REVIEW ARTICLE

Antibiotic Associated Diarrhea in Children

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Context: Keeping in view the recent flooding of the Indian market with antibiotic and probiotic combinations, we decided to look at the prevalence of antibiotic associated diarrhea (AAD) and *Clostridium difficile* infection (CDI) in children and reviewed evidence available for use of probiotics in the prevention of AAD.

Evidence acquisition: We did a PubMed, Medline and Cochrane libary search for literature available in last 25 years.

Results: Prevalence of antibiotic associated diarrhea (AAD) is around 11%. Children younger than 2 years and type of antibiotics are the two risk factors identified for AAD. For the pediatric population, CDI reportedly decreased in a tertiary care hospital in India, though number of suspected samples tested increased. The incidence of community acquired CDI is increasing in the pediatric population also. Detection of toxin A and B by enzyme linked immunosorbent assay (ELISA) and detection of toxin B by tissue culture form the mainstay in the diagnosis of *C. difficile*. Most of the AAD would respond to only discontinuation or change of the antibiotic. Oral metronidazole or oral vancomycin are drugs of choice for CDI. Probiotics reduce the risk of AAD in children and for every 7-10 patients one less would develop AAD. **Conclusion**: Prevalence of AAD is low and majority will respond to discontinuation of antibiotic. CDI is uncommon in children. Probiotics will prevent AAD in only 1 in 7 children on antibiotics. We need cost effectiveness studies to decide the issue of needing a probiotic antibiotic combination to prevent AAD.

Keywords: *Antibiotic associated diarrhea, C. difficile associated diarrhea, Children, Pseudomembranous colitis.*

Antibiotic associated diarrhea (AAD) is unexplained diarrhea occurring between 2 hours to 2 months after starting antibiotics, where diarrhea is defined as more than 2 unformed stools for ≥2 days. Sometimes patients may have mild illness due to antibiotics where diarrhea (duration less than 2 days) is not fulfilling AAD definition(1). We identified the following research questions for this review: how prevalent are childhood AAD and *Clostridium difficile* infection (CDI) in the world and especially in India? What is the management of the AAD and CDI? How justified it is to add probiotics to antibiotics to prevent AAD? We did PubMed, Medline and Cochrane library search using terms like antibiotic associated diarrhea (diarrhoea), *Clostridium difficile*, pseudomembranous colitis and probiotics/limiting data in the age group 0-12 years. Keeping in view the changes in the antibiotics policy and improvement in level of health care, we limited the search to past 25 years.

PREVALENCE

Pediatric data regarding the prevalence of AAD is scarce with very few studies all over the world and no Indian studies (***Table* I**). In a study from Thailand, 6.2% of 225 children had AAD, with amoxicillin and cloxacillin combination being the most commonly prescribed antibiotics. There was a trend towards a higher incidence of AAD in the amoxicillin/clavulanate group (16.7%) compared to amoxicillin (6.9%) and erythromycin (11.1%) groups, although it was not statistically significant. The study could not demonstrate an association between younger age or the high dosage of antibiotics used, and the development of AAD.

TABLE I PREVALENCE OF ANTIBIOTIC ASSOCIATED DIARRHEA (AAD) IN CHILDREN

Author (ref)	Place	Study type	Definition of AAD	Prevalence of AAD (%)	Age group	All or particular antibiotics	Outpatients or inpatients
Mitchell, *et al*.(9)	USA	Prevalence	adequate	22/76(28.9)	12-47 m	amoxicillin/ clavunate	outpatients
Vanderhoof, *et al*.(4)	USA	RCT*	adequate	25/95(26)	6 m 10 y	all	outpatients
Arvola, *et al*.(5)	Finland	RCT	adequate	9/58 (16)	2 weeks to 12.8 years	all, but 38 of 58 received amoxicillin	outpatients
Jirapinyo, *et al*.(6)	Thailand	CT**	not known	8/ 10 (80)	1-36 m	all	inpatients
Turke, *et al*.(3)	USA	Prevalence	adequate	71/650 (11)	1 m-15.4y	all	outpatients
La Rosa, *et al*.(7)	Italy	CT	inadequate	31/50 (62)	Mean age 6.6 y	all	outpatients
Sekhi H, *et al*.(8)	Japan	CT	not known	16/27 (59)	—	all	outpatients
Kotowska, *et al*.(10)	Poland	RCT	adequate	22/127 (17.3)	5 m -15 y	all	both
Damrongmanee and Karapol(2)	Thailand	Prevalence	adequate	14/225 (6.2)	3 m -14.5 y	all	outpatients
Ruszczynski, *et al*.(11)	Poland	RCT	adequate	20/120 (17)	3 m -14 y	all	both

