

## The role of probiotics as gastrointestinal infections treatment and prophylaxis: A review

Gabriel Gomes Vieira Ribeiro Leite<sup>1\*</sup>, Carlos Américo Veiga Damasceno<sup>2</sup>

<sup>1</sup> University of Itaúna, Itaúna, Minas Gerais, Brazil

<sup>2</sup> University of Itaúna, Department of Microbiology, Itaúna, Minas Gerais, Brazil

\* **Corresponding Author:** Gabriel Gomes Vieira Ribeiro Leite **E-mail:** [medgabrielvieira@gmail.com](mailto:medgabrielvieira@gmail.com)

### ABSTRACT

**Objective:** Probiotics are products that contain microorganisms capable of supporting symbiotic relations with native microbiota of many environments. They are widely used and studied due to their capacity to improve biological systems' overall health. Many hypothesis exist surrounding the mechanisms by which every microbe labelled as probiotic is the cause by which system health is enhanced by its presence. The aim of this review was to compile article's data concerning the role of different combinations of probiotics used to treat and prevent gastrointestinal conditions, such as antibiotic-associated diarrhea, pseudomembranous colitis, Helicobacter pylori infections, oral, pharyngeal and Salmonella infections. In general, other than presenting excellent safety records, several probiotic combinations registered in clinical trials could prove themselves capable of significantly preventing those infections and some proved to be capable to also treat them once established. The main challenge among the infections studies seems to be oral cavity infections, probably due to microbiota complexity. Nevertheless, probiotics seem to have good prospect for playing a major preventive and protective role in gastrointestinal infections with further investigation to gather sufficient evidence to base treatment protocols.

**Keywords:** Probiotics; Gastrointestinal Diseases; Clinical Protocols, review

### INTRODUCTION

The definition of probiotics was first produced in 1965 by Lilly and Stillwell (1) as bacteria who could increase other bacteria proliferation within biological systems, since then, they have had their definition and usage broadly expanded. Currently updated by Hill et al. in 2014, the meaning of probiotics is now fit to describe microorganisms that can improve the health of a system when ingested insufficient amounts (2).

Therefore, such definition is intended to include their effects on many human systems concerning medical sciences, mainly by impacting the resident microbiota, intestinal epithelium cells, the immune system, and cell-mediated response to infection and stress.

The most studied species include Lactobacillus, Bifidobacterium, and Saccharomyces (3), but even prior to the first steps investigating probiotics' potential, bacteria described as probiotic have been empirically added to dietary supplementation and foods due to the potential beneficial effects their action could produce for human health, and naturally clinical trials have been extensively conducted to measure and improve probiotic consumption and selection (4). Further than that, many studies nowadays have provided evidence to support probiotics' use as treatment and prophylaxis of a large array of infections, such as those produced by Helicobacter pylori, Clostridium difficile on the gastrointestinal tract, Streptococcus mutans on caries and periodontitis, many upper and lower respiratory tract infections, inflammatory bowel disease and diarrhea microbes, as well as other diseases.

Not only typical presentation cases management have shown to be improved by probiotics use, but also multi-drug resistant bacteria infections could potentially be considered for probiotics use, amplifying their relevance since those are universally important public health issues.

### Review Article

**Received** 01-09-2021

**Accepted** 09-09-2021

**Available Online:** 10-09-2021

**Published** 30-09-2021

Distributed under  
Creative Commons CC-BY-NC 4.0

**OPEN ACCESS**



The major role probiotics could play, if proven to be effective, is to decrease antibiotic use, which has the catastrophic side-effect of microbial resistance development, other than being a cause of many gastrointestinal conditions themselves, such as very common cases of antibiotic-associated diarrhea (AAB). Mitigating the burdens of diseases and antibiotic use could improve health care morbidity, mortality and cost worldwide (5).

Further on, the interest on probiotics is also inspired by high safety standards extensively recorded on literature (6) (7), even on immunocompromised HIV patients (8) and children (9).

We present this article as an endeavor to produce an updated compilation of current literature concerning probiotic use on several infections and its comparison to traditional antibiotic treatment on terms of prophylactic and treatment effectiveness, safety, and outcomes on gastrointestinal infections.

## MATERIAL and METHODS

The present review focused research on well-oriented clinical trials concerning probiotic use on AAD, *Clostridium difficile* infection (CDI), *Helicobacter pylori* infection, *Streptococcus mutans* oral infections, *Streptococcus* and *Bacilli* pharyngeal infections and *Salmonella* infection.

Article research was conducted on PubMed, Scielo, Science Direct and Medline bases. The following key-words were used: "probiotics", "treatment", "prevention", "*Clostridium difficile* infection", "*Helicobacter pylori*", "*Salmonella*", "oral infection", "microbiota", "pharynx infection", "antibiotic" as well as its equivalents in Portuguese. Boxes "AND" and "OR" were selected when they were present.

Enters and records identified in the electronic data banks were exported to the platform Rayaan, used in selection. Studies were initially filtered by title and abstract independently and those selected on a first filtration were evaluated regarding eligibility and inclusion in this review by full-text analysis.

Articles of opinion and isolated case reports were the only automatic exclusion criteria for article analysis, and no case complications were considered as to differ among infection presentations. Articles were also not excluded based on language, date or place of conduction.

## RESULTS

### 1. Probiotics use on Antibiotic-associated diarrhea (AAD)

AAD is a common and undesirable adverse effect of antibiotic treatment and can present itself disregarding previous patient conditions. It occurs in as many as 30% of patients (10) and is characterized by disruption of gut microbiota, decreased intestinal short-chain fatty acid (SCFA) concentrations, accumulation of luminal carbohydrates and colonic bile acids, altered water absorption, and ultimately diarrhea (11).

