Journal of Infectious Diseases and Therapy

Hirai et al., J Infect Dis Ther 2017, 5:5
DOI: 10.4172/2332-0877.1000333

Research Article OMICS International

Nosocomial *Clostridium difficile* Infection among Patients Over 90 Years Old

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Received date: August 25, 2017; **Accepted date:** September 05, 2017; **Published date:** September 09, 2017

Abstract

Aim: Ageing population trends indicate that the median life expectancy in Japan is increasing. *Clostridium difficile* infection (CDI) can be a fatal nosocomial infection among the geriatric population. We examined clinical outcome and risk factors associated with death due to CDI among patients >90 years old.

Methods: This retrospective observational study was performed to demonstrate the clinical characteristics of Patients >90 years who developed CDI between April 2010 and March 2015 at Tama-Hokubu Medical Center (a 344-bed community tertiary care hospital; average age of inpatients: 72 years). Diagnosis of CDI was confirmed *via* an enzyme-linked immunosorbent assay using stool sample. Multivariate analysis was performed to determine the independent risk factors associated with death.

Results: Twenty-nine patients with CDI confirmed were identified. The mean age was 93 (90–100) years and 37.9% were women. Patients presented with hypertension (37.9%) and diabetes (33%) as underlying diseases, and 93.1% were admitted from long-term care facilities. The median period from admission to onset of CDI was 14 (2–73) days. The average episodes of diarrhea was 3.96 (1 to 10) times per day. The overall 90-day mortality rate was 34.5%. Multivariate analysis revealed that arrhythmia followed by onset of CDI (Odds Ratio, 8.0; 95% Confidence Interval, 1.37–46.8; P=0.021) was an independent risk factor associated with death.

Conclusions: Arrhythmia followed by onset of CDI is a risk factor for death. Strict clinical management, including continuous monitoring of electrolyte and fluid balance and careful observation of patients >90 years old is crucial.

Keywords: *Clostridium difficile* infection; Geriatric population; Developing arrhythmia

Introduction

Clostridium difficile infection (CDI) is a fatal nosocomial infection among the geriatric population. In the United States, the mortality rate was reported to steadily increase, from 5.7 per million in 1999 to 23.7 per million in 2004. The median age of these deceased patients was 82 years [1]. In the United Kingdom, 81% of all patients with CDI were >65 years of age and 30% were >80 years [2]. Aging population trends indicate that the median life expectancy in Japan is increasing (80 years old in male and 82 years old in female). Patients >90 years of age admitted to tertiary care hospitals generally require intensive medical care. To date, CDI patients over 65 years of age have been described en bloc as a "geriatric population" [2-4]. The clinical characteristics of CDI within this group show further variation according to age sub-groups [2]. We aimed to demonstrate the clinical characteristics including risk factor associated with death of CDI among patients over >90 years of age in a tertiary care hospital.

Methods

This retrospective study reviewed the medical records of patients at Tama-Hokubu Medical Centre (a 344-bed community tertiary care hospital) between April 2010 and March 2015. Nosocomial CDI was defined as a positive enzyme-linked immunosorbent assay (ELISA; TOX A/B QUICK (from April 2000 to November 2011), C.DIFF QUICK CHECK COMPLETE, (from November 2011 to March 2015), Alere, Florida, USA) result using stool samples obtained >48 h after admission. Patients >90 years of age who developed nosocomial CDI were included in the study. Data recorded included age, sex, underlying diseases, cause of admission, initial antimicrobial agents used, Proton Pump Inhibitors (PPI) used, median time from admission to onset of CDI (days), daily episodes of diarrhea (times per day) at the onset of CDI, treatment of CDI, development of arrhythmia followed by CDI, vital signs at diagnosis of CDI, and overall mortality within 90 days of admission. Laboratory data, including white blood cell count (WBC) and serum C-reactive protein (CRP), brain natriuretic peptide (BNP), albumin, and electrolyte were also recorded. Continuous data were compared using the t test and categorical data were compared using Fisher's exact tests. Multivariate analysis was performed to determine the independent risk factors associated with death using forward stepwise logistic regression. All variables with P<0.1 in the univariate analysis were included in the multivariate model, with the level of significance set at P<0.05 Statistical analyses were performed using R version 3.3.1 for Microsoft Windows 10. The study protocol was approved by the Ethics Committee at Tama-Hokubu Medical Centre.

