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The incidence of Clostridium *Difficile* infection in diarrhea patients after receiving antibiotics at Dr. Soetomo Hospital Surabaya

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ABSTRACT

Introduction: Improper use of antibiotics is a risk factor for *C. difficile* infection. The increasing incidence of C. *difficile* infection is one of the indications of failure in infection prevention and control in hospitals. The aim of this study was to analyze the incidence of C. *difficile* infection in diarrhea patients after receiving antibiotics in the ICU and internal medicine ward of Dr. Soetomo Hospital Surabaya.

Methods: Stool samples were taken from 31 diarrhea patients with at least 2 x 24-hours of antibiotic use who were admitted to the ICU and hospitalized at Dr. Soetomo Hospital Surabaya from August 2017 to May 2018. Each sample was examined for glutamate dehydrogenase (GDH) and A and B toxins of *C. difficile*. The results of this study were analyzed descriptively.

Results: The average age of respondents was 48.94 (21 – 86) years old. In addition, based on demographic data, it was predominant by females (65%), diabetes mellitus and fever (16%), and ceftriazone usage (22%). The results showed one sample (3%) with positive results and 30 samples (97%) with negative results for both A/B toxins and GDH enzyme.

Conclusion: It can be concluded that the incidence of diarrhea in these patients was not due to *C. difficile* infection. The cause of diarrhea in these patients could be due to other causes such as a virus, fungus, or other bacterial infections. More sample collection is needed to provide more accurate data about *C. difficile* infection, so it can help to fulfill data for infection prevention and control in hospitals.

Keywords: *Clostridium difficile*, glutamate dehydrogenase, A/B toxins

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INTRODUCTION

Clostridium difficile (C. difficile) is an obligate anaerobe, gram-positive rod bacteria, which can cause diseases with clinical manifestations ranging from pseudomembranous colitis to severe fulminant colitis.[1] Irrational use of antibiotics is the most important risk factor for *C. difficile* infection.[2] The description of pseudomembranous colitis was first reported in 1893, and the association between the administration of clindamycin and pseudomembranous colitis was reported in 1974.[1] *C. difficile* infection is suspected to cause antibiotics-associated diarrhea in 10 – 35% of cases, and is the most common cause of nosocomial diarrhea with significant morbidity and mortality. About 80% of *C. difficile* infection are healthcare-associated infections (HAI), while 20% of cases are community-acquired.[3]

Several researchers in developed countries have reported the incidence of *C. difficile* infection, but it is still very limited in developing countries.[3] The increasing incidence of *C. difficile* infection in hospitals is an indication of failure in infection prevention and control in hospitals. In the past two decades, the incidence of *C. difficile* infection, both healthcare-associated infections and community-acquired, have increased. This problem has an impact on mortality, hospital care, and health costs.[3,4] Carriage of *C. difficile* occurs in around 5 - 15% of healthy adults, 84.4% of healthy infants and neonates, and 57% of hospitalized patients.[5]

The Joint Commission International (JCI) standard includes the number of *C. difficile* infections as the number of infections that must be monitored continuously. The increasing incidence of *C. difficile* infection in hospitals is one of the indications of failure in infection prevention and control in hospitals. This could be caused by several things, such as the lack of hand hygiene, inadequate decontamination of medical equipment, low quality of environmental cleaning, low awareness of human resources in the practice of preventing infection, and the use of antibiotics that are not indicated. Dr. Soetomo Hospital Surabaya has not routinely performed *C. difficile* checks as a parameter to evaluate HAI, which may be due to the difficulty of doing *C. difficile* culture.

The aim of this study was to analyze the incidence of *C. difficile* infection in diarrhea patients who received antibiotics in the intensive care unit (ICU) and the internal medicine ward of Dr. Soetomo Hospital Surabaya. It is hoped that knowing the rate of infection due to *C. difficile* can increase the awareness of infection prevention and control in the hospital.

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METHOD

This study was conducted at Dr. Soetomo Hospital Surabaya. Samples were taken from the ICU and internal medicine ward from August 2017 to May 2018. Samples were collected from male and female adult patients who experienced diarrhea after receiving antibiotics for at least two days in the inpatient room. The examination was carried out at the Clinical Pathology Laboratory using the Immuno Chromatography Test (ICT) method quantitatively to determine the presence of toxins and GDH enzymes of *C. difficile*.

