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Influence of Probiotics on Antibiotic Therapy

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ABSTRACT

Antibiotics are the most prominent advances in medicine and have provided great benefits in the treatment and control of infectious diseases. Antibiotics do not differentiate good and bad germs, disrupting normal microflora and causing vitamin deficiency in the human body. They also kill healthy bacteria in the gut on a large scale, weakening the host's defence mechanism. AAD is a common side effect of antibiotic usage, which affects up to 30% of patients. Probiotics are live microorganisms, belonging to the genera Lactobacillus and Bifidobacterium, although strains of other species are commercialized, that have a beneficial effect on the host. From the perspective of antibiotic use, probiotics have been observed to reduce the risk of certain infectious disease such as antibiotic associated diarrhea, respiratory tract infection and also prevent secondary infections. This may be accompanied with a reduced need of antibiotics for secondary infections with protective and therapeutic effects against diseases and infectious agents. Probiotics have generally been considered safe; however, there have been rare reports of sepsis and fungemia associated with probiotic use, especially in critically ill and immunosuppressed patients.

Keywords: Antibiotics, probiotics, lactobacillus, bifidobacterium

HISTORY

The history of probiotics suggests that centuries ago people drank fermented milk for their health benefit. A scientist named Henry Tessler in 1899, from the Pasteur Institute in Paris discovered bifidobacterium in the intestine of breast-fed infants. He reported that infants with bifidobacterium in their intestines had fewer diarrheal episodes. However, in 1907 a Russian scientist named Eli Metchnikoff was the one who first proposed the idea of using probiotics for health benefits. Then in 1917 a strain of Escherichia coli was isolated and was used to treat patients suffering from shigellosis outbreak. Since then, several others documented the use of probiotics and are available in the literature, but well-designed clinical studies and data are lacking.[1]

INTRODUCTION

The term probiotic is derived from the Latin, which means ‘‘for life.’’ Probiotics are non-pathogenic, beneficial, live bacteria, and yeast. According to the definition of the Food and Agriculture Organization of the United Nations/World Health Organization (FAO/WHO), probiotics are live microorganisms that confer health benefit to the host when administered in adequate amounts. Many probiotics are originally isolated from the gastrointestinal tract and are associated with gut microbiota.[2] The commonly used probiotics are Lactobacillus, Bifidobacterium, and Saccharomyces boulardii. Bifidobacterium and Lactobacillus are Gram-positive rods that are obligated facultative anaerobes and S boulardii is a yeast. Lactobacillus includes several individual species, the most notable of which include L acidophilus, L rhamnosus, L reuteri, L bulgaricus, and L casei. Similarly, the Bifidobacterium species

that are most commonly used in probiotics include B animalis, B infantis, B lactis, and B longum.[1]

Antibiotics are one of the most prescribed medications worldwide. They disturb the normal gastrointestinal microbiota and the common consequence is diarrhoea. This leads to prolonged hospital admissions, increased morbidity and mortality, and greater costs to the health system.[3] Bacterial probiotics are frequently administered to humans in order to prevent the gastrointestinal side effects associated with antibiotic therapy. It is a well-diffused concept that the ingestion of high quantities of bacteria for instance, Lactobacillus or Bifidobacterium species, or of bacterial spores (Bacillus species), is able to restore the intestinal microflora following the alterations induced by antibiotics.[4] Probiotics are believed to improve the microbial balance of the host and reduce colonisation by pathogenic bacteria. They can be delivered orally, are thought to adhere to target gastrointestinal epithelium and are stable in bile and acid. They are available in capsules, powders and fermented milk drinks and are promoted in health food shops and supermarkets, and in the media, for a multitude of purposes.[3]

The defence mechanisms that defend the mammalian GIT from bacterial colonization are extremely complicated. Intestinal inflammation, which is caused by the imbalance in gut flora between pathogenic and commensal bacteria, causes the mucus layer to thin or disappear, allowing bacteria and their metabolites to pass through the mucus layer and invade intestinal epithelial cells, resulting in a reduction in intestinal mechanical barrier function.[5] Most mammals' GI tracts are colonized by two types of bacteria: 1) invasive pathogenic germs and 2) native microflora. Sustaining intestinal immunity and homeostasis requires a healthy gut microbiota. A shift in this equilibrium could have negative pathophysiological consequences.[6]

