



Update on *Clostridium difficile* Infection in Patients with Solid Organ Transplantation

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Abstract

Clostridium difficile Infections (CDI) is increasing in recipients of Solid Organ Transplant (SOT). These patients are at a particularly elevated risk due to comorbid conditions, lengthy hospital stays, recurrent use of antibiotics and immunosuppressive status. CDI are more challenging to diagnose in this group of patients and contribute to a significantly increased mortality, morbidity and recurrence. Preventive measures and early diagnosis remain key in the management of CDI in transplant recipients in order to abort the associated complications.

Keywords: *Clostridium difficile*; Solid organ transplant; Antibiotic stewardship; Vaccination

Introduction

Clostridium difficile is an anaerobic, spore forming gram positive bacillus that colonizes the gastrointestinal tract and causes colitis in susceptible individuals who may have been exposed to antimicrobial therapy. Prior to the introduction of antibiotics, CD bacillus was first described in 1935 in the intestinal flora of healthy newborns [1]. It is not until the introduction of antibiotics (lincomycin and clindamycin) that CD was isolated from pseudo-membranes of patients with colitis [2]. Alteration in the intestinal flora and the gut microbiome is very important in the pathogenesis of antibiotic associated colitis and it is not surprising that almost every antibiotic has been implicated at least once.

Clostridium difficile diarrhea is the most common cause of nosocomial infections in the United States [3] and it has surpassed MRSA infections [4]. The incidence is rising and is reported in 147.2 cases per 100000 people in the US [5]. Most cases (64.8%) are associated with health care exposure [6] in relation to inpatient hospitalizations, nursing home dwelling and visits to outpatient clinics.

Incidence is more common in solid organ transplant SOT recipients and estimated at 1.5% to 31% depending on organ type compared to a 1.0% to 2.0% overall incidence in hospitalized patients.

C. difficile infections CDI pose increased mortality risk reaching 33% [7] in patients with diarrhea and in patients with organ transplants. They are associated with high recurrence rates and hospital costs [8]. Of 453,000 incident infections that occurred in 2011 29,000 deaths were reported in association with CDI [9]. Recurrence of CDI after initial episode was 21% in health care associated infection [6]. Rates of recurrence continue to increase with subsequent recurrences. Strain type plays a key role in the recurrence of CDI and there is emergence of newly virulent strains (NAP7/BK/078 and NAP1/B1/ribotype 027) [10]. For example, Ribotype 027 was described in people over 65 years and in those exposed to Fluoroquinolone antimicrobial therapy.

Total annual costs in the US during acute CDI is in the range of 1.2 to 5.9 billion dollars [9]. CDI contributes to 10% to 25% of the antibiotic associated diarrhea, and to 90% of Pseudomembranous colitis [11] induced by antibiotics [12]. Asymptomatic colonization of *C. difficile* is also increasing from 3% in healthy individuals to 10% to 21% among hospitalized patients [13].

Prevalence in Solid Organ Transplants

The prevalence of CDI in solid organ transplant is more common than in the general population. It is being reported at 7.4% among 21,683 organ transplant recipients [95%CI, (5.6% to 9.5%)] but may reach 30%. The prevalence is listed at 12.7% when more than one organ is transplanted and it varies with the organ transplanted. For example, in a study by Paudel et al. [14] the most common prevalence is seen with lung transplants, followed by liver, intestines, and pancreas and kidney transplants respectively. Prevalence is highest in the first 3 months post transplantation with a median time to infection of 51 days. In another study, liver transplant recipients had the shortest

OPEN ACCESS

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Received Date: 25 Jun 2018

Accepted Date: 13 Aug 2018

Published Date: 20 Aug 2018

Citation:

Nelson AD, Egtesad B, 'Wakim-Fleming J. Update on *Clostridium difficile* Infection in Patients with Solid Organ Transplantation. *Ann Digest Liver Dis.* 2018; 1(3): 1012.

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time to infection with a median of 35.6 days, and lung transplant recipients had the longest time to infection with a median of 136 days [15].

Risk factors and outcome

CDI requires the disruption of the GUT microbiome. Antibiotic exposure is the most important risk factor [16]. In recent studies, the most common antibiotics reported in association of CDI are Clindamycin, Cephalosporins and Fluoroquinolones. However, any antibiotic exposure is a risk factor for CDI [16-19]. Dose and duration of antibiotic use (Defined Daily Dose of >14 in the prior 3 months), further increase the risk of acquiring CDI [18].

In a healthy state, the intestinal microbiomes are dense and possess the ability to prevent colonization by pathogenic organisms such as *C. difficile*. This is known as colonization resistance. In CDI, the gut's colonization resistance is altered, and disruptions of microbiome density, structure and function have been described [20].

Risk factors specifically reported in patients with SOT include hypoalbuminemia (OR 10.6, 95% CI: 6.62-17.0), immunosuppression [21], gastrointestinal surgeries, tube feeding [22], and complications during post-operative course [11]. Decrease in humoral immunity due to immunosuppression causes decrease in mounting antibody response to CD toxins A and B [23]. The prolonged length of hospitalization during pre and post-transplant periods increases the risk of CDI proportionately [23].

Other risk factors for CDI include those reported in non-transplant patients. These involve advanced age beyond 65 years old, inpatient length of stay, severity of illness, gastric acid suppression, obesity and chemotherapy. Further, strain and virulence of CD toxin highly impact mortality from CDI [16,24]. PPI use increases risk of CDI and is associated with high rate of recurrence (50%) [5,17,25,26]. Recent hospitalization and healthcare exposure in the prior 12 weeks in addition to comorbid conditions such as liver and kidney disease [17] are common clinical conditions associated in SOT recipients and pose high risk for CDI and its recurrence [27].

In liver transplant recipients, CDI prevalence ranges from 3% to 8%. Specific risk in liver transplant are advanced liver failure (higher MELD score), pre-transplant renal impairment and complicated postoperative stay notably bile leak and major intra-abdominal bleeding [28,29].

In lung transplant, CD colitis developed in 7.4% of lung recipients with a cumulative incidence of 14.7%. Recent antibiotic use, recent hospitalization, and augmentation of steroid dosage were the most associated risk factors [30].

Reports on lung transplant recipients with cystic fibrosis, showed that 34% of patients developed multidrug resistance infections and 6% develop CDI within 90 days of the transplantation

In heart transplant recipients, CDI occur in about 10% of patients and most cases happen between 2 and 24 months post-transplant. Combined heart lung transplant, redo transplantation, augmentation immunosuppressive therapy, hypogammaglobulinemia and use of PPI were the most important risk factors in this group of patients [31].

In kidney transplants, Lionaki S et al. [32] found that 5.4% of transplant recipients developed CDI and 73.7% had exposure to antimicrobials within the previous 15 days.

Pathophysiology and Clinical manifestations

CD Bacillus produces toxins that infiltrate the intestinal mucosa and cause inflammation and colitis. Two toxins, A and B are the most commonly described. Toxin B is 10 times more virulent than toxin A. Both toxins can independently cause significant disease [33]. Other strains were linked to the epidemic of the 2000s [34,35]. They were more virulent and resistant to antibiotics

The pathophysiology of CDI is influenced by multiple factors. In addition to the strain and the virulence of toxins produced, other factors included the microbiome of the intestinal tract and the host inflammatory responses. Recipients of organ transplant are severely immunosuppressed and are at risk for invasion by CD toxins. Toxins A and B are encoded by genes *tcdA* and *tcdB*, respectively. Together with two regulatory genes (*tcdC* and *tcdD*) and a porin gene (*tcdE*), form the chromosomal pathogenicity locus. The expression of *tcdA* and *tcdB* is down-regulated by the *tcdC* gene. During the outbreak of 2003, a strain of *C. difficile* related to the partial deletion of the regulatory *tcdC* gene was noted in association with a resistance to fluoroquinolones and a high mortality of 24.8% [36]. When toxins infiltrate the enterocyte and the lamina propria, they impair mast cell and gut neuron functions and promote neutrophil chemotaxis. There is release of substance P and inflammatory cytokines, and a disruption of intestinal tight junctions. Abdominal pain and cell death ensue, and pseudo-membranes are formed [36].

Diarrhea is the main manifestation of CDI. It is defined as ≥ 3 loose stools per 24 hours. Other manifestations include development of megacolon or severe ileus, abdominal pain, low grade fever, nausea and vomiting.

The clinical manifestations are considered severe, when the Leucocyte count is >15,000 cells/ml or the serum creatinine is ≥ 1.5 mg/dl; or fulminant, when there is associated hypotension, megacolon, end organ failure or a lactate level >2.2.

Diagnosis

Clinical symptoms require confirmation with diagnostic testing. This can be accomplished by testing of liquid stool with and without endoscopic presence of pseudo-membranes. Pseudo-membranes are characteristic but not specific for CDI, and they can be seen in other conditions such as ischemic and collagenous colitis, NSAID intake, other bacterial infections and chemotherapeutic and pharmaceutical agents [37].

Laboratory studies demonstrating CD toxins in liquid stools are diagnostic of CDI in patients at risk and experiencing clinical symptomatology. These tests should not be done on solid stool or in patients taking laxatives due to high rate of asymptomatic carriers. Wanahita et al., suggest a prompt search for symptoms and signs consistent with CDI and a study to detect it in hospitalized patients with unexplained leukocytosis $\geq 15,000/\text{mm}^3$, because their symptoms may be missed and diarrhea is likely to develop within the next 2-3 days

Wanahita et al. [38] suggest a prompt search for symptoms and signs consistent with CDI in addition to laboratory testing for CD in hospitalized patients with unexplained leukocytosis.

