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THE INTERNATIONAL ARABIC JOURNAL OF ANTIMICROBIAL AGENTS

2014
Vol. 4 No. 1:5
doi: 10.3823/747

Probiotics versus antibiotics: Is this the only option?

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Abstract

The role of probiotics in potential prophylaxis of infectious disease has been studied for over a century, but until recently there has been no real interest in using these 'benign' bacterial species in place of or in combination with antibiotics. However, such suggestions are now commonplace and lead to a renewed interest in what has until recently been seen as a merely commercial branch of microbiology. This short review looks at the current literature in this area and attempts to identify if there is a scientific basis to inform the cautious clinical use of probiotics either alone or in combination with antibiotics. Whilst the evidence base is to date rather thin, there is sufficient to allow for a cautious support for such ideas. This review also identifies those areas in which further study is required before the general use of probiotics in the treatment of infection may be fully supported.

Introduction

Since the discovery of antibiotics less attention has been paid to older and more traditional treatments, such as probiotics [1]. Antibiotics, which were once considered to be *"miracle drugs"*, are now losing their effectiveness, particularly due to the overuse and misuse of antibiotics and subsequently to the increasing development of antibiotic resistance [1]. With each cycle of antibiotic-use the risk of recurrence due to resistance development increases by up to 60%, which is why alternative solutions are needed [2]. This has all led to the need for an alternative and safe long-term solution for the treatment of some infectious diseases [1]. Could probiotics be the solution to these problems and an effective alternative ? Several recent studies and clinical trials have exhibited potential significant benefits of probiotics in the prevention and treatment of infectious diseases. Probiotics also have the additional benefit of being generally considered as safe, with very

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few side effects. It is the aim of this brief review to investigate current opinion on the potential role of probiotics in the treatment of infectious disease and to attempt to identify the relationship between probiotics and antibiotics in clinical situations.

The history and resurgence of probiotics

Probiotics are not a new concept and their health benefits and clinical uses have been studied for many years [3]. Modern research on this topic began in 1908, when Eli Metchnikoff won the Nobel Prize for medicine for his work on immunology, which included studies on the role of probiotics in human health and longevity [3]. Metchnikoff was the first scientist to suggest that consuming certain bacteria found in sour milk and dairy products (used on the Eurasian steppe)could help replace harmful bacteria in the body and lead to increased longevity [3, 4].

In recent years the number of such products available has increased, as well as the modern consumer's familiarity with their proposed benefits and subsequently, this has generated much scientific research into the topic [5]. In 2006, over 600 commercial products were available using the term 'probiotic [5]. 'Probiotic' is a conflation of the Latin and Greek words *"pro"*and *"bios"*, which together mean *'for life"* [6]. A modern definition of the term includes " *probiotic drugs, probiotic food products (foods, food ingredients and dietary supplements), direct-fed microbials (probiotics for animal use) and designer probiotics (genetically modified probiotics)*" [7]. Probiotics are most commonly marketed as foods or dietary supplements [7].

Probiotics can be defined as "*live microorganisms which, when consumed in adequate amounts, confer a health benefit on the host beyond basic nutrition"* [5, 8-10]. Lactobacilli are some of the most widely used probiotic microorganisms [11]. Probiotic strains which have been studied most extensively include *Lactobacillus* GG and *Saccharomyces boulardii* [3]. Probiotic food is defined as "*a processed food product which contains viable probiotic organisms in a suitable matrix and sufficient concentration"* [5]. Lactic acid bacteria (LAB) can be found in fruit, vegetables and fermented food products. LAB are also present in the gastrointestinal tract and urogenital system of humans and animals [12] Probiotics are also commonly found in dietary supplements, milks, yogurts, powders and pills [3].

Probiotics and human health

According to Gomes da Cruz *et al.* [5], "*countless benefits to health are provided by the ingestion of foods containing probiotic cultures, some with scientific proof and other ones still needing more human studies*". Several ways have been suggested by which probiotics enhance human health. Various studies [6, 13, 14]. provide evidence of the benefits that probiotic formulations have with reference to the immune system, skin and allergies, surgical practice, urogenital infections, GI diseases such as diverticulitis, irritable bowel syndrome (IBS) and irritable bowel disease (IBD), *Helicobacter pylori* eradication, diarrhoea and carcinogenesis. One of the areas in which probiotics have received the most attention is in the prevention and treatment of various gastrointestinal diseases, including IBD, IBS, antibiotic-associated diarrhoea (AAD) and dysbiosis [15-17]. The overuse of vaccination and antibiotics has also been linked to dysbiosis [6]. Dysbiosis is said to occur when the normal profile of GI bacterial microflora becomes altered, which subsequently leads to an imbalance in the metabolic or immunological feedback of the host, possible rheumatoid arthritis and ankylosing spondylitis [6]. The use of probiotics has been investigated in the prevention and management of a wide range of infectious diseases, in particular infections of the GI tract. In a review conducted by Wolvers *et al.* [18], the following conditions were mentioned as possible side-effects of

