Clostridium Difficile Infection - A Review of Current Treatment Strategies

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Background

Clostridium difficile is an anaerobic, gram-positive, spore forming rod-shaped bacillus, spread via the fecal-oral route. The organism was first identified by Hall and O’Toole on 1935 in the stools of newborns, and referred to as Bacillus Difficilis in view of the difficulty in isolation and study [1]. The organism was subsequently renamed Clostridium difficile. The first reported case of toxin-producing Clostridium as a cause of antibiotic associated colitis was in 1978 [2,3].

Risk factors associated with C. difficile are previous antibiotic usage, age greater than 65 years, immuno compromised patients, use of laxatives, proton pump inhibitors or H2 blockers, chemotherapy, renal failure, gastrointestinal surgery, naso-gastric tube placement, mechanical ventilation, and prolonged hospital stay [4-6]. C. difficile colonizes 3-4% of healthy adults, and 30% of infants aged<12 months [7]. The normal gut flora acts as a colonization barrier that protects against C. difficile. This barrier may be compromised when the gut flora is disturbed by antibiotic therapy. Studies have indicated that 85% of patients with C. difficile infection had received antibiotics within 28 days of onset of symptoms [8]. Almost all antibiotics have been associated with C. difficile, however, the greatest risk is following treatment with Clindamycin, broad-spectrum cephalosporins, and fluoroquinolones [9-13].

Pathophysiology

After colonization, the organism secretes virulence factors toxin A (TcdA), and toxin B (TcdB) [14]. TcdA and TcdB are encoded with a positive transcriptional regulator tcdD, and a negative regulator TcdC. TcdA is an enterotoxin and TcdB is acytotoxin. The toxins are bound to receptors, and are internalized into the host cell by endocytosis [15,16]. Within the cell, the GTPases RhoA, Rac and Cdc42 are glycosylated, resulting in inactivation, actin condensation, eventual apoptosis and death of the target cell [14]. This results in disruption of tight junctions, inflammation, fluid and mucous secretion, and damage to the intestinal mucosa, with the characteristic “volcanic eruption” observed in pseudo membranous colitis. Some initial work indicated that TcdB was unable to elicit disease unless TcdA was also present [17]. Subsequent work, however, documented disease caused by TcdA-deficient strains [18]. A robust IgG antibody response to TcdA is associated with protection against C. difficile-associated disease.

Epidemiology

The epidemiology of C. difficile infection has changed dramatically since 2000, with significant increases in incidence and severity of infection in the USA, Canada and Europe [19]. Report from Quebec, Canada indicated that the incidence of C. difficile –associated disease increased from 35.6 cases per 100 000 persons in 1991, to 156.3 cases per 100 000 persons in 2003. This was associated with the emergence of a new hyper virulent strain B1/NAP1/027. The NAP1/B1/027 strain encodes a TcdC mutation which results in a truncated, inactive TcdC protein [20]. This results in unsuppressed and unregulated toxin production, and levels of toxins A and B 16 and 23 times higher in patients with this strain [21].

A recent Morbidity and Mortality Weekly Report (MMWR) documented 336 000 C. difficile infection-related hospital stays in the USA (110 600 as principal diagnosis) in 2009, resulting in 9.1% mortality, and an aggregate cost of 8.2 billion dollars [22]. This represented a three-fold increase from 139 000 cases a decade previously. Patients 85 years and older had the highest rate of 1089 cases per 100 000 population, and patients 65 years to 84 years 465 cases per 100 000 population. Patients under the age of 18 had a rate of 11 cases per 100 000 population.

Treatment

Treatment of C. difficile infection involves stopping systemic antibiotics if possible. Studies have indicated higher cure rates and decreased relapse in patients in whom antibiotics were discontinued [23,24]. Metronidazole and vancomycin are the principal drugs used to treat C. difficile infection. Patients with mild or moderate diarrhea are generally treated with metronidazole 500 mg TID for 10 to 14 days, as studies have indicated similar cure rates with either metronidazole or vancomycin [25]. Patients with severe diarrhea are treated with vancomycin 125 to 250 mg QID for 10-14 days, as patients with complicated C. difficile had a cure rate of 76% with metronidazole compared to 97% with vancomycin [25]. Recurrence rates were also higher with metronidazole. Adjunct therapy is with vancomycin enema 500mg in 10 ml saline and /or intravenous metronidazole. Surgery with total colectomy is indicated in severe colitis with significant toxemic symptoms.

Fidaxomycin is an antibiotic, which has been shown to be more active in-vitro than vancomycin, and has been found effective even in NAP1/B1/027 strains [24]. The recommended dose is 200mg every 12 hours for 10 days. The drug has minimal intestinal absorption, high fecal concentration, and does not change the intestinal microbiota [24]. Similar response rate to vancomycin were demonstrated, with lower recurrence rates in strains other than NAP1/B1/027 (16.9% compared to 29.2%).

Rifaximin is active against gram-negative, gram-positive, and anaerobic organisms. Like fidaxomycin, it is not absorbed from the intestine, has a high fecal concentration, and is highly effective against C. difficile, with a lower relapse rate [26]. The recommended dose is 400 mg TID for 10 days.

Nitazoxanide, an antiparasitic drug, has been shown to be as effective as metronidazole, and may be as effective as vancomycin in treating patients with C. difficile infection [27,28].

Probiotics found in fermented milk, yogurt, and capsule such as saccharomyces boulardi, bifidobacteria, and lactobacillus have been proposed as adjunctive therapy for C. difficile infection [29].
efficacy of this treatment remains controversial as the studies have been heterogeneous.

Recurrent C. difficile Infection

Recurrent Clostridium difficile infection is a significant issue for which there is currently no widely-practiced, effective therapy. Initial response to metronidazole and vancomycin is approximately 60%, with subsequent decreased response with subsequent relapses. Persistent alterations in the intestinal microbiota decrease natural colonization barriers and increase risk of relapse of C. difficile infection with the same, or different strain. A number reports since 1958, amounting to over 325 cases, including one systematic review, have described high cure rates of recurrent C. difficile infection with fecal transplantation performed via retention enema, colonoscopy, or nasogastric tube. A recent study further demonstrated that cure rates are sustained over long-term follow up of a mean of 17 months [30]. There has been, however, a lack of randomized controlled trials demonstrating efficacy [31].

In a recent study, the infusion of donor feces was shown to be significantly more effective for the treatment of recurrent C. difficile infection than the use of vancomycin [32]. In this open-label randomized controlled trial, van Nood et al. [32] compared three treatment regimens in patients with recurrent C. difficile infection. All patients had a relapse of C. difficile following an adequate course of antibiotics (≥ 10 days of metronidazole 500 mg three times a day or ≥ 10 days of vancomycin 125 mg four times a day). C. difficile infection was defined as diarrhea with ≥ 3 loose or watery stools per day for 2 consecutive days or ≥ 8 loose stools in 48 hours and a positive stool test for C. difficile toxin. Exclusion criteria included patients with prolonged immunodeficiency, critically ill patients admitted to an intensive care unit, and those requiring other antibiotics for other infections. Patients were randomized to one of three groups. One group received an abbreviated regimen of vancomycin 500 mg orally four times a day for 4 to 5 days, followed by bowel lavage with 4 litres of macrogol solution (Klean prep) on the last day of antibiotic treatment, and the infusion of a suspension of donor feces through a naso-duodenal tube the next day. Patients who developed recurrent C. difficile infection after the first infusion of donor feces were given a second infusion from a different donor. Another group received a standard vancomycin regimen (500mg orally four times daily for 14 days), and one group received a standard vancomycin regimen with bowel lavage on day 4 or 5.

Donors were screened initially with a questionnaire regarding risk factors for potentially transmissible diseases. Donor feces were screened for parasites (including Blastocystis hominis and Dientamoeba fragilis), C. difficile and enteropathogenic bacteria. Blood was screened for antibodies to HIV, human T-cell lymphotropic virus types 1 and 2, hepatitis A, B and C, cytomegalovirus, Epstein-Barr virus, Treponema pallidum, Strongyloides stercoralis and Entamoeba histolytica. A mean of ± 141 g of feces were collected from the donors on the day of infusion and diluted with 500ml sterile saline. Within 6 hours, the solution was infused through a naso-duodenal tube and patients were monitored for 2 hours.

The primary endpoint of the study was cure of infection with resolution of diarrhea associated with C. difficile infection without relapse after 10 weeks. Cure was defined as absence of diarrhea, or persistence of diarrhea that could be explained by other causes, with three consecutive negative stool tests for C. difficile toxin. Relapse was defined as diarrhea with a positive stool test for C. difficile toxin. For patients who received the second infusion of donor feces, follow-up was extended to 10 weeks after the second infusion.

The authors intended to enroll 40 patients per treatment group; however, the study was stopped after an interim analysis of 43 patients. One patient was excluded because he discontinued all medications due to heart failure and chronic obstructive pulmonary disease. Sixteen patients received the donor feces infusion. Of these, 13 (81%) had resolution of C. difficile-associated diarrhea after the first infusion. Three patients received an infusion from a different donor, with resolution in two patients, giving an overall response rate of 94%. Resolution of C. difficile-associated diarrhea occurred in four of 13 patients (31%) receiving vancomycin alone, and in three of 13 patients (23%) receiving vancomycin with bowel lavage (P<0.01). Five weeks after initiation of therapy, there was a recurrence of C. difficile infection in one patient in the donor feces infusion group (6%), eight in the vancomycin alone group (62%) and in seven of the group receiving vancomycin and bowel lavage (54%). Mild diarrhea occurred in all, except one patient receiving donor feces, with cramping in 31%, and belching in 19%. These symptoms all resolved within 3 hours. During follow-up, three patients (19%) who received donor feces developed constipation. One patient died from severe heart failure and chronic obstructive pulmonary disease, which was considered unrelated to the study drug. Following donor feces infusion, quantitative changes in relevant groups of intestinal bacteria were observed with an increase in fecal bacteria diversity, similar to that in healthy donors, with an increase in Bacteroides species and Clostridium clusters IV and XIVa and a decrease in Proteobacteria. The authors comment that their patients with C. difficile infection had reduced bacterial diversity, with changes in gut Firmicutes and Bacteroidetes, and that the success of the donor feces regimen is probably a consequence of the re-establishment of the normal microbiota as a host defense against C. difficile infection.

A number of questions remain unanswered. The optimal protocol for donor feces administration (naso-duodenal tube, enema or colonoscopy) is unknown. Furthermore, the efficacy of this modality in severe C. difficile infection, as well as in special populations such as patients with inflammatory bowel disease, cirrhosis, and immune compromised states, requires study. Bowel lavage was included to reduce the pathogenic bowel content in order to facilitate colonization of healthy donor microbiota. Whether this is indeed required is not known. This paper provides good evidence for efficacy of donor feces infusion, and given the increasing problem with recurrent C. difficile, the technique should be available in more areas. Further study is required, however, to determine the optimal protocol for donor feces administration.

References
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