A/B toxins were checked using the IMMUNOQUICK® Tox A/B, which is designed as a rapid lateral flow immunoassay to detect the presence of antigen A and B toxins in the form of fresh, frozen and stool specimens that have been stored. The IMMUNOQUICK® Tox A/B rapid test with nitrocellulose zone part of the test line coated with anti-toxin A and B antibodies. Anti-toxin A and B antibodies also bind to red latex particles inserted in the test strip below the zone of nitrocellulose. The presence of A and B toxins in a combination of samples with antibodies will be a complex form.

Table 1 Demographic data and clinical characteristics of patients (n = 31)

Parameter	Mean	N	%
Age (years)	48.94 (21 – 86)		
Sex			
Male		11	35%
Female		20	65%
Diagnosis			
Chronic kidney disease		2	7%
Diabetes mellitus		5	16%
Fever		5	16%
Typhoid fever		3	10%
Hepatitis B		3	10%
Pneumonia		4	13%
Urinary tract infection		2	6%
Abdominal colic		2	6%
Other		5	16%
Therapy			
Ceftriaxone		22	71%
Cefotaxime		5	16%
Ciprofloxacin		3	10%
Meropenem		1	3%
Length of stay (days)	7.65 (5 – 21)		
Duration of antibiotic administration (Days)	7.46 (4 – 18)		

Complex migration to the nitrocellulose strip will bind to antibodies in the test region and will be seen as a pink/red line. The appearance of two red/pink lines with varying intensity on the device in the test line position and the control line shows reactive results that are interpreted as positive results on the IMMUNOQUICK® Tox A/B. The appearance of one red/pink line with varying intensity on the device is in the position of the control line are interpreted as negative results. No line that appears on the device in the control line position indicates an invalid result and cannot be interpreted. If this condition occurs, the test must be repeated with a new kit.

Glutamate dehydrogenase (GDH) is a metabolic enzyme that is encoded by the gluD gene. All *C. difficile* isolates produce this antigen in high concentrations, for both toxigenic and non-toxigenic strains. *C. difficile* GDH IMMUNOQUICK is a qualitative lateral flow immunoassay to detect GDH antigens in feces. This test uses specific antibodies for GDH in the membrane on the test line. During the examination, the presence of GDH in fecal specimens will react with anti-GDH antibodies that are attached to gold particles. The mixture will move upward towards the membrane capillary and react with the anti-GDH contained in the test line. The appearance of a colored line on the line test (T) shows a positive result, whereas no line indicates a negative result. The results are declared invalid if a line does not appear in the control, so the test must be repeated.

Data were presented descriptively in tables and diagrams. Patients were descriptively presented based on inpatient rooms, gender, diagnosis, therapy, and *C. difficile* infection status.

RESULT

A total of 31 diarrhea patients with at least 2 x 24-hours of antibiotic use after admission to ICU and internal medicine ward were included in this study. Demographic data and clinical characteristics can be seen in Table 1.

As shown in Figure 1, two patients were obtained (6%) from the ICU, and 29 patients (94%) patients came from the internal medicine ward.

As shown in Figure 2, there were 20 females (65%) patients and 11 males (35%). The average age of patients from both the ICU and the inpatient ward was 48.94 years, with the youngest being 21 years old and the oldest being 86 years old. The shortest duration of antibiotic administration was four days, while the longest was 18 days. (Table 1)

As shown in Figure 3, patient diagnosis included chronic kidney disease, diabetes mellitus, febrile

observation, typhoid fever, hepatitis B, pneumonia, urinary tract infections, abdominal colic, and as many as 5 people (16%) suffered from other diseases, which were systemic lupus erythematosus, Ca caecum, pulmonary TB, HELLP syndrome and hypertension.

In Figure 4, 71% of the samples were treated with ceftriaxone, 16% received cefotaxime, 10% received ciprofloxacin, and one patient (3%) received meropenem therapy; all drugs were given through intravenous injection. The length of stay varied, with an average of 7.65 days. The shortest length of stay was five days from inpatient care, while the longest was 21 days from the ICU (Table 1).