Received 18 August 2014; accepted 22 August 2014 **This article is available from:** www.iajaa.org

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Vol. 4 No. 1:5
doi: 10.3823/747

GI microfloral imbalance: "*1. infectious diarrhoea in infants and children, 2. traveller's diarrhoea, 3. necrotizing enterocolitis in infants, 4. Helicobacter pylori infection, 5. respiratory tract infections in adults and children and ear, nose and throat infections.*"

Probiotics are also considered as useful in the treatment of post-operative infectious complications and infections in immuno-compromised patients [18]. Although most studies lack conclusive evidence and consistency, significant evidence has been found to support the use of probiotics in managing infectious diarrhoea in children, traveller's diarrhoea (TD), antibiotic-associated diarrhoea (AAD) and necrotizing enterocolitis (NEC) [18]. NEC is particularly common in pre-term infants, in comparison with healthy, full-term infants[18]. A study by Caplan *et al.* [18]. found that enteral administration of probiotics in pre-term infants could have significant benefits in reducing the risk of NEC and also reducing the associated use of antibiotics. Pre-term infants are often treated in intensive care units, receiving various broad spectrum antibiotics and this contributes to alterations in gastrointestinal tract colonization patterns[18]. It has been suggested that these alterations in pre-term infants play an important role in the pathogenesis of NEC and form a subsequent risk of increased infection [18]. However, in order for probiotic supplementation to become routine practice in the prevention of NEC in pre-term infants, it has been suggested that these results need to be validated by large, well-designed clinical trials in order to provide evidence for the efficacy and safety of probiotics in the prevention of NEC in pre-term infants [18].

Helicobacter pylori has been confirmed as a major cause of peptic ulcer disease and chronic gastric disease, as well as a contributing factor to the development of stomach cancer[18]. There are several difficulties involved in the eradication of *H. pylori*, which includes the rapid rate at which bacteria develop resistance to drugs and the unwanted side-effects that are associated with the use of these drugs, which subsequently increases the need for an effective alternative treatment [20-21]. Probiotics have been found to be effective in the eradication of *H. pylori* when used as an adjunct to antibiotic therapy and also, in reducing the undesirable side-effects associated with antibiotic therapy itself [18].

One of the most common medical concerns, particularly in women, are urogenital infections [6]. The most common urogenital complaints in women include recurrent urinary tract infections, which are most commonly caused by *E. coli,* recurrent bacterial vaginosis (BV) caused by *Gardnerella vaginalis* and also recurrent yeast vaginosis normally caused by *Candida albicans* [6]. However, lactobacilli have been shown to be the most predominant bacteria in the urinary tract of healthy females [18]. Usually these types of infections are treated with antibiotics and although they are generally effective, there is also a high incidence of recurrence [22]. Probiotics have been suggested as an alternative to antibiotic therapy for the treatment and prevention of urogenital infections, particularly since probiotics are effective in competing with pathogens for uroepithelial adhesion sites. They also produce substances that inhibit pathogen growth and secrete antimicrobial biosurfactants [6,23]. Another successful study by Anukam *et al.* [24]. showed that *L. rhamnosus* GR-1 and *L. reuteri* RC-14 were more effective than metronidazole treatment for bacterial vaginosis (BV) and this finding was reported as the first effective (90%) cure for BV [6]. It has also been reported that combinations of various probiotic strains may enhance or complement the health benefits that an individual strain exhibits [9]. The beneficial characteristics exhibited in one strain, when used in a combination with other probiotic strains, could have an effect on the mechanisms by which they inhibit or displace pathogens and compete for nutrients [9]. Current data supports the hypothesis that us-

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doi: 10.3823/747

ing combinations of probiotics or probiotics with antibiotics could have major health benefits and this topic needs to be further researched [9]. It has been suggested that "*Probiotic combinations that inhibit and displace pathogens may be good candidates in case of specific microbiota aberrancies related to disease risk reduction*" [9]. Results also indicate that when probiotic strains are used in combination with other probiotics and with antibiotics, this has an impact on pathogen adhesion properties, including inhibition, displacement and competition [9]. The study and control of such effects would be useful for the development of new probiotic combinations for treating specific diseases by preventing the adhesion of specific pathogens and have a massive impact on the disease [9]. However, the effects of health improvement depend on the strains present in the product and, so far, no probiotic strains have been shown to provide the complete range of the health benefits reported [5, 25]. Although several clinical trials have reported significant health benefits of probiotics, further trials are needed involving larger numbers of patients in order to provide conclusive evidence of their preventative and curative role in medical practice [6].

