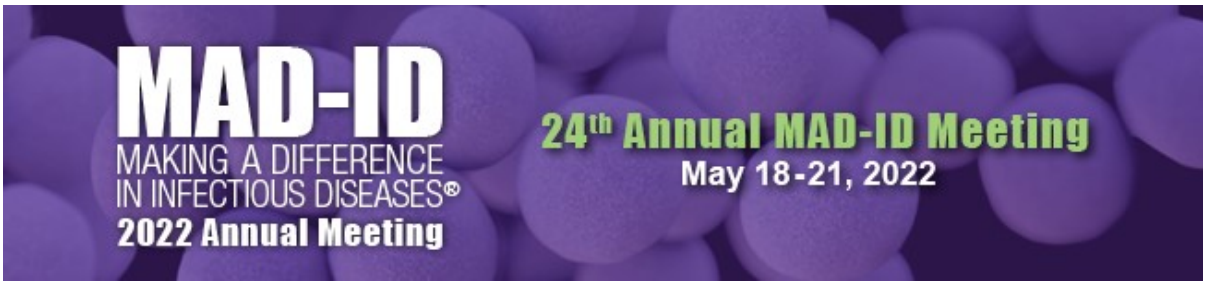
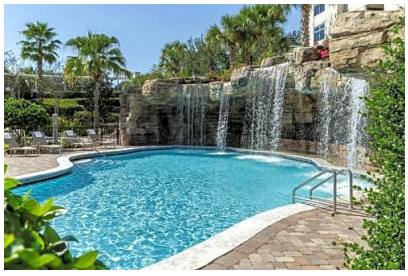




MAD-ID 2022 is Just Around the Corner

The MAD-ID Team is making final touches on plans for the 2022 Conference, May 18-21, 2022, at the Hyatt Regency Orlando in Orlando, Florida.

Click Here for the Full Announcement

Don't Miss These Outstanding Speakers Live at MAD-ID 2022!

Interactive Workshops

Wednesday Workshops

Leading Teams, Building Resilience
John Allen, PharmD

How to Implement the Science of AMS
Valeria Fabre, MD

How to Set Up Penicillin Delabeling Programs, Documenting Success
Bruce Jones, PharmD

How to Implement AMS in ED / UC Settings
Larissa May, MD, MSPH, MSHS

Plenary Session Speakers

Thursday Sessions

Keynote Presentation: Antimicrobial Stewardship for the Patients We Serve
Matthew B. Goetz, MD

What's New with COVID-19?
Payal Patel, MD, MPH
Amy Dzierba, PharmD

C. difficile Infections: Past, Present, and Future
Colleen Kelley, MD
Kevin Garey, PharmD

Scientific Poster Session and Reception

Friday Sessions

Thursday Workshops

How to Treat Patients Equitably and Influence People: Strategies for Infectious Diseases Engagement and Outreach
Erin McCreary, PharmD

Implementing Short Course Antimicrobial Therapy
David Ha, PharmD

HIV Stewardship, The Importance of Optimizing Therapy
Meshell Maxam, PharmD

How to Implement A Transitions of Care Program
Nick Mercuro, PharmD

Plus Special Events for Trainees Only, Wednesday afternoon!

Surviving Sepsis
Kee Kee Buckley, Patient advocate and survivor
John Allen, PharmD

Implementing Diagnostic Stewardship in 2022
Kimberly Claeys, PharmD
Kaede Ota Sullivan, MD, MSc

Gram Negative Pathogens, Optimizing Therapeutics
David van Duin, MD, PhD
Jason Pogue, PharmD

Carbapenem Therapy; What Does the Future Hold?
Katie Barber, PharmD
Jason Pogue, PharmD

