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Co-Prescribing Probiotics with Antibiotics for Prevention of Antibiotic-Associated Diarrhoea and *Clostridium difficile*-Associated Diarrhoea - A Position Statement

Introduction

Antibiotics are amongst the most commonly prescribed drugs in UK hospitals. However, as well as treating infection they can cause disruption to the gastrointestinal microbiota. This can lead to the relatively common side-effect of antibiotic-associated diarrhoea (AAD) which often delays discharge. More concerning is that a disruption to the normal gut microbiota can lead to reduced resistance to opportunistic pathogens such as *Clostridium difficile*, leading to *C. difficile* infection, a potentially severe or fatal infection. The annual number of *C. difficile* infection cases across England from September 2016-17 was 4708 (1).

Current Department of Health guidance recommends that a patient is only tested for the presence of *C. difficile* if they have diarrhoea (Bristol Stool Chart types 5-7) not clearly attributable to another cause or condition (2). Any patient with diarrhoea must then be isolated ideally in a side-room and contact precautions with gloves and aprons initiated until the results are back. If the diarrhoea is attributed to *C. difficile* it is then referred to as *C. difficile*-associated diarrhoea (CDAD).

In 2016/17 each case of CDAD in excess of the threshold for that trust incurred a sanction of £10,000 (3), and in 2016, 32 deaths were attributed to the infection (4). This figure has decreased over the last 10 years but CDAD remains an important public health concern.

Probiotics have been studied in antibiotic-consuming populations, including inpatient and outpatient children and adults, for prevention of both AAD and CDAD. Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. Probiotics are generally considered to be safe, have a long history of safe use and their use is generally without significant side-effects. However there have been rare, isolated cases of probiotic-related bacteraemia in immunocompromised patients.

Public Health England (PHE) and National Institute of Clinical Excellence (NICE) guidance suggest there is insufficient evidence at present to recommend the co-prescribing of probiotics with antibiotics for prevention of CDAD (5, 6). However, this guidance has not been updated for several years and in that time more substantial evidence has been published which suggests that co-prescribing probiotics with antibiotics can provide a safe and effective strategy to restrict the incidence of CDAD and AAD.

Evidence Summary

In 2017 a meta-regression of 6,261 patients showed a >50% reduction of risk of developing *C. difficile* infection when probiotics were taken within 2 days of starting antibiotics (5).

In 2016 a meta-analysis of 7,957 patients showed a 60.5% reduction of risk of developing CDAD when co-prescribing probiotics with antibiotics (6).

In 2013 a Cochrane meta-analysis of 4,213 patients showed a 64% reduction of risk of developing CDAD when co-prescribing probiotics with antibiotics. It also showed a decrease in the risk of developing side-effects related to antibiotics (7).

In 2012 a meta-analysis of studies using specific strains of probiotics showed a 60% reduction of risk of developing primary CDAD in patients co-prescribed a probiotic with antibiotic therapy (8).

Administration of *Saccharomyces boulardii* compared with placebo or no treatment reduced the overall risk of AAD in patients treated with antibiotics from 18.7% to 8.5% (NNT: 10). In children, *S. boulardii* reduced the risk of AAD from 20.9% to 8.8%; in adults, from 17.4% to 8.2%. *S. boulardii* also reduced the risk of CDAD but the reduction was significant only in children (9).

Recommendations

Based on the available evidence, probiotics are a safe and effective adjunct to antibiotics to reduce the risk of developing AAD and for the primary prevention of CDAD.

Which patient population?

There is evidence to support the use of probiotics in all age groups including children.

For preventing *C. difficile*, the evidence suggests probiotic usage in immunocompetent patients of all ages. However, inpatients receiving antibiotics who are >65 years of age are a group most at risk of developing *C. difficile* infection.

For preventing AAD, the evidence suggests probiotic usage in inpatients and outpatients, children and adults, receiving antibiotics.

Avoid use in immunocompromised patients.

When should they be given?

The probiotic should be started at the same time as antibiotic therapy or as soon afterwards as feasible and continue ideally for 7 days after antibiotic therapy has been discontinued.

Which probiotic formulation?

As the field is relatively new, there is currently no 'gold-standard' formulation. Probiotic formulations shown to be efficacious for the primary prevention of CDAD are listed below, however there are several others with a good evidence base:

- *Saccharomyces boulardii* (Biocodex)
- *Lactobacillus rhamnosus* GG (Culturelle)
- *Lactobacillus casei* DN-114 001 (Actimel)

Summary

The International Scientific Association of Prebiotics and Probiotics (ISAPP) has reviewed available data and supports several published assessments, which recommend probiotics as adjunctive therapy for prevention of AAD and CDAD.

Several medical organizations have recommended probiotic use for prevention of **AAD** [ESPGHAN (10), Latin-American Expert Consensus Group (11), Journal of Primary Health Care (12), J Family Practice (13), Pharmacists Letter (14)] and **CDAD** [J Family Practice (15), ESPGHAN (10), American Family Physician (16), Society for Healthcare Epidemiology of America and Infectious Diseases Society of America (17)]. Further, the World Gastroenterology Organisation has published guidelines for the use of specific probiotics, including for AAD and CDAD (18).

About ISAPP

ISAPP is a non-profit scientific organization dedicated to the advancing the science of probiotics and prebiotics (www.isappscience.org). ISAPP is funded by industry membership fees, but is governed by an independent all-academic unpaid board of directors who volunteer their time to accomplish ISAPP objectives. ISAPP does not endorse individual products. One priority of ISAPP is to encourage evidence-based use of probiotics in clinical settings. Toward this end, this document summarizing the evidence of probiotic use for the prevention of AAD and *C. difficile* has been prepared.

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