**RCT: Randomized controlled trial, **CT : Clinical Trial.*

A recent study done in USA to find the prevalence of AAD, reported 11% (71 of 650) of children on various antibiotics developed AAD and mild illness. More than two third of these 71 children developed AAD during the therapy and 15% in the week following stopping antibiotic. Seventeen percent presented with AAD during antibiotic treatment and continued after stopping the antibiotic. AAD was seen to begin 5.3±3.5 days after start of antibiotic and the mean duration was 4±3 days with none requiring hospitalization(3). The highest incidence (18%) of AAD was in the 2 months to 2 years age group. The antibiotics with which AAD was associated were: penicillin G and V (3%), penicillin A and M (11%), amoxycillin-clavulanate (23%), cephalosporins (9%), macrolides (8%), trimethoprim-sulphamethoxazole (6%) and erythromycin (16%). There was a statistically significant difference between the rate of onset of AAD associated with amoxicillin/clavulanate compared with all other antibiotics combined (P=0.003). The rate of AAD associated with parenterally administered antibiotics especially those with entero-hepatic circulation was similar to rates associated with oral antibiotics. The relative risk of onset of an episode of diarrhea in a child receiving amoxicillin/clavulanate was 2.43 (range, 1.4–4.21) and 3.5 (1.89–6.46) when the child was aged less than 2 years. Children younger than 2 years and type of antibiotic were the two risk factors identified for AAD. Other studies where we can find the prevalence of AAD and or mild illness are the clinical trials done to see the effect of probiotics. Vanderhoof, *et al*.(4) found 26 of 95 of the placebo group of children were having AAD albeit using a less severe definition. Higher prevalence was found either in studies with smaller samples(5-8) or in those where amoxy-clavunate was the only antibiotic used(9). Studies(6-8) which have not used the standard definition of AAD (and reported mild illness) found higher prevalence of AAD(6-8).

In two RCTs from Poland, 17 % of the children in the placebo group who received antibiotics had AAD(10,11). The sample size of the placebo group of the RCTs is small, which is not adequate for the interpretation of the prevalence of AAD. A survey by Kramer, *et al*.(12) evaluated the nature and incidence of gastrointestinal adverse effects in a cohort of 2,714 children receiving antibiotic treatment. They reported a 3.6% frequency of diarrhea but AAD was not defined. The relative risk of diarrhea was between 3 and 5 for penicillins V, amoxicillin, and nystatin; 6.5 for a first-generation cephalosporins;

and 10.2 for cloxacillin(12). More recently reported comparative analysis of prevalence, risk factors and epidemiology of AAD due to various organisms have found very few pediatric AAD cases(13). Almost all these studies have been done in the developed countries. There is no comparable data from the developing world.

The mild illness and AAD would present with only watery stools, occur sporadically and resolve on withdrawal of the antibiotic. They are usually *C. difficile* toxin negative and do not need any further treatment. Disruption of normal enteric flora caused by the antibiotic may lead to overgrowth of pathogens, functional disturbances of the intestinal carbohydrates and bile acids metabolism resulting in osmotic diarrhea. Other drugs might affect the intestinal mucosa and the motility. Erythromycin accelerates the rate of gastric emptying; amoxycillin-clavunate stimulates small bowel motility.

