

## Original Research Article

# Antibiotic associated diarrhoea in paediatric outpatient practice

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### ABSTRACT

**Background:** To document the profile of antibiotic associated diarrhoea (AAD) in children aged 6 months to 15 years receiving oral antibiotics.

**Methods:** Prospective study of children attending the out-patient department, who were started on oral antibiotic for indications other than gastrointestinal infections. Data collection was done with a questionnaire and follow up was done by telephone.

**Results:** Of the 1022 children, seven developed AAD (0.68%). Twenty-nine other children had loose stools but did not fulfil the criteria of AAD. Of 436 children who received Amoxicillin clavulanate, 4 developed AAD. One each from 361 on amoxicillin, 9 on ciprofloxacin and 8 on erythromycin developed AAD. Five of the seven children who had diarrhoea were less than two years (71.4%).

**Conclusions:** Incidence of AAD is very low in an out-patient setting. In all cases, diarrhoea subsided on stopping the antibiotic. Children below two years of age and those on Amoxicillin clavulanate have a significantly higher risk.

**Keywords:** Antibiotic associated diarrhoea, Amoxicillin clavulanate, Children

## INTRODUCTION

Antibiotics are one of the most common drugs prescribed in paediatric outpatient practice.<sup>1</sup> Antibiotic associated diarrhoea (AAD) is of concern to physicians and parents and often results in under-dosing of the antibiotic or addition of probiotics.<sup>1</sup> In most cases it is a self-limiting illness, but rarely does it lead to devastating diarrhoea or pseudomembranous colitis.<sup>1</sup> AAD is believed to occur due to alteration of the microbial flora in the gastrointestinal tract.<sup>2</sup> Over the years antibiotic manufacturing practices have improved with purer drugs, better bioavailability and safer additives.<sup>2</sup>

### Objective of the study

This study was done in the paediatric outpatient department of a tertiary care teaching hospital to find out the incidence, risk factors and outcome of AAD.

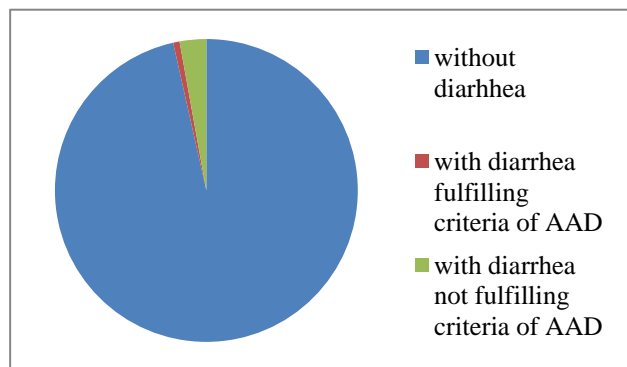
## METHODS

This is a cross sectional study conducted at the pediatric outpatient department, Government General Hospital, Siddhartha medical college, Vijayawada. The study was done over 6 months (from 1<sup>st</sup> June 2019 to 30<sup>th</sup> Nov 2019) and all children aged 6 months to 15 years who were started on an oral antibiotic for indications other than gastrointestinal infections were included in the study. Children who were immunocompromised, those with proven viral infections known to cause GI manifestations like dengue, IMN etc., those with history of any abdominal surgery, those with chronic intestinal disease, those who received multiple antibiotics and those who had received any antibiotic during the previous 4 weeks were excluded from the study. Antibiotic Associated Diarrhea (AAD) was defined as unexplained diarrhea occurring between two hours to one month after starting antibiotic where diarrhea is defined as more than 2 unformed stools for more than a day.<sup>1</sup>

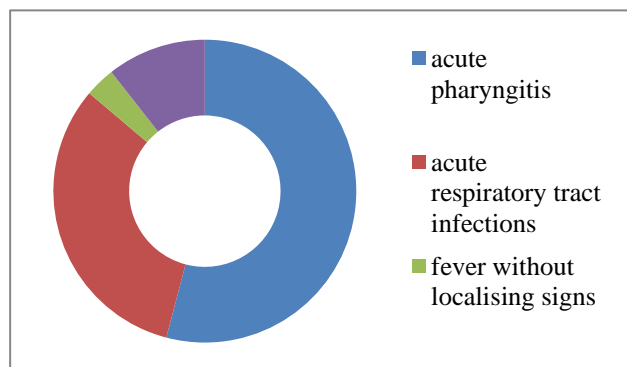
A questionnaire containing all relevant details was filled by the attending pediatrician. The details were explained to the child's attendant. Phone number of the author was given to all the parents. They were asked to report back any change in consistency of the stools in the next 4 weeks. Telephone calls were made between the 5<sup>th</sup> and 7<sup>th</sup> day and again on the 28<sup>th</sup> day after starting antibiotics. All those who developed diarrhea which persisted more than a day were asked to report back to the hospital and a stool culture and sensitivity was done. The antibiotic was stopped in all those in whom the diarrhea persisted for more than 48 hours. If the loose stools persisted beyond the 5<sup>th</sup> day and the stool culture was sterile, stool was tested for Clostridium difficile. The study approval was done by institutional human ethics committee, Siddhartha medical college, Vijayawada. Statistical analysis was done by using SPSS 16 software.

