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Risk Factors Associated with Suspected *Clostridium difficile* Infection (CDI) in Elderly Diarrhea Patients at Prof. Dr. I.G.N.G. Ngoerah Hospital

I Gusti Putu Suka Aryana^{1*}, Ni Nyoman Sri Budayanti², Ni Luh Putu Harta Wedari³

¹Geriatric Division, Internal Medicine Department, Faculty of Medicine, Universitas Udayana, Prof. Dr. I.G.N.G. Ngoerah Hospital, Bali, Indonesia

²Clinical Microbiology Department, Faculty of Medicine, Universitas Udayana, Universitas Udayana Hospital, Bali, Indonesia

³Clinical Microbiology Specialist Program, Faculty of Medicine, Universitas Udayana, Prof. Dr. I.G.N.G. Ngoerah Hospital, Bali, Indonesia

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ABSTRACT

Clostridium difficile infection (CDI) is a typical healthcare-associated infection that contributes to a significant proportion of morbidity and mortality among hospitalized patients. Anaerobe microbiological laboratory examinations cannot be performed at Prof. Dr. I.G.N.G. Ngoerah Hospital, leading to many undetected cases; therefore, it is crucial to determine the risk factors. Identification of cases may help to prevent, recognize, and appropriately treat CDI, reducing morbidity and mortality. This study aimed to determine the risk factors associated with suspected CDI in elderly patients with diarrhea due to their vulnerability to immunosenescence. This research used medical records as secondary data to determine the risk factors associated with suspected CDI in elderly diarrhea patients at Prof. Dr. I.G.N.G. Ngoerah Hospital during the year period of 2017 to 2021 with total of 70 samples who met inclusion criteria by purposive sampling technique. One hundred percent of all samples had a history of hospitalization for ≥ 48 h. There were 53 patients (77.1%) had a history of antibiotic use, 26 (37.1%) proton pump inhibitors (PPIs), 66 (94.3%) chemotherapy, 66 (94.3%) urinary tract infections, 6 (8.6%) kidney disease, and 7 (10%) myocardial infarction. Seven (10%) patients had vascular disease, and 11 (15.7%) had diabetes mellitus. Risk factors associated with suspected CDI in elderly patients with diarrhea at Prof. Dr. I.G.N.G. Ngoerah Hospital include hospitalization \geq for 48 hours, use of antibiotics in the last few months, proton pump inhibitors, decreased immune system, urinary tract infection, kidney disease, myocardial infarction, vascular disease, and diabetes mellitus.

Keywords: *Clostridium difficile* infection (CDI), risk factors, elderly, diarrhea, and immunosenescence.

Highlights: This is a preliminary descriptive study to determine risk factors of CDI among elderly patients that could be reference for further research in Indonesia.

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* Corresponding Author:
ptsuka_aryana@unud.ac.id



INTRODUCTION

Clostridium difficile is an anaerobic Gram-positive bacillus capable of forming spores and toxins that are transmitted to humans via the fecal–oral route. In the United States, *C. difficile* is the most commonly reported pathogen of HAIs, with a case fatality rate of 14% within 30 days of diagnosis.¹ In addition, the high health costs associated with *Clostridium difficile* infection (CDI) increase the government's financial burden on health spending. It was noted that half a million infections were associated with CDI in the United States in 2011, with an incidence rate of 8.75 cases/1,000 adults treated in 2009.^{2,3} A literature study by Collins et al. obtained CDI case data. The study found that The Japanese study only reported *C. difficile* ribotyping results without information on the prevalence or incidence of CDI in Japan; the incidence of CDI increased from 1.7/1,000 to 2.7/1,000 adults in Korea, and 17.1/10,000 hospitalized patients in Shanghai were associated with CDI. Meanwhile, approximately 44% and 14% of colitis patients were diagnosed as positive for *C. difficile* toxin in the Philippines and Malaysia.⁴ A more recent study showed that the prevalence of CDI was 9.2% in Thailand.⁵ There are few reports on the incidence or prevalence of CDI in Indonesia. One study reported that eight strains of *C. difficile* appeared in healthy people, while another study showed that the prevalence of *C. difficile* (toxin A) was 1.3% in communities and hospitals in Jakarta.^{6,7} The latest report from Central Java showed a CDI prevalence of 20.6% in 2017.⁸

Several risk factors, including advanced age, exposure to antibiotics, and hospitalization, are strongly associated with CDI.⁹ The ability of the elderly group's immunity to decrease with increasing age, including the speed of the immune response against infections. Elderly individuals with recent antibiotic treatment are at the highest

risk for CDI because they lack beneficial gut microbiota and have low immunity due to age and other comorbidities.¹⁰⁻¹³ This group is severely affected and has the highest mortality from CDI, with a 2% increase in risk each year after age 18 years. A report described that around one in ten deaths due to CDI in the elderly in the United States in 2010.¹⁴ There are no data on CDI in the elderly in Bali, Indonesia due to lack of surveillance of CDI cases followed by limited laboratory facilities in hospitals capable of diagnosing CDI. In addition, cases of relapse (relapse/reinfection) and death from CDI in the elderly will be higher due to inappropriate treatment.

One cohort study estimated that about 40% of CDI cases were community-acquired (CA-CDI).¹⁵ CA-CDI occurs in younger people, symptoms are less severe, hospital stays are shorter, relapse rates are lower, but no deaths have been reported due to CA-CDI.¹⁶ In addition, CDI was exacerbated by the discovery of hypervirulent strains and antibiotics that were resistant to quinolones, gatifloxacin, and not levofloxacin.¹⁷ The appearance of CA-CDI is a risk factor for domestic and foreign tourists visiting Bali. The identification of cases and appropriate treatment will reduce morbidity and mortality due to CA-CDI. Therefore, increasing the laboratory capacity to detect CDI and clinical awareness of the presence of CA-CDI is very important. Microbiological CDI diagnosis was not performed at Prof. Dr. I.G.N.G. Ngoerah Hospital, even though there are likely to be many undetected cases. Furthermore, if there is an underdiagnosis of CDI, the death rate of the elderly due to CDI will increase. Therefore, the modality of CDI examination is crucial. Owing to geriatric vulnerability to immunosenescence, this study aimed to determine the risk factors associated with *Clostridium difficile* infection (CDI) in elderly patients with diarrhea at Prof. Dr. I.G.N.G. Ngoerah Hospital.

METHODS

This type of research was a retrospective study using hospital medical records that aimed to determine the risk factors associated with suspected CDI in elderly patients with diarrhea at Prof. Dr. I.G.N.G. Ngoerah Hospital, Bali, Indonesia. The target population of this study included all elderly inpatients with suspected CDI. Based on the study of Collin *et al.*, the sample used in this study were all elderly inpatients (age 65 years and over) with suspected CDI at Prof. Dr. I.G.N.G. Ngoerah Hospital for the last 5 years (2017 to 2021), which included diarrhea patients with one or several risk factors: (i) pharmacotherapy: history of use of antibiotics (clindamycin, fluoroquinolones, second-generation cephalosporins or higher), chemotherapy, proton-pump inhibitors, and histamine type 2 blockers for at least two weeks; (ii) decreased host immunity: presence of comorbid diseases such as diabetes mellitus, chronic kidney disease, and human immunodeficiency virus; (iii) have experienced CDI previously.⁴ CDI was diagnosed based on the Infectious Diseases Society of America (IDSA) 2011 criteria.^{2,4} The sampling technique used was purposive sampling. The data-collection process began during the preparation stage. The processes

carried out from the preparation stage to the data collection process included: (i) administration of research ethics and permits at the ethics committee of the Faculty of Medicine, Universitas Udayana, Prof. Dr. I.G.N.G. Ngoerah Hospital; (ii) arrangement of permits for conducting research from the Education and Training Section of Prof. Dr. I.G.N.G. Ngoerah Hospital; and (iii) data collection was carried out from medical records.

RESULTS

The research sample totaled 70 participants for the last five years (2017–2021) who met the inclusion criteria. One hundred% of all samples had a history of hospitalization \geq for 48 h are showed on Table 1. Antibiotic use is frequently reported as a risk factor are showed on Table 2. A total of 53 patients (77.1%) had a history of antibiotic use. A total of 26 patients (37.1%) had a history of using proton pump inhibitors (PPIs), 66 samples (94.3%) had a history of chemotherapy, 66 samples (94.3%) had a history of urinary tract infections, 6 samples (8.6%) had a history of chronic kidney disease, 7 samples (10%) had a history of myocardial infarction, 7 samples (10%) had a history of vascular disease, and 11 samples (15.7%) had a history of diabetes mellitus.

Table 1. Risk Factors Associated with Suspected CDI in Elderly Diarrhea Patients at Prof. Dr. I.G.N.G. Ngoerah Hospital.

Variable	Percentage (%) (n=70)
History of hospitalization	
< 48 hours	0 (0)
\geq 48 hours	70 (100)
History of antibiotic usage	
Yes	53 (77.1)
No	16 (22.9)



History of proton pumps inhibitor usage

Yes	26 (37.1)
No	44 (62.9)

History of chemotherapy

Yes	4 (5.7)
No	66 (94.3)

History of human immunodeficiency virus

Yes	11 (15.7)
No	59 (84.3)

History of urinary tract infection

Yes	4 (5.7)
No	66 (94.3)

History of chronic kidney disease

Yes	6 (8.6)
No	64 (91.4)

History of myocardial infarction

Yes	7 (10)
No	63 (90)

History of vascular disease

Yes	7 (10)
No	63 (90)

History of diabetic mellitus

Yes	11 (15.7)
No	59 (84.3)

Table 2. Antibiotic Used in Elderly Diarrhea Patients at Prof. Dr. I.G.N.G. Ngoerah Hospital.

Antibiotic	Percentage (%) (n= 53)
Azithromycin	2 (3,8)
Doxycycline	1 (1,9)
Levofloxacin	7 (13,2)
Metronidazole	5 (9,4)



Cefoperazone	8 (15,1)
Ciprofloxacin	30 (56,6)

Eleven patients (15.7%) experienced diarrhea accompanied by blood and/or pus, 48 patients (68.6%) experienced cramps and abdominal pain, 16 patients (22.9%) experienced flatulence, 23 patients (32.9%) had fever, 16 patients (22.9%) experienced nausea, 23 patients (32.9%) experienced dehydration, 13 patients (18.6%) experienced decreased appetite, and 11 patients (15.7%) experienced decreased weight. Symptoms of suspected CDI in elderly diarrhea patients are showed on Table 3.

Table 3. Symptoms of Suspected CDI in Elderly Diarrhea Patients at Prof. Dr. I.G.N.G. Ngoerah Hospital.

Variable	Percentage (%) (n=70)
History of diarrhea	
With blood and/or pus	11 (15.7)
Without blood and/or pus	59 (84.3)
History of abdominal cramp and pain	
Yes	48 (68.6)
No	22 (31.4)
History of bloated stomach	
Yes	16 (22.9)
No	54 (77.1)
History of fever	
Yes	23 (32.9)
No	47 (67.1)
History of nausea	
Yes	16 (22.9)
No	54 (77.1)
History of dehydration	
Yes	23 (32.9)

No 47 (67.1)

History in decreased of appetite

Yes 13 (18.6)

No 57 (81.4)

History in decreased of body weight

Yes 11 (15.7)

No 59 (84.3)

DISCUSSION

Risk factors associated with suspected *Clostridium difficile* infection (CDI) in elderly diarrhea patients at Prof. Dr. I.G.N.G. Ngoerah Hospital

Previous studies have shown that most CDI cases are related to contact with healthcare facilities, and previous hospital admission has been widely described as a risk factor for CDI. *C. difficile* spores can survive for a long time on inanimate objects (resistant to heat, acids, and antibiotics), which is the main reason why these bacteria can cause infection in patients with long hospitalizations in health care facilities.^{3,5,7,9} *C. difficile* spreads via the fecal-oral route and causes disease in humans through the production of two protein exotoxins (toxin A and toxin B) that are cytotoxic to colonic epithelial cells.^{11,12}

Almost any antibiotic can increase susceptibility to CDI infection, but cephalosporins, fluoroquinolones, clindamycin and certain penicillins (eg co-amoxiclav) increase the risk to a greater extent.^{9,11,15,16} The impact of antibiotic on the gut microbiome remains the most important risk factor. Antibiotic-associated diarrhea is one of the most common side effects of antibiotic use. Most cases are mild, but *C. difficile* infection causes a spectrum of illnesses, ranging from diarrhea to colitis, toxic megacolon, and potentially death.¹⁷⁻¹⁹ Intestinal microbiota biology has been considered to play a role in the pathogenesis

of this condition as well as the role of gut microbiota manipulation as a new therapeutic approach. Antibiotic use can cause diarrhea through a variety of mechanisms, including osmotic diarrhea (through the loss of gut bacteria that absorb short-chain fatty acids) and colonization and overgrowth of toxin-secreting *C. difficile*.^{18,19}

Proton pump inhibitors (PPIs) are among the most prescribed outpatient and inpatient agents worldwide, with sales reaching billions of dollars worldwide. PPI has been shown to be effective in the treatment of stomach ulcers (including bleeding gastric ulcers), gastroesophageal reflux disease, *Helicobacter pylori* (in combination with antibiotic), Zollinger-Ellison syndrome, in prophylaxis of upper gastrointestinal complications with non-steroidal anti-inflammatory drugs (NSAIDs), ulcer prophylaxis stress in intensive care unit (ICU) patients, and functional dyspepsia.¹¹⁻¹⁷ The widespread use of PPIs over the last 25 years in clinical practice is a result not only of their high efficacy but also their excellent safety profile, proving to be one of the safest drug classes used in gastroenterology.¹⁸⁻²⁰ The relationship between the use of PPI and CDI is, at least theoretically, rational. Intestinal homeostasis is maintained by host defense mechanisms in which gastric acid plays an important role as a barrier to ingested bacteria and bacterial overgrowth. PPI therapy severely inhibits gastric acid production, leading to spore proliferation and transformation into the vegetative form of *C. difficile*. In addition, PPI impair leukocyte



function by inhibiting phagocytosis and acidification of phagolysosomes.^{21,22}

Chemotherapy that disrupts the gut microbiome and causes mucositis may make germination of *C. difficile* spores more common, leading to greater virulence.¹⁻⁷ While CDI rates in patients with cancer vary between studies, that is, 10% during chemotherapy and up to 20% risk overall.¹¹⁻¹⁵ A total of 59 patients (84.3%) had a history of decreased immune system. Immunocompromised patients have an increased incidence and poor prognosis when accompanied by CDI. Several studies have demonstrated clinical outcomes and risk factors for CDI and CDI relapse in haematological and haematological stem cell transplanted (HSCT) patients.¹⁵⁻¹⁹ The etiology for high CDI and rCDI rates in the immunocompromised population is multifactorial, consisting of repeated and prolonged exposure to broad-spectrum antibiotics, high-dose chemotherapy, acute graft-versus-host disease on HSCT, history of hospitalization, exposure to antibiotics, and repeated hospitalizations.^{15,17} In contrast to antimicrobials that disrupt the normal gut microbiome, facilitating *C. difficile* proliferation, and in contrast to PPIs that allow survival of the vegetative forms of *C. difficile*, the biological mechanism is the negative impact of corticosteroids on the integrity of the gastrointestinal mucosa.¹⁹⁻²²

Most comorbidities of CDI require polypharmacy and prolonged hospitalization, which directly influence the shift from *C. difficile* colonization to subsequent CDI.^{15,17} Previous studies comparing patients with and without underlying chronic kidney disease found that patients with chronic kidney disease had a higher risk for both initial and recurrent episodes of CDI. Similarly, this finding was supported by a recent study that observed a nearly four-fold increased risk (OR:3.68, CI:1.63-8.31, p=0.002) of developing CDI in patients with underlying chronic kidney disease.^{18,19} Reduced kidney function not only impairs the elimination of

toxins from the body but also alters the functioning of the gut microbiota and activates systemic inflammation. Hypertension affects gut microbiota dysbiosis. In contrast, antihypertensive drugs have been shown to improve or harm the gut microbiota. For example, verapamil protects cells from *C. difficile* toxicity.^{20,21}

Furthermore, several studies have shown that patients with diabetes are three times more likely to be at risk of CDI than non-diabetic patients.¹³⁻¹⁹ The relationship between CDI and diabetes has been extensively studied. Diabetes is a possible independent risk factor for primary and recurrent CDI. Diabetes causes structural remodeling of the colon, which affects various functions of the digestive tract, leading to impaired motility and changes in the composition of the gut microbiota, which can lead to *C. difficile* diarrhea.¹⁷⁻²¹ Similarly, an intervention study observed that metformin-treated diabetic patients experienced higher levels of *Clostridium* spp., which can significantly impact *C. difficile* colonization. The potential mechanism that has been investigated is that metformin alters secondary bile acid reabsorption and consequently inhibits spore development, vegetative growth, and toxin activity in *C. difficile* strains. Structural and functional changes in the colon caused by diabetes or diabetes treatment are likely to change the composition of the gut microbiota, consequently increasing or decreasing the risk of CDI; therefore, various measures have been implemented to limit potential exposure.^{11,12}

Symptoms of suspected CDI in elderly diarrhea patients at Prof. Dr. I.G.N.G. Ngoerah Hospital

The clinical manifestations of CDI are very heterogeneous, ranging from an asymptomatic carrier state, mild or moderate diarrhea, to life-threatening fulminant colitis.¹⁵⁻¹⁹ Although the incubation period is

not precisely defined, and according to some studies is 2-3 days, more recent studies have shown that the incubation period may be longer than 3 days and is highly individual-dependent. CDI can affect any part of the large intestine; however, the distal segment is the most frequently infected site.^{13,15} Most patients with CDI have mild diarrhea and recover spontaneously after 5-10 days of discontinuation of antibiotic therapy discontinuation. Diarrhea occurs in most cases during or immediately after antimicrobial therapy, although CDI onset may also occur several weeks later.^{17,19}

Clinical manifestations of CDI, apart from diarrhea, include abdominal pain, fever, nausea and vomiting, weakness, and appetite loss. Fecal occult blood tests are often positive, although active bleeding is rare. In the most severe clinical presentation of CDI, symptoms are life-threatening, and include significant dehydration, abdominal distention, hypoalbuminemia with peripheral edema, and subsequent circulatory shock, renal failure, systemic inflammatory response syndrome, septicemia, and death.²³⁻²⁵ Extracolonic manifestations of CDI are rare, and most often involve small intestinal infiltration, reactive arthritis, and bacteremia.^{25,27} The direct mortality rate due to CDI is estimated at 5%, while mortality due to complications of CDI reaches 15-25%, and reaches 34% in intensive care units (ICU). Mortality doubled in ICU patients with CDI compared to ICU patients without CDI. A poor prognosis is associated with older age, high leukocytosis, hypoalbuminemia, and high creatinine levels. The first episode of CDI also increases the overall risk of death.²⁸⁻³⁰

Relapses of CDI symptoms most often occur during the first week after the initial episode when treatment is completed.²⁵ After effective treatment of the first CDI episode, at least one new recurrent episode occurs in 10-25% of patients, and up to 65% in patients who have already had > 1 episode of recurrent CDI.^{26,27} Some studies

have shown that half of recurrent CDI cases are due to reinfection with the original strain, whereas the other half are due to reinfection with a different strain. Impaired immune responses to *C. difficile* toxins, as well as recent exposure to its spores, are thought to contribute to relapses.²⁹ However, antibiotic resistance does not appear to affect the risk of recurrence. Complications of *C. difficile* include electrolyte imbalance, renal failure due to severe dehydration, systemic inflammatory response syndrome, and sepsis.²⁵⁻²⁹ Bacteremia is rare, with few case reports of *C. difficile* bacteremia. Diagnosis is based on signs and symptoms of CDI, with confirmed microbiological evidence of toxin-producing *C. difficile* in the stool, or colonoscopic or histopathologic findings of pseudomembranous colitis, especially with the exclusion of other causes.²⁷ However, not all patients with CDI have pseudomembranes, especially those with mild or partially treated infections.²⁹

STRENGTH AND LIMITATION

The strength of this study is its representativeness, as the data were collected for five years. A limitation of this study is that it was conducted in only one hospital. This needs to be developed as a pilot study in more hospitals, especially referral center hospitals in Indonesia.

CONCLUSIONS

Several risk factors associated with suspected CDI in elderly diarrhea patients at Prof. Dr. I.G.N.G. Ngoerah, namely hospitalization \geq for 48 h, use of antibiotics in the last few months, use of proton pump inhibitors, decreased immune system, history of urinary tract infection, history of chronic kidney disease, history of myocardial infarction, history of vascular disease, and history of diabetes mellitus.

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ETHICAL CLEARANCE

This study was approved by the Research Ethics Committee of the Faculty of Medicine, Universitas Udayana, Prof. Dr. I.G.N.G. Ngoerah Hospital (reference letter number 1243/UN14.2.2VII.14/LT/2022).

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CONFLICT OF INTEREST

The authors affirmed that there were no conflicts of interest in this study.

AUTHOR CONTRIBUTION

Aryana IGPS determined the idea, provided guidance, conducted research, and was the guarantor and conceptor of the manuscript. Budayanti NNS conducted the research, reviewed drafts, and final contents of the manuscript. Wedari NLPH conducted the study, searched the literature, and wrote the manuscript.

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