

# Study on Incidence of Antibiotic Associated Diarrhoea in General Paediatric Ward

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## Abstract

**Objective:** To estimate the incidence rate and risk factors of developing Antibiotic Associated Diarrhoea (AAD) in paediatric patients in hospital setting. **Design:** Retrospective case records review. **Setting:** General paediatric ward of a regional acute hospital. **Methods:** Within a one month study period, the case records of all newly admitted paediatric patients with antibiotics prescribed after admission are reviewed. Diarrhoea is defined as loose stools three times or more per day, or watery stool. Patients who had no feature of prior infective gastroenteritis or nosocomial infection and developed diarrhoea after administration of antibiotic will be considered to have AAD. The demographic data of the patients, the duration of diarrhoea and the stool consistency will be recorded. The different classes of antibiotics prescribed will also be reported. **Results:** 18 out of 171 patients (10.5%) developed AAD and all patients with AAD were less than three years of age. The majority of AAD was mild and self-limiting. The relationships between incidence of AAD and different types of antibiotic prescribed cannot be clearly determined due to small patient number. **Conclusion:** The impact of the problem cannot be overlooked and further large scale prospective study is warranted to determine the true incidence and risk factors of AAD.

## Key words

Antibiotic associated diarrhoea; Incidence; Paediatric

## Introduction

Antibiotic is frequently prescribed for various infections but it can also cause unwanted effects. One of the common side effects is diarrhoea. The incidence of antibiotic associated diarrhoea (AAD) ranges from 5% to 25% according to the overseas literature.<sup>1</sup> The incidences vary with different antibiotics used. The severity of AAD is also variable. At one end of the spectrum, it only causes mild diarrhoea which is usually self limiting and is treated by stopping the causative antibiotic and occasionally requires fluid and electrolytes replacement. At the other end of the

spectrum, it can rarely cause potential life threatening colitis or pseudomembranous colitis which requires specific treatment. However, the data on the incidence and severity of AAD in paediatric age group is limited. In Hong Kong, prescription of antibiotics is a common practice especially in the private sector. Diarrhoea after taking antibiotics is also a well known phenomenon. Since the incidence of AAD is unknown and is not properly studied by scientific method in this locality, this study is designed to determine the incidence of AAD in paediatric population in this area.

## Methods

This is a retrospective study in which the case records of newly admitted paediatric patients (one month to 15 years old) with antibiotics prescribed in Paediatric Department Tuen Mun Hospital during a one month study period are reviewed. February 2000 was chosen by random selection. Diarrhoea is defined as loose stool three times or more per

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day, or watery stool. All acute admissions to the general paediatric ward during the study period will be included in the study.

Exclusion criteria:

1. History of diarrhoea or taking antibiotics before admission
2. History of taking anti-diarrhoeals before admission
3. Presence of Rotavirus or positive bacterial stool culture during hospitalization, i.e. Salmonella, Shigella, Campylobacter, Aeromonas and Pleidomonas
4. Oncology/ ICU/severely ill/ventilated cases
5. Hospitalization more than 15 days

Patients in categories 1 to 3 are excluded because they may suffer from infective gastroenteritis before admission and the diarrhoea therefore cannot totally be attributable to the antibiotic prescribed. For the categories 4 and 5 patients, they are excluded because of higher chance of nosocomial acquired infection.

Therefore, patients who had no feature of prior infective gastroenteritis or nosocomial infection and developed diarrhoea after administration of antibiotic will be considered to have AAD.

The demographic data of the patients, the duration of diarrhoea and the stool consistency will be recorded. The different classes of antibiotics prescribed (penicillin/cephalosporin/macrolide/aminoglycoside/others) will be reported. Statistical calculation will be performed by Chi-square test or other appropriate non-parametric methods.

## Result

### **Background Data**

One hundred eighty-five patients were prescribed with antibiotics during the study period in which 14 patients were excluded due to various reasons – three patients were excluded for presence of rotavirus in stool, two patients for positive Salmonella or Campylobacter culture, two patients for prolonged hospitalization and seven patients for diarrhoea before admission. The remaining 171 patients were involved in the study including 71 girls and 100 boys. Their age ranged from one month to 12 years with 90% less than six years old. They stayed in hospital from one to 12 days. 90% of them stayed less than five days.

Antibiotics were started within 48 hours in 90% of the case. Respiratory tract infections were the most common diagnosis. 35.7% of patients suffered from upper respiratory infection (excluded ear infection), and 36.3% had lower

respiratory infection. Ear infection accounted for 8.8% of cases and 19.3% had other different diagnoses. When the first antibiotic was taken into account, Penicillin group antibiotics were prescribed in 79% of cases. Amoxicillin/Clavulanate alone accounted for 45.6% of all antibiotic prescribed. Cephalosporins and Macrolides were prescribed in 14.1% and 6.4% respectively.

