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Factors Determining Physicians' Decision Making In Treatment and the Outcomes of Nosocomial Diarrhea in a Tertiary Care Hospital: A Prospective Cohort

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Abstract

Background: Patients with nosocomial diarrhea (ND) are empirically treated as if they have *Clostridium-difficile*-associated diarrhea (CDAD), even if their stool tests are negative for *C. difficile*. We determined the incidence, risk factors, and treatment outcomes of patients with ND in Siriraj Hospital.

Methods: All patients with ND were enrolled. Demographic data, clinical and laboratory and stool for *C. difficile* toxin were collected including severity and outcomes of ND. Descriptive analysis was performed using mean ± SD/ median ± IQR for continuous data and frequency for categorical data. χ^2/Fisher's exact tests were used to compare groups. Predictors that might determine the decision to prescribe empirical treatment were identified using regression analysis.

Results: We enrolled 105 patients (mean age 67 years), and 89.5% were non-CDAD. During ND development, 95.7% received antibiotics and 3.2% chemotherapy. Eleven patients had CDAD. Common findings included: fever 42.6%, abdominal pain and hemodynamic instability 7.4%; 11.7% had blood cells in their stools and 85.1% had low serum albumin. Median white blood cell count and serum creatinine were 11-880 cells/mm^3 and 1.4 mg/dl, respectively. CDAD treatment was prescribed in 48.9% regardless of the toxin result; 95.7% received metronidazole and 4.3% vancomycin. Response outcomes did not differ significantly between the two groups.

Conclusion: Incidence of ND was 4.7%, and 10.6% of these had CDAD. 43.8% of patients with ND were treated as CDAD although they were negative for *C. difficile* toxin. There were no significant differences in clinical and laboratory features and outcomes between treated and untreated groups. Further study is needed to determine if empirical treatment of CDAD is justified in all cases of ND.

Keywords: *Clostridium difficile*; Diarrhea; Nosocomial diarrhea; *Clostridium difficile* toxin

Introduction

Nosocomial diarrhea (ND) is a common complication in hospitalized patients, with an incidence of 0.7-32%. Diarrhea can predispose patients towards a greater risk of infection, which contributes to higher morbidity and mortality, increased length of stay and hospital costs. Physicians frequently focus on *Clostridium difficile* infection as a primary cause of ND. However, other causes including medication, enteral feeding, and underlying illness are probably more common [1-4].

The prevalence of *Clostridium-difficile*-associated diarrhea (CDAD) in Europe and the US is as high as 20-30%, and the incidence is 3.8-9.5 episodes/10,000 patients/day [5]. In Thailand, the incidence of CDAD was reported as 12.3% in Siriraj Hospital in 2008 [6] and 18.6% in King Chulalongkorn Memorial hospital in 2002-2005 [7].

Many risk factors of CDAD have been established, including age >65 years; prolonged duration of hospital stay; exposure to antibiotics, chemotherapy, immunosuppressants and acid-suppressive agents; HIV infection; bowel surgery and enteral feeding [6-5] Clinical manifestations of CDAD vary from mild and self-limited to severe diarrhea with potentially fatal colitis [1,5,9]. The Infectious Diseases Society of America recommends metronidazole or vancomycin as the first-line treatment for CDAD [5]. Empirical treatment of ND with metronidazole or vancomycin is a common practice, although there is no definitive diagnosis of CDAD [4]. This treatment leads to prolonged length of hospital stay and hospital costs. Moreover, it also results in overuse of antibiotics, which might increase drug resistance. The present study was conducted at Siriraj Hospital, Thailand to determine the incidence, risk factors, and treatment outcomes of ND.

Materials and Methods

Patient population

All patients who were admitted to the medical wards, Department of Internal Medicine, Siriraj Hospital between August 1, 2012 and February 20, 2013 were being vigilance for ND. Inclusion criteria included all patients who developed ND, with aged of ≥18 years and were capable to sign the consent form. Exclusion criteria included diarrhea lasted lesser than 3 days, alternate causes of ND were identified (eg. CDAD, bowel ischemia, acute appendicitis, acute diverticulitis, drug induced diarrhea) and pregnancy. Patients who met the criteria

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were prospectively enrolled. Clinical data were collected and recorded in a case record form. These included baseline characteristics (age, weight, height, BMI, comorbidity, medications, and modes of feeding); clinical features; investigations (analysis of stools for *C. difficile* toxin, stool examination, abdominal radiography, and colonoscopy); severity of ND; risk factors for CDAD [white blood cell (WBC) count, serum albumin and creatinine, and hemodynamic status]; management and outcomes. This study was approved from the ethic committee of the Faculty of Medicine, Siriraj Hospital, Mahidol University.

