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Clostridium difficile Infection Update for the Hospital-Based Physician

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Abstract *Clostridium difficile* infection (CDI) hospitalization and mortality rates increased rapidly over the first decade of the 21st century associated with the emergence of an "epidemic" *C. difficile* strain. Improved knowledge of this strain and its unique characteristics as well as *C. difficile* in general have heightened awareness to its virulence, recurrence risks, and transmissibility. The overuse of certain antimicrobials, which in turn disrupt the protective intestinal micro environment, may be driving CDI emergence. Newer treatments and those on the horizon have shown promise in their ability to reduce disease recurrence. Emergency and hospital-based physicians are frequently the first responders to patients with CDI. Therefore, the ability to identify an infected patient early, initiate appropriate medical and/or surgical management, and initiate preventative measures to impede spread and acquisition is imperative for the health of the entire hospital community.

Keywords *Clostridium difficile* · Epidemic · Pseudomembrane · Antibiotic · Colectomy

Introduction

Clostridium difficile, a gram positive, spore forming, toxin-producing bacillus, is the most common cause of hospital-acquired diarrhea and the most commonly reported hospital-acquired pathogen [1]. It leads to illness ranging from mild diarrhea to fulminant disease, associated with significant morbidity and mortality. Not only is the incidence increasing within the hospital setting, but it is also more frequently diagnosed within the community in those with or without previous healthcare exposure [2–5]. The increased incidence of CDI parallels the emergence of an "epidemic strain" of *C. difficile*, which has been linked to higher rates of recurrence, morbidity, and mortality [6••, 7]. Unfortunately, the mainstays of treatment for this infection, metronidazole and vancomycin, are associated with high rates of recurrence as their broad antimicrobial activity leads to further destruction of the protective intestinal microbiota.

With its increased frequency in the hospital and presentation within the community, it is of the utmost importance for emergency and hospital-based physicians to recognize an infected patient early, begin appropriate treatment, recognize the need for isolation to help prevent spread through the hospital community, and take precautions in uninfected patients to prevent acquisition.

Pathogenesis

C. difficile was discovered in the 1930s by Hall and O'toole when it was isolated from the meconium of stool in asymptomatic newborns [8]. Thinking it at first a commensal bacterium due to its commonality within the normal flora of newborns, it was not considered a pathogen until the 1970s when it was discovered to cause antibiotic-associated diarrhea [9]. It is a common colonizer, with up to 3–6 % of people outside the hospital setting colonized and 15–52 % within the acute care and long-term care settings, respectively [10–12]. Intestinal colonization resistance, through protective commensal bacteria and intestinal cell defense mechanisms, inhibits *C. difficile* growth, preventing the secretion of pathogenic toxins A

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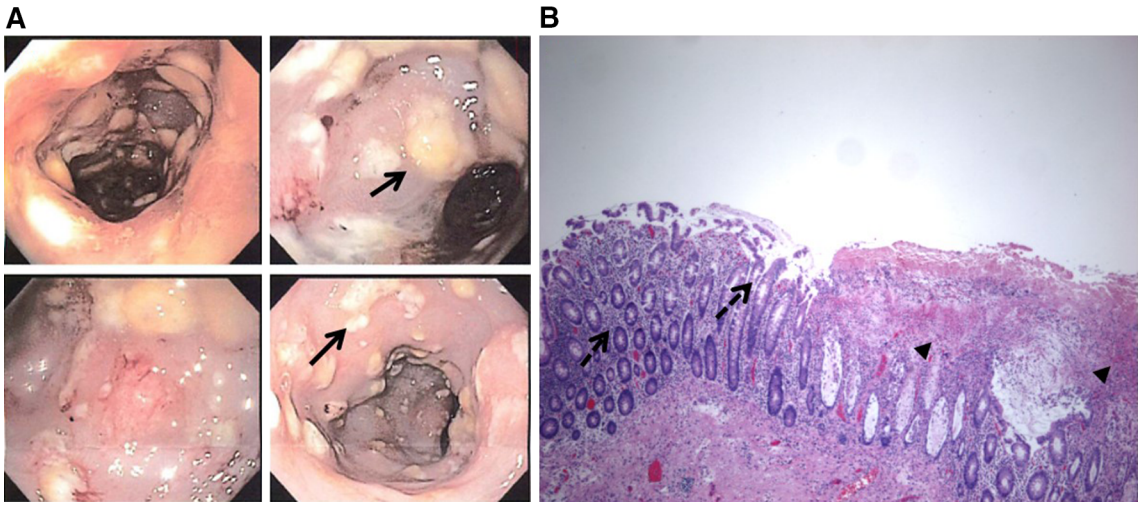

