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# A complementary medicine approach to augmenting antibiotic therapy: current practices in the use of probiotics during antibiotic therapy

## Abstract

Physicians and other healthcare providers have long posited that one of the functions of probiotics is to substitute and replenish the gut microbes destroyed by antibiotics during antibacterial therapy. Over time, mostly due to observation and anecdotal evidence, it became widely accepted that probiotics have a beneficial effect on the human body in reducing, or even eliminating, certain adverse effects and unwanted consequences of antibiotic treatment, as well as supporting the natural intestinal flora that may have been disrupted during the use of antibiotics. Much of the current research in this area supports these prior hypotheses and practices: that probiotic use is beneficial during antibiotic therapy; particularly in eliminating or limiting antibiotic-associated diarrhea (AAD), disruptions of the epithelium of the lower intestine tract due to *Clostridium difficile* infections (CDI), and even yeast (candida) infestation secondary to antibiotic therapy. Research on the beneficial effects of probiotics in AAD and CDI (aka, *C. difficile and C. diff*) is not limited to the United States. Research on the use of probiotics during antibiotic therapy for these conditions has been reported on in India, Pakistan, China, and Latin America and throughout Europe; thus making adjunctive probiotic use a global phenomenon.[1–6] As a result, the concurrence of probiotic administration and antibiotic treatment is increasing worldwide. Although, currently, there are no scientifically documented or medically endorsed guidelines regarding the administration of probiotics during a course of antibiotics–especially in the timing of the doses of each group (the probiotic and the antibiotic)–the consensus among researchers and physicians is to stagger the doses of the probiotic and the antibiotic to enhance efficacy. It is suggested to take the probiotic 2-6 hours after the antibiotic dose throughout the course of antibiotic treatment, and to continue with the probiotic 7-10 days after ending the antibiotic regime. It is also helpful to take probiotics before beginning antibiotic therapy, if possible. In this review, it is also noted that further research on the interaction of probiotics and antibiotics during concurrent use is requisite, and approved guidelines for the concomitant use of certain strains of probiotics with specific antibiotics should be considered. Herein, to address these concerns, two research projects are proposed.

**Keywords:** antibiotics, diarrhea, genetic stability, immunological, intestinal flora, microbiota, pathogenicity, probiotics, tight junctions, toxigenicity

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**Abbreviations:** AAD, antibiotic-associated diarrhea; CDC, Center for Disease Control and Prevention; CDI, clostridium difficile infection; cGMP, Current Good Manufacturing Practices; ECM, Albert Einstein College of Medicine; FDA, Food and Drug Administration; JAMA, Journal of the American Medical Association; JPH, Journal of Probiotics and Health; NCBI, National Center of Biotechnology Information; RAND, Research and Development Corporation

## Introduction

Probiotics are currently recommended by many healthcare providers (allopathic, homeopathic, chiropractic and naturopathic) for use during antibiotic treatment. The main supposition 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 used during antibiotic therapy not only to maintain the normal, health-promoting balance of intrinsic bacteria in the intestine, but also to avoid or lessen the unwanted side effects of antibiotic therapy; such as abdominal pain, flatulence and diarrhea, and Candida infestation.[7]

It is difficult to ascertain the prevalence of patients self-prescribing probiotics while taking antibiotics, but it is certain that the numbers are considerable and continuing to increase. However, to date, there are no identified protocols or sanctioned guidelines for the prescription and administration of probiotics in conjunction with antibiotic therapy. There are no circulating statistics on how many physicians prescribe–or even suggest–probiotics with antibiotics. In 2001, a study of physician practices regarding probiotics reported that the majority of the participating physicians did not prescribe probiotics during antibiotic therapy; and that 88% of those participating physicians felt that research is needed for probiotics concurrent use with antibiotics; and that medical guidelines for probiotic use should be established.[8]

This was a survey of 66 physicians in Nova Scotia. The report, *Clinical Use of Probiotics: A Survey of Physicians' Beliefs and Practice Patterns* stated that "peer practice patterns" influenced the group of physicians prescribing probiotics; whereas the group of physicians that did not prescribe probiotics cite the lack of evidenced-based research for not doing so.[9]

This survey was limited to 27 physicians at Danville Regional Medical Center in Danville, Virginia. Additional research findings in this survey are interesting:

> Those [physicians] who used probiotics were significantly more likely to agree that probiotics have clinically beneficial effects ($p<0.017$) and pose minimal risk ($p<0.003$) than those who don't use probiotics (n=12, 44.4%). Physicians using probiotics were also less likely to agree that more clinical evidence is needed to support the benefits of probiotics for their specialty ($p<0.012$), and more likely to indicate "peer practice patterns" ($p<0.032$) as prompting their use, whereas those not using probiotics were more likely to choose "original research ii i articles" ($p<0.006$) as a source of information that would potentially change their practice with regard to probiotics. . . . Physicians' beliefs regarding the use of probiotics differ between those who recommend their use in clinical practice and those who do not. Physicians not using probiotics feel that more evidence-based research is needed to support their use in clinical practice.[9]

What is missing from this research, however, are questions and responses from the antibiotic-prescribing group of physicians on the frequency of recommending probiotics during antibiotic treatment (as 32% of the physicians surveyed reported prescribing antibiotics); no data is reported regarding concurrent use of probiotics during antibiotic therapy.