Definitions

Diarrhea is defined as passing stools ≥3 times/day or bloody stools ≥1 time/day [5,8,10]. *Nosocomial* Diarrhea (ND) is defined as diarrhea that occurs at ≥48 h after hospitalization. *Clostidium Difficile* Associated Diarrhea (CDAD) is defined as diarrhea with a positive result for *C. difficile* toxin in stool assay and/or visualization of pseudomembranous colon by endoscopy or pathological examination. Severe ND is diagnosed by the presence of one of the following features: serum WBC count > 15,000 cells/mm^3, serum creatinine >1.5 mg/dl, serum albumin <2.5 g/dl, hemodynamic instability, toxic megacolon, and pseudomembranous colitis on endoscopy [5,8,10,11]. Response outcome is defined as a reduction in diarrhea within 7 days after initiation of treatment [12].

Statistical analysis

All statistics were performed using SPSS version 18 (SPSS Inc., Chicago, IL). Mean ± SD or median (minimum-maximum) were used to express continuous data, while frequency was used for categorical data. The χ^2 and Fisher's exact tests were used to compare categorical variables and Student's *t* test and Mann-Whitney *U* test were used for continuous variables. The predictive factors that might have influenced the decision to prescribe empirical treatment of *C. difficile* were compared between treated/untreated groups using univariate and multivariate binary logistic regression (backward stepwise) analysis.

Results

All 105 patients met the criteria and were enrolled during August 1, 2012 to February 20, 2013. Their mean age was 67 ± 17 years and 61 were female (58.1%). The incidence of ND was 4.7% (105 of 2233 patients), eleven (10.6%) of these patients had CDAD and were excluded from the main analysis. Common comorbidities were: 60 (57.1%) of patients had hypertension, 49 (46.7%) had renal disease, and 47 (44.8%) had diabetes mellitus. Upon occurrence of diarrhea, three (2.9%) patients received chemotherapy, seventeen (16.2%) was on corticosteroids, and four (4.8%) had immunosuppressive drugs other than corticosteroids. Proton pump inhibitor (PPI) use was common, in up to 96 (91.4%) patients with mean duration of 134 days. Eighty-seven (82.9%) patients received enteral feeding. Fifty (47.6%) patients had a previous history of hospitalization within 60 days. Ninety-two (87.6%) patients had previous antibiotic use within 60 days. Only 10 (9.5%) patients did not receive antibiotics while they developed ND. In the group of patients who received antibiotics, median duration of use was 5.4 days. In terms of types of antibiotics, 50 (47.6%) patients received a single agent, while the remainder had combined antibiotics. The most common antibiotic was carbapenem (44.8%), followed by β lactam/β-lactamase inhibitor (17.1%). Three (2.9%) patients received metronidazole and 20 (19%) received vancomycin while they developed diarrhea. Severe diarrhea was found in sixty four (61%) patients. Most of the patients up to 96.2% still needed to continue antibiotics while ND developed. The most common clinical finding when ND was diagnosed was fever (>38.3°C), which was found in 44 (41.9%) patients. Gastrointestinal manifestations, including abdominal pain, were found in eight (7.6%) patients. Two (1.9%) patients reported nausea and vomiting. The median number of bowel movements was five times/day (range 3-10). Watery stool was found in 61 (58.1%) patients, 43 (40.9%) of them had liquid stool while mucous bloody diarrhea was found in only one patient who also had rectal cancer. Only 8 (7.6%) of patients with ND had hemodynamic instability. The most common laboratory abnormality was mild hypoalbuminemia (serum albumin <3.5 mg/dl) with a median of 2.9 mg/dl. This was found in 90 (85.7%) patients. Red blood cells (RBCs) and/or WBCs were seen in the stools in 14 (13.3%) patients. Only three of them had CDAD. Median peripheral WBC count was 11,600 cells/mm^3 and median serum creatinine was 1.4 mg/dl. Only four (3.8%) of all patients had ileus on abdominal radiography. Amongst 105 recruited ND patients, only 11 of them had a positive result for stool *C. difficile* toxin assay and defined as CDAD. Considering in 94 ND patients, antibiotics for treatment of CDAD were empirically prescribed in 46 (49.5%) patients. Oral metronidazole was the most commonly used medication, in 44/46 (96.5%) of treated cases. Another 2/46 (3.5%) were treated with vancomycin orally. The median duration for antibiotic treatment was 10 days. Forty-eight (51.5%) of 94 patients did not receive any antibiotics for their ND. Table 1 compares treated/untreated groups in terms of demographic data, clinical characteristics, laboratory data, management and outcomes in ND patients (non-CDAD). There were no significant differences between the two groups in terms of clinical features and laboratory findings. Comorbidities between these treated/untreated groups are also comparable as demonstrated in (Table 2). In ND (non-CDAD) patients, response outcome was found in 33 (71.7%) patients in the treatment group, and 33 (70.2%) patients in the untreated group. Four (8.7%) patients died, which were two patients in each group. The median duration of response was 6 days in the treated group, and 5 days in the untreated group. The response outcome between the groups was not significantly difference ($p = 0.37$). Amongst 46 treated patients, the median duration of oral metronidazole was 10 days, and 33 (71.7%) patients responded well. Two (4.3%) patients were switched to receive vancomycin owing to non-response, and two (4.3%) received cholestyramine, while nine (19.7%) were observe without additional medication. There were 11 of 105 patients who had CDAD (positive for *C. difficile* toxin assay). Their median age was 62 years. Common comorbidities included diabetes mellitus, hypertension and dyslipidemia and were found in four, seven and three patients, respectively. Five patients had renal disease and two had gastrointestinal disease. Four of eleven patients currently used steroids; one used immunosuppressive drugs; 10 used PPIs (median duration of PPI use was 13 days); eight received enteral feeding; and three received oral feeding. Eight patients had previous history of hospitalization, and eight had previous antibiotic use. One patient did not receive antibiotics during development of ND; five received a combined antibiotic regimen; and five received a single antibiotic, of which carbapenem (63.6%) and colistin (27.2%) were commonly used. The median duration of antibiotic treatment in this group was 8 days.