Saturday Sessions

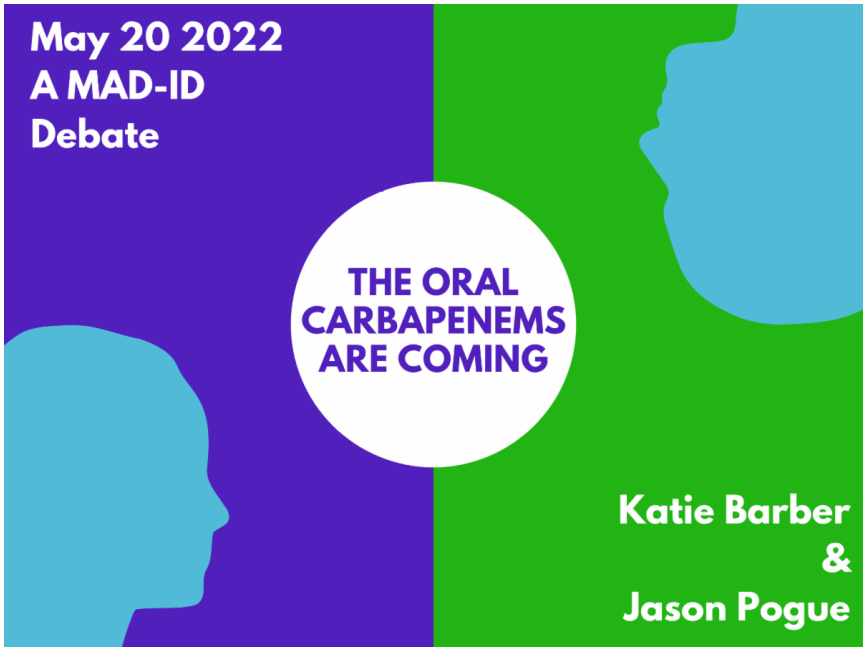
Coming Attractions: Innovations in HIV and Fungal Therapy
Meshell Maxam, PharmD
Greg Eschenauer, PharmD

Hot Topics and Burning Questions
Erin McCreary, PharmD
Emily Heil, PharmD, MS

Meet the Professors

Register for MAD-ID Here

Don't miss all the great topics happening at MAD-ID 2022. Keeping with tradition, this year's agenda will feature an epic debate to answer the question: The oral carbapenems are coming, are you excited or anxious?



Celebrating ID Pharmacists Day on May 22nd 2022

MAD-ID is excited to partner with the Society of Infectious Diseases Pharmacists and other organizations for the second year to celebrate ID Pharmacists Day. Share your stories and join in the activities!

SIDP's ID Pharmacist Day Resource Page

Continuing Education Feature

Secondary *Clostridioides difficile* prevention
To prophylax or not prophylax, that is the question

Authors: Amanda Lefemine, PharmD; Melanie Rae Schrack, PharmD

Disclosures: Doctors Lefemine and Schrack have no conflicts of interest to disclose relevant to this learning activity. This activity will discuss the unapproved use of oral vancomycin and fidaxomicin for *Clostridioides difficile* prophylaxis.

Learning Objectives:
At the end of this article, learners will be able to
1. Explain the benefits utilizing oral vancomycin for *Clostridioides difficile* prophylaxis

2. Explain the potential risks of utilizing oral vancomycin for *C. difficile* prophylaxis
3. Identify high-risk patients who may warrant *C. difficile* prophylaxis
4. Select an appropriate antimicrobial regimen for *C. difficile* prophylaxis

Disclaimer: The information contained in this newsletter is emerging and evolving because of ongoing research and is subject to the professional judgment and interpretation of the practitioner. We are not responsible for the continued currency of the information, for any errors or omissions, and/or for any consequences arising from the use of the information in any practice setting.

Introduction

Clostridioides difficile infections (CDIs) are commonly encountered by healthcare professionals in both the community and hospital setting. In 2017, hospital-associated CDIs alone were responsible for 12,800 associated deaths and one billion dollars in healthcare-associated costs. From 2001 to 2012, the annual incidence of CDI increased by 43%, and the annual rate of recurrent CDI increased by 189%.[1] Risk factors for recurrent CDI include antibiotic use, healthcare exposure, advanced age, immunocompromising conditions, chemotherapy, and gastric acid suppression therapy.[2] Due to the unavoidable risk factors and high incidence of recurrent CDI, secondary prophylaxis may have a role in select patient populations.

