HHS Public Access

Author manuscript

Infect Dis Clin Pract (Baltim Md). Author manuscript; available in PMC 2018 January 16.

Published in final edited form as:

Infect Dis Clin Pract (Baltim Md). 2016 January ; 24(1): 3–10. doi:10.1097/IPC.0000000000000350.

Diagnosis and Treatment of *Clostridium difficile* Infection (CDI)

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Abstract

Early and accurate diagnosis is essential for optimal treatment of individuals with *Clostridium difficile* infection (CDI) and for implementation of effective infection control procedures. The decision about which diagnostic test to use is an important one that should be based on test sensitivity, specificity, and predictive value. The challenges of CDI go beyond rapid identification and management of symptomatic patients. Asymptomatic carriage has long been suspected in *C.*

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Target Audience: Physicians and other healthcare professionals interested in effective diagnosis and treatment of *Clostridium difficile* infection (CDI).

Educational Objectives: Following the educational activity, participants will be able to recognize the warning signs and symptoms of CDI; identify the strengths and weaknesses of recommended tests to confirm a diagnosis of CDI; list the best practices for treatment of patients with CDI; and discuss the use of fecal transplant in the treatment of recurrent CDI.

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Marla Dalton, CAE (NFID staff, content reviewer) owns stock, stock options, or bonds from Merck & Co. Inc. Thomas M. File, Jr. MD (author) served as an advisor or consultant for Astellas, Cubist, Durata, GlaxoSmithKline, Nabriva, Pfizer Inc., and Tetraphase and received grant or research support from Cempra and Pfizer Inc. Dale N. Gerding, MD (author) holds patents for the treatment and prevention of *C. difficile* infection licensed to ViroPharma/Shire, and is a consultant or advisory board member for Merck & Co. Inc, Cubist, Actelion Pharmaceuticals Ltd, Sanofi Pasteur, Rebiotix Inc., Da Volterra, Pfizer Inc., Summit Pharmaceuticals International, and ViroPharma/Shire.William Schaffner, MD (NFID Medical Director, content reviewer) served as an advisor or consultant for Merck & Co., Inc., Pfizer Inc., and Novavax. All other planners and content reviewers have no funding or conflicts of interest to disclose.

difficile transmission, but it may play a larger role than previously thought. Emerging information also shows that patients treated for CDI remain colonized for many weeks after symptom resolution. In fact, stool culture positivity increases during the first weeks following treatment completion. Treatments that reduce the duration and degree of asymptomatic shedding could have added benefit for reduced transmission.

Keywords

Clostridium difficile; CDI; diagnostic test; treatment

Redefining The *Clostridium Difficile* Problem

Incidence of *Clostridium difficile* infection (CDI) increased dramatically in the first decade of this century and it is now the most common healthcare-associated infection in US hospitals. [Lessa NEJM 2015; CDC. MMWR 61(9), Dubberke CID 2012, Miller ICHE 2011, Stabler J Med Microbiol 2008] Much of the increase in CDI incidence, whether in hospitals or the community, is due to emergence of a toxin gene-variant strain, pulse field gel type NAP1 or PCR ribotype 027. [Stabler J Med Microbiol 2008, McDonald NEJM 2005, Akerlund J Clin Microbiol 2008, CID 2012] This strain is more virulent, producing more toxin A and B and in addition a third toxin, binary toxin, and it has been highly endemic in the US since about the year 2000. The increasing incidence and burden of CDI in the US and other countries (Table 1) has been well described in earlier publications [Lessa NEJM 2015, Dubberke CID 2012, Kwon Infect Dis Clin N Am, 2015], including a recent publication by two authors of this paper. [Gould IDCP 2015]

Prior antibiotic treatment is the single most important risk factor for CDI. [CDC MMWR 61(9)] Antibiotic treatment disrupts the normal colonic microbiota, leaving individuals susceptible to CDI when they come in contact with *C. difficile* spores, which can persist on any surface or device that becomes contaminated. Strategies to minimize inappropriate antibiotic exposure and decrease spore acquisition, essential components to reducing the burden of CDI, are also discussed in detail in an earlier companion CME article. [Gould IDCP 2015]