Fig. 1 **a** Pseudomembranes (*arrows*) throughout the colon in a patient with recurrent *C. difficile* infection (CDI). **b** A colon after subtotal colectomy for fulminant CDI. Note the necrotic cells (*arrowheads*) and disrupted epithelium with lymphocytic infiltration. (*dashed arrows*)

and B. When colonization resistance decreases, typically through the use of broad spectrum antibiotics, but occasionally with cytotoxic agents and disorders such as Crohns or Ulcerative Colitis, colonization can then progress to *C. difficile* infection (CDI).

Toxins A and B are secreted in highest numbers during the exponential growth of the bacterium and bind to receptors on colon cells, leading to a loss of barrier function, cell death, apoptosis, and release of numerous inflammatory molecules [13]. Through its direct activity on the colon cells and the ensuing release of cytokines, an inflammatory cascade occurs, which can progress quickly in spite of adequate antimicrobial treatment. Necrosis and neutrophil accumulation accounts for the pathognomonic pseudomembranes which develop along the colon (Fig. 1). In vitro studies reveal that toxin binding, followed by the release of inflammatory cytokines occur within several minutes of exposure to the toxin, with cascade progression even when the toxin is removed after several minutes, stressing the importance of early recognition and treatment [14].

Recent Epidemiologic Trends

Small CDI outbreaks affecting long-term care facilities and hospitals were recognized throughout the 1980s and 1990s, and an overall steady increase in disease was seen from the late 1980s to 2001, but it was not until 2001 that large-scale hospital outbreaks, associated with increased morbidity and mortality were recognized (Fig. 2) [15–17]. The upward trend in hospitalizations continued, until plateauing in 2009 [4, 18]. The upsurge in CDI has disproportionately affected older adults. Community-acquired CDI, defined as no healthcare facility exposure within 90 days of diagnosis, now accounts for as high as 10 % of cases [3]. The trend parallels the emergence of an "epidemic" strain of *C. difficile*, labeled 027/NAP1/BI (by typing methods), herein referred to as the BI strain. This strain has been shown to have increased transmissibility, a 16- and 23-fold increase in toxin A and B production, respectively, enhanced sporulation, expression of a binary toxin, and increased resistance to antimicrobials and disinfectants [7, 19–23]. Recent studies have associated the BI strain with higher rates of recurrence and a near two-fold increase in severe disease, severe outcomes, and mortality as compared to other strains [6••, 24••]. Though present since the 1980s, it was previously never implicated as a cause of outbreaks. Genotypically identical, phenotypically, it has greater resistance to fluoroquinolones, possibly implicating increased fluoroquinolone use as a cause for its emergence [7, 17]. With the aging of our population, elevated colonization rates, an overuse of antibiotics, and the emergence of a hypervirulent strain, it is not surprising that CDI has become more problematic.

Risk Factors and Prevention

A major strategy to reduce cases is to prevent acquisition within the hospital. Once colonized, patients can develop disease when exposed to antibiotics or other medications, such as acid-reducing medications, that are able to disrupt the balance of the protective microbiota. Aging additionally predisposes patients to disease acquisition. The risk factors and prevention strategies to reduce these risks will be discussed in the sections to follow (Table 1) [17, 25, 26].

