Metronidazole Resistant *Clostridium Difficile*

A Case Study

Elizabeth Gardner, RN, MSN, FNP-C, Texas Woman's University

Nosheen Meghani, RN, BSN, Texas Woman's University

Peggy Mancuso, PhD, RN, CNM, Professor and Coordinator, Doctor of Nursing Practice Program

Texas Woman's University

Anne Thomson, PhD, RN, FNP- BC Texas Woman's University

Nosheen Meghani

4004 Harvestwood CT. Grapevine, TX 76051

817-845-5882

Abstract

More than three million cases of *Clostridium difficile (C. difficile)* occur every year in the United States. An increasing number of cases are resistant to metronidazole. This case study describes a patient with recurrent episodes of metronidazole- resistant *C. difficile* and discusses the transmission, evaluation and treatment of this disease.

Metronidazole Resistant *Clostridium Difficile*

A Case Study

The patient is a fifty-three year-old single female who has a history of gastroesophogeal reflux disease, hypothyroidism, seasonal allergies, asthma and intermittent idiopathic gastroparesis. She does not smoke and is an occasional light drinker. She has worked in various hospitals and health care settings for thirty-five years.

This woman had been in her usual state of good health until about three weeks before her initial hospitalization. She underwent root canal surgery by her local dentist and was treated with a seven day course of Clindamycin (Cleocin) 300mg orally twice daily for a dental abscess. Approximately ten days after completing these antibiotics she developed nausea, intractable vomiting, fever, chills, abdominal cramping, and diarrhea, and was transported to the emergency room via ambulance.

Her vital signs upon arrival were as follows: blood pressure 105/58, pulse 106, temperature 100 degrees F (37.8 ^{0} C), respiratory rate 18, oxygen saturation 100% on room air. The physical exam was significant for dry mucous membranes and lower abdominal tenderness. A complete blood count with differential, metabolic profile and urinalysis were done, and abnormal results are listed in Table 1. The results of an abdominal series X-rays were negative.

Table 1: Abnormal Laboratory Results

Test	**Result**	**Normal Range**	**Test**	**Result**	**Normal Range**
CBC with Differential			**Urinalysis**		
White Blood Cells (mm3)	25,880	4,300- 10,800	Ketones	20	negative
Neutrophils %	93	54-62	Blood	trace	negative
Bands %	4	3-5	Protein	20	negative
Lymphocytes%	1	25-33	Red blood cells	4	<2-3
Monocytes%	2	3-7			

The initial differential diagnoses list included, infection, small bowel obstruction, urinary tract infection, hematuria, protienuria, and *C. difficile* colitis .She was admitted to the hospital and treated with intravenous fluids, ondansetron and intravenous metronidazole.

Pertinent laboratory values while hospitalized included negative blood cultures and stool for *salmonella, shigella, e. coli* 0:157, and *campylobacter* toxins. The stool was positive for *C. difficile* toxins with many fecal white blood cells present.

The patient's leukocystosis , nausea, vomiting, and fever improved within 48 hours. However, she developed anorexia and profound diarrhea requiring continuation of intravenous (IV) fluids and electrolyte replacements. On day three of hospitalization, metronizadole was changed to an oral form for better absorption and *Saccharomyces boulardii* (*S. boulardii*, Florastor) one capsule by mouth twice a day was added to the medication regimen. The intractable diarrhea persisted to day seven of hospitalization, when oral vancomycin (Vancocin) was added to her therapy. Following oral vancomycin therapy, there was a rapid improvement of diarrhea. On day nine she was discharged home with resolution of symptoms and feeling well. She was to continue oral vancomycin 125 mg four times a day for ten days and *S. boulardii* one capsule by mouth twice a day.

Three months later, the patient was treated with a five-day course of azithromycin (Zithromax) for an acute sinus infection. Two weeks after completing this therapy, she noted intermittent loose stools, which progressed to abdominal cramps and diarrhea. She was started on vancomycin 250 mg capsules one by mouth four times a day for seven days for presumptive *C. difficile* infection. Her stool was positive for *C. difficile* toxin. Her symptoms resolved rapidly on vancomycin.

