Can probiotics prevent antibiotic-associated diarrhoea in an 18 month-old boy? A Critical Appraisal of a Topic

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ABSTRACT
Diarrhoea is a common side effect in children on an antibiotic treatment. Antibiotic-associated diarrhoea can cause serious adverse effects such as dehydration and electrolyte disturbances, resulting in possible hospitalisation. This critical appraisal of a topic is focused on the question whether probiotics can prevent antibiotic associated diarrhoea in an 18 month-old boy. Four randomised controlled trials with a strong validity demonstrated the benefit of probiotics. Children that took probiotics in addition to antibiotics had a lower incidence of diarrhoea then children that took a placebo. Also, other positive effects of probiotics, concerning diarrhoea, were found.

Keywords
Probiotics, antibiotic-associated diarrhoea, children.

INTRODUCTION

Clinical scenario

An 18 month-old toddler was referred by the general practitioner to the paediatric emergency unit of a hospital in The Hague. Two weeks ago, the mother went swimming with the patient, and afterwards, he caught a cold. In the following days, he developed a fever of 39 ^{0}C and frequently grabbed both his ears. Because the boy was previously diagnosed with acute otitis media (ear infection), the mother went to see the general practitioner who prescribed analgesics (Paracetamol 4dd 240 mg) along with nose drops (Xylometazolin), because of one-sided otitis media acuta. After one week, unfortunately, the fever persisted and increased to 39.6 ^{0}C before the intake of Paracetamol. The patient was not drinking well and was agitated. Nonetheless, he had several wet diapers and there was a normal consistency to his faeces. On physical examination at presentation, he was asleep, but alert after stimulation and did not appear irritable. The patient had a pulse of 160/min, a breathing rate of 40/min and an O_2 saturation of 98% via pulse oximetry. His temperature was 39.1 ^{0}C (taken rectally). During otoscopy on both ears, a red bulging eardrum was seen on both sides. Broad spectrum antibiotic Amoxicillin-Clavulanate was started. However, previous treatment with this antibiotic resulted in antibiotic-associated diarrhoea (AAD). Therefore, the mother asked if this adverse side-effect could be overcome.

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In the gastrointestinal tract, several hundred competing bacteria reside in homeostasis, which are of key importance for the normal function of the gut.[1] However, through administration of antibiotics, the natural microbial balance is often disturbed in favour of harmful bacteria, resulting in AAD. The incidence of AAD in children treated with broad spectrum antibiotics varies from 11% up to 40%.[2,3] The symptoms of AAD include frequent watery bowel movements, abdominal cramps and pain. Moreover, mucosal integrity and vitamin/mineral adsorption can be compromised[4] and may even lead to electrolyte disturbances, depletion of volume (dehydration), pseudomembranous inflammation and toxic mega colon; but rarely death.[5] Although treatment with broad spectrum antibiotics such as Amoxicillin-Clavulanate is the “golden standard” for persisting otitis media, AAD is a serious side-effect, making it clinically relevant to determine whether it can be prevented.

Because of this clinical relevance, research has been conducted on the co-administration of probiotics alongside antibiotics. The main goal of administrating probiotics is to restore the natural microbial balance and reducing the risk of developing AAD. Besides restoring the balance, antibacterial and immune regulatory effects are reported.[6] Probiotics are comprised of (non-pathogenic) bacteria or yeast microbiotics. Probiotics consist of one to several strains[7] and are available in the form of either capsules, sachets, or even yoghurt. In some countries, such as Poland, the beneficial use of probiotic yoghurt is commonly accepted by the public,[8] whereas other countries differ in this practice. Nevertheless, whether or not probiotics prevent the occurrence of AAD is still controversial. Hence, a critical appraisal on this topic (CAT) was needed and the following clinical question was postulated: can probiotics prevent antibiotic-associated diarrhoea in an 18 month-old boy?

METHOD

Literature search

A combined search in the database PubMed Medline was conducted to extract relevant information regarding the clinical topic. The search strategy included several components. The first component comprised the patient population: “children” or “infants”. The second component, intervention, was covered by (prophylactic) “probiotics” and “antibiotics”. The third component was the comparison: “antibiotics”. The final component was the outcome: “diarrhoea”. More synonyms and related terms of these components were used as Mesh terms, in order to increase the number of search results. Subsequently, a filter for RCT and publication date up to 10 years from the time of search was applied. The combined search resulted in 94 hits from which 3 articles with high relevance to the subject were selected. Another

reference was identified through related articles by Fox et al.,[9] based on the target group (infants). At last, a reference older than 10 years that was mentioned in several studies was selected.