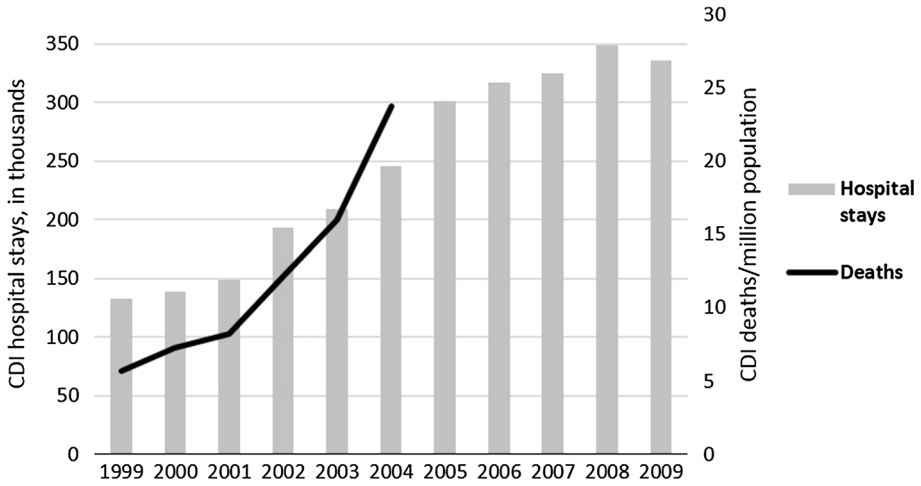

Fig. 2 Trends in hospitalizations (1999–2009) and mortality (1999–2004) associated with *C. difficile* infection (CDI)

Table 1 Risk factors for acquisition of CDI and strategies to decrease risk

Risk factors for acquisition of CDI	Strategies to decrease risk
Antimicrobial exposure	Development of an ASP or other program to encourage the appropriate use of antibiotics
Exposure to *C. difficile*	Active Infection Prevention program to promote isolation of patients with CDI and encourage gowning, gloving, and hand hygiene
	Environmental cleaning with effective sporicidal agents
Advanced age	Identification that age is a risk factor and avoid antibiotics and other medications associated with an increased risk of CDI
PPI use	Education and auditing by pharmacy to ensure appropriate use
Prolonged LOS	Early identification of patients safe to discharge

See Muto [17], Dellit [25], and Zilberberg [44]

CDI C. difficile infection, *ASP* Antimicrobial Stewardship Program, *PPI* proton pump inhibitor, *LOS* length of stay

Antibiotics

Antibiotics were first noted to be a risk factor for the development of CDI in the 1970s when it was observed that hamsters developed fatal colitis after exposure to clindamycin [9]. Antibiotic exposure is observed as a risk factor for CDI in 80–99 % of cases, but it should be noted that in cases of community-associated CDI, antibiotic exposure is frequently not encountered [27, 28]. The majority of antibiotics have been associated with CDI, most notably, fluoroquinolones, second and third generation cephalosporins, clindamycin, ampicillin, and amoxicillin [17, 27]. Fluoroquinolones and second and third generation cephalosporins are often the most frequently prescribed antibiotics hospital wide and have caused facility-wide clonal outbreaks associated with high mortality rates [17, 29]. During outbreak situations, infection control measures alone are not enough, and it often requires restriction of the implicated antibiotics through an antimicrobial stewardship program (ASP) or other means to control an outbreak. This was demonstrated by two studies that showed a 56 and 60 % reduction in incidence of CDI after targeting a decrease in the use of fluoroquinolones, cephalosporins, and clindamycin [17, 30, 31]. ASPs also effectively reduce CDI in non-outbreak setting [32, 33].

Studies indicate that more than half of hospitalized patients at any point in time are receiving antimicrobial therapy. Unfortunately, some studies suggest that up to 30 % are prescribed inappropriately [34, 35] (Table 2). Given that the pathogenesis of CDI primarily relies on the disruption of the colonic bacterial flora by antibiotics, the misuse of antibiotics in hospitalized patients has a direct influence on CDI; therefore, hospital-based physicians in conjunction with ASPs can have a direct impact on CDI acquisition by curbing the misuse of antibiotics.

Healthcare Exposure and Length of Stay

Exposure to acute care hospitals and long-term care facilities are a common risk factor for CDI. Reports as early as the 1980s indicate that up to 21 % of previously uncolonized patients acquire *C. difficile* during an acute care hospitalization and inpatient colonization rates are as high as 15 % [12, 36]. Increased acquisition occurs in hospital floors/settings with high *C. difficile* colonization pressure, a measurement of the proportion of patients colonized or infected with *C. difficile* within a defined hospital region (e.g., floor, ICU) during a specific time period [37].