Several articles evaluated probiotic treatment in children since they are particularly at risk with the incidence of AAD being as high as 35% (12), and all conclusive ones suggested probiotics to be effective in preventing and treating AAD,

despite previous theoretical conjectures which suggested that probiotic treatment was a logical flaw on AAD (13).

Compiling thirty-three studies with more than 6300 patients ranging from 0 to 18 years-old, organized in random groups for probiotic treatment, placebo, and no treatment at all it was recorded precise benefit for probiotics. Diarrhea incidence after five days to 12 weeks of follow-up was shown to be 8% in the probiotic group, in comparison to 19% in the control group (risk ratio RR 0.45, 95% confidence interval CI 0.36 to 0.56;  $P = 57%$ , 6352 participants; 95% CI 7 to 13). Low dose studies (< 5 billion CFUs per day) showed that the incidence of AAD in the probiotic group was 8% compared to 23% in the control group (4038 participants; RR 0.37; 95% CI 0.30 to 0.46;  $P = 0.06$ ) and high dose studies ( $\geq 5$  billion CFUs per day) recorded incidence rates of 13% in the probiotic group compared to 23% in control group (4425 participants; RR 0.54; 95% CI 0.42 to 0.70;  $P < 0.00001$ ;  $P^2 = 68%$ ) (14). The results suggested the effectiveness of treatment to be dose-dependent.

Comparing safety among 24 of those trials (4415 participants) which reported on adverse events, serious adverse events none reported attributable to probiotics.

Although also insensitive due to numerous subgroups consideration, another compilation of 82 randomized trials showed statistically significant AAD reduction results by associating probiotics to antibiotic treatment (relative risk, 0.58; 95% CI, 0.50 to 0.68;  $P < .001$ ; I(2), 54%) (15).

On the strands used, *Lactobacillus rhamnosus* GG (LGG) had the better record of effectiveness and tolerability on prevention of AAD, and even though *Clostridium difficile* is broadly known to cause around 20% of AAD as an opportunistic pathogen (16), it is better analyzed independently since a 2018 article reported that *Lactobacillus casei* was considered as presenting better efficacy and moderately better tolerance for its infections (17). Another strong recommendation strand is claimed to be *Saccharomyces boulardii*, although evidence is still lacking and current results are still behind LGG (18).

A double-blind randomized study conducted in Australia also confirmed LGG effectiveness combined with *Bifidobacterium lactis* (Bb-12) and *Lactobacillus acidophilus* (La-5). Children were given 200g/day probiotic yogurt versus pasteurized yogurt as placebo, with a narrower population consisting of 72 children of which 70 completed treatment, no severe diarrhea (stool consistency  $\geq 6$ ,  $\geq 3$  stools/day for  $\geq 2$  consecutive days) episodes were reported in probiotic group while six presented in placebo, and only one minor diarrhea (stool consistency  $\geq 5$ ,  $\geq 2$  stools/day for  $\geq 2$  days) episode was presented in probiotic group compared to 21 in placebo (19).

### 2. Probiotics use in *Clostridium difficile* infection (CDI)

The usual *Clostridium difficile* infection causes pseudomembranous colitis, and it is also the leading opportunistic pathogen to cause AAD. Disruption of gastrointestinal microbiota is the most evidence-based infection etiology, since normal conditions usually suffice for preventing *Clostridium* infection (20).

A recent consensus guidelines published by the British Society of Gastroenterology did mention probiotics as

relatively effective treatment to CDI, although it suggested that its use should be restricted to very uncommon scenarios and never as first line treatment or prophylaxis, opposing antibiotics, claiming evidence was lacking (21). Nevertheless, several articles were then conducted, including a Cochrane database article, indicating that guidelines should be revised, since probiotics have the highest quality evidence among cited prophylactic therapies (22).

In order to base this claim, the study compiled thirty-nine studies, concluding that probiotic prophylaxis should reduce the risk of *C. difficile*-associated diarrhea by 60%. The incidence of presentations was 1.5% in the probiotic group and 4.0% in the control (RR 0.40, 95% CI 0.30 to 0.52), which was considered to be statistically significant, even though it noted the heterogeneity of results when pooled.

Even prior to the guideline's publication, many articles suggested reasonable evidence that probiotics could indeed prevent CDI in many cases. New mechanisms were even discovered, suggesting probiotics health promotion worked not only through microbiome protection but also by directly inhibiting pathogen growth, neutralizing toxins, and modulating inflammatory response (23) (24).

The most successful treatment seems to be a multi-strand formula, combining *L. acidophilus* CL1285, *L. casei* LBC80R, *L. rhamnosus* CLR2, Bio-K+, which also showed an excellent safety profile, even in preventing *C. difficile* hospital infections (25).

These recent results should suffice safety evidence that concerned previous researchers who found great efficacy outcomes (26) (27) (28) (29).

### 3. Probiotics use in *Helicobacter pylori* infection (HPI)

*Helicobacter pylori* infections are relatively common, affect nearly half the world population, and its relevance relies not only on its relation with many gastrointestinal diseases, but also on extragastric manifestations (30). An alternative to antibiotic treatment is usually described as urgent, mainly due to bacterial resistance development (31). Thus, the role of probiotics seems to fit perfectly with *H. pylori* eradication treatment demands.

A recent Chinese study reviewed one hundred and forty results for probiotic eradication therapy in a massive population group (20,215 patients) in order to investigate different probiotics supplementation's effectiveness. All data considered, eradication rates were 84.1% in probiotic group while 70.5% in control, and adverse events rates were 14.4% in probiotic group while 30.1% in control (32).

