

Clostridium Difficile Infection: An Increasing Postsurgical Complication

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Abstract

Over the past decade the incidence of *Clostridium Difficile* infection has increased worldwide. Virulent forms of this organism have developed augmenting the morbidity and mortality of the disease.

Surgical patients, especially those undergoing gastrointestinal surgery and solid organ transplantation, express high rates of CDI.

Risk factors such as older age, prolonged preoperative hospital stay, use of broad spectrum antibiotics, and immunosuppression, have been identified.

Given the high morbidity and mortality rates in this group of patients, implementation of targeted strategies to reduce infection risk must be applied.

Keywords: *Clostridium difficile*; Surgery; Risk factors; Prevention measures

Introduction

Clostridium Difficile is a spore forming anaerobic gram positive bacillus. It accounts 20%-30% of cases of antibiotic associated diarrhea [1] and it is the leading cause of diarrhea in health care settings.

Most strains of *C. difficile* produce toxin A and B which are responsible for colonic mucosal injury and inflammatory diarrhea. There are strains that produce only toxin B and strains that do not produce any toxin so are not capable to cause *C. difficile* infection (CDI). Some strains produce also a binary toxin the role of which is still unknown [2].

The primary mode of *C. difficile* transmission is person to person through the fecal oral route, principally within inpatient care facilities, where the prevalence of asymptomatic colonization rises up to 26%. Environmental contamination also has an important role regarding the transmission in healthcare settings [3].

The usual presentation of CDI includes the following findings: 1. The presence of diarrhea defined as passage of 3 or more unformed stools in 24 or fewer consecutive hours 2. A stool test positive for the presence of toxigenic *C. difficile* or its toxins or colonoscopic or histopathologic findings demonstrating pseudomembranous colitis [3].

Testing for *C. difficile* and its toxins should be performed only in diarrheal stools, unless ileus due to *C. difficile* is suspected.

The laboratory gold standard for *C. difficile* toxin detection in stool is the cytotoxicity cell assay, and the gold standard for detecting toxin producing *C. difficile* is toxigenic culture, but they both rarely used due to slow turnaround time and cost.

Enzyme immunoassay (EIA) testing for *C difficile* and its toxins A and B is rapid but less sensitive (60-80%). To overcome this problem, a 2-step strategy is initiated. Testing the presence of glutamate dehydrogenase (GDH), a cell wall protein produced by toxigenic and non-toxicogenic strains, and subsequent toxin testing for those stool specimen that are GDH positive [3].

Clinical spectrum of the disease ranges from mild to severe or life threatening (ileus, toxic megacolon).

For non-severe CDI oral metronidazole or oral vancomycin or oral fidaxomicin is the treatment of choice [4].

For severe CDI oral vancomycin or oral fidaxomicin is the preferred treatment [4].

First recurrence is encountered with oral vancomycin or fidaxomicin, while second recurrence is cured with a tapering or a pulse regimen of oral vancomycin [3].

There is no evidence for anion-exchange resins (cholestyramine), probiotics (except maybe for *Sacharomyces boulardii*), immunoglobulins and monoclonal antibodies to *C difficile* toxins, to decrease the number of recurrences [3].

Instillation of stools from a healthy donor has been used with success in several uncontrolled case series [3].

Total abdominal colectomy with ileostomy should be performed in case of perforation of the colon, or systemic inflammation and deteriorating clinical condition not responding to antibiotic therapy [3,4].

Prevention strategies consist of antimicrobial restriction, hand hygiene, contact precautions and environmental cleaning using chlorine or other sporicidal agents in areas associated with increased rates of CDI [3].

Over the past decade the incidence of CDI has dramatically increased in Europe and North America experiencing hospital outbreaks with the hypervirulent strain NAP1/B1/027 [5].

Patients at risk are surgical patients especially those undergoing gastrointestinal surgery [6], the solid organ transplant recipients [7] orthopaedic patients [8] and patients undergoing vascular or cardiac surgery [9].

Herein we review the epidemiology, risk factors, clinical course, treatment and mortality rates of CDI for this surgical patient population.

CDI and Gastrointestinal Surgery

The incidence of CDI in patients undergoing gastrointestinal surgery ranges from 0.28% to 6.8% [6,9-15]. The highest percentage of CDI is referred to colorectal cancer surgery [14]. Patients who had an emergency procedure were at higher risk of developing CDI [6,12] whereas from all abdominal surgical procedures, colectomy, small bowel resection and gastric resection were associated with the highest risk [12,15].

Risk factors for CDI such as administration of antibiotics, older age, chemotherapy, impaired immune function, colorectal surgery and others, have been reported.

It is well known that normal bacterial flora in the intestine has been shown to be destroyed by antibiotics, thus *C. difficile* spores colonize the intestine and cause CDI. Prior antibiotic treatment [9], and even short courses of prophylactic antibiotics maybe associated with CDI. [16,17] From all antibiotics used, cefoxitin and exposure longer than 7 days to cefepime, piperacillin/tazobactam, and imipenem/cilastatin increased the risk for development of CDI [18]. However, in a large prospective study in the University of Michigan [6] and in other studies as well [11], perioperative antibiotic administration did not correlate with CDI after colectomy surgery.

Patients aged sixty and older seem to have a high risk of acquiring CDI [12,14] mainly due to comorbidities such as renal or neurological disease [6], diabetes mellitus, anaemia, congestive heart failure, malignancy [10,13,15].

Longer preoperative length of hospital stay (LOS) has been reported as a strong predictor of CDI [11,13,15,16] since the risk of colonization of *C. difficile* is increasing.

