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The Simple Predictors of Pseudomembranous Colitis in Patients with Hospital-Acquired Diarrhea: A Prospective Observational Study

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Background/Aims: As the incidence rate of and mortality from pseudomembranous colitis (PMC) are increasing worldwide, it is important to study the simple predictive risk factors for PMC among patients with hospital-acquired diarrhea (HAD). This study focused on identifying the clinical risk factors that can easily predict PMC. **Methods:** The presumed HAD patients were prospectively recruited at the Hallym University Kangdong Sacred Heart Hospital. **Results:** Age of 70 and older (adjusted odds ratio [OR], 1.76; 95% confidence interval [CI], 1.12 to 0.75), use of proton pump inhibitors (adjusted OR, 4.07; 95% CI, 2.512 to 6.57), use of cephalosporins (adjusted OR, 2.99; 95% CI, 1.82 to 4.94), and underlying cancer (adjusted OR, 1.72; 95% CI, 1.04 to 2.82) were independent risk factors for PMC in the multivariate logistic regression analysis. The prevalence of PMC was very low in the patients with HAD who exhibited no risk factors. **Conclusions:** The risk factors for PMC in patients with HAD included cephalosporin use, proton pump inhibitor use, old age, and cancer. Considering the strongly negative predictive values of these risk factors, endoscopic evaluation can be delayed in patients with HAD without risk of developing PMC. **(Gut Liver 2014;8:41-48)**

Key Words: Enterocolitis, pseudomembranous; *Clostridium difficile*; Risk factors; Predictors

INTRODUCTION

There are many causes of hospital-acquired diarrhea (HAD), including medications, nasogastric tube feeding, bowel ischemia, or constipation causing pseudodiarrhea. Antibiotics are the most common cause of HAD. Recently, the incidence of antibiotic-associated diarrhea (AAD) has increased rapidly due to use of broad-spectrum antibiotics.[1] In the preantibiotic era, pseudomembranous colitis (PMC) was associated with ischemic cardiovascular insufficiency, colonic obstructions, heavy metal intoxication, sepsis, shock, or uremia.[2] Since the 1970s, *Clostridium difficile* has been responsible for 90% to 99% of PMC cases.[3] There has been a worldwide increase in the incidence of *C. difficile*-associated diarrhea (CDAD). Several articles have described an epidemic increase in the incidence and severity of *C. difficile* colitis, which is related to crowded hospital wards, increased use of broad-spectrum antibiotics,[4,5] and/or relatively poor infection control.[6,7]

The clinical spectrum of HAD associated with antimicrobial agents varies from simple antibiotic-associated diarrhea (SAAD) to fatal PMC. Compared with SAAD or CDAD, PMC has a poor prognosis and more severe clinical manifestations, such as ascites and transmural inflammation of the colon,[8] although severe CDAD can be associated with significant mortality.[9,10] For these reasons, medical treatments, such as oral administration of metronidazole or vancomycin, are usually recommended for *C. difficile* toxin-positive patients who have diarrhea despite antibiotic discontinuation, cannot discontinue antibiotics, and/or show evidence of colitis on colonoscopy.[11] Furthermore, careful sigmoidoscopy or colonoscopy can be recommended in advance for selected patients with severe clinical features who cannot wait for the results of a *C. difficile*-toxin test.

Considering that the early diagnosis of PMC and urgent appropriate treatment are clinically crucial, it is important to assess simple predictors for PMC among HAD patients; however, many studies have focused on risk factors of AAD or CDAD. To the best of our knowledge, no prospective study has examined the risk factors of PMC. However, Lee *et al*.[12] published a retro-

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spective study assessing risk factors of PMC in 2006. The aim of this study was to identify the risk factors of PMC that can be easily applied to the treatment of patients with HAD.

MATERIALS AND METHODS

1. Definition

The HAD is defined as defecation of watery or loose stool more than three times a day for more than two days that started more than 48 hours after admission. SAAD was defined as antibiotic-related diarrhea without any other cause, and CDAD was defined as a positive result on a stool *C. difficile* toxin assay in a HAD patient. The definition of PMC included the presence of yellowish or milky-colored pseudomembranes on the colonic mucosa on endoscopy or characteristic pathologic findings, such as necrotic debris attached to the colonic wall or volcano lesions, regardless of the result of *C. difficile* toxin assay. *C. difficile* infection was defined as a positive *C. difficile* toxin result with clinical symptoms such as diarrhea, PMC, or occasionally toxic megacolon.

2. Study population

The study included adult patients 20 years or older with HAD. The exclusion criteria were as follows: 1) other causes of diarrhea, such as stool softeners, gastrointestinal (GI)-motility drugs, or anticancer drugs; 2) other GI disease-causing diarrhea, such as inflammatory bowel disease; and 3) diarrhea with an indefinite cause.

3. Study design

The HAD patients were recruited prospectively by consultation from the various medical or surgical departments, such as cardiology, orthopedics, neurosurgery, and general surgery, in Hallym University Kangdong Sacred Heart Hospital from June 2007 to September 2011.