MECHANISM OF ACTION

The mechanisms of action of probiotics involve colonization and normalization of perturbed intestinal microbial communities in both children and adults; competitive exclusion of pathogens and bacteriocin production; modulation of enzymatic activities related to metabolization of a number of carcinogens and other toxic substances; and production of volatile fatty acids, namely, SCFAs and BCFAs, which play a role in the maintenance of energy homeostasis and regulation of functionality in peripheral tissues. In addition, probiotics increase intestinal cell adhesion and mucin production and modulate the activity of gut-associated lymphoid tissue and the immune system. Similarly, probiotic metabolites are able to interact with the brain-gut axis and play a role in behavior.[7]

CLINICAL APPLICATION OF PROBIOTICS

Probiotics can help with a number of acute and chronic infectious disorders, in addition to stomach problems like normalising intestinal microbiota which includes, intestinal mucosal integrity; colonization resistance; control of irritable bowel syndrome; control of inflammatory bowel syndrome, immunomodulation that includes, stimulation of specific immune response; stimulate activity of macrophage; alleviate food allergy; induction of natural killer cells and metabolic effects include improved lactose tolerance; lower serum cholesterol; lower toxigenic/mutagenic reaction; supply of SCFA and vitamins to colon epithelium. Antibiotics therapy, may alter the usual flora makeup of the stomach. The goal of functional food products like probiotics is to improve cellular well-being and accelerate the implementation of cells natural defence mechanisms. Several studies suggests that probiotics should be incorporated in the treatment plan, Probiotics are known to have immune-modulatory effects on the host, making them promising therapeutic and preventive option for a variety of illnesses, including

inflammatory disease. Consumption of probiotics in the form of powder, capsules, and drinks helps to restore the beneficial microflora in the gut, which benefits humans by boosting their immune systems.[1]

PROBIOTICS INFLUENCE ON ANTIBIOTICS

Probiotics are currently recommended by many healthcare providers for use during antibiotic treatment. The main purpose for doing so is that while antibiotics kill the "bad" bacteria in the body, they also destroy the "good" bacteria in the body. It is put forth that probiotics help support the good bacteria and, therefore, should be administered during antibiotic therapy not only to maintain the normal, health-promoting balance of intrinsic bacteria in the intestine, but also to avoid or reduce the unwanted side effects of antibiotic therapy; such as abdominal pain, flatulence and diarrhea, and Candida infestation.[8] Importantly, probiotics have demonstrated the ability to be effective in the treatment of some chronic infections, against which most antibiotics are ineffective. So far, there are no prescriptive guidelines for probiotic use during antibiotic treatment. Most recent practices are based upon inferences, opinions, anecdotal evidence and peer-based practice patterns.

AMR AND PROBIOTICS

The overuse of antibiotics has led to the widespread development of antimicrobial resistance. AMR poses a growing challenge to healthcare and is proposed to cause 10 million deaths per year by 2050 at an estimated cost of 100 trillion USD. The coadministration of probiotics and traditional antibiotics therefore has the potential to overcome AMR and combat complex infections. However, technically this is very challenging since most probiotics, being bacteria themselves, are susceptible to antibiotics and cannot survive coadministration. The transformation of bacteria using genetically designed plasmids is a common method to confer antibiotic resistance for probiotics. However, this method is inefficient and results in permanently resistant strain that has not only the potential to cause pathology but also the propensity to transfer the resistance to other bacteria. Probiotics that possess intrinsic antibiotic resistance have the same risk.[9]