### **Antibiotic Associated Diarrhoea (AAD):**

#### ***Incidence of AAD***

In these 171 patients involved, 18 of them fulfilled our definition of AAD giving the incidence rate of 10.5% (Figure 1). Thirteen boys and five girls developed AAD. Sex is not a statistically significant risk factor for developing AAD ( $p=0.312$  by Fisher's Exact Test). All patients with AAD are below three years of age (11 infants, four patients aged 1 and three patients aged 2) which is significantly younger than the study population ( $p<0.001$  by Mann-Whitney Test).

#### ***Onset of AAD***

Their onset ranged from day 1 to day 5 with 94.4% occurring within the first three days after the prescription of antibiotics.

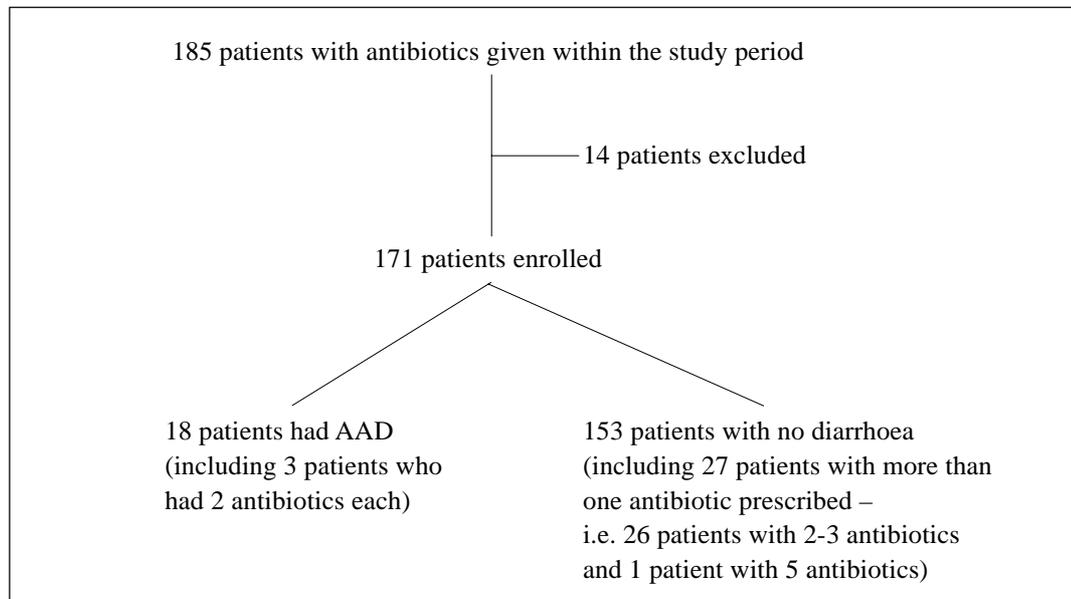
#### ***Severity of AAD***

Table 1 shows the stool consistency of these patients during the hospital stay. Two-third of patients presented with loose stools, 5/18 (27.8%) presented with watery stool, only one patient presented with blood and mucus in stool at the first day of diarrhoea. The Majority of these patients were discharged, allowed to have homeleave or the diarrhoea resolved so that data concerning stool consistency was not complete in subsequent days. All patients with AAD were discharged within five days either due to mild symptom or complete resolution of diarrhoea.

13/18 (72.2%) presented with stool frequency less than six times per day in the first day of diarrhoea. The most serious one passed stool 13 times per day. Since most of the diarrhoea was mild, 14/18 (77.8%) received no specific treatment. Only one patient received oral rehydration fluid and three patients received intravenous fluid for poor feeding. No significant dehydration was detected in all these cases.

#### ***Duration of AAD***

Table 2 shows the duration of AAD. Eight patients had diarrhoea resolved at discharge, seven patients had



**Figure 1** Flow chart showing patient recruitment and outcome of study.

**Table 1** Stool consistency of AAD

Stool consistency	Number of patients				
	Day 1	Day 2	Day 3	Day 4	Day 5
Loose stool	12	2	2	0	1
Watery stool	5	1	2	0	0
Blood in stool	1	0	0	1	0
Total number	18	3*	4	1	1

\*one patient was in homeleave so that information on stool consistency was not available.

Please also note that it did NOT mean 14 patients cleared up the diarrhoea in day 2/3 since some of them may be discharged or allow homeleave if the symptom is mild.

