Management of antibiotic-associated pseudomembranous colitis in Non-hospitalized and hospitalized patients

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Abstract: Proper management of antibiotic-associated pseudo membranous colitis is not clear. This article is to investigate proper treatment of antibiotic-associated pseudo membranous colitis. Data of 67 patients (aged 18-69 years, with 31 males and 46 females) with antibiotic-associated pseudo membranous colitis were retrospectively analyzed including the demography, antibiotics to induce and for treatment of the pseudo membranous colitis, and other supportive measures. All 67 patients had a positive cytotoxin test, which confirmed the pseudo membranous colitis. Antibiotics which induced the pseudo membranous colitis included clindamycin, ofloxacin, piperacillin, cefatriaxone, penbritin and ceftazidime. Once the correct diagnosis was made, the culprit antibiotics were discontinued immediately, and narrow-spectrum antibiotics like metronidazole and vancomycin were administered in combination with correction of fluid and electrolyte abnormalities, use of vitamins C and B complex to repair the intestinal mucosa, and avoidance of antispasmodic and antidiarrheal agents. After appropriate treatment for 2-20 days, all patients recovered with no sequela. Sixty-two patients were clinically cured while five (7.5%) had diarrhea recurrence within two months of the end of therapy. Retreatment with tapering and extended period of metronidazole and/or vancomycin led to complete recovery of the patients. Multiple antibiotic agents are associated with pseudo membranous colitis, and correction of fluid and electrolyte abnormalities and use of vitamins to repair the intestinal mucosa should be performed to speed up the cure process.

Keywords: Antibiotic-associated, Pseudo membranous colitis, Clostridium difficile, Narrow spectrum antibiotics.

INTRODUCTION

Antibiotic-associated diarrhea is now believed to be the most common intestinal infection in the hospitals of the United States (US), accounting for 10% of the symptomatic patients of infection (Lau & Chamberlain, 2016; Leal *et al*., 2016; Li *et al*., 2016; Roberts *et al*., 2016; Wiedel *et al*., 2016; Yoldas *et al*., 2016). The antibiotic-associated diarrhea is often caused by Clostridium (C.) difficile, which lives in the colon of human beings after the normal flora in the colon has been changed by use of antibiotics agents. The C. difficile then produces two exotoxins of protein (A and B) to bind to their coloncyte receptors for stimulating a substantial secretion of fluid (diarrhea) as well as necrosis of superficial mucosa, which was related to an acute infiltrate of inflammation. Some clinical responses are generated from infection of this bacterium, including static carrier without symptoms to acute enteritis of pseudo membrane (Castagliuolo & LaMont, 1999). However, this bacterium was originally believed to be harmless in the intestine since young babies with this organism demonstrated no signs or symptoms of sickness (Castagliuolo & LaMont, 1999). In 1978, *C. difficile* was discovered to be the cytotoxin source revealed in the feces of patients who had antibiotic-related pseudo membranous enteritis (Bartlett *et al*., 1978; McFarland *et al*., 1991) and this bacterium could cause immediate death of animals who were injected with *C. difficile* culture filtrate. This organism is now identified to be the primary hospital pathogen, which can cause massive morbidity in old patients in hospital and in nursing home since they use antibiotic agents more often in a circumstances, which is probably contaminated with the spores of *C. difficile*. It is estimated that 3-4 million cases of colitis and diarrhea caused by *C. difficile* will be newly developed in the US hospitals every year, affecting 10% of patients in hospital (McFarland *et al*., 1989). *C. difficile* usually attacks the elderly or debilitated patients in hospital. On the contrary, outpatients are rarely infected with this bacterium and the estimated infection rate is only 20,000 cases per year (Hirschhorn *et al*., 1994). Dangerous factors for *C. difficile* infection are exposure to various antibiotic agents or to an infected family member, gastrointestinal surgery, and enteral feeding. In our daily clinical practice, we have encountered some cases of both hospitalized and clinic patients of diarrhea caused by infection with *C. difficile* and reported our experience here.