There are several clinical practice guidelines that address the treatment of CDI but lack strong evidence to make recommendations regarding secondary prophylaxis. The 2017 Infectious Diseases Society of America (IDSA) CDI guidelines acknowledge the insufficient data to recommend restarting an anti-CDI agent empirically for patients on antibiotics.[2] The 2021 American College of Gastroenterology (ACG) CDI guidelines state that oral vancomycin prophylaxis could be considered in patients with a history of CDI at high risk for recurrence during a subsequent systemic antibiotic exposure, but this is a conditional, low quality evidence recommendation.[3] Finally, the 2021 European Society of Clinical Microbiology and Infectious Diseases CDI guidance recommends against routine prophylaxis except in patients with a history of multiple recurrent CDI.[4] This review will summarize key studies that either support or oppose the use of CDI prophylaxis.

Stewardship Opportunities

Antimicrobial stewardship is the cornerstone for CDI prevention and should be optimized prior to considering a prophylactic agent. It is important to assess if empiric antibiotics can be streamlined, the appropriate duration is utilized, or unwarranted antibiotics can be stopped. A recent, large-scale study of 192 hospitals in the United States assessed antimicrobial utilization and found that 56% of patients received unsupported antimicrobials. Inappropriate antibiotics were prescribed for 77% of the 452 urinary tract infections that were included and 80% of the 219 community-acquired pneumonias that were assessed.[5] A retrospective chart review of 210 patients with a diagnosis of CDI compared antibiotic prescribing pre- and post-CDI diagnosis and demonstrated that a history significant for CDI does not affect prescribing habits. The authors found that the rate of inappropriate antibiotics did not differ between the two groups: 40.6% pre-CDI versus 43.1% post-CDI ($p = 0.71$).[6] These studies further highlight the continued need for optimizing stewardship.

Support of Secondary Prophylaxis

Tolerability of *C. difficile*-targeted Antimicrobials

Treatment of *C. difficile* has historically included vancomycin, fidaxomicin, and metronidazole. Because of their site of action, these agents are consistently associated

with gastrointestinal (GI) side effects. However, this is often self-limiting with little impact on a patient's quality of life. Oral vancomycin and fidaxomicin both have low systemic absorption, but oral metronidazole has high bioavailability and exhibits additional systemic side effects including a potential for cumulative, irreversible neurotoxicity.[7] Because of the tolerability concerns with metronidazole and studies showing its inferior efficacy compared to vancomycin, it is no longer recommended first-line in the CDI treatment guidelines.[2,3] For these reasons, it is used infrequently for CDI prophylaxis, and the remainder of this review will focus on oral vancomycin and fidaxomicin

Major differences between vancomycin and fidaxomicin include their spectrum of activity and cost. Vancomycin is a broader spectrum agent which can lead to dysbiosis and loss of beneficial enteric flora compared to fidaxomicin.[2] However, vancomycin is more accessible with an average wholesale price (AWP) of $31.31 per dose compared to $268.51 for brand name fidaxomicin. This cost difference is likely to narrow as time passes from fidaxomicin's approval by the Food and Drug Administration in 2011.[7]

C. difficile Infection Recurrence

The estimated risk of CDI recurrence after an initial episode is 10-30%, and this risk increases further with the use of systemic antibiotics.[3] The goal of *C. difficile* secondary prophylaxis is to prevent recurrence, and several retrospective analyses evaluating the effect of oral vancomycin prophylaxis (OVP) on CDI recurrence rates have been published. A meta-analysis by Tariq and colleagues included ten studies from 2015 to 2019, accounting for a total of 713 patients who received OVP and 8,545 patients in the control group that received no prophylaxis. The pooled odds ratio for recurrence favored OVP at 0.34 (95% confidence interval (CI) 0.20 to 0.59). There was a notable degree of heterogeneity between the groups (I^2 = 59%), although seven of the studies independently showed a statistically significant lower odds of recurrence.[8]

One prospective study assessing OVP has been published by Johnson and colleagues. This was a single-center, randomized, open-label study in patients at high risk for developing CDI. Only one of these patients had a prior episode of CDI documented. Patients were considered high-risk if they were aged 60 years or older, were hospitalized within the prior 30 days, and received systemic antibiotics during the prior admission as well as the current admission. Patients randomized to the treatment group received OVP 125 mg daily until five days after completion of systemic antibiotics. A total of 50 patients were included in each group. Healthcare-onset CDI was defined as at least three loose stools in 24 hours plus a positive stool polymerase chain reaction (PCR) test for *C. difficile* at least 72 hours after admission. This occurred in 12% of the control group compared to none in the OVP group (p = 0.03).[9] These results support the use of low dose OVP in patients at high risk for CDI started on systemic antibiotics while inpatient. While this study focused on primary prophylaxis, it is the only prospective study published to date on this subject, and many patients with a history of CDI that are started on systemic antibiotics in the hospital would meet the inclusion criteria and could be predicted to have similar outcomes.