All samples were examined for A/B toxins and GDH enzymes using ICT. The results showed only one sample with positive results for A/B toxins and GDH enzyme. Therefore, it can be concluded that the incidence of diarrhea in this patient was due to *C. difficile* infection. A total of 30 samples (97%) had negative results for both A/B toxins and GDH enzyme. (Figure 5)

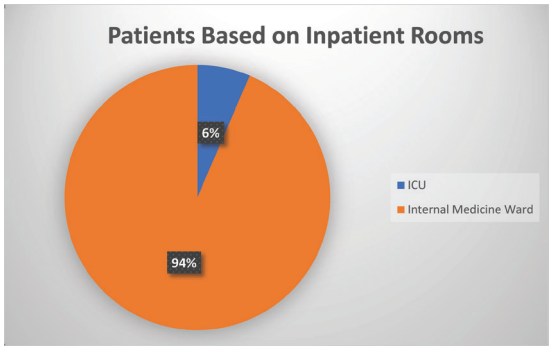

Figure 1 Diagram of patients based on inpatient rooms

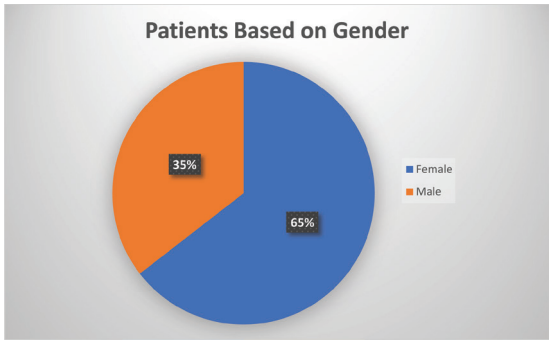

Figure 2 Diagram of patients based on gender

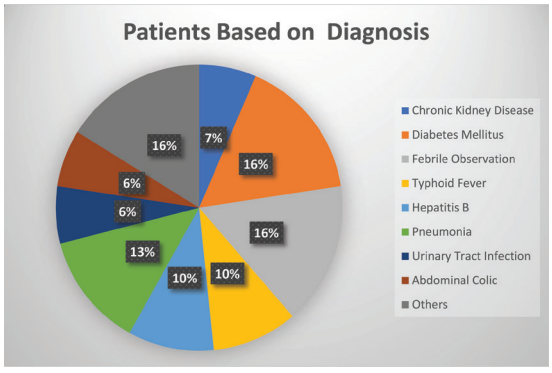

Figure 3 Diagram of patients based on diagnosis

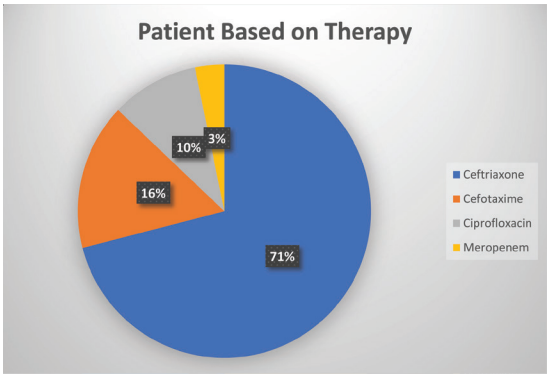

Figure 4 Diagram of patients based on therapy

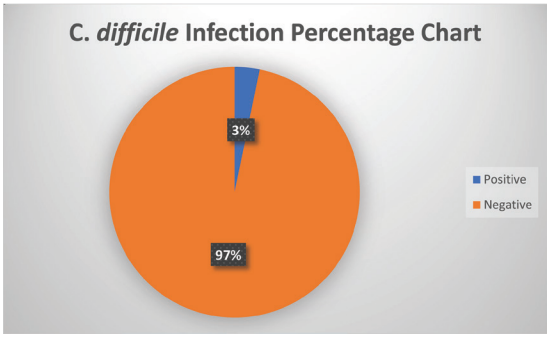

Figure 5 C. *difficile* infection percentage

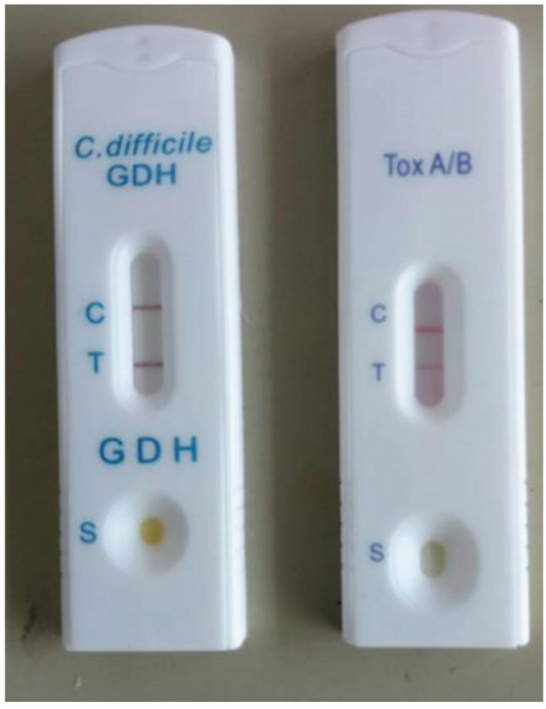

Figure 6 The positive result of C. *difficile* infection

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DISCUSSION

In humans, most of the normal flora bacteria are anaerobic bacteria. The most commonly found bacterium in the digestive tract is *C. difficile*. *C. difficile* in is found in about 3% of adults, 20 – 50% of infants, and 50 – 70% of neonates.[6] Rolfe et al. and Fekety et al. stated that ampicillin, penicillin, clindamycin, chloramphenicol, tetracycline, and cephalexin are antibiotics that were often associated with the onset of C. difficile infection. However, Allen et al. stated that almost all antibiotics, except vancomycin, bacitracin, and metronidazole, were often associated with *C. difficile* infection.

In 2015, the Centers for Disease Control (CDC) estimated that *C. difficile* infected nearly half a million Americans and caused 29,000 deaths in 2011. Forty percent of cases came from home care and community health services, while 24% occurred in hospitals.[7] In developing countries, *C. difficile* infection report is still uncommon. A study conducted by a hospital in Malaysia found that out of 175 fecal samples from patients suspected of being infected with *C. difficile*, 13.7% had positive results, with the majority occurring in patients over 50 years old.[8]

During the period of sample collection (August 2017 – May 2018), we obtained 31 samples. All samples were examined for A/B toxins and GDH enzymes using ICT. Only one sample (3%) was found to have positive results for A/B toxins and GDH enzyme, which meant that the incidence of diarrhea in this patient was due to *C. difficile* infection. A total of 30 samples (97%) had negative results for both for A/B toxins and GDH enzyme; hence it can be concluded that the incidence of diarrhea in these patients was not due to *C. difficile* infection. The cause of diarrhea in these patients could be due to a virus or other bacterial infections.

