Geriatric nutritional risk index as a risk-factor for \textit{Clostridioides difficile} infection relapse in elderly Japanese patients

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Abstract

\textbf{Objective:} Old age is a risk factor for \textit{Clostridioides difficile} infection (CDI). As the world’s aging population increases, identifying risk factors for CDI in elderly patients is a matter of urgency. This study examined the relationship between CDI relapse and nutritional status using the geriatric nutritional risk index (GNRI).

\textbf{Patients and Methods:} Between January 2016 and December 2021, 108 patients were diagnosed with CDI. Of the 108 patients, 19 were excluded because of younger age (<65 years), early death within 14 days of the initial CDI diagnosis, and insufficient data. The patients were divided into low- (<75) and high-GNRI groups (≥75) based on the receiver operating characteristic curve analysis. Variables associated with CDI relapse were also analyzed.

\textbf{Results:} The median GNRI scores in all patients and in the low- and high-GNRI groups were 74.9, 68.9, and 83.9, respectively. Of the 89 patients, 28 (31.8\%) experienced a CDI relapse. The log-rank test showed a significantly better relapse-free survival (RFS) in the high GNRI group (\textit{P}=0.002). Univariate analysis revealed that low GNRI (\textit{P}=0.004), chronic kidney disease (CKD) (\textit{P}=0.004), and beta-lactamase inhibitor administration before the initial diagnosis of CDI (\textit{P}=0.025) were significantly correlated with RFS. Multivariate analysis revealed that low GNRI (\textit{P}=0.008) and CKD (\textit{P}=0.010) were independent prognostic factors for RFS.

\textbf{Conclusion:} Among elderly patients, a low GNRI was strongly associated with CDI relapse. Our study may help clinicians to consider therapeutic strategies for elderly patients with CDI.

\textbf{Key words:} \textit{Clostridioides difficile} infection, elderly, relapse, nutritional status, geriatric nutritional risk index

Introduction

\textit{Clostridioides difficile} infection (CDI) is a disease characterized by fever and diarrhea and accounts for 20–30\% of antibiotic-associated diarrhea\textsuperscript{10}. The estimated number of incident CDI cases reached 453,000, and that of deaths within 30 days of the initial diagnosis of CDI reached 29,300 based on data from the Center for Disease Control and Prevention of the United States in 2011\textsuperscript{2}. Older age (>65 years) is an important risk factor for CDI\textsuperscript{1,3}. As the world’s aging population increases, identifying risk factors for CDI in elderly patients has become an urgent matter.

Many recent studies have reported an association between nutritional status and various diseases. The geriatric nutritional risk index (GNRI) is a simple and objective tool that uses serum albumin levels and body mass index (BMI) to assess the nutritional status of older patients\textsuperscript{4}. A low GNRI has been reported to be an adverse prognostic factor in elderly patients\textsuperscript{5–8}. Additionally, a low GNRI is also suggested to be related to the severity or mortality of infectious diseases such as aspiration pneumonia\textsuperscript{9} or coronavirus disease 2019\textsuperscript{10}. The relationship between CDI and nutritional status, including serum albumin levels\textsuperscript{1,10} and BMI\textsuperscript{12–13}, has also been reported. However, the relationship between CDI and the GNRI has not been re-
ported. This study aimed to elucidate whether a low GNRI would influence CDI relapse.

**Patients and Methods**

**Iwate Prefectural Senmaya Hospital**

Iwate Prefectural Senmaya Hospital is located in a rural area in Japan. The hospital has 148 beds and provides both acute- and chronic-phase treatment in accordance with regional needs.

**Study design**

The present study was conducted at a single institution. The requirement for written informed consent was waived because this was a retrospective observational study. The study protocol was approved by the ethics committee of Iwate Prefectural Senmaya Hospital (approval number: 4) and performed in accordance with the Declaration of Helsinki.