In general, more than ten strategies of probiotic treatment have experimented and no statistically significant difference was found amidst the strands. Combined therapy did not show better results or tolerance either. Differences among strands seems to rely on treatment length, being *Lactobacillus acidophilus* a slightly better choice in in triple therapy of 7 and 14 days, while *Saccharomyces boulardii* was more applicable for 10-day triple therapy.

Some notable strands properties should also be noted for further investigation, such as *L. pentosus* LPS16, which lactic acid production has been shown to inhibit both drug-sensitive and drug-resistant *H. pylori* strains *in vitro* (33). The same

effect could also be obtained from seven *L. bulgaricus* strains (34). The acid-resistant strain *L. johnsonii* No.1088, isolated from gastric juice of healthy volunteers could suppress *H. pylori* both *in vitro* and in a mouse model, and the heat-killed form of the strain also showed antibacterial effects (35) (36). Many hypotheses suggest mechanisms for the antagonism probiotics exert against *H. pylori*, although molecular studies are still pending for their confirmation (37).

From this review on, few interesting studies were conducted which led to new discoveries and hypothesis concerning probiotics treatment in HPI.

A research conducted on model animals showed a significant association of probiotic treatment with reduction on gastric inflammation secondary to HPI, and also suggested that long-term administration of probiotics might have favorable outcomes in *H. pylori* infection especially by decreasing the risk of development of diseases caused by increased levels of gastric inflammation, such as gastric ulcer (38). Other than that, the study also confirmed probiotics' colonization reduction capability previously observed.

Clinical researchers have yet failed to report on a probiotic treatment that could alone achieve *H. pylori* eradication. This is expected to be the great breakthrough of gastric probiotic therapy, and it is optimistically indicated to happen as further trials are conducted (39).

### 4. Probiotics use on oral infections

Probiotics are thoroughly studied in oral health problems mainly because periodontal diseases and dental caries are usually treated with systemic use of antimicrobial drugs<sup>39</sup>, which can trigger gastrointestinal conditions, as previously exposed, as well as promote bacterial resistance and allergic reactions (40).

Oral microbiota is a delicate subject in the clinics, since the oral cavity is a complex microbiological system that needs homeostasis (41). In order for microorganisms and toxins to attack oral tissues, they are usually organized in a thin film layer deposited on hard oral tissue (enamel and cementum) called biofilm (42), which is described to be the result of bacterial adhesion, aggregation and co-aggregation to colonize the oral cavity (43).

Although action mechanism for probiotic therapy in oral health is still obscure, they are widely correlated with decreased CFU counts of pathogens (44) (45). A review suggests the very interesting hypothesis of the microbiological dynamic of probiotics in the oral cavity competing for adhesion with pathogens, causing the latter's displacement (46).

A meta-analysis of articles concerning caries development with probiotic therapy recorded a significant decrease in CFU counts of *S. mutans* after bacteriotherapy, which does not happen with the CFU counts of *Lactobacilli*. In addition, after treatment with probiotics, the intervention group had a greater number of patients with low levels of *S. mutans* CFU counts (< 105 CFU/ml) and fewer patients with high levels (> 106 CFU/ml), which does not occur in the control group (47).

On the other hand, a double-blind clinical trial on 96 children divided into three groups receiving probiotics (*B. lactis* BB-12), xylitol or sorbitol for control, concluded that early

administration of this probiotic strain did not represent its permanent colonization in the oral cavity and that the CFU counts of *S. mutans* were not significantly affected (48). In addition, yet another three randomized clinical trials reviewed by Twetman, *et al.* (49) using *L. Rhamnosus* and milk as a vehicle for the prevention of dental caries concluded that despite encouraging results and given evidence collected, it is still premature to present probiotics as a preventive clinical recommendation, and indicated the need for long-term follow-up in order to establish needed confirmation for the therapy.

Another meta-analysis of 50 clinical trials suggested that probiotic therapy significantly reduces the *S. mutans* CFU counts (<104 UFC/ml), and that *Bifidobacteria* are the most significant contributor to this effect, but studies that brought up data to this conclusion has a high risk of bias, therefore, forcing researchers to conclude that current clinical evidence is inconsistent in order to make recommendations for the use of probiotics to treat or prevent dental caries (50).

Periodontal conditions and caries, being multifactorial diseases (51), seem to trouble trials with more variables to consider than it is possible to manage to organize data. That is one review's hypothesis to why despite the evidence, it is still impossible to make a statement towards probiotics recommendations in oral health (52).

Many other clinical trials (53) were conducted and are currently ongoing investigating other strands in oral health probiotics, such as *S. oralis*, *S. uberis*, *L. salivarius* and *S. rattus*, other pathogens' CFU counts are being considered as *Prevotella intermedia*, *Agregatibacter actinomycetemcomitans* and *Porphyromana gingivalis* and researchers struggle to extend follow-up time. Nevertheless, the main conclusion seems to remain that probiotics cannot replace daily oral hygiene technique (54).

### 5. Probiotics use in pharyngeal infections

Pharyngeal infections, notably the ones caused by *Streptococcus pyogenes*, also produces the previously described structure of biofilm. And as well as in the oral cavity, in the pharynx bacteria in biofilms are less sensitive to host defense mechanisms and antimicrobial agents, due to multiple strategies, that involve modulation of gene expression, controlled metabolic rate, intercellular communication, composition, and 3D architecture of the extracellular matrix (55).

In 2012, inspired by the probiotic potential to modulate cavity microbiota to protect it from infections, an *in vitro* research was conducted to experiment and investigate the functional and immunomodulatory properties of the strains *Lactobacillus helveticus* MIMLh5 and *Streptococcus salivarius* ST3 (56), which were highlighted previously by other studies (57) (58). This study concluded that strains MIMLh5 and ST3, alone and in combination, can efficiently adhere to pharyngeal epithelial cells, antagonize *S. pyogenes*, and modulate host innate immunity by inducing potentially protective effects. In addition, it also reported that their combination resulted in a synergistic effect, according to cytokine induction, that might help the host immune system react to potential pathogens while maintaining a balance between pro- and anti-inflammatory cytokines, thus preventing possible exaggerated responses.

