REVIEW

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Clostridium difficile Infection: A Worldwide Disease

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Clostridium difficile, an anaerobic toxigenic bacterium, causes a severe infectious colitis that leads to significant morbidity and mortality worldwide. Both enhanced bacterial toxins and diminished host immune response contribute to symptomatic disease. *C. difficile* has been a well-established pathogen in North America and Europe for decades, but is just emerging in Asia. This article reviews the epidemiology, microbiology, pathophysiology, and clinical management of *C. difficile*. Prompt recognition of *C. difficile* is necessary to implement appropriate infection control practices. **(Gut Liver 2014;8:1-6)**

Key Words: *Clostridium difficile*; Epidemiology; Review; Asia

INTRODUCTION

Clostridium difficile is a fastidious, gram-positive, spore-forming bacterium responsible for infectious diarrhea and pseudomembranous colitis with significant morbidity and mortality. Patients at highest risk for *C. difficile* infection include hospitalized individuals >65 years old with recent antibiotic exposure. Risk factors for *C. difficile* in these individuals include depletion of protective gut flora by antibiotics[1-3] and diminished immune response to *C. difficile* due to age and medical comorbidities.[4,5] Most epidemics occur in the hospital setting and in long-term care facilities,[6,7] but outpatient acquisition is also described. With the emergence of hypervirulent strains in both North America and Europe, the impact of *C. difficile* has broadened to affect a growing community-based population and younger individuals, even without previous exposure to antibiotics.[8] Though historically a rare entity in Asia, this pathogen can spread quickly and will likely grow in frequency in areas currently considered to be low prevalence. This article describes the pathophysiology and clinical aspects of *C. difficile* infection, and reviews its emergence in Asia.

MICROBIOLOGY

C. difficile colonizes the large intestine of humans and domestic and wild mammals. Both toxigenic and nontoxigenic strains exist, but only toxigenic forms produce disease in humans. Pathogenicity is dependent on the presence of one or both of two closely related diarrhea-producing toxins, named toxin A (TcdA) and toxin B (TcdB).[8] All toxigenic strains to date contain TcdB, with or without the presence of TcdA. TcdA and Tcd B share a common molecular mechanism of action: inactivation of Rho GTPases through enzymatic glucosylation of a conserved threonine residue. This pathway leads to actin depolymerization and cell death, and stimulates an inflammatory cascade that exacerbates tissue damage, diarrhea, and pseudomembranous colitis (Fig. 1).[9,10] A third pathogenic toxin, binary toxin, is produced by some strains of *C. difficile*. This toxin has been shown to enhance virulence of *C. difficile* through irreversible adenosine diphosphate-ribosylation of actin, inducing the formation of long host-cell microtubule protrusions that facilitate bacterial attachment.[11]

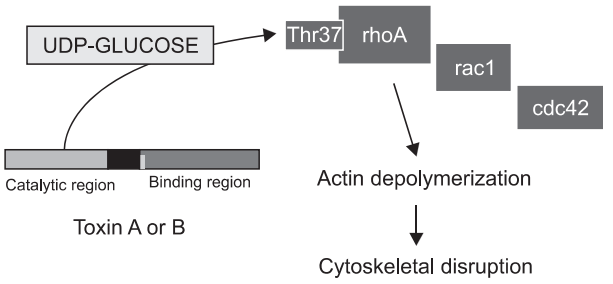

Fig. 1. *Clostridium difficile* toxins A and B monoglucosylate Rho GTPases. In the cytosol, the catalytic regions of toxin A and B glucosylate target Rho GTPases at the threonine residue (Thr), leading to disaffiliation of the actin cytoskeleton and eventual cell apoptosis.

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PATHOPHYSIOLOGY

The ability of *C. difficile* to cause enteritis is based upon two host features: colonization resistance and immune response to *C. difficile*. The large intestine is protected from invasive pathogens by indigenous flora composed of approximately 4,000 bacterial species,[12] collectively called the fecal microbiome. These microbes collectively provide colonization resistance against pathogenic species through competition for essential nutrients and attachment sites to the gut wall.[13] Antibiotics disrupt the barrier microflora and diminish colonization resistance, thereby providing a niche for colonization by intestinal pathogens.[1-3] Reduction of *Bacteroides* and Firmicutes phyla by antibiotics appears to be particularly important in the pathophysiology of *C. difficile*.[14]

The fecal flora of the newborn and infant lacks colonization resistance. As a result, 60% to 70% of healthy infants are asymptomatic carriers of *C. difficile* during the first 12 months of life.[15] During this infantile carrier state, serum immunoglobulin G (IgG) and IgA antitoxins first appear and protect against subsequent *C. difficile* disease. These antibodies may persist and bind *C. difficile* toxins in the lumen to prevent diarrhea and colitis. Kyne *et al*.[4] reported that serum antitoxin A IgG was higher in hospitalized patients who remained asymptomatic following *C. difficile* colonization, compared to those who developed acute infection.

