Treatment strategies for *C. difficile* associated diarrhea

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I. Introduction

C. difficile-associated diarrhea (CDAD) is the most common nosocomial cause of diarrhea in hospitalized patients. The causing pathogen is Clostridium difficile, a Gram positive anaerobic bacterium, which became recognized as an important pathogen when the antibiotics lincomycyn and clindamycin were widely used. The first outbreaks were described in the 1960's and although important progress has been made in diagnosis and control of outbreaks, CDAD continues to be a challenging gastrointestinal illness.

Diarrhea is a well-known complication of antibiotic use, with a wide range of clinical presentation from abdominal discomfort and mild diarrhea to severe colitis. The mechanisms involved in antibiotic-associated diarrhea are osmotic, increased gastrointestinal motility and secretory. C. difficile is responsible for 20% to 30% of all antibiotic – associated diarrhea cases, 50% to 70% of antibiotic – associated colitis and over 90% of pseudomembranous colitis.[1]

II. Epidemiology

The incidence of CDAD has increased in the past decade in the US, Canada and Europe, with a doubling of incidence rates in patients discharged from US short-stay hospitals in 2003 (61/100,000 population) compared with 1996 (31/100,000 population), and affecting especially older people.[2] The CDAD incidence rate from hospital discharge is up to 30 cases per 1000 discharges, with an overall estimate of 250,000 cases in the US, yearly. Rates are lower in the community and outpatient settings, where the estimate is 7.7 - 12 cases per 100,000 person-years.[3] Consequences of CDAD include extended hospital stay, increased rates of subsequent infections and additional treatment that add up to an estimated total cost for the US healthcare attributable to CDAD of more than $1.1 billion per year.[4] Recent epidemics have been reported in the US, Canada and Europe associated with a hypervirulent strain Nap IB1 which produces more toxins and has quinolone resistance. These epidemics have been associated with marked increases in morbidity and mortality.

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III. Clinical presentation and natural history

The prevalence of asymptomatic colonization ranges from 2-5% in the community to 20% in hospitalized patients.[5]

Symptomatic disease results in a wide spectrum, including mild self-limited diarrhea, severe diarrhea, pseudomembranous colitis or fulminant colitis which can be fatal. It usually begins during or up to 8 weeks after antibiotic therapy. Severe disease develops in less than 3% of CDAD and C. difficile has been identified as the direct cause of death for 1%-2% of affected patients, with a higher mortality rate in frail elderly people.[3] Diarrhea is usually watery, but rarely can be bloody. In addition, CDAD can also present with other complications such as toxic megacolon, colonic perforation, arthritis, and septicemia. Recurrent CDAD is one of the most challenging aspects and recent series show rates as high as 30-40%, compared with 10-20% as known a decade ago.

IV. Pathophysiology

C difficile is an anaerobic Gram positive bacillus, ubiquitously present in the environment and very

difficult to eradicate due to its ability to develop heat-resistant spores. *C difficile* produces toxins A and B, recognized as the main factors of virulence. In animal models, toxin A is enterotoxic causing increased intestinal permeability and fluid secretion, and toxin B is more cytotoxic, causing intense colonic inflammatory response. In 1988, an additional binary toxin was described but the pathogenic role or clinical relevance has yet to be determined. The strains secreting binary toxin may be associated with more severe disease as those strains were more often present in community-acquired diarrhea and resulted in more frequent hospitalization.[6] Previously detected in only 6% of clinical isolates, binary toxin producing strains are now found uniformly in the epidemic strain.[7]

The pathophysiology of CDAD involves a complex interaction between host factors (debilitating disease, immune deficiencies, and medication) and C difficile strains. During therapeutic exposure to broad-spectrum antibiotics, the normal bacterial flora of the colon is disrupted. Host immune response seems to determine whether C difficile causes diarrhea compared to remaining an asymptomatic carrier. A failure to mount an immune response of IgG to toxin A is associated with toxin production and diarrhea. In patients developing CDAD, shorter duration of the disease and decreased risk of recurrence correlates with higher concentration of anti-toxin A antibody.