C. difficile is not a normal part of the human lower intestinal microbiota except during early life, but neonates and infants appear to have a natural defense against CDI toxins. They often become colonized with *C. difficile* bacteria but do not develop infection; animal data suggest a relative lack of toxin receptors during microbiota establishment in the first year of life may be protective. [Eglow J Clin Invest 1992] But while colonization and asymptomatic carriage is not uncommon in these early years, it is rare from about age 4 until much later in life, when it increases due to healthcare and antibiotic exposures. [McDonald In Jarvis (ed) 2014]

C. difficile Transmission and the Role of Asymptomatic Carriers

Transmission of *C difficile* occurs often in inpatient healthcare settings. [Eyre NEJM 2013] Every day spent on a ward with CDI patients, places unaffected patients at a cumulative risk of becoming infected or colonized. In fact, the rate of colonization outpaces the rate of

infection. But patients also come to the hospital colonized; point prevalence estimates for colonization on admission range from 5% to 15%. [Eyre PLoS One 2013, Leekha Am J Infect Control 2013, Alasmari CID 2014]

There is increasing recognition of the role of asymptomatic carriers as a source for CDI. In a study of more than 1,200 CDI cases in hospitalized patients over a 3-year period, only 38% of new cases were linked to a symptomatic CDI infection source. [Eyre NEJM 2013] Another study using molecular subtyping linked 29% of new CDI cases in hospitalized patients directly to asymptomatic persons. [Curry CID 2013] One reason for the increased recognition of the role of asymptomatic carriers in disease transmission may be that improved infection control measures in symptomatic patients have decreased their role in *C. difficile* transmission. [McDonald In Jarvis (ed) 2014]

Signs, Symptoms, and Diagnosis of CDI

There are two critical questions in CDI diagnosis. First, what are the clinical characteristics that best identify a patient to test for CDI? And second, which test or combination of tests best identifies patients who are symptomatically infected with toxigenic *C. difficile*? That is to say, differentiating patients with actual CDI versus those who are colonized with the bacteria but whose diarrhea is not *C. difficile*-associated.

Diarrhea, the most common symptom of CDI, is usually watery, not bloody, and is accompanied by abdominal pain. The minimum symptom duration for suspected CDI should be at least 3 unformed or watery stools per day for 1 to 2 days. [Johnson CID 2014] More severe symptoms may include fever, shock or hypotension, and severe ileus in which diarrhea shuts down. Signs of severe CDI include leukocytosis (white blood cell count may be elevated to 15,000/microL or more) and elevated serum creatinine.

It is important to assess antibiotic exposure because the majority of CDI patients have had antibiotic exposure in the previous 3 months, and to discontinue any current antibiotics. [Hensgens 2012] The decision to treat empirically or to wait for diagnostic test results is dependent on the severity of patient symptoms.

Changing Diagnostic Criteria and Need for Rapid Diagnosis

There has been a progressive lowering in the number of unformed stools per day that defines potential *C. difficile*-associated diarrhea or that indicates whom to test. [Johnson 2014, Tedesco 1974, Teasley 1983, Fekety 1989, Wenisch 1996] In 1974 diarrhea was defined as a change in bowel habits leading to more than 5 loose movements per day. [Tedesco 1974] Criteria in 1983 called for at least 6 unformed stools over a period of 36 hours. [Teasley 1983] More recently, the definition of diarrhea has been changed to 3 or more bowel movements with a loose or watery consistency in a 24-hour period. [Johnson CID 2014]

The revised threshold for *C. difficile* testing, mirroring these lower numbers of unformed stools per day, is due at least in part, to the emergence of epidemic outbreaks caused by the NAP1/027 strain. Outbreaks have increased the urgent need to isolate and test patients with diarrhea early as an infection control measure. The more rapidly fatal CDI associated with this strain has also motivated clinicians to provide earlier and more empiric treatment.

