

Pseudomembranous Colitis :

A Clinical Report from Southern Taiwan

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Abstract

Pseudomembranous colitis is a disease commonly associated with hospitalization. This retrospective study shares the experience of treating pseudomembranous colitis in a Taiwanese hospital. From January 1996 to December 2005, fifty-nine patients, 33 males and 26 females with mean age of 60.9 ± 5.4 years (ranging from 26-84 years-old) were included into this retrospective study. The diagnosis was based on either by sigmoidoscopy or colonoscopy and confirmed by a pathologist and/or by a positive stool culture study. Patients were divided into 3 groups: group A with mild symptoms and diarrhea 3-5 times per day (n=8); group B having moderate symptoms with diarrhea more than 6 times per day, and stable vital signs but without massive or bloody diarrhea (n=41); group C having severe symptoms and signs of massive, watery or bloody diarrhea, and signs of toxic megacolon, and unstable vital signs implying hypovolemic shock (n=10). Several clinical variables and treatment outcomes were compared. Thirty-five of the patients had prior antibiotics exposure with cephalosporin most commonly associated (n=14). Significant variables were, age > 65 year-old, bloody diarrhea, fever, leukocytosis, and hypoalbuminemia. Twenty-five patients received oral vancomycin treatment, 76% were responders, and 6 were non-responders which included 2 recurrences. Four patients belonged to group C. Twenty-six patients received metronidazole treatment and 88.5% were cured. Three patients were treatment failures (one recurred) and all were cured by shifting to the alternate regimen, but 2 cancer patients with relapses died. The overall mortality rate was 3.4 %. We conclude that metronidazole is generally recommended as a first drug of choice in treating pseudomembranous colitis, which also has a cost-benefit. Age > 65 year-old and poor general health statuses are the relevant risk factors for developing into moderate to severe PMC. High suspicion is important in patients with gastrointestinal symptoms especially those with prior exposure to antibiotics or high-risks patients with long-term hospitalization. (J Intern Med Taiwan 2008; 19: 253-259)

Key Words : Pseudomembranous colitis, *Clostridium difficile*, Vancomycin, Metronidazole

Introduction

Pseudomembranous colitis (PMC) is a disease process commonly associated with hospitalization and prior antibiotic exposure¹⁻³ caused by toxins produced by *Clostridium difficile* (*C. difficile*)⁴. It is also referred to as *C. difficile* associated diarrhea, antibiotic-associated colitis and antibiotic-associated cases of diarrhea⁵⁻⁷. *C. difficile* can be carried asymptotically as normal gastrointestinal flora, and can be as high as 46% in the hospitalized patients. To date, at least 3 virulence factors are recognized: an enterotoxin (toxin A), a cytotoxin (toxin B), and a substance to inhibit bowel motility⁴. Toxin A is a potent enterotoxin that is lethal and cytotoxic. Toxin B is also lethal, and is much more cytotoxic than toxin A. Although the exact mechanisms by which these toxins cause damage to colonic mucosal cells are unknown, it is thought that the toxins can act synergistically⁸ and play a major role in the diarrhea and colitis caused by *C. difficile*⁷.

However, PMC can potentially cause significant morbidity and mortality⁹. Early diagnosis and appropriate treatment of PMC is very important in clinical practice. We can use readily available clinical and laboratory information to decide which patients are likely to have *C. difficile* disease and when it is appropriate and useful to order specific diagnostic tests for *C. difficile* toxin. This study shares our experiences of treating the disease over the past 11 years.

Material and Methods

Patients

Fifty-nine patients, 33 males and 26 females with mean age of 60.9 ± 5.4 years (ranging from 26-84 years-old) diagnosed as PMC from January 1996 to December 2005 were included into this study. The diagnosis of PMC was based on the following criteria: typical colonoscopic or sigmoidoscopic fluffy white-yellowish membranes caused by exudate on colorectal mucosa (Fig. 1). Microscopically, the lesions resemble small pseudomembranes composed of

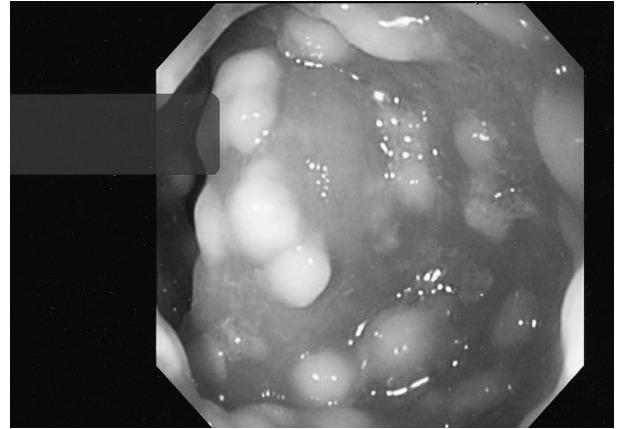


Fig.1. Typical colonoscopy shows fluffy white-yellowish membranes with exudates on colorectal mucosa.



