Antimicrobial Stewardship News

Volume 7, Number 3

March 2018

C the Diff: What's New in the 2017 IDSA/SHEA Clinical Practice Guidelines for *Clostridium difficile* Infection

Introduction

Clostridium difficile is a common hospital-acquired infection, representing a significant public health problem in the U.S and an important outcome to target for antimicrobial stewardship. The Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) recently published updated guidelines on the diagnosis and treatment of *C. difficile* infection (CDI).[1] This newsletter summarizes the updates that are most relevant for antimicrobial stewardship programs.

Updated Clinical Definitions:

The 2017 IDSA/SHEA guidelines provide updated clinical definitions for CDI severity based on risk factors previously correlated with disease severity and treatment outcomes.[1-4] Specifically, "mild-to-moderate" CDI is now referred to as "non-severe", and "severe and complicated" CDI is now referred to as "fulminant". Additionally, the serum creatinine (SCr) cutoff for determining severe versus non-severe disease was previously 1.5 times greater than baseline. This cutoff has been changed to an absolute value of 1.5 mg/dL, since baseline values are not always readily available.

Updated Treatment Recommendations:

1) Downgrade of metronidazole as "alternate" first-line therapy for non-severe CDI: This is the most dramatic practice change recommended in the new guidelines. For 30 years, metronidazole was considered a first-line agent for treatment of CDI. However, two randomized, placebo-controlled trials showed that oral vancomycin was superior to metronidazole across all degrees of disease severity.[5,6] The first study assessed clinical cure rates in 150 patients and demonstrated that clinical cure was superior for patients given oral vancomycin (97%) compared to metronidazole (84%, p<0.006).[6] Of note, clinical cure superiority was also observed in 69 patients with severe disease given vancomycin (97%) compared to metronidazole (76%, p=0.02).[6] The second study demonstrated that clinical response rates were inferior with metronidazole (72.7%) compared to vancomycin (81.1%, p=0.02).[5] More recently, two retrospective studies of hospitalized patients found that metronidazole was inferior to vancomycin for treatment response in patients with mild-to-moderate CDI.[7,8] Based on these data, the 2017 guidelines recommend oral vancomycin or fidaxomicin as first line agents for non-severe CDI.[1] Metronidazole is provided as an alternative agent only appropriate for non-severe disease in settings where access to vancomycin or fidaxomicin is limited (Table 1).

Table 1. CDI Treatment Recommendations for Adults[1]

Episode	2017 IDSA/SHEA Guidelines
Initial	**Non-severe**: WBC ≤ 15K ***and*** SCr ≤ 1.5 mg/dL ▪ vancomycin 125mg PO q6h x 10d ▪ fidaxomicin 200mg PO q12h x 10d ▪ *Alt:* metronidazole 500mg PO q8h x 10d[a]
	Severe: WBC > 15K ***or*** SCr > 1.5 mg/dL ▪ vancomycin 125mg PO q6h x 10d ▪ fidaxomicin 200mg PO q12h x 10d
	Fulminant: hypotension, shock, ileus, megacolon ▪ vancomycin 500mg PO/NG q6h ▪ *plus* metronidazole 500mg IV q8h ▪ *plus* vancomycin 500mg/100mL NS rectal enema q6h (if ileus)
First Recurrence	▪ vancomycin 125mg PO q6h x 10d[b] ▪ vancomycin 125mg PO q6h x 10-14d, q12h x 7d, q24h x 7d, q2-3d x 2-8w[c] ▪ fidaxomicin 200mg q12h x 10d[d]
Second Recurrence	▪ vancomycin in a tapered and pulsed regimen ▪ vancomycin 125mg PO q6h x 10d followed by rifaximin 400mg q8h x 20d ▪ fidaxomicin 200mg PO q12h x 10d ▪ fecal microbiota transplantation

WBC, white blood cells; SCr, serum creatinine; NS, normal saline; NG, nasogastric tube
[a] recommended only if access to vancomycin and/or fidaxomicin is limited
[b] if metronidazole used for the initial episode
[c] if a standard regimen (vancomycin or fidaxomicin) used for initial episode
[d] if vancomycin was used for the initial episode

2) Promotion of oral vancomycin as first-line therapy: Based on the studies described above demonstrating superiority of oral vancomycin over metronidazole in patients with CDI, oral vancomycin is now recommended as first-line therapy for an initial episode of CDI, regardless of severity.[1,5,6] We recognize that financial barriers to prescribing oral vancomycin exist, particularly in the outpatient setting. In order to reduce costs, pharmacies often compound an oral solution from vials of intravenous vancomycin. Unfortunately, compounded solutions may not be covered by insurance companies because it is not considered an FDA-approved medication. However, a new oral vancomycin reconstitution kit called FIR$_x$ST® by CutisPharma is available as an option for prescribers looking for a less expensive and FDA-approved vancomycin formulation covered by many insurance companies in the outpatient setting.[9,10]