C. difficile toxin assays using a polymerase chain reaction and stool culture were performed on all enrolled patients. Sigmoidoscopy or colonoscopy was performed, if possible, before the result of the toxin assay became available for patients with severe abdominal pain, dehydration, bloody diarrhea, age greater than 70 years, or a compromised immune system in order to obtain a prompt diagnosis of HAD etiology, according to textbook recommendations for the treatment of acute diarrhea.[13,14] Among 1,420 enrolled patients, 1,026 patients underwent sigmoidoscopy or colonoscopy. Others (n=394) could not undergo these procedures because of poor medical condition or refusal. History-taking, physical examination, and review of the medical records of the presumed HAD patients were performed by fellow trainees in gastroenterology to reach the differential diagnosis of HAD. The various parameters, such as age, sex, length of hospital stay before diarrhea, previous and current medication other than antibiotics (such as H_2-receptor blockers [H_2-blockers], proton pump inhibitors (PPI), or probiotics), endoscopic and pathologic findings, results of *C. difficile* toxin assays, and underlying disease, including diabetes mellitus, cancer, chronic kidney disease, and cerebrovascular disease, were reviewed. Moreover, we reviewed the type and number of antibiotics, the duration of antibiotic use before diarrhea, and any operative history, including GI, orthopedic, gynecologic, otorhinolaryngo-

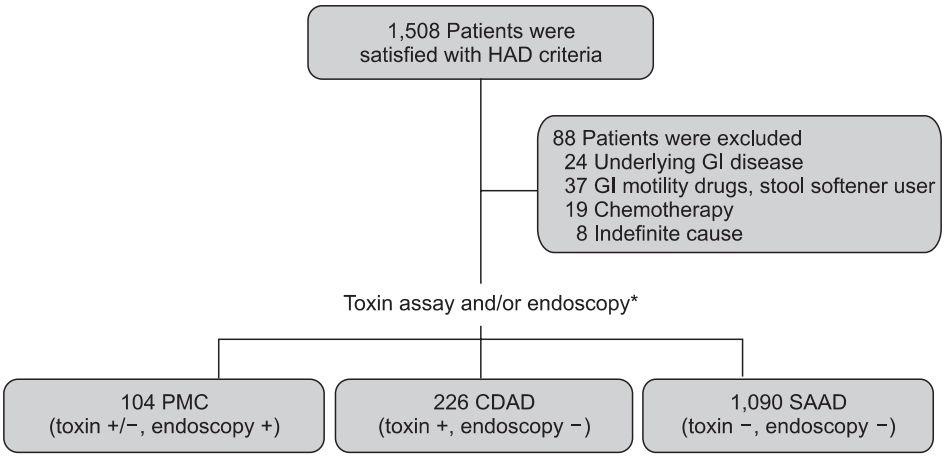

Fig. 1. Enrollment of and differential diagnostic flow chart for patients with hospital-acquired diarrhea (HAD). A total of 1,508 patients with diarrhea were identified after admission. Among them, 88 patients were excluded from the study because they had diarrheal disease other than pseudomembranous colitis (PMC), *Clostridium difficile*-associated diarrhea (CDAD), or simple antibiotic-associated diarrhea (SAAD) or because they were taking medicines causing diarrhea, such as stool softeners, gastrointestinal motility drugs, or anticancer drugs. Some patients suffered diarrhea before taking antibiotics. In total, 104 patients exhibited pseudomembranous colitis, and 226 exhibited *C. difficile*-associated diarrhea; 1,090 patients suffered from SAAD or other non-*C. difficile*-associated diarrheas.
*Endoscopic evaluation was performed, if possible, before the results of the toxin assay became available for the patients with severe abdominal pain, dehydration, bloody diarrhea, or fever.

logic, or neurosurgical operations.

In total, 1,508 patients with HAD were detected after admission. Among these patients, 88 were excluded from the study because they had GI disease causing diarrhea other than AAD, CDAD, or PMC (n=24) or were taking medicine causing diarrhea such as stool softeners, GI motility drugs (n=37), or anticancer drugs (n=19). Some patients were found to suffer from HAD with an indefinite cause (n=8). We depict the diagnostic flow chart applied in this study in Fig. 1.

The study protocol and exemption of informed consent were approved by the Institutional Review Board of the Kangdong Sacred Heart Hospital.

4. Statistical analysis

The enrolled patients were divided into PMC and non-PMC groups to assess predictors for diagnosing PMC. In addition, predictors for *C. difficile* infection were evaluated by dividing the patients into two groups: the SAAD group and the *C. difficile* infection group, which included patients with CDAD and PMC. Univariate analysis was performed to compare the clinical features of the two groups using the chi-square test for categorical variables and the independent sample t-test for continuous variables. Multivariate logistic regression analysis was performed to evaluate independent predictors of PMC or *C. difficile* infection. Statistical analyses were performed with IBM SPSS Statistics version 19 Doctor's Pack for Windows (IBM Co., Armonk, NY, USA), and a p-value less than 0.05 was regarded as significant.

