Presentation Number: 39658

Incidence and Mortality Associated with *Clostridium difficile* Infection at a Japanese Tertiary Care Center

Hitoshi Honda MD[1, 2], Akinori Yamazaki PharmD[2], Yumiko Sato RN CIC[2], Erik R Dubberke MD MSPH[3]
Department of Infection Prevention, Tokyo Metropolitan Tama Medical Center, Japan[1]
Department of Infection Prevention, Teine Keijinkai Medical Center, Sapporo, Japan[2]
Division of Infectious Diseases, Department of Internal Medicine, Washington University School of Medicine, St. Louis, MO[3]

Contact : Hitoshi Honda MD. Tokyo Metropolitan Tama Medical Center, Fuchu, Tokyo, Japan
Tel:+81-42-323-5111, Fax: +81-42-323-
hondah@hotmail.com

REVISED ABSTRACT

Background: Although increases in *Clostridium difficile* infection (CDI) incidence and severity have been observed in numerous countries, the incidence of CDI in Japan remains unclear. The goal of this study was to determine the incidence and outcomes of CDI at a Japanese tertiary care center.

Methods: Retrospective cohort study was performed at a 550-bed, tertiary care, academic centre in Sapporo, Japan from September 2010 through August 2012. CDI cases were categorized per internationally recognized surveillance definitions. Data on demographic characteristics, medication exposures, CDI presentation, and CDI treatment were collected on all CDI cases. Factors associated with 30-day all-cause mortality after the completion of CDI treatment were also investigated.

Results: There were 32,296 admissions and 350,074 patient-days from 22,863 patients during the study period; 126 patients were diagnosed with CDI. The median age of CDI case patients was 78 years. Healthcare facility-onset (HO) CDI accounted for 85% of CDI cases, with a HO-CDI incidence of 3.11 cases per 10,000 patient-days. Three patients underwent surgery for CDI (2.4%) and 19 patients (15%) died within a 30 days of completing CDI treatment. Factors independently associated with mortality were diabetes mellitus and shock at time of CDI diagnosis.

Conclusions: The CDI incidence was lower than that typically reported from North American hospitals, but the proportion of patients requiring surgical therapy and dying within 30 days of CDI in non-outbreak settings was higher. More study is needed to determine why CDI incidence is low relative to CDI-associated outcomes in Japan.

INTRODUCTION

- Increases in the incidence and severity of CDI have been observed in various countries including the United States, Canada, and several European countries.
- The incidence of CDI has disproportionately increased among the elderly, along with the associated CDI-attributable mortality and economic burden.
- Despite the importance of understanding the incidence and severity of CDI in the vulnerable elderly population, data are lacking on current trends of CDI in Japan.

METHODS

Study Design & Setting:
A retrospective cohort study at Teine Keijnkai Medical Center, 551-bed tertiary care center in Sapporo, Japan from from September 2010 through August 2012.

Identification of Study Patients:
CDI case patients were defined as patients with diarrhea and a positive stool toxin assay (either *C diff* Quick Chek complete®; Techlab, Blacksburg, VA/Alere Medical Co., Ltd., Tokyo, Japan or Xpect® *C. difficile* Toxin A/B; Remel, Renexa, KS/Kanto Chemical Co. Inc Tokyo, Japan) or the presence of pseudomembranous colitis on proctoscopy or colonoscopy.

Definition:
Cases of CDI were categorized according to published definitions with some modification. Healthcare facility (HCF)-onset (HO) CDI was defined as symptom onset > 3 days from admission. Community-onset (CO) CDI was defined as symptom onset prior to admission or ≤ 3 days from admission. CO CDI was further categorized as CO HCF-associated, attributable to the study hospital (CDI onset within 4 weeks of discharge from the study hospital with last inpatient HCF exposure from the study hospital), CO HCF-associated, not attributable to the study hospital (CDI onset within 4 weeks of discharge from a HCF with last inpatient HCF exposure not the study hospital), indeterminate CDI (CDI onset 5 to 12 weeks since discharge from last inpatient HCF exposure), and community associated (CA) CDI (CDI onset >12 weeks from last inpatient HCF exposure).

Incidence of CDI and Testing densities:
Denominator information to describe CDI rate was also adapted from the interim surveillance definition. Incidence of HO CDI and CO HCF associated, attributable to the study hospital was expressed per 10,000 patient-days, whereas the remaining cases of CO CDI incidence was expressed per 1,000 hospital-admissions. Testing densities were calculated by the number of toxin assays tested per 10,000 patient-days and the number of test performed per patient during the study period.

METHODS (cont)

Data Collection:
Data on demographic characteristics, medication exposures, CDI presentation, and CDI treatment were collected on all CDI cases. Factors associated with 30-day all-cause mortality after the completion of CDI treatment were also investigated.

Statistics
CDI rates (i.e., cases per 10,000 patient-days or per 1,000 admission as appropriate) during the study period were calculated for each CDI definition. Univariate comparisons among categorical variables were performed using the chi-square test or Fisher's exact test as appropriate to determine variables associated with mortality. Comparisons among continuous independent variables were performed using the Mann–Whitney U test. We considered variables with statistical significance of P value of <.05 in a univariate analysis as a candidate variable including in a forward stepwise multivariate logistic regression model. Variables were retained in the final model if P value was less than .05. Due to collinearity between the definition for severe CDI used and the individual components use to categorize patients as having severe CDI, only the individual components were included in the model building. All statistical analyses were performed using SPSS version 21 (IBM, Armonk, NY, USA).

