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Perspective

Global Health Preventive Medicine Overture: Select Probiotic Use in the Prevention of Antibiotic-Associated Diarrhea and the Treatment of C. Difficile and Distinct Tropical Diseases

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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 for Biotechnology Information; RAND: Research and Development Corporation

Abstract

Historically, in the absence of relevant independent scientific research, probiotics have become widely accepted and are being widely recommended and prescribed by healthcare providers and self-prescribed by patients and consumers. In antibiotic-associated diarrhea (AAD) and Clostridium difficile infection (CDI), probiotics appear harmless while providing certain benefits. Probiotic use in particular situations and conditions should be considered for a global health proposal.

Introduction

Physicians and other healthcare providers have long posited that one of the functions of probiotics is to substitute and replenish 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 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 in eliminating or limiting AAD, disruptions of the epithelium of the lower intestine tract due to CDI, and even yeast (Candida) infestation secondary to antibiotic therapy. Research into the beneficial effects of probiotics in AAD and CDI (aka C. difficile and C. diff) has not been limited to the United States. Studies on the use of probiotics during antibiotic therapy for these conditions have been reported in India, Pakistan, China, Latin America, and Europe making adjunctive probiotic use a global phenomenon [3-8].

The concomitant use 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 antibiotic treatment and to continue with the probiotic 7-10 days after ending the antibiotic regime. It is also offered to take probiotics before beginning antibiotic therapy, if possible.

Further research on the interaction of probiotics and antibiotics during concurrent use is bounden, and approved guidelines for the concomitant use of certain strains of probiotics with specific antibiotics should be considered.

Discussion

Probiotics are currently recommended by many healthcare providers (allopathic and naturopathic) for use during antibiotic treatment. The central 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 gut but also to avoid or lessen the unwanted side effects of antibiotic therapy; such as abdominal pain, flatulence, diarrhea, and Candida infestation [1].

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 current statistics on how many physicians prescribe, or even suggest, probiotics with antibiotics.

The Call for Research in Support of Select Probiotic Use

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 research was needed for concurrent probiotic use with antibiotics; and medical guidelines for probiotic use should be established [2].The study was a survey of sixty-six 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 that prescribed probiotics; whereas, the group of physicians that did not prescribe probiotics cited the lack of evidence-based research for not doing so [3]. This survey was limited to twenty-seven physicians at Danville Regional Medical Center in Danville, Virginia. Additional research findings in this survey are were as follows:

> 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 [3].

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 was reported regarding concurrent use of probiotics during antibiotic therapy.

There are no studies 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 is taken concurrently with a course of antibiotics. If the incidence of combined probiotic and antibiotic use is better documented, researchers could better assess outcomes of concurrent use and develop more specific and scientific guidelines for coadministration. As yet, there are no prescribed guidelines for probiotic use during antibiotic treatment. Most current practices are based on inferences, opinions, anecdotal evidence, and peer-based practice patterns. Conclusions regarding their conjunct use are drawn based on general understandings of the mechanisms of how the probiotic and antibiotic act independently but not based on a body of scientific research on how probiotics and antibiotics act and react together.

Current Antibiotic Prescriptive Use

In 2015, The Centers 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 [4]. However, there was no published data on how many times a physician may have prescribed probiotics for use with an antibiotic regime. There was no data that indicated how many times a pharmacist may have suggested probiotics to be taken with the antibiotics. There was no data on how many patients subsequently purchased probiotics if recommended by a physician; nor how many of those patients eventually followed through on taking probiotics with the antibiotics. Also, there was no data on the incidence of patients self-prescribing probiotics during their physician-prescribed antibiotic therapy. These are important and consequential data to explore.

If such data were available, research could evolve to investigate not only the efficacy of probiotic use with antibiotics but also the efficacy of particular strains, a combination of strains, and potencies of probiotics with different types of antibiotics. These topics are fertile ground for future research; for example, research to develop an analog to ascertain how many outpatients (who are recommended probiotics with antibiotics) follow through with the combine use, and what the outcomes are. This type of research could lead to the continued development of customized medicines containing both probiotics and antibiotics to augment or replace each stand-alone antibiotic of today.

