Original Article

Characterization and risk factors for recurrence of *Clostridioides (Clostridium) difficile* infection in Japan: A nationwide real-world analysis using a large hospital-based administrative dataset[☆]

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ABSTRACT

Objective: Recurrent *Clostridioides (Clostridium) difficile* infection (rCDI) is common and increases healthcare resource utilization. In this study, we assessed rCDI risk factors using an up-to-date, Japanese national hospital-based database.
Methods: *C. difficile* infection (CDI) episodes, occurring July 2014—June 2017, in patients aged $\geq$18 years were extracted from the database and a nested case-control analysis was performed. Cases were defined as rCDI episodes which required re-initiation of oral vancomycin or oral/intravenous metronidazole treatment within 8 weeks from the start of initial treatment. Cases were matched to 4 non-rCDI episodes at the timing of rCDI occurrence. Adjusted odds ratios (ORs) were estimated using multivariate conditional logistic regression model.
Results: Of 18,246 initial CDI episodes, 3250 (17.8%) had at least one rCDI. Approximately 90% of episodes occurred in inpatients and 65% were treated with metronidazole. Older age (<75 years vs 75—84 years and vs 85 + years) was associated with higher risk of rCDI (OR = 1.27, 95% confidence interval [1.15, 1.41] and 1.45 [1.30, 1.61], respectively). Use of systemic antibiotics (3.16 [2.90, 3.44]), probiotics (2.53 [2.32, 2.77]), chemotherapy (1.28 [1.08, 1.53]), or proton pump inhibitors (PPIs) (1.17 [1.07, 1.28]), and prior CDI history (1.22 [1.03, 1.43]) were also identified as rCDI risk factors. Vancomycin reduced the risk of rCDI compared with metronidazole treatment (0.83 [0.76, 0.91]).
Conclusion: This large, multicenter, nationwide study confirmed that older age, PPIs, antibiotics, probiotics, chemotherapy, and prior CDI history are risk factors for rCDI in Japan. There was a 17% decrease of rCDI risk with vancomycin vs metronidazole treatment.
Clinical trial registration number: N/A.

1. Introduction

Clostridioides (Clostridium) difficile infection (CDI) is a leading cause of hospital-acquired gastrointestinal illness and diarrhea [1—3]. Recurrence of CDI after initial treatment is a major cause of morbidity that places a considerable burden on patients and healthcare resources [4]. It is estimated that 12—64% of patients with CDI will experience at least one recurrent episode [5].

Compared with first episode CDI, recurrent CDI (rCDI) is associated with complications [6,7], as well as longer hospital stays and increased treatment costs [8,9].

Risk factors for rCDI are largely the same as CDI and include older age (>65 years) and the use of broad-spectrum antibiotics and proton pump inhibitors (PPIs) [5,10—13]. These treatments disrupt the gut microbiota, allowing overgrowth of *C. difficile* and subsequent infection [14,15]. The majority of rCDIs are relapses and are more likely to develop in patients with initial mixed CDI (infection with more than one strain) [16].

In Japan, a systematic review of CDI epidemiology has recently been undertaken [17] and new practice guidelines for CDI infection have been released [13]. The systematic review reported rCDI rates ranging from 3.3 to 27.3%, depending on factors such as setting,

population, CDI definition, and detection method [17]. Two of the 55 identified studies assessed risk factors for rCDI [12,18]. Factors found to be associated with increased rCDI risk included malignant disease, intensive care unit (ICU) hospitalization [18], and PPIs [12]. However, the association between initial CDI treatment and recurrence has not yet been reported.

The aim of the present study was to characterize CDI hospitalization with and without recurrence in Japan, and to assess the association between rCDI and identified risk factors using a nationwide, up-to-date hospital-based dataset.

2. Patients and methods

2.1. Study design and patients

This was a retrospective, nested case-control study using a hospital-based administrative database in Japan. Data for in- and outpatients from 342 Diagnosis-Procedure Combination (DPC, flat-fee payment system) hospitals were obtained from Medical Data Vision Co., Ltd. (Tokyo, Japan) [19]. All CDI episodes occurring between 1 July 2014 and 30 June 2017 in patients aged ≥18 years at the time of initial CDI were included. A single patient could have multiple initial CDI episodes during the study period. Patients with CDI episodes within 8 weeks from the start of the study period were excluded.