The safety of Probiotics

Although probiotics are generally considered safe [1, 6]. There have been reports of probiotic-related fungaemia and bacteraemia in severely immunocompromised patients [26, 27]. It has also been questioned as to whether they are safe for use in patients with severe inflammatory gut conditions and hence, this is a topic that requires further investigation [2]. Normally the safety assessment of dietary supplements is undertaken post-marketing [7] and the safety of probiotics is often assessed using animal models [28]. It is important for health care practitioners to have a clear understanding on the various uses of probiotics, as well as dosages and safety aspects in order to better educate patients and their families on the health benefits of probiotics [3]. Screening for specific probiotic strains will also allow the identification of strains without any potential oral health hazards [29]. Some studies have shown a risk of fungaemia in immunocompromised patients associated with *Saccharomyces boulardii* [1]. Other studies have shown that the risk of developing septicaemia in immunocompromised patients and of endocarditis in patients with damaged or artificial heart valves increases after their being treated with lactobacilli [1].

If a probiotic is to be considered for use in hospitalized patients, it has to be carefully assessed and the risks versus benefits should be carefully assessed [7] It is also important that probiotics are administered safely in order to ensure patient safety [7]. In addition to these reports it has been suggested that clinical studies on the use of probiotics fail to record any adverse effects of probiotics and their overall tolerability in patients [30]. There is also a lack of data on the long-term safety of probiotics, since most trials on the safety of probiotics are only of short duration [30]. Therefore, in a small proportion of patients, such as those with acute or co-morbid conditions or in hospitalized patients, the use of probiotics might not be suitable as a treatment regime [7, 30]. It has been suggested that more appropriately designed studies of sufficient duration are needed in order to determine the safety aspects and tolerability of probiotics [30]. However, Snydman reported in an article called '*The Safety of Probiotics'*,various concerns regarding their safety [31]. The first is the occurrence of disease due to bacteraemia, endocarditis and sepsis; secondly there is a possibility of toxic or metabolic effects on the gastrointestinal tract by probiotics [6]. The third concern that Snydman reported was the possibility of transfer of antibiotic resistance from probiotic species to potential pathogens in the GI flora [31]. However, cases of probiotic-related bacteraemia are very rare, with most epidemiological surveys suggesting

Received 18 August 2014; accepted 22 August 2014

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doi: 10.3823/747

that probiotics can be used safely in most clinical situations [6]. LAB have a GRAS-status (generally recognised as safe) and because of their health benefits as probiotics they have been widely researched [12]. In comparison to pharmaceutical agents they are generally regarded as safer, with less serious adverse side effects. However, in certain circumstances probiotic microorganisms can be infective and cause adverse health effects, for example in malnourished or immunosuppressed patients [32]. There have also been cases of bacteraemia following the intake of *Lactobacillus rhamnosus* GG in patients with underlying diseases [28]. According to Venugopalan*et al.* [7] the reporting of adverse events associated with the use of probiotics is very important to determine whether they are safe to be used in other than healthy populations.

In order to be an effective treatment for various infectious diseases, especially gastrointestinal infections, probiotics must be non-pathogenic and must act against pathogens by mechanisms differing from those of antibiotics, for example by competition[1]. Other essential qualities are that they have a rapid onset of action, are able to survive in the gastrointestinal tract and related environmental challenges (eg: the presence of bile salts, gastric acid and antibiotics) and also potentially modify the host's immune system in order to destroy the invading pathogen [1]. Hart *et al.* [33] suggested that probiotics need to be viable in order to demonstrate their beneficial effects. However, some studies have shown that even non-viable probiotic bacteria might have similar beneficial effects, as live probiotic strains. However, it is probably the case that probiotics must be viable at the time of consumption in order to achieve maximum health benefits. Many conventional types of lactobacilli are often inactivated by bile or low pH [6]. In order to be effective and considered a good probiotic, it has to meet the following requirements: "*1. being able to adhere to cells; 2. excluding or reducing pathogenic adherence; 3. being able to persist, multiply and produce acid, hydrogen peroxide and bacteriocins antagonistic to pathogen growth; 4. being able to be safe, non-invasive, non-carcinogenic and non-pathogenic; 5. being able to congregate as to form a normal balanced flora*" [6].

