

# Antibiotic Associated Diarrhea in Hospitalized Adult Patients

Marcellus Simadibrata\*, Lie Khie Chen\*\*, Diana Aulia\*\*\*, Ina Sutanto Timan\*\*\*

\*Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia/Dr. Cipto Mangunkusumo General National Hospital, Jakarta

\*\*Division of Tropical Medicine & Infectious Disease, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia/Dr. Cipto Mangunkusumo General National Hospital, Jakarta

\*\*\*Department of Clinical Pathology, Faculty of Medicine Universitas Indonesia/Dr. Cipto Mangunkusumo General National Hospital, Jakarta

## Corresponding author:

Marcellus Simadibrata. Division of Gastroenterology, Department of Internal Medicine, Dr. Cipto Mangunkusumo General National Hospital. Jl. Diponegoro No.71 Jakarta Indonesia. Phone: +62-21-3153957; Facsimile: +62-21-3142454. E-mail: prof.marcellus.s@gmail.com

## ABSTRACT

**Background:** Antibiotic associated diarrhea (AAD) occurs from the first initiation until 2 months of the end of antibiotic treatment. The aims of this study were to know the incidence of AAD, *Clostridium difficile* infection and other gastrointestinal symptoms in hospitalized adult patients.

**Method:** The study is a cross sectional study. We studied the antibiotic associated diarrhea (AAD), *Clostridium difficile* infection and other gastrointestinal symptoms in patients who were admitted in Cipto Mangunkusumo Hospital. Inclusion were male or female, age 18-75 years old, patients started receiving antibiotics maximal 2 x 24 hours prior to hospitalization, gave written informed consent.

**Results:** The incidence of AAD was 11.5%. The incidence of *Clostridium difficile* infection was 15.4%. The upper gastrointestinal symptom was present on 20 (38.5%) patients. Lower abdominal symptom was present on 10 (19.2%) patients.

**Conclusion:** The Incidence of AAD and *Clostridium difficile* infection were 11.5% and 15.4% respectively. The clinical manifestations of AAD were diarrhea, other upper and lower abdominal symptoms.

**Keywords:** incidence, antibiotic associated diarrhea (AAD), *Clostridium difficile*

## ABSTRAK

**Latar belakang:** Diare akibat antibiotik (DAA) terjadi sejak awal sampai 2 bulan setelah pengobatan antibiotik. Tujuan penelitian ini adalah untuk mengetahui insiden DAA, infeksi *Clostridium difficile*, dan gejala gastrointestinal lainnya pada pasien dewasa yang dirawat di rumah sakit.

**Metode:** Penelitian ini merupakan penelitian potong lintang. Kami meneliti diare akibat antibiotik (DAA), infeksi *Clostridium difficile*, dan gejala gastrointestinal lainnya pada pasien yang dirawat di Rumah Sakit Cipto Mangunkusumo. Inklusi adalah laki-laki atau perempuan usia 18-75 tahun. Pasien mulai menerima antibiotik maksimal 2 x 24 jam sebelum dirawat di rumah sakit, memberikan informed consent tertulis.

**Hasil:** Insiden DAA adalah 11.5%. Kejadian infeksi *Clostridium difficile* adalah 15.4%. Gejala saluran gastrointestinal atas terjadi pada 20 (38.5%) pasien. Gejala gastrointestinal bawah terjadi pada 10 (19.2%) pasien.

**Simpulan:** Insiden DAA dan infeksi *Clostridium difficile* masing-masing 11.5% dan 15.4%. Manifestasi klinis DAA yaitu diare, gejala gastrointestinal atas, bawah, dan lainnya.

**Kata kunci:** insiden, diare akibat antibiotik (DAA), *Clostridium difficile*

## INTRODUCTION

Antibiotic associated diarrhea (AAD) occurs from the first initiation until 2 months of the end of antibiotic treatment.<sup>1,2</sup> The prevalence of AAD is estimated 10 to 15% of all hospitalized patients treated with antibiotics.<sup>3</sup> Almost any antibiotic can cause an imbalance of bacteria in the body, and cause gastrointestinal symptoms with or without diarrhea. *Clostridium difficile* (CD) toxins can be found in the stool of 15-25% patients with AAD and more than 95% of patients manifested as pseudomembranous colitis.<sup>4,5</sup>

Risk factors of *Clostridium difficile* infection are age above 65 years old, hospitalization, antibiotics treatment, severe underlying illness, nasogastric intubation, antiulcer medications, receive multiple antimicrobial agents and undergo a longer course of therapy.<sup>6</sup> The clinical manifestation of antibiotic associated diarrhea or CD associated diarrhea may vary from mild diarrhea to fulminant colitis.<sup>6</sup>

The treatment of AAD or CD associated diarrhea include non-pharmacologic, pharmacologic including antibiotics (metronidazole, vancomycin, fidaxomicin), probiotics and surgery.<sup>3,7-12</sup> The aims of this study is to know the incidence of AAD, *Clostridium difficile* infection and other gastrointestinal symptoms in hospitalized adult patients.