Most prophylaxis studies have used oral vancomycin since this agent has historically been more accessible to patients. However, the new focus on fidaxomicin in the updated CDI treatment guidelines, along with its narrower spectrum, make fidaxomicin an attractive new option for CDI prophylaxis. The DEFLECT-1 study was a randomized, double-blind, placebo-controlled trial evaluating fidaxomicin as primary CDI prophylaxis after hematopoietic stem cell transplant.[10] All patients included were taking a fluoroquinolone for bacterial infection prophylaxis and randomized to receive placebo or fidaxomicin 200 mg daily until seven days after engraftment or completion of antimicrobials. CDI was defined

by greater than three loose stools in 24 hours plus a positive stool *C. difficile* toxin or PCR test. There were 301 patients included in the fidaxomicin group and 299 in the placebo group; 194 and 192 patients completed the prophylaxis treatment, respectively. There was no difference in the primary outcome of prophylaxis failure between the fidaxomicin and placebo groups (28.6% vs 30.8%; p = 0.278); however, in a sensitivity analysis, confirmed *C. difficile*-associated diarrhea (CDAD) was significantly lower in the fidaxomicin group at 4.3% compared to 10.7% with placebo (p = 0.0014).[10] This study supports the hypothesis that fidaxomicin decreases the risk of CDAD in patients on systemic antibiotics after hematopoietic stem cell transplant and encourages further evaluation of fidaxomicin as a CDI prophylaxis agent.

The majority of published data support the use of *C. difficile*-targeted antimicrobials as an effective measure to prevent CDI occurrence and recurrence in a variety of high-risk populations. This decrease in CDI has two major potential impacts: improved quality of life and decreased overall healthcare cost. Quality-of-life scores decrease further in patients with CDI recurrence compared to patients with an initial episode, making secondary prophylaxis a top priority.[2] Likewise, the cost of managing a CDI recurrence is significantly higher compared to a patient's initial episode.[11]

Cost-Effectiveness of Secondary Prophylaxis

Costs associated with treatment of a CDI recurrence include both diagnostic and therapeutic expenditures. The estimated total cost of managing a primary CDI episode has been reported to range from $2,871 to $4,846, compared to $13,655 to $18,067 for recurrent CDI.[11] This significant cost burden is notably more expensive than the cost of preventing one recurrence, which is estimated to range from $868 to $11,324 based on durations of prophylaxis and the number needed to treat from available studies (see Table 1). The stated cost of preventing one recurrence may be overemphasized since many institutions can procure oral vancomycin at a price less than AWP.[7] Nevertheless, this suggests that using OVP is a cost-effective intervention with the potential to save $2,331 to $17,199 in healthcare costs for every three to seven patients treated.

Table 1. Estimated Cost of Preventing One Recurrence

Number needed to treat to prevent one recurrence[12-16]	3.3 - 6.6 patients
Estimated duration of secondary CDI prophylaxis[13,17]	8.4 - 13.7 days
Daily cost of OVP 125 mg once to four times daily (based on AWP)[7]	$31.31 - $125.24
Estimated total cost of preventing one recurrence	$868 - $11,324

Pitfalls of Secondary Prophylaxis

Antibiotics are a well-known risk factor for causing *C. difficile* infections, so it can seem counterintuitive to add an additional antibiotic for secondary prophylaxis. Vancomycin and fidaxomicin are often used when prophylaxis is employed for patients with a history of CDI. Considerations for prophylactic antibiotics include the potential for dysbiosis and colonization with resistant organisms.