PROBIOTICS IN ANTIBIOTIC ASSOCIATED DIARRHEA

A rise in the use of antibiotics has resulted in a marked increase in antibiotic-associated diarrhea
(AAD). AAD is a common side effect of antibiotic usage that affects up to one-third of patients who are treated with antibiotics. Antibiotic-associated diarrhea (AAD) occurs in 5% to 39% of patients, from the beginning and up to two months after the treatment. In particular, aminopenicillins, cephalosporins, and clindamycin that act on anaerobes are associated with a high risk of AAD.[10] AAD is associated with high morbidity, mortality, and health care costs.
There are different mechanisms and factors by which antibiotics can not only cause but also increase diarrhea which include, altering the diversity of gut bacteria, age of patient as the pediatric population is particularly at risk since, the infant microbiome is not fully developed; Spectrum of antibiotics, broad-spectrum antibiotics such as clindamycin, which are particularly active against anaerobes, are associated with higher rates of AAD whereas, narrow-spectrum antibiotics typically produce lower rates of AAD, metabolic disturbances, loss of colonization resistance. Colonization resistance is the ability of bacteria to prevent pathogenic microbes from invading. The gut microbiome regulates many metabolites including bile acids, carbohydrates, and amino acids. These metabolites help to defend against pathogens. An example is the regulation of Clostridium difficile through secondary bile acids. Secondary bile acids are produced by gut bacteria and inhibit C.

difficile growth. Antibiotics destroy the gut microbiome, leading to the diminishment of secondary bile acids. This then allows C. difficile to flourish.[11],[12] The concurrent administration of probiotics with antibiotics has also been studied as a potential preventive intervention against AAD.[11],[12]

PROBIOTICS IN CLOSTRIDIUM DIFFICILE INFECTION

Clostridium difficile colitis is an opportunistic infection caused by antibiotic-induced changes in the normal gut flora. The most commonly associated antibiotics include clindamycin, fluoroquinolones, broad spectrum penicillin, and cephalosporin. Clostridium difficile colitis infection is a condition that ranges in severity, with the most severe instances requiring admission to an intensive care unit and being fatal. Probiotics are living non-pathogenic bacteria that colonize in the gastrointestinal system and create a lytic peptide that inhibits Clostridium difficile toxin activity. Saccharomyces boulardii produces a protease that inhibits Clostridium difficile toxin activity.[13],[14]

PROBIOTICS IN THE PREVENTION OF POST OPERATIVE INFECTIONS

The microbiome is now known to influence a wide range of pathologic and normal processes, and manipulating it may improve patient outcomes while also providing host health advantages. The goal of prophylactic probiotics is to keep "good" bacteria colonized in order to contend with Clostridium difficile overgrowth. Clostridium difficile toxins A and B are able to be neutralized by some probiotics. Probiotics have protective properties, according to data from in vitro and preclinical experiments.[15] Physical injury to the intestinal mucosa, which causes disruption of the gut barrier and increased intestinal permeability, as well as microbial imbalance and decreased immunodeficiency in the postoperative patient, are the most common cause of bacterial translocation. Patients undergoing abdominal surgery for medical conditions like as biliary cancer surgery, pancreaticoduodenectomy, and liver transplantation are at risk for urinary tract infection (UTI), pneumonia, wound infection, intra-abdominal abscess, and cholangitis.[6],[16] Clostridium difficile colitis rates are reduced when probiotics are given alongside antibiotics to adult patients with non-surgical infections. This is a promising infection-prevention strategy that could reduce morbidity, antibiotic therapy duration, hospital stay length, and the risk of antimicrobial resistance emergence.[6]

PROBIOTICS IN VENTILATOR ASSOCIATED PNEUMONIA

The most prevalent infection in the intensive care unit is ventilator-associated pneumonia (VAP), which is linked to a high rate of morbidity and mortality. Probiotics have lately emerged as a new weapon in the fight against ventilator associated pneumonia. By improving intestinal barrier function, regulating the composition of the intestinal flora, increasing host cell antimicrobial peptides and reducing pathogenic bacteria overgrowth and bacterial translocation through local and systemic actions, probiotic bacteria are thought to reduce the development of Ventilator associated pneumonia. Probiotics have been demonstrated to be safe and effective in the prevention and treatment of VAP in ICU patients in various trials. The study by Chang Hun Lee have shown some beneficial effects of certain strains of microbes on the recurrence of upper respiratory tract infections and nasal colonization. Several studies have reported the preventive effect of probiotics against VAP in patients who received mechanical ventilation.[2],[6]

Probiotics augment the role of antibiotics in the prevention and treatment of various microbial infections. Probiotics interfere with the invasion and adhesion of disease-causing microorganisms. Further, probiotics help in preventing bacteria from attacking cells that are exposed, and protect the gastrointestinal epithelium from further assault. Lactobacillus rhamnosus increases

the number of immunoglobulin secreting cells in the intestinal mucosa by stimulating interferon release. The study by Nicholas A Kerna shows that the coadministration of probiotics and antibiotics can help reduce the unwanted side effects of antibiotic therapy.[8]