RESULTS

Table 1. Demographic characteristics of 126 patients with *Clostridium difficile* infection

Patient characteristics	n (%)
Demographic data	
Male sex	76 (60)
Age; median (range)	78 (23-93)
Length of hospital stay; median (range)	42 (1-559)
Congestive heart failure	30 (24)
COPD	14 (11)
Malignancy	46 (37)
Peptic ulcer disease	31 (25)
Cerebrovascular accident	34 (27)
Diabetes mellitus	28 (22)
Hypertension	70 (56)
Collagen vascular diseases	5 (4)
Abdominal surgery prior to developing CDI	42 (33)
Hematologic malignancy	17 (14)
Mechanical ventilation prior to CDI	36 (29)
ICU admission prior to CDI	44 (35)
Medication exposures 2 month prior to CDI	
Steroid use	27 (21)
Chemotherapy	10 (8)
Histamine 2 blocker	22 (18)
Proton pump inhibitor	82 (65)
Laxative	40 (32)
Any antimicrobials exposure	120 (95)
Aminobenzyl Penicillin	15 (12)
Fluoroquinolone	22 (18)
Carbapenems	25 (20)
1st generation cephalosporin	17 (14)
2nd generation cephalosporin	6 (5)
Cefamycin	11 (9)
3rd generation cephalosporin	46 (37)
4th generation cephalosporin	23 (18)
Clindamycin	4 (3)
Vancomycin (intravenous)	27 (21)
BL/beta lactamase inhibitor	44 (35)

Clinical data	n (%)
Surveillance classification	
HO-CDI	109 (87)
CO-HCFA CDI	12 (10)
CA-CDI	4 (3)
Indeterminate CDI	1 (1)
Colonoscopy performed	12 (10)
Presence of pseudomembranous colitis	5 (4)
Acute kidney injury at the diagnosis of CDI	22 (18)
Required hemodialysis after CDI diagnosis	5 (4)
Shock at the diagnosis of CDI	14 (11)
Leukocytosis >15,000 cells / mm3	34 (27)
Temperature > 38.3 Celsius	30 (24)
Severe CDI	65 (52)
Outcome	
Cure (no recurrence > 30 days)	92 (73)
Death < 30 days	19 (15)
Recurrence < 30 days	8 (6)
Unknown for recurrence	7 (6)
Medical management	
Metronidazole 500 mg PO q8h	90 (71)
Vancomycin 125 mg PO q6h	8 (6)
Vancomycin 500 mg PO q6h	10 (9)
Metronidazole PO and vancomycin PO	3 (3)
Metronidazole PO and vancomycin PR	1 (1)
Vancomycin PO and vancomycin PR	2 (2)
No medical treatment	12 (10)
Surgical treatment required (colectomy or diverting loop ileostomy)	3 (2)
A 30-day all-cause mortality after the completion of CDI therapy	19 (15)

NOTE. COPD; chronic obstructive pulmonary disease, BL; beta lactams, HO; healthcare onset, CO-HCFA; community onset-healthcare facility associated, CA; community acquired.

RESULTS

- There were 32,296 admissions with 350,074 patient-days from 22,863 patients at the study institution during the 2-year study period.
- A total of 126 patients with CDI were identified.
- The median age of patients with CDI was 78.
- Testing densities for *C. difficile* were 44 patients tested per 10,000 patient-days.
- Healthcare-onset CDI was the most common form of CDI (87%), with the incidence density of CDI of 3.11 cases per 10,000 patient-days
- A 30-day all-cause mortality was approximately 15% (19/126) and 2.4% (3/126) of patients underwent surgery for CDI.

RESULTS

Table 2. Predictors of mortality 30 days or less after completing treatment of *Clostridium difficile* infection for 126 patients

Variable	Univariate analysis			Adjusted odds ratio (95% CI)
	Death (n=19)	Survived (n=107)	P	
Diabetes mellitus	8 (42.1)	20 (18.7)	.02	4.71 (1.46-15.18)
Fluoroquinolone use	6 (31.6)	16 (15.0)	.08	
AKI at the diagnosis of CDI	7 (36.8)	15 (14.0)	.02	
Shock at the diagnosis of CDI	7 (36.8)	7 (6.5)	<.001	11.82 (3.15-44.29)
Transfer to the ICU due to CDI	4 (21.1)	8 (7.5)	.08	
Leukocytosis >15,000 cells / mm3	9 (47.4)	25 (23.4)	.03	
Albumin <2.5 mg/dL at diagnosis of CDI	10 (52.6)	27 (25.2)	.02	
Severe CDI*	16 (84.2)	49 (45.8)	.002	

NOTE. CDI; *clostridium difficile* infection, AKI; acute kidny injury, ICU; intensive care units, CI; confidence Interval. * Severe CDI was defined by the criteria by Zar et al [*Clin Infect Dis*. 2007;45(3):302–307].

CONCLUSIONS

- Very few studies have investigated the incidence of CDI using surveillance definition due to the lack of national surveillance system in Japan.
- The CDI incidence was lower than that typically reported from North American hospitals, but the proportion of patients requiring surgical therapy and dying within 30 days of CDI in non-outbreak settings was higher.
- Factors associated with mortality in patients with CDI included underlying illness and severity of CDI at presentation.
- A major limitation was the lack of culture and molecular typing data. Given the relatively low sensitivity of *C. difficile* toxin tests, certain number of CDI cases were likely overlooked.
- More study is needed to determine why CDI incidence is low relative to CDI-associated outcomes in Japan.