The Dysbiosis Effect

Dysbiosis, the disruption of microbiota normal flora, can occur when a patient is exposed to an antimicrobial that disturbs the intestinal tract microbiome. Once disrupted, opportunistic intestinal pathogens, like *C. difficile*, have an optimal environment to

proliferate and outgrow other organisms. After CDI, time to microbiota recovery differs between patient to patient; one's microbiome may never fully recover before subsequent antibiotic exposure restarts the dysbiosis cycle.[18] Understanding dysbiosis caused by OVP is important to consider prior to initiation.

Multiple different vancomycin dosing regimens have been implicated with a negative effect on dysbiosis. A double-blind, randomized control trial characterized the effects of oral vancomycin 125 mg four times daily for 10 days on intestinal microbiota in patients colonized with *C. difficile.* Vancomycin was considered prophylactic as most patients received other antibiotics outside of the trial concomitantly. Patients who received vancomycin experienced a statistically significant microbiome shift compared to placebo ($p = 0.005$). Interestingly, 71% of patients in the vancomycin group had *C. difficile* cultured in their stool after 10 days of vancomycin, which indicates that oral vancomycin may not eradicate *C. difficile.*[19] The dysbiosis effect of vancomycin combined with the non-eradicated *C. difficile* hypothetically creates the perfect environment for a recurrent infection to occur when OVP is stopped.

Knowing the drastic change that vancomycin can have on intestinal microbiota, Isaac and colleagues sought to examine the time to microbiome recovery to distinguish if dysbiosis is a short- or long-term effect. Patients were included if they had no antibiotic exposure in the last 3 months and received oral vancomycin 250 mg four times daily for 2 weeks. When measuring the impact on operational taxonomic units in the patient's fecal analysis, the authors found that patients receiving vancomycin had a significant depletion of their Bacteroidetes phylum after 2 weeks of treatment ($p < 0.01$). They also noted that their operational taxonomic units of the Proteobacteria phylum, which are associated with human infections, significantly increased in the vancomycin group ($p < 0.01$). Ultimately these findings suggest that the slow microbiome recovery varies vastly from patient to patient, and vancomycin's negative effects can be seen up to 22 weeks after cessation of antibiotics.[20] Further studies are needed to characterize the dysbiosis effects and time to microbiome recovery of lower-dosed OVP.

Risk of Resistance

Another potential downfall of utilizing OVP is the risk of vancomycin-resistant *Enterococcus* spp. (VRE). A strong association with vancomycin treatment and VRE colonization has been described in a meta-analysis; however, a longer duration of hospitalization was observed in the VRE group which may have confounded these results.[21] In a retrospective cohort study, an automated alert was utilized to recommend oral vancomycin 125 mg twice daily in patients who were receiving systemic antimicrobials and had a history of CDI. Surveillance cultures were obtained from either urine or superficial wounds to monitor the acquisition of VRE isolates. The authors found a statistically significant increase in both VRE isolates in the 3 months following prophylaxis and in the ratio of VRE to vancomycin-susceptible *Enterococcus* in surveillance cultures (x^2, 0.003). During this study, there were 16 VRE-associated infections in the prophylaxis group versus 9 in the comparator group.[17] The rates of VRE colonization were also assessed in a more recent study of critically ill COVID-19 patients. An OVP protocol was implemented with a dose of 125 mg once daily compared to a pre-pandemic control group that received no prophylaxis. This study found a nonsignificant increase in VRE detection in non-gastrointestinal samples in COVID-19 patients who received prophylaxis ($p = 0.132$).[22] While OVP may be warranted in high-risk patients, it should be considered carefully due to a possible increased risk of VRE colonization.

Other studies have found no difference in VRE colonization rates when OVP is used. A study on secondary prophylaxis with oral vancomycin 125 mg twice daily in hematopoietic

stem cell transplant recipients with a hematologic malignancy evaluated the incidence of VRE compared to patients without secondary prophylaxis. The rate of recurrent CDI was significantly lower in the prophylaxis group without a statistically significant increase in rates of VRE ($p = 0.016$; $p = 0.686$).[16] Finally, a one-to-one randomized, prospective, open-label study of 100 patients receiving systemic antimicrobials evaluated OVP 125 mg once daily compared to no prophylaxis. The secondary endpoint was the incidence of VRE colonization by perirectal swab. 42% of the OVP group were colonized at baseline and no patients in this group developed new colonization prior to discharge. Unfortunately, only 64% of the patients were evaluated due to patient refusal or follow-up swab not being collected, limiting these results.[9] When reviewing the literature, it is important to note the differences in dosing strategies and whether colonization or infection was evaluated. Larger, randomized-controlled trials are needed to assess the risk of VRE, whether VRE colonization translates to an increase in VRE infections, and ultimately if the risk of VRE outweighs the benefit of preventing a recurrent CDI in patients who receive OVP.