MULTISTRAIN PROBIOTICS

Multi-strain probiotics consists of more than one species or strains of bacteria and sometimes, including some fungal species with benefits to human and animal's health. The mechanisms by which multi-strain probiotics exert their effects include interactions with the host tissues, cell–cell communications, and modulation of the immune systems. Multi-strain probiotics applications include alleviation of disease condition, inhibition of pathogens, and restoration of the gastrointestinal microbiome. Despite all these benefits, the potential of using multi-strain probiotics is still not fully explored.[17]

ADMINISTRATION OF PROBIOTICS

To enhance the advantageous effects of the probiotics, most researchers suggest staggering the doses; that is taking the probiotic 2-6 hours after the antibiotic dose, and continuing with the probiotic 7-10 days after ending the antibiotic treatment. It is also deemed helpful to take probiotics before beginning antibiotic therapy, if possible. This is expected to provide the best outcome; if a person observed a probiotic maintenance regime prior to beginning any treatment with antibiotics.

Since probiotics are not classified or regulated as drugs, their manufacture is not subject to the scrutiny of the FDA and the quality controls commensurate with those of the pharmaceutical industry. Hence, the quality and efficacy of different brands and different strains of probiotics can vary widely. It is advisable to investigate probiotic products thoroughly before prescribing or consuming them in order to maximize positive outcomes and minimize negative outcomes. The probiotics should, however, adhere to current Good Manufacturing Practices.

ADVERSE DRUG REACTION

According to some researchers, probiotics can cause rapid metabolism of certain drugs like sulfasalazine resulting in higher and consequential concentrations in the human body. Genetically modified probiotics increase the mortality rate of patients suffering from acute pancreatitis. Safety Assessment of Probiotics for Human Use suggests that Genetic stability of the probiotic over time, deleterious metabolic activities, and the potential for pathogenicity or toxigenicity must be assessed depending on the characteristics of the genus and species of the microbe being used. Immunological effects must be considered, especially in certain vulnerable populations, including infants with undeveloped immune system functions.

It is also important to note that antibiotic resistance determinants have been identified and characterized in Lactobacillus, Bifidobacterium and the probiotic Bacillus.[8]

SAFETY OF PROBIOTICS IN CRITICALLY ILL PATIENTS

Most probiotics are safe. Moreover, care should be taken when administering probiotics to severely ill or immunocompromised patients. There are some rare incidents of sepsis, endocarditis, and liver abscess during the use of Lactobacillus; additionally, fungemia has been reported with the use of S boulardii, primarily in patients with severe comorbidities. The risks and benefits of probiotics should be weighed before their use.[1]

According to Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient published in 2016, probiotics are not recommended for routine use for the general ICU patient population

however, the guidelines suggest that using probiotics in selected medical and surgical patients who benefit based on available evidence. The guidelines cite some studies demonstrating benefit of probiotics including prevention of antibiotic-associated, VAP, and pseudomembranous colitis in certain patient populations such as liver transplant, trauma, or pancreatectomy. The guidelines also suggest that probiotics can be considered for patients with severe acute pancreatitis who are receiving early enteral nutrition with the potential reduction in infection and hospital length of stay.[18],[19]

CONCLUSION

The best documented benefits of probiotics are in the relation to antibiotic use, with many probiotic strains having been reported to have beneficial effects. Most of these benefits are in relation to antibiotic associated diarrhea, and also maintenance of the intestinal and other microbiota composition and activity. Even though, the use of probiotics for the prevention of pneumonia in critically ill patients seem promising, there are a few serious concerns. Probiotics are regulated as a dietary supplement by the U.S. Food and Drug Administration; therefore, the manufacturer does not require to prove efficacy or safety of the probiotic before it is marketed to the public. For this reason, it is difficult to know with certainty the quality and the quantity and of the bacteria in probiotics. Also, there is no established standard dose or duration of therapy for probiotics and its various uses. These confounders make it difficult to examine the use probiotics for prevention and treatment of disease, including pneumonia in critically ill patients.