Moreover, patients who mounted an appropriate antibody response during an initial episode of *C. difficile* infection were at decreased risk for recurrent infection.[5] Conversely, Solomon *et al*.[16] demonstrated that patients with a low serum antitoxin A IgG were significantly more likely to die during the first 30 days of infection. Advanced age, malnutrition, female gender, and medical comorbidities tend to diminish host protective response to *C. difficile* in adults,[2] and may be associated with more severe infection.

EPIDEMIOLOGY

The geographic distribution of prevalent *C. difficile* strains is shown in Table 1. In 2003, the North American Pulse Field type 1 (NAP1)/ribotype 027 strain emerged as a source of *C. difficile* epidemics in Canada and the United States. This strain contains a mutation in the *C. difficile* toxin inhibitory gene tcdC, leading to increased toxin A and B production.[17-19] It also produces binary toxin. Due to these virulence factors, the 027 strain has been associated with higher morbidity, recurrence rates, and presence in the community. From 1998 to 2009, the number of United States hospitalizations with a principal diagnosis of *C. difficile* infection increased from 25,200 to 110,600, reaching a plateau from 2008 to 2009.[20] Similar to ribotype 027 in North America, ribotype 078 has been on the rise in Europe since 2005. This strain is also associated with increased community-acquired disease, younger age, and lack of preceding antibiotic therapy.[21]

Table 1. Distribution of Prevalent *Clostridium difficile* Ribotypes

Strain	Distribution
027	United States, Canada, across Europe (Netherlands, Ireland, Germany), Chile, few reports from East Asia
078	Europe (Spain, Germany, France)
017	China, Korea, Northern Europe (Netherlands, Scotland), Japan
018	Japan, Korea
014	United States, Spain, France, Japan, China, Korea
001	China, Japan, Korea, Spain, Germany, Scotland
002	Japan, Hong Kong, Korea

In Asia, *C. difficile* is reported as a low prevalence hospital pathogen, and its true prevalence remains unknown. A Korean study of 17 hospitals in 2008 found an increase in incidence from 1.7 cases/1,000 adult admissions in 2004 to 2.7 cases/1,000 adult admissions,[22] considerably lower than the rate of 8.75 cases/1,000 adult admissions in United States hospitals over the same period.[20] A 2007 to 2008 study in a single hospital in Shanghai, China found a similar incidence of *C. difficile* infection of 1.7 cases/1,000 admissions.[23] Though ribotype 027 is quite rare in Asia, variant $tdcA^-/tcdB^+$ ribotype 017 has emerged as the predominant strain in east Asia, accounting for between 23% and 48% of toxigenic strains in Korea,[24,25] China,[26,27] Japan, and Taiwan. Ribotype 018 has been responsible for *C. difficile* outbreaks in Tokyo and Korea.[28] Speciation of *C. difficile* in Hong Kong has revealed toxinotypes unique to east Asia. For example, Cheng *et al*.[29] reported that of 345 *C. difficile* isolates, ribotype 002 was the most prevalent, representing 10.1% of strains, with ribotype 017 representing only 0.6% of strains. Moreover, 70% of strains did not belong to any of the 23 ribotypes prevalent in North America and Europe, and 11.6% were nontypable.[29]

A prospective study of Indian patients with acute diarrhea in 2012 demonstrated *C. difficile* in 8% of hospitalized patients and in 1.3% of outpatients.[30] *C. difficile* was identified in 29% of patients with antibiotic associated diarrhea in Pakistan.[31] Surveys of hospitalized patients in Singapore reported a prevalence of 3.0 to 6.6 active *C. difficile* cases per 10,000 inpatient days.[32,33] In Malaysia and Thailand, recent reports suggest that *C. difficile* is more prevalent than previously appreciated, with rates of toxin A and B positivity of 14%[34] and 44% to 46%,[35] respectively, in patients with antibiotic-associated diarrhea. A recent report from the Philippines demonstrated that 44% of colitis cases were *C. difficile* positive, representing a paradigm shift as most cases in that country were previously attributed to amoebic or parasitic infections.[36]

