Clostridium difficile–associated Diarrhea: Brief Review and Update of Medical Management

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Abstract

In the past decade, the epidemiology and treatment of *Clostridium difficile*–associated diarrhea (CDAD) have significantly changed. *C. difficile* remains the most important cause of healthcare-associated diarrhea and is increasingly important as a community pathogen. The strains of *C. difficile* with hypervirulent BI-NAP1-027 and non- BI-NAP1-027 have been reported for after the use of nearly all systemic antibacterial agents worldwide, and strain with BI-NAP1-027 has been responsible for more severe cases of disease. The decreased effectiveness of metronidazole relative to vancomycin in the treatment of CDAD has been demonstrated. Areas of controversy still exist about the best treatment plans, despite the increasing quantity of available data in the literature. Here we review progress in antimicrobial therapy and review currently available non-antimicrobial strategies for CDAD management. The new approval agent, fidaxomicin, has the major benefit to treat CDAD, and has become the therapy of choice for recurrent CDAD. (J Intern Med Taiwan 2013; 24: 309-316)

Key Words: *Clostridium difficile*, Diarrhea, Management, Fidaxomicin

Introduction

Clostridium difficile, formerly known as *Bacillus difficilis*, is a gram-positive, cytotoxin-producing, anaerobic bacterium that was first described in 1935 by Hall and O'Toole as a component of the intestinal flora in healthy newborns[1]. Its name reflects the difficulties they encountered in its isolating and culturing it on conventional media[1]. *C. difficile* is a frequent cause of infectious colitis in elderly hospitalized patients that usually occurs as a complication of antimicrobial therapy[2]. The characteristics of this organism include a ''horse stable'' odor caused by *p*-cresol production and a golden-yellow fluorescence visible with Wood's lamp illumination when grown on a selective and differential agar medium that containing cycloserine, cefoxitin, fructose, and egg yolk (CCFA medium)[3].

Clostridium difficile–associated diarrhea (CDAD) is defined by the presence of symptoms that are usually diarrhea, abdominal pain, and fever; and either a stool test result positive for *C. difficile* toxins or toxigenic *C. difficile*, or colonoscopic findings demonstrating pseudomembranous colitis[4,5]. The clinical presentation of CDAD occurs in susceptible individuals who are unable to mount a

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sufficient anamnestic immune response and ranges from mild diarrhea to fulminant colitis[6].

Antimicrobial therapy is known frequently precedes CDAD and presumably contributes to its onset by altering the balance of the intestinal flora[6]. Many classes of antimicrobials have been associated with CDAD, including cephalosporins, penicillins, fluoroquinolones, aminoglycosides, carbapenems, and clindamycin[4,7]. Historically, clindamycin and cephalosporins has been most frequently associated with CDAD[8]. Other risk factors for CDAD include advanced age, increased severity of underlying illness, prior hospitalization, the use of feeding tubes, gastrointestinal surgery, and the use of proton-pump inhibitors[9,10]. Patients with fulminant disease frequently experience fail to respond to medical therapy with antimicrobials, so a subtotal colectomy is required as a life-saving measure[11]. Our purpose here is to review the progress in antimicrobial therapy and to review currently available non-antimicrobial strategies for CDAD management.

Epidemiology

In the past decade, reports have increased that describe healthcare-associated CDAD in the United States[12], Canada[4], and Taiwan[13,14], along with increased morbidity, mortality, complications of colectomy, and the need for long-term care facilities. After exposure to *C. difficile*, some patients remain asymptomatically colonized. The rate of *C. difficile* carriage is higher in hospitalized patients than in the general population[15-17].

From 2000 to 2009, the number of hospitalized patients with any CDAD discharge diagnoses more than doubled in U.S., from approximately 139,000 to 336,600, and the number with a primary CDAD diagnosis more than tripled, from 33,000 to 111,000[18]. Discharge rates increased among persons aged ≥ 65 years[5]. The estimated number of deaths attributed to CDAD increased from 3,000 deaths per year during 1999-2000 to 14,000 during 2006-2007, with more than 90% of deaths in persons aged ≥ 65 years[19]. From 2007 to 2008, the incidence was 42.6 cases per 100,000 patient-days, or 3.4 cases per 1,000 discharges, and was highest in intensive care units in a regional hospital in Taiwan[14]. Moreover, disease is occurring among healthy peripartum women, who have been previously at very low risk for CDAD[5]. Besides, the incidence might also be increasing among persons living in the community, including healthy persons without recent healthcare contact[5]. Fortunately, the incidence of healthcare-associated CDAD declined in the recent years (2008-2011) noted in England[20], and in Taiwan[21].