Table 2 Reasons for inappropriate antibiotic use

Reasons for unnecessary days of antibiotic therapy	No (%) of unnecessary days
Duration of therapy longer than necessary	192 (33)
Treatment of a non-infectious sequelae	187 (32)
Treatment of colonization or contamination	94 (16)
Redundant coverage	60 (10)
Spectrum of activity not indicated	25 (4)
Adjustments not made in a timely manner	20 (3)

See Hecker [35]

Hospital studies have shown that in rooms with asymptomatic colonizers, spores can be recovered in 29 % of cases, in 50 % of symptomatic cases, and in greater than 90 % of rooms with incontinent CDI patients [36, 38]. Spores are highly resistant to alcohol gel products and many commonly used environmental disinfectants. Accordingly, longer lengths of stay have been implicated in both the acute and long-term care setting as a risk factor for CDI and CDI recurrence, as exposure time to *C. difficile* spores increases [28].

Infection control programs are of the utmost importance to enforce early and correct isolation precautions (gowns, gloves, and hand washing rather than alcohol gel) for CDI patients and to recognize potential outbreaks. These efforts lead to reduced *C. difficile* pressure and decreased exposure. Length of isolation precautions vary; some institutions, particularly during an outbreak, favor isolation for an affected patient during the entire hospitalization, whereas other programs stop isolation when patients are no longer having diarrhea. However, patients clinically cured of CDI after treatment, still have skin and environmental *C. difficile* contamination of 58 and 50 %, respectively [39]. Environmental efforts to reduce contamination should include frequent and terminal cleaning with chlorine-based sporicides such as 10 % bleach [40••]. Hydrogen peroxide solutions, UV light and copper-based surfaces show promise, but should only be used adjunctively with chlorine-based sporicides [40••, 41–43].

Age

During the past decade, age >65 years old has been consistently found across multiple studies to be associated with increased rates of infection and more severe disease [18, 44, 45]. The reasons for this are likely due to a higher number of comorbidities, a dysregulated inflammatory state associated with aging, a depressed humoral response to antigenic stimuli, and a loss of intestinal barrier defenses, protective cellular signaling, as well as impaired reparative mechanisms. A lack of a systemic immunoglobulin G (IgG) response to CDI has been implicated as both a risk for disease recurrence and an increased 30-day mortality [46, 47]. Animal studies have shown an increased inflammatory cytokine response in aged mice as compared to young mice in response to CDI, associated with greater symptomatology [48]. Recognition that age is a risk factor for disease should guide the hospital-based physician not only in suspicion and early management but also to take measures to avoid unnecessary antibiotics in this vulnerable population.

Acid-Reducing Medications

Fifty percent of inpatients prescribed proton pump inhibitors (PPI) are done so inappropriately [49]. In 2012, the Food and Drug Administration (FD) issued a warning that stomach acid-reducing medications may be associated with an increased risk of CDI, with higher doses conferring a greater risk. This decision was based on twenty-three of twenty-eight studies that found a 1.4–2.8-fold increased risk of CDI with PPI exposure [50]. Additionally, histamine blockers have also been implicated though to a lesser extent. Not all studies, though, have found an associated risk of CDI with PPI use, so this data is somewhat controversial. However, targeted efforts to identify patients inappropriately prescribed acid-reducing medications should be undertaken to help decrease CDI incidence.

Diagnosis

There are several CDI diagnostic laboratory tests with wide ranges of both sensitivity and specificity available within the hospital setting (Table 3 [51–55]). Also, the presence of pseudomembranes on endoscopy is pathognomonic for CDI. In severe cases or in cases with a high clinical suspicion, it is imperative to initiate therapy and place on isolation precautions early even prior to establishing a laboratory diagnosis. Guidelines recommend testing only in patients that have three or greater loose watery stools within a 24-h period. Formed stools should not be tested as this is not clinically consistent with CDI and is a source of undue costs.