Clinical manifestations of CDAD included fever (>38.3°C) in four patients (median temperature was 38°C), and one of them had abdominal pain and hemodynamic instability. No patient had nausea and vomiting. The median number of bowel movements was five times/day; five patients had watery diarrhea and six had liquid diarrhea. Eight of them had severe diarrhea. Regarding laboratory findings in the CDAD group, three patients had RBCs or WBCs in their stools; three had ileus on abdominal radiography; but none had toxic megacolon. Ten patients had serum albumin <3.5 mg/dl (median 2.7 mg/dl), median WBC

Characteristics	Finding		*p* value
	Treated group	Untreated group	
Female: male	23:23	32:15	0.08
Age, years: mean (SD)	64.4±19	71.4±14.8	0.05
Fever (>38.3°C)	23	17	0.19
Abdominal pain	5	2	0.23
Hemodynamic instability	4	3	0.67
Median bowel movements (times/day)	5	5	0.38
Watery: liquid : mucous bloody diarrhea	30:16:0	26:20:1	0.42
Nausea/vomiting	2	0	0.15
Severe diarrhea	29	23	N/A
Presence of cells in stool	7	4	0.60
Median serum albumin (mg/dl)	2.9	2.8	0.61
Median WBC count (cells/mm^3)	13.765	11.340	0.39
Median serum creatinine (mg/dl)	1.6	1.32	0.60
Current antibiotic used	44	46	0.31
Median duration of use (days)	5	4	0.19
Median number of antibiotics used	1	1	N/A
PPI used: Median duration of use (days)	42:17.5	43:30	0.22
Previous antibiotic use	40	45	N/A
Median duration of previous use (days)	8	7	0.84
Enteral feeding	40	38	0.42
Median duration of investigation until treatment (days)	1	N/A	N/A
Metronidazole (oral route)	44	N/A	N/A
Vancomycin	2	N/A	N/A
Response	33	33	N/A
Median duration of response (days)	6	5	0.37

Table 1: Common clinical findings, laboratory data, managements and response outcomes in patients with ND (non-CDAD): Comparison between treated/untreated groups.

