A Study of *Clostridium difficile-Associated Disease* at King Chulalongkorn Memorial Hospital, Thailand

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Background: *Currently, in established antibiotic era, there is a widespread and increasing use of broad-spectrum antibiotics. Clostridium difficile, one of the troublesome intruders, flourishes when normal gut flora is altered by antibiotics. C. difficile is recognized as a frequent and leading cause of antibiotic-associated diarrhea and colitis. It causes substantial morbidity and mortality in hospitalized patients.*
Objective: *The present study was aimed at determining patient characteristics, clinical features, treatment, and outcomes of C. difficile-associated disease (CDAD) in hospitalized patients at King Chulalongkorn Memorial Hospital, Bangkok, Thailand.*
Material and Method: *From 2002 to 2005, 88 patients with positive latex immunoassay for C. difficile toxin A were identified. Data from medical records of 56 patients were available for analysis.*
Results: *Of 56 patients, there were 28 males and 28 females, with the mean age of 47.39 years (range: 4 months to 93 years). 50 (89.3%) patients had underlying illnesses with hematological malignancies (14 patients, 25%) and solid tumors (15 patients, 26.8%) being the most common. All patients had a history of antibiotic use including current (17 patients, 30.4%), recent (16 patients, 28.6%), or both current and recent uses (23 patients, 41.1%). Cephalosporins and carbapenems were the two most commonly prescribed antibiotics. 25 (44.6%) patients were receiving either omeprazole or ranitidine. 12 (21.4%) patients had received chemotherapy within two months before CDAD diagnosis. Of 50 stool specimens examined, only 26 (52%) had white or red blood cells. Colonoscopy was performed in only three patients, and pathological findings revealed non-specific colitis. Oral metronidazole, intravenous metronidazole, and vancomycin were prescribed for CDAD treatment in 38 (67.9%), 4 (7.1%), and 2 (3.6%) patients, respectively. 8 (14.3%) patients had no specific treatment, and the offending antibiotic was not discontinued in three of them. An overall initial response rate was 66.7%. 2 patients relapsed after metronidazole treatment.*
Conclusion: *The present study is the first in Southeast Asia to describe the decreased initial response rate of metronidazole treatment of CDAD. The reasons for this relatively poor response in the presented patients need to be determined in a future study.*

Keywords: *Clostridium difficile, Clostridium difficile-associated disease, Diarrhea, Antibiotic-associated diarrhea, Colitis, Pseudomembrane*

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Antibiotic-associated diarrhea (AAD) is defined as an unexplained diarrhea associated with the administration of antibiotics. The mechanisms by which antibiotics can cause AAD are not completely understood, but probably due to the direct effect of antibiotics to bowel motility function (i.e. erythromycin) or indirectly due to the disturbance of gut microflora leading to the overgrowth of pathogenic microorganisms. The onset of diarrhea ranges from a few hours after antibiotic therapy to 6-8 weeks after antibiotic discontinuation[1,2]. *Clostridium difficile* is the causative agents of AAD for only 10-20%, but is the major cause of antibiotic-associated colitis (AAC)[3-6].

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Almost all antibiotics, including vancomycin and metronidazole, have been linked to *C. difficile*-associated disease (CDAD). Clindamycin, cephalosporins, amoxicillin, and ampicillin are the antibiotics most frequently associated with CDAD[7,8]. Although fluoroquinolones are not usually associated with CDAD, several reports have recently published the association between the new fluoroquinolones especially with anti-anaerobic activity and CDAD[9]. In addition to antibiotics, antineoplastic chemotherapy[10-12] and gastric acid-suppressive agents[13] have been reported to be associated with CDAD.

The incidence of *C. difficile* infection has been increasing dramatically in the established antibiotic era, and is currently an important cause of nosocomial diarrhea. Certain uncommon features of CDAD have been reported increasingly. Recently, the severity of CDAD and the proportion of CDAD in community-acquired diarrhea are increasing[14-17]. In Thailand, one of the countries where antibiotics and gastric acid-suppressive agents have been overused, there have been a few published studies about CDAD. A recent study reported the prevalence of *C. difficile* isolated from the stools in Thai adult patients with suspected AAD was 18.64%[18]. The present study was aimed at determining patient characteristics, clinical features, treatment, and outcomes of CDAD in hospitalized patients at King Chulalongkorn Memorial Hospital, Bangkok, Thailand.