Eight days after completing the outpatient course of vancomycin, the patient developed abrupt onset of fever, rigors, nausea, and vomiting. She was unresponsive to promethazine

(Phenergan) and ondansetron and was transferred to the emergency room via ambulance. On admission, her blood pressure was 141/71, pulse 135, respiratory rate 24, temperature 105.3 degrees F (40.7 C), oxygen saturation 96% on 2 liters of oxygen, and she reported pain perception of 3 on a scale of 10.The physical exam was remarkable for tachycardia, rigors, abdominal distension, and abdominal tenderness. A complete blood count was done, with the abnormal results listed in Table 2. A metabolic panel and urinalysis were normal. A CT scan of the abdomen and pelvis showed mild and prominent small bowel loops in the left upper quadrant. There was a large amount of fluid throughout the colon, particularly in the right colon associated with mild thickening of the cecal wall.

Table 2. Abnormal Laboratory Results		
Test	**Result**	**Normal Range**
CBC with Differential		
White Blood Cells (mm3)	19,300	4,300- 10,800
Neutrophils %	92	54-62
Bands %	7	3-5
Lymphocytes% Monocytes%	1 0	25-33 3-7

Her admission diagnoses were nausea , vomiting, fever, bacteremia, and systematic inflammatory response syndrome. She was started on intravenous fluids, antiemetics, intravenous metronidazole, oral vancomycin, and intravenous piperacillin and tazobactam (Zosyn). The Zosyn was discontinued after *C. difficile* infection was confirmed by a positive stool toxin. *Giardia, cryptosporium, campylobacter,* and *e. coli* 0:157 toxins were negative. Blood cultures were negative. Hypotension and hypovolemia were treated with volume and electrolyte replacements. Her symptoms resolved after three days, and she was discharged on vancomycin 500 mg orally four times a day for two weeks, and Florastor, one capsule by mouth twice a day.

A gastrointestinal specialist saw the patient two weeks after discharge. He prescribed prescribed pulsed therapy consisting of vancomycin 250 mg orally four times a day for seven days, then two times a day for seven days, once a day for seven days, every other day for seven days, then every three days for fourteen days. She was also advised to continue Florastor one capsule by mouth twice a day for a total of three months.

At a follow-up appointment six weeks later, she felt well and had no diarrhea. To prevent further episodes of *C. difficile*, she was advised to avoid antibiotics unless absolutely necessary. If placed on antibiotics, she could be treated concurrently with oral metronizadole and Florastor.

What Is *Clostridium Difficile* and How Does it Spread?

Clostridium. difficile is a gram positive, anaerobic, spore-forming bacteria. It is the most common cause of healthcare-associated diarrhea in developed countries. At least three million cases of *C. difficile*-associated diarrhea (CDAD) and colitis occur in the United States every year. CDAD usually only occurs when normal intestinal flora has been disrupted by antibiotic use. The eradication of the normal flora creates an environment that allows spores to vegetate, multiply, and secret toxins. Symptoms of infection range from mild diarrhea to severe colitis with fever, leukocytosis, abdominal cramps, and bloody diarrhea. Complications may include toxic megacolon (especially in patients treated with antimotility agents), intestinal perforation, sepsis, and death. Endoscopy reveals pseudomembrane formation in about half of cases.[1,2] Chow [2,para13]explained the effect of two toxins secreted by the bacteria that cause CDAD and its complications:

> Toxin A causes intestinal fluid secretion, mucosal injury, and inflammation. Toxin B has no demonstrable effect on cell permeability and fluid secretion, but like toxin A, it disrupts tight junctions in human epithelial cell monolayers. Toxin B is ten times more potent on a molar basis than toxin A in mediating damage to human colonic mucosa.

Symptoms may develop within the first few days of antibiotic therapy to four to six weeks after antibiotics have been discontinued. In hospitalized patients, risk factors include prolonged hospitalization, age greater than sixty- five years, antibiotic use, underlying medical conditions, neoplastic disease, gastrointestinal surgery, use of nasogastric tubes, tube feedings, gastrointestinal disorders including inflammatory bowel disease, and proton-pump inhibitors. Chemotherapy for cancer is an independent risk factor for development of CDAD.[3]

The propensity of patients to obtain *C. difficile* infection while in the hospital is due to difficulty eradicating the bacteria. *C. difficile* has the uncommon ability to sporulate, and these spores may exist for months on surfaces. As a result, hospitals and chronic care facilities may be heavily contaminated. The spores are resistant to killing by alcohol-based hand hygiene products, antimicrobial soaps, and most disinfectants.[3] Moreover, low levels of some disinfectants may promote increased sporulation. Bleach has sporicidal activity, but it has several disadvantages, including being corrosive to many materials, irritating to some patients and staff members, and dependent on correct application by staff. New approaches are being developed to control the infection. One approach consists of inducing spore germination through application of nutrients, followed by application of ultraviolet light to kill the vegetating forms of bacteria.[4]

How Was the Infection Acquired?