The hypervirulent BI-NAP1-027 (toxinotype III) strain of *C. difficile* has caused several CDAD epidemics in recent years[2,4]. Toxins A and B are the major determinants of virulence strain, and they are transcribed from the pathogenicity locus, *tcd*A (toxin A) and *tcd*B (toxin B)[2]. The presence of a *tcdC* gene mutation is associated with enhanced synthesis of both toxin A and toxin B[2,22], and the highly virulent BI-NAP1-027 strain is known for producing both toxins A and B[2,4,12]. This strain has a higher incidence and an increased severity of CDAD[23], which have contributed to increasing mortality rates[4,12,24]. Asymptomatic colonization with a non-BI-NAP1-027 strain may result in the development of antibodies against toxin B that are protective against the acquisition of the BI-NAP1-027 strain[17].

Laboratory Diagnosis of CDAD

Accurate diagnosis is crucial to the overall management of CDAD. Empirical treatment without diagnostic testing is inappropriate if diagnostic tests are available[5]. Traditionally, the use of tissue culture cell lines to detect the cytopathic effect of *C. difficile* cytotoxin (toxin B) followed by neutralization of the effect with *C. sordelli* antitoxin or *C. difficile* antitoxin has been used as the definitive diagnostic test[25]. The description of CCFA medium provided a selective culture system for recovery of

C. difficile[3]. Optimal results require that culture plates be reduced in an anaerobic environment prior to use. Culture followed by detection of a toxigenic isolate is considered the most sensitive methodology, but it takes 2 days or more to obtain results[5].

Subsequent tests have used antigen detection with enzyme immunoassay (EIA), testing for *C. difficile* toxin A and B[5]. Although the ease of use and lower labor costs, it is a suboptimal alternative approach for diagnosis due to less sensitive (63% to 94%) than the cell cytotoxin assay[5]. One potential strategy to overcome this problem is using EIA detection of *C. difficile* common antigen, glutamate dehydrogenase (GDH), with a sensitivity of 85% to 95% and a specificity of 89% to 99%[5]. The high negative predictive value making this method useful for rapid screening if combined with another method that detects toxin[26].

Pseudomembranous colitis has been used as a marker of severe disease, which can only be diagnosed by direct visualization by lower gastrointestinal endoscopy or by histopathologic examination[5]. Polymerase chain reaction (PCR) tests for toxigenic *C. difficile* is stool samples are now available from several manufacturers[27], but more data on utility are necessary before this methodology can be recommended for routine testing.

Management of CDAD

C. difficile is well-recognized as the etiologic agent of pseudomembranous colitis and has been implicated in about 20%-30% of cases of diarrhea associated with antibioitcs[5]. Patients with severe CDAD should be evaluated early by a gastrointestinal surgeon, since timely subtotal colectomy can be lifesaving[28]. High colectomy and case-mortality rates have prompted clinicians to seek better approaches to this disease[28]. Medical management of CDAD can be subdivided into therapeutic categories of antibiotics, immunomodulation, and miscellaneous adjuvant therapies.

General Considerations

The risk of CDAD increases as antimicrobial therapy increases in frequency, number of doses, and duration[5]. When CDAD occurs, clinicians might discontinue all inciting antimicrobial agents and allow the normal bowel microflora to restore itself[2]. Although asymptomatic *C. difficile* carriers can be effectively treated with vancomycin, no available data to supports treatment of asymptomatic carriers with vancomycin to control hospital transmissions[5]. Thus, a positive assay in patients without significant symptoms might not prompt treatment[2]. Further, another causes should be considered in patients with persistent diarrhea despite several weeks of treatment with metronidazole or vancomycin[2]. Anti-peristaltic agents can obscure symptoms and precipitate toxic megacolon, so these agents should be avoided[5].

Standard Antibiotics

Antimicrobials have been the agents of choice for treatment of CDAD for more than 30 years, with the standard therapies being either metronidazole or oral vancomycin[11]. Despite the increasing incidence and severity of *C. difficile* infection during the past decade, these two agents remain the initial treatments of choice for almost all patients with CDAD[2]. Treatments of CDAD occurring before the year 2000 had virtually identical cumulative failure rates for treatment with metronidazole or with vancomycin. However, since 2000, metronidazole therapy has had decreased responses and higher rate of failure, especially when treating CDAD caused by the hypervirulent strains[29-31]. For example, 26% of patients failed to respond to metronidazole treatment during a CDAD outbreak in Quebec[30]. Another retrospective study also reported that patients treated with metronidazole had a significantly longer time to resolve diarrhea than those treated with vancomycin[32]. These data sustain an ongoing debate as to whether vancomycin is superior to metronidazole as initial therapy for CDAD. Because a small

incremental increase in efficacy may be critical in patients with fulminant disease, a number of professional societies advocate vancomycin as the first-line agent for patients with a severe infection[33]. These recommendations are supported by the findings of a recent prospective, randomized, placebo-controlled trial that compared metronidazole with vancomycin in 172 patients stratified according to the severity of CDAD[34]. These two agents showed similar efficacy for mild infections, though vancomycin had a greater response rate than metronidazole. In patients with severe infections, vancomycin was significantly more effective[34]. Markers of severe CDAD include fever, pseudomembranous colitis, a marked peripheral leukocytosis, acute renal failure, and hypotension[35-37].