V. Diagnostic testing

CDAD should be suspected in any patient with diarrhea which develops during or after antibiotic treatment, especially in the elderly, in hospitals and in those with compromised immunity. For the diagnosis, three criteria have to be fulfilled: clinical presentation of diarrhea, presence of the organism/toxins and exclusion of other causes of diarrhea. Stool tests require detecting toxin A and/or B, using one single unformed stool specimen. Tissue culture cytotoxicity assay for detection of toxin B has long been the gold standard for CDAD with sensitivity of 94-100% and specificity of 99%. However it is expensive and time-consuming and thus it has been largely replaced with the enzyme immunoassay tests (EIA) for toxin A or B or both, with the advantage of results available within a few hours. Sensitivity and specificity range from 60% to 80% and some strains produce a toxin A not detected by EIA tests.

Polymerase chain reaction (PCR) is a promising new diagnostic test with 100% specificity and 92% to 97% sensitivity.

VI. Management strategies for the first episode of CDAD

Management should focus on two aspects: improvement of the clinical condition and prevention of spread of the infection. The management should start by discontinuing the offending antibiotic, if possible, and rehydration. If the antibiotic can not be discontinued, the recommendation is to change to one with more a narrow spectrum.

Treatment requires oral antimicrobial therapy. Metronidazole is the recommended first line drug; the regimen is 500 mg 3 times a day, for 10-14 days. Vancomycin is second-line therapy, reserved mostly for cases with metronidazole intolerance/contraindication or first trimester pregnancy or metronidazole failure. In the past, both antibiotics had similar rates for symptomatic and bacteriologic cure, with more than 90% positive response rate.[8] In the last several years, several studies reported a decreasing response rates to metronidazole to 60-70%. Due to this change in response to metronidazole, vancomycin can be used as first line therapy in severely ill patients,[1] especially in patients with severe CDAD and chronic renal failure or severe leukocytosis. Irrespective of which drug was used as a first line therapy, the rates of recurrent CDAD ranged approx 15% to 25%.

A better bacteriologic cure rate than vancomycin and borderline superior effectiveness in terms of symptomatic cure was seen with teicoplanin, but this drug is not available in the United States.

VII. Recurrent C. difficile – associated diarrhea

Recurrent *C difficile*-associated diarrhea (RCDAD) is a challenging illness with a great impact on quality of life for those patients. Rates of RCDAD were approx 15-25% between 1991 and 2002, but some studies have reported increased rates up to 47% in 2003-2004. The diagnosis of RCDAD is considered when diarrhea recurs within 2 months of the initial diagnosis and the repeat stool specimen is positive for *C difficile* toxin. After one episode of RCDAD, further episodes are even more common and some patients have had recurrences for years.[12] The rate of recurrences in patients with previous episodes of RCDAD ranges from 45% to 65%.[13]

RCDAD defines both reinfection and relapse.

Reinfection is caused by a different strain and it is thought to be responsible for the majority of recurrences. Relapse is caused by the same strain of C difficile, presumably the result of intraluminal persistence of *C difficile* spores.

Risk factors associated with RCDAD are: age greater than 65 years, previous CDAD recurrence, concomitant debilitating diseases, hospital acquisition of infection, low serum antibody response (IgG) to toxin A during the first episode of CDAD and continuous antibiotic use after CDAD diagnosis.[9,10]

Antibiotic therapy

The current strategy to treat the first recurrence of CDAD is to give a repeat trial of the same or different antibiotic. Metronidazole is most commonly used to treat the first recurrence. During the outbreak in Quebec, Canada, in 2003-2004, vancomycin was used to treat the first relapse after completion of metronidazole therapy,[9] due to increasing rates of incidence, severity and relapse. Studying the outcome of first recurrence of CDAD in Quebec during 1991 to 2005, Pepin et al[11] reported that both metronidazole (250 mg 4 times daily for 10-14 days) and vancomycin (125-500 mg 4 times daily for 10 days) therapies for the first recurrence of CDAD had the same risk of developing second recurrences. Severe complications such as shock, megacolon, perforation, colectomy, and death were present in 11% of those with a first episode of RCDAD. The study suggested a lower frequency of complications associated with vancomycin treatment, but these results were based on a single health care center experience during an epidemic with a hypervirulent strain.