Results

Twenty-nine patients with CDI were included in the study (Table 1). The mean age was 93 (90–100) years, and 11 (37.9%) patients were women. Patients presented with the following underlying conditions: hypertension (37.9%); diabetes (33%); chronic heart failure (27.5%), renal impairment (24.1%); orthopedic diseases, such as femoral neck fracture (20.7%); dementia (13.8%); ischemic heart diseases (13.8%), and malignancy (12.2%). No one had cardiovascular surgery, coronary intervention therapy, and Cardiac Implanted Electric Devices (CIED) was found among study population. Out of 29 patients, 27 (93.1%) were transferred from long-term care facilities (LTCF) or nursing homes (NH) and 6.9% were admitted from home. All of case had been admitted LTCF. The cause of admission in 58.6% of patients was community-acquired or aspiration pneumonia. Initial treatment consisted of penicillin mono therapy or in combination with beta-lactamase inhibitors (58.6%) (ampicillin-sulbactam, piperacillin-tazobactam) and carbapenems (20.7%). Thus, 65.5% of patients were administered antimicrobials to which anaerobic organisms are generally susceptible. No one took oral or intravenous fluoroquinolone during or before admission as far as description of medical records. And 48.3% of patients took PPI. The initial clinical presentation was watery diarrhea (100% of cases). The median period from admission to onset of CDI was 14 (2–73) days. The average number of episodes of diarrhea was 3.96 (1 to 10) per day at the day of onset CDI. Vital signs at diagnosis of CDI were as follows: median body temperature, 36.3 (35.8-38.1) °C, with 58.6% of patients having a body temperature <37 °C; median heart rate was 79 (52-108) beats per minute. A new episode of arrhythmia (paroxysmal atrial fibrillation (n=5), non-sustained ventricular tachycardia (n=1), incomplete right bundle branch block (n=1), complete atrial ventricle block (n=1), or ventricular premature complexes (n=1)) was followed by CDI in 31.3% of patients. The median days from onset CDI to developing arrhythmia was 4 (1-11) days. All cases demonstrated positive ELISA results (TOX A/B QUICK until November, 2011, C.DIFF QUICK CHECK COMPLETE, Alere, Florida, USA). Laboratory test results were as follows: median WBC count, 8700 (3500–24500) cells/μL; median CRP level, 2.91 (0.2–21.2) mg/dL; median BNP level (n=9), 899.7 (66.7–2777.3) pg/mL; and blood urine nitrogen level, 20.1 (3.2–98.2) mg/dL. Oral metronidazole was administered in 82.3% of patients while oral vancomycin was administered in 6.9% of patients. Overall mortality rate was 34.5% over 90 days. The median time from onset to death was 20.5 (4–55) days and 60% of deaths were associated with serum electrolyte imbalances, such as hyponatremia and hypopotassemia. In the univariate analysis, no significant difference in the clinical characteristics of the participants was observed between survivors and deceased patients. Multivariate analysis indicated that arrhythmia followed by onset of CDI (Odds Ratio (OR), 8.0; 95% Confidence Interval (CI), 1.37–46.8; P=.021) was an independent risk factor for death (Table 1). No recurrent cases of CDI were found among the study population.

	Overall (n=29)	Survived (n=19)	Died (n=10)	Univariate Analyses	Multivariate Analyses OR (95%CI; p value)
Median Age (years old)	93 (90 - 100)				
Gender (male)	11 (37.9%)	7	3	1	
Underlying Diseases					
Hypertension	11 (37.9%)	7	4	1	
Renal Impairment	7 (24.1%)	3	4	0.193	
Dementia	4 (13.8%)	3	1	1	
Malignancy	6 (20.7%)	3	3	0.633	
Diabetes	1 (3.3%)	0	1	0.345	
Proton Pump Inhibitor Use	14 (48.3%)	9	5	1	
Heart Failure	8 (27.5%)	4	4	0.445	
Ischemic Heart Disease	4 (13.8%)	2	2	0.592	
Cause of Admission					
Pneumonia	17 (58.6%)	10	7	0.449	
Orthopedic Diseases	6 (20.7%)	4	2	1	
Colorectal Diseases	4 (13.8%)	4	0	0.268	
Others	6 (20.7%)	6	0	0.0676	
Initial Antimicrobial Used					
PC +/- BLI	17 (58.6%)				