Although recent study reported the reduced susceptibility to metronidazole in *C. difficile*[38], metronidazole remains the first-line agent to treat mild-to-moderate infections because of its lower cost and because of concerns about proliferating vancomycin-resistant pathogens. Moreover, the similar report of antimicrobial susceptibilities of *C. difficile* in Taiwan described that all enrolled isolates were susceptible to metronidazole[39]. And, more than 90% of isolates were inhibited by vancomycin at 1μg/ml[39]. For severe infections, vancomycin is recommended as the first-line agent because of its more prompt symptom resolution and a significantly lower risk of treatment failure[35]. Because of coexisting ileus or toxic megacolon, oral vancomycin may not be suitable for some patients with severe or fulminant infections. Intravenous metronidazole is used in this situation and should, if possible, be supplemented with vancomycin administered through a nasogastric tube or by enema[35].

Other Antibiotics

Rifaximin has US Food and Drug Administration (FDA) approval for indications other than CDAD but it has been used as an adjunct agent to treat patients with multiple CDAD recurrences[40]. A 2-week course of rifaximin immediately following the last course of vancomycin treatment lowers the recurrence of CDAD[40]. However, the increasing numbers of clinical *C. difficile* isolates with high-level resistance to rifaximin may limit its efficacy[41,41].

Fidaxomicin was compared with vancomycin in patients with *C. difficile* infection in a prospective, multicenter, double-blind, randomized, parallel-group trial that was conducted between May 9, 2006, and August 21, 2008[42]. In May 2011, the US FDA approved fidaxomicin, the first drug of the macrocyclic class of antimicrobial agents, to treat CDAD[32]. This important new drug is inactive against Gram-negative organisms, fungi, and protozoa pathogens, yet has appreciable *in vitro* activity against aerobic and anaerobic Gram-positive pathogens that include *C. difficile*[44]. The major benefit of using fidaxomicin to treat CDAD is the significantly reduced rate of recurrence and the correspondingly improved rate of global cure[42]. Theoretically, fidaxomicin also reduces the likelihood of selecting for the overgrowth of vancomycin-resistant enterococci[42]. Fidaxomicin also has a prolonged post-antibiotic effect in treating CDAD, which is not observed with vancomycin[42]. Since fidaxomicin has minimal systemic absorption, high fecal concentrations, and high activity both *in vitro* and *in vivo* against clinical isolates of *C. difficile*, it is a promising candidate that may become the therapy of choice for CDAD[45-51].

Other agents that have been evaluated to treat CDAD, including bacitracin, teicoplanin, fusidic, nitazoxanide, tigecycline, and ramoplanin[5,11,39], but none of these agents have been approved by the US FDA to treat CDAD[5].

Immunomodulation

Several non-antimicrobial approaches have been proposed and under development, some of which have entered clinical trials[11]. Patients with

multiple recurrences have been treated with active or passive immunization against *C. difficile* toxins. Though passive immunization with intravenous immunoglobulin (IVIG) has been reported, its efficacy is unproven[52,53]. Active immunization with a vaccine containing denatured *C. difficile* toxins may elicit high levels of antitoxin antibodies[54]. Anti-toxin immunoglobulins seem important in reducing the recurrence of CDAD, according to a recent randomized, double-blind, placebo-controlled study[55]. Thus, immunization for recurrent infections appears promising, but more prospective, controlled trials are needed to establish the efficacy of both active and passive immunization treatments.

Miscellaneous Adjuvant Therapies

Probiotics have long been touted as a plausible means of preventing CDAD[28]. Currently, administrating probiotics is not recommended to prevent primary CDAD[5], and the role of probiotics in preventing CDAD is dubious[56]. However, one exception exists in a single study of *Saccharomyces boulardii* to prevent relapses, which was administered sequentially after therapy with high-dose oral vancomycin[57]. Larger trials are required before this practice can be recommended.

Summary

During the past decade, the clinical profile of *C. difficile* infection has worsened, with increased numbers of cases, greater morbidity, an increased incidence of complications requiring colectomy, and rising mortality[42]. An approach to the medical management of CDAD is presented in Table 1[2,5,28,40,42,43,55,58,59].