MATERIALS AND METHODS

Patients who were 18 years or older with C. difficile-caused diarrhea were assessed retrospectively and this

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study was approved by the Ethics Board for Scientific Research of our institution, with waived requirement of the informed consent. Sixty-seven patients with pseudo membranous colitis caused by *C. difficile* infection were retrospectively included in this study between June 2010 and July 2013, including 31 males and 46 females with an age range of 18-69 years (mean 53) (fig. 1 and table). Twenty-eight patients initially had common diarrhea, which was defined as 3 or more bowel actions per day and were treated with antibiotics (ofloxacin 2 capsules, 3 times daily), which induced the pseudo membranous colitis. In nineteen patients with car accidents, pseudo membranous colitis occurred following treatment with clindamycin and/or multiple antibiotics including piperacillin and cefatriaxone. Nine patients with diabetes and 7 patients with cerebral infarction all had pseudo membranous colitis while on systemic antibiotics. Two patients had pseudo membranous colitis after treatment with ofloxacin for herpes zoster and skin ulceration. In the last two patients with subarachnoid hemorrhage resulted from a ruptured cerebral aneurysm, which was embolized endovascularly with coils, pseudo membranous colitis ensued after treatment with ceftazidime.

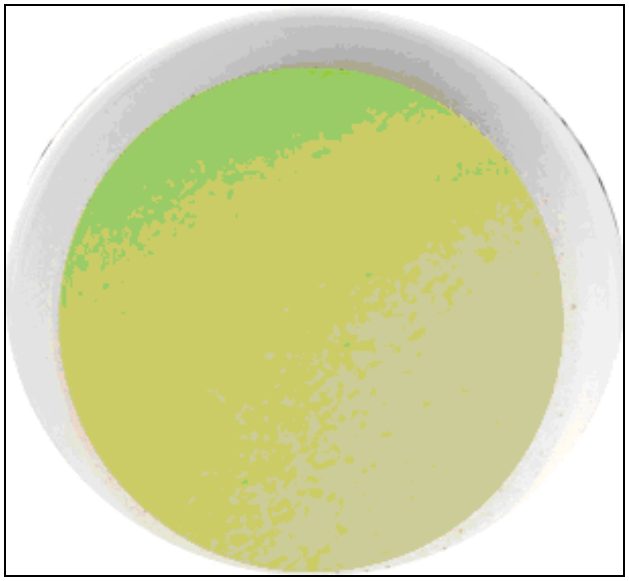

Fig. 1: Stool from patients with antibiotic-associated pseudo membranous colitis.

STATISTICAL ANALYSIS

The data were presented as mean ±SD (standard deviation) unless stated otherwise and were compared with Student's t-tests. The significance of P value was set at <0.05. All analyses were studied by use of SPSS 16.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

All patients had the cytotoxin test which confirmed the diagnosis of pseudo membranous colitis (table). Once the correct diagnosis was made, the original antibiotics which induced the pseudo membranous colitis were stopped immediately and metronidazole and/or vancomycin applied in combination with other supportive measures like vitamin B-complex and folic acid to repair the intestinal mucosa, correction of fluid and electrolyte abnormalities, and avoidance of antispasmodic and antidiarrheal agents. After treatment with metronidazole and/or vancomycin for 2-20 days, all patients recovered with no sequela. The definition of recovery of diarrhea was well-formed or <3 unformed defecation daily for two days while relapse was defined to be repeated diarrhea within two months of the end of treatment with a positive toxin test of *C. difficile*. Sixty-two patients had clinical cure but five (7.5%) had recurrence of diarrhea. The five had continued exposure to systemic wide-spectrum antibiotic agents during the treatment for the *C. difficile*-associated diarrhea. For recurrent diarrhea, the systemic wide-spectrum antibiotic agents were stopped and gradual tapering of metronidazole and/or vancomycin led to the recovery of the patients.

DISCUSSION

The *C. difficile* colonizes the intestinal lumen and causes pseudo membranous colitis because some organisms which can prevent the colonization of the *C. difficile* in the normal intestinal bacterial flora has been destroyed by antibiotic agents (Lau & Chamberlain, 2016; Leal *et al*., 2016; Li *et al*., 2016; Roberts *et al*., 2016; Wiedel *et al*., 2016; Yoldas *et al*., 2016). More than 90% of the fecal flora is Bacteroides which probably inhibit the colonization of *C. difficile* because some of them disappeared during *C. difficile* colitis and diarrhea but repopulated after the patient was recovered from the infection (Tvede & Rask-Madsen, 1989). Both antibiotics and some cancer therapeutic agents can readily make it easy for *C. difficile* to colonize the intestinal tract (Anand & Glatt, 1993; Kelly *et al*., 1994), but some antibiotic agents can bring about symptomatic infection by *C. difficile*, probably because of their specific effects on the normal bacterial flora in the colon. Clindamycin is probably the commonest antibiotic agent to cause colitis and diarrhea, but chemical agents like penicillins and cephalosporins with a broad spectrum can frequently cause *C. difficile* colitis. In this study, the antibiotics leading to pseudo membranous colitis included clindamycin, ofloxacin, piperacillin, cefatriaxone, penbritin and ceftazidime.