Current Probiotic Consumption

Antibiotic use can be tracked with some certainty as in the CDC statistics mentioned in the previous section, 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 namely yogurt and other fermented products. The tracking of this data is further hindered as probiotics are not covered by health insurance [5]. If health insurance covered probiotics, then it would be much easier to track the use of probiotics with antibiotics by studying such data obtained from the insurance industry. Tracking concurrent probiotic and antibiotic intake is an essential step (to determine the incidence of concurrent probiotic and antibiotic use); and would aid in a more meaningful discussion regarding this relevant topic, and could support the establishment of guidelines regarding the use of probiotics with antibiotics including any determined contraindications.

One of the few probiotic statistics that is available to examine are sales figures. In 2014, the University of Berkeley reported the annual global sales of all probiotic products were expected to hit $42

billion by 2016 [6]. 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 does not work. However, from these numbers, it can safely be surmised that there are a plethora of antibiotics being prescribed (849 antibiotic prescriptions per 1,000 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. This combined use is projected to multiply. Herein is 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 joint use.

Growing Acceptance of the Clinical Use of Probiotics

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 [7-9]. The catalog of research regarding probiotics (live bacteria) and prebiotics (specialized fiber that promotes the growth of specific microorganisms in the intestines) continues to expand. Today, there are scientific and medical publications and journals dedicated to probiotic research. The availability of research is promising for the many challenges that lie ahead in local health care concerns and global healthcare initiatives. However, a note of caution needs to be sounded.

Probiotics: Proceed with Caution

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, psychology, and in restoring health and preventing disease. Therefore, contrary effects of certain probiotic strains in specific disorders should be investigated, and evidence-based guidelines for the combined use of probiotics and antibiotics should be reconciled.

Antibiotics in Causing AAD

Antibiotic use can result in the development of gastrointestinal discomfort or disease that can range from mild diarrhea to severe colitis. In the adult population, AAD occurs in 5-35 percent of patients taking antibiotics. The severity of the symptoms depends on the specific type of antibiotic, the health of the patient, and the exposure to and type of pathogens. The pathogenesis can occur through the disturbance of the intrinsic microbiota resulting in pathogen overgrowth or metabolic imbalances [10]. In children over the age of two, the prevalence of AAD is 11 percent. A study found that probiotics reduce the risk of AAD in children: for every 7-10 patients, one less would develop AAD [11]. A RAND study found that probiotics reduced the risk of AAD by 42 percent [12]. Combined treatment (probiotics and antibiotics) has been successful in postoperative Crohn's disease and, less so, in secondary pancreatic infections [13,14]. However, these are particular conditions 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 studies mentioned above, not one study noted how and when the probiotics were administered.

Benefits of Concurrent Probiotic Administration During Antibiotic Therapy

The therapeutic 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; there is evidence to support this application [15]. Antibiotics kill microbes in the digestive system reducing competition and creating a suitable environment for fast growing Candida to fill the gap.

Probiotics and Candida Infestation

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 probiotics promote natural microbial balance in the gut. An effective mechanism of probiotics in the gut is through competition. As antibiotics disrupt the natural intestinal flora, 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 exert a positive influence on the immunological system which, when strengthened, can counter Candida. Yeast proliferation in the gut can have deleterious effects on tight junctions resulting in leaky gut syndrome [16]. Probiotics may alter the gastric environment making it less hospitable to Candida. A marked reduction in Candida results from the gut's exposure to strains of acidophilus and bifidus [17]. In all cases, yeast or bacteria, the application of appropriate strains and dose and dosage of probiotics is all-important.

Probiotics and AAD, CDI, and Chron's

Current research supports that probiotics in some ways and in certain conditions (AAD, CDI, Crohn's, and secondary pancreatitis) benefit patients taking antibiotics or have recently completed a course of antibiotic therapy. Despite killing the "bad" bacteria, antibiotics may also kill the "good" bacteria in the gastrointestinal system which may result in diarrhea. Probiotics promote microbial balance [18]. Probiotic strains like Lactobacillus rhamnosus and Saccharomyces boulardii help in preventing diarrhea and certain infections that may arise from using antibiotics.

Rationale and Support for Probiotic Use in AAD

A study at the Albert Einstein College of Medicine (ECM) supported the select use of probiotics. ECM scientists reported "that up to one in five people stop taking their antibiotics due to diarrhea". Also, they reviewed medical literature and found seven, high-quality studies in which probiotics were administered to people undergoing antibiotic treatment. The researchers concluded that studies supported the use of probiotics in preventing diarrhea that results from antibiotic use or gastrointestinal (viral or bacterial) infections[19]. Also, 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", said Dr. Benjamin Kligler, a co-author of the study and Associate Professor of Clinical Family and Social Medicine at ECM. Dr. Kligler also noted that the effects of probiotic doses were short-lived, so they [probiotics] should be taken throughout antibiotic therapy. "Probiotics will not diminish the effectiveness of antibiotics", he added [19].