More often than the physician, it may well be the pharmacist that suggests probiotics for the patient when the patient is filling their antibiotic prescription. According to an article by pharmacist Scott:

> There's reasonably good evidence that probiotics, when taken with antibiotics, will reduce the risk of antibiotic-associated diarrhea. There is still much to be learned about how these products can be used most effectively, which means it's unlikely we will see routine use recommended for some time. However, the reassuring lack of side effects, and potential to reduce potentially serious complications of antibiotic treatment, suggests that probiotics may become a valuable addition to antibiotic therapy.[10]

The pharmacist may recommend probiotics when a patient expresses concern about antibiotic side effects, such as abdominal discomfort or bowel disturbance; or the pharmacist may simply take the initiative and explain to the patient the benefits of taking a probiotic during the antibiotic regime, such as supporting natural gut flora and reducing abdominal discomfort.

There are no statistics indicating how many times probiotics are taken with a course of antibiotics when the probiotics are self-prescribed by a patient undergoing antibiotic therapy. Therefore, it is impossible at this time to determine how many times a "course" of probiotics has been taken concurrently with a course of antibiotics. If the incidence of combined probiotic and antibiotic use was better documented, researchers could better assess outcomes of concurrent use and develop more specific and scientific guidelines for such coadministration. As yet, there are no prescriptive guidelines for probiotic use during antibiotic treatment. Most current practices are based upon inferences, opinions, anecdotal evidence and peer-based practice patterns. Conclusions regarding their conjunct use are drawn based on the general understanding of the mechanisms of how the probiotic and antibiotic each act independently, but not based on a wide body of scientific research on how probiotics and antibiotics act and react together.

## Discussion

In 2015, the Center for Disease Control and Prevention (CDC) reported that outpatient antibiotic prescriptions in the United States (in 2013) were 268.6 million prescriptions which, at the time, was the equivalent of 849 antibiotic prescriptions per 1,000 people.[11] However, there is no published data on how many times probiotics may have been prescribed by the physician for use with the antibiotic regime. Nor is there any data that indicates how many times a pharmacist may have suggested probiotics to be taken along with the antibiotics. Nor is there any data on how many patients subsequently purchased the probiotics if recommended by a physician; nor how many of those patients eventually followed through on taking the probiotics with the antibiotics. Nor is there any data on the incidence of patients self-prescribing probiotics during their physician-prescribed antibiotic therapy. These are important and consequential data to explore. From such data further research could evolve to investigate not only the efficacy of probiotic use with antibiotics, but also the efficacy of particular strains, combination of strains, and potencies of probiotics with different types of antibiotics. This is fertile ground for future research; for example, to develop an analog to ascertain how many of those 268.8 million outpatients given antibiotic prescriptions were recommended probiotics; and how many of those followed through with the combined use; and what the outcomes were. If the outcomes were favorable, this could lead to the further development of customized medicines containing both probiotics and antibiotics to augment or replace each stand-alone antibiotic of today.

Antibiotic use can be tracked with some certainty as in the aforementioned CDC statistics, but it is difficult to do so for probiotics. It is also challenging to quantify probiotic use because, unlike antibiotics which usually come in the form of capsules or pills, the term "probiotics" refers to an assortment of dietary supplements; such as tablets, capsules, powders, lozenges and gums, and come in foods like yogurt and other fermented products. The tracking of this data is further hindered as probiotics are not covered by health insurance.[12] If probiotics were covered by health insurance, then it would be much easier to track the use of probiotics with antibiotics by studying such data obtained from the insurance industry.

A second research suggestion is to conduct surveys of physicians, physician assistants, nurse practitioners and pharmacists regarding the frequency of concurrent probiotic use and antibiotic therapy; and/or surveys or questionnaires from retailers of probiotics on the consumer use of probiotics with antibiotics. This would be an important first step (to determine the incidence of concurrent probiotic and antibiotic use) and would aid in a more meaningful discussion regarding this relevant topic; and support the establishment of guidelines regarding the use of probiotics with antibiotics, including any determined contraindications.