Another *in vitro* article observed that *S. salivarius* 24SMB and *S. oralis* 89a are able to inhibit the biofilm formation capacity of selected pathogens and even to disperse their preformed biofilms. Diffusible molecules secreted by the two streptococci and lowered pH of the medium revealed to be implied in the mechanisms of anti-biofilm activity (59).

New strands other than *Streptococcus salivarius*, probiotic candidates *Lactobacillus acidophilus* and *Lactobacillus plantarum* were tested for the same protective properties in a *in vitro* pharynx cosmos, showing promising results together with many other bacteria native to the natural environment (60). The article purposes itself to be a preclinical towards future probiotic trials, and no clinical trials were published yet to this review's making date concerning probiotics use in pharyngeal infections that would suffice inclusion criteria, even though given laboratory evidence it poses as a great prospect for a safe upper respiratory infections treatment.

### 6. Probiotics use in *Salmonella* spp. Infections

*Salmonella* spp. Infections are one of the leading causes of acute diarrhea worldwide (61). As a long known disease, efforts to employ microorganisms therapy, which would today be called probiotic therapy, started even before the first definition of the word itself, in 1959, when Nissle published an article with records of an *E. coli* strain isolated from a soldier which appeared to be resistant to a diarrhea outbreak and seemed to establish persistent intestine colonization, therefore, suggesting its potential to compete with intestinal infections (62).

Nissle hypothesis' success mechanisms were explained in 2017, when a trial in rats infected with *S. enterica* serovar Typhimurium showed *E. coli* strain Nissle 1917 outcompeted the pathogen for iron acquisition (63) which is established as the most important micronutrient for its virulence (64).

Further on, many other probiotics were suggested to alleviate salmonellosis as time progressed. A study identified two non-*Saccharomyces* species - *K. marxianus* and *Metschnikowia gruessii* - as significantly capable of protecting host's intestinal epithelium against disrupting activity from the same *Salmonella* strain (65).

Animal trials in newly hatched broiler chicken with a multi-species probiotic consisting of *Lactobacillus crispatus*, *Lactobacillus salivarius*, *Lactobacillus gallinarum*, *Lactobacillus johnsonii*, *Enterococcus faecalis* and *Bacillus amyloliquefaciens* showed better and safer results than traditional antibiotic therapy with oxytetracycline, used as control. Results were significant to the point which probiotic therapy were suggested as preferred choice of treatment (66). Other studies with other strands were also published studying probiotics in poultry and rats, many of which were absolutely successful, through different biochemical mechanisms of pathogen inhibition (67) (68) (69) (70).

In fact, microbiota seems to play an extraordinarily important role in *Salmonella* infections, being shown that slight variation in endogenous *Enterobacteriaceae* could importantly determine host's susceptibility to infection, even in genetically similar organisms (71). Confirming probiotics effectiveness, several clinical trials in humans replicated *in vitro* and *in vivo* animal trials (72). A randomized controlled trial showed *Lactobacillus plantarum* 299 could accelerate

clearance of non-typhoid *Salmonella* and reduce infection-related symptoms, which was influenced by gender (73).

Recently, that first *E. coli* strand isolated by Nissle (62) was subject to bioengineering and successfully inhibited *Salmonella* colonization via tetrathionate-induced production of microcin H47. The strand seems to greatly outcompete *Salmonella*, using an environmental signal indicative of intestinal inflammation as an inducing molecule, resulting in a considerable increase in fitness advantage (74).

## CONCLUSION

The quality of evidence for the use of probiotics to treat or prevent gastrointestinal tract infections seems to be uneven. While its usage on AAD, CDI and *Salmonella* infections have shown reasonably positive clinical results and are already incorporated to protocol therapies, it remains unclear which exact mechanisms, microbiological interactions and method approaches could account for many discrepant results in some trials. The main challenge seems to present in oral infections applications, due to the microbiota dynamics complexity.

In assessing safety, probiotics seem to exceed traditional antibiotic treatment, given almost no record of adverse events from all evaluated studies in comparison to the known problematic and often iatrogenic drug therapies. Overall, probiotics seem to have increasingly good prospects in clinical use, even though further research is needed in order to produce evidence for strain selection and effectiveness in specific diseases.

**Acknowledgements:** We are thankful to DD Juliana Gomes Vieira and former cytology technician José Atanásio Vieira for technical support and scientific partnership. We are also grateful to University of Itaúna's higher administration.

**Author Contributions: GGVRL, CAVD:** Literature Search, Data collection, Article writing and revisions

**Financial & competing interest's disclosure:** The authors have no relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

**Ethical approval:** The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee

**Conflict of interest:** The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive and specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## REFERENCES