Declaration by Authors

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REFERENCE

1. Islam SU. Clinical uses of probiotics. Medicine. 2016;95(5).
2. Lee CH, Choi Y, Seo SY, Kim SH, Kim IH, Kim SW *et al*. Addition of probiotics to antibiotics improves the clinical course of pneumonia in young people without comorbidities: A randomized controlled trial. Scientific reports. 2021;11(1):1-9.
3. Goodman C, Keating G, Georgousopoulou E, Hespe C, Levett K. Probiotics for the prevention of antibiotic-associated diarrhoea: a systematic review and meta-analysis. BMJ open. 2021 Aug 1;11(8):e043054.
4. Courvalin P. Antibiotic resistance: the pros and cons of probiotics. Digestive and Liver Disease. 2006;38:S261-5.
5. Pickard JM, Nunez G. Pathogen colonization resistance in the gut and its manipulation for improved health. The American Journal of Pathology. 2019; 189(7) 1300–10.
6. Tegegne BA, Kebede B. Probiotics, their prophylactic and therapeutic applications in human health development: A review of the literature. Heliyon. 2022:e09725.
7. Plaza-Diaz J, Ruiz-Ojeda FJ, Gil-Campos M, Gil A. Mechanisms of action of probiotics. Annals of nutrition and metabolism. 61: 160-74.
8. Kerna NA, Brown TL. A complementary medicine approach to augmenting antibiotic therapy: current practices in the use of probiotics during antibiotic therapy. International Journal of Complementary and Alternative Medicine. 2018;11(2):62-6.
9. Li Z, Behrens AM, Ginat N, Tzeng SY, Lu X, Sivan S *et al*. Biofilm-inspired encapsulation of probiotics for the treatment of complex infections. Advanced Materials. 2018;30(51):1803925.
10. Blaabjerg S, Artzi DM, Aabenhus R. Probiotics for the prevention of antibiotic-associated diarrhea in outpatients—a systematic review and meta-analysis. Antibiotics. 2017 ;6(4):21.
11. Kopacz K, Phadtare S. Probiotics for the Prevention of Antibiotic-Associated Diarrhea. Healthcare 2022;10 (8) 1450.
12. Silverman MA, Konnikova L, Gerber JS. Impact of Antibiotics on Necrotizing Enterocolitis and Antibiotic-Associated Diarrhea. Gastroenterology Clinics.2017; 46(1):61–76.

13. Goldenberg JZ, Mertz D, Johnston BC. Probiotics to prevent Clostridium difficile infection in patients receiving antibiotics. Jama. 2018;320(5):499-500.
14. 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 Medicine. 2013;7(2):e56.
15. Franko J, Raman S, Krishnan N, Frankova D, Tee MC, Brahmbhatt R *et al*, Randomized trial of perioperative probiotics among patients undergoing major abdominal operation, Journal of the American college of Surgeons.2019;229(6) 533–40.
16. Pitsouni E, Alexiou V, Saridakis V, Peppas G, Falagas ME. Does the use of probiotics/synbiotics prevent postoperative infections in patients undergoing abdominal surgery? A meta-analysis of randomized controlled trials. European journal of clinical pharmacology. 2009;65(6):561-70.
17. Kwoji ID, Aiyegoro OA, Okpeku M, Adeleke MA. Multi-Strain probiotics: synergy among isolates enhances biological activities. Biology. 2021;10(4):322.
18. Kalabalik J, Ozdener AE. The Role of Probiotics in Critically Ill Adult Patients with Pneumonia. International Journal of Critical Care and Emergency Medicine. 2018;4(2):049.
19. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR *et al*. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition Journal of Parenteral and Enteral Nutrition. 2016;40(2): 159-211.
20. Venugopalan V, Shriner KA, Wong-Beringer A. Regulatory oversight and safety of probiotic use. Emerging Infectious Diseases.2010; 16(11):1661-65.
21. Liao W, Chen C, Wen T, Zhao Q. Probiotics for the Prevention of Antibiotic-associated Diarrhea in Adults: A Meta-Analysis of Randomized Placebo-Controlled Trials. Journal of Clinical Gastroenterology. 2021;55(6):469.

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