The usual route of transmission is oral-fecal however, there is some evidence that *Clostridium* may aerosolize.[5] In this case, the patient had been a healthcare worker for many years. It could be speculated that she had had harbored the clostridium spores obtained in a health care setting for many years until clindamycin eradicated her normal gut flora. There is no data about the number of healthcare workers who are asymptomatic carriers.

Which Medications Increase Susceptibility to *Clostridium Difficile*? What Could Account for the Presumed Resistance to Metronidazole In This Case?

Clindamycin is the antibiotic most frequently associated with CDAD, followed by the broad-spectrum penicillins, cephalosporins, and floroquinolones .Drugs that are used to treat CDAD infections, metronidazole and vancomycin, may also rarely induce infection.[6] Use of proton –pump inhibitors is associated with the development of CDAD. It is thought that that a decrease in stomach acidity prevents destruction of ingested vegetative bacteria.[7]

Metronidazole has been a first line treatment due its low cost, high cure rate, and concern about the risk of vancomycin resistance; however, increasingly high failure rates, re-occurrence rates, and increase in mortality suggest that metronidazole may be losing effectiveness.[8] Dubberke, Albert and Wertheimer compared metronidazole and vancomycin for the treatment of CDAD in three areas: length of hospital stay, length of stay in the intensive care unit, and in-hospital deaths. Length of stay was 12.8 days with metronidazole vs. 11.5 days with vancomycin. Length of stay in the ICU was at 23.2 days with metronidazole vs. 17.7 days with vancomycin. In- hospital deaths were at 7.9% with metronidazole vs. 6.8% with vancomycin (2008) Metronidazole also had a lower response rate (62%-74%) and a higher re-occurrence rate (47.2%) as compared to previous trials.[9] This decrease in effectiveness of metronizadole is linked to the emergence of a more virulent strain of *C. difficile*. In 2005, the Centers for Disease Control (CDC) documented the presence of a strain of *C. difficile* that was found in hospitals from six states.[10] This strain, known as BI/NAP1, was also found to be resistant to fluoroquinolones unlike other C. difficile strains. BI/NAP1 produces about twenty times as much of each of the two main toxins of *Clostridium difficile* as well as an additional toxin. As of October 2008, the more- toxic strain has been documented in forty states in the United States.[11]

What Is The Initial Outpatient Treatment? When Would the Patient Need to Be Hospitalized?

Metronidazole is the appropriate first-line therapy for most cases. Initially, the patient can be treated with metronidazole 500mg by mouth three times a day or 250 mg orally four times a day for ten to fourteen days. If there is a high suspicion for *C. difficile* infection due to signs and symptoms of the disease, treatment should be started before results of stool toxins are available.[12] Severely ill or known metronizadole- resistant patients should be started on vancomycin 125mg orally four times a day.[13] Vancomycin achieves significantly higher response rates (97%) than metronidazole (76%). For patients with recurrent disease, a six- week tapering dose regimen of vancomycin should be initiated after the initial therapy is completed. One regimen consists of 125mg orally four times a day for fourteen days; twice a day for seven days; once a day for seven days; every other day for seven days and every third day for seven days. Probiotic therapy is recommended for patients with relapsing disease.[14] Regardless of what therapy is used, patients should be carefully monitored to be sure they are responding to therapy and that there is no deterioration in their condition.[10]

The patient requires hospitalization if there is dehydration, ileus, hypotension, marked leukocytosis or if the patient is unable to take oral antibiotics. Excessive gastrointestinal fluid loss can lead to hypovolemic shock and/or electrolyte imbalance.[13] Treatment includes replacement of fluids and electrolytes and intravenous metronidazole with vancomycin administered either orally or by enema for better absorption.[14]

What Role do Probiotics Play in Treating This Infection?

