Hospitalized patient receiving broad-spectrum antibiotics are at risk of developing Clostridium difficile infection (CDI). Antibiotics change the normal colonic bacterial flora and C. difficile colonizes the colon in these patients. C. difficile produces toxins that cause inflammation of the colonic mucosa. Even though clindamycin has been traditionally linked to the development of C. difficile colitis, almost all antibiotics can cause the disease.

Introduction

Clostridium difficile infection (CDI), also called antibiotic-related diarrhea, often occurs after receiving broad spectrum antibiotics, especially in hospitalized patients. In most cases, the presentation consists of diarrhea, abdominal colic, and fever. Less commonly, patients can develop fulminant colitis.

Epidemiology of C. Difficile Infection

Clostridi um difficile is a Gram-positive, anaerobic, spore-forming bacteria, which is also a normal enteric flora in about 5 % of the population. It is important to differentiate...
between mere colonization with *C. difficile* and the development of CDI, as **treatment of asymptomatic persons with C. difficile colonization is not recommended.**

In the United States, CDI is responsible for at least 3 million cases per year. Additionally, those who received an antibiotic in the last three months and present with diarrhea should be evaluated for possible *C. difficile* colitis. While the majority of the cases are hospital-acquired, up to 40 % of *C. difficile* colitis cases are community acquired.

CDI is relatively more common in the elderly. It is important to note that *C. difficile* is becoming more common among hospitalized children with predisposing conditions such as **inflammatory bowel disease.**

The recurrence rate of CDI is high, 40 %, and can be attributed to metronidazole or vancomycin resistance.

**Pathophysiology of C. Difficile Infection**

The human colon is colonized by the bacterial flora. The use of broad-spectrum antibiotics (such as clindamycin, beta-lactams, and fluoroquinolones) disturbs the normal colonic bacterial flora to varying degrees. While, in most patients, these changes are not severe enough to cause a problem; in the elderly and patients with pre-existing conditions such as inflammatory bowel disease, *C. difficile* colonization of the colon can happen. Once the colon is colonized with *C. difficile*, the bacteria can release **cytotoxic toxins** that cause inflammation and mucosal damage, leading to colitis.

*C. difficile* forms heat-resistant spores that can survive in the environment for quite some time. Outbreaks of *C. difficile* diarrhea are most prevalent in hospitals and outpatient facilities where there is contamination with spores. Even though normal gut flora resists colonization with *C. difficile*, increased use of broad-spectrum antibiotics, alters the normal flora, allowing a proliferation of *C. difficile*, diarrhea and toxin synthesis.

The *C. difficile* produces two different types of high–molecular weight toxins that play a crucial role in the pathogenesis of CDI. The **toxin A, an enterotoxin**, binds to certain receptors in the cellular lining of the intestine and the **toxin B, a cytotoxin**, has a direct effect on the same cells that result in **apoptosis**. The ultimate result is mucosal inflammation and necrosis which causes diarrhea and abdominal pain.

A specific strain of *C. difficile*, NAP1, is responsible for fulminant colitis that is associated with leukocytosis, **acute renal injury** and toxic megacolon. The judicious use of fluoroquinolone antibiotics may have played a major role in the development and proliferation of the NAP1 strain. Unfortunately, this form of life-threatening colitis can only be managed by colectomy. Fecal bacteriotherapy and immunotherapy are also accompanied treatment strategies for this kind of strain.

**Etiology of C. Difficile Infection**
Since the disturbance of normal colonic flora and colonization of *C. difficile* is central to the pathogenesis of CDI, the use of broad-spectrum antibiotics and presence of certain medical conditions increase the likelihood of this disease.

The **use of broad-spectrum antibiotics** is the most commonly implicated etiology in *C. difficile* colitis. **Cephalosporins**, **Penicillins**, and **clindamycin** have been associated with *C. difficile* infection, and the recent expanding use of **fluoroquinolones** is thought to be responsible for the emergence of the **NAP1 strain** that is implicated in fulminant colitis.

**Proton pump inhibitors**, when used in older patients who are also receiving antibiotics, put them at even higher risk of developing *C. difficile* infection. An increased risk of CDI in adults has also been associated with taking the antidepressants mirtazapine and fluoxetine.

Genome studies have found an association between a common polymorphism in the upstream promoter of the interleukin (IL)-8 gene and an increased risk for both the initial occurrence and the recurrence of CDI. Neutrophil recruitment to the intestine is thought to be coordinated by IL-8, and the polymorphism in the IL-8 promoter is thought to influence the manner in which neutrophils are recruited to the intestines when CDI is present.

Patients with **suppressed immunity**, due to malignancies or chemotherapy, are known to have a disturbance in their normal colonic flora and are at risk of developing CDI. Patients with **inflammatory bowel disease**, **necrotizing enterocolitis**, and **Hirschsprung disease** are also at increased risk of developing CDI.

**Rare associations include the following:**

- Antineoplastic agents, principally methotrexate
- **Hemolytic-uremic syndrome**
- Intestinal ischemia
- **Chronic kidney disease**
- Nonsurgical gastrointestinal procedures, including placement of nasogastric tubes
Clinical Presentation of CDI

The typical clinical presentation of CDI varies from mild diarrheal disease to pseudomembranous colitis and fulminant life-threatening colitis.

