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MANAGING ANTIBIOTIC ASSOCIATED AND CLOSTRIDIUM DIFFICILE ASSOCIATED DIARRHOEA WITH PROBIOTICS

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The human intestinal tract harbours a diverse and complex microbial community which plays a central role in human health (14). This gut microbiota is defined as 'an assortment of micro-organisms inhabiting the length and width of the mammalian gastrointestinal (GI) tract' (32).

There is a growing body of evidence which proposes that alterations in GI microbiota composition are associated with the pathogenesis of some GI disorders, including inflammatory bowel disease, constipation, antibiotic associated diarrhoea (AAD) and Clostridium difficile associated diarrhoea (CDAD) (7,17,26).

Moreover, the aberration of gut microbiota is also associated with an increased risk of developing other chronic long-term health problems, including Alzheimer's disease, obesity and Type 2 diabetes (24). Therefore, this clearly shows that host physiology and intestinal microbiota are intimately connected. However, Gerristen et al (12) argue that, since there are substantial inter-individual and intra-individual variations in the composition of the intestinal microbiota, it is difficult to establish the individual's inherent risk of developing specific GI and other chronic diseases.

Promising beneficial therapeutic effects have been demonstrated with targeted manipulation of gut microbiota composition through the use of probiotics (29). The aim of this article is to provide an overview of the science on probiotics and discuss their use in the management of antibiotic associated diarrhoea (AAD) and Clostridium difficile associated diarrhoea (CDAD) given that there is an inextricable link between the two conditions and, more importantly, increased risks of patient suffering and, in some circumstances, increased risk of morbidity and mortality (35,23).

PROBIOTICS: AN OVERVIEW

Probiotics have been defined as 'live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host' (10). In order to qualify as a probiotic, certain criteria need to be met. A bacterial strain must be fully identified, be safe for ingestion, adhere to the luminal mucosa, colonise the gut and possess documented health benefits, the results of which should be reported from randomised controlled clinical trials (39).

The GI tract in a newborn is considered to be sterile and bacteria from the mother colonise the gut during birth. Moreover, the microbiota composition differs between infants born by caesarean section (CS) and by vaginal delivery. In particular, children born by CS have demonstrated a delayed colonisation of the genus Bacteroides (25,18). Bacteroides are of clinical significance given that they have an excellent symbiotic relationship with the human host (41).

However, new evidence is emerging which challenges this transmission theory. Data from a recent and extensive study, found that the faecal microbiota of children was no more similar to that of their mothers or their biological fathers and was also genetically unrelated (42). This therefore suggests that the environment may have a significant impact on the development of the gut microbiota in children.

Indeed, it is well documented that the biodiversity of microbiota will also vary considerably depending upon whether the child is breast or bottle fed and the subsequent weaning process (40). It is also proposed that when the child reaches the age of four, the gut flora is fully mature and is unique to the individual (19). However, it is also argued that microbial signatures stabilise and start to resemble the 'adult state' when the infant reaches one to two years of age (32).

Although intestinal micro-organisms carry out essential

Table 1: Factors which can cause gut dysbiosis (Adapted from 34)

Intrinsic factors	Extrinsic factors
Gastric acid	Diet/prebiotics and probiotics
02 consumption	Proton Pump Inhibitors, (PPI) H2 blockers
Gut motility	Antibiotics
Mucus membrane	Prokinetics
GI secretions/enzymes	Laxatives
Antimicrobial peptides	Opioids
Immunity Peyer's patches (IgA secretion as first line of immune defence)	Non-steroidal anti-inflammatory drugs (NSAID)

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Box 1: Clostridium difficile: who is at risk? (Adapted from 6 and 34)

Recent hospital stay
Elderly individuals in long-term residential care settings
Individuals who have recently taken antimicrobials
Immuno-compromised individuals
PPI therapy
Those with poor health secondary to chronic disease
Pregnant woman

functions for their hosts, it is important to be aware that they also pose a constant threat of invasion owing to their sheer numbers and the large intestinal surface area (15).

Gut dysbiosis is defined as 'a state of imbalance in the gut microbial ecosystem, including overgrowth of some organisms and loss of others' (27). This dysbiosis is thought to be attributed to many factors which are shown in Table 1 and has a significant impact on the development of disease which may be acute or chronic (5).

As previously discussed, the range of pathological conditions arising from gut dysbiosis can range from those of localised GI conditions or can be more widespread exerting their effects systemically.

ANTIBIOTIC ASSOCIATED DIARRHOEA

Antibiotic-associated diarrhoea (AAD) is diarrhoea that occurs in association with antibiotic treatment and without an alternative cause (2). AAD occurs most frequently in older (≥65 years) inpatients exposed to broad-spectrum antibiotics, the risk increases progressively with longer treatment courses and it can occur up to 12 weeks after antibiotic exposure (3). Other risk factors associated with the development of AAD include; dysbiosis of gut microbiota, a direct effect of the antibiotic, for example erythromycin which can enhance gastric emptying and, finally, overgrowth of Clostridium difficile bacteria in the gut (8).

The main treatment for managing AAD is to prescribe metronidazole, a powerful antimicrobial drug which also has the potential to cause many unpleasant GI side effects, including diarrhoea and vomiting in some individuals (8).