Management strategies for consecutive recurrences

Standard treatment relies on metronidazole or vancomycin, but when recurrent episode, the choice is not as clear for patients with RCDAD and in some cases resolving the RCDAD could take months of antibiotic treatment.[14] In these cases, vancomycin is probably safer long-term than metronidazole or where there is a risk of irreversible peripheral neuropathy.

Vancomycin has no systemic absorption and few side effects. It might be a better option for multiple recurrences of CDAD due to increasing fecal levels of vancomycin with duration of therapy. The limitations of a widespread use are the cost and the risk of selection of vancomycin-resistant Enteroccocus in hospitalized patients.

There have been very few studies comparing antibiotic treatments in patients with RCDAD and even fewer randomized trials. In 1985, Tedesco et al. treated 22 patients with vancomycin in pulse therapy followed by vancomycin in tapering therapy for 21 days, with no documented relapse.[15] In 1987, Buggy et al. treated seven patients with vancomycin and rifampin, resulting in just one recurrence.[16] Both studies are limited because of the very small number of subjects. In a large study of 163 patients with RCDAD, McFarland et al. compared metronidazole and vancomycin, in different doses and different prolonged strategies. The study showed overall similar failure rates (46.2% for vancomycin versus 42.1% for metronidazole) with significant differences in recurrence rates depending upon the dose of vancomycin and the type of vancomycin therapy.[17] The lowest recurrence rate was obtained with high dose vancomycin (2 g/day). Regimens with tapering or pulsing vancomycin decreased the recurrence rates even more (31% versus 14%). Tapering strategy is gradually decreasing doses over a period of several days. Pulse therapy involves alternating treatment days with days off therapy, gradually increasing the interval number of days between antibiotic doses. Once antibiotics are taken only every tenth day, recurrences are usually unlikely and antibiotics can be discontinued. One other option with encouraging results is a combination approach that starts with a high dose 10-day vancomycin treatment, followed by tapering doses over several days that is followed by pulse therapy for several weeks. Presumably time off antibiotics allows the spores to germinate and the new vegetative forms are killed by the next antibiotic dose. Also, between doses the intestinal flora may start to normalize.

For CDAD, various clinical trials have compared different antibiotic therapies, trying to identify new drugs capable of erradicate C. difficile and to decrease the recurrence rates. Among those antibiotics, teicoplanin proved to have similar rates of initial cure with vancomycin, but with a significant lower rate of recurrence compared with vancomycin (7% versus 20%). However, no studies have been reported on patients with RCDAD.

For RCDAD, a combination of rifampicin and oral vancomycin has been used with some success in patients with multiple recurrences, but the studies were small and uncontrolled.

In 2006, Johnson et al used rifaximin following standard therapy in seven patients with RCDAD, resulting in six patients having no further CDAD episodes during the follow-up period of 2 to 12 months.[18]

Probiotics

The term "probiotic" defines a variety of mono- and mixed-cultures of live non-pathogenic microorganisms, including yeasts and lactic acid bacteria, which have a beneficial effect on intestinal flora. The mechanisms seem to involve repopulation of normal flora disturbed by antibiotics, suppression of the growth and attachment of potential pathogens, enhancement of gut barrier function, modulation of immune function, and production of antimicrobial substances.[19] Various probiotics have been evaluated in the prevention and treatment of antibiotic-associated diarrhea. The nonpathogenic yeast *Saccharomyces boulardii* and lactic-acid fermenting bacteria, *Lactobacillus rhamnosus* GG (LGG) prevent antibiotic-associated diarrhea, but with unknown effect on CDAD prevention. Both are generally safe and well tolerated, but probiotics should be used cautiously in immunocompromised patients in whom various complications such as fungemia or bacteremia have been reported.