'Definite' CDI was defined as hospitalization with CDI treatment (oral vancomycin [VCM] or oral/injectable metronidazole [MNZ]) and with a CDI diagnosis code (International Classification of Diseases 10th revision [ICD-10] = A04.7, without suspicion flag) on the month of CDI treatment, plus an enzyme immunoassay (EIA) positive test result obtained ±1 day from initiation of the CDI treatment. However, as EIA test results were only available from nine hospitals, a broader definition of 'probable' CDI was used for the primary cohort: those treated with VCM or MNZ and with diagnosis code in the month of CDI treatment. Patients with a CDI diagnosis, but without prescription record for VCM or MNZ, were included in a secondary cohort and defined as having 'possible' CDI.

The first date of the prescription of VCM or MNZ during the episode was used as the CDI onset date because the diagnosis date was not available in this dataset. CDI treatment must have continued for a minimum of 3 days unless the patient was discharged, transferred or deceased. A treatment episode could have an interval of 1–2 days with no medication: i.e., if the next treatment started within 3 days of the end of prior treatment, it was considered as a continuous treatment (one episode). When no medication was received (Possible CDI cohort), the 'Treatment Initiation Date' in the medical claims was used as the onset date.

Cases were defined as rCDI episodes (not patients): those with CDI diagnosis and re-initiated CDI treatment within 8 weeks (56 days) from the initial CDI episode treatment initiation [20,21]. Where a patient had multiple recurrent episodes, only the first episode was used in the analysis. Controls were defined as initial CDI episode without rCDI (non-rCDI group).

2.2. Risk factors

The following risk factors, based on those identified from the literature, were assessed: older age; CDI treatment (MNZ, VCM); Charlson Comorbidity Index score (for comorbidities recorded during the CDI onset month and during the hospital stay); probiotics and non-CDI treatment (including systemic antibiotics, PPI/H_2 blocker or chemotherapy) from initial CDI treatment completion until rCDI onset for cases, until Day 56 for non-matched controls, or until the matching date for matched controls (details below); prior

hospitalization within 6 months; prior CDI within 6 months (but not 8 weeks); and ICU hospitalization [5,17,22–29].

2.3. Analysis

Study endpoints were the prevalence of pre-defined risk factors in CDI with and without rCDI episodes and the adjusted odds ratios (ORs) for the association between risk factors and rCDI. The median time to rCDI was also assessed.

Cases and controls were matched at the time of rCDI onset to adjust for exposure period [30]. For each rCDI, up to 4 control episodes were selected at random from the group of episodes in the same sex and with the same calendar year/month of initial CDI and which had not developed rCDI at the timing of matching (i.e., days between the start of the initial treatment to rCDI). If no control could be identified, a potential control was sought within ±1 month of initial CDI and within 1 day of the recurrence. Age was categorized into 3 tertiles (<75 years, 75–84 years, and ≥85 years).

Conditional logistic regression analyses of the matched cohort were performed. As a reference, logistic regression was also performed in the non-matched cohort. For the Possible CDI cohort, MNZ vs no treatment and MNZ or VCM vs no treatment for initial CDI were also assessed. ORs with 95% confidence intervals (CIs) were obtained.

3. Results

3.1. Patients and CDI episodes

The Probable cohort (primary cohort) included 18,246 episodes in 16,701 patients and the Possible cohort (secondary cohort) included 22,997 episodes in 20,434 patients (Table 1). Given the small number of episodes in the Definite cohort (n = 146), data from this cohort are not presented.

Overall, the baseline characteristics were similar in the Possible and Probable cohorts. Characterization of CDI episodes in the Probable cohort (Table 2) revealed that inpatients accounted for around 90% of non-rCDI and rCDI episodes. Approximately two thirds of episodes were treated with MNZ and one third with VCM. More than one third of patients with rCDI were in the oldest age category of 85 years or older. PPI use after initial CDI treatment completion was reported for around half of rCDI episodes, and systemic antibiotics and probiotics had each been used in around

Table 1
Disposition of *Clostridioides (Clostridium) difficile* infection episodes and patients.