Probiotics *versus* Antibiotics in the prevention and treatment of infectious diseases

According to D'Souza *et al.* the "*increasing availability, lower costs and relative lack of side effects of probiotics contrasts with the problems associated with current antibiotic regimens*." Probiotic microorganisms that have been isolated and studiedto date include *Streptococcus thermophilus, Lactobacillus bulgaricus, Bifodobacterium* spp*., B. longum, Enterococcus faecium, Saccharomyces boulardii, L. acidophilus, L. casei and Lactobacillus* GG [1]. Some of the advantages of probiotic microorganisms, such as *S. boulardii*,over antibiotics include: being readily available, easy to administer and cost-effective when compared to antibiotics such as vancomycin [1]. The use of broad spectrum antibiotics has also been associated with several side effects, including disruption of the normal human microflora, leading to bacterial overgrowth and infections such as yeast vaginitis [22]. A common side effect associated with the long-term use of antibiotics is antibiotic-associated diarrhoea (AAD) [1,18]. AAD has been defined as "*otherwise unexplained diarrhoea occurring in association with antibiotic administration*" and it has been estimated that the incidence AAD in the paediatric population is between 11 and 40% between the initiation of antibiotic therapy and up to two months after completion of antibiotic therapy[18]. Several studies have shown that probiotics are effective in preventing and treating antibiotic-associated diarrhoea, particularly in the adult population [1, 3, 18]. Several probiotics have been studied in the prevention and treatment of

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antibiotic-associated diarrhoea (AAD). These include *Saccharomyces boulardii*,which produces a protease that destroys the receptor site for *Clostridium difficile* toxin A and B, preventing its attachment [1]. In *C. difficile* infections probiotics "*aim to restore the gut's colonisation resistanceby providing a barrier of relatively low-virulence microorganisms, mainly yeasts or Lactobacillus species – that compete with C. difficile for essential nutrient, mucosal adherence sites and space*" [2].

Other benefits of individual probiotic strains include reducing fever and incidence of rhinorrhoea and duration of cough and the subsequent requirement for antibiotic prescription [9]. Certain probiotics have been found to inhibit enteropathogenic *Escherichia coli* (EPEC) adherence by inducing the expression of an intestinal mucin gene[10]. It has been suggested that probiotics could offer an alternativeto the conventional antimicrobials in the treatment and prevention of enteric infections [10]. Various studies have also accessed the effectiveness of probiotic combinations such as VSL#3 and SCM-III (*L. acidophilus, L. helveticus* and *Bifidobacterium* spp.) in the treatment of irritable bowel disease (IBD) [30]. Most studies showed that probiotic combinations were effective in reducing the severity of IBD symptoms, such as abdominal pain, distension, flatulence and discomfort [30].

A study by Zuccotti *et al.* found that probiotics could be effective alternatives to antibiotic therapy in the treatment of urogenital infections in women [23]. The use of antibiotics in urogenital infections is often accompanied by several unwanted side effects, such as reducing the general counts of lactobacilli causing GI symptoms. Antibiotics are also ineffective in restoring the urinary tract's natural barrier against infection [6, 23]. According to Reid and Bruce , patients are often frustrated with repeatedly being prescribed antibiotics, which are becoming less effective due to the development of antibiotic resistance [22]. The type of antibiotic used and also the individual patient's risk factors are important factors that play a role in the incidence of AAD and not all antibiotics are equally likely to cause AAD [18]. According to Venugopalan *et al.*, due to the recent increases in the incidence and severity of *Clostridium difficile* infections, particularly in hospitalized patients, there is an urgent need for a safe and effective alternative to antibiotic therapy [7]. Subsequently, clinicians are considering the use of probiotics, either alone or in combination with antibiotic therapy for the treatment and prevention of *C. difficile* infection [7]. Antibiotics are generally effective in reducing the symptoms from *C. difficile* infection, although often the disease frequency relapses since antibiotics also disrupt the microflora of the gut [2]. This is one reason why non-antibiotic strategies such as probiotics have been investigated in the prevention and treatment of *C. difficile* infections [2].

Summary

In conclusion, considering all the evidence that has been given in this review it is clear that there is a scientific basis for the use of probiotics in the treatment and prevention of several infectious diseases, as an alternative or co-therapy to conventional antibiotic treatments. Probiotics have the benefit of being relatively safe in comparison to antibiotics, with fewer side effects and they are particularly cost effective. Probiotics offer various other additional health benefits and, when used alongside antibiotics, can reduce the incidence and severity of a range of side-effects normally associated with antibiotic therapy. Although there have been several studies providing evidence to suggest that probiotics could provide an effective alternative to antibiotic therapy or even be used alongside antibiotic therapy, more up-to-date clinical trials and studies are needed to provide conclusive evidence in order to validate

Received 18 August 2014; accepted 22 August 2014 **This article is available from:** www.iajaa.org

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doi: 10.3823/747

these findings. Future research could also focus on the possibility of probiotics being prescribed in general practice and on educating physicians on the role that probiotics have in the prevention and management of disease. It is apparent that clinical trials are needed to assessthe possible consequences of AAD, by looking at alternatives such as discontinuing antibiotic therapy, hospitalization or intravenous rehydration .

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Comment on this article:

Received 18 August 2014; accepted 22 August 2014