Material and Method

Patient population

All patients hospitalized at King Chulalongkorn Memorial Hospital from January 2002 to July 2005, whose stool specimens were positive for *C. difficile* toxin A, were included in the present study. The authors then retrospectively reviewed all available inpatient records of these patients.

Data collection

Clinical data including gender, age, comorbidities, clinical manifestations, medication exposure in the preceding 90 days (antibiotics, gastric acid-suppressive agents, and chemotherapeutic agents), treatment, and outcomes were recorded. Laboratory investigations including stool examination, stool cultures, colonoscopic and pathological findings were also recorded.

Microbiological examination

Stool specimens of all CDAD-suspected patients sent to the microbiology laboratory were analyzed for *C. difficile* toxin A by the latex immunoassay method (Oxoid®, Basingstoke, Hamshire, United Kingdom). According to the manufacturer's instructions, its sensitivity, specificity, positive predictive value, and negative predictive value were 90.4%, 97.8%, 94.2%, and 96.3%, respectively. All stool samples were tested within three hours after collection. If the samples could not be tested within this time, they were stored in a refrigerator at 2-8°C, and tested within 72 hours.

Statistical analysis

Continuous data were described as mean, median, and standard deviation; and categorical variables were described as number and percentages.

Results

Demographic data and clinical manifestations

From January 2002 to July 2005, 88 patients hospitalized to King Chulalongkorn Memorial Hospital, whose stool were positive for *C. difficile* toxin A, were enrolled in the present study. Of all 88 patients, 56 inpatient records (63.6%) were available for data analysis.

There were 28 males and 28 females with the mean and median ages of 47.39 and 53 years, respectively (range: 4 months to 93 years). 50 (89.3%) patients had underlying illnesses including hematologic malignancies (14 patients, 25%), solid tumors (15, 26.8%), diabetes mellitus (11, 19.6%), chronic renal failure (4, 7.1%), cirrhosis (2, 3.6%), steroid use (2, 3.6%), HIV infection (2, 3.6%) and others (7, 12.5%) (Table 1). Seven (12.5%) diabetic patients had more than one comorbidity. Only six (16.7%) patients had no underlying illness.

All 56 patients had diarrhea, with or without colitis. Two of them had recurrent diarrhea, 20 and 30 days after completion of CDAD treatment, respectively. There were no asymptomatic *C. difficile* toxin A carriers in the present study.

Laboratory findings

Stool examination was performed in 50 patients. Gross findings were mucous and/or bloody in only 17 (34%) patients. Stool leukocytes and erythrocytes were not present in 25 (50%) and 40 (80%) patients, respectively. Numerous white blood cells could be detected in the stool of nine (18%) patients. Enteric pathogens including *Pseudomonas aeruginosa* and *Salmonella* group C were isolated from the stool of two patients, and parasites including *Strongyloides stercoralis* and

Table 1. Comorbidities of all 56 patients with *Clostridium difficile*-associated diseases

Comorbidities	Number of cases (%)
Hematologic malignancies	14 (25.0)
Acute myeloid leukemia	6
Acute lymphoblastic leukemia	5
Non-Hodgkin's lymphoma	1
Multiple myeloma	2
Solid tumors	15 (26.8)
Teratoma with germinoma	1
Retinoblastoma	1
Nasopharyngeal cancer	1
Thyroid cancer	1
Breast cancer	1
Lung cancer	1
Hepatocellular carcinoma	1
Pancreatic adenocarcinoma	2
Insulinoma	1
Cervical cancer	2
Colonic cancer	3
Diabetic mellitus	11 (19.6)
Chronic renal failure	4 (7.2)
Cirrhosis	2 (3.6)
Steroid use	2 (3.6)
HIV infection	2 (3.6)
Others	7 (12.5)
Hypertension	2
Combined variable immunodeficiency	1
Griscelli syndrome	1
Biliary atresia	1
More than 1 comorbidities	7 (12.5)
No underlying disease	6 (16.7)

Table 2. Current and recents use of antibiotic(s) in 56 patients with *Clostridium difficile*-associated diseases

Number of antibiotic use	Number of cases (%)
Current use*	40 (71.4)
1 agent	27
2 agents	12
3 agents	0
> 3 agents	1
Recent use	16 (28.6)
1 agent	11
2 agents	4
3 agents	1
> 3 agents	0

* 23 patients with the history of both current and recent antibiotic use were categorized as patients with the history of current antibiotic use

Entamoeba histolytica were identified from another two patients.

Colonoscopy was performed in only three patients. Endoscopic findings were non-specific colitis in all of these patients. No typical pseudomembrane was noted in the presented patients. Biopsies were performed in two patients, and the pathological findings also revealed non-specific colitis.

History of antibiotic use

All patients had a history of antibiotic use including current use (40 patients, 71.4%) and recent use (16, 28.6%). 23 patients of the former group also received antibiotic(s) within the preceding 60 days (Table 2). Antibiotics were discontinued, 1-27 days (mean: 7.4 days) before the diagnosis of CDAD in all patients of the latter group. 38 (67.9%) patients received only one antibiotic. Two and three antibiotics were prescribed for 16 (28.6%) and one patient, respectively. The mean duration of antibiotic(s) prescribed were 8.6 days (range: 1 to 60 days) in the current-use group and 10.8 days (range: 3 to 38 days) in the recent-use group.

Antimicrobials agents commonly prescribed for the presented patients were cephalosporins (31 patients, 55.4%) and carbapenems (15, 26.8%) (Fig. 1). Metronidazole and vancomycin were suspected as the offending agents causing CDAD in two and four patients, respectively.

History of gastric acid-suppressive agent use

31 (55.4%) patients had not received gastric acid-suppressive agents. Of 25 patients receiving gastric acid-suppressive agent, 19 (33.9%) patients received omeprazole, and six (10.7%) patients received ranitidine. Both agents were given to the patients for 5-170 days (mean: 26.0 days) before the diagnosis of CDAD.

History of chemotherapy

12 (21.4%) patients had a history of receiving chemotherapeutic agents before the diagnosis of CDAD. No patients received chemotherapy treatment while they were having diarrhea. Patients received chemotherapeutic agents for 5-48 (mean: 21.75 days) before the diagnosis of CDAD. Chemotherapeutic agents most commonly prescribed for the presented patients were cytarabine plus idarubicin (six patients, 50%), followed by vincristine plus doxorubicin (2, 16.7%), cyclophosphamide plus busulfan (1, 8.3%), etoposide plus cisplatin (1, 8.3%), 5-fluorouracil plus cisplatin (1, 8.3%), and capecitabine (1, 8.3%) (Table 3).

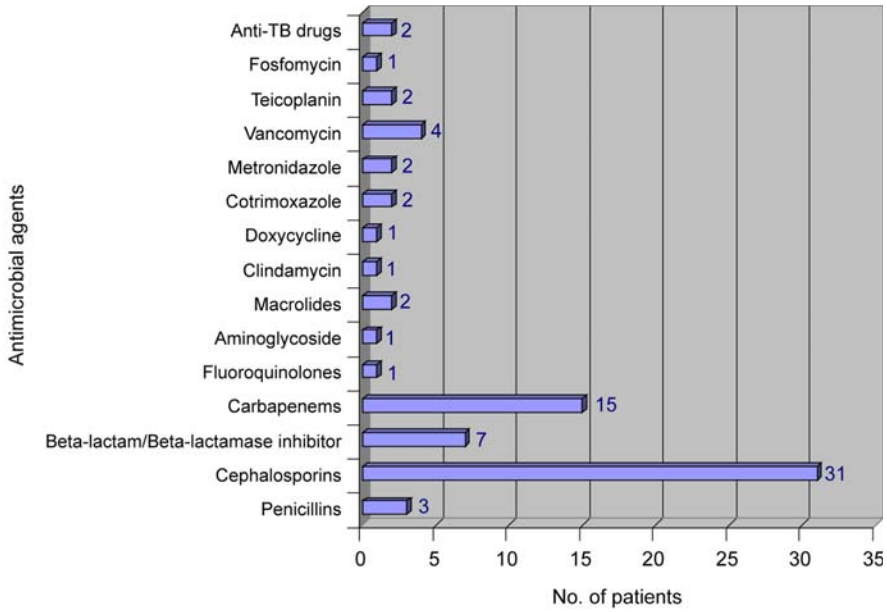

Fig. 1 Antimicrobial agents prescribed in 56 patients with *Clostridium difficile*-associated diseases

Treatment and outcomes

48 (85.7%) and 8 (14.29%) patients received and did not receive specific antibiotic treatment for CDAD, respectively (Table 4). The offending antimicrobial agents were discontinued at a mean duration of 2.2 days (range: 0 to 7 days) after the diagnosis of CDAD in 26 of 40 (65%) patients with current antibiotic use. Of these 26 patients, five (12.5%) patients did not receive the specific antibiotic treatment for CDAD. Of 48 patients with specific antibiotic treatment, no patients received intracolonic vancomycin, and no colectomy was performed in the presented patients. The most commonly prescribed antibiotic was oral metronidazole (38 patients, 67.9%), followed by intravenous metronidazole (4, 7.1%), and vancomycin (2, 3.6%). One patient received intravenous metronidazole in combination with oral vancomycin for the treatment of CDAD, but he eventually died from septicemia. Three patients did not improve after treatment with oral metronidazole, and a good clinical response was observed after a switch to intravenous metronidazole (Table 4).

Table 3. History of chemotherapy in 12 patients with *Clostridium difficile*-associated diseases

History of chemotherapy	Number of cases (%)
Ara-C plus idarubicin	6 (50)
Vincristine plus doxorubicin	2 (16.7)
Cyclophosphamide plus busulfan	1 (8.3)
VP-16 plus cisplatin	1 (8.3)
5-FU plus cisplatin	1 (8.3)
Capecitabine	1 (8.3)
Total	12 (100)

Ara-C: cytarabine, VP-16: etoposide, 5-FU: 5-fluorouracil

There was no improvement in 12 patients receiving specific treatment for CDAD including nine with oral metronidazole treatment, one with intravenous metronidazole treatment, one with oral vancomycin treatment, and one with intravenous metronidazole plus oral vancomycin (Table 5). Of these 12 patients, four patients did not discontinue the offending agents for CDAD.

Only one of eight (12.5%) patients without specific treatment had clinical improvement, in contrast to 32 (66.7%) patients with specific treatment being clinical response (Table 5). Overall 32 of 48 (66.7%) patients with clinical improvement, the mean duration of diarrhea resolution was 4.4 days (range: 1 to 11 days). Two patients with oral metronidazole treatment had recurrent CDAD. Overall mortality rate was 37.5% (21 of 56 patients). There was no CDAD-associated death in the presented patients. The most common cause of death was septicemia (14 patients, 66.7%), followed

Table 4. Treatment of 56 patients with *Clostridium difficile*-associated diseases

Treatment*	Number of patients (%)
1. No specific treatment	8 (14.3)
2. Specific treatment	48 (85.7)
Oral metronidazole	38 (67.9)
Intravenous metronidazole	4 (7.1)
Oral vancomycin	2 (3.6)
Intravenous metronidazole plus oral vancomycin	1 (1.8)
Oral metronidazole, and switched to intravenous metronidazole	3 (5.4)

* The offending antibiotics were discontinued in 26 of 40 (65%) patients with current antibiotic use

Table 5. Treatment in 56 patients with *Clostridium difficile*-associated diseases

Outcomes	Patients without specific treatment (n = 8) (%)	Patients with specific treatment (n = 48) (%)
Improved	1 (12.5)	32 (66.7)
Not improved	6 (75.0)	12 (25.0)
Unknown	1 (12.5)	4 (8.3)

n: number of patients

by hospital-acquired pneumonia (6, 28.6%), and acute renal failure (1, 4.8%).

Discussion

Risk factors for developing CDAD include extreme age, severe underlying comorbidities, hospitalization, and exposure to broad-spectrum antibiotic(s) particularly prolonged and combined antibiotic treatment[3,19]. In the present study, 89.3% of the patients had comorbidities, and 12.5% had more than one comorbidities. Only 16.7% had no underlying condition. All patients had been receiving or received antibiotic treatment within 60 days before the diagnosis of CDAD. A clinical spectrum of CDAD can vary from nuisance diarrhea to severe colitis with or without typical pseudomembrane formation, or toxic megacolon[3,20]. Most of the presented patients had mild watery diarrhea, and only 34% had mucous and/or bloody stool. Thus, colonoscopy was performed in a few patients, and all revealed mild colitis without typical pseudomembrane formation.

Cephalosporins and carbapenems were the most commonly prescribed antibiotics in the presented patients. However, most of them also received other non-antimicrobial agents attributable to CDAD including chemotherapeutic and gastric acid-suppressive agents. 44.6% of the presented patients were receiving either omeprazole or ranitidine when CDAD was diagnosed. 21.4% of the presented patients had received chemotherapy within two months before the diagnosis of CDAD. However, most of them received cytarabine and idarubicin which have never been reported to be associated with CDAD.

In the present study, the authors identify *C. difficile* toxins using the latex immunoassay method in the stool specimens to exclude false-positive patients (carriers with other causes of diarrhea). However, the presented toxin assay detected only toxin A. 1-2% of patients with CDAD could be caused by *C. difficile* that produced only toxin B[3].

In the present study, overall initial response rate was 66.7% with oral metronidazole being the most common drug prescribed. Four of 12 patients without clinical response still received the offending antibiotic without discontinuation after CDAD diagnosis. Two patients relapsed after metronidazole treatment. In the literature, metronidazole and vancomycin have similar rates of efficacy, with initial response rate ranging from 90 to 97%[3,20,21]. However, the reduced initial response rates to metronidazole were recently reported in the studies at Quebec, Canada by Muscher et al (78%)[22] and at Houston, the United States by Pepin et al (74%)[23]. In addition to an increased rate of failure, an increasing incidence, an increased relapse/recurrence rate, disease severity, and severe disease in non-traditional hosts (for example younger age, otherwise healthy, non-institutionalized individuals, and some without apparent antimicrobial exposure). The reasons for these are unknown, and are the subject of further investigations.

The main limitation of the present study was related to its retrospective nature. CDAD may be under-diagnosed in the institute study because of lack of awareness of the disease among clinicians and diagnostic method used.

In summary, the present study is the first in Southeast Asia to describe the decreased initial response rate of the metronidazole treatment of CDAD. The reasons for this relatively poor response in the presented patients need to be determined in a future study.

Potential conflicts of interest: No conflicts of interest exist among the authors.

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การศึกษาโรคเนื่องจาก Clostridium difficile ที่โรงพยาบาลจุฬาลงกรณ์ ประเทศไทย

จักรพันธ์ ภู่ไพบูลย์, มยุรี ขันติพงศ์, ชุษณา สวนกระต่าย

ภูมิหลัง: *ในปัจจุบันซึ่งเป็นยุคของการใช้ยาปฏิชีวนะ มีการเพิ่มขึ้นของการใช้ยาปฏิชีวนะที่มีการออกฤทธิ์อย่างกว้างขวาง และนำมาใช้อย่างแพร่หลาย Clostridium difficile ซึ่งเป็นแบคทีเรียที่อยู่ในลำไส้มนุษย์จะมีจำนวนเพิ่มขึ้นและสามารถก่อให้เกิดโรคได้จากผลกระทบจากการให้ยาปฏิชีวนะนี้*

วัตถุประสงค์: *การศึกษานี้เพื่อศึกษาข้อมูลทางระบาดวิทยา ลักษณะทางคลินิก การรักษา และผลการรักษาในผู้ป่วยที่เป็นโรคเนื่องจาก Clostridium difficile ที่รับไว้รักษาตัวในโรงพยาบาลจุฬาลงกรณ์ กรุงเทพมหานคร ประเทศไทย*

วัสดุและวิธีการ: *ในระหว่างปีพุทธศักราช 2545-2548 มีผู้ป่วย 88 ราย ที่ได้รับการวินิจฉัยโรคเนื่องจาก Clostridium difficile โดยวิธี latex immunoassay สำหรับ toxin A แต่มีเพียง 56 (64%) ราย ที่ได้ข้อมูลมาวิเคราะห์อย่างครบถ้วนสมบูรณ์*

ผลการศึกษา: *ในผู้ป่วย 56 ราย มีผู้ป่วยชาย 28 ราย และผู้ป่วยหญิง 28 ราย โดยมีอายุเฉลี่ย 47.39 ปี (ค่าพิสัยระหว่าง 4 เดือน – 93 ปี) ผู้ป่วย 50 ราย (ร้อยละ 89.3) มีโรคประจำตัว โดยเป็นโรคมะเร็งทางโลหิตวิทยา 14 ราย (ร้อยละ 25) และโรคมะเร็ง 15 ราย (ร้อยละ 26.8) ที่พบบ่อยสุด ผู้ป่วยทั้งหมดมีประวัติการใช้ยาปฏิชีวนะ โดยจำแนกเป็นการใช้ในปัจจุบัน 17 ราย (ร้อยละ 30.4) การใช้เร็ว ๆ นี้ 16 ราย (ร้อยละ 28.6) และมีการใช้ทั้งในปัจจุบัน และในเร็ว ๆ นี้ 23 ราย (ร้อยละ 41.1) โดยเป็นการใช้ยาปฏิชีวนะในกลุ่ม cephalosporins และ carbapenems มากที่สุด นอกจากนั้นยังมีผู้ป่วย 25 ราย (ร้อยละ 44.6) ที่มีการใช้ omeprazole หรือ ranitidine และผู้ป่วย 12 ราย (ร้อยละ 21.4) ได้รับยาเคมีบำบัดภายใน 2 เดือน ก่อนการวินิจฉัยโรคเนื่องจาก Clostridium difficile นี้ จากการตรวจอุจจาระในผู้ป่วย 50 ราย พบ 26 ราย (ร้อยละ 52) มีอุจจาระที่มีเม็ดเลือดขาวหรือเม็ดเลือดแดง การตรวจด้วยกล้อง ผ่านทางทวารหนัก (colonoscopy) ในผู้ป่วย 3 ราย พบการอักเสบของลำไส้ใหญ่ที่ไม่จำเพาะ สำหรับการรักษาจำแนกเป็นการให้ยา metronidazole รับประทาน metronidazole ทางหลอดเลือดดำ และ vancomycin ในผู้ป่วย 38 ราย (ร้อยละ 67.9) 4 ราย (ร้อยละ 7.1) และ 2 ราย (ร้อยละ 3.6) ตามลำดับ ผู้ป่วย 8 ราย (ร้อยละ 14.3) ไม่ได้รับการรักษาด้วยยาปฏิชีวนะ และผู้ป่วย 3 ใน 8 รายนี้ที่ไม่ได้หยุดยาปฏิชีวนะที่น่าจะเป็นสาเหตุของโรคเนื่องจาก Clostridium difficile นี้ โดยสรุปมีการตอบสนองต่อการรักษาในครั้งแรกเป็นร้อยละ 66.7 และมีผู้ป่วย 2 รายมีการกลับเป็นโรค ใหม่หลังได้ยา metronidazole*

สรุป: *การศึกษานี้เป็นการศึกษาแรกของทวีปเอเชียตะวันออกเฉียงใต้ที่แสดงถึงการลดลงของอัตราการตอบสนองต่อการรักษาด้วยยา metronidazole ในโรคเนื่องจาก Clostridium difficile สำหรับสาเหตุของผลการรักษาที่ลดลงในผู้ป่วยเหล่านี้คงต้องรอการศึกษาในอนาคตเพิ่มเติม*