CLINICAL PRESENTATION

The clinical presentation of *C. difficile* ranges across a wide spectrum from asymptomatic carrier state to toxic megacolon. Typical signs and symptoms of acute *C. difficile* infection include watery diarrhea (≥3 unformed stools/24 hours), anorexia, nausea, and leukocytosis with a neutrophilic predominance. Disease severity is used to guide antibiotic therapy.[37] Disease is characterized as severe if associated with hypoalbuminemia (< 3 g/dL), and leukocytosis exceeding 15,000 cells/mm^3 or abdominal tenderness.[38] Immunocompromised state, presence of inflammatory bowel disease,[39-41] and acute kidney injury[42] related to *C. difficile* also portend a worse prognosis and should be treated as severe in practice. The presence of associated leukocytosis above 35,000 cells/mm^3, fever, hypotension, mental status changes, elevated serum lactate levels > 2.2 mmol/L, end-organ failure, or admission to the Intensive Care Unit, define severe-complicated disease,[38] with predicted 20% to 30% mortality. Rarely, *C. difficile* may result in an ileus with abdominal distention but little to no diarrhea. This presentation tends to herald a more severe course and should also be treated as severe-complicated disease.[38]

DIAGNOSIS

The diagnosis of *C. difficile* infection is based on the presence of typical signs and symptoms, in addition to identification of *C. difficile* organisms/toxin in stool or pseudomembranous colitis on colonoscopy (Fig. 2). Several laboratory tests are available for the diagnosis of *C. difficile* (Table 2). Nucleic acid amplification tests are most commonly employed in the United States, as they have the highest sensitivity and specificity, and provide quick results. A step-wise approach using a screening glutamate dehydrogenase assay followed serially by confirmatory immunotesting for toxins A and B may also be employed for diagnosis, but has lower sensitivity than polymerase chain reaction-based testing.[38] Toxin-based testing should always include both toxin A and B, as the predominant ribotypes in Asia are toxin A negative.[24,43]

PREVENTION

C. difficile is spread via the fecal-oral route by ingestion of acid-resistant spores. Therefore, appropriate hand-hygiene of healthcare workers by washing with soap and water to help remove spores and isolation of patients with acute diarrhea can limit spread in the hospital. Much effort has been focused on patient therapies to prevent symptomatic disease. Probiotics are generally well-tolerated and have been found in a recent Cochrane review including 23 randomized controlled trials to be associated with decreased incidence of *C. difficile*-associated diarrhea.[44] Novel *C. difficile* vaccines based on inactived toxins A and B are also currently in development, and have been

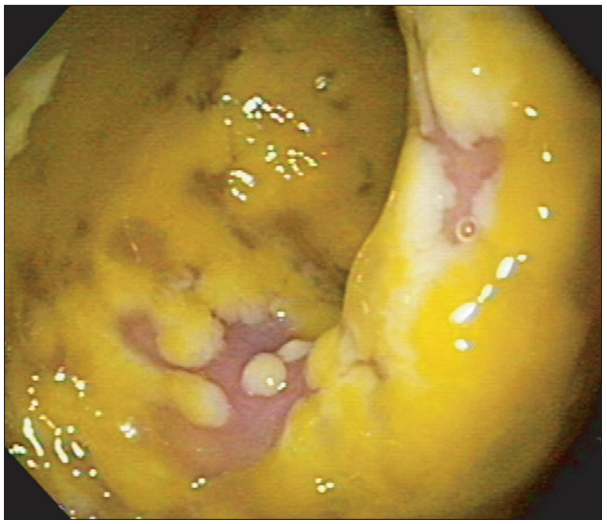

Fig. 2. Pseudomembranous colitis. Appearance of pseudomembranes on colonoscopy confirms the diagnosis of *Clostridium difficile*, though is not required for diagnosis.