**Patients**

Between January 2016 and December 2021, the total hospitalization, mean patient age, and length of hospital stay (LOS) in Iwate Prefectural Senmaya Hospital were 219,022, 79.4 years, and 21.0 days, respectively. During the same period, 108 patients with fever and diarrhea were diagnosed with CDI during hospitalization. Of the 108 patients, three were excluded because they were aged <65 years, 10 were excluded because of early death (within 14 days) after the initial diagnosis of CDI, and 6 were excluded because of insufficient data. Then, 89 patients were enrolled in this study (Figure 1). The diagnostic criteria for CDI were as follows: glutamate dehydrogenase antigen and toxin A/B were positive using a detection kit (C. DIFF QUIK CHEK COMPLETE®, Abbott Diagnostics Medical Co., Tokyo, Japan), and toxin A/B was negative using the kit, but the toxin B gene was positive using the nucleic acid amplification test.

**Data collection**

We examined the data of all enrolled patients, including age, sex, body mass index (BMI), duration of hospitalization prior to the initial diagnosis of CDI, medical condition, antibiotics administered prior to the initial diagnosis of CDI. In addition, laboratory findings at initial diagnosis of CDI, severity of CDI, treatment for CDI, relapse of CDI, and length of hospital stay (LOS). This study defined chronic kidney disease (CKD) as a medical condition. CKD was diagnosed by a decreased estimated glomerular filtration rate (eGFR, <60 mL/min/1.73 m^2) for three or more months. Leukocyte count, lymphocyte count, C-reactive protein (CRP) level, albumin level, and total cholesterol level were evaluated as laboratory parameters. The severity of CDI was assessed using the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) criteria 2018 as follows: non-severe was defined as leukocytosis with a leukocyte count of ≤15,000 × 10^3 cells/µL and a serum creatinine level <1.5 mg/dL. Furthermore, severe was defined as leukocytosis with a leukocyte count of ≥15,000 × 10^3 cells/µL or a serum creatinine level >1.5 mg/dL; fulminant was defined as hypotension or shock, ileus, and megacolon. CDI relapse was defined as CDI that occurred within 2–8 weeks of its initial onset.

**Calculating GNRI and setting cut-off of GNRI**

GNRI during the initial CDI episode was also evaluated. Serum albumin level (g/dL) and BMI were used to calculate GNRI. The GNRI formula was as follows: GNRI = 14.89 × serum albumin (g/dL) + 41.7 × BMI (kg/m^2) / 24.7. The appropriate cut-off was set using receiver operating characteristic curve analysis (Figure 2). The area under the curve was 0.628 (95% confidence interval [CI]: 0.499–0.757), and the most appropriate cut-off value was calculated to be 74.670. The sensitivity and specificity of the cut-off values were 0.714 and 0.607, respectively. We determined that the cut-off value of the GNRI was 75 and divided it into two groups: a low GNRI (GNRI <75) and a high GNRI group (GNRI ≥75).

**Statistical analysis**

Data are presented as median (range) for continuous variables and number (%) for categorical variables. Statistical analysis was performed using the t-test or Mann–Whitney U test for continuous variables and Fisher’s exact test for categorical variables. Relapse-free survival (RFS) was determined using the Kaplan–Meier method and analyzed using the log-rank test. Univariate and multivariate analyses with Cox proportional model was used to also analyze the risk factors associated with CDI relapse. All statistical analyses were performed using the EZR software (Jichi Medical
Results

Patient characteristics

Table 1 summarizes the patient characteristics. The median GNRI in all patients and in the low- and high-GNRI groups were 74.9, 68.9, and 83.9, respectively. In the low GNRI group, age was significantly higher ($P=0.009$), and LOS was longer ($P=0.003$) than in the high GNRI group. Body mass index (BMI) and serum albumin levels, which are components of the GNRI, were significantly lower in the low GNRI group than in the high GNRI group.

Comparison of RFS between the low and high GNRI groups

Of the 89 patients, 28 (31.8%) experienced a CDI relapse. The recurrence rates in the low- and high-GNRI groups were 45.5% (20/44) and 17.8% (8/45), respectively. Figure 3 shows the Kaplan–Meier curves of RFS between the low- and high-GNRI groups. The log-rank test showed that RFS in the high GNRI group was significantly better than that in the low GNRI group ($P=0.002$).

Multivariate analysis for relapse CDI

Table 3 shows the multivariate analysis for relapse CDI. We determined the analysis variables by referring the univariate analysis and previous reports. Cox proportional hazard model showed that low GNRI ($P=0.008$) and patients with CKD ($P=0.010$) were independent RFS prognostic factors.

Discussion

We found that a low GNRI strongly influenced CDI relapse in elderly patients. The relationship between GNRI and various diseases, including solid tumors, heart failure, and hemodialysis, has been reported. Similarly, a relationship between the GNRI and infectious diseases has been reported. However, the relationship between GNRI and CDI has not yet been reported, and we believe that this study is the first report on the relationship between low GNRI and CDI relapse in elderly patients.
GNRI is a simple and objective tool that can be used to assess nutritional status in elderly patients. Nutritional status is usually classified into four groups: major risk (GNRI <82), moderate risk (GNRI: 82–92), low risk (GNRI: 92–98), and no risk (GNRI >98). Most studies on the GNRI have used this classification. However, the GNRI values in the present study were lower than those reported previously. The median age of the study population was 88 years and the study population was completely different. Therefore, a new cut-off value was set for GNRI in accordance with our study population.

The GNRI has two components: serum albumin level and BMI. Albumin is a well-known predictive marker for CDI incidence, recurrence, and mortality. Among elderly patients, a low albumin level (≤2.5 g/dL) influences CDI mortality. Reports on the association between BMI and CDI are increasing. A recent meta-analysis suggested that high BMI may be a protective factor against CDI. Furthermore, Suzuki et al. reported that low BMI (<18.5 kg/m²) is a risk factor for CDI among older patients with pneumonia in Japan. Therefore, the GNRI, calculated using serum albumin levels and BMI, can be a reasonable and strong tool for predicting the risk of CDI in elderly patients.

Older age (>65 years) is a known risk factor for CDI incidence, relapse, and mortality. Additionally, Linsky et al. reported that older age (>80 years) was a risk factor for CDI.

### Table 1  Characteristics of analyzed patients in low and high GNRI groups

| Variable                                      | All patients (n=89) | Low GNRI (n=44) | High GNRI (n=45) | P-value |
|-----------------------------------------------|--------------------|-----------------|------------------|---------|
| GNRI                                          | 74.9 (51.0–97.6)   | 68.9 (51.0–74.7)| 83.9 (75.3–97.6) | <0.001* |
| Age, years                                    | 88 (66–103)        | 90 (73–103)     | 87 (66–99)       | 0.009*  |
| Age category                                  |                    |                 |                  |         |
| 65–74                                         | 7 (7.9)            | 1 (2.3)         | 6 (13.3)         |         |
| 75–84                                         | 17 (19.1)          | 8 (18.2)        | 9 (20.0)         |         |
| 85–94                                         | 54 (60.7)          | 28 (63.6)       | 26 (57.8)        |         |
| 95 and over                                   | 11 (12.4)          | 7 (15.9)        | 4 (8.9)          |         |
| Gender, Male/Female                           | 39/50              | 20/24           | 20/26            | 0.832   |
| BMI, kg/m²                                    | 20.2 (14.4–32.6)   | 17.8 (14.6–24.1)| 21.5 (14.4–32.6) | <0.001* |
| Duration of hospitalization prior to initial diagnosis of CDI, days | 22 (1–117)         | 26 (1–117)      | 20 (1–110)       | 0.235   |
| Medical condition                             |                    |                 |                  |         |
| Neurological disease                          | 52 (58.4)          | 28 (63.6)       | 24 (53.3)        | 0.392   |
| Chronic kidney disease                        | 37 (41.6)          | 16 (36.4)       | 21 (46.7)        | 0.392   |
| Malignancy                                    | 16 (18.0)          | 10 (22.7)       | 6 (13.3)         | 0.281   |
| Tube feeding                                  | 15 (16.9)          | 11 (25.0)       | 4 (8.9)          | 0.051   |
| History of gastrointestinal surgery           | 14 (15.7)          | 8 (18.2)        | 6 (13.3)         | 0.573   |
| Antibiotics prior to initial diagnosis of CDI |                    |                 |                  |         |
| Ceftriaxone                                   | 48 (53.9)          | 23 (52.3)       | 25 (55.6)        | 0.833   |
| Ampicillin/Sulbactam                          | 23 (25.8)          | 14 (31.8)       | 9 (20.0)         | 0.233   |
| Piperacillin/Tazobactam                       | 15 (16.9)          | 10 (22.7)       | 5 (11.1)         | 0.167   |
| Ceftoperazone/Sulbactam                      | 12 (13.5)          | 7 (15.9)        | 5 (11.1)         | 0.550   |
| Levofloxacin                                  | 11 (12.4)          | 7 (15.9)        | 4 (8.9)          | 0.353   |
| Multiple antibiotics                          | 37 (41.6)          | 22 (50.0)       | 15 (33.3)        | 0.135   |
| Severity of CDI, Mild/Severe/Fulminant        | 66/23/0            | 35/9/0          | 31/14/0          | 0.334   |
| Laboratory parameters                         |                    |                 |                  |         |
| Leukocytes, ×10⁶ cells/µL                     | 8.7 (1.0–38.0)     | 9.3 (1.0–22.3)  | 8.4 (2.6–38.0)   | 0.990   |
| Lymphocytes, ×10⁶ cells/µL                    | 1.0 (0.2–3.3)      | 0.9 (0.2–3.3)   | 1.0 (0.2–3.3)    | 0.777   |
| CRP, mg/dL                                    | 4.6 (0.2–36.5)     | 4.6 (0.3–22.0)  | 4.5 (0.2–36.5)   | 0.705   |
| Albumin, g/dL                                 | 2.5 (1.3–3.8)      | 2.2 (1.3–2.9)   | 2.9 (2.1–3.8)    | <0.001* |
| Total cholesterol, mg/dL                     | 139.6 (71.5–270.0) | 139.2 (87.1–217.9) | 146.0 (71.5–270.0) | 0.987   |
| Treatment for CDI                             |                    |                 |                  |         |
| Metronidazole                                 | 70 (78.7)          | 38 (86.4)       | 32 (71.1)        | 0.120   |
| Vancomycin                                    | 19 (21.3)          | 7 (15.9)        | 12 (26.7)        | 0.302   |
| Length of hospital stay, days                 | 66 (10–727)        | 79(19–727)      | 56 (10–220)      | 0.003*  |

*Parameters with P-value <0.05. Data are expressed as the median (range) or number (%). GNRI: geriatric nutritional risk index; BMI: body mass index; CDI: Clostridium difficile infection; CRP: C-reactive protein.
In the present study, prognostic factors associated with CDI relapse in elderly patients were analyzed. As stated above, the median age of our study population was 88 years, which was much higher than that reported in previous studies. Among elderly patients, age may be less relevant to CDI relapse.

However, it is uncertain whether CKD reduced the risk of CDI relapse in this study. CKD is also a well-known risk factor for CDI. We considered the following hypotheses: First, this was a single-institutional study in a Japanese rural area; therefore, selection bias may have affected this result. Second, most patients in this study were initially treated with metronidazole. Most metronidazole is metabolized by the liver; approximately 80% and 15% of the metabolites are eliminated via the urine and feces, respectively. Metabolites of metronidazole in the blood increased more among patients with renal failure than among healthy volunteers. In patients with CKD, excretion of metronidazole metabolites via feces may increase because of the increased blood concentration of its metabolites. Thus, administration of metronidazole may have increased the risk of CDI relapse.

### Table 2 Univariate analysis for relapse CDI using cox proportional hazard model

| Variable                                      | HR (95% CI)     | P-value |
|-----------------------------------------------|-----------------|---------|
| GNRI <75                                      | 3.388 (1.475–7.783) | 0.004*  |
| Age, years                                    | 1.047 (0.990–1.077) | 0.105   |
| Gender, Male                                  | 0.541 (0.249–1.173) | 0.120   |
| BMI, kg/m²                                     | 0.932 (0.833–1.043) | 0.218   |
| Duration of hospitalization prior to initial diagnosis of CDI, days | 0.995 (0.982–1.009) | 0.490   |
| Medical condition                             |                 |         |
| Neurological disease                          | 2.034 (0.890–4.649) | 0.092   |
| Chronic kidney disease                        | 0.214 (0.074–0.617) | 0.004*  |
| Malignancy                                    | 0.792 (0.301–2.088) | 0.637   |
| Tube feeding                                  | 1.300 (0.527–3.210) | 0.569   |
| History of gastrointestinal surgery           | 0.248 (0.059–1.051) | 0.058   |
| Antibiotics prior to initial diagnosis of CDI |                 |         |
| Ceftriaxone                                   | 0.684 (0.325–1.439) | 0.317   |
| LevoFlaxacin                                  | 1.960 (0.744–5.166) | 0.174   |
| Beta-lactamase inhibitor                      | 2.485 (1.123–5.498) | 0.025*  |
| Multiple antibiotics                          | 1.456 (0.694–3.057) | 0.320   |
| Severe CDI                                    | 0.800 (0.339–1.887) | 0.610   |
| Treatment for CDI                             |                 |         |
| Metronidazole                                 | 2.061 (0.713–5.954) | 0.182   |
| Vancomycin                                    | 0.5832 (0.221–1.539) | 0.276   |
| Laboratory parameters                         |                 |         |
| Leukocytes, ×10³ cells/µL                     | 1.000 (1.000–1.000) | 0.641   |
| Lymphocytes, ×10³ cells/µL                    | 1.000 (0.999–1.000) | 0.282   |
| CRP, mg/dL                                    | 1.018 (0.972–1.066) | 0.453   |
| Albumin, g/dL                                 | 0.497 (0.249–0.991) | 0.047*  |
| Total cholesterol, mg/dL                      | 1.004 (0.994–1.014) | 0.456   |