	Episodes, N (%)	Patients, N (%)
Unique patients with CDI diagnosis codes[a]	–	20,823 (100)
Reason for exclusion		
CDI within 8 weeks from the start of study	–	95 (0.5)
<18 years of age	–	294 (1.4)
Included	22,997 (100)	20,434 (98.1)
Cohorts		
Possible cohort[b]	22,997 (100)	20,434 (98.1)
Probable cohort[c]	18,246 (79.3)	16,701 (80.2)
Definite cohort[d]	146 (0.6)	139 (0.7)

CDI, *Clostridioides (Clostridium) difficile* infection; EIA, enzyme immunoassay; MNZ, metronidazole; VCM, vancomycin.
[a] International Classification of Diseases 10th revision [ICD-10] = A04.7.
[b] Possible CDI cohort: all episodes diagnosed.
[c] Probable CDI cohort (primary cohort): episodes diagnosed and treated with VCM or MNZ.
[d] Definite cohort: episodes diagnosed, positive laboratory (EIA) test, and treated with VCM or MNZ.

Table 2
Baseline characteristics of the Probable Cohort.

	Probable cohort[a]	
	Non-rCDI	rCDI
Episodes, N	14,996	3250
Patients, N	13,942	3157
Sex, N (%)		
Female	6938 (46.3)	1541 (47.4)
Male	8058 (53.7)	1709 (52.6)
Age, median (Q1–Q3)	78 (67–86)	81 (71–87)
Age categories, years, N (%)		
<75	6003 (40.0)	1022 (31.4)
75–84	4535 (30.2)	1074 (33.0)
≥85	4458 (29.7)	1154 (35.5)
Visit, N (%)		
Inpatient	13,328 (88.9)	2989 (92.0)
Outpatient	1668 (11.1)	261 (8.0)
CDI treatment, N (%)		
Oral MNZ[b]	9795 (65.3)	2074 (63.8)
IV MNZ[b]	622 (4.1)	121 (3.7)
Oral VCM[b]	4687 (31.3)	1073 (33.0)
Probiotics[c]	6703 (44.7)	2252 (69.3)
Non-CDI treatment, N (%)[c]		
PPI	6270 (41.8)	1656 (51.0)
H_2 blocker	2014 (13.4)	452 (13.9)
Antibiotics	5621 (37.5)	2109 (64.9)
Chemotherapy	1049 (7.0)	219 (6.7)
Prior hospitalization[d]	4522 (30.2)	1046 (32.2)
CDI history[e]	963 (6.4)	239 (7.4)
Comorbidity score, mean (SD)	2.4 (2.1)	2.6 (2.0)
ICU admission	346 (2.3)	87 (2.7)

CDI, *Clostridioides (Clostridium) difficile* infection; ICU, intensive care unit; MNZ, metronidazole; rCDI, recurrent *Clostridioides difficile* infection; VCM, vancomycin.
  [a] CDI diagnosed ([ICD-10] = A04.7) and treated with VCM or MNZ.
  [b] For initial episode.
  [c] Between initial CDI treatment completion date and treatment re-initiation date.
  [d] Number of discharges within 6 months prior to treatment initiation date for initial episode.
  [e] Between 8 weeks and 6 months prior to treatment initiation date for initial episode.

two thirds of rCDI episodes. These risk factors (older age, PPIs, systemic antibiotics and probiotics) were more prevalent in the rCDI group than the non-rCDI group, whereas CDI treatments, prior hospitalization, ICU admission, and mean comorbidity score were similar between the groups.

Characterization of the Possible CDI (secondary) cohort can be found in the supplementary materials (Table S1). In the Possible cohort, 22.2% of CDI episodes were not treated with MNZ or VCM, 54.8% were treated with MNZ and 25.0% were treated with VCM.