3) Addition of fidaxomicin for treatment of CDI: Fidaxomicin received FDA-approval for treatment of CDI shortly after the last guideline update in 2010. FDA-approval was based on the results of two randomized controlled trials that compared oral vancomycin to fidaxomicin.[11,12] These trials demonstrated that resolution of diarrhea was similar in patients treated with fidaxomicin (88%) or vancomycin (86%, RR: 1.0; 95% CI: 0.98-1.1), but sustained clinical response at 25 days following treatment was superior for fidaxomicin (88%) compared to vancomycin (57%, RR: 1.2; 95% CI: 1.1-1.4). Based on these data, fidaxomicin was added as a first-line agent to be considered along with vancomycin as the drugs of choice for an initial episode of CDI (Table 1).[1]

   Studies have shown that approximately 25% of patients treated with oral vancomycin for an initial episode of CDI will experience at least one recurrence and that recurrence rates are significantly lower following treatment with fidaxomicin.[11-13] Fidaxomicin is significantly more expensive than vancomycin; therefore, it should be reserved for patients with the greatest risk for recurrence. A recent retrospective cohort study in 340 patients with CDI identified risk factors for recurrence and developed a risk prediction tool.[14] Five factors were identified, including: 1) CDI at admission; 2) fever > 37.8°C on admission; 3) leukocytosis; 4) nosocomial acquisition of CDI; and 5) abdominal distention on CDI presentation (1 point assigned for each factor present).[14] A score of $\leq$ 2 was found to have a negative predictive value of 91%, and a score of $\geq$ 4 had a positive predictive value of 70%.[14] While this risk prediction tool has not been validated externally, we believe a tool such as this may allow clinicians to identify patients at high risk for recurrent CDI that could potentially benefit from fidaxomicin therapy.

4) Updated Treatment Duration Recommendations: The 2010 guidelines recommended a treatment duration of 14 days, largely because patients treated with metronidazole may have delayed response. However, nearly all randomized trials have demonstrated that 10 days should be sufficient to resolve symptoms in most patients. Therefore, the new guidelines recommend treating for 10 days.[1] Of note, it is appropriate to extend the treatment duration to 14 days in patients that have improved but have not had symptom resolution at day 10.

Treatment duration for patients with an initial episode of CDI has been reduced to 10 days

Primary Prophylaxis

Several recent meta-analyses suggested probiotics may be effective at preventing CDI when given to patients on antibiotics that do not have a history of CDI.[15-17] However, the studies with the greatest influence on the results of these meta-analyses had a CDI incidence of 7 to 20 times higher in the control arms than would be expected, which may have biased the results to favor probiotics. In addition, probiotic administration is not without risks. Several studies demonstrated the potential for organisms in probiotic formulations, such as *S. boulardii*, to cause infections in hospitalized patients.[18-20] Cost effectiveness analyses for routine use of probiotics are also not available. The 2017 guidelines

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Secondary Prophylaxis

Some patients require systemic antibiotics while receiving treatment for CDI. This increases the risk of recurrence. Strategies to mitigate this risk such as continuing anti-CDI treatment at traditional or lower doses until all antibiotics are discontinued have been adopted by some clinicians, but these practices remain unproven.

Similarly, initiating broad-spectrum antibiotic therapy in a patient with a recent case of CDI raises concern for relapse of CDI. Two retrospective cohort studies have addressed this issue comparing vancomycin to no anti-CDI treatment at a variety of doses and durations. Both of these demonstrated a decreased risk of subsequent CDI for a portion of the patients treated empirically with vancomycin.[21,22] However, there are no prospective, randomized studies evaluating this approach. Also, risks of subsequent MDRO infection (e.g. VRE) have not been assessed.

The current guidelines suggest that providers prescribing secondary prophylaxis consider a lower dose of anti-CDI agents. Patient-specific factors that may influence the decision to initiate secondary CDI prophylaxis include the length of time from previous CDI treatment, the number and severity of previous CDI episodes, and the underlying frailty of the patient. The efficacy of secondary prophylaxis for prevention of recurrent CDI remains an open question in need of future study to guide practice.

Restricting Proton Pump Inhibitors (PPIs)

To date, three meta-analyses demonstrated an association between gastric acid suppression with PPIs and increased risk of CDI using data from 47 studies in over 300,000 patients.[23-25] Most studies reviewed found that the risk of CDI ranged from 1.4 to 2.75 times higher among patients with PPI exposure. No randomized controlled studies or quasi-experimental studies have evaluated the relationship between discontinuing or avoiding PPI use and risk of CDI. Therefore, the 2017 guidelines note that a recommendation to globally discontinue PPIs in patients at high risk for CDI or recurrent CDI regardless of need for PPI is not supported by current evidence.[1] However, the authors concluded that stewardship activities addressing unnecessary PPIs are warranted.

Take Home Points:

1) Metronidazole is no longer recommended as first-line therapy for patients with CDI, regardless of severity. However, in settings where access to oral vancomycin or fidaxomicin is limited, it may be used as an alternative agent.
2) Oral vancomycin is now recommended as first-line therapy in all patients with an initial episode of CDI.
3) Fidaxomicin is recommended as first-line therapy in patients with non-severe or severe CDI; however, it is significantly more expensive than oral vancomycin. Therefore, it should be reserved for patients at highest risk for recurrent disease.
4) Probiotics are not recommended for primary prevention of CDI.
5) Stewardship efforts focused on limiting unnecessary use of PPIs are warranted.

For more information on *C. difficile* diagnostic testing, please see our February 2018 DICON Newsletter.

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