Issues In Diagnostic Testing

The decision about which test to use for *C. difficile* diagnosis is not inconsequential, but there is considerable debate about which test is best. Using more sensitive diagnostic tests may reduce transmission but lead to unnecessary treatment. Data are accumulating that detection of toxin is necessary to diagnose clinically important CDI whereas more sensitive tests that detect the toxin genes, such as the Nucleic Acid Amplification Test (NAAT), may lead to over-diagnosis by detecting colonized patients with diarrhea from another cause. [Polage JAMA Int Med 2015, Planche Lancet Inf Dis 2013, Longtin CID 2013]

To be useful in ruling out CDI and determining with certainty who does not require either treatment or isolation precautions to prevent onward transmission, a diagnostic test must have a high negative predictive value, which is a function of the test's inherent characteristics (ie, sensitivity and specificity) and the prevalence of CDI in the population in which it is being used. In contrast, if what is valued most is to avoid treating and isolating patients who do not have CDI as if they do, a high positive predictive value is needed, which again is a function of the test's inherent characteristics and the prevalence of CDI. If the incorrect population is tested (ie, a low prevalence group), then obtaining a high positive-predictive test value will be restricted. Positive-predictive test value can change dramatically based on disease prevalence. Planche et al described the positive and negative predictive values of a theoretical *C. difficile* toxin assay in populations with true disease rates ranging from 3% to 25% (Figure 1). [Planche Lancet Infect Dis 2008]

Testing has advanced considerably since the first two gold-standard tests, cell cytotoxicity and culture, were defined for diagnosis of *C. difficile* in 1979. [Chang 1978;22(2), George 1979] Just 4 years later these tests were replaced by enzyme immune assay (EIA) for toxin A, which provided a relatively quick, simple, and inexpensive means for CDI diagnosis. [Lyerly 1983]

In the next decade, the latex agglutination test, which was designed to detect Toxin A, was found to detect another key enzyme in CDI diagnosis, glutamate dehydrogenase (GDH). [Lyerly 1991]. This test was resurrected as an EIA and continues to be used today as a screening test for *C. difficile*. However, because GDH occurs in both toxigenic and non-toxigenic *C. difficile*, this test lacks adequate sensitivity and must be accompanied by another test to confirm presence of a toxigenic strain. [Lyerly 1991]

In 2000 a toxin A-/B+ strain was identified and associated with outbreaks worldwide. These strains were missed by the EIA for toxin A, which greatly limited the usefulness of the test. An EIA for both Toxin A and B replaced it, but there was no monoclonal antibody for Toxin B. A polyclonal antibody serum was used, but it was less sensitive than monoclonal antibody for Toxin A. [Alfa 2000]

A 2006 survey found that the most common laboratory test for CDI diagnosis was EIA for toxins A and B (201 of 350 responses, 57%). [Gerding IDCP 2009] Today, polymerase chain reaction (PCR) is by far the most common test. Kato et al [Kato 1993] first described PCR in 1993, but it did not become clinically available for laboratory diagnosis of *C. difficile*-associated diarrhea and colitis until 2010.

Table 2 lists *C. difficile* tests in order from most to least sensitive. The most sensitive test in use today is culture plus toxin confirmation, but it is too slow to be of practical use. NAAT (real time PCR, LAMP [Loop Mediated Isothermal Amplification]) is nearly as sensitive and much faster. GDH EIA is very sensitive but not specific, and cell cytotoxin is also too slow for practical use today. At the lower end of sensitivity are Toxins A and B EIA, Toxin A EIA, GDH latex test, and endoscopy, which is about 50% sensitive. [Cohen et al ICHE 2010]

Studies continue to spur debate and discussion about CDI testing and diagnosis, and the connection between testing method and clinical outcome. In a prospective cohort study that tested 1,321 stool samples during a test period of 95,750 patient days, Longtin et al [Longtin CID 2013] found that cases detected by PCR alone were less likely to have a complication of CDI compared with cases detected by EIA/CCA (3% vs. 39%, $p<0.001$). PCR compared with EIA/CCA detection was also associated with a lower chance of CDI readmission (0 vs. 20%, $p=0.01$) and a lower 30-day mortality rate versus EIA/CCA (3% vs. 18%, $p=0.09$). [Longtin 2013 CID] A later and larger study by this same group [Beaulieu 2014] confirmed that there are far fewer complications of CDI for patients diagnosed by PCR only (19% vs. 44%, $p=0.02$). Still, it is not clear how or if differences in diagnostic methods should drive different clinical approaches to patient care.