Clostridium difficile associated AAD

CDI (Clostridium difficile infection) is responsible for 10-20% cases of AAD, and almost all cases of colitis associated with antibiotic therapy. For the Indian pediatric population, 3.6% of the AAD were *Clostridium difficile* associated about a decade back(14). But recently in a study undertaken to find out the role of stool culture and toxin detection in the diagnosis of CDI in 250 hospitalized children aged 5-12 years, the overall positivity has been reported to be 18%(15). Severe diarrhea, liquid stool with mucus and blood, fecal leucocytes >5/high power field, altered flora and presence of Gram-positive bacilli with oval subterminal spores were sensitive predictors for diagnosis of CDI. The increase in incidence of CDI could be due to better diagnostic tests available now. A retrospective chart review at an Indian tertiary care hospital reported 60 pediatric cases in the five year period of which 4 (6.3%) were CDI positive(16). This may be due to stringent surveillance and an improved antibiotic policy followed at the tertiary care hospital. Of the 30 and 51 inpatient and outpatient Brazilian children with AAD, 2 (6.6%) and 6 (11.7%) were CDI positive, respectively(17). An observational, retrospective cohort study that included children who visited or were admitted to Children's Medical Center in USA during the period from 2001 to 2006 found 513 patients with CDI. The proportion with CDI in more than 2 years age group had increased from 46% to 64%. The incidence of CDI increased significantly in the outpatient setting, particularly in the emergency department (1.18 cases versus 2.47 cases per 1,000 visits; P=0.02). The incidence among inpatients decreased during the study period (1.024 cases versus 0.680 cases per 1,000 patient-days; P=0.004)(18).

These studies suggest that the incidence of community acquired CDI is also increasing in the pediatric population. Some cases of nosocomial CDI can be expected to occur in the weeks or even months following discharge. In addition, the increased circulation of *C. difficile* within hospitals will increase the rate of asymptomatic *C. difficile* carriers within the population. Contact with such cases will in the end lead to some cases of community acquired CDI. Furthermore, it has been suggested that an animal reservoir may play a role in the emergence of community-acquired CDI. The pediatricians need to keep this in mind while treating difficult diarrhea in the hospital and the community. Comparable Indian data is not available.

Pseudomembranous colitis usually presents with abdominal cramps, fever, leucocytosis, fecal leucocytes, hypoalbuminemia, colonic thickening on CT and widely spread punctate yellow plaques seen on endoscopic examination. This form of colitis follows administration of antibiotics including clindamycin, cephalosporins and penicillin, occurring as an epidemic or endemic in a hospital with usually no previous history of antibiotic intolerance. Most of these cases are *C. difficile* toxin positive. The major risk factors for CDI include advanced age, hospitalization and exposure to antibiotics.

C. difficile associated diarrhea have a symptomatic recurrence of 15-35%(19). This is a serious problem since they increase the length and overall cost of hospitalization. The longer hospitalization is also responsible for re-infection due to a different strain from the hospital environment. Handwashing, iso-lation and environmental decontamination are the factors which can prevent recurrences and

reinfec-tion. Avoiding usage of rectal thermometers, usage of vinyl gloves and hospital antibiotic policies are other factors which can help. Change from cefotaxime to ceftriaxone for initial treatment of severe sepsis or pneumonia led to the average number of patients with CDI to increase from 16 to 39 but shift to levofloxacin brought it down to 5 cases a year later in an Irish hospital(20). The delay in the decline of CDI after withdrawal of cephalosporins may reflect a slowly diminishing environmental reservoir. Decrease in intravenous cephalosporins usage from 210 to 28 defined daily doses with corresponding increase in Piperacillin- Tazobactum and moxifloxacin led to significant decrease in the relative risk (RR 3.24, 95%CI 1.07- 9.84, *P*=0.03) of developing of CDI(21).

The cytotoxin assay that uses tissue culture is the gold standard for diagnosis. It is very sensitive test detecting as little as 10 pg of toxin B. The ELISA available for detection of CDI has a false negative rate of 10-20% since about 100-1000 pg of the toxin A and B are needed for the test to be positive. Few of the strains just produce toxin B so the test which detect both toxin A and B should be preferred. ELISA is more easily available, results are available within hours and the cost is about $40 per test. Therefore, detection of toxin A and B by ELISA and detection of toxin B by tissue culture form the mainstay in the diagnosis of *C. difficile*. Stool culture is not easily available but has high sensitivity with low specificity. *C. difficile* was isolated on culture from stool specimen of 16/80 (20%) patients, while 23 (28.8%) stool specimens were positive for *C. difficile* toxin(22) *C. difficile* has been isolated in 7.2 % by culture whereas the overall positivity was 18% by ELISA(15). Diagnosis of CDI by culture is difficult and time consuming because of strict anerobic nature of organism. Moreover, mere isolation of *C. difficile* on culture is not sufficient to establish the pathogenic role of these isolates. Therefore, ELISA for detection of toxin A and B is recommended for rapid diagnosis of CDI. A two-step algorithm evaluated in 1,468 stool specimens first screened the specimens by an immunoassay for *C. difficile* glutamate dehydrogenase antigen (C.DIFF CHEK-60). Later screen-positive specimens underwent toxin testing by a rapid toxin A/B assay (TOX A/B QUIK CHEK); toxin-negative specimens were subjected to stool culture. This algorithm allowed final results for 92% of specimens with a turn around time of 4 hours(23).