**Table 2** Duration of AAD

Duration of diarrhoea (days)	Diarrhoea persisted after discharge	Diarrhoea cleared up on discharge	Diarrhoea cleared up before discharge	Total
1			1	1
2		6	4	10
3		1	2	3
4		1		1
>6	1*			1
>10	1*			1
>16	1*			1
	3	8	7	18

\*this three patients was discharged before complete resolution of diarrhoea but they are still having diarrhoea according to the data obtained during follow up in day 6, day 10 and day 16 after the onset of diarrhoea.

diarrhoea resolved before discharge and other three patients still had diarrhoea after discharge according to the information obtained during clinical follow up (at 6, 10 and 16 days after onset of diarrhoea respectively). Therefore, 14/18 patients (77.8%) had AAD that lasted less than four days but the longest one could have lasted for more than 16 days.

#### Association Between AAD and Disease Diagnoses

Table 3 shows the relative incidences of AAD in different disease diagnoses, the incidence of AAD were

9.8% in upper respiratory tract infection including pharyngitis and tonsillitis, acute bronchitis and bacterial tracheitis, 9.7% in lower respiratory tract infection including different bacterial pneumonia, 13.3% in ear infection including otitis media and otitis externa. No specific pattern or relationship was detected.

#### Relationship Between AAD and Type of Antibiotic Used

Table 4 shows the incidence of AAD in different types of antibiotics prescribed. Among the 171 patients, the mean antibiotic prescribed was 1.26 times/patient. Thirty of them

**Table 3** Relationship between grouped disease diagnoses and AAD

Grouped diagnoses	Diarrhoea absent	Diarrhoea present
Upper respiratory tract	55 (90.2%)	6 (9.8%)
Lower respiratory tract	56 (90.3%)	6 (9.7%)
Ear infections	13 (86.7%)	2 (13.3%)
Others	29 (87.9%)	4 (12.1%)
Total	153 (89.5%)	18 (10.5%)

**Table 4** Relationship between antibiotics prescribed and AAD

#### Table 4a Penicillins group

Antibiotic	Total prescription	Diarrhoea absent	Diarrhoea present	Percentage (95% CI)
Penicillin V	28	23	5	17.9 % (6-36%)
Ampicillin/Amoxicillin	27	23	4	14.8 % (4-33%)
Cloxacillin	4	3	1	25.0%(1-81%)
Amoxicillin/Clavulanate	86	82	4	4.7% (1-12%)
Amoxicillin/Sulbactam	2	1	1	50.0% (1-99%)
Cumulative	147	132	15	<b>10.2%</b> (6-17%)

#### Table 4b Cephalosporins group

Antibiotic	Total prescription	Diarrhoea absent	Diarrhoea present	Percentage (95% CI)
Cefuroxime axetil	28	24	4	14.3% (4-32%)
Cefuroxime sodium	14	13	1	7.1% (0.2-34%)
Cefaclor	3	3	0	0% (0-71%)
Cefotaxime	2	2	0	0% (0-84%)
Ceftibuten	2	2	0	0% (0-84%)
Ceftazidime	1	1	0	0% (0-98%)
Cumulative	50	45	5	<b>10.0%</b> (3-22%)

#### Table 4c Macrolides group

Antibiotic	Total prescription	Diarrhoea absent	Diarrhoea present	Percentage (95% CI)
Erythromycin	6	6	0	0% (0-47%)
Clarithromycin	8	7	1	12.5% (0.3-53%)
Cumulative	14	13	1	<b>7.1%</b> (0.2-34%)

#### Table 4d Others

Antibiotic	Total prescription	Diarrhoea absent	Diarrhoea present	Percentage (95% CI)
Nitrofurantoin	1	1	0	0% (0-98%)
Metronidazole	1	1	0	0% (0-98%)
Cumulative	2	2	0	0% (0-84%)

had received more than one antibiotic(s) concomitantly or sequentially (ranged from 2 to 5 antibiotics). In these 30 patients, three of them fulfilled our criteria of AAD and all of them received two different antibiotics. All the other 141 patients received a single antibiotic only (Figure 1). Since it was difficult to judge which antibiotic was responsible for the diarrhoea in patients with AAD on multiple antibiotics, the symptom was assumed to be due to either antibiotic in our calculation (Table 4). Total number of antibiotics prescribed was 203 times in 171 patients, the incidence of AAD was 10.2% in Penicillin group, 10.0% in Cephalosporin group and 7.1% in Macrolide group. However, the number of patients in other individual antibiotics groups was too small for meaningful statistical calculation.

## Discussion

The incidence of antibiotic associated diarrhoea is 5% to 25% according to overseas literature.<sup>1</sup> Different diagnostic definition of diarrhoea is one of the factors which accounted for the different figures quoted.<sup>3</sup> The definition of diarrhoea varies from three loose stools for one day to two/three loose/watery stools for two to three consecutive days. It has been suggested that AAD is clinically significant when there are three mushy or watery stools per day.<sup>1</sup> The incidence rate will be lower if a stricter definition of diarrhoea is used. The incidence rate of AAD in our case series is 10.5% which is in line with the figure quoted by the literature. This can be an underestimation since the majority of our patients were hospitalized for less than five days while the onset of AAD can occur up to two months after the antibiotic exposure. Therefore those patients with diarrhoea after discharge would not be included in the study. On the other hand, some children with acute infection other than infective gastroenteritis can also develop diarrhoea. This can result in over-estimation of the true incidence. Although the onset of this kind of diarrhoea can occur a few days after the initial presentation, majority of them present in the first few days. Since not all the patients are admitted at the time of onset of symptom so majority of them should have already developed diarrhoea at the time of admission and therefore will be excluded from the study. The overall impact is expected to be minimal.