Toxin enzyme immunoassays (EIA) test for the presence of both toxins A and B and were frequently the only available diagnostic test in the hospital setting. Sensitivity and specificity in comparison to gold standard cytotoxin neutralization assays are 58 and 95 % with a positive (PPV) and negative predictive value (NPV) of 70 and 92 % [54]. Newer antigen kits testing for the presence of

Table 3 Common *C. difficile* diagnostic tests available in the hospital setting

Test	Sensitivity (%)	Specificity (%)	Advantage	Disadvantage
Toxin A/B EIA	58	95	Cheap	Low NPV-High number of false negative tests
GDH antigen	>90	80–100	High NPV-good screening tool	Low PPV-High number of false positive tests
2-Step algorithm: GDH +PCR (Can also be combined with EIA)	94	99	Cheaper than screening all stools with PCR	Time intensive
Toxin B PCR	90–100	94–97	Rapid turnaround time. Option to test for the BI strain	Expensive

See Goldenberg [51, 52], Huang [53], Novak-Weekley [54], Shetty [55]

EIA enzyme linked immunoassay, *NPV* negative predictive value, *GDH* glutamate dehydrogenase, *PPV* positive predictive value, *PCR* polymerase chain reaction

glutamate dehydrogenase (GDH), an antigen present in both toxigenic and non-toxigenic *C. difficile*, are now available. Its NPV is >99 % with a PPV of 50 % making it a useful screening test [56]. A two-step algorithm, utilizing a screening GDH test combined with a polymerase chain reaction (PCR) test for the presence of the tcdB gene (transcribes toxin B) has a sensitivity and specificity of 94 and 99 %, respectively [51]. Because of their high sensitivity and specificity (94–100 and 96–97 %, respectively) and ability to test for the BI strain, many facilities are utilizing tcdB PCR without screening tests [52, 54]. The downside to the use of PCR only without the two-step algorithm is that it's expensive, but the benefit is that there is decreased testing time as compared to the two-step algorithm.

Early recognition of disease and diagnostic testing is essential for accurate epidemiologic surveillance. A standardized case definition, based on the timing of infection in relation to healthcare exposure (hospital, long-term acute care hospital, rehabilitation center) is now recommended by the Society for Healthcare Epidemiology or America/Infectious Disease Society of America (SHEA/IDSA) as follows [40••]:

1. Healthcare facility (HCF)-onset, HCF-associated CDI: Onset and diagnosis after 48 h of inpatient facility hospital admission and prior to discharge.
2. Community-onset, HCF-associated CDI: Onset and diagnosis within 4 weeks after inpatient facility discharge.
3. Community-associated CDI: Onset and diagnosis 12 weeks after inpatient facility discharge.
4. Indeterminate: Onset between 4–12 weeks after facility discharge.

Understanding these acquisition trends can help identify hospital-wide outbreaks and are crucial to hospitals since financial reimbursement for hospital-acquired infections will diminish and hospital onset CDI rates will be made public.

Disease Presentation and Definition

Symptoms of CDI range from mild, watery to profuse diarrhea, leading to profound dehydration and shock. Presentation typically occurs days to weeks after antibiotic exposure, but as previously stated, can occur with no antibiotic or healthcare exposure and at time months after antibiotic exposure. When patients present with symptoms of abdominal distention, abdominal pain, and lack of bowel movements, it indicates a more severe case. Disease severity is generally graded as mild to moderate, severe, and severe with complications. Various definitions of disease severity exist, with some including a combination of physical symptoms and lab work. SHEA/IDSA defines disease as follows [40••]:

Mild to Moderate Disease

1. White blood cell (WBC) less than 15,000 cells/uL
2. Cr of less than 1.5-fold the premorbid state.

Severe disease

1. WBC greater than 15,000 cells/uL
2. Cr of greater than 1.5-fold the premorbid state

Severe disease with complications

1. Presence of severe disease
2. Ileus
3. Toxic megacolon
4. Shock

Additional indicators of disease severity include a comorbid state, immunosuppression, bandemia, the use of

vasopressor therapy, hypoalbuminemia, and an elevated lactate level [27, 57•, 58]. Early recognition of severe disease and a fulminant state is of the utmost importance in order to start antibiotics and involve surgical colleagues when colectomy is deemed necessary (see Treatment: Fulminant Disease section below).

Treatment

CDI treatment varies depending on the severity of illness, which is defined above. In 2008, SHEA/IDSA published evidence-based recommendations for the treatment of CDI based on severity of the illness and/or recurrence (Table 4). Newer agents, associated with higher cure rate, less recurrence, and less microbiota disturbance are now available or in trial.

