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REVIEW

Probiotics for the prevention of antibiotic-associated diarrhoea in older patients: A systematic review

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Summary *Objective:* Here, we evaluated the efficacy of probiotic interventions in prevention of antibiotic-associated diarrhoea (AAD) and *Clostridium difficile* diarrhoea (CDD) in older patients.
Methods: PubMed, Embase, CENTRAL, CINAHL, and Web of Science were comprehensively searched from their dates of inception to May 2014. Only randomised controlled trials reporting data on probiotics including *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, and *Bacillus*—alone or in combination—versus placebo or absence of treatment in older patients (age ≥65 years) were included. Risk ratios (RRs) for AAD and CDD relative to placebo or absence of treatment were estimated.
Results: Six trials with a total of 3562 patients were included. Only one trial showed that *Bacillus licheniformis* was effective for preventing AAD in older patients. However, there was no preventive effect for AAD and CDD with *Lactobacillus acidophilus (Florajen)*, *Lactobacillus casei Shirota*, *Saccharomyces cerevisiae (boulardii) lyo*, mixture of *Lactobacillus acidophilus* and *Bifidobacterium bifidum (Cultech strains)*, and mixture of *Lactobacillus acidophilus CUL60*, *CUL21*, *Bifidobacterium bifidum CUL20* and *B. lactis CUL34*.
Conclusions: Our findings indicate that probiotics may not reduce the risk of AAD and CDD in older patients. However, with current published data, it is difficult to draw concrete conclusions. To

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confirm these findings, sample sizes, multi-centre, double-blind studies that consider factors such as probiotic strains and types of antibiotics are required.

1. Introduction

Antibiotics are commonly used for treatment of numerous infectious diseases. Unfortunately, their use can lead to potential clinical complications, such as the misuse or inappropriate use of antibiotics, the emergence of antibiotic-resistant microorganisms, poor compliance, and increasing rates of disease related to antibiotic use [1—3]. Antibiotic-associated diarrhoea (AAD) is one of the most common intestinal complications of antibiotic use when antibiotic-mediated disturbance results in altered function of the microbiota [3]. This occurs in 5%—39% of patients, depending on the population and type of antibiotic: it is more common in older patients (age $\geq$ 65 years), and broad-spectrum antibiotics, such as clindamycin, cephalosporins and fluoroquinolones impart a greater risk than narrow-spectrum drugs [4—6]. Older patients are at greater risk of AAD because the incidence and prevalence of acute and chronic illnesses, drug consumption, and polypharmacy all increase with age. In addition, age may be associated with changes to the microbiota of the gut [7], which makes older patients are more susceptible to the effects of antibiotics [8]. *Clostridium difficile*, an important infectious cause of AAD, accounts for 15—39% of all AAD cases [2,9]. Compared with adults, the increased risk of acquiring *C. difficile* infection in the older patients may be due to age-related changes in faecal flora, immune senescence, or the presence of other underlying diseases [10].

The clinical presentations of AAD may range from mild, uncomplicated diarrhoea to more severe colitis, and may even result in toxic megacolon or death, particularly in *C. difficile* infections [2,11]. The severity of the diarrhoea generally determines whether a physician will discontinue or change antibiotics, and whether a stool specimen is analysed for the presence of *C. difficile* toxins. Older patients with AAD have higher rates of *C. difficile* infection, and these older patients with AAD typically have longer hospital stays [8,12]. AAD may also put patients at risk for developing other nosocomial infections, hospital stays, medical care costs, and diagnostic procedures [2,13—15].

Probiotics are microorganisms intended to have a health benefit when consumed in adequate amounts [16]. They help maintain normal gut flora and help reduce colonization by pathogenic organisms through competitive inhibition of epithelial and mucosal adhesion [17]. Therefore, probiotics have been widely used to treat a variety of conditions affecting the gastrointestinal tract, including travellers' diarrhoea, inflammatory bowel disease, irritable bowel syndrome, bacterial overgrowth, and *C. difficile* infection [18]. Due to this, there is an increasing interest in probiotic interventions, and there is increasing evidence for the effectiveness of probiotics in preventing or treating AAD [19,20]. Prevention and treatment of AAD with probiotics has been evaluated in two prior meta-analyses, and the results indicate some efficacy with this treatment [21,22]. However, these findings are confounded by substantial statistical heterogeneity in pooled results, which are attributed to variation in individual study results. Furthermore, a recent, multicentre, randomised, double blind, placebo-controlled trial that evaluated a multi-strain preparation of *lactobacilli* and *bifidobacteria* in prevention of AAD and CDD in older patients failed to show efficacy of the treatment [23]. Given this conflicting evidence, a determination of the patient populations that benefit most from probiotic intervention must be completed.

Further confounding our understanding of treatment of AAD with probiotics is the fact that the mechanisms by which probiotics might ameliorate AAD are complex. Creation of an unfavourable local pH for invading pathogens, enhancement of intestinal barrier function, competition for adhesion and production of bacteriocins to inhibit pathogens are all possible mechanisms [24—27]. These mechanisms can vary between populations, so it is important to note that the preventive effect is specific to the population [3]. At present, several meta-analyses and systematic reviews have been conducted to evaluate the efficacy of probiotics in prevention of AAD in adult and paediatric patients [21,22,28,29], but such a study of older patients has not been carried out. This is necessary, since older people are at greater risk of AAD. The aim of this study is to address this shortfall by systematically reviewing the literature on the effectiveness of probiotics interventions for the prevention of AAD and CDD in older patients.

2. Methods

2.1. Data sources and literature search strategy

A comprehensive search of PubMed, EMBASE, CENTRAL, CINAHL, and ISI Web of Science from date of their inception to May 2014 was conducted with the following keywords: probiotics, diarrhoea, antibiotic therapy, older, and randomised controlled trials (RCTs), *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, and *Bacillus*. For example, the PubMed search text was: [(probiotics OR *lactobacillus* OR LGG OR *bifidobacterium* OR *Saccharomyces boulardii* OR *saccharomyces* OR *streptococcus* OR *enterococcus* OR *bacillus*) AND (antibiotic*) AND (diarrhoea OR diarrhoea) AND (aged OR elderly OR senior* OR geriatric* OR retire* OR pension* OR old*)] AND (Clinical Trial [ptyp]). No language restrictions were applied. Additional trials were obtained by scanning the reference lists of all identified records.