Carbapenems	6 (20.7%)				
Susceptible to Anaerobe	19 (65.5%)	12	7	1	
CDI					
From Admission To Onset Of CDI (days)	14 (2-73)	14 (2-73)	19 (8-54)	0.679	
Diarrhea (times per day) at diagnosis	3.96 (1- 10)	4 (1-10)	2 (1-5)	0.0555	
Oral MNZ Treatment	24 (82.3%)	15	9	0.633	
Oral VCM **Treatment**	2 (6.9%)	0	2	0.111	
At Diagnosis Of CDI					
Median Body Temperature ()	36.3 (35.8-38.1)				
Body Temperature<37	17 (58.6%)	9	8	0.126	
Median BP (mmHg)	120 (91-172)	120 (96-168)	116.5 (91-172)	0.765	
Heart Rate (/min.)	79 (52-105)	80 (52-105)	74 (60-108)	0.945	
Heart Rate>80 (/min.)	14 (48.3%)	10	4	0.7	
WBC (× 10^3/μL)*	8.7 (3.5-24.5)	8.6 (4.6-25.0)	9.4 (3.5-16.9)	1	
WBC>8000 (/μL)	20 (69%)	14	6	1	
Serum Albumin*	2.8 (1.7-4.4)	2.9 (2.1-4.4)	2.7 (1.7-3.3)	0.25	
CRP (mg/dL)*	2.91 (0.2-21.2)	2.91 (0.4-21.25)	3.22 (0.02-13)	0.636	
CRP>10 (mg/dL)	5 (17.2%)	3	2	1	
BNP (pg/mL)*	899.7 (66.7-3136)	450 (66.7-3136)	1867.5 (771-2793)	0.286	
BNP>500 (pg/mL)	5 (17.2%)	1	4	0.0476	OR 9.26 (0.72-119; p=0.087)
Serum BUN (mg/dL)	20.1 (3.2-98.2)	14.9 (3.2-59.2)	38.05 (7.7-98)	0.119	
BUN>20 (mg/dL)	15 (51.7%)	8	7	0.245	
Hyponatremia (Na<135 mEq/L)	10 (34.5%)	7	3	1	
Hypopotassemia (K<3.5 mEq/L)	7 (24.1%)	3	4	0.193	OR 5.32 (0.59-47.6; p=0.135)
A New Arrhythmia Followed By CDI	9 (31%)	3	6	0.0317	OR 8.0 (1.37-46.8; p=0.021)
Days From Onset CDI to Arrhythmia*	4 (1-11)	3.5 (1-11)	4 (2-9)	1	
Overall Mortality In 90 days	10 (34.5%)				
Days From Onset CDI To Death*	20.5 (4-55)				

CDI: *Clostridium difficile* Infection; BNP: Brain Natriuretic Peptide; BLI: Beta-Lactamase Inhibitor; PC: Penicillin; BP: Blood Pressure; MNZ: Metronidazole; VCM: Vancomycin; WBC: White Blood Cell Count; CRP: C-reactive Protein; BUN: Blood Urine Nitrogen; CI: Confidence Interval; OR: Odds Ratio; *: median

Table 1: Characteristics of patients over 90 years of age with CDI, Univariate/ Multivariate analyses.

Discussion

CDI can be fatal among elderly patients. The median life expectancy is reaching 90 years (80 years in male and 82 years in female) in Japan. The incidence of exposure to antibiotics among elderly people is increasing, due to community-acquired or nosocomial infections, such as pneumonia. The extreme geriatric population (patients >90 years old) [3] may have a higher incidence of developing CDI compared to

the younger geriatric population [2]. Out of the total study population, 93% of patients were transferred to our hospital from a LTCF or NH. The incidence of CDI in NHs ranged 0.52–0.67 per 10,000 resident care days [5]. Although the carriage rate of *C. difficile* among residents at LTCF or NHs remains unclear, health care workers and patients residing in LTCF or NHs may be reservoirs for *C. difficile* [6,7]. Antibiotic stewardship programs (ASP) have shown a significant protective effect (pooled risk ratio 0.48; 95% CI 0.38-0.62) on CDI in recent meta-analyses [8,9]. Therefore, strengthening ASP and promoting strict infection control can reduce the incidence of CDI in the elderly population in NHs and LTCF. In addition, the economic burden of CDI in developed countries, including the United States and Canada [10,11] have been reported. Of note, the median cost of pharmacological treatment for patient with recurrent CDI while hospitalization was much higher than that of primary CDI (US$140 *vs.* US$60, P=0.0013) [12].