Critical evaluation

Four randomised controlled trials were critically evaluated. These articles were selected during the literature search based on the most relevance to answer the clinical question. The main criteria were the use of antibiotics, probiotics as an additive compared to a placebo, children as the target group and the incidence of diarrhoea as an outcome measure.

The validity items of the JAMA guidelines[10] were scored in order to measure the strength of validity for each article. Furthermore, articles were scanned for possible bias or other irregularities to conclude whether an article was applicable in answering the clinical question.

RESULTS

All four articles were found to be of strong validity, based on the JAMA guidelines (Table 1). However, the incidence of AAD in the study by Szymański et al.[11] (3.8%) was quite low in contrast with normally reported incidence of AAD (11%-40%),[2,3] despite the intake of antibiotics susceptible to AAD. The authors suspected the use of other probiotics during the study, against recommendation, since the use of probiotics combined with antibiotics is very popular in Poland, where the study took place. For this reason, the authors questioned the clinical importance of their conclusion. Consequently, these results were only partially applicable in answering the clinical question.

Table 1: Critical evaluation of articles by JAMA guidelines

	Fox et al.	Szymański et al.	Corrêa et al.	Vander-hoof et al.
Were patients randomised?	Yes	Yes	Yes	Yes
How was the randomisation performed?	Computer	Computer	Not clear	Computer
Were all included patients reported?	Yes	Yes	Yes	Yes
Follow-up complete?	97%	100%	93%	93%
'Intention-to-treat' analysis?	No	Yes	No	No
Randomisation double blinded?	Yes	Yes	Yes	Yes
Groups similar at baseline?	Almost (boy/girl ratio not)	Almost (age not)	Yes	Yes
Were groups treated the same?	Yes	Yes	Yes	Yes

The study by Vanderhoof et al. was supported by the supplier of the probiotic capsules, and Vanderhoof himself serves as a consultant in that firm. Therefore, there could be some conflict of interest. Still, the overall validity of the study was strong and the results were taken into account to conclude an answer on the clinical question.

The four evaluated studies were quite comparable. The sum of the study population consisted of children treated with antibiotics within an age range of 5 months to 16 years. Corrêa et al.[12] was the only study focussing on infants from the age of 6 months up until 3 years. The interventions consistently included the use of probiotics in a wide range of probiotic type as well as different fashions of intake (yoghurt, capsule, sachet). Outcome measures varied slightly per study, while diarrhoea was the common denominator. All articles determined the incidence of diarrhoea, which was the most important outcome to answer the clinical question of this CAT. Beside this primary endpoint, other outcome measures such as stool frequency, stool consistency, duration of diarrhoea, onset of diarrhoea and dehydration were established.

All of the studies concluded that probiotics were beneficial in the prevention of AAD (Table 2). Fox et al., classified diarrhoea in four grades, based on stool consistency and stool frequency. They found a lower incidence of diarrhoea in all their classifications of diarrhoea in the probiotic group in comparison to the placebo group ($p<0.001$). Additionally, no children in the probiotic group suffered from severe diarrhoea, compared to 6 children in the placebo group ($p=0.025$).

Table 2: Results: incidence diarrhoea

Author	Population	Intervention	Results
Fox et al. (2015)	Children (1-12 years) N=70	Yoghurt (*LGG*, *Bifidobact. lactis*, *Lactobacillus acidophilus*, resp. $5.2x10^9$, $5.9x10^9$, $8.3x10^9$ CFU*/day)	Any type of diarrhoea: 1/34 probiotic vs 27/36 placebo group, P<0.001 Severe diarrhoea: 0/34 probiotic and 6/36 placebo group, P=0.025
Szymański et al. (2008)	Children (5 months – 16 years) N=78	*Bifidobact. longum*, *Lactobacillus rhamnosus*, *Lactobacillus plantarum* (10^8 CFU/day)	1/40 probiotic vs 2/38 placebo group, not significant (95% CI 0.06 ; 3.5)**
Corrêa et al. (2005)	Infants (6 – 36 months) N=157	Supplemented formula (*Bifidobact. lactis* and *Streptococcus thermophiles,* minimal 10^7 CFU/g)	16% probiotic vs 31% placebo group, P=0.044, 95% CI 0.29 ; 0.95
Vanderhoof et al. (1999)	Children (6 months – 10 years) N=188	Capsules (*LGG,* $1x10^{10}$ – $2x10^{10}$ CFU/day)	8% probiotic vs 26% placebo group***