Planche et al [Planche Lancet Infect Dis 2013] provided similar findings using different diagnostic tests. In their study, group 1 patients had positive cell cytotoxin tests (i.e., toxin in the stool); group 2 had culture-positive and cell cytotoxin-negative tests (i.e., *C. difficile* in stool but no toxin detected in the stool); and group 3 had both cell- and culture-negative tests (i.e., no CDI). Mortality was significantly higher in group 1 (72/435 [16.6%]) compared with group 2 (20/207 [9.7%], $p=0.044$) and group 3 (503/5880 [8.6%], $p<0.001$). However, when a multivariate analysis accounted for confounding, only the difference between group 1 (positive cell cytotoxin test) and group 3 (no CDI) remained statistically significant for 30-day mortality (OR 1.61, 95% CI 1.12-2.31, $p=0.01$). [Planche Lancet Inf Dis 2013]The multivariate analysis also showed that many of the confounding risk factors were more strongly associated with increased odds of mortality than the test type. Confounders included: age >65 years (OR 2.52, 95% CI 1.98-3.21, $p<0.0001$), WBC $>15 \times 10^9$/L (OR 1.94, 95% CI 1.52-2.47, $p<0.0001$), >50% rise in serum creatinine (OR 2.25, 95% CI 1.69-2.99, $p<0.0001$), and serum albumin <20 g/L (OR 2.72, 95% CI 1.90-3.91, $p<0.0001$). [Planche Lancet Infect Dis 2013] Similar findings of Longtin and Planche were confirmed in a subsequent study by Polage et al. [Polage JAMA Int Med 2015]

In summary, if laboratories have no clinical input and accept any unformed stool for testing, it may be most appropriate to use a test that better identifies likely CDI, such as a relatively sensitive test for toxin in the stool (e.g., cell cytotoxin or GDH coupled with EIA for toxin). Conversely, if patients are screened carefully for clinical symptoms associated with CDI (e.g., at least 3 unformed or loose stools in a 24-hour period plus a history of antibiotic exposure), then a highly sensitive test such as NAAT or toxigenic culture, or GDH plus toxin detection, may be best. Neither of these approaches has been established, however, and appropriate testing strategy remains a dilemma.

Management Approaches To Cdi

There are several management strategies for CDI, including “inside the box” treatments (i.e., antimicrobial therapy that spares the normal microbiota), and “outside the box” non-antibiotic treatments such as live organism biotherapeutics (eg, nontoxigenic *C. difficile*, fecal transplants and their derivatives) or treatments focusing on supplementing or increasing the antibody response to *C. difficile* toxins (e.g., actively through vaccines or passively through monoclonal antibodies). Treatment using luminal (oral) toxin binders have not been successful to date and will not be discussed in this paper.

Current Recommendations for Treatment of CDI

Current recommendations for treatment of CDI are presented in Table 3. These recommendations are based on the 2010 guidelines from IDSA/SHEA [Cohen ICHE 2010] but include some alternative treatments based on emerging information and drug availability since the guidelines were published.

Recommended treatment for initial episodes is stratified based on severity (mild-moderate or severe) of CDI assessed by white cell count (above or below 15,000 cells/μL), serum creatinine level (above or below 1.5 times the pre-morbid level), and hypotension or shock, ileus, and megacolon which characterize severe complicated (also called fulminant) CDI. There are separate treatment recommendations for first and subsequent recurrences. [Cohen 2010]

Current guidelines call for metronidazole treatment for mild to moderate cases and vancomycin for severe cases. However, preferred treatment is moving toward oral vancomycin for all except the mildest cases, which may be treated with metronidazole. For severe cases, oral fidaxomicin, which was not available at the time the guidelines were published, is an alternative. Fidaxomicin uptake has been slow, largely due to its high cost. However, it may be the best drug available today because it has a similar treatment effect as vancomycin with a significantly lower recurrence rate.