The initial therapeutic approach to a newly diagnosed case of *C. difficile* infection is to discontinue the antibiotic that precipitated the *C. difficile* infection[5]. One of the most problematic aspects of infection with *C. difficile* is the rate of recurrence. A higher rate of recurrence and more failures are associated with metronidazole therapy than with vancomycin therapy, especially among severely ill patients[34,60]. During metronidazole therapy, clinicians should pay attention to the risk of neurotoxicity[5]. In contrast, orally administered vancomycin is relatively free of systemic toxicity, and it is poorly absorbed, so that fecal levels of

Table 1. Suggested Management of Symptomatic *C. difficile*-Associated Diarrhea*

Replace fluid and electrolyte losses
If clinical situation allows, discontinue offending antibiotics.
Avoid antiperistaltic agents
plus
Initial Episode or First Recurrence
Mild-to-moderate infection
metronidazole 500 mg orally 3 times daily for 10 to 14 days
Severe infection or unresponsiveness to or intolerance of metronidazole
Vancomycin 125 mg orally 4 times daily for 10 to 14 days
Second Recurrence
Vancomycin in tapered and pulsed doses
125 mg orally 4 times daily for 14 days
125 mg orally twice daily for 7 days
125 mg orally once daily for 7 days
125 mg orally once every 2 days for 8 days (4 doses)
125 mg orally once every 3 days for 15 days (5 doses)
Third Recurrence
Vancomycin 125 mg orally 4 times daily for 14 days, followed by rifaximin 400 mg orally twice daily for 14 days
Other Options for Recurrent infection
Intravenous immunoglobulin, 400 mg/kg of body weight once every 3 weeks for a total 2 to 3 doses
Therapy with other microorganisms, such as "fecal transplantation"
Vancomycin combined with Probiotics, such as *Saccharomyces boulardii*.§
New approval antibiotic
Fidaxomicin 200 mg twice daily for 10 days

*Data are from reference 2, 5, 28, 40, 42, 43, 55, 58, 59.
§ Efficacy of *S. boulardii* and other probiotics in recurrent *C. difficile* infection is mixed. Serious complications may due to the use of probiotics in immunocompromised patients and in critically ill patients, particularly those with central venous lines or feeding tubes.

vancomycin are maintained throughout the duration of therapy[5].

Because of the appearance of the hypervirulent form of CDAD and because of the increasingly frequent reports of severe disease and death resulting from CDAD, initiatives have been undertaken to find alternative and improved antimicrobials, probiotics, immunomodulating agents, and adjuvant measures to control CDAD[5,28]. Currently, no single regimen can be recommended for the patient with multiple relapses of CDAD, though some algorithms exist that consist of high-dose or tapered-dose oral vancomycin that is combined with either concomitant sequential IVIG or else probiotics such as *Lactobacillus rhamnosus* GG and *S. boulardii*[28].

Fidaxomicin has the major benefit to treat CDAD and reduced rate of recurrence[42]. It is a promising candidate that become the therapy of choice for CDAD[45-51]. Additionally, increasing awareness of the possibility of severe *C. difficile* infection should facilitate earlier diagnosis and treatment. The great hope of clinicians who care for those with this infection, along with the patients who have CDAD, is that one or more approaches will be shown to be highly effective in controlling the disease itself, decreasing the associated serious morbidity and high mortality, and preventing the frequent relapses that make so many patients ill for such a long period.

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困難梭狀芽孢桿菌相關腹瀉：簡短文獻回顧與藥物治療新進展

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摘　要

近二十年的期間，困難梭狀芽孢桿菌相關腹瀉在流行病學與治療方面都有顯著的改變。在醫療相關腹瀉的個案中，困難梭狀芽孢桿菌扮演著重要的致病因，且社區型感染有增加的趨勢。現今全世界廣泛探討著更具毒力之困難梭狀芽孢桿菌種BI-NAP1-027和非BI-NAP1-027所引發病情，而這幾乎與所有類別的抗生素使用有關，特別菌種BI-NAP1-027所引起的感染更是嚴重。近幾年的文獻指出，硝基甲嘧唑乙醇(metronidazole)在治療困難梭狀芽孢桿菌相關腹瀉成效上相較於萬古黴素(vancomycin)有減弱的趨勢，是否因此無法使用該藥與尋求較佳治療藥物，在文獻上仍是一個具爭議的議題。因此我們藉由文獻回顧，探討該疾病在藥物治療上的進展，值得注意的是新核准使用的藥物Fidaxomicin，除了對該疾病有顯著的療效，更用以選擇在治療復發性的感染。