**RESULTS**

A total of 1022 children completed the study and were eligible for statistical analysis. There were 554 boys and 468 girls. Seven children developed diarrhoea that fulfilled the criteria for Antibiotic associated diarrhoea (I-0.68%). Twenty-nine other children had episodes of loose stools during the course of antibiotics but did not fulfil the criteria of AAD (Figure 1).



**Figure 1: Incidence of Antibiotic associated diarrhoea.**

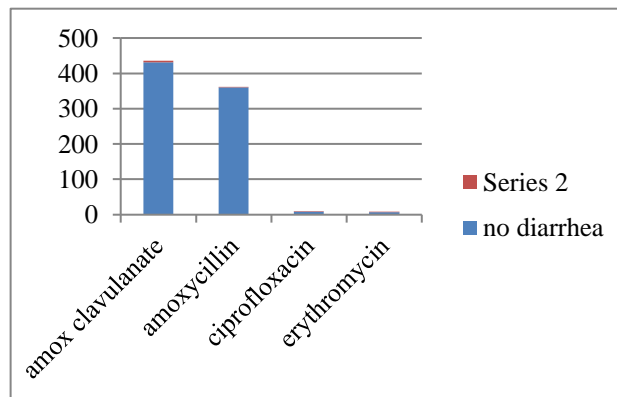


**Figure 2: Indications for prescribing antibiotics.**

The indications for antibiotics were acute pharyngitis (54.1 %), Acute respiratory tract infection (32.09 %),

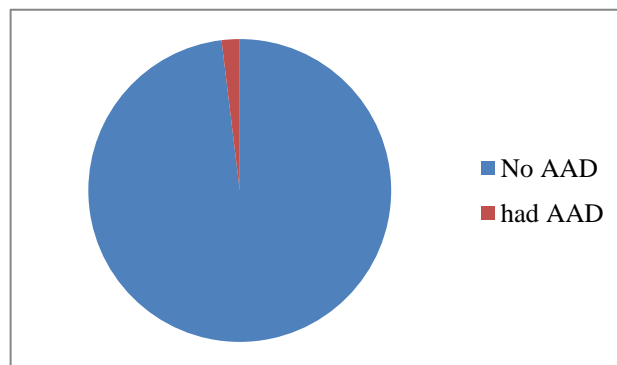
fever without localizing signs (3.22 %) and others (10.59%) (Figure 2).

Of the 436 children who received Amoxicillin-clavulanic acid combination 4 developed AAD. One child each from the 361 who received amoxicillin, 9 who received ciprofloxacin and 8 who received erythromycin developed AAD (Figure 3).



**Figure 3: Incidence of AAD based on type of antibiotic used.**

Five out of seven children (71.4%) who had diarrhoea were less than two years old. Among the two hundred and fifty-five children below two years, AAD was reported in five children (p<0 .0002) (Figure 4).



**Figure 4: Antibiotic associated diarrhoea in less than 2 years.**

**DISCUSSION**

AAD is not uncommon, but generally over-emphasised in practice. It is a diagnosis of exclusion and most cases have little clinical consequence. Mild cases are due to reduced carbohydrate fermentation and impaired metabolism of bile acids or alteration in gut motility. In severe cases, changes in the gut ecosystem allow pathogens to proliferate.<sup>2</sup>

The incidence of antibiotic associated diarrhoea in our study was only 0.68%. Damrongmanee in their study on 225 children in Thailand, reported an incidence of

6.2%.<sup>3</sup> Turke et al in their study from France on 650 children aged 1 month to 15 years, reported that 11% had an episode of AAD. No child required hospitalization.<sup>4</sup> While the incidence reported from Japan was 59% it was only 16% in Finland.<sup>5,6</sup> Mitchell et al in a study from the US showed a prevalence of AAD as 28%.<sup>3,7</sup> Kramer et al in a study in 1985 on 2,714 children receiving antibiotic reported that 3.6% of them developed diarrhoea but AAD was not clearly defined.<sup>8</sup>

Higher prevalence was found in studies with smaller samples or those which did not follow the standard definition or in those where amoxy-clavunate was the only antibiotic used.<sup>9</sup> In general, the incidence of AAD is higher in developed countries, with older studies reporting higher numbers than recent ones.<sup>10</sup> The possible reasons for this variation in incidence may be genetic factors, differences in the micro biota or the technological advances in the drug manufacturing techniques.

In our study, the incidence of AAD was higher in children less than 2 years ( $P < 0.0001$ ). Turke et al have also observed that the incidence was significantly higher in children less than 2 years (18%) compared to those more than 2 years (3%).<sup>4</sup> In the study by Damrongmanee, no correlation with age was observed.<sup>5</sup> The overall high incidence of AAD in the study from US was attributed to the younger study population.