RESULTS

1. Predictive factors of PMC

In total, 1,420 patients were analyzed (mean age, 66 years; 47.25% were female). The PMC group consisted of 104 patients and the non-PMC group was composed of 1,316 patients. Of 23 parameters, nine were significantly associated with PMC after univariate analysis. The mean number of administered antibiotics before starting diarrhea was 3.77 and 2.87 in the PMC and non-PMC groups, respectively (p=0.001). The use of cephalosporins (70/104, 67.31% vs 441/1,316, 33.51%) and clindamycin (13/104, 12.50% vs 87/1,316, 6.61%) was more common in the PMC group than in the non-PMC group; both differences were statistically significant (cephalosporins, p<0.0001; clindamycin, p=0.013). The PMC group was significantly older than the non-PMC group (69.77 vs 61.62 years; p<0.0001), reflecting the increasing incidence of PMC with age. The number of postoperative patients was greater in the PMC group (44/104, 42.31% vs 393/1,316, 29.86%; p=0.004). The patients were also divided by surgery type (orthopedic: PMC 18.27%, non-PMC, 9.12%, p=0.002; otorhinolaryngologic: PMC 8.65%, non-PMC 4.79%, p=0.04). The number of PPI use in the PMC group was significantly more than that of the non-PMC group (41/104, 39.42% vs 145/1,316, 11.02%; p<0.0001), although there is no significant difference between the two groups in terms of the dose or length of PPI administration. Regarding underlying disease, 28.85% (30/104) of the PMC group and only 17.02% (224/1,316) of the non-PMC group had cancer (p=0.002). Chronic renal failure was more common in the PMC group than in the non-PMC group (11/104, 10.58% vs 81/1,316, 6.16%; p=0.04), and cerebrovascular disease was more common in the PMC group than in the non-PMC group (17/104, 16.35% vs 130/1,316, 9.88%; p=0.02) (Table 1).

Multivariate logistic regression analysis was performed for these nine variables. Age greater than 70 years (adjusted odds ratio [OR], 1.76; 95% confidence interval [CI], 1.12 to 2.75; p=0.01), use of PPI (adjusted OR, 4.07; 95% CI, 2.52 to 6.59; p<0.0001), use of cephalosporins (adjusted OR, 2.99; 95% CI, 1.82 to 4.94; p<0.0001), and underlying cancer (adjusted OR, 1.72; 95% CI, 1.04 to 2.82; p=0.03) were the predictors of PMC (Table 2).

To determine how well the final model predicted PMC, we developed risk groups based on the number of predictive clinical factors. When no predictors were present, 1.54% (7/454) of the patients developed PMC; when only one was present, 5.39% (29/538) developed PMC; when two, three, and four were present, 10.42% (32/307), 29.73% (33/111), and 30.0% (3/10) developed PMC, respectively. There was a significant difference in the morbidity rate of PMC between the group with no predictors and that with one or more predictors (OR, 7.13; 95% CI, 3.28 to 15.48; p<0.0001) (Table 3).

The positive predictive value (PPV) and the negative predictive value (NPV) of age older than 70 years were 0.11 and 0.94, respectively. The PPV and NPV were 0.22 and 0.95 for PPI use, 0.14 and 0.96 for the use of cephalosporins, and 0.12 and 0.94 for underlying cancer, respectively. The NPV was better than the PPV for all of the evaluated predictors of PMC. For predicting PMC, the sensitivity and the specificity of age older than 70 years were 45.00% and 60.49%, respectively. They were 39.42% and 88.98% for PPI use, 67.31% and 66.49% for the use of cephalosporins, and 28.85% and 82.98% for underlying cancer, respectively (Table 4).

2. Predictive factors of *C. difficile* infection

The *C. difficile* infection group and *C. difficile* noninfection group consisted of 330 patients and 1,090 patients, respectively. Of 23 parameters, 15 were significantly associated with PMC after univariate analysis. The infection group was significantly older than the noninfection group (67.12 vs 60.73; p<0.0001). The duration of hospital stay in the infection group was significantly longer than in the non-infection group (39.91 days vs 30.37 days; p=0.03). The number of antibiotics used in the infection group was higher than in the noninfection group (3.59 antibiotics vs 2.73 antibiotics; p<0.0001). The number of postoperative patients was greater in the infection group (139/330,

42.12% vs 298/1,090, 27.34%; p<0.0001). The patients were also divided by surgery type in the infection and noninfection groups: orthopedic operations, 14.24% vs 8.44% (p<0.0001); otorhinolaryngologic operation, 9.70% vs 3.67% (p<0.0001); and neurosurgery, 8.18% vs 4.13% (p<0.0001), respectively. Compared with 48.99% (534/1,090) of the noninfection group, 56.67% (187/330) of the infection group was female, and this difference was statistically significant (p=0.01). The number of probiotics used in the infection group was higher than in the noninfection group (108/330, 32.73% vs 295/1,090, 27.06%; p=0.03). Other medications were also significantly different between the groups: H_2-blocker, 139/330, 42.12% vs 372/1,090, 34.13% (p=0.006); PPI, 73/330, 22.12% vs 113/1,090, 10.37% (p<0.0001); cephalosporins, 177/330, 53.64% vs 334/1,090, 30.64% (p=0.009); and clindamycin, 33/330, 10.00% vs 67/1,090, 6.15% (p=0.009), respectively. In terms of underlying disease, 23.33% (77/330) of the infection group had diabetes mellitus vs only 16.88% (184/1,090) of the noninfection group (p=0.005); 24.24% of the infection group had cancer vs 15.98% of the noninfection group (p=0.001). Findings were similar for chronic kidney disease at 9.39% (31/330) and 5.60% (61/1,090; p=0.008) and for cerebrovascular disease at 15.76% (52/330) and 8.72% (95/1,090; p<0.001), respectively (Table 1).