## METHOD

This study was a cross sectional study. We studied the antibiotic associated diarrhea (AAD) and other gastrointestinal symptoms in patients with antibiotic treatment who were admitted in Cipto Mangunkusumo Hospital 2010-2013.

Diagnosis AAD was made if  $\geq 3$  abnormal loose bowel movement and 3 unformed stool in 24 hours for a minimum 2 days, and occur from initiation to 2 months end of antimicrobial treatment (mostly 2 weeks). Other gastrointestinal symptoms were recorded such as upper gastrointestinal symptoms (nausea, vomiting, bloating, epigastric pain), and lower gastrointestinal symptoms (abdominal pain, constipation, and flatulence). *Clostridium difficile* infection was examined with the stool's test of *Clostridium difficile*'s toxin (toxin A & B) using Enzyme immunoassay (EIA) tests.<sup>1,3,5</sup>

The SPSS 12 software was used for the statistical analysis. The inclusion criteria were male or female, age 18-75 years old, patients started receiving antibiotics maximal 2 x 24 hours prior to hospitalization, gave written informed consent. The exclusion criteria were diarrhea symptoms during admission and maximal 7 days prior to hospitalization, receiving antibiotic 2 weeks prior to hospitalization, pregnant women, non-reassuring vital sign (severe condition, worse condition, shock), non-functioning gastrointestinal tract (severe vomiting, acute pancreatitis), severe immunocompromised patients: chemotherapy, HIV (+) and AIDS.

## RESULTS

The characteristics of patients in this study could be seen in Table 1. The most frequent characteristic of the patients was male (59.6%), age  $48.9 \pm 16.5$  years old, respiratory tract infection (35.1%) and using Cephalosporin antibiotic (90.4%).

**Table 1. Patient's characteristics**

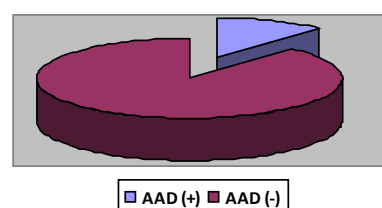
Variable	n (%)
Sex	
Male	31 (59.6)
Female	21 (40.4)
Age (mean $\pm$ SD) year	48.9 $\pm$ 16.5
Respiratory tract infection	18 (35.1)
Antibiotic types	
Cephalosporin	47 (90.4)
Non-cephalosporin	5 (9.6)

The incidence of antibiotic associated diarrhea (AAD) was 6 (11.5%). The *Clostridium difficile* total incidence in both groups was 8 (15.4%) (see Table 2, Table 3).

**Table 2. Incidence of antibiotic associated diarrhea (AAD)**

AAD	n (%)
Yes	6 (11.5)
No	46 (88.5)

AAD: antibiotic associated diarrhea



**Figure 1. Incidence of antibiotic associated diarrhea (AAD)**

AAD was present on 6 patients (11.5%). *Clostridium difficile* was present on 8 patients (15.4%). Upper gastrointestinal symptoms were present on 20 (38.5%) patients. Lower gastrointestinal symptoms were present on 10 (19.2%) patients. The upper gastrointestinal symptoms included nausea, vomitus, epigastric pain & bloating. The lower abdominal symptoms included abdominal pain, constipation & flatulence.

**Table 3. Incidence of of antibiotic associated diarrhea (AAD) and other characteristics**

Variable (total n = 52)	n (%)
AAD	6 (11.5)
<i>C. Difficile</i> infection	8 (15.4)
Upper gastrointestinal symptoms	20 (38.5)
Lower abdominal symptoms	10 (19.2)
Mean duration using antibiotic	16.41 ± 28.52
Mean length of hospital stay	12.79 ± 9.37

AAD: antibiotic associated diarrhea

## DISCUSSION

The most frequent sex of the patients in this study was men, and most patients suffered respiratory tract infection. This result was inline with the result of Elseviers MM' study which also revealed that the largest characteristic in the study was also men (52%) and in about half of the patients have respiratory tract infection as the indication for antibiotic treatment.<sup>13</sup> Age of patients receiving antibiotics in this study had mean age of  $48.9 \pm 16.5$  years old, somewhat different from the study of Elseviers MM which found that the average age of the patients was 68 (range 16-99) years old.<sup>13</sup>

