REVIEW ARTICLE

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Probiotics and its Impact on Antibiotic-associated Diarrhea (AAD) and *Clostridium difficile* Infections (CDI) in Adult and Pediatric Patients: A Review

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Abstract

A common adverse effect of antibiotic use is diarrhea. Probiotics are living micro-organisms, which may prevent antibiotic-associated diarrhea (AAD) by the normalization of an unbalanced gastrointestinal flora. The objective of this review was to assess the benefits and harms of probiotics used for the prevention of AAD in patients based on literature findings. Thus review of the literature using bibliographic databases and abstracting systems such as PubMed (1978- 2020) and Cochrane was conducted to find the effects of probiotics and compare AAD and CDI in both pediatric and adult populations and determine significant differences and similarities that might impact clinical decisions. In general, pediatric AAD and CDI have a more rapid onset of symptoms, a shorter duration of disease and fewer CDI complications (required surgeries and extended hospitalizations) than in adults. Literature studied revealed the finding that suggests that probiotic use in both adult and populations may be beneficial in the prevention of AAD among patients. Furthermore, the use of probiotics appears to be safe. The narrative review adds value to the current knowledge owing to the fact that adult and pediatric differences of AAD and CDi have not been studied in many review focusing on current evidence before ours. The differences in treatment modality across age groups should be taken into account when rating severity of disease and prescribing antibiotics. However, any differences should be taken into account when rating severity of disease and prescribing.

Key words: Antibiotics, Antibiotic-associated diarrhea, *Clostridium difficile* infections, probiotics, Lactobacillus, Bifidobacterium, Saccharomyces.

INTRODUCTION

The clinical presentation and response to treatments often differ radically in pediatric compared to adult patient populations. Although antibiotic-associated diarrhea (AAD) and *Clostridium difficile* (*C. difficile*) infections (CDI) are widely studied in adult populations, a comparison of the disease processes in the pediatric population is not as well described, especially for *C. difficile* infections.[1]

The use of probiotics may be an important clinical concern, as global guidelines are typically based on adult patients, not children.[2,3] Results from clinical trials performed in adults might be extrapolated to pediatric populations if the response is similar in these two populations. Currently, there are limited comprehensive comparisons of these two populations for AAD and CDI. The national prevalence of both pediatric[4-6] and adult cases of CDI[7,8] are increasing over time, but the secular trends for pediatric and adult rates of AAD have not been documented. The impact of AAD and CDI on healthcare systems is high. In the United States, an estimated number of about 45000 cases of incident CDI occurred in 2013, associated with 29300 deaths and increased costs of healthcare.[9,10]

Many incident cases of adult CDI generally recur and these cases are associated with higher costs.[10] The burden and costs of pediatric AAD have not been documented by national surveillance studies. AAD is also associated with longer hospitalizations, higher healthcare costs, increased risks of mortality and acquiring other nosocomial infections.[11]

Generally for AAD, the pediatric population is defined as aged one month to 18 years of age, but for pediatric CDI, the reported age range shifts to 1-21 years old.[12-14] For pediatric CDI, infants younger than one year old are typically excluded from being defined as CDI cases due to their high asymptomatic carrier rate associated with the lack of toxin A/B receptors in the immature colon and high prevalence of other etiologies of diarrhea (most commonly viral causes).[15]

Adults are usually defined as ≥ 21 years old, but published studies have included ages as young as 16 years old. The lower limit for pediatric AAD is difficult to define without knowing more about asymptomatic carriage of other etiologies of AAD. Although it is appreciated that the intestinal microbiome is in an active stage of change during early life, few studies report clinical data by finer age strata other than either pediatric or adult. For this review, we include all ages under 21 years as pediatric AAD and ages 1-21 years old as pediatric CDI. Diarrhea The World Health Organization defined diarrhea in adults and children as the passage of three or more loose or liquid stools per day, or more frequently than is normal for the individual.[16] In clinical studies, diarrhea in adults is usually defined as more than 3 liquid stools/d for at least two days.[17]

Pediatric diarrhea is typically defined using the WHO definition,[16] but one study defined pediatric diarrhea as more than 5 stools/d.[18] Antibiotic-associated diarrhea AAD is defined as diarrhea associated with antibiotic exposure, either while on antibiotics or for up to eight weeks after antibiotics have been discontinued[19,20] Although the etiologies for AAD are varied and

not all the pathogens are identifiable, nearly one-third of AAD cases are due to *C. difficile*. In paediatric AAD, etiologies may include viruses (25% in one study)[21] or *C. difficile* (22%-30%), but also may be due directly to osmotic imbalances in the intestines brought about by antibiotic exposure and microbiota disruption. In adults with AAD, identifiable pathogens include *C. difficile* (13%-28%), *C. perfringens* (3%-21%), *Staphylococcus aureus* (1%-28%) and less commonly *Klebsiella oxytoca*.[22] *C. difficile* infections CDI diagnosis is based on standard definitions in practice guidelines, which are based on a positive result in two factors: (1) presence of *C. difficile* in the stool (e.g., microbial culture, cytotoxin assay, enzyme immunoassay, nucleic acid amplication test, or polymerase chain ribotyping); and (2) the presence of gastrointestinal symptoms (e.g., diarrhea, colitis, etc.) without another etiology being present.[23]