C. difficile can excrete potent toxins to act against cultured fibroblast and other cells and to bind the glycoprotein receptors on the brush border of human colonocytes. The resultant cell rounding and dysfunction of tight junctions were brought about by filamentous actin disaggregation and dysfunction of the GTP-binding Rho of protein (Just *et al*., 1995). Then, the epithelial cells

Table 1: Demography, data and antibiotics before and after treatment

Variables	Values
No. of patients	67
Outpatient	22
Inpatient	45
Age (y)	18-69 (mean 53)
Male: Female	31:46
Pre-CD diarrhea diseases	
Common diarrhea	28
Car accidents	19
Diabetes	9
Cerebral infarction	7
Subarachnoid hemorrhage	2
Herpes zoster and skin ulceration	2
No. of patients on systemic antibiotics	
Before diagnosis of CD diarrhea	
Ofloxacin	28
Clindamycin	12
Piperacillin	9
Penbritin	7
Ceftazidime	6
Cefatriaxone	5
After correct diagnosis	
Metronidazole	11
Metronidazole and berberine	28
Metronidazole and vancomycin	19
Vancomycin and fungicidin	9
No. of daily bowel movements	3-8 (mean 5)
Cytotoxin test	All positive
Time to resolution postdiagnosis (d)	2-20 (mean 5)
No. of patients with clinical cure	62
No. of patients with diarrhea recurrence	5

necrosed and dropped into the enteric lumen. However, toxin A rather than toxin B was demonstrated to induce inflammatory diarrhea in animal experiments. Rodent animal studies revealed that toxin A induced acute diarrhea of inflammation if injected into closed loops of intestine, leading to substantial fluid production, damage of mucosa and prominent infiltration of neutrophils (Kelly *et al*., 1994; Triadafilopoulos *et al*., 1987). The complex interaction among the epithelial and inflammatory cells, and sensory nerves in the intestine accounts for the pathophysiology of this toxic inflammation.

The cytotoxin test of the stool is the gold standard for correct diagnosis of infection with *C. difficile* and is in light of the elicitation of cell rounding by the toxins *of C. dfficile* in stool. Because of no direct correlation in the levels of stool toxin B with the disease severity, this test is commonly marked as positive or negative, and stool culture is less specific for correct diagnosis of infection with *C. dificile* because the *C. difficile* non-toxigenic strains can also be identified with this method (Tabaqchali, 1990). For correct diagnosis, the value of sigmoidoscopy and rectal biopsy is limited because of their technical difficulty and the fact that the rectum may not be affected by pseudo membranous in some patients.

The first step in treating patients with infection of *C. difficile* is to try to stop the initial antibiotic agents. The discontinuation of the culprit antibiotics is usually sufficient to gain recovery for patients with mild symptoms. For severe or persistent symptoms or patients in whom the culprit antibiotics cannot be stopped, specific measures are required to get rid of the *C. difficile*, including the use of metronidazole and vancomycin. Both vancomycin and metronidazole have similar effects on colitis caused by *C. difficile* and can get a rapid symptomatic improvement within three days, with the colitis and diarrhea resolved totally after continued treatment for 10 days. If the patients cannot tolerate oral administration, intravenous dripping of metronidazole can be performed to eradicate the bacteria by excretion and exudation of this medicine into the bile and the intestinal lumen (Bolton & Culshaw, 1986). The treatment approaches for antibiotic-associated colitis have been

suggested in the following order: discontinuation of the initial antibiotics, correction of fluid and electrolyte abnormalities, use of metronidazole or vancomycin, avoidance of antidiarrheal agents, and strict contract isolation plus stool precautions (Castagliuolo & LaMont, 1999).