Severe, complicated or fulminant cases are treated with higher doses of oral vancomycin plus metronidazole IV. [Cohen 2010] Tigeclycline IV may be used in place of either vancomycin or metronidazole but has only anecdotal evidence to support its use. Vancomycin may also be given via rectal retention enema for patients with complete ileus. Colectomy and ileostomy should be reserved for patients with severe disease who are not responsive to medical management.

First recurrences are treated based on severity following the same guidelines as the initial episode. Subsequent recurrences, however, are treated with vancomycin in a tapered or pulsed regimen for 5 to 7 weeks. Alternatives include fidaxomicin, vancomycin followed by rifaximin, or a fecal transplant (discussed below). Metronidazole should not be used beyond the first recurrence or for long-term therapy due to cumulative neurotoxicity. [Cohen 2010]

Tolevamer Trial Provides Data Comparing Vancomycin and Metronidazole

A large, multicenter, randomized, prospective study compared tolevamer (a non-antibiotic, toxin-binding polymer), vancomycin and metronidazole. [Johnson 2014] The trial included patients >18 years with primary CDI or recurrent CDI defined as ≥3 loose or watery bowel movements within a 24-hour period along with a positive *C. difficile* toxin assay result or pseudomembranes on endoscopy, and no other likely etiology for the diarrhea. The primary efficacy endpoint was resolution of diarrhea and absence of severe abdominal discomfort due to CDI for >2 consecutive days. [Johnson 2014]

While tolevamer was inferior to both vancomycin and metronidazole for the treatment of CDI, vancomycin was significantly better than metronidazole for all patients. Previously, vancomycin superiority data were limited to patients with severe CDI. [Johnson 2014]

This study also showed a better outcome for treatment naïve versus treatment experienced patients (OR 1.814, 95% CI 1.196-2.753, p=0.0051) and for mild to moderate versus severe CDI (OR 1.6, 95% CI 1.032-2.479, p=0.0356). The latter finding would be expected, but provides additional confirmation of the clinical utility of the current definitions of mild to moderate and severe disease. These findings will likely be incorporated into future guidelines but a shift toward increased use of vancomycin and decreased use of metronidazole may already be warranted.

Surgical Options for Severe, Complicated CDI

Surgery is recommended for patients with severe, complicated CDI not responding to medical treatment. Colectomy, the current surgical clinical standard, should be performed before serum lactate reaches 5 mmol/L or WBC is >50,000/mm^3 to reduce the risk of mortality. Even then, while colectomy has been shown to improve survival, mortality in this population remains high. [Neal Ann Surg 2011]

An option to colectomy is diverting loop ileostomy followed by intraoperative lavage of 8 L of warmed polyethylene glycol and 500 mg vancomycin q 8 hours. In a case control study, Neal et al [Neal Ann Surg 2011] reported reduced mortality in patients treated with diverting loop ileostomy compared with historic mortality with colectomy (19% vs. 50%, OR 0.24, p=0.006). Preservation of the colon was achieved in 39 of 42 patients (93%) and 35 (83%) of these surgeries were performed laparoscopically.

Fecal Transplants for Recurrent CDI

Based on limited data, fecal microbiota transplantation (FMT) appears to be very effective for treatment of recurrent CDI. Ina systematic review of FMT research, Drekonja et al reported on 2 randomized controlled trials with limited numbers of patients, in which 27 of 36 (75%) patients did not have further recurrence. [Drekonja Ann Intern Med 2015] They also discussed case reports in which 85% of 480 patients had symptom resolution without further recurrence.