One of the few probiotic statistics that are available to examine are sales figures. In 2014, the University of Berkeley reported that the annual global sales of all probiotic products were expected to hit $42 billion by 2016.[13] Of course, comparing 268.6 million outpatient antibiotic prescriptions with $42 billion in probiotic sales to extrapolate the incidence of concurrent probiotic and antibiotic use is inherently flawed. Such formulation simply does not work. However,

from these numbers, it can safely be surmised that there are a plethora of antibiotics being prescribed (849 antibiotic prescriptions /1000 people in the U.S.) and legions of probiotics being purchased ($42 billion worth) and consumed; and quite likely, a small percentage of the amounts of each are being consumed concurrently. It is projected that this combined use will continue to multiply. Therein lies the basis of the need for a better understanding of the interactions of probiotics with antibiotics in treating illness and disease, and the need for upgraded guidelines and revised recommendations for their concerted use.

Currently, there is growing body of scientific evidence establishing links between probiotics and physical health, probiotics and mental health, the beneficial effects of probiotics in certain diseases, the role of probiotics in the gut epithelium and tight junctions and leaky gut, the relationship of probiotics to the human microbiome, and more.[14–16] The catalogue of research regarding probiotics (live bacteria) and prebiotics (specialized fiber that promotes the growth of certain microorganisms in the intestines) continues to expand. Today, there are scientific and medical publications and journals dedicated solely to research regarding probiotics. This is all very promising for the many challenges that lie ahead in local healthcare concerns and in global healthcare initiatives. However, a note of caution needs to be sounded. It is easy to become bewildered when foreseeing the numerous benefits and applications of probiotics; and, it is easy for the mind to divagate when contemplating the vastness of the human microbiome and its far-reaching effects on human physiology, immunology and psychology, and in restoring health and in preventing disease. Therefore, contrary effects of certain probiotic strains in certain disorders should be investigated; and evidence-based guidelines for the combined use of probiotics and antibiotics should be reconciled.

Antibiotic use can commonly result in the development of gastrointestinal discomfort or disease. This can range from mild diarrhea to severe colitis. In the adult population, AAD occurs in 5-35% of patients taking antibiotics. The severity depends upon the specific type of antibiotic, the health of the patient, and exposure to and type of pathogens. The pathogenesis can occur through the disturbance of the intrinsic microbiota resulting in pathogen overgrowth or metabolic imbalances.[17] In children over the age of two, the prevalence of AAD is 11%. A study found that probiotics reduce the risk of AAD in children, and for every 7-10 patients one less would develop AAD.[18] A RAND study found that probiotics reduced the risk of AAD by 42 percent.[19] Combined treatment (of probiotic and antibiotics) has been used successfully in post-operative Crohn's disease and, less so, in secondary pancreatic infections.[20,21] But, these are particular conditions and special cases wherein outcomes may not readily transfer to other conditions with differing pathophysiologies. From these trials and studies, inferences can be drawn but conclusions cannot be confirmed concerning concurrent probiotic and antibiotic use in other conditions. Regarding the aforementioned studies, not one noted how and when the probiotics were administered.

The remedial use of probiotics is considered a means to restore and boost the beneficial microbes in the human body. The use of probiotics to prevent vaginal infections following antibiotic therapy is worthwhile if the antimicrobial drug adversely affects the vaginal microbiota; and there is evidence to support this application.[22] Antibiotics kill microbes in the digestive system reducing competition and creating a suitable environment for fast growing candida to fill the gap. The use of probiotics during antibiotic treatment slows the growth of candida by supplying the gastrointestinal system with beneficial microbes. Probiotics reduce the side effects of antibiotics since they promote intrinsic microbial balance in the gut. An effective mechanism of probiotics in the gut is through competition. As antibiotics disrupt the intrinsic intestinal flora, the candida can rapidly infiltrate and spread within the gut. Probiotics stimulate the elemental flora causing this flora to compete for space within the gut. Probiotics can also exert a positive influence on the immunological system which, when strengthened, can counter the candida. Yeast proliferation in the gut can have deleterious effects on the tight junctions resulting in leaky gut syndrome. Probiotics may alter the gastric environment making it less hospitable to candida. A marked reduction in candida is resultant to its exposure to strains of acidophilus and bifidus.[24] In all cases, yeast or bacteria, the application of appropriate strains and dose and dosage of probiotics is all-important.