* CFU = colony-forming units
** Results should be interpreted with caution because of the low number of overall AAD
*** No p-value or CI was mentioned in the study

Likewise, in the study by Corrêa et al., significantly more patients of the placebo group (31.2%) developed AAD compared to the probiotic group (16.3%) (p=0.044). Vanderhoof et al.,[13] also found a difference in diarrhoea incidence (seven children (8%) in the probiotic group and 25 children (26%) in the placebo group), though no p-value or CI was mentioned in the article. The sole study without a significant difference in the incidence of

diarrhoea (Szymański et al.) was partial applicable given their low overall incidence of AAD.

In addition to diarrhoea incidence, differences in secondary outcome measures were also found with regard to diarrhoea between probiotic and placebo groups. Groups that co-administered probiotics had decreased stool frequency,[10,11,13] better stool consistency,[10,13] shorter duration of diarrhoea,[13] delayed onset of diarrhoea[10,12] and less dehydration.[12]

CONCLUSION

Based on the results of the evaluated studies it can be concluded that probiotics are effective in preventing diarrhoea in children that are treated with antibiotics. All studies found differences in diarrhoea incidence between the probiotic group and the placebo group in favour of the probiotic group. Although one study found no significant difference between groups, the clinical relevancy was questioned by the authors themselves. Beside the decrease in developing AAD while taking probiotics as an additive to antibiotics, other benefits regarding diarrhoea were shown in the studies. And important as well, none of the studies reported negative side-effects of probiotics.

The evidence presented in this CAT suggests a benefit of probiotics in the prevention and reduction of AAD in children. However, no conclusions can be drawn about the most effective probiotic strain (or combination of several strains) and what doses ensure the best results. The four evaluated studies included different types of probiotics in different doses, but it cannot be concluded which type and/or doses was most effective because of the different study designs and patient populations, as well as the variations in definitions of diarrhoea. A recently published systematic review on this topic,[8] including 23 RCTs, concluded that the two probiotics that were most effective are *Lactobacillus rhamnosus spp.* and *Saccharomyces boulardii* at a dose of 5 to 40 billion colony-forming units/day. These strains were only very rarely associated with adverse events and side-effects. Three out of the four evaluated studies of this CAT included *Lactobacillus rhamnosus* as (one of) the probiotic(s).[10,11, 13]

No side-effects or adverse effects of probiotics were found or reported in the evaluated studies; yet, it cannot be completely ruled out. A systematic review by Goldenberg et al.,[8] stated that no serious adverse events were reported among otherwise healthy children in any of the 23 RCTs that they reviewed. In contrast, probiotics have not yet been proven safe in children that are immuno-compromised, severely debilitated or neonatal. It is therefore suggested not to prescribe probiotics to children in these high risk situations until further research is performed.

The outcome of the different studies depends greatly on the definitions of diarrhoea, varying in time frame, frequency and consistency. Fox et al., classified four definitions of diarrhoea, and found that the benefit of probiotics is higher in case of a more severe type of diarrhoea, while mild forms of diarrhoea benefit relatively less. Due to this conclusion even the results of meta-studies and systematic reviews that compare studies with various definitions of diarrhoea must be met with the necessary criticism.

To conclude, more research is necessary in order to gather more evidence about the most effective type of probiotic(s) and doses. Also, more knowledge is required concerning the effect of probiotics on children with differences in age, weight, and type of antibiotic administered to them. In order to draw a valid conclusion about the most effective type of probiotics, comparisons within, instead of between, RCTs should be considered. This would result in more equal variables.

In the clinical scenario presented here, an 18 month-old boy was prescribed antibiotics because of an otitis media. The results of the evaluated articles were applicable to the patient, since all patient populations included children within the age of 18 months. It can therefore be concluded that the 18 month-old boy should be treated with probiotics, as an additive to his antibiotic treatment, to endeavour to prevent diarrhoea. From the analysis of this CAT, the type of probiotic does not seem to matter, as long as one kind is used.

ROLE OF THE STUDENT

Anand Biharie was an undergraduate medical student working under the supervision of Dr. A. Roest, a pediatrician in LUMC. A Critical Appraisal of a Topic in medicine is an evaluation of the best available evidence to answer a specific clinical question. The topic was proposed by the supervisor, while the clinical scenario was written by the student, based on the situation of his own son at that moment. The rest of the critical appraisal was performed by the student as well.

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