Multivariate logistic regression analysis was performed for the 15 significantly associated variables. Age older than 66 years (adjusted OR, 1.66, 95% CI, 1.23 to 2.44; p=0.001), number of used antibiotics (adjusted OR, 1.08; 95% CI, 1.02 to 1.15; p=0.009), sex (adjusted OR, 1.38, 95% CI, 1.03 to 1.86; p=0.03), use of PPI (adjusted OR, 1.92; 95% CI, 1.34 to 2.75; p<0.0001), use of cephalosporins (adjusted OR, 1.87; 95% CI, 1.37 to 2.55; p<0.0001), underlying cancer (adjusted OR, 1.58; 95% CI, 1.13 to 2.22; p=0.008), and cerebrovascular disease (adjusted OR, 1.55; 95% CI, 1.03 to 2.33; p=0.04) were the predictors of *C. difficile* infection (Table 2).

To determine how well the final model predicted *C. difficile* infection, we developed predictive groups based on the number

Table 1. Univariate Analysis of Risk Factors for Pseudomembranous Colitis or *Clostridium difficile* Infection among Patients with Hospital-Acquired Diarrhea

	PMC (n=104)	Non-PMC (n=1,316)	p-value	*Clostridium* infection (n=330)	*Clostridium* noninfection (n=1,090)	p-value
Mean age, yr	69.77±13.46	61.62±17.11	<0.01	67.12±14.80	60.73±17.34	<0.0001
Mean hospital stay, day*	30.53±35.75	33.02±77.21	0.38	39.91±62.71	30.37±78.11	<0.0001
No. of antibiotics used	3.77±2.82	2.87±2.50	<0.01	3.59±2.77	2.73±2.42	<0.0001
Surgical procedures	44 (42.31)	393 (29.86)	0.004	139 (42.12)	298 (27.34)	<0.0001
GS	3 (2.89)	88 (6.69)	0.064	19 (5.76)	72 (6.61)	0.291
OS	19 (18.27)	120 (9.12)	0.002	47 (14.24)	92 (8.44)	0.001
OBGY	1 (0.96)	9 (0.68)	0.372	1 (0.30)	9 (0.83)	0.160
ENT	9 (8.65)	63 (4.79)	0.042	32 (9.70)	40 (3.67)	<0.0001
NS	8 (7.69)	64 (4.86)	0.103	27 (8.18)	45 (4.13)	0.002
CS	4 (3.85)	40 (3.04)	0.324	13 (3.94)	31 (2.84)	0.157
Abdominal surgery	5 (4.81)	96 (7.29)	0.167	18 (5.45)	83 (7.61)	0.085
Female sex	61 (58.65)	660 (50.15)	0.055	187 (56.67)	534 (48.99)	0.011
Use of probiotics	26 (25.00)	377 (28.65)	0.202	108 (32.73)	295 (27.06)	0.028
Use of H_2-blocker	40 (38.46)	471 (35.79)	0.310	139 (42.12)	372 (34.13)	0.006
Use of PPI	41 (39.42)	145 (11.02)	0.000	73 (22.12)	113 (10.37)	<0.0001
PPI dose (full)	28 (68.29)	107 (73.79)	0.259	49 (67.12)	86 (76.11)	0.198
PPI duration	16.58±16.48	11.88±15.83	0.055	14.55±14.20	11.90±17.04	0.146
Use of cephalosporin	70 (67.31)	441 (33.51)	0.000	177 (53.64)	334 (30.64)	<0.0001
Use of clindamycin	13 (12.50)	87 (6.61)	0.013	33 (10.00)	67 (6.15)	0.009
DM	23 (22.12)	238 (18.09)	0.162	77 (23.33)	184 (16.88)	0.005
Cancer	30 (28.85)	224 (17.02)	0.002	80 (24.24)	174 (15.96)	0.001
CRF	11 (10.58)	81 (6.16)	0.041	31 (9.39)	61 (5.60)	0.008
CVA	17 (16.35)	130 (9.88)	0.020	52 (15.76)	95 (8.72)	<0.0001

Data are presented as mean±SD or number (%).
PMC, pseudomembranous colitis; GS, general surgery; OS, orthopedic surgery; OBGY, obstetrics and gynecology; ENT, ear, nose, and throat (otolaryngology); NS, neurosurgery; CS, chest surgery; PPI, proton pump inhibitor; DM, diabetes mellitus; CRF, chronic renal failure; CVA, cerebrovascular accident.
*Duration of hospital stay indicates days until the onset of diarrhea after admission.