- Lilly DM, Stillwell RH. Probiotics: growth-promoting factors produced by microorganisms. *Science*. 1965 Feb 12;147(3659):747-8.
- Hill C., Guarner F., Reid G., Gibson G. R., Merenstein D. J., Pot B., et al. (2014). Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat. Rev. Gastroenterol. Hepatol.* 11, 506–514. [10.1038/nrgastro.2014.66](https://doi.org/10.1038/nrgastro.2014.66)
- Wilkins T, Sequoia J. Probiotics for Gastrointestinal Conditions: A Summary of the Evidence. *Am Fam Physician*. 2017 Aug 1;96(3):170-178. PMID: 28762696.
- Doron S, Gorbach SL. Probiotics: their role in the treatment and prevention of disease. *Expert Rev Anti Infect Ther*. 2006 Apr;4(2):261-75. doi: 10.1586/14787210.4.2.261. PMID: 16597207.
- Pattani R, Palda VA, Hwang SW, Shah PS. Probiotics for the prevention of antibiotic-associated diarrhea and *Clostridium difficile* infection among hospitalized patients: systematic review and meta-analysis. *Open Med*. 2013 May 28;7(2):e56-67. PMID: 24348885; PMCID: PMC3863752
- Stadlbauer V. Immunosuppression and probiotics: are they effective and safe? *Benef Microbes*. 2015;6(6):823-8. doi: 10.3920/BM2015.0065. Epub 2015 Aug 19. PMID: 26287986..
- Sanders ME, Akkermans LM, Haller D, Hammerman C, Heimbach J, Hörmannspurger G, Huys G, Levy DD, Lutgendorff F, Mack D, Phothirath P, Solano-Aguilar G, Vaughan E. Safety assessment of probiotics for human use. *Gut Microbes*. 2010 May-Jun;1(3):164-85. doi: 10.4161/gmic.1.3.12127. Epub 2010 Mar 4. PMID: 21327023; PMCID: PMC3023597.
- Happel AU, Barnabas SL, Froissart R, Passmore JS. Weighing in on the risks and benefits of probiotic use in HIV-infected and immunocompromised populations. *Benef Microbes*. 2018 Feb 27;9(2):239-246. doi: 10.3920/BM2017.0106. Epub 2018 Jan 18. PMID: 29345159.
- Jin L, Deng L, Wu W, Wang Z, Shao W, Liu J. Systematic review and meta-analysis of the effect of probiotic supplementation on functional constipation in children. *Medicine (Baltimore)*. 2018 Sep;97(39):e12174. doi: 10.1097/MD.00000000000012174. PMID: 30278490; PMCID: PMC6181519.
- Barbut F, Meynard JL. Managing antibiotic associated diarrhoea. *BMJ*. 2002;324(7350):1345-134612052785
- Mekonnen SA, Merenstein D, Fraser CM, Marco ML. Molecular mechanisms of probiotic prevention of antibiotic-associated diarrhea. *Curr Opin Biotechnol*. 2020 Feb;61:226-234. doi: 10.1016/j.copbio.2020.01.005. Epub 2020 Feb 19. PMID: 32087535; PMCID: PMC7096272.
- McFarland LV, Ozen M, Dinleyici EC, Goh S: Comparison of pediatric and adult antibiotic-associated diarrhea and *Clostridium difficile* infections. *World J Gastroenterol* 2016, 22: 3078–3104.
- Gould K, Short G. Probiotics and antibiotic-associated diarrhoea—a logical flaw? *J Antimicrob Chemother*. 2008 Mar;61(3):761. doi: 10.1093/jac/dkm534. Epub 2008 Jan 28. PMID: 18227093.
- Guo Q, Goldenberg JZ, Humphrey C, El Dib R, Johnston BC. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. *Cochrane Database Syst Rev*. 2019 Apr 30;4(4):CD004827. doi: 10.1002/14651858.CD004827.pub5. PMID: 31039287; PMCID: PMC6490796.
- Hempel S, Newberry SJ, Maher AR, Wang Z, Miles JN, Shanman R, Johnsen B, Shekelle PG. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. *JAMA*. 2012 May 9;307(18):1959-69. doi: 10.1001/jama.2012.3507. PMID: 22570464.
- Song HJ, Shim KN, Jung SA, Choi HJ, Lee MA, Ryu KH, Kim SE, Yoo K. Antibiotic-associated diarrhea: candidate organisms other than *Clostridium difficile*. *Korean J Intern Med*. 2008 Mar;23(1):9-15. doi: 10.3904/kjim.2008.23.1.9. PMID: 18363274; PMCID: PMC2686956
- Cai J, Zhao C, Du Y, Zhang Y, Zhao M, Zhao Q. Comparative efficacy and tolerability of probiotics for antibiotic-associated diarrhea: Systematic review with network meta-analysis. *United European Gastroenterol J*. 2018 Mar;6(2):169-180. doi: 10.1177/2050640617736987. Epub 2017 Oct 4. PMID: 29511547; PMCID: PMC5833232