We observed a higher incidence of AAD with Amoxicillin Clavulanate, though it was not statistically significant in view of small numbers. Turke et al have also reported that AC had the highest risk. There also observed a statistically significant difference between the rate of onset of AAD associated with amoxicillin/clavulanate compared with all other antibiotics combined.

Damrongmanee et al have also reported the highest incidence with amoxicillin/clavulanate (16.7%) compared to amoxicillin (6.9%) and erythromycin (11.1%), although it was not statistically significant. In the study by Kramer et al, the relative risk of diarrhoea was low for penicillins and amoxicillin and highest for cloxacillin, with amoxclav being not available at the time of study.

Pseudomembranous colitis due to *Clostridium difficile* is the most dreaded form of AAD. In a study in 1989 on hospitalized children there were 111 cases of AAD, in which only 4 stool samples were positive for CF, while 3 of the 111 controls also showed CF.<sup>11</sup> They concluded that CF was not an important pathogen for AAD in children in India. Among the 544 cases of antibiotic associated diarrhoea during a 5 years period in a tertiary hospital in India in 1994, there were only 37 positive cases, two thirds of whom were from Oncology.<sup>12</sup> The majority of cases were above 60 years of age and there were only 3 children. They also reported a gradual decline in the incidence of CD over the years. There were no cases of *Clostridium difficile* in our study.

Our study shows that the incidence of antibiotic associated diarrhoea in children is very low in out-patient setting. In all cases it was a self-limiting illness and children below two years of age and those on Amoxicillin Clavulanic acid were at higher risk. The current practice of combining probiotics with oral antibiotics as a routine does not appear rational or evidence based.

### Limitations

The sample size is less. The sample taken doesn't represent multiple ethnicities and global population. It is not randomized and doesn't have a control group.

### CONCLUSION

Incidence of antibiotic associated diarrhea in children is very low in out-patient department setting (I-0.68%). In all cases diarrhea is self-limiting without any complications. Children below two years of age had a statistically significant higher incidence AAD ( $p$  value-0.0002). Antibiotic associated diarrhea is uncommon with oral antibiotics in outpatient practice. Children below two years of age and those on Amoxicillin clavulanate have a significantly higher risk than others.

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### REFERENCES

1. Dominique T, Bernet JP, Jacques M, Helene K, Patrick G, Olivier W, et al. Incidence and risk factors of oral antibiotic-associated diarrhea in an outpatient pediatric population. *J Pediatr Gastroenterol Nutr.* 2003;37:22-26.
2. Wistrom J, Norby SR, Myhre EB, Eriksson S, Granstorm G, Lagergren L, et al. Frequency of antibiotic associated diarrhea in 2462 antibiotic treated hospitalized patients: a prospective study. *J Antimicrob Chemother.* 2001;47:43-50.
3. Clausen MR, Bonnen H, Tvede M, Motensen PB. Colonic fermentation to short-chain fatty acids is decreased in antibiotic-associated diarrhea. *Gastroenterology.* 1991;101:1497-504.
4. Damrongmanee A, Ukarapol N. Incidence of antibiotic-associated diarrhea in a pediatric ambulatory care setting. *J Med Assoc Thai.* 2007;90(3):513-7.
5. Seki H, Shiohara M, Matsumura T, Miyagawa N, Tanaka M, Komiyama A, et al. Prevention of antibiotic-associated diarrhea in children by *Clostridium butyricum* MIYAIRI. *Pediatr Int.* 2003;45:86-90.
6. Arvola T, Laiho K, Torkkeli S, Mykkanen H, Salminen S, Maunula L, et al. Prophylactic *Lactobacillus GG* reduces antibiotic-associated

- diarrhea in children with respiratory infections: a randomized study. *Pediatrics*. 1999;104:64.
7. Mitchell DK, Van R, Mason EH, Norris DM, Pickering LK. Prospective study of toxigenic *Clostridium difficile* in children given amoxicillin/clavulanate for otitis media. *Pediatr Infect Dis J*. 1996;15:514-9.
  8. Kramer MS, Hutchinson TA, Naimark L, Contardi R, Flegel KM, Leduc DG. Antibiotic-associated gastrointestinal symptoms in general pediatric outpatients. *Pediatrics*. 1985;76:365-78.
  9. Alam S, Mushtaq M. Antibiotic Associated Diarrhea in children. *Indian Pediatrics*. 2009;46: 491-6.
  10. Asha NJ, Tomkins D, Wilcox MH. Epidemiology of antibiotic-associated diarrhoea due to *clostridium difficile*, *Clostridium perfringens*, and *Staphylococcus aureus*. *J Clin Microbiol*. 2006;44:2785-91.
  11. Dutta P, Niyogi SK, Mitra U, Rasaily R, Bhattacharya MK, Chakraborty S, et al. *Clostridium difficile* and antibiotic associated pediatric diarrhea. *Indian Pediatr*. 1994;31:121-6.
  12. Chaudhry R, Joshy L, Kumar L, Dhawan B. Changing pattern of *Clostridium difficile* associated diarrhoea in a tertiary care hospital: A 5 years retrospective study. *Indian J Med Res*. 2008;127:377-82.

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