Table 2. Multivariate Regression Analysis of Risk Factors for Pseudomembranous Colitis or *Clostridium difficile* Infection among Patients with Hospital-Acquired Diarrhea

Risk factor	Adjusted OR	95% CI	p-value
PMC			
Age ≥70 yr*	1.76	1.12-2.75	0.014
Use of PPI	4.07	2.52-6.57	<0.0001
Use of cephalosporin	2.99	1.82-4.94	<0.0001
Cancer	1.72	1.04-2.82	0.033
C. difficile infection			
Age ≥66 yr*	1.66	1.23-2.44	0.001
No. of antibiotics used	1.08	1.02-1.15	0.009
Female sex	1.38	1.03-1.86	0.034
Use of PPI	1.92	1.34-2.75	<0.0001
Use of cephalosporin	1.87	1.37-2.55	<0.0001
Cancer	1.58	1.13-2.22	0.008
CVA	1.55	1.03-2.33	0.037

OR, odds ratio; CI, confidence interval; PMC, pseudomembranous colitis; PPI, proton pump inhibitor; CVA, cerebrovascular accident.
*Evidence for selecting elderly patients: Age increases both the sensitivity and specificity of the receiver operating characteristic curve.

Table 3. Model for Predicting Pseudomembranous Colitis and *Clostridium difficile* Infection according to the Presence of Risk Factors and the Number of Risk Factors

	Events of PMC	Events of *Clostridium* infection
Risk factors present		
No	7/454 (1.54)	24/232 (10.34)
Yes	97/966 (10.04)*	306/1,188 (25.76)†
No. of risk factors‡		
0	7/454 (1.54)	24/232 (10.34)
1	29/538 (5.39)	25/204 (12.25)
2	32/307 (10.42)	70/354 (19.77)
3	33/111 (29.73)	66/245 (26.94)
4	3/10 (30.00)	66/230 (28.70)
5	-	70/139 (50.36)
6	-	9/16 (56.25)
7	-	-§

Data are presented as number (%).
PMC, pseudomembranous colitis.
*Odds ratio 7.1279, 95% confidence interval 3.2822 to 15.4795, p<0.0001; †Odds ratio 3.0068, 95% confidence interval 1.933 to 4.678, p<0.0001; ‡p<0.0001; §There is no patient who exhibits all of the *C. difficile* infection risk factors.

of clinical predictors. When no predictors were present, 10.34% (24/232) of the patients developed *C. difficile* infection. With more predictors, a greater percentage of the patients developed *C. difficile* infection (12.25%, 19.77%, 26.94%, 28.70%, 50.36%, and 56.25% at one to six predictive-factor groups, respectively; p<0.0001). There was a significant difference in the morbidity rates for *C. difficile* infection between the group with no predictive factors and that with one or more of the predictors (adjusted OR, 3.01; 95% CI, 1.93 to 4.68; p<0.0001) (Table 3).

The PPV and NPV of age older than 66 years were 0.30 and 0.82, respectively. The PPV and NPV were 0.28 and 0.86 for the number of antibiotics used; 0.26 and 0.80 for female sex, 0.39 and 0.79 for use of PPI, 0.35 and 0.83 for use of cephalosporins, 0.31 and 0.79 for underlying cancer, and 0.35 and 0.78 for underlying cerebrovascular disease, respectively. The NPV was better than the PPV for all of the evaluated predictors of *C. difficile* infection. For predicting *C. difficile* infection, the sensitivity and the specificity for age older than 66 years were 63.94% and 52.94%, respectively. They were 81.52% and 35.60% for number of antibiotics used, 56.67% and 51.01% for the sex (female), 22.12% and 89.63% for use of PPI, 53.64% and 69.36% for use of cephalosporins, 24.24% and 84.04% for cancer, and 15.76% and 91.28% for cerebrovascular accident (CVA), respectively (Table 4).

DISCUSSION

When HAD patients are in poor clinical condition, it is impossible to wait for the result of *C. difficile* culture and toxin assays because PMC presents a poor prognosis compared to SAAD or CDAD.[8] Therefore, the patients at high risk for PMC must be given an early endoscopic evaluation and treatment before the results of the toxin assay are reported. Considering the importance of early diagnosis and medication for PMC, it is vital to research predictors of PMC.

This study design focuses on the predictors that can easily predict PMC in a clinical setting. The independent predictors of PMC were old age (≥70 years), use of PPI, use of cephalosporins, and history of cancer. Additionally, the predictors of CDAD were old age (≥66 years), use of PPI, use of cephalosporins, history of cancer, number of used antibiotics, female sex, and previous history of CVA. The good NPVs of the independent predictors (0.94 to 0.96) suggest that the patients without any of the predictors described above may not have a risk of PMC. Importantly, the fewer predictors the HAD patients had, the lower the risk of PMC or CDAD. We depict the suggested algorithm (based on these results) in Fig. 2. This preemptive treatment algorithm may not be applicable to all HAD patients without risk factors for PMC. In fact, among 104 patients with PMC, seven patients did not have any risk factor and three patients showed negative toxin assay, though there was no patient that showed both negative toxin assay and did not have any risk factor. However, sigmoidoscopy or colonoscopy cannot be done in a considerable proportion of hospitalized patients with diarrhea because of their medical conditions. The suggested algorithm may be more valuable in those situations. In brief, if HAD patients may have acute infectious diarrhea (fever >38.5°C, severe abdominal pain, bloody diarrhea, severe volume depletion, diarrhea lasting >48

