

Risk factors for recurrent hospital-acquired *Clostridium difficile* infection in a Japanese university hospital

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Background: *Clostridium difficile* infection (CDI) is a highly prevalent hospital-associated infection. Although most patients respond well to discontinuation of antibiotics, 20%–30% of patients relapse. To initiate early therapeutic measures, the risk factors for recurrent CDI must be identified, although very few Japanese studies have used standard surveillance definitions to identify these risk factors.

Methods: We retrospectively reviewed the medical records of patients with health care facility-onset CDI between August 2011 and September 2013. Patients with diarrhea who were positive for *Clostridium difficile* (via an enzyme immunoassay) were defined as having CDI. Clinical data (eg, demographics, comorbidities, medication, laboratory results, and clinical outcomes) were evaluated, and multivariate analysis was used to identify risk factors that were associated with recurrent CDI.

Results: Seventy-six health care facility-onset CDI cases were identified, with an incidence rate of 0.8 cases per 10,000 patient-days. Fourteen cases (18.4%) were recurrent, with 13 patients having experienced a single recurrent episode and one patient having experienced three recurrent episodes. The 30-day and 90-day mortality rates were 7.9% and 14.5%, respectively. Multivariate analysis revealed that recurrent patients were more likely to have underlying malignant disease (odds ratio: 7.98; 95% confidence interval: 1.22–52.2; $P=0.03$) and a history of intensive care unit hospitalization (odds ratio: 49.9; 95% confidence interval: 1.01–2,470; $P=0.049$).

Conclusion: Intensive care unit hospitalization and malignancy are risk factors for recurrent CDI. Patients with these factors should be carefully monitored for recurrence and provided with appropriate antimicrobial stewardship.

Keywords: *Clostridium difficile*, recurrent infection, risk factors

Introduction

Clostridium difficile (CD) is a spore-forming anaerobe, and the toxin-producing strain is known to cause *Clostridium difficile* infection (CDI), which is one of the most prevalent of the health care-associated infections. CDI is characterized by symptoms such as diarrhea, fever, and enteric pain,¹ and severe CDI can be fatal in patients with hypotension, renal failure, sepsis, colic ileus, and toxic megacolon.² The diagnosis of CDI is based on the clinical manifestation and laboratory test results, which include testing the stool sample for CD toxin, stool cultures, and polymerase chain reaction testing.³ Furthermore, CDI is clinically important, as CD can be transmitted person-to-person, especially in health care facilities, and can cause nosocomial outbreaks. Therefore, symptomatic patients in health care facilities should be placed and treated under an appropriate quarantine.

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Although most patients respond well to the discontinuation of antibiotics and administration of oral metronidazole or vancomycin, 20%–30% of patients experience recurrence.⁴ Therefore, the management of recurrent CDI is often challenging, given the infection control aspect, combined with the increase in the related morbidity, mortality, and health care expenditures.^{5–9} Several studies have reported that various risk factors are associated with recurrence, including advanced age, concurrent use of antibiotics, chronic renal insufficiency, elevated white blood cell counts, low serum albumin levels, gastric and acid anti-secretory medications, and prolonged hospitalization.^{10–14}

Despite the increasing awareness of CDI, an appropriate surveillance methodology has not been established in Japan, and very few Japanese studies have surveyed the prevalence of CDI using standard surveillance definitions. One exception is a study that investigated the incidence rate of health care facility-onset CDI (HO-CDI) in a Japanese tertiary care center.¹⁵ Therefore, the currently available information is insufficient to indicate an appropriate clinical practice, and the collected data are of little practical use. Furthermore, it is important to identify the risk factors for recurrent CDI, as these can be used to develop early preventative measures and therapeutic interventions.

Given these limitations in our knowledge of recurrent CDI, this study's first purpose was to investigate current status of CDI in health care settings using standard surveillance definitions.³ The second purpose was to identify the risk factors that were associated with recurrence in a Japanese health care facility.

Materials and methods

Target patients

This retrospective study was carried out between August 2011 and September 2013, at the Tokyo Women's Medical University Hospital (TWMUH), which is a 1,423-bed teaching hospital. Medical records were used to collect all clinical data, including demographic information, comorbidities, medications (immunosuppressive agents, chemotherapies, and gastric acid suppressions), laboratory test results, severity of the CDI (defined as leukocytosis with a white blood cell count of 15,000/ μ L or higher or a serum creatinine level greater than or equal to 1.5 times the premorbid level), initial medication that was prescribed for the CDI (oral metronidazole or vancomycin), and clinical outcomes. CDI cases were defined based on the Society for Healthcare Epidemiology of America (SHEA) and the Infection Diseases Society of America (IDSA) guideline, as diarrheal patients with stool samples

that were positive for CD toxin,³ as detected via enzyme immunoassay (EIA) (C. DIFF QUIK CHEK COMPLETE[®] test, Alere, Tokyo, Japan).

All hospitalized patients who were >2 years old were considered eligible. We categorized the timeline for case definition according to the SHEA/IDSA guideline³ and our inclusion criteria for HO-CDI cases were either 1) patients who had developed CDI hospitalized for more than 3 days or 2) patients who had developed CDI within 48 hours of admission to TWMUH with history of admission in health care facilities in previous 12 weeks. However, patients who were diagnosed with CDI within 48 hours after admission to TWMUH and had no history of hospitalization in the previous 12 weeks were classified as having community-acquired CDI. Patients with community-acquired CDI and patients who were only positive for glutamate dehydrogenase were excluded from our analysis.

Recurrent CDI was defined as a subsequent episode of CDI within 8 weeks from the previous episode, and its diagnosis was based on the same criteria as the first episode of CDI. Patients with recurrence after their discharge were excluded from our analysis. We grouped the patients into recurrent and non-recurrent groups, and investigated the risk factors that were associated with recurrence.

Statistical analysis

To identify the factors that were associated with CDI recurrence, categorical variables were evaluated using Fisher's exact test, while continuous independent variables were evaluated using the Mann–Whitney *U* test. A two-sided *P*-value of <0.05 was considered to be statistically significant, and variables were subsequently used in the multivariate logistic regression model. All analyses were performed using R 3.0.2 software (The R Foundation for Statistical Computing Platform).

Ethical consideration

This study was approved by the Ethics Committee of the TWMUH.

Results

Patients and background

During the 26-month study period, 2,193 specimens from inpatients and outpatients were tested for CD toxin, and 107 specimens were found to be positive for CD toxin. Seventy-six hospitalized patients were diagnosed with HO-CDI, with an incidence rate of 0.8 cases per 10,000 patient-days (Figure 1).

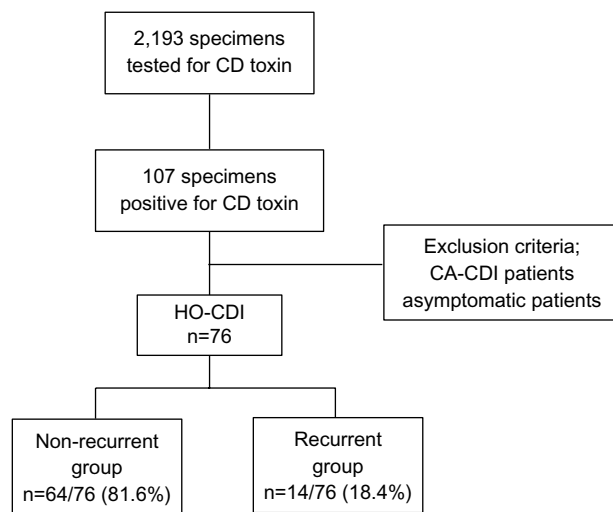


Figure 1 Patient disposition.

Abbreviations: CD, *Clostridium difficile*; HO-CDI, health care facility-onset *Clostridium difficile* infection; CA-CDI, community-acquired *Clostridium difficile* infection.

Among the cases of HO-CDI, the median patient age was 69.5 years (range, 2–95 years), and 50 patients (65.8%) were >65 years old (Table 1). Thirty-nine patients (51.3%) were men and 37 (48.7%) were women. The median duration of hospitalization before the diagnosis of CDI was 28 days (range, 1–155 days). Forty-one patients (53.9%) had malignant disease, 24 patients (31.6%) had heart disease, eleven patients (14.5%) had gastrointestinal disease, and four patients (5.3%) had received a transplant. Among the 41 patients with malignant disease, ten patients had gastrointestinal tumors and eight patients had hematological tumors.

All the enrolled patients had diarrhea, but none of them had ileus or toxic megacolon. The mean temperature was 37.1 Celsius (range, 35.9–41.2) and 13 patients (17.1%) had fever with temperature of 38.0 Celsius or over.

To treat the CDI, 49 patients (64.5%) received oral metronidazole and 27 (35.5%) received oral vancomycin, with a median treatment duration of 14 days (range, 6–52 days). Fourteen cases of CDI (18.4%) were recurrent, which included 13 patients who had experienced single recurrent episode and one patient who had experienced three recurrent episodes. Six patients (7.9%) were categorized as having severe CDI, per the SHEA/IDSA guideline.³ The 30-day mortality rate was 7.9% (n=6) and the 90-day mortality rate was 14.5% (n=11); none of these deaths were related to CDI.

Risk factors for recurrent CDI

Among the 76 patients with HO-CDI, 14 patients (18.4%) were included in the recurrent group and the remaining

Table 1 Demographic and clinical characteristics of the patients with HO-CDI

| Variables | n (%) |
|---|-------------------|
| Age; mean (range) | 69.5 (2–95) |
| Age ≥65 yr | 50 (65.8) |
| Sex, male | 39 (51.3) |
| Underlying disease | |
| Malignant disease | 41 (5.3) |
| Heart disease | 24 (31.6) |
| Gastrointestinal disease | 11 (14.5) |
| Transplantation | 4 (5.3) |
| Medication | |
| Immunosuppressive agents | 18 (23.7) |
| Chemotherapy | 20 (26.3) |
| Gastric acid suppression | |
| Histamine H2 blockers | 13 (17.1) |
| Proton pump inhibitors | 47 (61.8) |
| Clinical parameters | |
| Temperature (Celsius); mean (range) | 37.1 (35.9–41.2) |
| Temperature ≥38 Celsius | 13 (17.1) |
| Peripheral white blood cell count (/ μ L); mean (range) | 6,505 (70–43,660) |
| Serum albumin (g/dL); mean (range) | 2.6 (1.9–4.7) |
| Serum CRP (mg/dL); mean (range) | 4.1 (0.04–24.3) |
| Duration from admission to diagnosis, days; mean (range) | 28 (1–55) |
| ICU admission | 3 (3.9) |
| Recurrent CDI | 14 (18.4) |
| Severe CDI | 6 (7.9) |
| Medication for CDI | |
| Metronidazole | 49 (64.5) |
| Vancomycin | 28 (36.8) |
| Treatment duration for CDI, days; mean (range) | 14 (6–52) |
| 30 days mortality | 6 (7.9) |
| 90 days mortality | 11 (14.5) |

Abbreviations: HO-CDI, health care facility-onset *Clostridium difficile* infection; ICU, intensive care unit; yr, years.

62 patients (81.6%) were included in the non-recurrent group. However, none of the factors that we examined were statistically significant in the univariate analysis (Table 2). In contrast, the multivariate analysis revealed that the recurrent group had significant underlying malignant disease (odds ratio: 7.98; 95% confidence interval: 1.22–52.2; $P=0.03$) and were more likely to be hospitalized in the intensive care unit (ICU) (odds ratio: 49.9; 95% confidence interval: 1.01–2470; $P=0.049$).

Discussion

Incidence rate of HO-CDI in Europe has been reported at 4.1 cases per 10,000 patient-days,¹⁶ which is lower than the American incidence rate of 7.8¹⁷ and the Canadian incidence rate of 6.5.¹⁸ However, only a few epidemiological surveys have examined Asian populations. Among these studies,

Table 2 Univariate and multivariate analysis of risk factors for recurrent CDI

| Variables | Recurrent group (N=14) | Non-recurrent group (N=62) | P-value | Multivariate analysis OR (95% CI), P-value |
|--|---------------------------|-------------------------------|---------|---|
| Age; mean (range) | 69 (31–86) | 69.5 (2–95) | 0.33 | |
| Age \geq 65 yr | 9 (64.3) | 41 (66.1) | 1 | |
| Sex, male | 6 (42.9) | 33 (53.2) | 0.56 | |
| Underlying disease | | | | |
| Malignant disease | 9 (64.3) | 32 (51.6) | 0.55 | 7.98 (1.22–52.2), 0.03 |
| Heart disease | 6 (42.9) | 18 (29.0) | 0.35 | |
| Gastrointestinal disease | 3 (21.4) | 8 (12.9) | 0.41 | |
| Transplantation | 1 (7.1) | 3 (4.8) | 0.57 | |
| Medication | | | | |
| Immunosuppressive agents | 4 (28.6) | 14 (22.6) | 0.73 | |
| Chemotherapy | 4 (28.6) | 16 (25.8) | 1 | |
| Gastric acid suppression | | | | |
| Histamine H2 blockers | 4 (28.6) | 9 (14.5) | 0.24 | |
| Proton pump inhibitors | 8 (57.1) | 39 (62.9) | 0.76 | |
| Clinical parameters | | | | |
| Temperature (Celsius); mean (range) | 36.9 (35.9–37.8) | 37.1 (36.2–41.2) | 0.11 | |
| Peripheral white blood cell count (μ L); mean (range) | 7,020 (260–16,450) | 6,315 (70–43,660) | 0.66 | |
| Serum albumin (g/dL); mean (range) | 2.4 (1.9–3.7) | 2.6 (1.9–4.7) | 0.28 | |
| Serum CRP (mg/dL); mean (range) | 5.1 (0.04–10.3) | 3.87 (0.13–24.3) | 0.88 | |
| Duration from admission to diagnosis, days; mean (range) | 31.5 (1–112) | 27.5 (1–155) | 0.68 | |
| ICU admission | 2 (14.3) | 1 (1.6) | 0.085 | 49.9 (1.01–2,470), 0.049 |
| Severe CDI | 1 (7.1) | 5 (8.1) | 1 | |
| Medication for CDI | | | | |
| Metronidazole | 9 (64.3) | 40 (64.5) | 1 | |
| Vancomycin | 5 (35.7) | 22 (37.1) | 1 | |
| Treatment duration for CDI, days; mean (range) | 14 (10–24) | 12 (6–52) | 0.88 | |
| 30 days mortality | 1 (7.1) | 5 (8.1) | 1 | |
| 90 days mortality | 3 (21.4) | 8 (12.9) | 0.41 | |

Abbreviations: CDI, *Clostridium difficile* infection; CI, confidence interval; OR, odds ratio; yr, years; ICU, intensive care unit.

Korea's reported incidence rate was 7.16,¹⁹ Taiwan's was 4.5,²⁰ Singapore's was 2.99,²¹ and a Japanese survey reported an incidence rate of 3.11 cases per 10,000 patient-days.¹⁵ In our study, the HO-CDI incidence rate was 0.8 cases per 10,000 patient-days, and this rate is noticeably lower than those reported in Europe, the US, and other Asian countries. Although EIA detection of CD toxin is rapid, convenient and low-cost (compared to other diagnostic testing methods), the EIA method has been reported to have limited sensitivity and/or specificity. In addition, diagnosis with low sensitivity testing alone could misdiagnose some CDI cases; therefore, changes in the laboratory methods that are used may lead to a higher reported incidence rate. Unfortunately, in Japan, the EIA method is the only commercially available method for CD toxin detection; therefore, diagnoses that were made using only the low sensitivity test may have affected our observed incidence rate. Furthermore, recent data from the US indicate that a \geq 30% increase in the incidence of CDI

may be observed after the adoption of more sensitive nucleic acid amplification tests.²² Therefore, the CDI incidence rate might be underestimated in Japan, as not all diarrheal patients are routinely evaluated; greater awareness and improved surveillance may increase the number of reported CDI cases. Finally, there might also be differences in the CD toxicity that may have influenced our patients' sensitivity to infection as well as CDI-related mortality, as the CDI incidence and mortality varies depending on time and location. For example, there has been a well-documented increase in the incidence of CDI in the US and European countries, which is largely attributed to the spread of the ribotype 027 strains.^{23,24}

In our study, the recurrence rate for HO-CDI was 18.4%, and ICU stay and malignant diseases were the only significant risk factors that were associated with recurrence. In contrast, previous studies have identified various predictors of recurrent CDI, including advanced age, concurrent use of antibiotics, chronic renal insufficiency, elevated white

blood cell count, low serum albumin level, gastric and acid anti-secretory medications, and prolonged hospitalization.^{10–14} Although these factors did not reach statistical significance in our study, it is possible that those previously known risk factors could have coexisted in extended ICU stay and malignant disease. Similar to our results, Salva et al have reported that ICU patients have a higher recurrence rate and risk of recurrence, which were associated with a prolonged ICU stay.²⁵ Furthermore, ICU patients experience multiple antibiotic exposures, due to a high number of nosocomial infections, which include ventilator-associated infections, catheter-related urinary tract infections, and catheter-related bloodstream infections. Patients with malignant diseases are also at risk for acquiring CDI, due to their immunosuppressive state, exposure to broad-spectrum antibiotic treatment and/or chemotherapies. In addition, several chemotherapeutic agents are associated with development of CDI.²⁶ Patients who are undergoing stem cell transplantation are also susceptible to CDI and substantial gastrointestinal damage, due to their conditioning regimens and radiation, graft-versus-host disease in the gastrointestinal tract and prolonged neutropenic state.²⁷ Therefore, the severity of their underlying medical condition and low nutritional state, combined with their disrupted gastrointestinal environment (due to antibiotic, chemotherapy, and radiation therapy), could lead to a higher incidence, recurrence, and complication rate for CDI.

This study has several limitations. First, this was a single-center study with a relatively small number of patients. Although this is one of the few studies to provide recent data regarding the status of CDI in Japan, the data may not generalize to other Japanese hospitals; therefore, additional studies should be conducted in different settings. Second, the retrospective design may have led to an under-diagnosis of CDI cases, and molecular typing was not performed. Since the 1990s, a hypervirulent CD strain has become common in the US and several European countries, and it is associated with a significant risk of recurrence.^{28,29} As our diagnosis was only based on EIA detection of CD toxin, comparison of our data with those from previous studies (which used more sensitive tests) may lead to misinterpretation of our results. In addition, discharged patients were not under close follow-up, which may have led to underestimated recurrent cases.

In conclusion, our study is one of the few surveys to report the current incidence of CDI in Japan, and was the first study to investigate cases of recurrent CDI. Based on our results, ICU hospitalization and malignancy were significant risk factors for recurrence. Therefore, patients with malignancy

and history of ICU hospitalization should be closely monitored for recurrence, and appropriate antimicrobial stewardship is needed to reduce CDI recurrence. However, both ICU hospitalization and malignancy are potentially under immunocompromised situation and would be highly challenging to put appropriate antimicrobial stewardship. Further studies are needed to assess the comprehensive features of CDI, as well as the prevalence of recurrent cases in Japan.

Disclosure

The authors have no conflicts of interest to disclose.

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