Fig.2.A characteristic volcano lesion may be seen in which crypts erupt as mucus and neutrophils stream from destroyed gland. Surrounding crypts may appear normal. (H&E, 40X)



Fig.3.Small pseudomembrane is composed of fibrin, inflammatory debris with superficial necrosis in underlying mucosa. (H&E, 100X)

fibrin, inflammatory debris with superficial necrosis underlying mucosa (Fig. 2 and Fig. 3). Routine fresh stool culture positive for *C.difficile*, negative for *salmonella*, *shigella*, *campylobacter* and *ameba histolytica* is also used as a diagnostic test in these symptomatic in-patients.

We then classify PMC according to the severity of the diseases as: group A having mild symptoms with diarrhea 3 to 5 times diarrhea per day (n=8); group B having moderate symptoms with diarrhea more than 6 times per days, stable vital signs but without massive or bloody diarrhea (n=41); group C having severe symptoms and signs of massive, watery or bloody diarrhea, and signs of toxic megacolon, and unstable vital signs implying hypovolemic shock (n=10). The definition for complete cure of the disease is passage of less than 3 episodes of formed stool each day for more than 3 weeks. Treatment failures are those patients who suffered from 3 or more episodes of loose stool per day despite 7 days of treatment. Relapse means reappearance of the symptoms of diarrhea 3 or more episodes per day within 3 weeks after initial response to the first treatment.

Treatments

Patients with mild symptoms were treated with symptomatic supportive care such as intravenous fluid supply and anti-diarrhea agent avoiding antiperistaltic agents and opiates. Oral form vancomycin were administrated at 250 milligrams(mg) qid for 10-14

days in some patients while metronidazole 500 mg qid per oral or by intravenous infusion in the others for 10-14 days. For those who were treatment failures or when relapses occurred, we shifted to the other alternative antibiotic for another course of 14 days.

Statistical analysis :

Each possible relevant variable such as the age, laboratory results, and treatment outcome between using different antibiotics of patients in each severity group were compared by using Fisher exacts test and Chi-square test. A p value < 0.05 was considered as statistical significance.

Results

Among the 59 patients of PMC in this study, thirty-nine patients were 65 years-old or above (66%) with mean age of 60.9 ± 5.4 years. Our results also showed only 35 patients had used antibiotics within 6 weeks of diagnosis of PMC. Sixteen patients received antibiotics during admission at our hospital due to infections such as pneumonia, cellulites, biliary tract infection, and pelvic inflammatory disease. Nineteen patients had antibiotics treatment at local clinics within 6 weeks prior to the diagnosis of PMC but 13 of them were uncertain about the exact antibiotics regimens. On the whole, the most commonly involved antibiotic was cephalosporin (n=14), followed by the penicillin group of antibiotics (n=5), and clindamycin (n=4). According to the available chart-

Table 1. Comparisons of Clinical Variables in Each Group of Patients with PMC

Variables	n (%)	Group A n=8 (%)	Group B n=41 (%)	Group C n=10 (%)
Age > 65 year-old	39 (64.4)	2(25.0)	37(90.2)	10(100) ^{*1}
Fever	37 (62.7)	1(12.5)	26(63.4)	10(100) ^{*2}
Hypoalbuminemia (< 2.5 g/dL)	36 (61.0)	2(25.0)	24(58.5)	10(100) ^{*3}
WBC > 10000/mm ³	23 (39.0)	1(12.5)	14(34.1)	8(80.0) ^{*4}

^{*1} : A versus C: p<0.001; and B versus C: p <0.001

^{*2} : A versus C: p<0.001; A versus B: p=0.016; B versus C: p=0.026

^{*3} : A versus C: p<0.018; B versus C: p=0.024

^{*4} : A versus C: p=0.015; B versus C: p=0.013

Statistical analysis: Fisher's exact test

Abbreviations: PMC: Pseudomembranous colitis

recording, only 5 patients could confirm prior exposure to the gastric acid suppression drug and 19 to the anti-inflammatory drugs before PMC occurred. Aged, hypoalbuminemia, leukocytosis (WBC > 10000/mm³) and fever were the significant relevant factors indicating the disease severity (Table 1).

