Journal of HOSPITAL MEDICINE www.journalofhospitalmedicine.com

REVIEWS

Meeting the Challenge of Recurrent *Clostridium difficile* Infection

Stuart Johnson, MD*

Division of Infectious Diseases, Department of Medicine, Loyola University Medical School, Maywood, Illinois.

Recurrent *Clostridium difficile* infection (CDI) is a growing problem that poses significant management challenges. There is no strong evidence to support a particular treatment strategy for recurrent CDI, especially those with multiple recurrences. However, a key strategy for reducing recurrent CDI is prompt diagnosis and treatment, facilitated by early recognition of patients at risk for recurrence. *Journal of Hospital Medicine* 2012;7:S11–S13. © 2012 Society of Hospital Medicine

As noted elsewhere in this supplement, recent studies show a high rate of recurrent *Clostridium difficile* infection (CDI) despite the availability of evidence-based guidelines for CDI treatment.[1,2] Treatment with vancomycin has been associated with recurrence in 25% or more of patients. The risk for recurrence increases with each episode, and is greater than 60% in patients with more than 2 episodes.[1,3,4] Identification of patients at risk for recurrence is critical to early diagnosis and prompt treatment.[5] Because recurrent CDI is so widespread, it should be common practice to educate patients about this complication, including:

- The risk for continued exposure to *C. difficile* in the hospital or home environment and strategies for appropriate hygiene to minimize reinfection.
- When to contact a healthcare professional for recurrent symptoms.[1]

CASE STUDY CONTINUED. . .

In the previous article in this supplement, a case study for patient A.L. was presented. A.L. is an 87-year-old woman who developed initial inpatient CDI in a rehabilitation facility. She was empirically started on oral metronidazole, 500 mg 3 times a day. Her symptoms improved but she became febrile with an elevated white blood cell (WBC) count. She was transferred to an acute care facility where her treatment was switched to oral vancomycin 125 mg 4 times daily. A proctoscopic exam confirmed pseudomembranous colitis, and her treatment regimen was increased to oral vancomycin 500 mg 4 times daily plus intravenous (IV) metronidazole 500 mg every 8 hours. The CDI responded to therapy and she was discharged to home care.

***Address for correspondence and reprint requests:** Stuart Johnson, MD, Division of Infectious Diseases, Department of Medicine, Loyola University Medical School, 2160 S First Ave, Bldg 54, Room 149, Maywood, IL 60153; Telephone: 708-216-3232; E-mail: sjohnson@lumc.edu

Additional Supporting Information may be found in the online version of this article.

Received: August 17, 2011; **Revised:** December 12, 2011; **Accepted:** December 23, 2011
 DOI 10.1002/jhm.1914
Published online in Wiley Online Library (Wileyonlinelibrary.com).

Ten days after her hospital discharge, A.L. noted a change in the character of her stools, which became looser and increased in frequency, accompanied by a foul odor that she recalls was present during her previous episode. The following day, she developed frank watery stools occurring every 1-2 hours and had 2 incontinent episodes. Her family brought her to the emergency department because she was also lightheaded, confused, and had increased abdominal cramping. Intravenous fluid resuscitation was started, along with oral vancomycin, 125 mg every 6 hours for 14 days, followed by a vancomycin taper and pulse, which consisted of 125 mg twice daily for 7 days, once daily for 7 days, once every other day for 7 days, then every third day. Stool was sent to the lab for *C. difficile* testing in the middle of the taper regimen. The result was negative. Ten days after tapering the oral vancomycin regimen to every third day, she developed loose stools with the same odor, followed by increased frequency and frank watery stools.

This case illustrates several aspects of recurrent CDI. First, the recurrent episode may be severe, as evidenced by the need for IV fluid resuscitation in addition to specific anti-*C. difficile* treatment. Second, although the patient was treated appropriately with standard 4 times daily vancomycin followed by a taper, subsequent recurrences may still occur, usually near the end of the taper/pulse (as in this case) or shortly after finishing the regimen. Finally, "test of cure" stool testing (either toxin testing, culture, or polymerase chain reaction [PCR]) may be misleading and is NOT recommended for managing recurrent CDI. Although subsequent management of this case was not addressed, repeating the standard vancomycin regimen, followed again by a taper/pulse would be a realistic option, as vancomycin resistance in *C. difficile* has not been reported and the patient would be expected to respond. Other management options should also be considered and are discussed below.

SHEA/IDSA RECOMMENDATIONS

There is no strong evidence to support a particular treatment strategy for recurrent CDI.[5] The Society for Healthcare Epidemiology of America/Infectious Diseases

Society of America (SHEA/IDSA) guidelines[6] recommends the following:

- When severe or complicated CDI is suspected, initiate empiric treatment as soon as the diagnosis is suspected (C-III).
- Treatment of the first recurrence is usually with the same regimen as for the initial episode (A-II), but should be stratified by disease severity (C-III).
- Do not use metronidazole beyond first recurrence or for long-term chronic therapy (B-II).
- Treatment of second or later recurrences with vancomycin using a taper and/or pulse regimen is the preferred next strategy (B-III).
- No recommendations can be made regarding prevention of recurrent CDI in patients requiring continued antimicrobial therapy (C-III).

