CLINICAL UPDATE

Advances in *Clostridium difficile* Infection

Evidence-Based Approach to *Clostridium difficile* Infection

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G&H How common is *Clostridium difficile* infection in the United States?

SJ In 2009, the Centers for Disease Control and Prevention (CDC) started active surveillance for *Clostridium difficile* infection as part of the Emerging Infections Program. Initially, 10 sites were used across 34 counties that were representative of the US population as a whole, and several other counties have been added since then. The CDC estimated that 453,000 cases of *C difficile* occurred in the United States in 2011, along with an estimated 29,300 deaths, making this infection an important public health issue in the United States.

G&H What are the challenges or complexities associated with antimicrobial stewardship in *C difficile* infection?

SJ *C difficile* infection is intimately associated with antibiotics. There are 2 particular aspects to this. One is that antibiotics clearly have collateral damage to the colonic normal flora, meaning that they might be effective for treating pneumonia or urinary tract infection, but they often disrupt the normal protective host defense provided by the resident microbiota of the colon. The other aspect, which has been more recently realized, is that certain antibiotics can select for particular strains of *C difficile* that are highly resistant to those antibiotics.

Thus, the challenge for antimicrobial stewardship programs (ASPs) is to first understand the epidemiology of *C difficile* in one's own institution. If there is an outbreak or increased incidence, it is helpful to know (although this is not always possible) the prevailing strain in the institution and its susceptibility pattern. If this information is available, then ASPs can look at their antibiotic usage patterns. For example, since 2000 there has been a widespread epidemic strain referred to as REA Strain BI or Ribotype 027, which is highly resistant to fluoroquinolones. There are multiple lines of evidence indicating that fluoroquinolones facilitated the numerous outbreaks of this strain in North America and Europe. Thus, in institutions where this strain has been a problem, identifying and limiting the use of fluoroquinolones can be an effective measure.

The other issue to keep in mind is that certain classes of antibiotics have historically been known to precipitate *C difficile*, such as clindamycin and second- and third-generation cephalosporins. Fluoroquinolones can now be added to this list. A general ASP may be to limit all of these agents, but it is important to understand local patterns. This was done in the United Kingdom in a top-down manner, in which increased rates of *C difficile* infection were noticed between 2004 and 2006, leading to the establishment of a strict ASP to avoid clindamycin and cephalosporins and minimize the use of fluoroquinolone, carbapenem, and aminopenicillins. This plan helped in a nationwide, rather than institutional, manner. A post-hoc review of this intervention, which included whole genome sequencing of clinical *C difficile* isolates obtained during this time period, showed that restricting fluoroquinolones was the key intervention responsible for the decline in the incidence of *C difficile* infection.

G&H Based on the evidence currently available, how effective are the current treatment options for an initial episode of *C difficile* infection?

SJ Traditionally, metronidazole and vancomycin have been the drugs used. However, there is increasing evidence that metronidazole is not as effective as vancomycin, and although the 2010 Infectious Diseases Society of America/

Society for Healthcare Epidemiology of America guidelines suggested that metronidazole was effective for patients with mild to moderate disease, the use of metronidazole is decreasing. Vancomycin and fidaxomicin (Dificid, Merck) are very active against *C difficile*, and prospective, randomized, controlled data have shown that those agents are both effective for treating initial infection of *C difficile*. Clinical cure rates were 86% to 88% by modified intent-to-treat (mITT) analysis and 90% to 92% by per protocol (pp) analysis for these agents. In addition, fidaxomicin was shown to be noninferior to vancomycin for initial cure in these studies, which included mostly (~84%) patients with a first episode of *C difficile* infection.

G&H What are the dosing schedules usually used with these agents?

SJ The typical schedule is 10-day treatment, with 125 mg of vancomycin 4 times a day or 200 mg of fidaxomicin 4 times a day. For an initial infection, that treatment should be sufficient. The regimen for metronidazole is 500 mg 3 times a day if used for an initial episode of *C difficile* infection, but extending the treatment up to 14 days is frequently recommended because patients often respond slower to treatment with this agent.

G&H How common is recurrence of *C difficile* infection, and what are the associated risk factors?

SJ Recurrence is a significant problem with *C difficile* infection. Approximately 1 in 4 patients who respond to initial treatment will have another episode of *C difficile* infection usually within several weeks of stopping treatment for the first episode. In addition, once a patient has a recurrence, the risk for a subsequent episode is higher still. Compared to a risk of 25% for an initial recurrence, the risk of a subsequent episode can be as high as 30% to 40%. Some patients may have multiple recurrences, which typically respond to any of the agents used, but they develop recurrent diarrhea after stopping treatment, usually within the first 2 weeks after treatment.