Patients usually complain of diarrhea, which is often watery but could also be bloody. Abdominal pain, fever, and malaise are common. The vomiting is less common. These symptoms are nonspecific and a high degree of suspicion is needed to diagnose CDI, especially if there is a known history of recent antibiotic’s exposure or hospitalization.

In mild cases, a physical examination may be normal or could only reveal fever and diffuse abdominal tenderness. In more severe cases, tenderness and rebound tenderness become more pronounced. Patients with severe dehydration, abdominal distension, decreased bowel sounds and perhaps rigidity could have fulminant C. difficile colitis or pseudomembranous colitis.

The presence of 3 or more of the following factors indicates moderate-to-severe CDI:

1. Leukocytosis (white blood cell count > 20×10^9/L)
2. Fever (temperature > 38°C)
3. Hypotension (systolic blood pressure < 100 mm Hg)
4. Creatinine level > 50 % of baseline
5. Plasma albumin level < 30 g/L
6. Abdominal pain and distension
7. Radiological evidence of colonic dilation, ascites or ileus

Sign and symptoms of C. Difficile Infection (Antibiotics):

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<thead>
<tr>
<th>Frequently</th>
<th>Infrequently</th>
<th>Rarely</th>
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<tr>
<td>Ampicillin</td>
<td>Tetracyclines</td>
<td>Aminoglycosides</td>
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<td>Amoxicillin</td>
<td>Sulfonamides</td>
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<td>Cephalosporins</td>
<td>Erythromycin</td>
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<td>Clindamycin</td>
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<td>Fluoroquinolones</td>
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Diagnostic Workup of C. Difficile Colitis

Laboratory investigations in C. difficile infection are helpful. The complete blood counts show leucocytosis. Kidney function and electrolytes should be checked as C. difficile severe infection can cause dehydration and kidney injury.

Stool analysis is recommended in symptomatic patients with diarrhea. Fecal leukocytes are common and found in 50 % of the patients. The gold standard to diagnose C. difficile is stool culture but this examination is time-consuming and enzyme immunoassay testing for toxins A and B in the stool is recommended in order to not delay treatment.
In patients with more severe disease and especially if pseudomembranous colitis is suspected, an abdominal computed tomography (CT) is indicated that reveals colonic wall thickening, and may also reveal other intraabdominal pathologies, such as an abscess, colonic perforation and/or fluid accumulation in the abdominal cavity.

Colonoscopy can also be used but is not needed to make the diagnosis of C. difficile. If colonoscopy is performed, the yellowish plaques overlying the inflamed mucosa, pseudomembranes, could be visualized, see figure. This is not a true membrane as it contains mucin, fibrin, necrotic cells, and neutrophils but not viable epithelium.

Complications

Fulminant colitis is a rare form of CDI, occurring in few of patients but accounting for most of the serious complications which are associated to toxic megacolon, colonic perforation, and death. Colectomy is usually required in patients who develop fulminant colitis.

Toxic megacolon is an acute toxic colitis with dilatation of the colon. This condition is diagnosed clinically with signs and symptoms of severe toxicity, the presence of a tender abdomen, and a dilated colon on a plain radiograph of the abdomen.

Colonic perforation is associated with abdominal rigidity, involuntary guarding, rebound tenderness, and absent bowel sounds. Free air may be revealed on abdominal radiographs. Any suspected perforation in this case should prompt immediate colectomy consultation.

Management of CDI

Since CDI has various presentations depending upon the degree of severity, various guidelines have been proposed for its treatment.

As a rule of thumb, the broad-spectrum antibiotics causing the CDI should be stopped. The asymptomatic carriers should not be treated or tested. The symptomatic CDI should receive antibiotic treatment, with the suitable treatment options being metronidazole, oral vancomycin or fidaxomicin. Additional measures include fluids and electrolytes replacement, avoidance of antimotility agents, limiting the use of PPIs, hand hygiene, and
standard contact precautions (wearing gowns and gloves).

- For mild CDI, it may be acceptable to observe clinically for 48 hours after stopping the culprit antibiotics.
- For mild/moderate disease, oral metronidazole is recommended as an initial treatment.
- For severe CDI, oral (not IV/IM) vancomycin with or without metronidazole or fidaxomicin is recommended.
- For patients with life-threatening colitis, toxic megacolon, colonic perforation and/or deteriorating clinical condition despite antibiotic treatment, surgical intervention may be needed. The recommended approaches are total/subtotal colectomy, combined with colonic lavage and ileostomy.
- The use of probiotics is not recommended.

The Center for Disease Control (CDC) has also put forward some guidelines to prevent CDI in hospitalized patients.

- Antibiotics should be restricted only to patients with presumed infections.
- Narrow-spectrum antibiotics should be used when possible.
- The cultures should be sent before starting the empiric antibiotics and the antibiotics should be appropriately downregulated or stopped depending upon the culture results.

References

Clostridium Difficile Colitis via medscape.com


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