Table 2. Utility of Stool Laboratory Tests for *Clostridium difficile* Infection

Test	Sensitivity	Specificity	Utilization
C. difficile culture	Low	Moderate	Not useful in the clinical setting. Cannot differentiate between toxigenic and nontoxigenic *C. difficile*.
Toxigenic culture	High	High	Gold-standard in defining sensitivity and specificity of other testing modalities. Not useful in clinical setting due to slow time to result.
Cell culture neutralization assay	High	High	Diagnostic utility limited by labor-intensity and time to result.
Glutamate dehydrogenase assay (GDH)	High	Low	High sensitivity, but cannot differentiate between toxigenic and nontoxigenic strains. Must use sequentially with toxin EIA confirmatory testing for toxigenic strain.
Toxin enzyme immunoassay (EIA)	Low	High	Fast and specific for toxigenic strains. Must detect toxins A+B. Limited by low sensitivity. Used in combination with GDH.
Nucleic acid amplification testing	High	High	Fast PCR-based toxin gene testing. Preferred diagnostic method in United States. Only useful in patients that have acute diarrhea.

PCR, polymerase chain reaction.

Table 3. Treatment of *Clostridium difficile* Infection

Episode	Therapy
Initial episode and first recurrence	Mild-moderate infection: metronidazole 500 mg PO 3 times daily for 10–14 days or fidaxomicin 200 mg twice daily for 10–14 days
	Severe infection: vancomycin 125 mg PO 4 times daily for 10–14 days
	Severe complicated infection: metronidazole 500 mg IV 3 times daily and vancomycin 500 mg PO 4 times daily for 10–14 days
Second recurrence	Pulsed and tapered doses of vancomycin
	125 mg 4 times daily for 14 days
	125 mg 2 times daily for 7 days
	125 mg once daily for 7 days
	125 mg once every 2 days for 8 days (total 4 doses)
	125 mg once every 3 days for 15 days (total 5 doses)
Third or more recurrences	Vancomycin 125 mg PO 4 times daily for 14 days, followed by rifaximin 400 mg twice daily or fidaxomicin 200 mg twice daily for 14 days
	Fecal microbiota transplantation

Adapted from Kelly CP, et al. N Engl J Med 2008;359:1932-1940, with permission from Massachusetts Medical Society.[8]
PO, orally; IV, intravenously.

shown in early clinical trials to diminish the effects of *C. difficile* through enhancement of antitoxin A and B response.[45-48]

TREATMENT

The approach to treatment of *C. difficile* is outlined in Table 3. The inciting antibiotics should be stopped if possible to allow regeneration of the normal gut microflora, and an antibiotic with activity against *C. difficile* should be started. Initial therapies based on severity of disease include metronidazole for mild-moderate disease, vancomycin for severe disease, or a combination of the two for severe-complicated disease.[8] All antibiotics are given orally, with the exception of metronidazole, which is active by the intravenous route owing to an active enterohepatic circulation.[8] In 2011, fidaxomicin was shown to be non-inferior to vancomycin for the first or second episode of *C. difficile*[49,50] and was approved in the United States for the treatment of mild-to-moderate *C. difficile*. The major advantage of fidaxomicin is its lower recurrence rate (15.4%) as compared to vancomycin (25.3%).[50] However, widespread use of this antibiotic has been constrained by both cost[51] and limited trial data. Treatment for the first episode of recurrent *C. difficile* is identical to that for initial treatment. Antibiotic therapies for subsequent recurrences include prolonged pulse-dosed vancomycin tapers, with an additional 14 days of rifaximin[52] or fidaxomicin[53] following the vancomycin taper (Table 3). Fecal microbiota tranpslantation, by which donor feces is infused into a patient's gastrointestinal lumen, results in a cure rate of approximately 90% in recurrent *C. difficile* infection.[54] In the first randomized controlled trial of stool transplantation for recurrent *C. difficile*, van Nood *et al*.[55] recently demonstrated that duodenal infusion of healthy donor feces was significantly more likely to result in cure (81%) than vancomycin with bowel lavage (31%) or vancomycin alone (23%) for the treatment of recurrent *C. difficile*. Fecal transplant is becoming the preferred treatment for patients with multiple recurrences of *C. difficile* infection.

SUMMARY

C. difficile, a pathogen responsible for severe infectious colitis that leads to significant morbidity and mortality worldwide, has established a foothold in Asia. The recent uptrend in *C. difficile* prevalence with increasingly pathogenic strains in North America and Europe likely heralds a similar pattern in Asia over time. Though testing for *C. difficile* is common in some parts of Asia, the paucity of literature supports the need for further clinical and laboratory awareness of this disease. Prompt recognition of this pathogen will support the essential development of infection control practices to thwart the propagation of *C. difficile* in Asia.

CONFLICTS OF INTEREST

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

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