In recent several years, wide use of broad-spectrum antibiotics and immunosuppressants has brought about a rising incidence of antibiotic-associated pseudo membranous colitis. Diabetes, cerebral infarction and depression may all predispose to pseudo membranous colitis after antibiotic therapy. For prevention of pseudo membranous colitis, narrow-spectrum antibiotics which do not metabolize through the intestine should be administered. The treatment of this disease is to use narrow-spectrum antibiotics, which are specific to *C. difficile* including metronidazole and vancomycin. Avoidance of antispasmodic and antidiarrheal agents is also suggested to prevent retention of cytotoxins within the body. Some vitamins like vitamins B complex and vitamin C can be administered to repair the intestinal mucosa. However, even with these measures, some patients may experience reecurrence of diarrhea and various measures have been proposed for these relapses, including gradual tapering of antibiotic treatment (Lapointe-Shaw *et al*., 2016), administration of cholestyramine (Silva, 1989), bateriotherapy and oral use of nontoxigenic *C. difficile* (Tvede & Rask-Madsen, 1989). Continuation of systemic wide-spectrum antibiotic agents is a well-recognized risk factor for therapeutic failure of the *C. difficile*-caused pseudo membranous colitis and disease relapse (Clutter *et al*., 2013). Other factors may also play a role including older age, use of *C. difficile*-provocative antibiotic agents after right diagnosis, hospital-acquired disease, and comorbid conditions like severe underlying illness, poor scores of quality of life and previous relapse (Lupse *et al*., 2013). *Saccharomyces boilardii* is a yeast which is harmless and may be used together with metronidazole to decrease recurrence of pseudo membranous colitis in patients with repeated relapses (McFarland *et al*., 1994) because this yeast contests with *C. difficile* in the microflora of the colon and probably produces factors to decrease the toxic effects of the toxins of the *C. difficile* bacterium (Castagliuolo *et al*., 1996). The yeast itself can be cleared spontaneously after discontinuation of the treatment.

The universe rose incidence and severity of *C. difficile* infection in the past two decades may be caused by many factors including the advent of hyper-virulent strains like BI/NAP1/027, the elevated use and misuse of antibiotic agents, and the rise of susceptible populations (Mullane, 2014). In our study, twenty-two patients were from the outpatient department accounting for 32.8%. This may indicate severe misuse of antibiotics in China because only 20,000 cases of *C. difficile* infection were estimated yearly in a report (Hirschhorn *et al*., 1994). In fact, the misuse of antibiotics was severe in China and any antibiotics can be purchased almost at any pharmacy without prescription.

Recently, fidaxomicin was available in the US in 2011(Clutter *et al*., 2013). This is a macrocyclic antibiotic agent with a narrow spectrum of activity and showed good effects in treating *C. difficle*-caused pseudo membranous colitis. The phase III trials of fidaxomicin had demonstrated that the clinical effect of fidaxomicin was similar to that of 10-day oral administration of vancomycin, with significantly smaller risk for disease relapse for fidaxomicin (Cornely *et al*., 2012; Louie *et al*., 2011). A further analysis of the 1,164 patients who took part in the two phase III trials demonstrated that long-term diarrhea, diarrhea relapse and even deaths were significantly ($P<0.0001$) decreased by 40% in the cohort treated with fidaxomicin compared to the oral vancomycin cohort (Crook *et al*., 2012). In a meta-analysis (Cornely *et al*., 2012), fidaxomicin had a similar clinical response to vancomycin in patients with first relapse of *C. difficile*-infected diarrhea. Moreover, patients who had the first diarrhea relapse and received fidaxomicin treatment had decreased risk for more relapse than patients who had vancomycin orally. Thus, fidaxomicin may stand for an important step forward in managing *C. difficile*-caused pseudomembranous colitis with great advantages compared to other antibiotic agents in lower rates of diarrhea relapse and minimal side effects.

This study has some limitations including single center design, non-control, non-randomization and single race involved in China. In the future, a randomized, controlled study involving multiple centers should be designed to test the conclusion of this study.

CONCLUSION

Multiple antibiotic agents are associated with pseudo membranous colitis whose incidence and severity are on the rise, and this infection may no longer be hospital acquired as traditionally viewed and should be taken seriously in daily life and health care practice. When treating this infection with narrow-spectrum antibiotics, it is very important to apply supportive measures like correction of fluid and electrolyte abnormalities and use of vitamins to repair the intestinal mucosa for speeding up the cure process.

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