18. Szajewska H, Canani RB, Guarino A, Hojsak I, Indrio F, Kolacek S, Orel R, Shamir R, Vandenplas Y, van Goudoever JB, Weizman Z; ESPGHAN Working Group for Probiotics/Prebiotics. Probiotics for the Prevention of Antibiotic-Associated Diarrhea in Children. *J Pediatr Gastroenterol Nutr.* 2016 Mar;62(3):495-506. doi: 10.1097/MPG.0000000000001081. PMID: 26756877.
19. Fox MJ, Ahuja KD, Robertson IK, Ball MJ, Eri RD. Can probiotic yogurt prevent diarrhoea in children on antibiotics? A double-blind, randomised, placebo-controlled study. *BMJ Open.* 2015 Jan 14;5(1):e006474. doi: 10.1136/bmjopen-2014-006474. PMID: 25588782; PMCID: PMC4298112.
20. Mullish BH, Williams HR. Clostridium difficile infection and antibiotic-associated diarrhoea. *Clin Med (Lond).* 2018 Jun;18(3):237-241. doi: 10.7861/clinmedicine.18-3-237. PMID: 29858434; PMCID: PMC6334067.
21. Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, Hayee B, Lomer MCE, Parkes GC, Selinger C, Barrett KJ, Davies RJ, Bennett C, Gittens S, Dunlop MG, Faiz O, Fraser A, Garrick V, Johnston PD, Parkes M, Sanderson J, Terry H; IBD guidelines eDelphi consensus group, Gaya DR, Iqbal TH, Taylor SA, Smith M, Brookes M, Hansen R, Hawthorne AB. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut.* 2019 Dec;68(Suppl 3):s1-s106. doi: 10.1136/gutjnl-2019-318484. Epub 2019 Sep 27. Erratum in: *Gut.* 2021 Apr;70(4):1. PMID: 31562236; PMCID: PMC6872448.
22. Goldenberg JZ, Yap C, Lytvyn L, Lo CK, Beardsley J, Mertz D, Johnston BC. Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. *Cochrane Database Syst Rev.* 2017 Dec 19;12(12):CD006095. doi: 10.1002/14651858.CD006095.pub4. PMID: 29257353; PMCID: PMC6486212.
23. Bermudez-Brito M, Plaza-Díaz J, Muñoz-Quezada S, Gómez-Llorente C, Gil A. Probiotic mechanisms of action. *Ann Nutr Metab.* 2012;61(2):160-74. doi: 10.1159/000342079. Epub 2012 Oct 2. PMID: 23037511.
24. McFarland LV. Use of probiotics to correct dysbiosis of normal microbiota following disease or disruptive events: a systematic review. *BMJ Open.* 2014 Aug 25;4(8):e005047. doi: 10.1136/bmjopen-2014-005047. PMID: 25157183; PMCID: PMC4156804.
25. McFarland LV, Ship N, Auclair J, Millette M. Primary prevention of Clostridium difficile infections with a specific probiotic combining Lactobacillus acidophilus, L. casei, and L. rhamnosus strains: assessing the evidence. *J Hosp Infect.* 2018 Aug;99(4):443-452. doi: 10.1016/j.jhin.2018.04.017. Epub 2018 Apr 24. PMID: 29702133.
26. Barker AK, Duster M, Valentine S, Hess T, Archbald-Pannone L, Guerrant R, Safdar N. A randomized controlled trial of probiotics for Clostridium difficile infection in adults (PICO). *J Antimicrob Chemother.* 2017 Nov 1;72(11):3177-3180. doi: 10.1093/jac/dkx254. PMID: 28961980; PMCID: PMC5890711.
27. De Wolfe TJ, Eggers S, Barker AK, Kates AE, Dill-McFarland KA, Suen G, Safdar N. Oral probiotic combination of Lactobacillus and Bifidobacterium alters the gastrointestinal microbiota during antibiotic treatment for Clostridium difficile infection. *PLoS One.* 2018 Sep 28;13(9):e0204253. doi: 10.1371/journal.pone.0204253. PMID: 30265691; PMCID: PMC6161886.
28. Mills JP, Rao K, Young VB. Probiotics for prevention of Clostridium difficile infection. *Curr Opin Gastroenterol.* 2018 Jan;34(1):3-10. doi: 10.1097/MOG.0000000000000410. PMID: 29189354; PMCID: PMC6335148.
29. Evans CT, Johnson S. Prevention of Clostridium difficile Infection With Probiotics. *Clin Infect Dis.* 2015 May 15;60 Suppl 2:S122-8. doi: 10.1093/cid/civ138. PMID: 25922397.
30. Gravina AG, Zagari RM, De Musis C, Romano L, Loguercio C, Romano M. Helicobacter pylori and extragastric diseases: A review. *World J Gastroenterol.* 2018 Aug 7;24(29):3204-3221. doi: 10.3748/wjg.v24.i29.3204. PMID: 30090002; PMCID: PMC6079286.