Probiotics are live bacteria or yeast. Some of common types of bacteria include *Lactobacillus rhamnosus GG, Streptococcus thermophilus, Lactobacillus casei* and *Lactobacillus acidophilus*. Bacterial probiotics are believed to inhibit pathogen adhesion, block the production of microbial toxins, and stimulate the immune system. The yeast *Saccharomyces bouldardii* produces a protease that decreases the toxicity of *C. difficile* toxins A and B. Probiotics are administered as capsules or powders or added to foods such as yogurt, butter, milk, cheese, and sauerkraut.[15, 17] Probiotics may be beneficial both by preventing CDAD and by rapidly restoring the normal intestinal flora after and infection. A recent study showed that prophylactic administration of *Lactobacillus casei, Lactobacillus bulgaricus*, and *Streptococcus thermophilus* to hospitalized patients receiving antibiotics reduced the incidence of *C. difficile* associated diarrhea from 34% to 12% [14] Another study showed that *S. boulardii* in combination with metronidazole, vancomycin, or both significantly reduced the reoccurrence of *C. difficile* infection.[15] The evidence of the effectiveness of probiotics has not been established. A Cochrane review of four randomized prospective studies evaluated the effectiveness of probiotics alone or in conjunction with conventional antibiotics for the treatment of documented C. *difficile* colitis. The authors concluded that was insufficient evidence to recommend probiotics as adjunct to antibiotic therapy for *C. difficile* .[18]

In the event that this patient has another episode of CDAD, other therapies may be helpful. These include anion-binding resins, such as colestipol and cholestyramine. These resins bind to *C difficile* toxins and are fecally excreted. Alternative antibiotics (ie, rifaximin, nitazoxanide, tinidazole) have been considered in addition to metronidazole and vancomycin.

Intravenous immunoglobulin has been effectively used in the treatment of several severe, recurrent, or refractory cases of CDAD.[15]

An highly effective treatment for severe or relapsing infection may already exist. Bacteriotherapy, or fecal transplant, consists of administering fecal material from a healthy donor into the colon of the patients with the disease.[19 pg 4] Since the first transplant was performed 1958, there have been over 200 reported cases, with a success rate of 90% and no side effects.[19] Despite its apparent efficacy, fecal transplant it has been slow to gain widespread acceptance. This is thought to be due to the nature of and lack of profitability of the procedure.[20] Because of the increasing number of CAD infections and the emergence of more toxic strains, it is important that every effective modality be utilized to treat this disease. Well designed clinical studies are advocated to prove the value of the procedure and bring about its widespread acceptance in the medical community.[19]

References

1 Gerding DN, Johnson S. *Clostridium difficile*-associated disease, including pseudomembranous colitis. In: Fauci AS, Kasper DL, Longo DL, Braunwald E , Hauser SL ,eds. *Harrison's Principles of Internal Medicine.* 17th ed. New York, NY: McGraw-Hill. 2008: chap 123. http://ezproxy.twu.edu:2723/Results/Results.aspx?SessionID=139B304WQLVUSLOP&UseStemming=false&FilterType=0&query=clostridium%20difficile&list=55. Accessed October 2, 2010.

2 Chow AW. Anaerobic infections. In: Dale D, ed. *Infectious Diseases: The Clinician's Guide to Diagnosis, Treatment and Prevention.* New York, NY: Web MD; 2010:chap 17. *http://ezproxy.twu.edu:2723/Results/Results*.aspx?SessionID=139B288TTWJCNGWF&UseSte UseStemming=false&FilterType=0&query=Anaerobic infections&list=65. Accessed September 29, 2010.

3 Yoo J, Lightner AM. *Clostridium difficile* infections: What every clinician should know. *Perm J. Summer 2010; 14 (2):35-40. htt*p.//www.thepermanentejournal.org. Accessed September 26, 2010.

4 Nerandzic MM, Donskey CJ. Triggering germination represents a novel strategy to enhance killing of *Clostridium difficile* spores. *PLoS One.* 2010; 19(5). doi:10.1371/journal.pone.0012285.

5 Best EL, Fawley WN ,Parnell P, Wilcox MH. The potential for airborne dispersal of *Clostridium difficile* from symptomatic patients. *Clin Infect Dis.* June 1, 2010;1(50): 1450-1457. http://www.ncbi.nlm.nih.gov/pubmed/20415567 Accessed September 28, 2010

6 Wieczorkiewicz JE , Lopansri BK, Tomich AZ, Zurkowski E, Sambol SP, Gerding DN. Fluoroquinolone use is a specific risk factor for *Clostridium difficile* infection due to the highly fluoroquinolone resistant epidemic strain BI/NAP1 [Abstract].In :*Fifth Decennial International Conference on Healthcare- Associated Infections*]. March 18-22, 2010. Atlanta, GA.