One risk factor for recurrence is older age. In addition, concomitant antibiotic use has been shown to be a large influence on recurrence. Other reported risks for recurrence include infection with the epidemic BI/027 strain, severe underlying illness, immunocompromise, gastric acid reduction therapy (ie, proton pump inhibitors), intensive care unit stays, and prolonged hospitalization.

G&H Are there any ways to reduce recurrence of this infection, including the use of any new or emerging therapies?

SJ The advantage of fidaxomicin over vancomycin is not in the initial response to treatment, but in the sustained response. Thus, the incidence of recurrent *C difficile* infection after treatment with fidaxomicin is significantly less than with vancomycin. Randomized trials of fidaxomicin and vancomycin showed an approximately 10% lower rate of recurrence with fidaxomicin, which translated to a higher global cure, or sustained response, with fidaxomicin (75% vs 64% in the mITT and 78% vs 67% in the pp groups for fidaxomicin and vancomycin, respectively).

In addition, bezlotoxumab (Zinplava, Merck), a monoclonal antibody directed against toxin B produced by *C difficile*, was approved by the US Food and Drug Administration (FDA) several months ago. The trials that led to FDA approval, the results of which were recently reported in the *New England Journal of Medicine*, included bezlotoxumab as an adjunctive treatment. This meant that patients with *C difficile* infection received standard antibiotic treatment (vancomycin, metronidazole, or, in some cases, fidaxomicin) in addition to 1 intravenous infusion of bezlotoxumab or placebo. The combination of bezlotoxumab and antibiotics reduced the absolute risk of recurrence by 10%, or a 38% relative reduction. The best use of this new agent and the specific setting where this agent will likely be used are still not clear. Bezlotoxumab is currently FDA-approved as adjunctive therapy for the prevention of recurrence in patients who are at high risk for recurrence.

G&H How should multiple recurrences be treated?

SJ Although there are limited comparative data available, the best way of handling patients with multiple recurrences, in my experience, is to wean patients off treatment. This is typically done with vancomycin after a standard 10-day course of treatment; when the patient's symptoms resolve, the doctor should taper the dose and then pulse it (ie, administer it every other day and then every third day). Thus, a typical tapered pulse regimen for vancomycin would be twice a day for a week, once a day for a week, every other day for several weeks (up to a month), and then every third day, depending on the patient's history. This is a slow process, but it works for most patients. If patients do have a recurrence, they will typically have it when they are on their every-second-day dosing, every-third-day dosing, or just after they finish treatment. They usually respond to treatment again with vancomycin, and clinically important resistance to vancomycin has not yet been demonstrated.

I have also had experience using fidaxomicin in the same way, although in a smaller number of patients. Again, the idea is that after a treatment course of fidaxomicin,

the drug can be administered in a tapering and pulsed fashion. Anecdotally, this has been very effective.

G&H What is the role of fecal microbiota transplantation for the treatment of *C difficile* infection?

SJ In fecal microbiota transplantation, feces from a healthy volunteer is screened for pathogens, processed, and administered via enema, colonoscopy, or upper gastrointestinal tube with the aim of restoring a protective gut flora. This procedure was rare 10 to 15 years ago, but now has become fairly widespread practice. However, a challenge with this procedure is that it is not FDA-approved. A draft guidance was issued last year from the FDA indicating that it will continue to exercise enforcement discretion regarding the investigational new drug requirements for the use of fecal microbiota transplantation. This is provided that the licensed health care provider treating the patient obtains adequate consent, the fecal product is not obtained from a stool bank, and the stool donor and stool are qualified by screening and testing under the direction of the provider. Stool banks have made fecal microbiota transplantation logistically possible for many physicians by offering reasonably priced screened stool specimens that are frozen, shipped, and then thawed; however, follow-up on these patients has been minimal, and it is unclear how this practice will have to change to comply with the FDA guidance. Based on uncontrolled anecdotal and case series reports, this procedure was thought to be over 90% effective, but more recent randomized, controlled trial results indicate much more modest results. In my experience, outside of research protocols, this treatment should be reserved for the small group of patients who do not respond to antibiotic therapy.

G&H Has there been any comparative analysis on the efficacy of the various treatment options for recurrent *C difficile* infection?

SJ Within the phase 3 registration trials for fidaxomicin, there was a subset of patients with a first recurrence of *C difficile* infection who were randomized to fidaxomicin and vancomycin. Fidaxomicin was found to be superior for sustained response in that group of patients. The number of patients examined was not large, so additional research is needed.