Application to Clinical Practice

Evidence supporting secondary CDI prophylaxis for patients on systemic antibiotics has increased, and with this new interest, additional questions have arisen. Questions that remain include which patient populations stand to benefit the most, optimal dosing, and duration of secondary prophylaxis.

Patient Selection

The definition of “high-risk” in relation to CDI recurrence has various interpretations throughout the literature. Populations of interest include immunocompromised patients, patients over the age of 65 years, and those with frequent or recent antimicrobial exposure. This is reflected in the ACG guidelines, which recommend consideration of prophylaxis for patients that have been hospitalized for severe CDI within the prior 3 months and are aged 65 years or immunocompromised.[3] The IDSA guidelines recommend considering the length of time from previous CDI treatment, number and severity of previous CDI episodes, and underlying frailty of the patient when making the decision of whether to start prophylaxis.[2] An additional factor to consider is current antimicrobial therapy since longer durations, multiple antibiotics, and broader-spectrum agents are associated with higher risk of developing CDI. Antibiotics identified to be the highest risk include clindamycin, fluoroquinolones, third- and fourth-generation cephalosporins, and carbapenems.[2] Because the ideal target patient population for CDI prophylaxis is not well defined, it would be prudent to use a patient-specific approach when evaluating risks and benefits in patients with a history of CDI. Patient age, immunocompromised status, details of prior CDI episode(s), and current antimicrobial therapy should be assessed when making the decision of whether to use prophylaxis.

Oral Vancomycin Prophylaxis Dosing

The IDSA guidelines recommend oral vancomycin 125 mg once daily or fidaxomicin 200 mg once daily for secondary prophylaxis while antibiotics are administered, while the ACG guidelines recommend OVP 125 mg once daily to be continued until 5 days after completion of systemic antibiotics.[2,3] A wide range of dosing strategies have been reported in studies and are summarized in table 2. The doses and duration from these eleven studies are consolidated in tables 3 and 4. The most common OVP dose used was 125 mg, ranging from one to four times daily. The duration of OVP was most commonly five to seven days after completion of systemic antibiotics. Based on the guidelines and published studies,

using OVP 125 mg one or two times daily for five to seven days after completion of systemic antibiotics is reasonable.

Table 2. Oral Vancomycin Prophylaxis Dosing Strategies

Study	Population	Prophylaxis	Systemic Antibiotics	# Patients in Study	Dose	Duration
Carignan 2016[12]	-	Secondary	✓	190	125 mg QID	Median = 7 days
Connor 2020[15]	Critically ill	Secondary	✓	7	125 mg BID	
				5	125 mg QID	
				4	250 mg QID	
Ganetsky 2018[23]	HSCT	Primary	Not reported	90	125 mg BID	Duration of admission Median = 28.5 days
Johnson 2020[9]	Age ≥ 60 years + recent admission with antibiotics	Primary	✓	50	125 mg QD	5 days after antibiotic complete Mean = 12 days
Knight 2020[14]	-	Secondary	✓	22	250 mg QID	Duration of antibiotics
				10	125 mg QID	Median = 8.5 days
Morrisette 2019[16]	Hematologic malignancy	Secondary	✓	21	125 mg BID	≤ 7 days after antibiotic complete
Papic 2018[24]	≥ 65 years	Primary	✓	71	125 mg QD	Median = 9 days
Splinter 2018[25]	Renal transplant	Secondary	✓	12	125 mg BID	Mean = 19 days
Van Hise 2016[13]	-	Secondary	✓	29	125 mg BID	≤ 7 days after antibiotic complete Mean = 13.7 days
				42	250 mg BID	
Zachariodakis 2020[17]	-	Secondary	✓	264	125 mg BID	Mean inpatient = 8.4 days