Mild to Moderate Disease

Metronidazole (500 mg orally three times a day for 10 days) is still recommended for a first presentation of mild to moderate disease according to the SHEA/IDSA guidelines. Evidence to support this comes from a small study performed prior to the prevalence of the BI strain and demonstrated that treatment with metronidazole or oral vancomycin for 10 days led to clinical cure in 90 and 98 % of patients, respectively ($p = .36$) [59]. Recurrence rates of 15 % were seen in both groups. Since then, a larger scale study demonstrated cure rates for metronidazole and vancomycin of 75 and 82 %, respectively [60•]. The lower cure rate in the latter study is thought to be due to the presence of the BI strain whereas the first study was undertaken prior to the widespread distribution of the strain. Though this newer study did not reach statistical significance, the trends in improved outcomes in this and other studies have led some to suggest vancomycin over metronidazole even in mild to moderate cases [61].

Severe Disease

Vancomycin (125 mg orally four times a day for ten to 14 days) is recommended for severe disease. It was previously shown to lead to clinical cure in 97 % of cases as compared to 76 % given metronidazole ($p = 0.02$) [59]. Better cure rates were also seen in a larger scale study with vancomycin being more effective than metronidazole for clinical cure (78.5 vs 66.3 %, $p = .059$) [60•]. Similarly, the difference in clinical cure between the two studies has been hypothesized to be due to the presence of the BI strain in the latter study.

Severe Disease with Complications

High dose vancomycin dosed 500 mg orally four times a day by mouth or nasogastric tube combined with metronidazole 500 mg intravenously three times per day is recommended for severe disease with complications such as ileus, toxic megacolon, or shock [40••]. Intravenous metronidazole is utilized as it is secreted into the bowel even in the presence of an ileus. If an ileus is present, then 500 mg of vancomycin in 125 ml of normal saline by retention enema every 6 h, rather than orally, is recommended in addition to the metronidazole. If clinical conditions worsen, surgical intervention is needed.

Fulminant Disease

Even despite antimicrobial treatment, CDI can progress to fulminant disease in 9 % of cases [17]. Signs of progressive disease include increasing number of bowel movements, increasing white blood cell count, worsening abdominal distension, more pronounced shock, and increasing lactate levels. Recognizing these signs and the urgent need for surgical intervention is of great importance as increased time to surgery is associated with a higher mortality [57•, 62, 63]. Mortality in fulminant cases can be as high as 60 % in those treated medically and 50 % in those undergoing total or subtotal colectomy [58]. Admission of fulminant patients to a Medicine as opposed to a Surgical service is associated with an increased mortality risk, thought to be due to an increased time to surgery [57•]. Other predictors of mortality in fulminant cases include WBC >50,000 cells/uL (87 % mortality), vasopressor use (66 % mortality), immunosuppression (73 % mortality), and/or a lactate >5 mmol/L (93 % mortality), even if a colectomy is undertaken, whereas a colectomy in patients with WBC of greater than 20,000 cells/uL, age greater than 65, immunocompetent state, and lactate between 2.2 and 4.9 mmol/L are associated with a mortality benefit [57•, 58] (Table 5 [57•, 58, 64]). The use of a loop ileostomy with colonic lavage and direct infusion of vancomycin into the colon has shown promise, dropping one center's mortality in fulminant cases from 50 % in those undergoing colectomy to 19 % in those with a loop ileostomy ($p = 0.006$) [65]; the use of loop ileostomy additionally decreases morbidity associated with colectomy with end ileostomy.

Recurrent Disease

CDI recurs in 25–30 % of patients, with the BI strain associated with a greater recurrence risk. A lack of an IgG

Table 4 Treatment strategies based on severity of CDI

Disease severity	Clinical and laboratory data	Treatment
1st Episode-mild/mod	WBC <15,000 cells/uL, Cr <1.5 times premorbid state	Metronidazole 500 mg PO TID × 10d
1st Episode-severe	WBC >15,000 cells/uL, Cr >1.5 times premorbid state, Consider if >65 years	Vancomycin 125 mg PO QID × 10–14 d
Severe, complicated	Hypotension, shock, ICU, megacolon, ileus	Vancomycin 500 mg PO QID + Metronidazole 500 mg IV TID. Vancomycin retention enema QID (500 mg mixed in 125 ml of normal saline) with ileus Early involvement of Surgery
1st Recurrence		Same as initial treatment
2nd Recurrence		Vancomycin taper with pulse[a]

See Cohen [40••]

CDI C. difficile infection, *WBC* white blood cell count

[a] Vancomycin 125 mg PO 4x/day × 14 d, then 125 mg PO TID × 7 d, then 125 mg PO BID × 7 d, then 125 mg PO q day × 7 d, then 125 mg PO qod × 14 d

response to infection and/or a continued drop of colonization resistance due to microbiota elimination with vancomycin and metronidazole is a possible reason for this recurrence [46]. SHEA/IDSA guidelines recommend for a first recurrence, a course identical to the first antibiotic course. With a second recurrence, a tapering course of vancomycin over several weeks is recommended (Table 4) [40••].