In an open-label controlled trial, van Nood et al [van Nood NEJM 2013] randomized 43 patients ≤18 years of age with recurrent CDI to one of three treatments: FMT preceded by an abbreviated regimen of vancomycin and bowel lavage (n=17), a standard vancomycin

regimen (n=13), and a standard vancomycin regimen with bowel lavage (n=13). The primary endpoint, cure without relapse within 10 weeks of initiation of therapy was met by 81.3% of patients in the FMT group, 30.8% in the vancomycin group, and 23.1% for the vancomycin plus lavage group (p=0.003 for FMT versus both vancomycin regimens). [van Nood NEJM 2013] An additional FMT for those who did not meet the endpoint in the FMT group led to a 94% cure rate. Repeat FMT is often successful after failure, but with limited data, the focus for now should remain on initial FMT treatment results.

More recently, fecal material has been delivered via frozen FMT capsules. This oral therapy resolved symptoms for 14 of 20 (70%) patients (95% CI 47%-85%). [Youngster JAMA 2014] Investigators are working to identify and isolate the live bacterial organisms that can be used in a mixture of defined bacteria to treat recurrent CDI with FMT. [Pardi ICAAC 2014]

Administration of Nontoxigenic *C. difficile* Spores to Prevent CDI Recurrence

Gerding et al [Gerding JAMA 2015] reported a phase 2 study assessing the effect of administration of non-toxigenic *C. difficile* spores on CDI recurrence in patients who had clinically recovered following treatment with vancomycin or metronidazole. This double-blind, placebo-controlled, dose-ranging study randomized 173 patients ≥18 years of age to placebo for 14 days (n=44), or one of three doses of oral liquid formulation of non-toxigenic *C. difficile* strain M3 (NTCD-M3): 10^4 spores/day for 7 days (low dose, n=43), 10^7 spores/day for 7 days (high dose/short course, n=44), or 10^7 spores/day for 14 days (high dose/long course, n=42). [Gerding JAMA 2015]

All doses of NTCD-M3 met the primary outcome—they were well tolerated and appeared to be safe. [Gerding JAMA 2015] Secondary outcomes measured fecal colonization with NTCD-M3 from end of study drug through week 6, and recurrence of CDI from day 1 through week 6. NTCD-M3 colonized the gastrointestinal tract and significantly reduced CDI recurrence. The lowest rate of recurrence seen was in the high dose, 7-day (short course) treatment arm. CDI recurrence rates were: placebo (30%), NTCD-M3 low-dose (15%), NTCD-M3 high-dose/short course (5%), and NTCD-M3 high dose/long course (15%).

Conclusion

CDI incidence has increased dramatically in the US since 2000. Reducing the burden of CDI begins with rapid and accurate testing of patients exhibiting its known signs and symptoms and including recent antibiotic exposure in the patient history. Choosing the right diagnostic test based on the true disease rates in the population at hand is an important but challenging decision. Treatment advances include new information about optimal diagnostics, newer antibiotics, FMT for recurrent CDI, surgical options to colectomy, and administration of non-toxigenic *C. difficile* spores to reduce disease recurrence.

Acknowledgments

This publication is based on presentations by Dr.Gerding and Dr. McDonald during an NFID webinar held in July 2015 (www.nfid.org/archived-webinars). The findings and conclusions in this report are those of the authors and do

not necessarily represent the official position or views of the Centers for Disease Control and Prevention or the US Department of Veterans Affairs.

This activity is supported by an unrestricted educational grant from Merck & Co., Inc.

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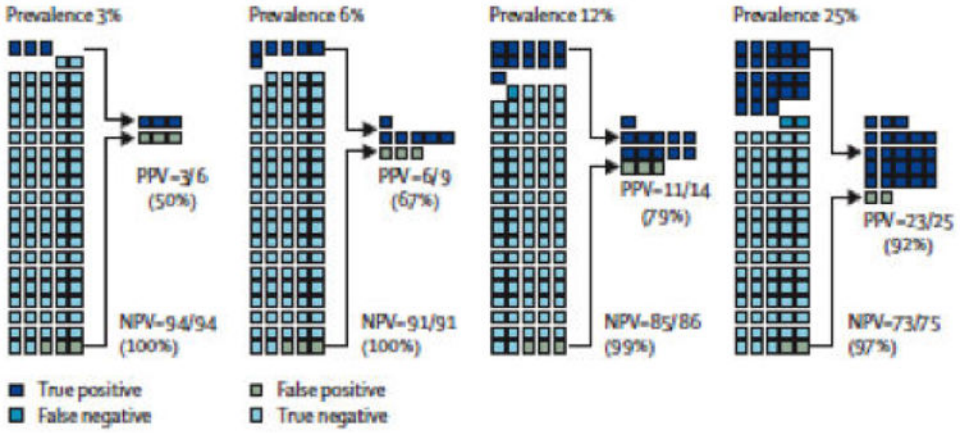