Table 4. Positive Predictive Value, Negative Predictive Value, Sensitivity, and Specificity of the Risk Factors for Pseudomembranous Colitis and *Clostridium difficile* Infection

Risk factor present	PPV (A/B)	NPV (C/D)	Sensitivity (A/E)	Specificity (C/F)
PMC				
Old age ≥70 yr	0.11 (63/574)	0.94 (796/846)	45.00 (63/104)	60.49 (796/1,316)
Use of PPI	0.22 (41/186)	0.95 (1,171/1,234)	39.42 (41/104)	88.98 (1,171/1,316)
Use of cephalosporin	0.14 (70/511)	0.96 (875/909)	67.31 (70/104)	66.49 (875/1,316)
Cancer	0.12 (30/254)	0.94 (1,092/1,166)	28.85 (30/104)	82.98 (1,092/1,316)
C. difficile infection				
Old age ≥66 yr	0.30 (211/715)	0.82 (577/705)	63.94 (211/330)	52.94 (577/1,090)
No. of antibiotics used	0.28 (269/971)	0.86 (388/449)	81.52 (269/330)	35.60 (388/1,090)
Female sex	0.26 (187/721)	0.80 (556/699)	56.67 (187/330)	51.01 (556/1,090)
Use of PPI	0.39 (73/186)	0.79 (977/1,234)	22.12 (73/330)	89.63 (977/1,090)
Use of cephalosporin	0.35 (177/511)	0.83 (756/909)	53.64 (177/330)	69.36 (756/1,090)
Cancer	0.31 (80/254)	0.79 (916/1,166)	24.24 (80/330)	84.04 (916/1,090)
CVA	0.35 (52/147)	0.78 (995/1,273)	15.76 (52/330)	91.28 (995/1,090)

Data are presented as percentage (number). A, the number of PMC or *Clostridium difficile*-associated diarrhea (CDAD) patients with the respective risk factor; B, the number of patients with the respective risk factor; C, the number of non-PMC or non-CDAD patients without the respective risk factor; D, the number of patients without the respective risk factor; E, the number of PMC or CDAD patients; F, the number of non-PMC or non-CDAD patients.
PPV, positive predictive value; NPV, negative predictive value; PMC, pseudomembranous colitis; PPI, proton pump inhibitor; CVA, cerebrovascular accident.

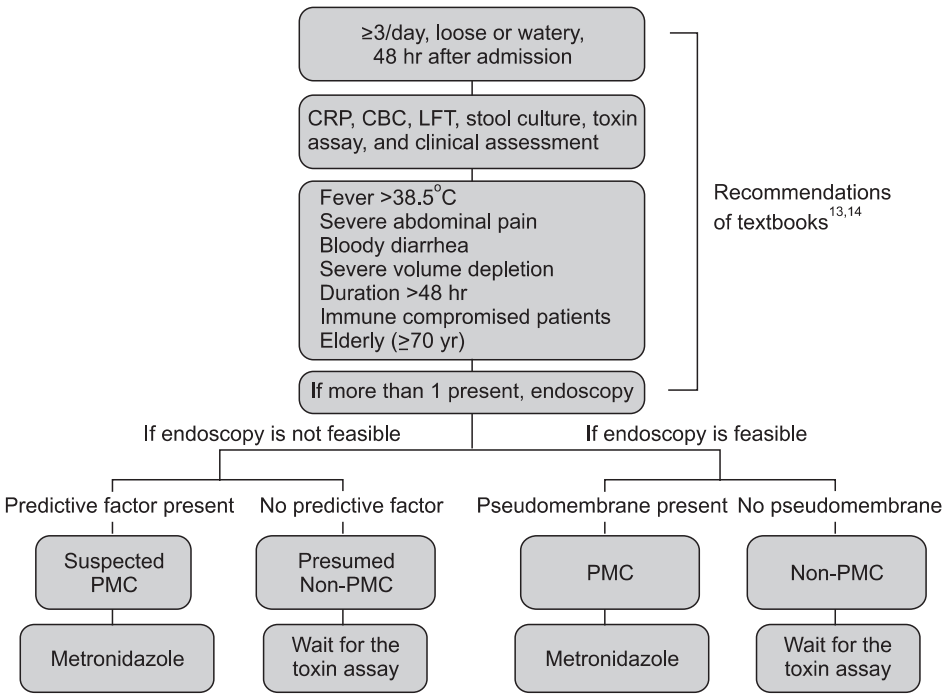

Fig. 2. Suggested algorithm for the management of hospital-acquired diarrhea. If patients with hospital-acquired diarrhea exhibit infectious diarrhea (fever >38.5°C, severe abdominal pain, bloody diarrhea, severe volume depletion, duration >48 hours, immunocompromised, or age >70 years), it is better to perform an endoscopy. Endoscopy, however, may be unsuitable due to the patient's condition. Based on our results, we suggest that antibiotic treatment can be delayed in patients with hospital-acquired diarrhea who lack the predictors of pseudomembranous colitis (PMC) until the results of the *Clostridium difficile* toxin assay and culture are available.
CRP, C-reactive protein; CBC, complete blood cell count; LFT, liver function test.

hours, compromised immune system or age >70 years), endoscopy should be considered first, according to the well-known recommendation of textbooks;[13,14] however, when endoscopy is not available because of the patients' conditions, without the predictors of PMC revealed in this study, antibiotic treatment may become delayed in HAD patients until the results of the *C. difficile* toxin assay or culture become available.