Table 3. Summary of OVP Dosing Regimens

Dosing Regimen	N
125 mg QD	121
125 mg BID	423
125 mg QID	205
250 mg BID	42
250 mg QID	26

Table 4. Summary of OVP Duration

Duration	N
Duration of antibiotics	32
5 days after	50
Up to 1 week after	92

Conclusion

The use of secondary prophylaxis for *C. difficile* remains a clinical grey area, but emerging data are now available to assist with selection of patients at highest risk for recurrence. The use of OVP may help decrease the risk of CDI recurrence and should be considered in patients with a history of CDI started on systemic antibiotics. Special consideration should be given to patients with an age 65 years and older, immunocompromising conditions, recent or severe prior CDI episodes, and those on broad-spectrum antibiotic therapy. Future studies addressing the optimal population, dose, and duration of OVP would be beneficial. Additionally, further evaluation of fidaxomicin as a prophylactic agent is warranted.

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This is Knowledge-based activity.
Target audience: pharmacists and other healthcare providers

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Self-Assessment Questions

To be completed online (http://mad-idtraining.org/newsletter/) or, in the case of non-MAD members, printed and mailed. You must achieve a grade of 80% of better to receive continuing education credit. Please also provide your honest assessment of the value of this learning activity so that we can continue to improve our offerings.

Read this patient case to answer questions 1 through 2:

JM is a 66-year-old male with a past medical history significant for a left renal transplant 4 months ago. He continues on triple immunosuppressive therapy with tacrolimus, mycophenolate mofetil, and prednisone. JM had a recent admission 4 weeks ago for treatment of pyelonephritis that was complicated by a severe CDI. He completed 10 days of vancomycin for this and was doing well until his current presentation with fever, dysuria, and altered mental status. He denies any diarrhea, nausea, or abdominal pain. The patient's chart notes a history of vancomycin infusion reaction. The team starts him on ceftriaxone empirically, and given his history, asks you about oral vancomycin for secondary CDI prophylaxis.

1. Which of the following is true?
a. Oral vancomycin should be avoided in this patient since they have history of an adverse reaction to intravenous vancomycin
b. Oral vancomycin prophylaxis could help decrease the risk of CDI recurrence
c. Oral vancomycin prophylaxis should not be used since it is not cost-effective
d. Since the patient came in with a fever and had a recent CDI, they should be started on CDI treatment

2. Which of the following potential risks would you consider when deciding whether to use oral vancomycin prophylaxis?
a. Dysbiosis
b. Increased risk of side effects including neurotoxicity
c. Acquisition of resistant organisms
d. A & C

Read this patient case to answer questions 3 through 5:

PT is a 59-year-old female with a past medical history significant for acute myeloid leukemia, major depressive disorder, treatment for community-acquired pneumonia 4 weeks ago, and 2 previous *C. difficile* infections with the most recent infection 3 weeks prior that required hospitalization. She is now admitted to the hospital for febrile neutropenia. She is febrile to 104°F on admission, hypotensive requiring IV fluids, and two blood cultures were collected prior to starting empiric cefepime. Gram-negative rods are identified on the blood culture gram stain and rapid diagnostic testing identifies *Pseudomonas aeruginosa*.

3. PT is at high-risk for a recurrent *C. difficile* infection. Which of the following is not one of PT's risk factors?
a. Immunocompromised

b. Age
c. Broad spectrum antibiotic
d. History of severe CDI

4. The team would like to start oral vancomycin prophylaxis since the patient is at high-risk for a recurrent episode, what dosing regimen would you recommend?
a. Vancomycin 125 mg PO QID
b. Vancomycin 125 mg PO QD
c. Vancomycin 250 mg PO QID
d. Vancomycin 250 mg PO BID

5. PT has just completed therapy for her *P. aeruginosa* bloodstream infection. The team asks you how much longer she should remain on her prophylactic vancomycin now that she has completed her systemic treatment?
a. Stop prophylaxis when the systemic antibiotic is completed
b. Continue for 14 days after completion of the systemic antibiotic
c. Continue for 5-7 days after completion of the systemic antibiotic
d. Continue prophylaxis for the remainder of her chemotherapy

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