The vancomycin taper/pulse regimen is one of the most widely used regimens for treatment of recurrent CDI.[5] A tapered oral vancomycin regimen consists of a stepwise decrease in dose over a period of time. Intermittent or "pulsed" vancomycin therapy consists of administering the drug every few days.

A standard course of antibiotic therapy eradicates vegetative cells of *C. difficile*, but is not effective against spores. Administering antibiotics over an extended time period at decreasing doses (tapered regimen) or intermittent delivery (pulsed regimen) gradually clears *C. difficile* by eradicating cells as the spores germinate.[5] Thus, a taper/pulse regimen of vancomycin, in theory, leads to a decreased rate of recurrence and may aid restoration of the normal microflora.[5]

Evidence for efficacy of the tapered dosage regimen is based on a post hoc analysis of patients treated for recurrence in 2 trials of probiotic treatment with *Saccharomyces boulardii*. When standard-dose oral vancomycin (125 mg 4 times daily) was compared with high-dose vancomycin (500 mg twice daily for 7 to 14 days), recurrence rates were not statistically different. However, a tapered regimen of vancomycin resulted in significantly fewer recurrences (31%, $P = 0.01$), as did a pulsed dose of vancomycin (14.3%, $P = 0.02$).[4] One empiric pulsed-dose regimen consists of oral vancomycin, 125 mg every 6 hours for 14 days, followed by tapering to 125 mg every 12 hours for 7 days, then 125 mg once daily for another 7 days, followed in turn by pulse-dosed vancomycin (125 mg once every 2 days for 4 doses, then once every 3 days for 5 doses, or longer).[1] Prolonged courses of metronidazole are not recommended because of potential adverse effects, including peripheral neuropathy.[1]

Management of patients with multiple recurrences of CDI is difficult, and no regimens are supported by adequate clinical evidence.[5] Various strategies have been tried, including probiotics, antibiotics, toxin binders, and immune-based treatments.[1] The strategy behind use of probiotics is to augment colonization resistance. The probiotic *S. boulardii*, 1 g daily for 4 weeks, decreased recurrence compared with placebo in a small study of 60 patients when given during and after standard treatment (ie, metronidazole or vancomycin). In patients receiving high-dose vancomycin plus *S. boulardii*, 3 of 18 (16.7%) had a recurrence compared with 7 of 14 (50%) receiving high-dose vancomycin plus placebo ($P = 0.05$).[7] However, a larger follow-up study did not show a significant overall benefit of *S. boulardii* over placebo.[1,7] In addition, there have been a few case reports of systemic infections in immunocompromised patients treated with probiotics.[8] Overall, the results of studies with probiotics, including *Lactobacilli*, have been inconsistent.

Another approach to restoring a normal gastrointestinal microflora is fecal transplantation, where a small amount of fresh feces from a healthy donor (ideally someone who lives with the patient), is suspended in saline, filtered, and administered through a nasogastric tube, by colonoscope, or by enema. In a recent case series of 18 patients, this approach showed a 94% success rate.[9]

Another potential strategy to prevent recurrence is to block colonization of pathogenic *C. difficile* strains by administration of nontoxigenic and nonpathogenic strains of *C. difficile*. Researchers have identified a nontoxigenic strain that is being developed as a targeted biotherapeutic probiotic for human use.[1] Because patients with recurrent CDI lack a strong immune response to *C. difficile* toxins, IV immunoglobulin (IVIG) has been used empirically to provide passive immunotherapy. It has shown benefit in some case series of patients with multiple recurrences.[1,10,11]

Other antibiotics have also been investigated in conjunction with vancomycin for recurrent infection. Rifaximin has good in vitro activity against *C. difficile*, and is not absorbed from the gastrointestinal tract. Oral rifaximin, 400 to 800 mg daily for 14 days following discontinuation of vancomycin, was shown to prevent further recurrence in 7 of 8 patients with a history of 4 to 8 CDI recurrences.[1,12] It is important to note that rifaximin resistance has been reported in clinical isolates of *C. difficile*, and may be more common than initially thought, particularly among epidemic strains.[13]

Fidaxomicin, a narrow-spectrum macrocyclic antibiotic, was also compared with vancomycin in 2 multicenter, randomized, double-blind Phase 3 clinical trials of 1105 adults with confirmed CDI.[14] Patients were treated with either oral fidaxomicin (200 mg every 12 hours) or oral vancomycin (125 mg every 6 hours) for 10 days.[15,16] The clinical cure rate with fidaxomicin was comparable to vancomycin in both studies.[14] In the more recent study, 59.8% of subjects (N = 535) were receiving concomitant antibiotics during CDI treatment; among this group, treatment with fidaxomicin was associated with a significantly lower recurrence rate than treatment with vancomycin

(17.6% vs 29.5%, $P = 0.027$).[15] In addition, there was a sustained clinical response. Global cure, also a secondary endpoint, was defined as patients who were cured and did not have a recurrence during a subsequent 4-week period, compared with treatment with vancomycin (67.5% vs 53.4%, $P = 0.020$).[15] These results confirm the findings from the first fidaxomicin Phase 3 study[16] and suggest that even when concomitant antibiotics are administered, fidaxomicin may be more effective than vancomycin in preventing CDI recurrence.