Comorbidities	Finding		*p* value
	Treated group	Untreated group	
DM	21	22	0.91
HT	23	30	0.18
DLP	8	21	0.005
Neurological disease	20	20	0.93
Respiratory disease	16	13	0.46
Renal disease	19	24	0.35
CVS disease	17	20	0.54
GI disease	10	6	0.25
Connective tissue disease	3	2	0.63
Hematologic malignancy	4	2	0.38
Solid tumor	5	5	0.79
HIV infection	1	1	0.99
Current steroid used	6	7	0.8
Current immunosuppressive drug used	1	2	0.57
Serum albumin < 3.5 g/dl	38	42	0.35

DM= diabetes mellitus, HT= hypertension, DLP= dyslipidemia, CVS = cardiovascular system disease, GI = gastrointestinal disease, HIV = Human Immunodeficiency Virus

Table 2: Comorbidities in patients with ND (non-CDAD), between treated/untreated groups.

count was 10,570 cells/mm^3, and median serum creatinine was 1.67 mg/dl. Ten patients were receiving antibiotics during development of diarrhea. The median duration from the first day of diarrhea until stools were sent for examination was 2 days. Six patients were treated within

Discussion

ND is a common condition in clinical practice. The etiologies are varied including drug induced diarrhea and enteral feeding which were simply corrected. In our study, we selected only patients with ND who had negative test of stool for *C.difficile*. There is no standard treatment in this group of the patients. Various treatment were given depend on physician determination and judgement. CDAD is another possible cause of ND and was often empirically treated whether the results of stool for *C.difficile* was positive or negative. In the present study, we found that the incidence of ND was 4.7% of admission, while the

No. of patients	Management	Result
4	Oral metronidazole for 10 days	Response within 5 days
1	Oral metronidazole for 8 days	Response within 3 days
1	Oral metronidazole for 5 days	Response within 5 days
1	Oral metronidazole for 14 days	No response but doctor observed (diarrhea stopped within 13 days)
1	Oral metronidazole for 14 days then switch to oral vancomycin for 7 days	No response to metronidazole Response to vancomycin within 5 days
1	Oral metronidazole for 7 days then switch to oral vancomycin for 10 days	No response to metronidazole Response to vancomycin
1	Oral metronidazole for 10 days then combined oral metronidazole for 5 days with cholestyramine then switch to oral vancomycin for 8 days and loperamide	No response
1	Observe	Diarrhea improved without antibiotics within 6 days

Table 3: Treatments and outcomes in CDAD patients.

Factor	Univariate analysis		Multivariate analysis	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value
Sex	0.47 (0.20-1.09)	0.08	0.43 (0.17-1.08)	0.07
Age	0.98 (0.95-1)	0.05	0.97 (0.947-1)	0.05
Fever	1.76 (0.77-4.04)	0.18	-	-
Antibiotic-free day	0.99 (0.97-1.02)	0.55	-	-
Current antibiotic use	1.06 (0.979-1.143)	0.16	-	-
HT	0.57 (0.25-1.3)	0.18	-	-
DLP	0.26 (0.1-0.68)	0.006	0.339 (0.123-0.935)	0.04

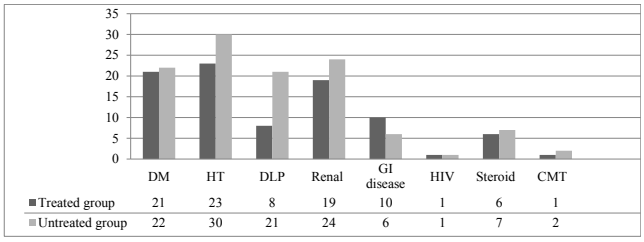
CI = confidence interval; OR = odds ratio

Table 4: Univariate and multivariate analyses of factors associated with treated and untreated ND (non-CDAD).