Probiotics constitute a new and emerging therapeutic measure for both the prevention and effective management of AAD and to date are deemed to be safe with no side effects (NICE 2008 and 1). However, the evidence regarding the use of probiotics in AAD is equivocal (44). It is thought that the equivocal nature of the literature may be due to several reasons. Firstly, it is important to note that the therapeutic effects of probiotics are strain specific and furthermore, the efficacy will also depend on many environmental factors that make the immune system receptive or not to the influences of a given probiotic strain (28). This effect is illustrated with data from the PLACIDE Trial which concluded that there is currently no evidence to support the use of a multi-strain preparation of lactobacilli and bifidobacteria as being effective in the prevention of AAD (3). Moreover, one study has also suggested that probiotic treatment is not compatible with pharmacological treatments (4). However this is an extreme view and therefore the results from this study cannot be applied to the population as a whole. There are also several flaws identified in the methodology of many of the studies which examine the effects of probiotics and AAD (20).

In summary, whilst probiotics are useful in the prevention and management of ADD to ensure effective treatment of AAD, more research is needed to determine which probiotics are associated with the greatest efficacy and for which patients receiving which specific antibiotics (44).

CLOSTRIDIUM DIFFICILE ASSOCIATED DIARRHOEA

Clostridium difficile is a gram positive spore-forming anaerobic bacterium (6). Whilst Kaneria & Paul (21) argue that rampant use of broad spectrum antibiotics has increased CDAD, Varughese et al (37) propose that this organism only accounts for a small percentage of CDAD. Most recently, the European Society for Microbiology and Infectious Disease (ESCMID) suggest that mild CDAD is more likely to be caused by antibiotic use. However, one can argue what is 'mild CDAD' and how the word 'mild' can be defined in this instance (9).

The number of individuals with Clostridium difficile infection is reported to be falling on an annual basis (16). But it is still important to be aware that in severe cases Clostridium difficile infection can lead to pseudomembranous colitis and toxic mega colon; both of which can ultimately result in death (8). Furthermore, there is also a growing body of data to suggest that some individuals may also suffer with recurrent Clostridium difficile infections (33). Relapses may be secondary to germination of residual Clostridium difficile spores which have not been eradicated from the colon, therefore remaining in situ post the initial treatment (6). There are many individuals who are deemed to be at high risk of re-infection and these are highlighted in Box 1.

Ironically, unless the infection is deemed to be 'mild', the mainstay of treatment for Clostridium difficile infection is antibiotics, including metronidazole, vancomycin and more recently fidaxomicin (9). A recent review has concluded that fidaxomicin, one of the new generations of antibiotics, is a valuable emerging option for both the treatment of first episode and recurrent episodes of C. difficile-associated diarrhoea (31). However, given that recent antimicrobial therapy is deemed to be an increased risk factor for both developing and recurrent Clostridium difficile infection, it is prudent to suggest that there needs to be an alternative therapy in the prevention and management of this condition. Due to increasing antibiotic resistance and an increase in hypervirulent strains of C. diff infection where treatment with vancomycin and metronidazole has at times proven to be ineffective (38), this also highlights the

importance of discovering new treatments in order to eradicate this bacterium.

There is increasing data to suggest that probiotics may be useful in both the prevention and management of CDAD (39). Again, when analysing the literature, it is important to be aware that the effectiveness of the probiotic will be determined by both the strain and the dosage and that data is not transferable to other probiotic studies (43). A recent Cochrane Review which pooled data from several systematic reviews and meta-analysis of 23 randomised controlled trials, including 4213 patients deemed as 'moderate quality evidence', suggests that probiotics are both safe and effective for preventing CDAD (13). However, whilst probiotics are also reported to be safe and potentially effective in the prevention of CDAD, additional studies of higher power and rigorous design are needed to clarify these findings (20).

Whilst it is fair to say that the use of probiotics in the prevention and management of C. difficile infection remains controversial, there is now evidence to suggest that faecal microbiota transplantation may be beneficial in treating this highly unpleasant disease (30). Faecal transplants are meant to restore the healthy complement of gut bacteria that would normally keep C. difficile at bay. Despite their unappealing nature, the transplants have been used to treat hundreds of patients with C. diff infection and results highlight that more than 90 percent of patients have recovered (36). This form of therapy has been found to be most effective in those individuals who suffer a relapse of C. diff infection (22). At the present time, there is no clear evidence base regarding the mode of delivery of the faecal microbiota (30), but there is new and emerging data that proposes the use of a pill which encapsulates faecal microbiota which may remove the need for transplantation via nasal tubes or enemas (27).

CONCLUSION

Whilst it can be argued that the incidence of CDAD is decreasing, the risks of recurrent infection remain high in some vulnerable individuals. Furthermore, whilst there are certain hyper virulent strains of CDAD that are not responsive to the main antibiotics used to treat this disease, it is important that healthcare professionals are aware of good safe evidenced based alternatives. Given that probiotics are relatively cheap and are deemed to be safe, then their use in the prevention and treatment of both AAD and CDAD is certainly worth considering as an alternative therapeutic target. An improved understanding of the pathophysiology in both AAD and CDAD will help to guide further studies.

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Questions relating to: *Managing AAD and CDAD with probiotics*
Type your answers below and then **print for your records.** Alternatively print and complete answers by hand.

Q.1	What are probiotics and what criteria need to be met for classification?
A	
Q.2	What are the main influences on GI microbiota in infants?
A	
Q.3	Define gut dysbiosis giving examples of factors that influence its development.
A	
Q.4	What are the risks of Antibiotic Associated Diarrhoea (AAD) and how is it managed?
A	
Q.5	What factors play a part in the efficacy of probiotics as a treatment for AAD?
A	
Q.6	Define Clostridium Difficile Associated Diarrhoea (CDAD) and explain the main cause.
A	
Q.7	Who is at risk of Clostridium Difficile (C. Diff)?
A	
Q.8	What are the risks of severe C. Diff?
A	
Q.9	Why are probiotics useful in the prevention and management of C. Diff?
A	

Please type additional notes here . . .