Figure 1. Predictive Value for a Theoretical Test Based on True CDI Disease Prevalence [Planche Lancet Infect Dis 2008]

Effect of varying prevalence on the PPV and NPV of a theoretical *Clostridium difficile* toxin assay with a sensitivity of 92% and a specificity of 97%

NPV=negative predictive value. PPV=positive predictive value.

Table 1

Annual Burden of *C. difficile* Infection in the US [Lessa NEJM 2015, Kwon Infect Dis Clin N Am 2015]

- 453,000 cases annually
  - Approximately two-thirds of cases are categorized as (inpatient) healthcare associated, but only 24% have hospital onset (23% have nursing home onset, 18% have post-discharge onset)
  - More than 8 in 10 (82%) patients with “community-associated” CDI report recent healthcare exposures such as doctor or dentist visits
- 29,000 deaths within 30 days of CDI diagnosis
- 83,000 annual recurrences within 8 weeks of the initial case
- Rate of colectomies increasing; as high as 6.2% in epidemic periods
- CDI extends inpatient hospital stays by 2.3 to 12 days and increases the financial burden by $2,454 to $27,160 per case

Table 2

Relative Sensitivity of *C. difficile* Tests from Highest to Lowest Sensitivity.

- Culture + Toxin Confirmation: a “gold standard”, but is labor intensive and also has a slow turnaround
- Nucleic Acid Amplification Test (NAAT), which includes Polymerase Chain Reaction (PCR) and Loop Mediated Isothermal Amplification (LAMP), detects the genes for toxin production, but does not detect toxin itself.
- Enzyme Immuno Assay (EIA) for Glutamate Dehydrogenase (GDH): rapid test that detects presence of an enzyme found in toxigenic and non-toxigenic *C. difficile*; must be used in conjunction with a test for toxin or toxin genes.
- Cell Culture Cytotoxin Assay – more difficult and slower turnaround time than EIA, even though more sensitive, leading to limited usefulness in clinical setting, but is one of the “gold standard” tests
- EIA for toxin – to detect toxins A and B in stool (lower sensitivity compared to Cell Culture Cytotoxicity)
- GDH Latex Test (very low sensitivity)
- Endoscopy (very low sensitivity)

Table 3
CDI Current Treatment by Infection Severity and Recurrence [Cohen 2010]

Organism	Antibiotic	Dose	Alternatives
C. difficile (mild to moderate)	Metronidazole	500 mg po tid × 10-14d	Vancomycin 125 mg po qid × 10-14d
C. difficile (severe)	Vancomycin	125 mg po qid × 10-14d	Fidaxomiciri 200 mg po bid × 10d
C. difficile (severe complicated or fulminant)	Vancomycin + Metronidazole	500 mg po qid × 10-14d 500 mg iv tid × 10-14d	Tigecycline 50 mg iv bid × 10-21d in place of metronidazole or vancomycin Additional vancomycin via rectal retention enema, 500 mg in 100 ml NS q 6h if complete ileus present Colectomy or Ileostomy
C difficile (first recurrence)	Same as primary CDI based on severity of disease		
C. difficile (>1 recurrence)	Vancomycin	125 mg po qid × 10d, then 125 mg po bid × 7d, then 125 mg po qd × 7d, then 125 mg po qod or q3d × 14-28d, then stop	Vancomycin 125 mg po qid × 10d followed by rifaximin 400 mg po bid × 14d, Fidaxomicin 200 mg po bid × 10d Fecal Transplants (FMT)

Adapted from SHEA/IDSA 2010 clinical practice guidelines [Cohen 2010]