SUMMARY

Because hospitalists take a leadership role and often coordinate care for patients with CDI, they can take an active role to ensure that clinicians are aware of evidence-based treatments for recurrent CDI, and the importance of routine follow-up and persistence. The most important considerations in managing patients with recurrent CDI are to:

- Continue to try new or previous approaches, beginning with those that are evidence-based, followed by options that have been shown to work but are not backed by strong clinical evidence.
- Provide consistent follow-up and ongoing support.
- Be sympathetic—because this condition has significant detrimental impact on quality of life.

Disclosure: Consultant: Astellas Pharma, Bio-K+, Cubist Pharmaceuticals, Pfizer, Optimer Pharmaceuticals, and ViroPharma. The author received support for travel and an honorarium from Paradigm Medical Communications for time and expertise spent writing this article.

References

1. Kelly CP. A 76-year-old man with recurrent Clostridium difficile-associated diarrhea: review of C difficile infection. *JAMA*. 2009; 301(9):954–962.
2. Norén T. Clostridium difficile and the disease it causes. *Methods Mol Biol*. 2010;646:9–35.
3. McFarland LV, Surawicz CM, Greenberg RN, et al. A randomized placebo-controlled trial of Saccharomyces boulardii in combination with standard antibiotics for Clostridium difficile disease. *JAMA*. 1994;271(24):1913–1918.
4. McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent Clostridium difficile disease. *Am J Gastroenterol*. 2002;97(7):1769–1775.
5. Johnson S. Recurrent Clostridium difficile infection: a review of risk factors, treatments, and outcomes. *J Infect*. 2009;58(6):403–410.
6. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infect Control Hosp Epidemiol*. 2010;31(5):431–455.
7. Surawicz CM, McFarland LV, Greenberg RN, et al. The search for a better treatment for recurrent Clostridium difficile disease: use of high-dose vancomycin combined with Saccharomyces boulardii. *Clin Infect Dis*. 2000;31(4):1012–1017.
8. Riquelme AJ, Calvo MA, Guzmán AM, et al. Saccharomyces cerevisiae fungemia after Saccharomyces boulardii treatment in immunocompromised patients. *J Clin Gastroenterol*. 2003;36(1):41–43.
9. Aas J, Gessert CE, Bakken JS. Recurrent Clostridium difficile colitis: case series involving 18 patients treated with donor stool administered via a nasogastric tube. *Clin Infect Dis*. 2003;36(5):580–585.
10. Leung DY, Kelly CP, Boguniewicz M, et al. Treatment with intravenously administered gamma globulin of chronic relapsing colitis induced by Clostridium difficile toxin. *J Pediatr*. 1991;118(4 pt 1): 633–637.
11. Wilcox MH. Descriptive study of intravenous immunoglobulin for the treatment of recurrent Clostridium difficile diarrhoea. *J Antimicrob Chemother*. 2004;53(5):882–884.
12. Johnson S, Schriever C, Galang M, Kelly CP, Gerding DN. Interruption of recurrent Clostridium difficile-associated diarrhea episodes by serial therapy with vancomycin and rifaximin. *Clin Infect Dis*. 2007; 44(6):846–848.
13. O'Connor JR, Galang MA, Sambol SP, et al. Rifampin and rifaximin resistance in clinical isolates of Clostridium difficile. *Antimicrob Agents Chemother*. 2008;52(8):2813–2817.
14. Crook D, Miller M, Louie T, Cornely O, Shue Y-K, Gorbach S. Efficacy and safety of fidaxomicin (FDX) vs. vancomycin (VAN) in *Clostridium difficile* infection (CDI) in 2 randomized controlled trials (RCT) with 1105 patients [abstract 1417]. Presented at: The 48th Annual IDSA Meeting; October 21–24, 2010; Vancouver, BC, Canada.
15. Johnson S, Crook DW, Cornely DA, High KP, Miller M, Gorbach SL. Randomized clinical trial in *Clostridium difficile* infection confirms superiority of fidaxomicin over vancomycin [abstract 828630]. Presented at: Digestive Disease Week 2010; May 4, 2010; New Orleans, LA.
16. Louie TJ, Miller MA, Mullane, KM, et al for the OPT-80–003 Clinical Study Group. Fidaxomicin versus vancomycin for Clostridium difficile infection. *N Engl J Med*. 2011;364(5):422–431.