Recently, there have been several randomized trials of fecal microbiota transplantation that have been published. One of the more recent trials examined fecal microbiota transplant via an enema vs a standard vancomycin taper-and-pulse regimen. This study was discontinued for futility at an interim analysis when fecal microbiota transplant did not show any benefit over the vancomycin taper-and-pulse regimen. In fact, the vancomycin regimen's outcome was better, although the difference was not statistically significant. The largest randomized, controlled trial of fecal microbiota transplantation found that the efficacy of 1 transplant by enema was approximately 50%, but increased to approximately 70% with 2 transplants and approximately 90% with more than 2 transplants.

G&H According to the data currently available, how do these approaches compare in terms of safety and tolerability?

SJ The 2 mainstay antibiotic treatments for *C difficile* infection, vancomycin and fidaxomicin, are not absorbed. Thus, there is little systemic exposure to these drugs, and their safety profiles are very good. On the other hand, metronidazole is highly absorbed and not as well tolerated. The drug reaches the colon in modest amounts. Many people experience gastrointestinal symptoms with metronidazole.

As for fecal microbiota transplantation, the long-term consequences are not yet known. My main concern is the use of this procedure in children, in whom it is already being used. This group needs to be watched very carefully for potential long-term metabolic or infectious complications.

The new agent bezlotoxumab was well tolerated during the trials that led to FDA approval, and the agent did not have a higher incidence of side effects than that of the placebo group. However, the studies were limited in their ability to detect potentially serious but infrequent events because of the limited number of patients who received bezlotoxumab.

G&H Has there been any cost-effectiveness analysis on any of these agents?

SJ There have been estimates on cost-effectiveness, but I do not think that there has been a very good cost study on these agents. Fidaxomicin is an expensive drug, which may be problematic depending upon the patient's insurance, although the manufacturer does offer a patient-assistance program. Interestingly, even though vancomycin capsules are available in at least 4 generic formulations, the price has not dropped for 4 years. An alternative is to use the solution form of vancomycin. Many pharmacies take vancomycin powder that is used for intravenous administration and compound it into an oral solution for treating *C difficile* infection, which is much less costly but still effective.

G&H In general, are there any benefits to using targeted therapy as opposed to broad-spectrum therapy for *C difficile* infection?

SJ Trials comparing fidaxomicin to vancomycin have looked at the microbiome of the subjects who were treated. There was a profound effect on bacterial groups that are thought to be correlates of a protective microflora with vancomycin (eg, *Bacteroides* sp and certain Clostridia), unlike with fidaxomicin. Thus, the data suggest that fidaxomicin is a narrower-spectrum agent, which is probably the reason that fewer recurrences are seen after treatment with fidaxomicin.

G&H Are there any particular patients in whom using a targeted therapy would be especially beneficial?

SJ I think that any patient with *C difficile* infection would benefit from a narrow-spectrum agent, although cost may be an issue. Thus, doctors and institutions often try to triage fidaxomicin use in particular by looking at the risk for recurrence. The issue then becomes how to reliably predict the risk of recurrence. Certainly, age and continuing or additional antibiotic use are major risk factors, as previously mentioned, so patients with those factors might receive particular benefit.

G&H Why is there a need to update the *C difficile* guidelines?

SJ The 2 main issues that necessitate an update of the guidelines involve cumulative data on the treatment agents fidaxomicin, vancomycin, and metronidazole as well as changes in the laboratory diagnosis of this infection. In the United States, there is fairly widespread use of molecular methods to make a diagnosis of *C difficile* infection, which means that the organism is not cultured, and importantly, the polymerase chain reaction amplification assays will identify a toxigenic strain but do not detect toxin. Polymerase chain reaction is much more sensitive, so it may detect patients who may be colonized with *C difficile* but who do not necessarily have the disease.

G&H Are there any other important recent or ongoing studies in this area?

SJ Additional treatment agents are in development. Phase 3 trial results for cadazolid should be available soon. Another drug that looks promising is ridinilazole, which has recently completed phase 2 testing. In addition to antibiotic agents, a nontoxigenic strain of *C difficile* looks to be a promising adjunctive therapy. However, this therapy has not yet moved into phase 3 testing. Finally, several vaccines are being developed, but it is too early to know whether they are efficacious.

G&H What are the most important remaining research needs?

SJ The efficacy and limitations of the various treatment options for *C difficile* infection need to be better understood. In addition, there is currently a good deal of data on the treatment of first episodes of *C difficile* infection, but recurrence is less well studied. A few randomized studies have been conducted in this area, but for the most part, there is only anecdotal evidence. A randomized trial of 3 different treatments for recurrent *C difficile* infection is currently being conducted through the VA Cooperative Studies Program, which will hopefully provide better guidance for the treatment of recurrent disease in the future.

Dr Johnson is on the advisory boards of the following companies that are developing treatments or prevention approaches for C difficile *infection: Summit Therapeutics, Seres Therapeutics, and Bio-K+.*

Suggested Reading

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