Saccharomyces boulardii is a nonpathogenic yeast that survives gastric passage and reaches a steady level in the stool in 3-5 days. In animal model, *S boulardii* demonstrated various mechanisms: production of a protease which inactivates *C difficile* toxin receptors, diminished ileal fluid secretion and stimulation of the intestinal immunoglobulin A response to toxin A.

The role of *S boulardii* as an adjunct to antibiotic therapy in RCDAD has been investigated in several studies. In 1994, a randomized study on the combined therapy of *S boulardii* and vancomycin or metronidazole showed the efficacy of combined therapy in patients with recurrent CDAD: recurrence rate was 34.6%, compared with 64.7% on placebo. In patients with an initial episode of CDAD, the recurrence rate was 19.3% compared with 24.2% on placebo, with no statistical difference.[20]

In 2000, a controlled trial showed that *S boulardii* significantly reduced the occurrence of RCDAD when it was used as an adjunct with high-dose vancomycin (2 g/day), but not with metronidazole or lower dose vancomycin (16.7% of patients receiving S. boulardii and high-dose vancomycin versus 50% of patients receiving placebo and vancomycin).[21]

Lactobacillus GG is resistant to gastric acid and bile, survives the gastrointestinal passage and adheres to intestinal epithelium. It also produces an antimicrobial substance with potent inhibitory activity against a wide range of bacteria, including *C difficile*. LGG is not yet proved to be effective in RCDAD management. One randomized controlled trial using a combination of LGG with either vancomycin or metronidazole reported similar rates of recurrence: 36.4% for probiotic and 35.7% for placebo.[14] Another double-blind, placebo-controlled trial analyzed a different Lactobacillus specie, *L plantarum* 299v, in prevention of further recurrences in RCDAD. The combined therapy of *L plantarum* and metronidazole resulted in 35% recurrence rate compared with 66% for metronidazole and placebo, but the small sample size did not allow definitive conclusions.[22]

There are numerous limitations to the studies using probiotics for management of RCDAD such as different definitions of CDAD/RCDAD, different probiotic products and doses. Further studies of probiotics, including large, randomized controlled dose-ranging trials, comparative trials are necessary.

Toxin binding agents

The most common toxin binding agents are cholestyramine and colestipol. They could be used as an adjunctive therapy in CDAD, for their putative mechanism of binding *C difficile* toxins. The anion exchange resins may also help by their nonspecific constipation effect. Clinical efficacy is not established. One study involving eleven patients with recurrent PMC treated with colestipol and tapering trial of vancomycin showed a complete response and no relapse for a follow-up period of six weeks.[23] A placebo-controlled trial showed that colestipol made no difference on fecal excretion of *C difficile* toxin.[14]

The therapeutic effect might be compromised by their ability to bind drugs such as vancomycin, teicoplanin and theoretically metronidazole. Due to this interaction, the resins should be administered at different times from antibiotics, at least 2-3 hours before or after the antibiotics. Large randomized controlled trials would be needed to determine the role of resins in the treatment of CDAD and to address the timing of their use.

Alternative therapies

Fecal enema and bowel irrigation

Part of the management of RCDAD is to restore the colonic flora disturbed by the antibiotics. In attempt to replenish the colon with healthy bacteria, some have used donor stool enemas. The benefits of using stool transplantation over repeated therapy with antibiotics are: recovery of the intestinal flora, no antibiotic-resistant enteric strains and lower cost. Besides the aesthetically unappealing issues, no adverse effects have been reported to date. The drawbacks are the risks of transmission of infectious pathogens and the limited experience with stool bacterial flora replacement.