The results obtained in this study are lower than the study conducted in four hospitals in Semarang from 2014 to 2015. The study used fecal samples taken from 340 patients suspected of being infected with *C. difficile*. As many as 19 (5.6%) samples had positive results for toxins and GDH examination.[9] Diagnosing *C. difficile* infection is difficult because of the lack of laboratories that can provide anaerobic culture facilities.

The patient who had positive results in this study was admitted to the hospital with a diagnosis of hepatitis B. The patient was 54 years old. The patient was treated in the inpatient of the internal medicine ward and received a treatment of 3rd generation cephalosporin injections twice per day along with other therapies according to the treatment protocol for hepatitis B. On the third day of antibiotic administration, the patient began to have diarrhea, yet the antibiotic treatment continued until the seventh day. The patient's fecal sample was examined on the fifth day of antibiotic administration and showed positive results. Two days after the antibiotic was stopped, the patient no longer had diarrhea. Three days later, or on the 12th day, the patient was discharged from the hospital. The results of the examination for A/B toxins and GDH enzymes have also been reported to the clinician. This supports the theory that diarrhea in hospitalized patients who received at least 2 x 24-hour antibiotic therapy can be a sign of *C. difficile* infection.

Further research examining *C. difficile* infection should be conducted in a wider range of hospitals with longer periods, considering how difficult it is to collect the samples. It is expected that with more sample collection and anaerobic culture examination, more accurate data on *C. difficile* infection can be obtained to help fulfill data for infection prevention and control in hospitals.

CONCLUSION

Only one sample showed positive results, while the remaining 30 samples showed negative results. Therefore, it can be concluded that diarrhea in these patients was not due to *C. difficile* infection, but could be due to other causes such as viruses, fungi or other bacterial infections. Stool examination in patients suffering from diarrhea after receiving antibiotics for at least two days can help establish a diagnosis of whether the patient is suffering from *C. difficile* infection. Controlling *C. difficile* infection is very critical because the increasing incidence of *C. difficile* infection in hospitals is one of the indicators of failure in infection prevention and control in hospitals.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding manuscript

ETHICAL CLEARANCE

This study has been received ethical approval by the Ethics Committee prior study was carried out.

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AUTHOR CONTRIBUTION

All authors are contributed equally to the content of study from data preparation, statistical analysis, results, and data synthesis.

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