31. Suzuki S, Esaki M, Kusano C, Ikehara H, Gotoda T. Development of Helicobacter pylori treatment: How do we manage antimicrobial resistance? *World J Gastroenterol.* 2019 Apr 28;25(16):1907-1912. doi: 10.3748/wjg.v25.i16.1907. PMID: 31086459; PMCID: PMC6487377.
32. Wang F, Feng J, Chen P, Liu X, Ma M, Zhou R, Chang Y, Liu J, Li J, Zhao Q. Probiotics in Helicobacter pylori eradication therapy: Systematic review and network meta-analysis. *Clin Res Hepatol Gastroenterol.* 2017 Sep;41(4):466-475. doi: 10.1016/j.clinre.2017.04.004. Epub 2017 May 25. PMID: 28552432.
33. Zheng P.X., Fang H.Y., Yang H.B., Tien N.Y., Wang M.C., Wu J.J. Lactobacillus pentosus strain LPS16 produces lactic acid, inhibiting multidrug-resistant Helicobacter pylori. *J. Microbiol. Immunol. Infect.* 2016;49:168-174. doi: 10.1016/j.jmii.2014.04.014.
34. Boyanova L., Gergova G., Markovska R., Yordanov D., Mitov I. Bacteriocin-like inhibitory activities of seven Lactobacillus delbrueckii subsp. bulgaricus strains against antibiotic susceptible and resistant Helicobacter pylori strains. *Lett. Appl. Microbiol.* 2017;65:469-474. doi: 10.1111/lam.12807.
35. Aiba Y., Nakano Y., Koga Y., Takahashi K., Komatsu Y. A highly acid-resistant novel strain of Lactobacillus johnsonii No. 1088 has antibacterial activity, including that against Helicobacter pylori, and inhibits gastrin-mediated acid production in mice. *Microbiologyopen.* 2015;4:465-474. doi: 10.1002/mbo3.252.
36. Aiba Y., Ishikawa H., Tokunaga M., Komatsu Y. Anti-Helicobacter pylori activity of non-living, heat-killed form of lactobacilli including Lactobacillus johnsonii No.1088. *FEMS Microbiol. Lett.* 2017;364 doi: 10.1093/femsle/fnx102.
37. Ji J, Yang H. Using Probiotics as Supplementation for Helicobacter pylori Antibiotic Therapy. *Int J Mol Sci.* 2020 Feb 8;21(3):1136. doi: 10.3390/ijms21031136. PMID: 32046317; PMCID: PMC7037652.
38. Chakravarty K, Gaur S. Role of Probiotics in Prophylaxis of Helicobacter pylori Infection. *Curr Pharm Biotechnol.* 2019;20(2):137-145. doi: 10.2174/1389201020666190227203107. PMID: 30827235.
39. Becker DE. Drug allergies and implications for dental practice. *AnesthProg.* 2013;60:188-97.
40. Becker DE. Antimicrobial drugs. *AnesthProg.* 2013;60:111-22
41. Zarco MF, Vess TJ, Ginsburg GS. The oral microbiome in health and disease and the potential impact on personalized dental medicine. *Oral Diseases.* 2012;18:109-20.
42. Zijne V, van Leeuwen MB, Degener JE, Abbas F, Thurnheer T, Gmür R. Oral biofilm architecture on natural teeth. *PLoS One.* 2010;5:e9321
43. Piwat S, Sophatha B, Teanpaisan R. An assessment of adhesion, aggregation and surface charges of Lactobacillus strains derived from the human oral cavity. *LettApplMicrobiol.* 2015;61:98-105.
44. Laleman I, Yilmaz E, Ozcelik O, Haytac C, Pauwels M, Herrero ER. The effect of a streptococci containing probiotic in periodontal therapy: a randomized controlled trial. *J Clin Periodontol.* 2015;42:1032-41.
45. Morales A, Carvajal P, Silva N, Hernandez M, Godoy C, Rodriguez G. Clinical Effects of Lactobacillus rhamnosus in Non-Surgical Treatment of Chronic Periodontitis: A Randomized Placebo-Controlled Trial With 1-Year Follow-Up. *J Periodontol.* 2016 Aug;87(8):944-52.
46. Faran Ali SM, Tanwir F. Oral microbial habitat a dynamic entity. *J Oral Biol Craniofac Res.* 2012;2:181-7.
47. Laleman I, Detailleur V, Slot DE, Slomka V, Quirynen M, Teughels W. Probiotics reduce mutans streptococci counts in humans: a systematic review and meta-analysis. *Clin Oral Investig.* 2014;18:1539-52.
48. Taipale T, Pienihäkkinen K, Salminen S, Jokela J, Söderling E. Bifidobacterium animalis subsp. lactis BB-12 administration in early childhood: a randomized clinical trial of effects on oral colonization by mutans streptococci and the probiotic. *Caries Res.* 2012;46:69-77.

