PSNet
PATIENT SAFETY NETWORK

Clostridium Difficile Relapse Secondary to Medication Access Issue

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The Case

A 24-year-old woman with history of HIV/AIDS [human immunodeficiency virus/acquired immunodeficiency syndrome] and diffuse B-cell lymphoma, actively receiving chemotherapy, was admitted with diarrhea and abdominal pain. The patient reported recent antibiotic use, and a stool sample was positive for *Clostridium difficile* toxin. As she had prior episodes of *Clostridium difficile*–associated diarrhea (CDAD), she was treated with oral vancomycin. She improved quickly and was discharged with a plan to complete a 14-day course of oral vancomycin. After being discharged, the patient took her discharge prescriptions to her usual retail pharmacy. However, the pharmacy informed her that the oral vancomycin solution had not been approved by her insurance, and she was unable to afford the considerable cost of paying for the medication out of pocket.

The patient contacted her primary care physician, and over the next 4 days, the nurses at the patient's primary care clinic spent many hours on the phone attempting to obtain coverage for the vancomycin solution. Despite contacting the medical director of the insurance plan, the approval was never finalized and during this time the patient received no treatment. Soon, her symptoms recurred. She was instructed to return to the emergency department, where a computed tomography scan was suggestive of toxic megacolon (marked dilation and inflammation of the colon secondary to uncontrolled infection). She was readmitted and re-started on oral vancomycin and intravenous metronidazole for treatment of severe CDAD. Fortunately, she improved with this regimen and did not require surgery. The plan again was to discharge her with a long course of oral vancomycin with a taper, as per the infectious disease service's recommendation.

During the readmission, a pharmacist was consulted in order to help the patient gain access to oral vancomycin in advance of discharge. The pharmacist contacted the patient's insurance and was informed that the vancomycin oral solution could only be filled at a compounding pharmacy, and that the patient's usual retail pharmacy (part of a national chain) could not perform this service. Eventually, after much effort,

an independent pharmacy was identified that could compound the medication and was contracted with the patient's insurance. Given the issues after her prior hospitalization, the patient remained hospitalized until a clear plan was in place to ensure her access to medication.

The independent pharmacy filled the oral vancomycin solution, which was delivered to the patient, and she was able to complete her treatment course. However, after the second discharge the inpatient pharmacist was contacted by the pharmacist at the patient's usual retail pharmacy. The outpatient pharmacist informed the inpatient pharmacist that a prescription for vancomycin oral capsules (not vancomycin solution) could have easily been filled after the initial discharge and would have been covered by the patient's insurance. Had this information been available, the patient might have been able to access the medication after the first discharge, potentially avoiding the patient's return of symptoms, the readmission, and the subsequent treatment costs.

The Commentary

Clostridium difficile infection (CDI) is the most common hospital-acquired infection and accounts for 250,000 cases, approximately 14,000 deaths, and an estimated 1 billion dollars of excess medical cost per year in the United States.(1) The treatment paradigm for CDI has shifted the last 10 years and will likely continue to change with the introduction of novel antibiotics, adjunct therapies, and vaccinations in clinical development. The utilization of oral vancomycin has become first-line therapy for patients with severe CDI, and utilization has increased by more than 200% the last decade.(2,3)

The definition of severe CDI is not universally consistent, and there are significant differences between Infectious Diseases Society of America, American College of Gastroenterology, and European Society of Clinical Microbiology and Infectious Diseases guidelines (Table).(4,5) However, all three guidelines advocate for vancomycin as first-line therapy for patients with severe disease. Zar and colleagues conducted the only randomized trial comparing vancomycin with metronidazole, stratifying results by CDI disease severity.(6) They demonstrated that vancomycin and metronidazole were equivalent for mild disease, but vancomycin was associated with improvements in clinical cure for severe disease (86% vs. 76%, p=0.02). No differences in the rate of recurrent disease were seen between agents. Disease severity was defined using a point system; patients with a score of ?2 were considered to have severe CDAD. (One point each was given for age >60 years, temperature >38.3° C, albumin level 15,000 cells/mm^3 within 48 hours of enrollment, and two points were given for endoscopic evidence of pseudomembranous colitis or treatment in the intensive care unit.) For the presented case of CDI in a 24-year-old immunosuppressed patient with diarrhea and abdominal pain, the utilization of vancomycin may have been appropriate depending on her laboratory markers and which CDI guideline the prescriber was following. However, the primary literature suggesting vancomycin is superior to metronidazole in immunocompromised patients is limited, and published correspondence questions the superiority of vancomycin.(7,8)

Compounding oral vancomycin suspension from the intravenous (IV) product is common practice at most hospitals as a method of delivering cost-effective therapy with equivalent outcomes to vancomycin capsules.(9) Oral vancomycin is now available as generic product; however, the average wholesale price is still approximately $30 per 125 mg capsule or $1,680 per 14-day treatment course.(10) Compounding oral vancomycin from the IV product reduces the cost to approximately $40 per 14-day treatment course, which

can save hospitals hundreds of thousands of dollars per year.