Current Practices in the Use of Probiotics During Antibiotic Therapy

How should patients take—or physicians prescribe—probiotics during antibiotic therapy?

(It is fundamental to recognize that probiotics must act against pathogens by mechanisms that differ from those of antibiotics, for example, by competition. They should be nonpathogenic. Also, probiotics must act rapidly and survive any challenges presented by antibiotics, gastric acid, and bile.)

It is advised to administer the antibiotic and the probiotic at different times. This difference 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 advised to continue taking the probiotics for ten days after the antibiotics are finished or stopped. Other practitioners suggest to separate 4 hours between the intake of probiotics and the intake of antibiotics [20].

Summary

Probiotics for Gastric Disorders and Candida Infestation

Current studies have shown that coadministration of probiotics and antibiotics can reduce the unwanted side effects of antibiotic therapy; in particular, gastric disorders, 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. Also, 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.

Probiotics: Coadministration Guidelines

Most research suggests staggering the doses (to enhance the advantageous effects of the probiotics); 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 [11, 21].

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 advised to investigate probiotic products thoroughly before prescribing or consuming them to maximize positive outcomes and minimize adverse effects [22]. The probiotics should, however, adhere to current Good Manufacturing Practices (cGMP).

Probiotics: Contraindications and Precautions

It is the opinion of many researchers that probiotics do not adversely affect the potency of antibiotics and that antibiotics do well in the presence of probiotics while their efficacy remains uncompromised. 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 [23]. Some patients with Crohn's disease, an autoimmune disease, have shown unpleasant outcomes after probiotic administration [4]. (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 beneficial in some cases.) Also, according to some researchers, probiotics can cause rapid metabolism of certain drugs, like sulfasalazine, resulting in higher and consequential concentrations in the human body [24]. Genetically modified probiotics increase the mortality rate of patients suffering from acute pancreatitis (as differentiated from the aforementioned secondary pancreatitis).

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 [25].

It is also relevant to note that antibiotic resistance determinants have been identified and characterized in Lactobacillus, Bifidobacterium, and the probiotic Bacillus [26,27].

Probiotics: Future Research

These precautions regarding probiotic use warrant evaluation. Also, 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 with 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.

The concurrent use of probiotics during antibiotic treatment is proving useful in reducing or eliminating the symptoms of AAD in the treatment of C. difficile and in certain tropical diseases caused by pathologic bacteria in the intestinal tract or requiring treatment with antibiotics.

In-depth research regarding certain strains of probiotics (and combinations thereof) as applied to specific conditions is beyond the scope of this paper, and is offered for 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 as an alternative treatment for certain bacterial infections and as complementary therapy in the treatment of distinct intestinal conditions and tropical diseases.

Conclusion

Overture for the Coadministration of Probiotics as a Global Health Proposal

Quality probiotics are affordable to produce and feasible to distribute on a global basis. Certain forms of probiotic foods can be produced locally. The simple addition of probiotic foods to the essential diet along with probiotic supplementation can result in a wide range of health benefits to people and thereby lessen the burden on their respective healthcare system and society. The prescriptive use of probiotics during antibiotic treatment may not only lessen the prevalence of AAD but may also aid in the patient tolerating and complying with antibiotic treatment resulting in improved outcomes of medical treatment.

The development of prescriptive and customary guidelines for probiotics in augmenting antibiotic treatment (particularly in preventing or lessening AAD and other side effects of antibiotics and in the treatment of C. diff, Chron's, and certain tropical infections) is a practical and promising project and should be considered within a structured public health proposal.

Conflict of Interest Statement

The author declares that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

Supplementary Note

This paper is based on prior unpublished research: Kerna, NA. (2017) Current Practices in the Use of Probiotics During Antibiotic Treatment (unpublished doctoral dissertation). Chapter I, pages 1-3; Chapter II, pages 9-27. ©2017 Nicholas A Kerna; and on published research: Kerna NA. A complementary medicine approach to augmenting antibiotic therapy: current practices in the use of probiotics during antibiotic therapy. Int J Complement Alt Med. 2018; 11: 62-66.

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