The incidence of AAD in this study (11.5%) is almost equal to the AAD prevalence of Elseviers MM's research which revealed 9.6%.<sup>13</sup> AAD in this study was more related to the use of cephalosporin, this is different if compared to the Elseviers MM's study, in which the most frequent antibiotics used were penicillin.<sup>13</sup>

In this study, a total of *Clostridium difficile* infection in both groups was 15.4%, this is in accordance with the results of other studies.<sup>13</sup> In this study, beside diarrhea there were also other clinical manifestations such as upper and lower gastrointestinal symptoms. Lower gastrointestinal symptoms that patients complained were abdominal pain, constipation & flatulence, diarrhea. This was similar to the results of other studies which found the AAD symptoms such as watery diarrhea, abdominal cramping, abdominal tenderness and pain, blood or pus in bowel movements, fever, nausea, loss of appetite and dehydration.<sup>14</sup>

## CONCLUSION

The Incidence of AAD and *Clostridium difficile* infection were 11.5%. and 15.4% respectively. The clinical manifestations of AAD were diarrhea, other upper and lower gastrointestinal symptoms.

## REFERENCES

1. MayoClinic.Com. Antibiotic-associated Diarrhea [serial online] [cited 2010 July 26]. Available from: URL: <http://www.mayoclinic.com/health/antibiotic-associated-diarrhea/DS00454>.
2. Cremonini F, Di Caro S, Nista EC, Bartolozzi F, Capelli G, Gasbarrini G, et al. Meta-analysis: the effect of probiotic administration on antibiotic-associated diarrhoea". *Aliment Pharmacol Ther* 2002;16:1461-7.
3. Deshpande A, Pimentel R, Choure A. Antibiotic-Associated Diarrhea and *Clostridium difficile* [serial online] [cited 2017 July 8]. Available from: URL: <https://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/gastroenterology/antibiotic-associated-diarrhea/>.
4. Mcfarland LV. Meta-analysis of probiotics for the prevention of antibiotic associated diarrhea and the treatment of *Clostridium difficile* disease. *Am J Gastroenterol* 2006;101:812-22.
5. Ohio health online. Antibiotic-associated diarrhea [serial online] [cited 2010 July 27]. Available from: URL: <http://www.ohiohealth.com/body mayo.cfm?xyzpdqabc=0&id=6&action=detail&ref=1262>.
6. Szajewska H, Mrukowicz J. Meta-analysis: non-pathogenic yeast *Saccharomyces boulardii* in the prevention of antibiotic-associated diarrhoea. *Aliment Pharmacol Ther* 2005;22:365-72.
7. Meier RF. Probiotics: a new treatment for antibiotic-associated diarrhea? *Digestion* 2005;72:49-50.
8. Nelson RL, Suda KJ, Evans CT. Antibiotic treatment for *Clostridium difficile*-associated diarrhoea in adults. In *Cochrane database of systematic review* [serial online] [cited 2017 July 8]. Available from: URL: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004610.pub5/abstract>.
9. Cimperman L, Bayless G, Best K, Diligente A, Mordarski B, Oster M, et al. A randomized, double-blind, placebo-controlled pilot study of *Lactobacillus reuteri* ATCC 55730 for the prevention of antibiotic-associated diarrhea in hospitalized adults. *J Clin Gastroenterol* 2011;45:785-9.
10. Kolodziej M, Szajewska H. *Lactobacillus reuteri* DSM 17938 in the prevention of antibiotic-associated diarrhoea in children: protocol of a randomised controlled trial. *BMJ open*. [serial online] [cited 2017 June 28]. Available from: URL: <http://bmjopen.bmj.com/>.
11. Guandalini S. Probiotics for Prevention and Treatment of Diarrhea. *J Clin Gastroenterol* 2011;45:S149-S153.
12. Georgieva M, Pancheva R, Rasheva N, Usheva N, Ivanova L, Koleva K. Use of the probiotic *Lactobacillus reuteri* DSM 17938 in the prevention of antibiotic-associated infections in hospitalized Bulgarian children: A randomized, controlled trial. *J of IMAB* 2015;21:895-900.
13. Elseviers MM, Elseviers MM, Van Camp Y, Nayaert S, Dure K, Annermans L, et al. Prevalence and management of antibiotic associated diarrhea in general hospitals. *BMC Infect Dis* 2015;15:129.
14. Justad J. Health and Safety Guidelines *Clostridium difficile*. *Clostridium difficile antibiotic-associated diarrhea* [serial online] [cited 2017 July 8]. Available from: URL: <https://dphhs.mt.gov/Portals/85/dsd/documents/DDP/MedicalDirector/Health%20and%20Safety%20Guidelines%20-%20Clostridia%20difficile.pdf>.