Clinical Infectious Diseases

EDITORIAL COMMENTARY

Potential Risks and Rewards With Prophylaxis for *Clostridium difficile* Infection

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(See the Brief Report by Van Hise et al on pages 651–3.)

Keywords. prophylaxis; *Clostridium difficile*; CDI.

Antibiotics have long been recognized as a major risk factor for symptomatic infection with *Clostridium difficile* [1]. Antibiotics have also been shown to adversely affect both the cure rate of treatment for *C. difficile* infection (CDI) when given concurrently with specific treatment for CDI as well the subsequent recurrence rate when given shortly after treatment for CDI [2]. Antibiotics have profound effects on the richness, diversity, and evenness of the host microbiota, which can lead to loss of "colonization resistance" normally provided by the microbiota [3]. Given the importance of concomitant antibiotics on the outcome of CDI treatment, the Society for Healthcare Epidemiology of America/Infectious Diseases Society of America clinical practice guidelines for CDI considered the following clinical situations but had no evidence on which to base specific recommendations on extension of CDI treatment or reinstitution of empiric CDI treatment [4]. It is recognized that some patients will be continued on systemic antibiotics after completion of treatment for CDI in order to finish treatment for infections requiring prolonged antibiotic administration (eg, osteomyelitis and endocarditis). Based on opinion only, the Expert Panel suggested that if clinicians chose to prolong CDI treatment in this situation, vancomycin was the preferred agent given the lack of detectable metronidazole fecal concentrations after resolution of diarrhea. The other frequently encountered situation is after successful resolution of CDI when patients are readministered systemic antibiotics for a new incident infection. The guidelines were silent on recommendations for empiric CDI treatment in this second scenario.

Is there a downside to extension of treatment for CDI in patients who cannot discontinue systemic antibiotics or in reinitiating empiric CDI treatment in patients in whom systemic antibiotics are reintroduced? While there is a consensus that vancomycin would be preferable over metronidazole in these situations, increasing evidence shows that vancomycin itself has a profound effect on the microbiota of the host and delays recovery of a protective microflora [5–8]. In the early 1990s we attempted to eradicate asymptomatic *C. difficile* colonization (fecal excretion) in a group of patients as a potential infection control intervention in the hospital [9]. Thirty patients were randomized to a 10-day course of vancomycin, metronidazole, or placebo. On day 10 only 1 of the vancomycin-treated patients had detectible *C. difficile* in the stool by culture, and high fecal levels of vancomycin were documented. However, 8 of 9 vancomycin-treated patients began to excrete *C. difficile* again within 3 weeks of treatment completion. At the end of the 2-month follow-up period, vancomycin-treated patients were more likely to be positive for *C. difficile* than the placebo-treated patients (67% vs 11%). The results of the metronidazole-treated group mirrored the placebo results. The reasons for this paradoxical increased susceptibility to CDI or colonization following vancomycin treatment was elucidated recently in a detailed study of the microbiota of mice pretreated with vancomycin and/or metronidazole followed by sequential challenge with *C. difficile* spores [8]. Unlike metronidazole, vancomycin facilitated colonization with *C. difficile* from 3 days to >2 weeks after treatment cessation. This loss of colonization resistance was even more profound and long-lasting after combination treatment with vancomycin and metronidazole. In parallel to the susceptibility to *C. difficile* colonization, vancomycin treatment resulted in major changes in the murine microbiota; Bacteroidales S24-7 taxa became undetectable and overgrowth occurred with *Enterococcus*, Proteobacteria, and some *Lactobacillus* and *Clostridium* members. Pretreated mice were also challenged in separate experiments with vancomycin-resistant *Enterococcus faecium*, carbapenem-resistant *Klebsiella pneumoniae*, and *Escherichia coli*. Again, vancomycin treatment facilitated colonization with all 3 of these nosocomial pathogens.

Despite these potential concerns of vancomycin prophylaxis for subsequent antibiotic exposure in patients with prior CDI, Van Hise et al conducted a

Received 21 June 2016; accepted 22 June 2016; published online 28 June 2016.

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Clinical Infectious Diseases® 2016;63(5):654–5

 DOI: 10.1093/cid/ciw424

retrospective cohort study, published in this issue of *Clinical Infectious Diseases*, in a large community teaching hospital which suggested that this approach may be beneficial . This electronic medical record review identified 580 patients over a 5-year time period who had evidence of prior CDI and who were subsequently hospitalized and given systemic antibiotics. A recurrent CDI episode was defined as a positive stool *C. difficile* polymerase chain reaction assay and documentation of loose stools or diarrhea within 4 weeks of stopping the systemic antibiotics. The rate of recurrent CDI (4.2%) among patients given oral vancomycin prophylaxis (OVP) was significantly lower than the rate among patients not given OVP (26.6%). Although the authors state that the decision to give OVP was left up to the individual practitioners, it appears that some OVP protocol was in place at this hospital as the OVP cohort included only 2 specific regimens, 125 mg twice daily and 250 mg twice daily. It is interesting to note that among the 3 recurrent CDI cases in the OVP group, 2 of these cases had received the higher-dose OVP regimen. As pointed out by the authors, the major limitation of this study was its retrospective nature, and the results may have been subject to unknown biases that dictated administration of OVP. Nevertheless, this study gives impetus to design a prospective, randomized trial that could confirm or reject these findings and potentially define an optimal regimen for OVP.

What might be the optimal drug, regimen, and appropriate patient population for prophylaxis? With the increasing recognition of vancomycin's effect on the host microbiota [5–8] and clinical experience showing that symptoms can be suppressed following treatment with doses as low as 125 mg once daily [10], using a low dose of vancomycin seems prudent. There was a hint in this study that higher doses of vancomycin were less effective, but could the effective dose be even lower than the lowest dose used in this study (eg, 125 mg once daily)? The optimal duration of prophylaxis is also unknown, but the mean duration following discontinuation of systemic antibiotics in this study was 0.8 days and limiting the duration of vancomycin might also be important. How long is a patient at risk for recurrent CDI when subsequently given systemic antibiotics? The mean period of time between the previous CDI episode and subsequent hospitalization and antibiotic exposure in this study was between 6 and 7 months. Whereas most spontaneous CDI recurrences occur within weeks of stopping treatment for the prior episode [11], many patients who are successfully treated for CDI are still at risk for an unknown period of time (but at least for several months) if given subsequent antibiotics [10].

Finally, could fidaxomicin be even a better choice for prophylaxis? This drug has less effect on the host microbiota than vancomycin and recurrent CDI is less frequent following treatment with fidaxomicin [6]. A prospective, randomized, placebo-controlled trial of fidaxomicin prophylaxis among a very challenging population has recently been reported in abstract form [12]. This study (DEFLECT-1, ClinicalTrials.gov identifier NCT01691248) compared fidaxomicin 200 mg daily to placebo in 600 patients undergoing hematopoietic stem cell transplant and receiving fluoroquinolones. Full analysis of data from this trial may point toward a role for fidaxomicin in prophylaxis against CDI.

Note

Potential conflict of interest. Author certifies no potential conflicts of interest. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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