The well-known predictors associated with CDAD are grouped into host and drug factors. Age older than 65, severe underlying disease, compromised immune system, history of GI surgery, history of stay at an intensive care unit, long duration of stay and insertion of nasogastric tube are noted host factors.[11,15] The type of antibiotics, length of antibiotic course, and history of using multiple antibiotics are drug factors.[16]

In patients that use PPI, there were approximately 4- and 2-fold increases in the risk for PMC and CDAD, respectively. PPI use showed the highest AOR for both PMC and CDAD in this comparison. The single case-control study reported that patients with PPI had a 2.5-times higher risk of CDAD compared with those without PPI.[17] A meta-analysis conducted in 2012 showed a 65% increase in the incidence of CDAD among PPI users;[18] however, the association between use of PPI and the development of CDAD has not been conclusive until now because the results of some reports do not coincide.[1,19,20] Although the mechanism of this association between PPI and *C. difficile* infection is unclear, when inhibition of gastric-acid production alters the acidic environment of the gastric cavity, a physiological barrier, *C. difficile* easily passes through the stomach and colon, allowing colonization. After colonization, *C. difficile* can overcome host immunity and cause PMC.[20] More specifically, the dose and length of administered PPI were evaluated for a relationship with *C. difficile* infection or the prevalence of PMC; however, no association was found, possibly because a PPI, irrespective of the dose or the duration, alters the acid environment. This change can increase the prevalence of PMC.

In addition, elderly patients were prone to CDAD and PMC. This result of the present study was similar in this respect to that of another study.[21] Elderly patients, compared with younger patients, are more likely to be exposed to *C. difficile* because of their relatively longer hospital stays, which are due in part to severe underlying disease, decreased host immunity and/or frequent use of antibiotics.[11]

Interestingly, no type of surgery increased the risk of PMC and CDAD in this study; however, there were reports that GI surgery, which is known to contribute to changes in the normal intestinal flora due to the required pretreatment (e.g., bowel preparation, nasogastric tube insertion, and empirical antibiotic use), increases the risk of CDAD.[15,16,22] Moreover, McCarter *et al*.[23] reported that for pretreated patients, the risk of CDAD was 4.2 times higher than that of the control group, regardless of the type of surgery. Furthermore, probiotic use was not an independent preventive factor in the multiple logistic regression analysis, although some studies showed that probiotics might help to prevent *C. difficile* infection.[24-26] These discordant results regarding the effect of probiotics should be studied further.

In this study, surprisingly, female sex was another independent predictor of *C. difficile* infection. Although some studies have suggested that female sex may be one predictor,[27,28] it is difficult to explain the relationship between sex and *C. difficile* infection. Future studies should examine bowel-wall immunity with regard to sex to investigate the significance of this finding.

There are several limitations in this study. First, PMC may have been misclassified as CDAD because not all enrolled HAD patients underwent colonoscopy because of poor general condition or patient refusal. Therefore, the PPVs of PMC predictors might be underestimated; however, considering that most patients with PMC are in debilitated condition, unjustified endoscopic examination would be harmful and unethical because bowel preparation or air inflation during endoscopy could aggravate the colonic inflammation. Second, this study did not investigate the performance of cancer patients. The performance of cancer patients is varied. Some patients with localized curable cancer show normal performance, but others may perform very poorly due to progression of the cancer or systemic chemotherapy. Although there was approximately a 1.5-fold increase in the risk for both PMC and CDAD in cancer patients, this result could be altered if the performance scale of the cancer patients was to be evaluated. Third, selection bias is a possibility, although this study was conducted prospectively. We could not include nasogastric-tube feeding as a variable (although it is reported as a CDAD predictor in other studies) because we classified the patients with tube feeding as having other or indefinite causes of diarrhea and excluded these patients in the study design.

In conclusion, the independent predictors of PMC in HAD patients were PPI use, cephalosporins use, old age (≥70 years), and history of cancer. In particular, PPI use had the highest adjusted OR (4.07) for PMC. Therefore, we suggest the implementation of a preemptive management algorithm; based on the good NPVs of these predictors, endoscopic evaluation can be delayed in HAD patients without any predictors of PMC.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Lowe DO, Mamdani MM, Kopp A, Low DE, Juurlink DN. Proton pump inhibitors and hospitalization for Clostridium difficile-associated disease: a population-based study. Clin Infect Dis 2006;43:1272-1276.
2. Trnka YM, Lamont JT. Clostridium difficile colitis. Adv Intern Med 1984;29:85-107.
3. Surawicz CM, McFarland LV. Pseudomembranous colitis: causes and cures. Digestion 1999;60:91-100.
4. Muto CA, Pokrywka M, Shutt K, et al. A large outbreak of Clostridium difficile-associated disease with an unexpected proportion of deaths and colectomies at a teaching hospital following increased fluoroquinolone use. Infect Control Hosp Epidemiol 2005;26:273-280.
5. Dachs R. Interventions to improve antibiotic prescribing practices for hospital inpatients. Am Fam Physician 2008;77:618-619.
6. Ward CO. Diagnosis, treatment, and prevention of Clostridium difficile colitis. Consult Pharm 2003;18:1050-1054.
7. Weiss K. Poor infection control, not fluoroquinolones, likely to be primary cause of Clostridium difficile-associated diarrhea out-

