EDUCATIONAL COMMENTARY – *CLOSTRIDIUM DIFFICILE* UPDATE

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LEARNING OBJECTIVES

On completion of this exercise, the participant should be able to

- discuss recent changes in the epidemiologic features of *Clostridium difficile*-associated disease
- compare and contrast laboratory methods for detecting *C difficile*
- describe conventional and emerging treatments for *C difficile*-associated disease

Introduction

Clostridium difficile was first detected in the feces of healthy infants in 1935, but it was not recognized as a pathogen until 1978, when it was found to cause pseudomembranous colitis in patients who had been treated with antibiotics Since 2000, the epidemiologic picture of *C difficile*-associated disease (CDAD) has changed rapidly Recent data indicate that *C difficile* has surpassed methicillin-resistant *Staphylococcus aureus* as the most frequent cause of health care-associated infection,[1] and increasing numbers of outbreaks involve strains of *C difficile* that are more virulent and resistant to conventional therapy In particular, these changes have been attributed to the emergence of a previously rare strain of *C difficile*, B1/NAP1/027, which is resistant to fluoroquinolones and produces large amounts of both toxin A and toxin B [1,2] The B1/NAP1/027 strain also produces a third toxin, termed *binary toxin*, which may cause more severe diarrhea [1,2]

Persons who harbor *C difficile* but show no symptoms of disease are said to be *colonized* rather than *infected* Colonization rates range from less than 5% of healthy adults to as many as 25% to 55% of hospitalized patients and nursing home residents [1] *Clostridium difficile*-associated disease appears less likely to develop in persons who are colonized, owing to natural immunity or the presence of a nontoxigenic strain

Researchers have identified two essential requirements for the development of CDAD exposure to antibiotics and new acquisition of *C difficile* [1,2] Although all classes of antibiotics have been implicated in the development of CDAD, broad spectrum antibiotics, such as cephalosporins, clindamycin, and fluoroquinolones, confer the greatest risk However, not all persons who have been treated with antibiotics and harbor *C difficile* become ill For this reason, experts believe that host factors, such as advanced age, hospitalization, compromised immunity, gastrointestinal surgery, nasogastric tubes, and treatment with proton pump inhibitors, also play a role in the development of CDAD [2] Finally, only

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C difficile strains that produce toxin A or toxin B cause disease In general, CDAD should be suspected in patients with the following six features [3]

1 Diarrhea is the main symptom

2 Diarrhea begins 2 to 3 days after hospitalization without obvious exposure to other pathogens

3 Diarrhea persists for more than 3 days without identification of the cause

4 The patient has been treated with antibiotics

5 The patient is older than 65 years, has compromised immunity, or has gastrointestinal disease or other severe disease

6 The patient has been frequently exposed to *C difficile*

Laboratory Diagnosis

Testing for *C difficile* or its toxins should be performed only on unformed stool specimens [4] Testing stool specimens from asymptomatic persons is not useful and is not recommended for any reason except epidemiologic studies Testing multiple stool specimens during the same episode of diarrhea is likewise not recommended, except to confirm a negative enzyme immunoassay (EIA) for toxins, because it is not cost-effective and is unlikely to improve diagnosis of CDAD [2-4]

Enzyme immunoassay to detect *C difficile* toxins is used by more than 90% of laboratories in the United States to detect pathogenic *C difficile* strains, because it is inexpensive, rapid, and easy to perform [4] Available assays can detect toxin A alone or toxin A and toxin B directly from stool specimens However, testing for toxin A only is not recommended, because this will not detect strains of *C difficile* that produce only toxin B [3] Also, studies have demonstrated that the sensitivity of EIA is variable, ranging from 45% to 95% [2,3] For this reason, the test should be repeated on 2 or 3 subsequent stool specimens if the initial result is negative and the clinical diagnosis is CDAD [2,3] Because of its low sensitivity, expert consensus is that toxin detection using EIA is not the best method to diagnose CDAD [4,5]

Another EIA method to detect *C difficile* involves screening stool specimens for the enzyme glutamate dehydrogenase (GDH) Also known as the C difficile *common antigen*, GDH is secreted into the feces by *C difficile* The absence of GDH strongly indicates that *C difficile* is not present in the specimen However, because other organisms may also produce GDH, the presence of this enzyme does not reveal whether *C difficile* toxins are present For these reasons, confirmatory testing with cell cytotoxin assay, toxin A/B EIA, or toxigenic culture is recommended [3,4] Commercially available EIA assays for GDH have a sensitivity of 85% to 95% and a specificity of 89% to 99% [4]

Culture for *C difficile* is highly sensitive, but culture alone cannot differentiate strains that produce toxins from those that do not However, many experts believe that culture followed by testing for toxins in suspicious colonies (*toxigenic culture*) is the most sensitive method to diagnose CDAD, and this has the advantage of providing isolates for epidemiologic studies [2,4,5] Despite these advantages, toxigenic culture is not used in most laboratories, because it is expensive and labor intensive and it has a lengthy turnaround time of 2 to 9 days