In the Probable cohort, 17.8% of the CDI episodes had rCDI episodes within 8 weeks from the start of prior treatment. In general, the frequency of recurrence increased during the first 3 weeks after the initial episode, then started to decline (Fig. 1). The median time to rCDI was 25 days (interquartile range [IQR], 18–34). Similar results were obtained for the Possible cohort (23.5% of episodes with rCDI; median time to rCDI 30 days [IQR 22, 31]).

3.2. Risk factors for rCDI

In the Probable cohort, multivariate analysis identified older age, probiotics, PPI, antibiotics, chemotherapy, and CDI history (within 6 months, but not within 8 weeks, of initial episode) as risk factors for rCDI (Fig. 2). Of the identified risk factors, use of antibiotics (OR, 3.16; 95% CI, 2.90, 3.44) and probiotics (OR 2.53; 95% CI, 2.32, 2.77) had the strongest positive association with rCDI. These risk factors also showed a strong association with rCDI in the Possible cohort.
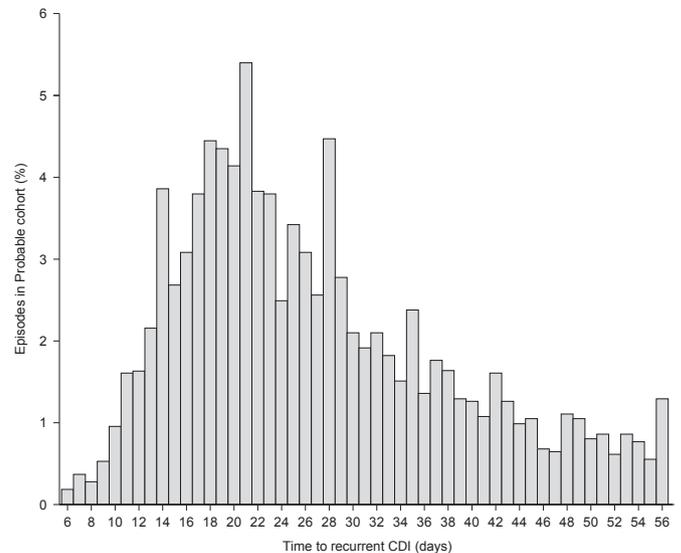

Fig. 1. Time to *Clostridioides (Clostridium) difficile* infection recurrence in the Probable cohort[a]: days between initiation of initial and recurrent *C. difficile* infection treatment. [a]Patients with *Clostridioides (Clostridium) difficile* infection diagnosed ([ICD-10] = A04.7) and treated with vancomycin or metronidazole. CDI, *Clostridioides (Clostridium) difficile* infection; ICD-10, International Classification of Diseases 10th revision.

H_2 blockers, comorbidity score, prior hospitalization (within 6 months), and ICU admission had no association with increased rCDI.

In the Probable cohort, initial treatment with VCM was associated with a decreased risk of rCDI, compared with MNZ (OR, 0.83; 95% CI, 0.76–0.91). In the Possible cohort, CDI treatment, either by VCM or MNZ, reduced the risk of rCDI by 74% (univariate OR, 0.26; 95% CI, 0.24–0.28) compared with no treatment (see supplementary materials, Table S2).

4. Discussion

This study using a large, nationwide hospital-based dataset confirmed that established risk factors for CDI are also risk factors for rCDI in a Japanese setting. Furthermore, we found that initial CDI treatment can prevent rCDI. Of the ten potential risk factors investigated, the following were identified as increasing the risk for rCDI: older age at initial CDI episode; use of probiotics, antibiotics, PPIs or chemotherapy; and prior CDI within 6 months. Treatment with VCM was associated with a reduced rCDI risk compared with MNZ. Comorbidity score, use of H_2 blockers, prior hospitalization, and ICU admission had no impact on rCDI risk.

In the Probable cohort, 18% of CDI episodes had rCDI, which was within the range reported by a recent Japanese systematic review (3–27%) [17]. Although inpatients represented 90% of the episodes in our study, the rate of recurrence is similar to that of a study using a U.S. veterans database (16%), where one third of the cohort were outpatients [31].