breaks in Quebec. Clin Infect Dis 2006;42:725-727.
8. Changela U, Cannon JP, Aneziokoro C, Shah PS, Thottapurathu L, Lentino J. Risk factors and mortality associated with Clostridium difficile-associated diarrhoea at a VA hospital. Int J Antimicrob Agents 2004;24:562-566.
9. Dylewski J. The value of repeat Clostridium difficile toxin testing during and after an outbreak of C difficile-associated diarrhea. Can J Infect Dis Med Microbiol 2011;22:e12-e15.
10. Cunningham R, Dial S. Is over-use of proton pump inhibitors fuelling the current epidemic of Clostridium difficile-associated diarrhoea? J Hosp Infect 2008;70:1-6.
11. Bartlett JG. Clinical practice. Antibiotic-associated diarrhea. N Engl J Med 2002;346:334-339.
12. Lee KS, Shin WG, Jang MK, et al. Who are susceptible to pseudomembranous colitis among patients with presumed antibiotic-associated diarrhea? Dis Colon Rectum 2006;49:1552-1558.
13. Longo DL, Fauci AS, Kasper D, Hauser S, Jameson J, Loscalzo J. Alteration in gastrointestinal function. In: Longo DL, Fauci AS, Harrison TS, et al., eds. Harrison's principles of internal medicine. 18th ed. New York: McGraw Hill, 2012:311-312.
14. Feldman M, Friedman LS, Brandt LJ. Diarrhea. In: Sleisenger MH, Fordtran JS, Feldman M, Friedman LS, Brandt LJ, eds. Sleisenger and Fordtran's gastrointestinal and liver disease. Volume 1. 9th ed. Philadelphia: Saunders/Elsevier, 2010:211-232.
15. Southern WN, Rahmani R, Aroniadis O, et al. Postoperative Clostridium difficile-associated diarrhea. Surgery 2010;148:24-30.
16. Spencer RC. Clinical impact and associated costs of Clostridium difficile-associated disease. J Antimicrob Chemother 1998;41 Suppl C:5-12.
17. Cunningham R, Dale B, Undy B, Gaunt N. Proton pump inhibitors as a risk factor for Clostridium difficile diarrhoea. J Hosp Infect 2003;54:243-245.
18. Janarthanan S, Ditah I, Adler DG, Ehrinpreis MN. Clostridium difficile-associated diarrhea and proton pump inhibitor therapy: a meta-analysis. Am J Gastroenterol 2012;107:1001-1010.
19. Jayatilaka S, Shakov R, Eddi R, Bakaj G, Baddoura WJ, DeBari VA. Clostridium difficile infection in an urban medical center: five-year analysis of infection rates among adult admissions and association with the use of proton pump inhibitors. Ann Clin Lab Sci 2007;37:241-247.
20. Shah S, Lewis A, Leopold D, Dunstan F, Woodhouse K. Gastric acid suppression does not promote clostridial diarrhoea in the elderly. QJM 2000;93:175-181.
21. Taslim H. Clostridium difficile infection in the elderly. Acta Med Indones 2009;41:148-151.
22. Zerey M, Paton BL, Lincourt AE, Gersin KS, Kercher KW, Heniford BT. The burden of Clostridium difficile in surgical patients in the United States. Surg Infect (Larchmt) 2007;8:557-566.
23. McCarter MD, Abularrage C, Velasco FT, Davis JM, Daly JM. Diarrhea and Clostridium difficile-associated diarrhea on a surgical service. Arch Surg 1996;131:1333-1337.
24. Allen SJ, Wareham K, Bradley C, et al. A multicentre randomised controlled trial evaluating lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhoea in older people admitted to hospital: the PLACIDE study protocol. BMC Infect Dis 2012;12:108.
25. Hickson M. Probiotics in the prevention of antibiotic-associated diarrhoea and Clostridium difficile infection. Therap Adv Gastroenterol 2011;4:185-197.
26. Dendukuri N, Costa V, McGregor M, Brophy JM. Probiotic therapy for the prevention and treatment of Clostridium difficile-associated diarrhea: a systematic review. CMAJ 2005;173:167-170.
27. Khanna S, Pardi DS, Aronson SL, et al. The epidemiology of community-acquired Clostridium difficile infection: a population-based study. Am J Gastroenterol 2012;107:89-95.
28. Kuntz JL, Chrischilles EA, Pendergast JF, Herwaldt LA, Polgreen PM. Incidence of and risk factors for community-associated Clostridium difficile infection: a nested case-control study. BMC Infect Dis 2011;11:194.