One of the earliest reports was in 1981, when fecal enemas were used to treat PMC not responsive to standard therapy (thirteen of 16 patients of the study responded to treatment).[24] Overtime, several cases of RCDAD have been reported cured by stool transplantation of stool donated from family members or healthy volunteers.[25,26] Persky and Brandt suggested that Polyethylene glycol (PEG) bowel preparation may allow the elimination of residual *C difficile* organisms and spores before stool administration and this might help the success of this procedure.[27] They also suggested that administration during colonoscopy may be more effective than by enema, due to the ability to administer organisms proximal to the splenic flexure. An alternative to stool transplantation rectal installation of mixtures of facultative aerobic and anaerobic bacteria, which helped a few patients to clear *C difficile*.[26]

Stool transplantation has also been delivered via nasogastric tube. In a retrospective study, 18 patients with more than two documented episodes of RCDAD were pretreated with at least 4 days of oral vancomycin followed by stool transplantation therapy via nasosogastric tube. The cure rate was 94%, with only one patient presenting with an additional episode of CDAD within 90 days after stool transplantation.[28]

Whole-bowel irrigation with polyethylene glycol solution alone is another therapeutic option with even more limited experience. It has been successful in two children with RCDAD who had failed antibiotic regimens. Treatment was followed by a 3-week course of oral vancomycin and Lactobacillus therapy. It is unclear whether the clinical response was due to the whole-bowel irrigation or not, but the authors postulated that whole-bowel irrigation cleared the intestine of *C difficile* organisms, toxins, and spores.[29]

Immune therapy

Host immune response to *C difficile* is an important factor in the pathology of CDAD and is a predictor of recurrence of CDAD. Various studies have shown that a low level of serum IgG against toxin A and low fecal IgA antitoxin A are associated with RCDAD. Also, there seems to be a correlation between higher IgG titers to toxin B and clinical recovery without relapse.[30] The antibody level does not correlate with the likelihood of colonization with *C difficile*, but it correlates with the likelihood of symptomatic disease. Patients who develop RCDAD had lower concentrations of serum IgM against toxin A on day 3 and of IgG to toxin A on day 12 after the onset of symptoms.[31] New therapeutic approaches are being developed to correct this defective humoral response by active and passive immunization against *C difficile*.

Passive immunization uses intravenous human immunoglobulin (IVIG). Normal pooled human immunoglobulin preparations contain significant levels of *C difficile* antibody. The experience with this therapy is limited to several case series. Patients enrolled for therapy with IVIG usually were previously treated with metronidazole, vancomycin or both, but continued to have recurrences. Although the number of patients involved in those studies was small, immunoglobulin therapy seemed to be successful for RCDAD. Leung et al treated five children with RCDAD (1991);[32] Hassett et al treated one patient with IgG deficiency, using IVIG and S. boulardii (1995);[33] Salcedo et al treated two patients with PMC (1997)[34] and Beales reported successful treatment in four patients (2002).[35] Wilcox reported five patients receiving IVIG therapy for RCDAD with three successes, one case of RCDAD within 6 weeks and one patient died of intractable CDD (2004).[36] The IVIG therapy results in clinical resolution of gastrointestinal symptoms and a significant increase in IgG antitoxin A levels, except in patients with immunodeficiency in whom the increase was modest.

An alternative approach to IVIG is an oral antibody product, bovine immune whey powder. The product derives from the milk of gestating cows immunized with *C difficile* toxoid. Immune whey powder concentrate contains a high concentration of specific IgA antibodies. These antibodies have been proven to neutralize the cytotoxic effects of toxins A and B in vitro and to confer protection from otherwise lethal *C difficile*-associated cecitis in

hamsters. The major limitation of this therapy is the degradation of bovine IgG during transit by intestinal proteases, which substantially reduces the activity of anti-C difficile antibodies recovered in stool. In a recent study, 16 patients with CDAD (9 with a history of RCDAD) received immune whey powder concentrate for 2 weeks after standard antibiotic therapy. At the end of therapy, 15 patients had no detectable fecal *C difficile* toxins and no further recurrences were reported during a follow-up period of median 333 days.[37] The treatment was also very well tolerated.

Active immunization includes the development of a vaccine containing inactivated toxins A and B. This parenteral toxoid vaccine was recently tested in healthy volunteers for safety and immunogenicity, showing good tolerance.[38] After therapy, all subjects seroconverted, with ELISA positive for serum IgG antitoxin A and the levels were 42- to 92- fold increased over baseline. Positive anti-toxin B IgG responses were seen in 90% of volunteers. Anti-toxin fecal IgA levels increased less frequently than in serum, expected upon parenteral vaccination. The vac-cine was tested in combination with vancomycin in three patients with multiple episodes of RCDAD, without further recurrence.[39] The vaccine elicited potent immune responses which suggests that it might prove useful as an immunological alternative to antimicrobial therapy.

VIII. New therapies

Tolevamer is a soluble, high-molecular weight, anionic polymer that binds *C difficile* toxins A and B. A multicenter, randomized, double-blind study compared tolevamer with vancomycin in patients with initial and recurrent CDAD. Resolution of diarrhea was achieved in 67% of patients receiving 3 g of tolevamer per day, 83% of patients receiving 6 g of tolevamer per day and 91% of patients receiving vancomycin. Tolevamer administered at a dosage of 6 g per day was as effective as vancomycin administered at a dosage of 500 mg per day and was associated with a trend toward a lower recurrence rate. Tolevamer therapy was associated with an increased risk of hypokalemia, due to its anionic properties that cause it to bind to potassium, but overall it was very well tolerated.[40] Phase 3 has yet to be done.

Nitazoxanide is a nitrothiazolide that blocks anaerobic metabolism in eukaryocytes and has been used to treat intestinal infections such as giardiasis. In a prospective study, Musher enrolled patients with *C difficile* colitis, who were randomly assigned to metronidazole 250 mg 4 times daily for 10 days, nitazoxanide 500 mg twice daily for 7 days, and nitazoxanide 500 mg twice daily for 10 days. After 7 days, 82.4% in the metronidazole group and 89.5% in the nitazoxanide groups had responded to therapy. Recurrence occurred in 4 cases in the metronidazole group, in nine and four cases in the nitazoxanide groups after a month from the treatment initiation.[41] No adverse effects were attributed to nitazoxanide.

Tiacumicin B is a nonabsorbable macrolide antibiotic in phase III clinical trials for the treatment of CDAD. It is a narrow-spectrum antibiotic with good activity against *C difficile* (it is 8 to 10 fold more active than vancomycin against *C difficile*) but with minimal activity against other gut microflora. Because of its specificity, the natural balance of intestinal flora is maintained, providing resistance to recolonization and reducing the relapse rate. Initial clinical evaluation has shown tiacumicin B to be effective in the treatment of CDAD, with a relapse rate of only 5%.[42] A phase 2B/3A is now underway, with a study of 500 patients, comparing tiacumicin with vancomycin.[43]

Rifaximin is a synthetic antibiotic, rifamycin derivate, resistant to the gastric acidity and not-absorbed through the intestinal mucosa. The drug has a wide bactericidal effect. Its effectiveness in CDAD treatment was evaluated over the time. In 1990, Boero et al compared its effectiveness with vancomycin and demonstrated that rifaximin was efficacious as a treatment of *C difficile colitis*, but less efficacious than vancomycin.[44] In 2005, Kokkotou et al showed that rifaximin and vancomycin have comparable activity in prevention and treatment of CDAD in an animal model. The study also showed rifaximin resulting in a significant lower relapse of CDAD compared with vancomycin.[45]

Tinidazole is a structural analogue of metronidazole. It has been used as an antiprotozoal agent in Europe for more than 20 years. In vitro, tinidazole exhibits antiprotozoal and anti-C. difficile activity. Metronidazole seems to be slightly more active than tinidazole in vitro.[46,47] Although there is no study in humans, its activity against *C difficile* in vitro, the available MIC data, its slower absorption and elimination, make tinidazole a worthy option to evaluate in future clinical trials.

Ramoplanin is a lipoglycodepsipeptide antibiotic obtained from the fermentation of an *Actinoplanes* strain. It is a nonabsorbable agent designed for the gastrointestinal decontamination of patients infected or colonized with vancomycin-resistant enterococci. Its bactericidal activity consists of blocking peptidoglycan synthesis. The hamster model showed that vancomycin and ramoplanin reduced *C difficile* and produced symptomatic resolution. In both animal and in vitro models vancomycin was associated with the persistence of *C difficile* spores, but in the gut model, after 2 days of ramoplanin therapy, neither vegetative cells nor spores were detected. Spores were recovered sporadically after cessation of ramoplanin,[48] thus reducing the likelihood of CDAD relapse in comparison with vancomycin therapy. A Phase II trial demonstrated the equivalence of ramoplanin compared with vancomycin for the treatment of *C difficile* colitis[49] and the results of Phase III trial will decide its clinical value and its place in CDAD treatment. No cross-resistance has been documented with vancomycin and other glycopeptides.

Oligofructose is a prebiotic that occurs in some fruits and vegetables rich in inulin such as artichoke, onion and asparagus. It is poorly digested in the human intestinal tract and it seems to stimulate selectively the growth of bifidobacteria in vivo and in vitro.[50] In 2005, a combined therapy of antibiotics and oligofructose in patients with CDAD resulted in decreased likelihood of developing relapses than placebo group (8.3% relapse rate for oligofructose versus 34.5% for placebo). Stool culture showed an increase in fecal bifidobacteria in patients receiving the oligofructose.[51] Lewis also conducted a study on oligofructose in prevention of AAD, showing no protection in elderly patients receiving broad-spectrum antibiotics from antibiotic-associated diarrhea whether caused by *C difficile* or not.[52]

Summary and conclusions

Clostridium difficile-associated diarrhea usually occurs as a complication of antibiotic treatment. Recent data shows an increase in incidence rate of CDAD and higher rates of morbidity, colectomy and death. The management of CDAD involves discontinuing the inciting antibiotic agent and treatment with metronidazole or vancomycin. The reduced response rates and higher recurrence rates with metronidazole treatment reported in recent studies raise the question of the effectiveness of metronidazole therapy. After each recurrence, the risks for further relapses grow even bigger (after two recurrences, the risk being greater than 50%) and the management of recurrent CDAD becomes a challenge.

Even after a careful review of available data on various drugs and having the experience of managing many cases of CDAD, one might find difficult to present with a successful "recipe" for treating severe CDAD. Every case is different and different management plans can lead to full recovery. First episode are metronidazole. If there is no improvement in three days or white blood cell count is more than 12,000 or creatinine level is high, metronidazole should be discontinued and vancomycin should be started. The latest trend of CDAD with more severe cases and increasing morbidity and mortality may be an incentive for using vancomycin as first line in some ases for RCDAD. Adding *S boulardii* to vancomycin or metronidazole from the first or second relapse and using pulse/tapering vancomycin therapy have been beneficial in decreasing the relapse rate. For patients with RCDAD, vancomycin therapy followed by rifaximin for two weeks looks promising.

New therapies with, nitazoxanide, tinidazole, tiacumicin, rifaximin and ramoplanin are being evaluated and future reports and trials will show their efficacy. Immune therapy is also a promising option treatment in evaluation, showing seroconversion and protective antibody levels in initial tests in healthy volunteer. Passive immunization is also considered but for all these new therapy options, further randomized studies are needed.

Prevention is also very important in controlling this disease: first by limiting the use of broad spectrum antibiotics and secondly by controlling the environmental spreading through gloves, handwashing and disposable thermometers.

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