As in previous studies [5], older age and antibiotic use were identified as robust risk factors for rCDI in our study. The association of PPI use with rCDI (1.17; 95% CI, 1.07–1.28) was also consistent with a recent systematic review of studies in PPI-treated patients (pooled OR 1.73; 95% CI, 1.39–2.15; p = 0.02) [12]. These risk factors were very common among total CDI hospitalizations (61.5% were 75 years or older, 42.4% had been treated with antibiotics and 43.4% with PPIs).

No previous studies had investigated the association between initial CDI treatment and recurrence in Japan [17]. In the present study, CDI treatment (VCM or MNZ) decreased the risk of rCDI by
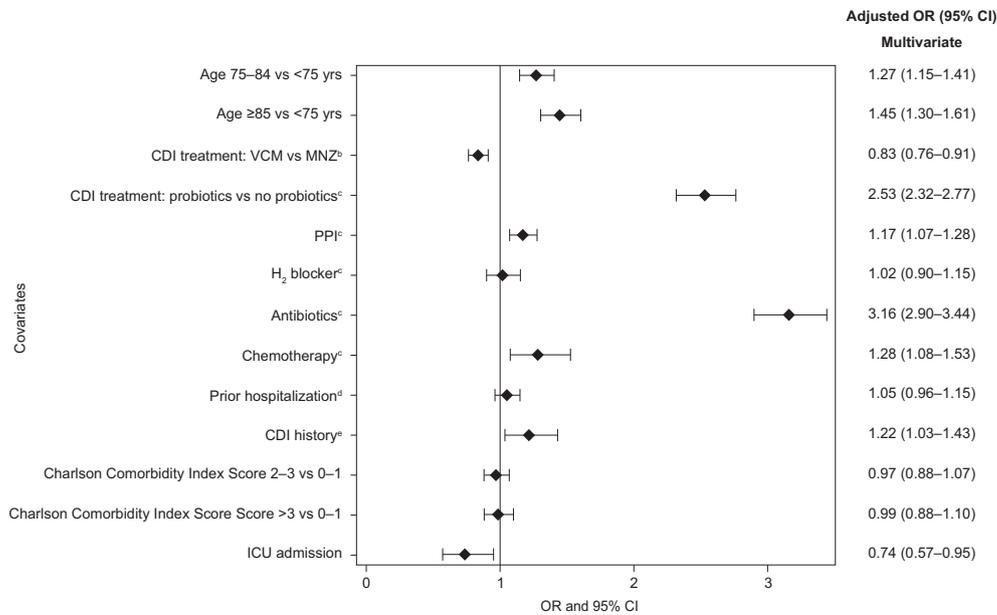
Fig. 2. Forest plot (multivariate analysis) and adjusted odds ratios for recurrent *Clostridioides (Clostridium) difficile* infection in the Probable cohort[a]. CDI, *Clostridioides (Clostridium) difficile* infection; CI, confidence interval; ICD-10, International Classification of Diseases 10th revision; ICU, intensive care unit; MNZ, metronidazole; PPI, proton pump inhibitor; OR, odds ratio; VCM, vancomycin. [a]CDI diagnosed ([ICD-10] = A04.7) and treated with VCM or MNZ. [b]For initial episode. [c]Between initial CDI treatment completion date and treatment re-initiation date. [d]Number of discharges within 6 months prior to treatment initiation date for initial episode. [e]Between 8 weeks and 6 months prior to treatment initiation date for initial episode.

74% vs no CDI treatment. Furthermore, VCM treatment decreased the risk of rCDI by 17% vs MNZ. This is in contrast to a recent study in the U.S., which found no difference in recurrence rates among patients treated with VCM and MNZ [31].

In Japan, risk factors identified previously for initial and/or recurrent CDI included malignant disease, use of PPIs, and ICU hospitalization [12,18]. Matsumoto et al. found that, in addition to antibiotics, initiation of treatment with acid-suppressive agents, anticancer drugs or steroids shortly after completing CDI therapy was also associated with a greater risk of CDI recurrence [26]. In our study, ICU admission was not associated with rCDI risk, but chemotherapy was marginally associated with rCDI risk, as was PPI use after adjusting for exposure period. Malignant disease was not assessed as an independent risk factor, but we found no difference in baseline incidence between rCDI and CDI episodes in the crude analysis (23.4% versus 24.6%, respectively).