Onset of symptoms Laboratory testing and surveillance data allows both the setting (location of disease onset) and the time of onset (incubation time) to be determined. If an etiology can be determined (e.g., *C. difficile*), the source of the infection may be determined. AAD or CDI cases may begin exhibiting symptoms at healthcare settings (including hospitals and long-term care facilities) or in community settings (home etc.), but the setting is typically only defined for CDI cases. The incubation time for AAD (defined as the time between antibiotic initiation and the onset of diarrhea) falls into two groups: early onset, occurring during antibiotics and delayed onset, which may occur from 2-8 weeks after the antibiotics have been discontinued.[20,21]

The incubation time for CDI should best be measured from the first day of the inciting antibiotic to the first day of diarrhea associated with a positive *C. difficile* assay, but most studies of CDI have not collected data related to the first day of antibiotic for all their patients. As a consequence, the incubation time for CDI is typically measured starting from either the first day of healthcare facility admission or first positive laboratory test for *C. difficile* and ending at the first day of defined diarrhea.

Probiotics are live micro-organisms which when administered in adequate amounts confer a health benefit on the host.[23] The rationale behind the administration of probiotics in gastrointestinal disorders is based on the hypothesis that they may assist a normalization of an unbalanced gastrointestinal flora. There are many proposed mechanisms by which probiotics enhance intestinal health, including the stimulation of immunity, competition for nutrients, the inhibition of the epithelial and mucosal adherence of pathogens, the inhibition of epithelial invasion, and the production of antimicrobial substances.[24]

Epidemiology

Incidence and setting Pediatric AAD incidence: National surveillance studies have not been done documenting the incidence of pediatric AAD in the general population. From a meta-analysis of 22 clinical trials of children exposed to antibiotics, AAD in the controls ranged from 4.3% to 80%, with a median incidence of 22%.[19] The incidence of pediatric AAD varies largely due to two main factors: the age of the child and the type of antibiotic to which the child is exposed. As infants are transitioned to solid food, the incidence of AAD seems to increase, perhaps reflecting a shift in the normal intestinal microbiome.

Few studies of pediatric AAD have provided age, gender or racial distribution of their cases, but one study reported no significant differences by gender.[24]

Adult AAD incidence: The literature presents different results for proton-pump inhibitors, some showing significant risk, while others do not. Further research may help to define the role of proton pump inhibitors and pediatric CDI. Adult CDI risk factors: The risk factors that are common for adult CDI also include the same triad of factors: host factors (age, co-morbidities), disruptive factors (exposure to antibiotics or other medications) and increased exposure to *C. difficile* spores (prolonged lengths of stay at healthcare facilities). A broader range of antibiotics have been identified as high-risk in adults, but there are not as many studies done in children (Table). However, many additional types of risk factors were identified in several studies using multivariate models to adjust for other simultaneous risk factors.

DISCUSSION

Antibiotic-associated diarrhea (AAD) occurs in 5% to 39% of patients, from the beginning and up to two months after the end of treatment.[21] Any type of antibiotics can cause AAD. In particular, aminopenicillins, cephalosporins, and clindamycin that act on anaerobes are associated with a high risk of AAD.[22] The symptoms range from mild and self-limiting diarrhea to severe diarrhea, the latter particularly in *Clostridium difficile* infections.

The primary care sector is responsible for the bulk of antibiotic consumption in humans.[23] Reports suggest that a major part of this antibiotic use may, in fact, be inappropriate, and efforts to reduce and target antibiotics are rightly promoted. However, when antibiotic therapy is deemed necessary, it is useful to have an easily available, cost effective, and safe method to prevent side effects associated with the issued antibiotic.

Numerous probiotic species have been tested, most commonly the *Lactobacillus* genus, *Bifidobacterium* genus, and *Saccharomyces* genus. Previous reviews suggest that probiotics are useful in the prevention of AAD. However, most reviews of the reviews have mainly focused on the prevention of AAD in inpatients from secondary care settings, which was likely influenced by the intensity of antibiotic treatment (intravenous versus oral), the type of infection, and the microbial pathogens, in turn making the translation complicated.

CONCLUSION

Our review findings point out to the fact that adding probiotic agents may be useful in preventing antibiotic associated diarrhoea, but it provides little support for a role of probiotics in the treatment of such diarrhoea. The increasing availability, lower costs, and relative lack of side effects of probiotics contrast with the problems associated with current antibiotic regimens. Data from trials have provided with clear evidence on the efficacy of some strains in the gut, but we still need to see confirmation of their clinical benefit.

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