* Parameters with P-value <0.05. HR: hazard ratio; CI: confidence interval; GNRI: geriatric nutritional risk index; BMI: body mass index; CDI: *Clostridioides difficile* infection; CRP: C-reactive protein.

### Table 3 Multivariate analysis for relapse CDI using cox proportional hazard model

| Variable                                      | HR (95% CI)     | P-value |
|-----------------------------------------------|-----------------|---------|
| GNRI <75                                      | 3.705 (1.411–9.728) | 0.008*  |
| Age, years                                    | 1.025 (0.964–1.091) | 0.429   |
| Chronic kidney disease                        | 0.224 (0.071–0.701) | 0.010*  |
| Administration of beta-lactamase inhibitor prior to initial diagnosis of CDI | 1.864 (0.805–4.317) | 0.146   |
| Severe CDI                                    | 1.613 (0.624–4.168) | 0.324   |
| Administration of MNZ for initial CDI         | 1.184 (0.391–3.586) | 0.765   |

* Parameters with P-value <0.05. HR: hazard ratio; CI: confidence interval; GNRI: geriatric nutritional risk index; CDI: *Clostridium difficile* infection; MNZ: metronidazole.
of metronidazole for CDI may have a high therapeutic effect in patients with CKD. Third, serum creatinine level, which is used to calculate eGFR, is related to skeletal muscle mass\textsuperscript{27, 29}. Among elderly patients, skeletal muscle mass decreases with age\textsuperscript{29}, which leads to decreased serum creatinine levels. Thus, the eGFR is often estimated to be higher than the actual value in elderly patients, and the number of patients diagnosed with CKD may decrease. The same can be said about CDI severity. CDI severity is categorized by leukocyte counts and serum creatinine levels according to the SHEA/ISDA guidelines\textsuperscript{2018}\textsuperscript{15, 16}. In the present study, many elderly patients with less skeletal muscle mass were classified into the non-severe group for the reasons mentioned above. These factors might have affected this study’s results.

Oral antibiotics including metronidazole, vancomycin, and fidaxomicin are usually administered to treat CDI. Fidaxomicin is recommended as the first-choice treatment for initial non-severe CDI according to the Japanese Clinical Guidelines\textsuperscript{2018}\textsuperscript{2016}. Metronidazole is less expensive; however, it is recognized to have a higher risk of treatment failure or CDI relapse compared to other medications\textsuperscript{25, 26}. Our study demonstrated that the administration of metronidazole for initial CDI tended to be related to CDI relapse. Conversely, vancomycin or fidaxomicin is the first-choice treatment for initial CDI, even if the patient is considered non-severe in the SHEA/ISDA guidelines\textsuperscript{2018}\textsuperscript{15}. Additionally, the SHEA/ISDA guidelines\textsuperscript{2021} recommended fidaxomicin as the first-choice treatment for initial CDI instead of vancomycin\textsuperscript{27}. Fidaxomicin is an expensive drug but has some excellent characteristics. First, fidaxomicin is superior to metronidazole or vancomycin preventing CDI relapse\textsuperscript{26, 28}. Second, \textit{Clostridioides difficile} with resistance to fidaxomicin is rare\textsuperscript{27, 29}. Third, fidaxomicin is a narrow-spectrum drug and there are no treatment indications other than CDI\textsuperscript{27, 30}. Among older patients with low nutritional status, that is, among those with a high risk for relapse, vancomycin or fidaxomicin should be considered as the initial treatment for CDI.

This study had some limitations. First, this was a retrospective observational study conducted at a single institution. Accordingly, the analysis was performed with limited sample size. Second, our study population was much older than those in the previous reports, as stated above; therefore, this study had the possibility of selection bias. Third, most patients with CDI are treated with oral metronidazole. Vancomycin or fidaxomicin is mainly used as a treatment for CDI in the United States and European countries; thus, the treatment situation can differ greatly.

## Conclusion

We identified a strong relationship between nutritional status and CDI relapse in elderly patients in Japan. Our study may help clinicians to consider therapeutic strategies for elderly patients with CDI. The GNRI is a simple and strong tool to assess the nutritional status of elderly patients; administration of vancomycin or fidaxomicin, which has a lower risk of treatment failure or relapse of CDI than metronidazole, should be considered for patients with CDI with low GNRI.

## Conflicts of interest

The authors declare that they have no competing interests.

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## References

1. Abou Chakra CN, Pepin J, Sirard S, et al. Risk factors for recurrence, complications and mortality in \textit{Clostridium difficile} infection: a systematic review. PLoS One 2014; 9: e89400. [Medline] [CrossRef]
2. Lessa FC, Mu Y, Bamberg WM, et al. Burden of \textit{Clostridium difficile} infection in the United States. N Engl J Med 2015; 372: 825–834. [Medline] [CrossRef]
3. Eze P, Balsells E, Kyaw MH, et al. Risk factors for \textit{Clostridium difficile} infections - an overview of the evidence base and challenges in data synthesis. J Glob Health 2017; 7: 010417. [Medline] [CrossRef]
4. Bouillanne O, Morineau G, Dupont C, et al. Geriatric Nutritional Risk Index: a new index for evaluating at-risk elderly medical patients. Am J Clin Nutr 2005; 82: 777–783. [Medline] [CrossRef]
5. Yamana I, Takeno S, Shimaoka H, et al. Geriatric Nutritional Risk Index as a prognostic factor in patients with esophageal squamous cell carcinoma -retrospective cohort study. Int J Surg 2018; 56: 44–48. [Medline] [CrossRef]
6. Sasaki M, Miyoshi N, Fujino S, et al. The Geriatric Nutritional Risk Index predicts postoperative complications and prognosis in elderly patients with colorectal cancer after curative surgery. Sci Rep 2020; 10: 10744. [Medline] [CrossRef]
7. Dong CH, Chen SY, Zeng HL, et al. Geriatric nutritional risk index predicts all-cause mortality in patients with heart failure: A systematic review and meta-analysis. Clinics (São Paulo) 2021; 76: e2258. [Medline] [CrossRef]
8. Xiong J, Wang M, Zhang Y, et al. Association of geriatric nutritional risk index with mortality in hemodialysis patients: a meta-analysis of cohort studies. Kidney Blood Purif 2018; 43: 1878–1889. [Medline] [CrossRef]
9. Araki T, Yamazaki Y, Goto N, et al. Prognostic value of geriatric nutritional risk index for aspiration pneumonia: a retrospective observational cohort study. Aging Clin Exp Res 2022; 34: 563–571. [Medline] [CrossRef]

10. Song F, Ma H, Wang S, et al. Nutritional screening based on objective indices at admission predicts in-hospital mortality in patients with COVID-19. Nutr J 2021; 20: 46. [Medline] [CrossRef]

11. Leibovici-Weissman Y, Atamna A, Schlesinger A, et al. Risk factors for short- and long-term mortality in very old patients with Clostridium difficile infection: a retrospective study. Geriatr Gerontol Int 2017; 17: 1378–1383. [Medline]

12. Charoenngam N, Ponvilawan B, Thongpya J, et al. Body mass index and risk of Clostridioides difficile infection: a systematic review and meta-analysis. Infection 2022; 50: 725–737. [Medline] [CrossRef]

13. Suzuki R, Sakata N, Fushimi K. Association of body mass index with Clostridioides difficile infection among older patients with pneumonia in Japan. Geriatr Gerontol Int 2022; 22: 63–67. [Medline] [CrossRef]

14. Kim JW, Lee KL, Jeong JB, et al. Clinical practice guidelines for Clostridium difficile infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis 2018; 66: e1–e48. [Medline] [CrossRef]

15. McDonald LC, Gerdin DN, Johnson S, et al. Chronic kidney disease and end-stage renal disease are risk factors for poor outcomes of Clostridium difficile infection: a systematic review and meta-analysis. Int J Clin Pract 2015; 69: 998–1006. [Medline] [CrossRef]

16. Kim JW, Lee KL, Jeong JB, et al. Proton pump inhibitors as a risk factor for recurrence of Clostridium difficile-associated diarrhea. World J Gastroenterol 2010; 16: 3573–3577. [Medline] [CrossRef]

17. Keddis MT, Khanna S, Noheria A, et al. Nutritional screening based on objective indices at admission predicts in-hospital mortality in patients with chronic kidney disease. Kidney Int Suppl 2013; 3: 1–150.

18. Thongprayoon C, Cheungpasitporn W, Phatharacharukul P, et al. Chronic kidney disease and end-stage renal disease are risk factors for poor outcomes of Clostridium difficile infection: a systematic review and meta-analysis. Int J Clin Pract 2015; 69: 998–1006. [Medline] [CrossRef]

19. Schwartz DE, Jeunet F. Comparative pharmacokinetic studies of ornidazole and metronidazole in man. Chemotherapy 1976; 22: 19–29. [Medline] [CrossRef]

20. Lamp KC, Freeman CD, Kltman NE, et al. Pharmacokinetics and pharmacodynamics of the nitroimidazole antimicrobials. Clin Pharmacokinet 1999; 36: 353–373. [Medline] [CrossRef]

21. Kreeft JH, Ogilvie RJ, Dufresne LR. Metronidazole kinetics in dialysis patients. Surgery 1983; 93: 149–153. [Medline]

22. Wang ZM, Gallagher D, Nelson ME, et al. Total-body skeletal muscle mass: evaluation of 24-h urinary creatinine excretion by computerized axial tomography. Am J Clin Nutr 1996; 63: 863–869. [Medline] [CrossRef]

23. Janssen I, Ross R. Linking age-related changes in skeletal muscle mass and composition with metabolism and disease. J Nutr Health Aging 2005; 9: 353–373. [Medline] [CrossRef]

24. Kunishima H, Ohge H, Suzuki H, et al. The Japanese clinical practice guidelines for management of Clostridium (Clostridium) difficile infections. Jpn. J Chemother 2018; 66: 645–690 (in Japanese).

25. Vardakas KZ, Polyzos KA, Patouni K, et al. Treatment failure and recurrence of Clostridium difficile infection following treatment with vancomycin or metronidazole: a systematic review of the evidence. Int J Antimicrob Agents 2012; 40: 1–8. [Medline] [CrossRef]

26. Okumura H, Fujikuma A, Taieb V, et al. Fidaxomicin compared with vancomycin and metronidazole for the treatment of Clostridium (Clostridium) difficile infection: a network meta-analysis. J Infect Chemother 2020; 26: 43–50. [Medline] [CrossRef]

27. Johnson S, Laverne V, Skimmer AM, et al. Clinical practice guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of Clostridiodes difficile infection in adults. Clin Infect Dis 2021; 73: e1029–e1044. [Medline] [CrossRef]

28. Louise T, Miller MA, Mullane KM, et al. OPT-80-003 Clinical Study Group Fidaxomicin versus vancomycin for Clostridium difficile infection. N Engl J Med 2011; 364: 422–431. [Medline] [CrossRef]

29. Goldstein EJ, Babakhani F, Citron DM. Antimicrobial activities of fidaxomicin. Clin Infect Dis 2012; 55(Suppl 2): S143–S148. [Medline] [CrossRef]

30. Louise T, Cannon K, Byrne B, et al. Fidaxomicin preserves the intestinal microbiome during and after treatment of Clostridium difficile infection (CDI) and reduces both toxin reexpression and recurrence of CDI. Clin Infect Dis 2012; 55(Suppl 2): S132–S142. [Medline] [CrossRef]