TREATMENT

Discontinue or change implicated antibiotic and give supportive management with fluid and electrolytes, if required. Most of the AAD would respond to only discontinuation or change of the antibiotic. Avoid usage of any anti-peristaltic drug and control the infection in the patient with other antibiotics. In some of cases of CDI, withdrawal of the inciting agent will lead to resolution of clinical signs in three days(24). Oral metronidazole or oral vancomycin are drugs of choice for CDI for 10 days with > 90% cure rates for both of them(24). Using metronidazole allows the treatment cost to be low and also prevents the development of vancomycin-resisitant enterococci. Vancomycin should be reserved for those with severe illness, or intolerance or failure to metronidazole. Treatment regimens may also include probiotics, bile-acid sequestrants and intravenous immunoglobulin (IVIG). Most recurrences also respond to this line of management. A prolonged treatment with low dose vancomycin is preferred for the repeated recurrences.

PREVENTION

Probiotics like *Sacchyromyces boulardii* or *lactobacillus* strain GG have also been used for prevention of AAD. A Cochrane review reporting on the incidence of diarrhea in nine studies on children suggest that probiotics are effective for preventing AAD (RR 0.49; 95% CI 0.32 to 0.74)(25). However, intention to treat analysis showed non-significant overall results (RR 0.90; 95% CI 0.50 to 1.63). The number needed to treat to prevent one case of diarrhea is ten (NNT 10; 95% CI 7 to 18). Regarding safety, no trials reported a serious adverse event although only 5/10 trials included reporting on adverse events. Research done till date does not permit determination of the effect of age (*e.g.,* infant versus older children) or antibiotic duration (*e.g.,* 5 days versus 10 days).

In another meta-analysis(26), treatment with probiotics compared with placebo reduced the risk of

AAD from 28.5% to 11.9% (RR, 0.44, 95% CI 0.25 to 0.77). Preplanned subgroup analysis showed that reduction of the risk of AAD was associated with the use of *Lactobacillus* GG (RR 0.3, 95% CI 0.15 to 0.6), *S. boulardii* (RR 0.2, 95% CI 0.07-0.6), or *B. lactis* and *S. thermophilus* (RR 0.5, 95% CI 0.3 to 0.95). The reviewers concluded that probiotics reduce the risk of AAD in children. For every 7 children that would develop diarrhea while being treated with antibiotics, one fewer will develop AAD if also receiving probiotics(26). Another meta-analysis(27) with a per-protocol method reported signi-ficant benefit for the use of probiotics over placebo (RR 0.43, 95% CI 0.25–0.75) in reducing the incidence of AAD in children. In contrast, results from intention-to-treat analysis were overall non-significant (RR 1.01, 95% CI 0.64–1.61). Subgroup analysis on 4 studies (with *Lactobacillus* GG, *L. sporogens* or *Saccharomyces boulardii*) showed strong evidence for the preventive effects of probiotics for AAD (RR 0.36, 95% CI 0.25–0.53)(27). It is important to note here that we need to now concentrate on specific probiotics individually when assessing their role in AAD or in other disorders, because clubbing together the effective strains with ineffective ones might actually be diluting the effect of the former. These meta-analyses raise the issue of how cost-effective is the addition of probiotics to antibiotics in the developing world. We need more studies to have a definite answer.

To conclude, the prevalence of AAD in children is lower than that in adults and we need data from India. Majority suffer from mild illness. Five to 18 % of AAD in children is CDI. There is an increase in community acquired CDI in children in the Western literature and no corresponding Indian data is available. Certain antibiotics like amoxycillin–clavunate combination have higher risk. Most of the children with AAD respond to discontinuation of antibiotic. Probiotics may have a role to play in the prevention of AAD. Since the prevalence of AAD is low and the addition of probiotics is going to prevent only 1 in 7-10 cases of AAD, we need cost effectiveness studies to decide the issue of routine supplementation of probiotics to antibiotics in diarrhea.

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