49. Twetman S, Keller MK. Probiotics for caries prevention and control. *Adv Dent Res*. 2012;24:98–102.
50. Gruner D, Paris S, Schwendicke F. Probiotics for managing caries and periodontitis: Systematic Review and Meta-Analysis. *J Dent*. 2016;48:16–25.
51. Iheozor-Ejiofor Z, Worthington HV, Walsh T, O'Malley L, Clarkson JE, Macey R. Water fluoridation for the prevention of dental caries. *Cochrane Database Syst Rev*. 2015;6:CD010856.
52. Seminario-Amez M, López-López J, Estrugo-Devesa A, Ayuso-Montero R, Jané-Salas E. Probiotics and oral health: A systematic review. *Med Oral Patol Oral Cir Bucal*. 2017 May 1;22(3):e282–e288. doi: 10.4317/medoral.21494. PMID: 28390121; PMCID: PMC5432076.
53. Shimauchi H, Mayanagi G, Nakaya S, Minamibuchi M, Ito Y, Yamaki K. Improvement of periodontal condition by probiotics with *Lactobacillus salivarius* WB21: a randomized, double-blind, placebo-controlled study. *J Clin Periodontol*. 2008;35:897–905
54. Morales A, Carvajal P, Silva N, Hernandez M, Godoy C, Rodriguez G. Clinical Effects of *Lactobacillus rhamnosus* in Non-Surgical Treatment of Chronic Periodontitis: A Randomized Placebo-Controlled Trial With 1-Year Follow-Up. *J Periodontol*. 2016 Aug;87(8):944–52.
55. Alves-Barroco C, Paquete-Ferreira J, Santos-Silva T, Fernandes AR. Singularities of Pyogenic Streptococcal Biofilms - From Formation to Health Implication. *Front Microbiol*. 2020 Dec 23;11:584947. doi: 10.3389/fmicb.2020.584947. PMID: 33424785; PMCID: PMC7785724.
56. Taverniti V, Minuzzo M, Arioli S, Junttila I, Hämäläinen S, Turpeinen H, Mora D, Karp M, Pesu M, Guglielmetti S. In vitro functional and immunomodulatory properties of the *Lactobacillus helveticus* MIMLh5-*Streptococcus salivarius* ST3 association that are relevant to the development of a pharyngeal probiotic product. *Appl Environ Microbiol*. 2012 Jun;78(12):4209–16. doi: 10.1128/AEM.00325-12. Epub 2012 Apr 13. PMID: 22504812; PMCID: PMC3370528.
57. Wescombe PA, et al. 2011. Salivaricin 9, a new lantibiotic produced by *Streptococcus salivarius*. *Microbiology* 157:1290–1299
58. Guglielmetti S, et al. 2010. Oral bacteria as potential probiotics for the pharyngeal mucosa. *Appl. Environ. Microbiol*. 76:3948–3958
59. Bidossi A, De Grandi R, Toscano M, Bottagisio M, De Vecchi E, Gelardi M, Drago L. Probiotics *Streptococcus salivarius* 24SMB and *Streptococcus oralis* 89a interfere with biofilm formation of pathogens of the upper respiratory tract. *BMC Infect Dis*. 2018 Dec 13;18(1):653. doi: 10.1186/s12879-018-3576-9. PMID: 30545317; PMCID: PMC6292094.
60. Humphreys GJ, McBain AJ. Antagonistic effects of *Streptococcus* and *Lactobacillus* probiotics in pharyngeal biofilms. *Lett Appl Microbiol*. 2019 Apr;68(4):303–312. doi: 10.1111/lam.13133. Epub 2019 Mar 13. PMID: 30776138.
61. Popa GL, Papa MI. *Salmonella* spp. infection - a continuous threat worldwide. *Germes*. 2021 Mar 15;11(1):88–96. doi: 10.18683/germes.2021.1244. PMID: 33898345; PMCID: PMC8057844.
62. Nissle A. Explanations of the significance of colonic dysbacteria & the mechanism of action of *E. coli* therapy (mutaflor) *Medizinische*. 1959;4:1017–1022.
63. Deriu E, Liu JZ, Pezeshki M, Edwards RA, Ochoa RJ, Contreras H, Libby SJ, Fang FC, Raffatellu M. Probiotic bacteria reduce salmonella typhimurium intestinal colonization by competing for iron. *Cell Host Microbe*. 2013 Jul 17;14(1):26–37. doi: 10.1016/j.chom.2013.06.007. PMID: 23870311; PMCID: PMC3752295.
64. Crouch ML, Castor M, Karlinsey JE, Kalthorn T, Fang FC. Biosynthesis and IroC-dependent export of the siderophore salmochelin are essential for virulence of *Salmonella enterica* serovar Typhimurium. *Molecular microbiology*. 2008;67:971–983.
65. Smith IM, Baker A, Arneborg N, Jespersen L. Non-Saccharomyces yeasts protect against epithelial cell barrier disruption induced by *Salmonella enterica* subsp. *enterica* serovar Typhimurium. *Lett Appl Microbiol*. 2015 Nov;61(5):491–7. doi: 10.1111/lam.12481. Epub 2015 Sep 22. PMID: 26280244.
66. Neveling DP, van Emmenes L, Ahire JJ, Pieterse E, Smith C, Dicks LMT. Effect of a Multi-Species Probiotic on the Colonisation of *Salmonella* in Broilers. *Probiotics Antimicrob Proteins*. 2020 Sep;12(3):896–905. doi: 10.1007/s12602-019-09593-y. PMID: 31784950.
67. Carter A, Adams M, La Ragione RM, Woodward MJ. Colonisation of poultry by *Salmonella* Enteritidis S1400 is reduced by combined administration of *Lactobacillus salivarius* 59 and *Enterococcus faecium* PXN-33. *Vet Microbiol*. 2017 Feb;199:100–107. doi: 10.1016/j.vetmic.2016.12.029. Epub 2016 Dec 26. PMID: 28110775.
68. Levkut M, Pisl J, Lauková A, Revajová V, Herich R, Sevcíková Z, Stropfová V, Szabóová R, Kokincáková T. Antimicrobial activity of *Enterococcus faecium* ef 55 against *Salmonella* enteritidis in chicks. *Acta Vet Hung*. 2009 Mar;57(1):13–24. doi: 10.1556/AVet.57.2009.1.2. PMID: 19457770.
69. de Oliveira JE, van der Hoeven-Hangoor E, van de Linde IB, Montijn RC, van der Vossen JM. In ovo inoculation of chicken embryos with probiotic bacteria and its effect on posthatch *Salmonella* susceptibility. *Poult Sci*. 2014 Apr;93(4):818–29. doi: 10.3382/ps.2013-03409. PMID: 24706958.
70. Mazkour S, Shekarforoush SS, Basiri S, Nazifi S, Yektaseresht A, Honarmand M. Effects of two probiotic spores of *Bacillus* species on hematological, biochemical, and inflammatory parameters in *Salmonella* Typhimurium infected rats. *Sci Rep*. 2020 May 15;10(1):8035. doi: 10.1038/s41598-020-64559-3. PMID: 32415253; PMCID: PMC7229222.
71. Velazquez EM, Nguyen H, Heasley KT, Saechao CH, Gil LM, Rogers AWL, Miller BM, Rolston MR, Lopez CA, Litvak Y, Liou MJ, Faber F, Bronner DN, Tiffany CR, Byndloss MX, Byndloss AJ, Bäuml AJ. Endogenous Enterobacteriaceae underlie variation in susceptibility to *Salmonella* infection. *Nat Microbiol*. 2019 Jun;4(6):1057–1064. doi: 10.1038/s41564-019-0407-8. Epub 2019 Mar 25. PMID: 30911125; PMCID: PMC6533147.
72. Gut AM, Vasiljevic T, Yeager T, Donkor ON. *Salmonella* infection - prevention and treatment by antibiotics and probiotic yeasts: a review. *Microbiology (Reading)*. 2018 Nov;164(11):1327–1344. doi: 10.1099/mic.0.000709. Epub 2018 Aug 23. PMID: 30136920.
73. Lönnemark E, Lappas G, Friman V, Wold AE, Backhaus E, Adlerberth I. Effects of probiotic intake and gender on nontyphoid *Salmonella* infection. *J Clin Gastroenterol*. 2015 Feb;49(2):116–23. doi: 10.1097/MCG.000000000000120. PMID: 24667592.
74. Palmer JD, Piattelli E, McCormick BA, Silby MW, Brigham CJ, Bucci V. Engineered Probiotic for the Inhibition of *Salmonella* via Tetrathionate-Induced Production of Microcin H47. *ACS Infect Dis*. 2018 Jan 12;4(1):39–45. doi: 10.1021/acsinfectdis.7b00114. Epub 2017 Sep 20. PMID: 28918634; PMCID: PMC5766358.