Most recent guidelines [5] recommend a multi-step approach to diagnosis. Initial testing with Nucleic Acid Amplification Test (NAAT) is recommended due to its high sensitivity. When positive it should be followed by confirmatory Enzyme Immunoassay

(EIA) or a Glutamate Dehydrogenase (GDH) + toxin EIA. If results are discordant, a reassessment of the clinical condition is suggested. Cell Culture Cytotoxicity Neutralization Assay (CCCNA) requires incubating stool filtrate on a specific culture medium. It is cumbersome and has a wide range of sensitivity but can be used if diagnosis remains questionable.

In recipients of SOT, the clinical symptoms can be muddled by the use of non-antibiotic medications that can cause diarrhea, other bacterial or viral infections affecting this group of patients, HIV status and in graft versus host disease. In these situations, a stepwise diagnostic approach is advised and a combination of tests such as NAAT along with GDH and toxin EIA instead of NAAT alone [5] is preferred. The diagnostic yield of repeat testing within 7 days is only 2% [39] and is discouraged. Also testing when symptoms abate after therapy and in asymptomatic patients is also not recommended due to colonization.

Treatment

Treatment of CDI must involve a three-prong approach. The primary focus is to reduce inappropriate antibiotic use and to emphasize infection control practices in the outpatient and the inpatient settings [40].

The second approach is to withhold the offending agent.

Thirdly and once infection occurs, antibiotic therapy targeting *C. difficile* is recommended [5]. Either vancomycin or fidaxomicin is recommended for first episode of *C. difficile*. The dosage of vancomycin is 125 mg orally 4 times a day or fidaxomicin 200 mg twice daily for a total of 10 days. Metronidazole was once the first line of therapy but has lost favor due to drug resistance, and waning efficacy [41]. However, Metronidazole can be used in setting where access to vancomycin and fidaxomicin is limited. The suggested dosage is 500 mg 3 times daily for 10 days. Fidaxomicin has proven to reduce persistent diarrhea and CDI recurrence [42] and to decrease growth of VRE and Candida infections[43] .

In patients with fulminant CDI and ileus, vancomycin at higher doses orally (500 mg QID) and rectal vancomycin (500 mg in 100 ml of normal saline as a retention enema) are recommended by Society of Health Care Epidemiology of America/ Infectious Disease Society of America Clinical practice guidelines [5]. Addition of IV Metronidazole (500 mg IV every 8 hours) to oral or rectal vancomycin decreases the mortality of fulminant CDI [45]. Subtotal colectomy with preservation of the rectum has shown benefit when clinically feasible in patients with megacolon, acute abdomen and septic shock with multiple organ failure [45]. Loop ileostomy and antegrade vancomycin flush is less invasive and may help preserve the colon in these situations [46].

The risk of recurrence of CDI in patients treated with vancomycin is approximately 25% [47]. Recurrence of CDI can either be treated with tapered and pulsed vancomycin regimen for 4 weeks, or a standard course of oral vancomycin followed by rifaximin or fidaxomicin for 10 days. These regimens are preferable over metronidazole especially if it had been used for first recurrence. Fidaxomicin is more effective in reducing subsequent recurrence when compared to vancomycin (19.7% to 35.5%; p=0.045) [48].

Fecal Microbiota Transplantation (FMT) has recently shown to be a safe and effective treatment for recurrent and refractory CDI in the general population. Many case reports and case series studies

have also shown efficacy of FMT in SOT. A retrospective case series of 14 SOT patients with antibiotic refractory CD found an overall 79% success rate with initial FMT [49]. A few case reports followed and showed resolution of diarrhea, but safety data is limited to short term follow up. Kelly et al. showed an increase in cure rate of 78% with single FMT in patients with recurrent, refractory and severe CDI in SOT and in IBD patients on immunosuppression. Recent guidelines do not recommend FMT in transplant recipients [50].

Bezlotoxumab is a fully human monoclonal IgG1 antibody approved by FDA to reduce recurrence of CDI in patients on antimicrobial therapy [51]. Bezlotoxumab binds to the N-terminal domain of toxin B (TcdB) and neutralizes its effect by inhibiting its binding to cellular surface receptors [52]. Recurrence rates decreased significantly with bezlotoxumab (17%) when compared to placebo (28%). There is insufficient data on the combination of bezlotoxumab and actuozumab [53].

Prevention Techniques

Isolation techniques that include admitting patients to private rooms, contact precautions and use of gloves and gowns by healthcare personnel have shown to decrease rates of CDI [54]. Washing with soap and water or alcohol-based wipes is recommended [55]. Antibiotic stewardship that involves minimizing the duration, frequency and number of antibiotics showed reduction in the CDI incidence rates [56-58].

Statin use was reported to decrease risk of CDI by unknown mechanisms however, there was a significant heterogeneity among studies [59]. Patients without gastric acid suppression have reduced risk of CDI [60].

Conclusion

Recipients of SOT are at increased risk for *C. difficile* infection. The highest risk is in lung transplants and the lowest risk is in kidney transplants. Exposure to antibiotics is the most important risk factor. Diagnosis is challenging due to comorbid conditions but should be entertained when a clinical suspicion arises because of associated morbidity, mortality and recurrence in this group of patients.

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