Inflammatory bowel disease (IBD) has been linked to CDI due to antibiotics and immunosuppressants used by that group of patients [19]. Additionally, IBD has been recognized as risk factor for *C. difficile* enteritis [10,20-22] which is associated with higher case-fatality rates than that reported with *C. difficile* colitis.

Although some authors claim that preoperative oral antibiotics along with mechanical bowel preparation, increase the rate of *C. difficile* colitis [23], other studies support the use of oral antibiotics with bowel preparation [24,25] and believe that antibiotics such as metronidazole or rifaximin [26,27] may decrease the colonization rate of *C. difficile*.

Colorectal surgery has been reported as a risk factor for CDI in many studies. It has been suggested that functional intestinal obstruction predisposes in *C. difficile* infection by altering the normal bacterial flora of the intestine and thus facilitates the colonization from the bacterium [9,14]. On the other hand the environmental changes

within the colon after surgery, maybe important in the occurrence of CDI in patients with gastrointestinal surgeries [11].

The clinical course of the disease in surgical patients is from mild to fulminant colitis. Of note, symptoms related to the disease such as fever or abdominal pain, are often result from a complication from the surgical procedure. However, cytotoxin titer should be sent in all patients with postoperative diarrhea and the treatment should be withheld until a positive cytotoxin assay is obtained [9,14] Only if there are systemic signs and a high suspicion of CDI, treatment is immediately initiated.

The CDI surgical patients have a 3.4 fold increase in mortality rate compared with patients without CDI [10,12,16].

Moreover, patients with CDI are more likely to have postoperative complications, require ICU level care or reoperation, and to be readmitted within 30 days of initial discharge [10].

CDI in Solid Organ Transplantation

Infections are the leading cause of morbidity and mortality in the early post-transplant period. CDI is an increasing problem in Solid Organ Transplant population (SOT).

The incidence of the disease is estimated to be 3-19% in liver recipients [28-30], 3.5-16% in kidney recipients [28,29,31-33] 1.5-7.8% in pancreas kidney recipients [28,29,31,32] 9% in intestinal recipients, 8-15% in heart recipients and 7-31% in lung recipients [28,29,34].

The highest incidence of CDI is observed during the first three months of transplantation, attributed maybe to treatment with broad spectrum antibiotics, intense immunosuppression and prolonged exposure to the health care setting [35].

Vancomycin resistant Enterococcus colonization before transplant, high risk transplant recipient defined as ABO or/and HLA incompatible, increasing age, increasing comorbidity, female gender, intra-abdominal graft placement, severe hypogammaglobulinemia [30,32,33,36], are some of the risk factors for CDI, along with prolonged antibiotics administration, especially in previous month [31] and immunosuppression.

The clinical course of the disease is often mild but some patients may develop fulminant colitis. Of note, less than 3% of immunocompetent patients with CDI develop fulminant colitis that require colectomy, compared to 13% of SOT recipients [35]. There are reports concerning that lung allograft recipients are eight times more likely to express fulminant disease [37].

The mortality rate ranges from 0.7% to 7.4% for SOT recipients [30,38,39].

Regarding treatment, metronidazole and vancomycin show equivalent efficacy for mild to moderate disease. The disadvantage of metronidazole for this group of patients, is the interaction with sacrolimus or tacrolimus, so the levels of them should be monitored. Fidaxomicin has been evaluated in patients with no or 1 prior episode of CDI, but there is no data for SOT recipients. There is still insufficient evidence to support the use of intravenous immunoglobulin, probiotics or toxin binding resins for the treatment of initial or recurrent CDI [7,40]. Surgical intervention should be considered for complicated CDI.

CDI in Orthopaedic Surgery

In orthopaedic surgery CDI is linked with total joint arthroplasty as well as with fracture repair and spine surgery [8,41-45].

The incidence of CDI in this group of patients ranges from 0.11% to 7.1%, with highest incidence recorded in hip fractures and low incidence recorded in spine surgery [41,42,44,45].

Risk factors for CDI include advanced age, more than 2 antibiotics preoperatively, prolonged antibiotic use in the postoperative period, multiple medical comorbidities, lumbar fusion revision, urban hospitals, revision arthroplasty, and surgery >24 hours after admission [8,43-45].

There is an overall 36.4 fold increase in mortality in patients acquiring postoperative *C. difficile* infection compared with those without infection [44].

Clinical course and treatment are similar to the other groups of surgical patients.

CDI in Vascular and Cardiac Surgery

There are very few studies concerning CDI in vascular and cardiac surgery.

The incidence of infection in cardiac surgery seems to be low, ranges from 0.75% to 1.09% [46,47] whereas in aortic surgery the incidence of CDI comes up to 8.4% [48].

Regarding cardiac surgery, advancing age, longer preoperative length of stay, female sex, blood products transfusion, large hospital, multiple comorbidities, female gender and increasing cumulative days of antibiotic administration, are associated with high risk of acquiring CDI [46,47]. Prolonged prophylactic cephalosporin administration in vascular surgery is also associated with CDI [48].

In cardiac surgery, mortality for CDI patients was 12% vs 7.2% for controls and the consequence of the infection are also longer median (nearly double) hospital stay and greater median hospital charges [46].

In a cohort study consisting of patients undergoing open abdominal vascular surgery, evaluation of infectious complications after surgery showed that the highest 30-day mortality rates after discharge (30%) were found after CDI with sepsis [49].

Conclusion

CDI has grown into an increasingly prevalent infection. The high mortality and costs associated with postsurgical CDI indicate the necessity of prompt identification of high risk patients so that rapid diagnosis and timely treatment being applied. Implementation of measures such as reduction of preoperative hospital stay, restrictions of broad spectrum antibiotics and strict policy of surgical chemoprophylaxis, may contribute to further reduction of this infectious disease.

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