Ticinesi et al. [13] studied 505 elderly (≥ 65 years old) hospitalized patients and found that the incidence of developing CDI was 8.5% (43/505) and that a Cumulative Illness Rating Scale (CIRS) score ≥ 17 (OR 5.07, 95% CI; 1.28-20.14, P=0.02) and antibacterial therapy (OR 2.61, 95% CI; 1.21-5.64, P=0.01) are independent risk factors associated with developing CDI in the multivariate logistic regression model. The CIRS score is focused on geriatric population and is a risk factor for CDI comorbidity and mortality. Where CDI is suspected among geriatric patients, CIRS may be a useful tool for clinical diagnosis and appropriate infection control management. The majority of hospitalized patients with CDI were treated with antibiotics for infectious diseases, such as pneumonia. Predict to a complicated clinical course in CDI was discussed. 12% among 395 CDI hospitalized patients had a complicated course. Age over 85 years (OR 4.96, 95% CI; 1.4-17.6, P= 0.01) is a significant and strong independent predictor of CDI in multivariable analyses [14]. Thus extreme age, such as over 90 years old, is an important risk factor for CDI [15] and for developing complications or recurrence of CDI [12].

A study involving 72 patients (mean age 81 years old) at 4 NHs found that 69% of patients developed CDI within 30 days (10.5 ± 2.5 days) of admission to hospital, corroborating our results [5]. Generally, increased WBC and fever (>38) have been reported in patients with CDI. However, our results showed that only 41.4% of 90 year old patients developed a body temperature >37 and 31% had elevated WBC (>8000/μL). Therefore, except for diarrhea, clinical symptoms among elderly patients with CDI are atypical, compared to general population. Furthermore, difficulty in defecation, such as chronic constipation and diarrhea, are common in geriatric patients. The incidence of CDI among elderly patients may be underestimated because of this atypical presentation [16] and, as a result, in general practice, only 40% of all cases of CDI were detected. Multivariable analysis revealed that use of antibiotics (OR, 6.88; 95% CI, 3.97-11.9; P<0.01) and cancer (OR, 4.04; 95% CI, 1.47–11.1; P<0.01), which were recognized as general risk factor, were strongly associated with CDI. Age ≥ 50 years old was not a significant risk factor (OR, 1.41; 95% CI, 0.79–2.52; P<0.25) [17].

Our results showed a mortality rate of 34.5% among patients >90 years old with CDI. This is comparable to the reported mortality rate among patients with CDI >65 years [18]. Generally, age >65 years in patients with CDI was considered a risk factor associated with death [19]. However, to date, risk factors other than age, hyper-virulent *Clostridium difficile* strain, antibiotic use, or PPI use [20] remain unclear. Approximately a half of study population took PPI. The use of PPI may affect to develop or recurrence of CDI20. Similar to ASP, appropriate use of PPI, if I was to say 'PPI stewardship', should be considered to prevent CDI.

This is the first report to show that arrhythmia followed by onset of CDI is an independent risk factor associated with death. A previous study involving patients >80 years of age, reported an association between coronary artery disease (OR 5.5, 95% CI; 1.2-23, P=0.02) and death in 90-days among patients [21]. This may corroborate our results. Dehydration, with serum electrolyte imbalance, caused by CDI, can strongly affect the development of a new episode of arrhythmia. Therefore, intensive general care, including strict management of fluid and electrolyte balance, is required for *Clostridium difficile*-infected patients aged >90 years.

This study has four limitations. First, it was an observational retrospective study with only 29 patients. Further multi-institutional studies are required. Second, according to guidelines, the indication for ELISA test for stool samples is generally recognized that patients develop diarrhea (≥ 3 times per day) with Bristol score more ≥ 5. However, geriatric patients with CDI develop atypical clinical symptoms. Thus, patients with diarrhea ≥ 1 time per day at ELISA test were also included our study. Third, hyper-virulent *Clostridium difficile* strains (i.e. B1/NAP1/027), have recently spread across North America; however, these are extremely rare in Japan. To detect these strains was not performed in this study. Finally, some of arrhythmias followed by onset of CDI may be a simple result of altered electrolyte and fluid balance in combined with underlying heart diseases of patients.

In conclusion, this study has shown that strict and continuous clinical management, including management of electrolyte and fluid balance, and careful observation of patients >90 years with CDI is crucial. With the current ageing population trend, further investigations to establish infection control measures for LTCF, NHs, and home environments, are required.

Acknowledgements

The results of this study were presented as a poster (Abstract number P1103) at the European Conference of Clinical Microbiology and Infectious Diseases (ECCMID) 2016, Amsterdam, Netherlands, April 9-12, 2016. The authors thank for Mrs. Shinobu Tase, and Dr. Hideki Akiyama.

Disclosure Statement

Dr. Yuji Hirai received research funding from Daiichi Sankyo Company Limited, as relevant financial activities outside the submitted work.

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