Current research supports that probiotics do in some ways and in certain conditions (AAD, CDI, Crohn's and secondary pancreatitis) benefit patients that are taking antibiotics or have recently completed a course of antibiotic therapy. Antibiotics, despite killing the "bad" bacteria, may also kill the "good" bacteria in the gastrointestinal system which may lead to diarrhea. Probiotics promote microbial balance.[25] Probiotic strains like *Lactobacillus rhamnosus* and *Saccharomyces boulardii* help in preventing diarrhea and certain infections that may arise from using antibiotics. A study done at the Albert Einstein College of Medicine (ECM) supports the use of probiotics. ECM scientists reported "that up to one in five people stop taking their entire course of antibiotics due to diarrhea." In addition, they reviewed the medical literature and found seven, high- quality studies in which probiotics were administered to people undergoing antibiotic treatment. The researchers concluded that the studies support the use of probiotics in preventing diarrhea which usually results from antibiotic use or from gastrointestinal (viral or bacterial) infections. In addition, the probiotics used in these studies were found to rarely cause adverse effects, even in children. "With the level of evidence that probiotics work and the large safety margins for them, we see no good reason not to prescribe probiotics when prescribing antibiotics," says Dr. Benjamin Kligler, a coauthor of the study and Associate Professor of Clinical Family and Social Medicine at ECM. Dr. Kligler also notes that the effects of probiotic doses are short-lived, so they should be taken throughout a course of antibiotic therapy. "Probiotics will not diminish the effectiveness of antibiotics," he adds.[26] Here again, however, there is no mention of what strains of probiotics were administered in the studies; and no mention of the dose and, in particular, the timing of the administration of the probiotic relative to the antibiotic.

How should patients take–or physicians prescribe–the probiotic during antibiotic therapy? To determine a reasonable protocol, it is fundamental to recognize that probiotics must act against pathogens by mechanisms that differ from those of antibiotics, for instance by competition. They should also be nonpathogenic. In addition, probiotics must act rapidly and survive any challenges presented by the antibiotics, gastric acid and bile. It is advisable to administer the antibiotic and the probiotic at different times. This is due to the concern that the antibiotic may reduce the efficacy of the probiotic microorganisms.

Some physicians recommend the intake of probiotics six hours after taking an antibiotic dose. Moreover, it is advisable to continue taking the probiotics for a period of ten days after the antibiotics are

finished or stopped. Some of the adverse effects of the antibiotics are counteracted by probiotics; for instance, dysbiosis caused by a loss of lactobacillus from the gastrointestinal tract. Therefore, it is advisable to separate 4 hours between the intake of probiotics and the intake of antibiotics.[27]

## Conclusion

Current studies have shown that the coadministration of probiotics and antibiotics can help reduce the unwanted side effects of antibiotic therapy; in particular gastric disorders and diarrhea, and candida infestation. Probiotics augment the role of antibiotics in the prevention and management of various microbial infections. Probiotics interfere with the invasion and adhesion of disease-causing microorganisms. In addition, 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.

To enhance the advantageous effects of the probiotics, most research suggests 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.[35,36] This stratagem 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 (in the USA) and the quality controls commensurate with those of the pharmaceutical industry. Therefore, 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.[28] The probiotics should, however, adhere to current Good Manufacturing Practices (cGMP).

It is the opinion of many researchers that probiotics do not adversely affect the potency of antibiotics and that antibiotics fair well in the presence of probiotics without their efficacy being compromised. Nevertheless, caution must be observed as probiotics can have disadvantageous effects; such as in patients who are immunocompromised, and in certain infections that are resistant to antibiotic therapy.[29] Some patients suffering from Crohn's Disease, an autoimmune disease, have shown unpleasant outcomes after probiotic administration. (This is differentiated from the aforementioned studies regarding Crohn's, wherein it was the postsurgical application of combined probiotic and antibiotic therapy that was determined to be beneficial in some cases.) In addition, according to some researchers, probiotics can cause rapid metabolism of certain drugs like sulfasalazine resulting in higher and consequential concentrations in the human body.[30] Genetically modified probiotics increase the mortality rate of patients suffering from acute pancreatitis (as differentiated from the aforementioned secondary pancreatitis).[32] According to an NCBI report, *Safety Assessment of Probiotics for Human Use:*

> 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 function.[31]

It is also relevant to note that antibiotic resistance determinants have been identified and characterized in Lactobacillus, Bifidobacterium and the probiotic Bacillus.[33,34]

These precautions regarding probiotic use warrant further evaluation. In addition, further investigation into the pharmacokinetics of concurrent probiotic and antibiotic intake is rational. Developing guidelines for appropriate and efficacious use of particular strains of probiotics with different types of antibiotics is a long- term, but invaluable, project. The future is promising for the integration of probiotics into medical regimens and personal supplementation programs. For the time being, the use of high-quality probiotics during and after antibiotic therapy, staggering the probiotic dose 4-6 hours after ingesting the antibiotic, continuing in this way throughout the course of antibiotic therapy, and sustaining probiotic intake for 7-10 days beyond the completion of the antibiotic regime (especially in those groups prone to candida and diarrhea) is deemed safe and beneficial–and is recommended–by many researchers and practitioners.

In-depth research regarding certain strains of probiotics (and combinations thereof) as applied to specific conditions is beyond the scope of this review, and is left for further speculation and investigation. Regarding the current use of probiotics during antibiotic therapy (and probiotics in other human applications): so far, so good; but future research is vital in determining more efficacious applications and in developing more specific guidelines for their use.

## Conflict of interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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