New Treatments

Fidaxomicin, a new macrocyclic antibiotic, dosed 200 mg orally twice a day for 10 days, is associated with a lower recurrence rate as compared to vancomycin (15.4 vs. 25.3 %, $p = 0.005$) [24••]. Whereas vancomycin and fidaxomicin are equally effective in resolving CDI symptoms, fidaxomicin preserves the microbiota, likely leading to the decreased recurrence [66]. The lower recurrence trend is similar when treating a first recurrence as well (20 % fidaxomicin vs 36 % vancomycin, $p = 0.045$) [67]. Fidaxomicin's costs have led some practitioners and hospitals to restrict its use, but a recent analysis has shown that it may be a more cost-effective treatment as compared to vancomycin [68].

Table 5 Clinical and laboratory findings associated with mortality in fulminant CDI

Increased time to surgery
Admission to a medical rather than surgical service[a]
Shock requiring vasopressor use
Immunosuppression
Age greater than 75 years
Lactate greater than 5 mmol/L
Respiratory failure
WBC greater than 35,000-50,000 cells/L or less than 4,000 × cells/L
Greater than 10 % bandemia
Multi-organ failure
Mental status changes

See Sailhamer [57•], Lamontagne [58], Perera [64], Byrn [61]

[a] Associated with an increased length of time prior to surgery

The most effective treatment for CDI recurrence remains fecal microbiota transplant (FMT), in which stool from a healthy donor is "transplanted" into the patient, restoring colonization resistance. Prior to a randomized controlled trial showing a cure rate of 94 % with FMT by nasoduodenal infusion, there were numerous case series and reports, as early as 1958, proving its benefit by colonoscopy and/or retention enema instillation, with cure rates ranging from 84 to 100 % [69–71••, 72]. Self-administered FMT has even been proven effective [72]. The biggest barrier to its implementation is the FDA's lack of clear guidance as to the necessity of an investigational new drug (IND) application. In June 2013, the FDA said an IND is not necessary to utilize FMT, but there is still concern it may be needed in the future. Additional barriers to implementation include institutions unwilling to adopt its use, lack of reimbursement by insurance plans, high costs associated with screening donors and recipients, and a lack of doctors, nurses, and/or ancillary staff willing to participate. Cost analysis, however, has shown it to be the most cost-effective treatment for CDI recurrence making it difficult for these barriers to be justified [74].

Surotomycin, an anti-*C. difficile* lipopeptide, currently in Phase 3 trials, has shown comparable cure rates to vancomycin and improved recurrence rates (17 vs 36 %, $p < 0.035$) [75]. Additional promising treatments include toxin A- and B-specific monoclonal antibodies, frozen fecal inocula for instillation, and stool substitute preparations of purified intestinal bacteria [76–78].

Conclusion

The turn of the century saw a surge in CDI prevalence and CDI-associated deaths. This has now plateaued as we further understand disease pathogenesis and epidemiology

associated with the "epidemic" BI strain. Our understanding of the preservation of the intestinal microbiota for disease prevention is greater and major efforts are being undertaken by some hospitals to reduce inappropriate antimicrobial use in the hopes of reducing CDI incidence. Newer studies are showing a trend toward improved outcome with vancomycin as compared to metronidazole. New anti-*C. difficile* drugs have shown promise in reducing recurrence, but by far the most promising treatment remains FMT and restoration of a healthy intestinal microbiota. Emergency room and hospital-based physicians can be at the forefront of battling this disease by initiating appropriate management early, recognizing factors associated with disease acquisition, facilitating the acceptance of ASP and infection control programs, and advocating for the approval of FMT in the hospital setting.

Compliance with Ethics Guidelines

Conflict of Interest Sean W Pawlowski has no reported conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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