7 Jump RLP, Pultz MJ, Donskey CJ. Vegetative *Clostridium difficile* survives in room air on moist surfaces and in gastric contents with reduced acidity: A potential mechanism to explain the association between proton pump inhibitors and C. difficile-associated diarrhea. *Antimicrob Agents Chemother*. June 11, 2007; 51(8):2883-2887. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1932506/. Accessed October 4, 2010.

8 Dubberke E, Wertheimer A. Review of current literature on the economic burden of *Clostridium difficile* infection. *Infect Control Hosp Epidemiol* .January 1, 2009; 30 (1): 57-66. http://www.ncbi.nlm.nih.gov/pubmed/19049438. Accessed October 6, 2010.

9 Razavi B, Apisarnthanarak A, Mundy L. *Clostridium difficile*: Emergence of hypervirulence and fluoroquinolone resistance. *Infection.* October 2007 ; 35(5): 300-307. http://www.springerlink.com/content/v01078u117u14w83/fulltext.pdf. Accessed October 2, 2010.

10 Centers for Disease Control and Prevention(CDC). Information about the current epidemic strain of *Clostridium difficile*. Centers for Disease Control and Prevention Web site. http://www.cdc.gov/ncidod/dhqp/id_CdiffFAQ_newstrain.html. Updated October 18, 2010. Accessed November 1, 2010

11 Consumers Union. Consumers Union policy brief: Hospital-acquired *C.difficile* infections. Available at http://www.consumersunion.org/pub/Final%20Cdiff%20Policy%20Brief%2011-11-08.pdf. Accessed Oct 2, 2010.

12 Kelly CP, LaMont JT. Patient information: Antibiotic-associated diarrhea (*Clostridium difficile).* http://www.uptodate.com/patients/content/topic.do?topicKey=~6y86CpJTTR1ZzRx. Updated Feb 11, 2008. Accessed Oct 4, 2010.

13 Higginson R. Infection control and IV therapy in patients with *Clostridium difficile*. *Br J Nurs.* September 10-23 ,2009;18 (16):962-969 http:// www.Britishjournalofnursing.com. Accessed Oct 5, 2010.

14 McQuaid KR. Gastrointestinal Disorders. In: Mcphee SJ ,Papadakis MA, eds. *Current Medical Diagnosis and Treatment*.49th ed. New York, NY: McGraw Hill; 2010: 503-597.

15 Williams N. Probiotics. *Am J Health Syst Pharm.*March 2010; 67(6):449-458. http://ezproxy.twu.edu:2053/ehost/pdfviewer/pdfviewer?vid=2&hid=15&sid=6db9f131-289b-455c-9a18-e5e10ccebde6%40sessionmgr14. Accessed October 11, 2010.

16 Bakken JS. Resolution of recurrent *Clostridium difficile*-associated diarrhea using staggered antibiotic withdrawal and kefir. *Minnesota Medicine.* July 2009. http://www.minnesotamedicine.com/CurrentIssue/tabid/3581/Default.aspx**.** Accessed November 13, 2010.

17 Johnson BC Thorlund K. Probiotics for the prevention of *Clostridium difficile*- associated diarrhea in adults and children (Protocol). *Cochrane Database of Systematic Reviews*,2009 (1). DOI:10.1002/14651858.CD006095.pub2. Accessed October 11, 2010.

18. Pillai A, Nelson RL. Probiotics for treatment of *Clostridium difficile*-associated colitis in adults. *Cochrane Database of Systematic Reviews* 2008, Issue 1. Art. No.: CD004611. DOI: 10.1002/14651858.CD004611.pub2.

19. Khoruts A, Sadowski M J. Therapeutic transplantation of the distal gut microflora. *Mucosal Immunol*. January 2011; 4(1):4-7. DOI: 10.1038/mi.2010.79

20. Ho N, Prasad V. Lacking the incentive to cure? Recurring Clostridum difficile diarrhea and our reluctance to use fecal transplantation. *J Clin Gastroenterol.* January 26, 2011. (Epub ahead of print). Accessed February 17, 2011.

Deleted: