Case Report

Recurrent/Refractory Antibiotic Associated Colitis

Background

C. difficile associated diarrhea (CDAD), also known as antibiotic-associated colitis (AAC) is a medical condition that has potentially fatal outcomes. It is increasing in incidence worldwide due to well known reasons as well as new and emerging ones. C.difficile is a spore forming, gram positive bacillus that was given its name because of its difficulty to grow and isolate in culture. It can either be in the vegetative form which is very sensitive to oxygen or the spore form which is very hardy and heat stable. The spores can survive under harsh environmental conditions and withstand antimicrobial therapy. Therefore, strict hand washing and contact precautions are imperative measures in preventing the spread of the organism. Development of CDAD requires several factors. The first two factors are treatment with antimicrobials and colonization of C.difficile which may or may not lead to infection. (7) The end result may depend on host susceptibility or immunity, the virulence of the particular C.difficile strain, or the type and timing of antimicrobial exposure. Almost every antibiotic has been linked to AAC, most commonly the beta-lactams as a class and clindamycin. (10) The pathogenesis of C.difficile involves the production of two toxins, A and B, which are both high molecular weight proteins that are heat labile. Toxin A is primarily an enterotoxin whereas Toxin B is primarily cytotoxic. The standard for C.difficile diagnosis is the cytotoxin assay which detects the principal toxin, toxin B. It has a sensitivity of 94% to 100% and a specificity of 97%. However, it requires a tissue culture facility, which is not widely available in most hospitals. It also takes 24-48hrs to perform. The method used most widely in the clinical setting to diagnose C.difficile infection is the enzyme linked immunosorbent assay (ELISA). It only takes 2-6hrs to perform and has a sensitivity of 85% with a specificity of 100%. (1) Signs and symptoms that lead to further confirmation of this condition include fever, elevated white blood cell count, abdominal cramping and frequent loose and bloody stools. The severity can range from mild to fulminant pseudomembranous colitis and even a sepsis syndrome that can lead to toxic megacolon. The drugs of choice for treatment are oral metronidazole or vancomycin for ten days. The most cost effective option, however, is metronidazole. (5) If these are ineffective, parenteral agents or enemas may be used, however, their efficacy are unknown. In addition, there are a number of investigational agents that are optional for use.

Case

On June 12, 2007 a 48 year old man, KS, presented to an outside hospital with severe abdominal pain and persistent, bloody diarrhea. Prior to outpatient admission, KS was mobile and independent. On physical exam patients’ abdomen was soft and nondistended. Diagnostic studies showed colitis, bilateral pleural effusions and atelectasis. Microbiology reports tested positive for C. difficile toxin on 6/15/07 and treatment was initiated. Patient was subsequently admitted to New York Presbyterian Hospital (NYPH) on 6/20/07 for further work-up.

KS has a significant past medical history of a double lung transplant (6/12/06) secondary to Sarcoidosis complicated by severe gastroaparesis, hypertension, end stage renal disease and recurrent CDAD. In addition, he has a past history of fungal infection by Scediosporom, Psudallescheria Boydii. KS is at high risk for cytomegalovirus (CMV) being that his donor was CMV positive and he, as the recipient was CMV negative. He has allergies to heparin (heparin induced thrombocytopenia) and reglan (reglan induced tremor). His at home medications were the following: Tacrolimus 0.5mg twice daily, Prednisone 10mg daily, Pentamidine 300mg INH once a month, Voriconazole 200mg twice daily, Lansoprazole 30mg daily, Ondansetron 4mg twice daily, Lisinopril 20mg daily and Nephrocaps 1 capsule daily. His discharge medications from the outside hospital (OSH) were the same, however, he received Loperamide as well before leaving to stop the diarrheal episodes.

Physical examination revealed a very fragile, fatigued AA male in very severe pain with loose bloody stools. His vitals include a temperature that was 99.5 degrees F, heart rate 105bpm and blood pressure of 143/96. Pertinent labs on admission to NYPH revealed the following: WBC 10.5 (3.2-9.8*10^9/L), platelet count 96,000 (130,000-400,000/mm^3), hemoglobin 10.5 (14-18g/dL), hematocrit 31.5 (39-49%) and tacrolimus level 3.8 (8-10).

Based on patient’s clinical presentation, physical examination and laboratory tests, he was diagnosed with recurrent C.difficile associated diarrhea complicated by pseudomembranous colitis (PMC). On day 1 of this clinical course at NYPH, KS was treated with metronidazole. On day 2 he was given vancomycin in addition to the metronidazole.
His condition was still refractory and an investigational agent for CDAD, Rifaximin, was added to his therapy. In addition, he was administered intravenous immunoglobulin on day 18. Unfortunately, the patient’s recurrent CDAD was so severe that he had to have a flexidex sigmoidoscopy which lead to a temporary recovery. Unfortunately, a day later he spiked a temperature of 100 degrees F with an elevated WBC of 12.0 and was transferred to the intensive care unit for further care. He was diagnosed on the floor with refractory CDAD and referred to surgery. Ultimately, he received a subtotal colectomy and has recovered since with no symptoms.

Discussion

During the course of therapy, KS was diagnosed with the more severe form of CDAD, pseudomembranous colitis (PMC). Risk factors for this condition and CDAD in general include recent antibiotic therapy, advanced age, hospitalization, surgical and non-surgical GI procedures and immunosuppression. KS is a post lung transplant patient that has been in and out of the hospital due to several complications mentioned in the case. Hence, he has several of the risk factors including advanced age, hospitalization and immuno-suppression. His first incidence of CDAD was post lung transplant surgery, in which several antibiotics are used as prophylactic agents pre and post surgery.

Unfortunately, before KS was discharged from the outside hospital he was administered a dose of loperamide to stop the diarrheal episodes. It is important to note that antidiarrheals should be avoided in these patients as well as any other anti-motility agents such as opiates. These agents prolong transit time, hence delaying toxin removal and worsen the illness. As a result, although this may not have effected KS’ final outcome it is still important to recognize as an inappropriate therapy option for patients with CDAD.

The symptoms of patients with CDAD are very significant. In fact, patients that are asymptomatic are usually not treated. Treatment for mild to moderate C. difficile colitis with or without pseudomembranes is standard. The first step is to discontinue the offending agent and use the drug of choice metronidazole 250 mg by mouth four times daily or 500 mg by mouth three times daily for 10 to 14 days. An alternative is vancomycin 125 mg to 500 mg by mouth four times a day for 10 to 14 days. These are the drugs of choice since their cure rate is 90-97%. Studies have shown that they are equally effective for the treatment of mild CDAD, but vancomycin is superior for treating patients with severe CDAD. (1)

Midway through therapy, Mr. KS required non-oral therapy (NPO) due to his multiple bowel movements and inability to absorb anything orally. As a result, he was given IV Metronidazole 500mg every 8 hours. Another option would be vancomycin rectal 500mg every 4-8 hours to 1,000 mg/L every 8 hours. It can not be given IV since it is not absorbed into the GI tract. (11) However, this was not an option for KS due to the voluminous amounts of diarrheal episodes he had daily. Reasons why Vancomycin might be used besides metronidazole in the treatment for CDAD include Metronidazole failure or resistance, pregnancy, intolerance, <10 years of age and if the person is critically ill. Major limitations to using Vancomycin are its cost, being that it is very expensive in comparison, as well as the fear for the development of vancomycin resistant organisms.

Emerging therapies for refractory CDAD include rifaximin, nitazoxinide, tolevamer, tinadazole and vaccinations. (8) Research has shown some improvement with the use of rifaximin and vancomycin, however, the development of more trials are warranted to provide more evidence in its benefit. (3) In a retrospective review, intravenous immunoglobulin was also used to assess the response of patients with refractory C. Difficile diarrhea. The findings were that it may be beneficial as well. (4)

Both of these treatments were, however, administered to KS and no overall improvement was seen unfortunately.

Nitazoxanide’s proposed mechanism of action is that it inhibits pyruvate-ferredoxin oxidoreductase (an enzyme essential to anaerobic energy metabolism). There are some studies out there that have published nitazoxanide being atleast as effective as metronidazole for the treatment of CDAD with few side effects. (2) Although, I did recommend this therapeutic option to the Infectious Disease team, they considered it but decided against it since they have had no experience with the medication. All of the other therapies have very little data published supporting their use in CDAD.

A more recent theory for the increasing incidence of recurrent refractory CDAD is the North American PFGE type 1 strain (NAP-1). This strain has been identified from pulse field gel electrophoresis (PFGE) and is known to exclude
large amounts of toxins. It is extremely resistant to our available antibiotic drug therapies and is believed to have enhanced morbidity. (6)

10-20% of CDAD cases relapse and usually treatment of the first relapse is successful. However, additional relapses occur that are typically refractory and hence much more difficult to treat. Possible reasons for the reoccurrence of CDAD include resistance to metronidazole, reinfections from the environment and persistence of spores in the GI tract after treatment of vegetative forms. (9)

Management strategies for recurrent AAD include oral vancomycin, pulse dose/tapered vancomycin regimen, vancomycin plus rifampin, donor stool transplantation and non-toxigenic C.difficile strains. However, since KS is experiencing very refractory CDAD that has been unresponsive, surgery was the last option and he was scheduled for a subtotal colectomy which lead to his complete recovery.

References

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