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

Clostridium 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.

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. Unfortunately, this form of life-threatening colitis can only be managed by colectomy.

Etiology of C. Difficile Infection

Etiology of C. Difficile Infection

Image: "Scanning electron micrograph of Clostridium difficile bacteria from a stool sample. Obtained from the CDC Public Health Image Library." by Transferred from en.wikipedia to Commons. This media comes from the Centers for Disease Control and Prevention’s Public Health Image Library (PHIL), with identification number #6260. License: Public Domain
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.

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.

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 mmHg)
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

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
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.

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](https://medscape.com) via medscape.com


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