Cytotoxicity testing of cell cultures is both highly sensitive (94%-100%) and specific (99%) [3] However, most cytotoxicity assays detect only toxin B, because special cells are needed to detect toxin A [3,4] This is a disadvantage, because, although most *C difficile* strains produce either both toxins A and B or neither toxin, an increasing number of strains produce only toxin A [4] Also, the toxin-induced cytotoxicity must be neutralized to ensure the specificity of the assay [3] Finally, like culture, cell culture cytotoxicity testing is expensive and labor intensive, and results may not be available for up to 2 days [3]

Polymerase chain reaction (PCR) assays have been developed that detect the genes that encode for toxins A and B and other genes that are specific for *C difficile* [3] Since this assay does not detect actual toxin, a positive result is not always indicative of active disease and could lead to inappropriate therapy The combination of short turnaround time and high sensitivity (84%-94%)[1] make PCR an attractive alternative to other methods, but experts caution that more studies are needed before PCR can be recommended for routine testing [4] Also, because it is expensive and requires technical expertise in molecular methods, PCR may not be feasible for many laboratories

Treatment of CDAD

In all cases of CDAD, the antibiotic that triggered the disease should be discontinued as soon as possible [2,4] Further recommendations for treatment of CDAD depend on whether the disease is an initial episode or a recurrence and on the severity of the illness Levels of severity are defined as follows [2]

- Mild to moderate disease is characterized by mild to moderate diarrhea and a white blood cell count of fewer than 16,000/µL
- Severe disease is characterized by fever, profuse diarrhea, abdominal pain, elevated creatinine, and a white blood cell count of more than 16,000/µL
- Severe, complicated disease is characterized by hypotension, shock, toxic megacolon, and ileus

Metronidazole and vancomycin are highly effective treatments for CDAD [2] However, vancomycin is more expensive, and it can promote development of vancomycin-resistant enterococci For these reasons, initial episodes of mild to moderate CDAD should be treated with metronidazole [2,4] On the other hand, because treatment failure can occur with metronidazole, initial episodes of severe CDAD should be

treated with vancomycin [2,4] Severe, complicated cases of CDAD may be treated with a combination of vancomycin and metronidazole [2,4]

The first recurrence of CDAD is usually treated with the same antibiotic as the initial episode, provided the severity has not changed If the severity of the disease has changed, treatment should follow the recommendations for treating initial episodes by severity Subsequent recurrences should not be treated with metronidazole Instead, a tapered or pulse regimen with vancomycin is recommended [2,4]

Drug therapy for CDAD continues to evolve, and several new antibiotics have been found effective, although they are not yet recommended as primary treatments Researchers have investigated therapy with tolevamer, a nonantibiotic drug that binds to toxins A and B, but this has not yet proved as effective as vancomycin [2]

Researchers have also investigated the use of probiotics, immunotherapy, and fecal transplant as treatments for CDAD Studies have shown some benefit from administering probiotics, such as *Lactobacillus* species, *Streptococcus thermophilus*, or *Saccharomyces boulardii*, however, evidence does not yet support the routine use of probiotics to prevent or cure CDAD [2] Case reports have indicated that intravenous administration of immunoglobulin G antibodies to neutralize *C difficile* may be effective, but much more research is needed to determine if immune therapy is a viable approach [2] Similarly, fecal transplant from healthy donors has been reported as effective,[2,6] and recently published results of a randomized trial appear to support the efficacy of this method [6]

Summary

Clostridium difficile is now the most frequent cause of health care-associated disease in the United States The emergence of more virulent strains has led to outbreaks of more severe disease Methods currently available to diagnose CDAD include culture of the organism, cell culture cytotoxin assay, EIA to detect *C difficile* toxins, EIA to detect the antigen GDH, and PCR Currently, no single test for *C difficile* or its toxins is sufficiently sensitive, specific, timely, and cost-effective to meet every laboratory's needs For this reason many laboratories use 2-step algorithms, but the best testing strategy remains controversial Metronidazole and vancomycin are the antibiotics currently recommended for treating CDAD, but researchers are investigating other drugs as well as unconventional therapies, such as probiotics, immunotherapy, and fecal transplant

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References

1 Lessa FC, Gould CV, McDonald LC Current status of *Clostridium difficile* infection epidemiology *Clin Infect Dis* 2012,55(suppl2) S65-S70 http //www ncbi nlm nih gov/pmc/articles/PMC3388017/pdf/cis319 pdf Accessed June 12, 2013

2 Gould CV, McDonald LC Bench-to-bedside review *Clostridium difficile* colitis *Crit Care* 2008,12 203 http //ccforum com/content/12/1/203 Accessed June 12, 2013

3 Stevens DL, Bryant AE, Berger A, von Eichel-Streiber C *Clostridium* In Versalovic J, ed *Manual of Clinical Microbiology.* Vol 1 10th ed Washington, DC ASM Press, 2010 834-857

4 Cohen SH, Gerding DN, Johnson S, et al Clinical practice guidelines for *Clostridium difficile* infection in adults 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) *Infect Control Hosp Epidemiol* 2010,31(5) 431-455

5 Baron EJ Approaches to identification of anaerobic bacteria In Versalovic J, ed *Manual of Clinical Microbiology* Vol 1 10th ed Washington, DC ASM Press, 2010 799-802

6. van Nood A, Vrieze A, Nieuwdorp M, et al Duodenal infusion of donor feces for recurrent *Clostridium difficile N Engl J Med* 2013,368(5) 407-415

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