Probiotics were included in our analysis in order to investigate their role as a protective factor for rCDI. While the degree of protective effect of probiotics to reduce CDI varies [32,33], an elevated risk of rCDI in our analyses was likely to reflect the protopathic bias, a well-known source of bias for case-control studies where a medication is prescribed for early disease, prior to a formal diagnosis [34]. In this situation, patients at higher risk of rCDI might be more likely to be prescribed probiotics. Application of lag-time into exposure definitions can help control for protopathic bias [35], but we used no such methodology, which therefore constitutes a limitation of the current study.

The neutral impact of comorbidities might be surprising given the increased risk for complicated CDI, which is strongly associated with rCDI [5]. In this study, because diagnosis dates were not available, complications after CDI were not assessed separately from baseline comorbidities, and this may warrant investigation in future studies. Furthermore, a previous evaluation of the same type of administrative data revealed that, while the specificity of diagnosis records in identifying the Charlson diseases was high, the sensitivity was low and varied across conditions [36]. This potential under-reporting of disease is another limitation of the present study.

A further limitation is that the findings from this database may not be generalizable to the entire Japanese CDI population. Based on the Statistics of Medical Care Activities in Public Health Insurance (2017), there were 2,265,933 hospitalizations in June 2017 in Japan. This database captured 292,260 hospitalizations (12.9%) during the same period. Although this dataset has been widely used in Japan [19,37–40] and is sufficiently large to assess hospitalized patients in Japan, our dataset includes only DPC hospitals which are largely acute care facilities. No non-DPC hospital or long-term care facilities were included, which will affect generalizability to the entire Japanese CDI population. Indeed, differences in CDI treatment have been observed between DPC and non DPC-implemented hospitals (MNZ treatment is more frequent in DPC hospitals while VCM is predominant in non-DPC hospitals) [41]. All episodes that were diagnosed and treated were used for the primary analysis, knowing that not all CDI cases were treated with VCM or MNZ: for example, some episodes may be resolved by ceasing antibiotic treatment. Although the baseline characteristics and results from the crude analysis were similar to those in the Possible cohort, which also includes non-treated CDI, our findings may not reflect the representative cases in Japan.

The use of this administrative database also poses challenges with regard to CDI diagnosis. In the majority of CDI episodes, laboratory confirmation of CDI was unknown; such episodes may consequently be misclassified. As our definition for CDI did not include confirmed diarrhea symptoms, some asymptomatic CDI episodes may have been included in the cohort. However, the sensitivity of the diagnosis code-based case definition was low (51.2%), meaning that only half of the CDI test-positive cases had a diagnosis of CDI (ICD-10 = A04.7). We therefore considered that the diagnosis code and treatment were given only on the basis of clinical need. rCDI episodes may also be misclassified if the initial CDI episode was undiagnosed in the panel hospitals or else diagnosed out of the panel hospital. rCDI rate may thus be underestimated as a result of the missing rCDI episodes. Alternatively, despite allowing 1–2 days of treatment holiday, it is still possible that

some rCDI might be persistent diarrhea caused by the initial CDI episode, leading to overestimation of rCDI.

A notable strength of our research is that it is the largest study to date assessing rCDI risk factors in Japan, where previous evidence was sparse. To minimize the burden of rCDI in Japan, additional investigation of the risk for rCDI is warranted, with further characterization of episodes and outcomes in the inpatient, outpatient, acute, and long-term care settings.

5. Conclusion

In a large, current, hospital-based dataset in Japan, older age, prior CDI within 6 months, and use of probiotics, antibiotics, PPIs, and chemotherapy were identified as risk factors for rCDI. Treatment with VCM, compared with MNZ, was associated with a significantly reduced risk of rCDI.

Conflicts of interest

TK and TS are employees of Astellas Pharma, Inc.
RS is an employee of Astellas Pharma B.V.

Data sharing

Access to anonymized individual participant level data will not be provided for this trial as it meets one or more of the exceptions described on www.clinicalstudydatarequest.com under "Sponsor Specific Details for Astellas."

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2019.03.011.

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