Apparently, 18 patients developing AAD in one month may not be a significant figure. However, if one considers the vast number of patient receiving antibiotics from the hospital and private sector and if 10% of them develop

diarrhoea, the impact of this issue cannot be overlooked. The clinical impact of AAD is reflected by potential severity of the illness like severe colitis and possible consequence of disruption in the treatment of the primary infection since the causative antibiotic may need to be stopped. It may also result in higher medical costs, increased hospital stays and unnecessary parental inconvenience and anxiety.

Most cases of AAD can be classified in two categories – cases in which *Clostridium difficile* is implicated (*C. difficile* associated diarrhoea) and cases in which there are no putative agents or the pathophysiological mechanism is not clearly established (enigmatic AAD).<sup>5</sup> In the enigmatic AAD, the patient usually presents with mild watery diarrhoea with no evidence of colitis and minimal constitutional disturbance. The symptoms seem to be related to the dose of antibiotic given and usually respond to antibiotic withdrawal. While *Clostridium difficile* causes a spectrum of disease ranging from asymptomatic carriage to its most serious form, pseudomembranous colitis. The diarrhoea ranges in severity from a brief, self limited episode of loose stools to those of frequent watery stools for more than 20 times per day. It was estimated that approximately 10-20% of AAD without colitis is ascribed to *Clostridium difficile*.<sup>3</sup> Findings like fever, lower quadrant abdominal pain, leukocytes in stool and peripheral leukocytosis are distinguishing features from enigmatic cases. Serious complications such as toxic megacolon, hyperpyrexia, leukaemoid reaction, hypoalbuminaemia with anasarca and chronic diarrhoea can also occur despite the discontinuation of the inducing agent.<sup>5,6</sup> The categorization of *C. difficile* associated AAD and enigmatic AAD bears important implications on the management and prognosis of AAD since *C. difficile* associated AAD can be a potentially life-threatening illness.

Fortunately, most of our cases suffered from mild diarrhoea and presented with loose stool only. Blood in stool is a rare presentation. Despite the fact that the stool frequency could be as high as 13 times per day, all of them had no significant dehydration or electrolyte disturbance. Constitutional disturbance was also minimal. The exact incidence of *C. difficile* associated diarrhoea is unknown in our case since thorough work up including stool culture and toxin detection for *Clostridium* was usually not necessary in these cases, but most of them are believed to be enigmatic cases. The exact pathophysiology in this group of patient is not well defined. The proposed mechanisms include disturbance of normal gut flora, or disturbance of intestinal carbohydrate or bile acid metabolism. It may also be due to allergic and toxic effects of antibiotics on intestinal

mucosa or due to pharmacological effect on motility.<sup>2,4</sup>

One of the pitfalls of this study is related to its retrospective nature so that some of the patients were not completely followed up and the data on stool consistency and frequency after the patient was discharged was not available. However, apparently the severity of diarrhoea improved in subsequent days since diarrhoea cleared up in the majority of patients within three days and no patient was readmitted due to worsening diarrhoea.

Any antibiotics can lead to AAD and the risk is the highest for those resulting in high intestinal drug concentration. The incidence of AAD also varies with different antibiotics, which depends on their antimicrobial spectrum and pharmacokinetic properties like the rate of gastrointestinal absorption and enterohepatic circulation. The incidence quoted was 5-10% for ampicillin, 2-5% for cephalosporins and 2-5% for macrolides.<sup>3,5</sup> They are comparable to our study. 10-25% of patient will develop diarrhoea when Amoxycillin/ clavulanate is given according to literature.<sup>3</sup> It is probably largely due to clavulanate which increases bowel motility. However, the incidence rate of AAD is only 4.7% for Amoxycillin/clavulanate in our series. Since the number of patients involved is too small for definitive conclusion, further large scale study is required to determine whether this observed difference in our locality is genuine.

## Conclusion

Around 10% of patient receiving antibiotics developed antibiotic associated diarrhoea in our study. This is likely to be an under-estimation. All patients who developed AAD were aged less than three years of age. The majority of AAD were mild and resolved spontaneously without specific treatment. The relationship between the incidence and antibiotic prescribed was inconclusive due to small number of patients studied. Further large scale prospective study is required to determine the true incidence and risk factors of the disease.

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