However, several potential problems may arise when a patient transitions out of the hospital while continuing oral vancomycin therapy. First, vancomycin suspension or capsules may not be covered by insurance providers or the co-pay may be unaffordable for patients. Second, some pharmacies cannot provide compounding services and are unable to direct the patient to a pharmacy that does offer this service, as seen in this case. Finally, vancomycin suspension can taste bitter and unpleasant, which may contribute to decreased compliance (flavoring can be added to improve tolerability). The resulting discontinuities in care often lead to post-discharge adverse events that cause morbidity and readmission, as in this patient.(11,12) Two-thirds of adverse events experienced by patients are adverse drug events, most of which could be prevented or ameliorated through better communication and coordination of care.(7)

When patients are discharged on oral vancomycin or with other unusual or nonstandard medication needs, there are several opportunities to minimize gaps in therapy and prevent adverse events. First, proactively identify unusual medication needs through medication review and discharge medication reconciliation—preferably performed by a pharmacist—and determine resources to meet those needs prior to discharge.(13,14) In this case, for example, discharge planning and the pharmacy department could be asked to create a list of area pharmacies that compound vancomycin. Pharmacies that offer compounding services prepare customized medications from pharmaceutical grade ingredients to accommodate a patient's specific medication needs that cannot be met by commercially available products. This includes preparing medications in alternative strengths or dosage forms when the commercially available products are not suitable, such as the oral vancomycin required for this patient. These pharmacies provide more flexibility and customization of medication therapy than typically available from pharmacies not offering compounding services.

Discharge planning and pharmacy should also create a list of insurance providers that cover compounded vancomycin suspension (or the unusual/nonstandard medication in question) and determine if prior authorization is needed. Information should be disseminated to medical staff, posted on hospital intranet sites, linked to institutional CDI treatment guidelines, and displayed in work areas for medical staff. Where possible, obtain prior authorization before discharge and engage discharge planners or the pharmacist actively following individual patients to assist with determining the co-pay for vancomycin capsules or suspension. If vancomycin is unaffordable or intolerable, consider alternative agents such as metronidazole or fidaxomicin. Fidaxomicin is a reasonable alternative for patients with mild and severe CDI. The pharmaceutical manufacturer of fidaxomicin currently offers a patient assistance program for those unable to afford medication.

At discharge, patients like the one in this case should be counseled about their medication and advised where to have unusual or nonstandard prescriptions filled. Telephone follow-up has been recommended as a means to reduce readmissions, particularly with high-risk patients; follow-up within 72 hours of discharge may help identify and resolve medication issues before adverse events ensue.(15)

Even if patients are able to access medications and are adherent to medications after discharge, approximately 20% of patients will have recurrent CDI, and some are highly likely to have multiple

recurrences. Limited data characterize the best treatment course for patients with multiple recurrences, but stool transplantation appears to be very effective. A prospective trial comparing stool transplant to vancomycin was stopped after interim analysis when the stool transplant group demonstrated significant improvement in clinical cure (93.8% vs. 30.8% with oral vancomycin and 23.1% with rectal vancomycin, p16) Stool transplant is not a substitute for appropriate antibiotic therapy for the treatment of acute CDI, but can be considered following resolution of symptoms. The process for transplantation varies among institutions and a consultation with a specialist performing stool transplantation could be considered for patients with multiple recurrences. However, in most cases of CDI—including severe episodes—appropriate antibiotic therapy should result in complete resolution of symptoms.

Take-Home Points

- Determine if vancomycin is appropriate therapy based on institutional or national guidelines. Patients might be candidates for oral metronidazole, which eliminates potential problems with outpatient oral vancomycin.
- Proactively identify unusual or nonstandard medication needs prior to discharge and collaborate with discharge planning and pharmacy to help identify resources to meet those needs. They can provide information regarding where to obtain unusual or nonstandard medications, such as oral vancomycin suspension, and determine affordability of these medications for patients with insurance coverage.
- If vancomycin is unaffordable or intolerable, consider alternative agents such as metronidazole or fidaxomicin.
- Consider post-discharge telephone follow-up to identify and resolve potential medication issues early.

Paul C. Walker, PharmD Clinical Professor and Director, Experiential Education and Community Engagement Manager, Pharmacy Patient Outcomes The University of Michigan College of Pharmacy The University of Michigan Hospitals and Health System

Jerod Nagel, PharmD, BCPS (AQID) Clinical Pharmacist, Infectious Diseases Adjunct Clinical Assistant Professor The University of Michigan College of Pharmacy The University of Michigan Hospitals and Health System

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Table

Table. Definitions of Severe Disease secondary to *Clostridium difficile* colitis.(4,5)

	Infectious Diseases Society of America Guidelines	**Gastroenterology Guidelines**	**European Society of Clinical Microbiology and Infectious Diseases Guidelines**
Severe Disease	• Leukocytosis with a white blood cell count of 15,000 cells/mm^3 or higher • Serum creatinine level greater than or equal to 1.5 times the premorbid level	Serum albumin • White blood cell count ? 15,000 cells/mm^3 • Abdominal tenderness	• Age >65 • Leukocytosis with a white blood cell count of 15,000 cells/mL • Albumin < 30g/L • Serum creatinine level greater than or equal to 1.5 times the premorbid level • Comorbidity (severe underlying disease and/or immunodeficiency)
Severe Disease with Complications	• Severe disease plus hypotension • Shock, ileus, megacolon	Any of the following attributable to CDI: • Admission to intensive care unit for CDI • Hypotension with or without required use of vasopressors • Fever ? 38.5° C • Ileus or significant abdominal distention • Mental status changes • White blood cell count > 35,000 or 3 • Serum lactate levels > 2.2 mmol/L • End organ failure	Not Categorized

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