Thirty-four patients received colonoscopy examinations and only 5 of them had lesions involving the entire colon and all of them belonged to group C patients. The other 25 patients were reluctant to receive colonoscopy and signed informed consent for sigmoidoscopy examinations only. Despite the reluctances of these 25 patients, all the 59 patients were involved at least both the rectum and sigmoid colons.

All the eight patients in group A had recovered after symptomatic supportive care such as intravenous fluid supply and anti-diarrhea agents avoiding anti-cholinergic agents (Table 2). Twenty-five patients received oral vancomycin treatment and twenty-six were given metronidazole treatment. Only 19 patients that were prescribed by vancomycin achieved complete cure (76 %). For the other 6 patients (24 %), 4 treatment failures were cured after shifting to metronidazole for a course of 14 days. Two patients suffered from relapses 4 to 5 weeks after initial treatment success (8 %) but only the one in group

B was cured after shifting to the metronidazole treatment, also for 2 weeks. The other cancer patient who had suffered from relapse and expired due to terminal stage of the disease. Twenty-three of the patients treated with metronidazole them were cured (88.5 %). Two were treatment failures, both of them were cured after shifting to vancomycin treatment for 2 weeks. One patient with underlying terminal stage of metastatic colon cancer disease, relapse occurred 4 weeks after initial success also died of toxic co-morbidities during the later course of the hospital stay. There was no statistical significance in comparing each severity groups whether or not the patients were using vancomycin and metronidazole (p=0.252). The overall mortality in this study was about 3.4 %.

Discussion

In recent years there has been a marked increase in the incidence of PMC^{1,2}. PMC is more common in patients over 65 years of age and can cause significant morbidity¹⁰. The majority of *C. difficile*-positive patients were treated previously by antibiotics^{2, 11}. Although most people who develop *C. difficile* infection do so in one of two general ways: antibiotics, chemotherapy, invasive bowel procedures (such as surgery or colonoscopy), or any other factors that dis-

Table 2. The Treatment Outcome in Each Group of PMC

Initial treatment option	Outcome	Group A	Group B	Group C	Total
Vancomycin n=25 (%)	Complete cure	-	17(68.0)	2(8.0)	19(76.0)
	Treatment failure	-	1(4.0)	3(12.0)	4(16.0)
	Relapse ※	-	1(4.0)	1(4.0)※	2(8.0)
Metronidazole n=26 (%)	Complete cure	-	22(84.6)	1(3.9)	23(88.5)
	Treatment failure	-	-	2(7.7)	2(7.7)
	Relapse ※	-	-	1(3.8)※	1(3.8)
Supportive care n=8 (%)	Complete cure	8(100)	-	-	-
Overall mortality					2(3.4)

Complete cure Versus treatment failures including relapses: (vancomycin / metronidazole): p=0.252 (Using Chi-Square test)

※: Both relapses in each group did not respond by shifting to the alternate antibiotics but expired after developed into toxic diseases.

Abbreviations: PMC: Pseudomembranous colitis

rupt normal bowel flora and cause an overgrowth of *C. difficile*; or the organism is acquired from a health care worker's contaminated hands or from direct contact with environmental surfaces contaminated with *C. difficile*¹².

According to some studies, 15% to 20% of hospital patients may be colonized with *C. difficile*¹³⁻¹⁶. While most colonized hospital patients won't develop *C. difficile* disease, they represent a large reservoir of *C. difficile* with the potential to contaminate the environment and health care workers' hands. Poor hand hygiene and erratic disinfection practices can then easily result in the transmission of *C. difficile* to susceptible patients^{12,17}. There have been studies reporting that 26-63 % of patients had not received any antibiotics within the three months prior to diagnosis^{18,19}. Some of them claimed that the risk of PMC was increased by the use of proton pump inhibitor gastric acid suppressants and the use of non-steroidal anti-inflammatory drugs but the response was inconsistent among researchers^{17,18,20}. In our series, only thirty-five of the patients were exposed to prior antibiotics. The limitation of this retrospective study does not allow us to have sufficient evidences to explain the exact source of infection for this group of patients. We can neither correlate the disease to gastric acid suppressor nor non-steroidal anti-inflammatory agent users.

Diagnosis now tends to be made by detecting toxin and so laboratories no longer culture *C. difficile*. This hampers wider public health control of outbreaks and monitoring of antibiotic sensitivities because there may be a delay in detecting emerging epidemic strains^{20,21}. In one study, cytotoxin is absent from the stools of a small proportion of endoscopically proved cases²². We were very careful with the diagnosis of PMC in the past because our diagnosis was made by using endoscope diagnosis and fresh stool culture results. However, no episodes of infectious colitis occurred during the same period of hospitalizations in that particular ward where patients

with PMC was admitted. Of course, there could be asymptomatic carriers of *C. difficile* in the same ward but there has not been any outbreak of the disease in our hospital to date. The antibiotic prescription habits of doctors were also strictly controlled in our hospital's policy and this could contribute to the results.

Treatment can be divided into treating the *C. difficile* associated diarrhea and the measures to prevent other patients developing it. Therapy for patients with *C. difficile* associated diarrhea comprises supportive measures with adequate fluid and electrolyte replacement, withdrawal of current antibiotic therapy if possible, and antibiotic treatment to eradicate *C. difficile*. The major treatment antibiotics used are still metronidazole or vancomycin. Resistance to metronidazole and vancomycin is not reported, but changing antibiotics is often tried empirically after one week if symptoms have not resolved²⁰. One study suggested vancomycin should be used as first line treatment for patients with albumin < 2.5 g/l or for patients who are in intensive care²³. In our studies, we found patients with age > 65 years, hypoalbuminemia, fever, and leukocytosis are relevant to severe disease which imply that poor health status and the severity of the disease among these patients. No statistical significance exists in comparing patients with complete cures, treatment failures (relapses included) between those who were treated by using vancomycin and metronidazole (p=0.252) could be due to the small sample size of this study. Nevertheless, metronidazole has great much more cost-benefit savings than vancomycin in Taiwan and is therefore preferred to be used as the first line antibiotics in treating PMC.

Relapse could occur in up to one third of cases, and is mostly associated with older age and poor immunity status of the patient^{20,24} like the 3 of our patients. It is sometimes difficult to determine whether this is due to failure of eradication of *C. difficile* and subsequent recolonisation with normal colonic bacterial flora, or to a new infection of a susceptible patient. Colonisation with more than one strain is not

uncommon²⁰. Besides, the role of spores in the recurrence could be responsible for not being sensitive to the antibiotics²³. It is not unusual for an initial episode of *C. difficile* associated diarrhea to affect the patient's nutritional status and for the serum albumin to remain low at the time of recurrence. The overall mortality is about 3.4 % which is much lower than most reports (8-20 %) ²⁵.

In conclusion, metronidazole is generally recommended as the initial drug of choice for PMC in Taiwan, which has clear cost savings. Aged patients older than 65 years-old and those with poor general health status are at higher risks of developing into moderate to severe PMC once infected. High suspicion is important in patients with gastrointestinal symptoms especially those with prior exposure to antibiotics or high-risk patients with long-term hospitalization.

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偽膜性大腸炎：南台灣之臨床報告

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摘 要

偽膜性大腸炎是一種常與住院相關的疾病。本篇回顧性研究是南台灣治療偽膜性大腸炎的臨床經驗。從1996年1月至2005年12月共收集59位偽膜性大腸炎病人(33男性,26女性;平均年齡 60.9 ± 5.4 歲,年齡分佈26-84歲)。雖然本院無法檢測cytotoxin,主要診斷依據是乙狀結腸鏡或大腸鏡發現配合糞便培養陽性。病患分成三群:A群8位具有輕度症狀,B群41位具有中度症狀,C群10位具有嚴重症狀。35位病患先前有使用抗生素治療,其中14位使用cephalosporin。重要的影響因素包括年齡大於65歲,血性腹瀉,發燒,白血球增加與低白蛋白血症。24位接受口服vancomycin治療,76%有反應,6位無反應,包括2位復發,4位病患屬於C群。26位接受metronidazole治療,88.5%有反應,3位無反應,包括1位復發。所有無反應者除2位癌症病患死於復發,其餘皆靠改變治療抗生素治癒。全部死亡率為3.4%。我們建議metronidazole應作為治療偽膜性大腸炎的首選藥物,因其較符合治療經濟效益。年齡大與較差健康狀況者較易從中度症狀進展至嚴重症狀。