the first day of diarrhea. Treatment regimen in 10 of 11 patients with CDAD was oral metronidazole. Seven (63.6%) of them respond well; three were switched to vancomycin due to no clinical response (one received vancomycin combined with cholestyramine and loperamide, but he still had diarrhea); and one had no response. One patient was left untreated although he had a positive result for *C. difficile* toxin assay because his diarrhea was self- resolved before returning result of the stool examination. These were summarized in (Table 3). Univariate and multivariate factors associated with treatment and non-treatment of ND (non-CDAD) are shown in (Table 4). There are correlations between age, dyslipidemia and ND (non-CDAD) management.

incidence of CDAD was 10.6% amongst ND patients. This is similar to a previous study in Siriraj Hospital [6]. Considering only patients with ND but no CDAD, we analyzed whether any factors influenced the decision of physicians to treat CDAD empirically. Surprisingly, risk factors for CDAD, for instance, sex, malnutrition, previous hospitalization, antibiotic use, proton pump inhibitor use, immune status, and modes of feeding, as well as clinical manifestations and severity of diarrhea, did not influence treatment decision making for ND. On the contrary, we observed that age and dyslipidemia were associated with the decision to prescribe empirical antibiotics for CDAD. The results showed that physicians tend to prescribe CDAD regimen in younger more than in elderly patients ($p = 0.047$), although the difference was only marginally significant. Patients with dyslipidemia who developed ND tend to be treated as if they have CDAD ($p = 0.037$). This might be explained by the fact that this study had a small sample size and dyslipidemia was a common comorbidity (which might not reflect a true association). Unlike prior studies [6,8], there is no evidence from our study to support that old age, prolonged duration of hospital stay, antibiotics, chemotherapy, immunosuppressive drugs, HIV infection, bowel surgery, enteral feeding and proton pumps inhibitors are risk factors for CDAD. However, we did observe that four of eleven patients with CDAD had blood cells in their stools, and eight of them had severe diarrhea, although the numbers are too small to draw a final conclusion. Metronidazole was used as an initial antibiotic in most CDAD patients (90.9%), with a mean duration of treatment of 10 days. The response rate was 60%, which is lower than previous studies 66.7% [13] and 74.5% by Thipmontree et al. [6] Again, our finding was based on a small number of patients.

In the non-CDAD group (Figure 1), up to 50% of patients were treated as if they had CDAD, regardless of the result for *C. difficile* toxin assay. There was a comparable clinical outcome between the treated and untreated groups. Diarrhea stopped within 7 days in 71.7% of the treated group and 70.2% of the untreated group. This difference was not significant. The median durations of response in the treated and untreated group of non-CDAD patients were 6 and 5 days, respectively. This does not differ greatly from the duration of response to treatment in CDAD patients in our study as well as that of Chirag et al. [4] (4.2 days). In our study, the decision of physicians to treat or not to treat ND empirically with antibiotics as CDAD was not associated with the risks of CDAD. However, the treatment outcomes in both groups were comparable. This suggests that empirical treatment of all cases of ND as CDAD might not be justified. We did not collect data regarding the adverse effects of treatment, which might have increased the unfavorable outcomes in the treated group, as metronidazole frequently causes gastrointestinal irritation, including diarrhea. The main limitation of our study was its small sample size. In addition, we did not collect data regarding confounding factors (such as switch mode/concentration of feeding, elixir KCl feeding). Moreover, the incidence of CDAD may have been underestimated because of the process of specimen collection and transportation. *C. difficile* toxin degrades at room temperature and may be undetectable within 2 h after collection [6]. We did not have information regarding time intervals from specimen collection to reach the laboratory room. Most stool specimens were not kept in the refrigerator or an iced container. Our study found that the incidence of ND of all admissions was 4.7%, and 10.6% of ND patients had CDAD. Concurrent antibiotic use was common (95.7%). 43.8% of nosocomial diarrhea cases were treated as CDAD, even if they had a negative result for *C. difficile* toxin in the stools. The most common antibiotic used was metronidazole. There were no significant differences in terms of clinical, laboratory and treatment outcomes between the treated and untreated groups. This raises the issue of cost-effectiveness if we should treat ND empirically as CDAD. Further study is needed to determine if empirical treatment of CDAD is justified in all cases of ND.



DM= diabetes mellitus, HT= hypertension, DLP= dyslipidemia, Renal = renal disease, GI = gastrointestinal disease, Steroid = steroid used, CMT= chemotherapy

Figure 1: Common comorbidities in non-CDAD patients.

Declaration of Interest

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