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## Clostridia Difficile Diarrhea

Enoch Lule  
*Medical Center Of Central Georgia*  
USA

### 1. Introduction

The term antibiotic associated diarrhea is usually reserved for diarrhea caused by infection with the organism *Clostridia Difficile*. Infection is thought to take place after the normal intestinal flora is altered by antibiotic use allowing for proliferation of *Clostridia Difficile*. Worryingly, the incidence and severity of illness caused by *Clostridia Difficile* is on the increase.

### 2. Pathophysiology

*Clostridia difficile* is a gram positive, spore forming anaerobic bacilli<sup>1</sup> Infection occurs when the organism is ingested. Though initially thought of as a nosocomial infection, community acquired *clostridia difficile* infection is increasingly recognized.<sup>2</sup>

*Clostridia Difficile* produces a variety of toxins, toxin A (enterotoxin) and B (cytotoxin) are the toxins most frequently linked to disease. They cause inflammation and disrupt cell cytoskeleton synthesis leading to colonic cell disruption.<sup>3,4,5</sup> A new strain, termed NAP1 or BI or 027 (depending on the technique used to identify it) was identified in the early 2000s the cause of selected outbreaks. This strain of *clostridia difficile* is associated with clinically more severe disease, innate resistance to quinolones and higher amounts of toxin production.<sup>6</sup>

### 3. Epidemiology

*Clostridia difficile* infection was linked to the development of pseudomembranous colitis in the 70's.<sup>7</sup> Initial cases were mostly linked to clindamycin but since then the range antibiotics linked with development of *Clostridia Difficile* has widened and cephalosporins and floroquinolones are thought to be the major causes.<sup>8</sup>

Though less often thought of as a cause of diarrhea in developing countries, pathogenic *C. Difficile* has been noted in South Africa<sup>9</sup> and India.<sup>10</sup>

The incidence rate of *C. Difficile* infection in the US was about 30 to 40 cases per hundred thousand.<sup>11</sup>

One research group noted an increasing rate of colectomies following *C. Difficile* infection.<sup>12</sup> Canadian authors noted a four fold increase in background prevalence of *C. Difficile* between when the period before 2002 was compared to 2003.<sup>13</sup>

#### 4. Clinical presentation

Presentation may range from asymptomatic carrier state<sup>14</sup> to fulminant colitis.<sup>15</sup> Symptomatic patients typically present with watery diarrhea and lower abdominal pain.<sup>16</sup> Severe diarrhea with leucocytosis, fever, abdominal pain and distention occurs in the severely ill<sup>16,17</sup>. Surgical management with colectomy may be required in severe cases<sup>18</sup>. *C. Difficile* colitis was increasingly listed as the cause of death in an English population.<sup>19</sup> Rises in white cell count to above 30,000 or a doubling of serum creatinine have been suggested as harbingers of complicated disease.<sup>20</sup>

#### 5. Diagnosis

*C. Difficile* diagnosis is usually done with laboratory testing in a patient suspected to be having the infection.

One of the most sensitive and specific tests available is the cell cytotoxicity assay, which had a sensitivity of 98% and specificity of 99% when compared to clinical and laboratory criteria.<sup>21</sup> This test is unfortunately technically demanding and may not be the first choice of many laboratories.

Many laboratories will use EIAs for detection of toxin A and B. These tests are insensitive when compared to cell culture or cytotoxicity assay but they are cheaper and produce results in hours rather than days.<sup>22</sup> Due to the lower positive predictive value of these tests a 2 step approach with a sensitive screening test followed by confirmation by culture or cell cytotoxicity may be appropriate.<sup>23</sup>

Testing for glutamate dehydrogenase, an enzyme produced by *C. Difficile* is sensitive (96 to 100%)<sup>24</sup>, cheap, and rapid but it only detects presence of organism rather than toxin production.

Though its usually unnecessary, direct visualization of colitis by endoscopy is virtually diagnostic as they are few other infections that would cause pseudomembrane formation.<sup>25</sup> Endoscopy carries the risk of perforation in fulminant colitis.

#### 6. Treatment

First line therapy for *C. Difficile* infection has long been considered to be a choice between metronidazole or vancomycin. Resolution of disease was seen in over 90% of patients taking a 10 day course of either therapy.<sup>26</sup>

More recently, metronidazole has been associated with therapeutic failure rates as high as 50 percent if persistence of disease and recurrence are combined.<sup>27</sup> That said, oral metronidazole at a dose of 500mg, three times daily for ten to fourteen days remains the initial recommended therapy for mild disease.<sup>28</sup> Oral or rectal vancomycin (500mg four times a day) is recommended for more severe disease.<sup>28</sup> Patients who cannot tolerate oral therapy may be treated with intravenous metronidazole.<sup>29</sup>

Up to 25% of patients may have recurrent infection<sup>16</sup> believed to occur because of germination of spores or ingestion of new spores.

Many approaches have been taken to recurrent symptomatic *C. Difficile* infection. A tapered or pulsed course of oral vancomycin may reduce recurrence rates<sup>30</sup>.

Other approaches include fecal transplants<sup>31</sup>, immunization against C difficile toxins<sup>32</sup>, cholestyramine<sup>33</sup>, rifampin<sup>34</sup> or probiotics<sup>35</sup>. There isn't sufficient data to recommend any of these approaches.

Recently fidaxomicin (200 mg oral, twice daily for ten days), a macrolide antibiotic, was shown to be non inferior to vancomycin.<sup>36</sup> During the trial referenced, patients were noted to have a lower recurrence rate when they were treated using fidaxomicin rather than vancomycin (13.3% vs. 24.0%)

## 7. Prevention

Judicious use of antibiotics has been shown to reduce the rates of C. difficile infection.<sup>37, 38</sup> Washing hands with soap and water, using gloves when touching patients and use of disposable thermometers have been recommended as control measures with good quality evidence of efficacy.<sup>39</sup> Alcohol hand washing gels are not effective in preventing disease spread.<sup>40</sup>

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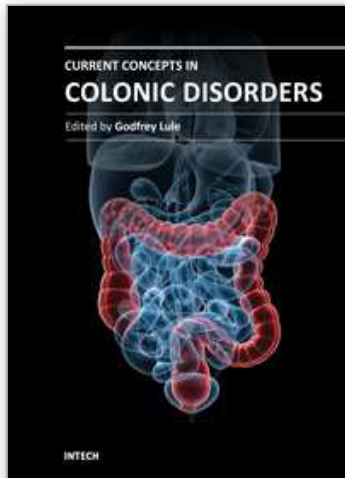
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The 21st Century has seen a resurgence of research of the gastrointestinal tract, especially since it was established that it plays a central role as an immune system organ and consequentially has a huge impact on causation, impact and transmission of most human ailments. New diseases such as the Acquired Immunodeficiency Syndrome, hepatitis and tumours of the gastrointestinal tract have emerged and they are currently subjects of intensive research and topics of scientific papers published worldwide. Old diseases like diarrhea have become extremely complex to diagnose with new and old pathogens, drugs, tumours and malabsorptive disorders accounting for the confusion. This book has set out algorithms on how to approach such conditions in a systematic way both to reach a diagnosis and to make patient management cheaper and more efficient. "Current Concepts in Colonic Disorders" attempts to put all the new information into proper perspective with emphasis on aetiopathogenesis and providing rational approach to management of various old and new diseases. As the book editor, I have found this first edition extremely interesting and easy to understand. Comments on how to improve the content and manner of presentation for future editions are extremely welcome.

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