**Slide 1**
***Current and Evolving* Clostridium difficile *Treatment Strategies***
Stuart Johnson, MD, DTM&H
Thank you, Dale.

**Slide 2**
**Disclosures**
These are my disclosures, if you will. I also work for the VA and do not represent them. So this is not the spokesperson from the VA hospital. I do have funding through the VA.

**Slide 3**
**Overview**
So what I'd like to talk about is treatment of first episode of CDI, treatment of severe CDI—you already heard the problems we've had with the diagnosis or defining that—and treatment of severe, complicated CDI, recurrent CDI, and then I'll finish up with some unresolved treatment issues.

**Slide 4**
**Treatment Options Prior to 2000**
If you look at options that were available before 2000, I listed here studies where randomized comparative trials have been done. You can see vancomycin, metronidazole, teicoplanin, which is not available here, and then fusidic acid, which is rarely used and probably has no other helpful reason to do it, rifaximin I'll talk about at the end—there's a very small study that was done in Italy many years ago—bacitracin, probably does not offer anything that the other options have, and then colestipol; when it was studied, was about the same as placebo. So please don't use colestipol.

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**Prospective, Randomized CDI Trials of Vancomycin and Metronidazole, Prior to 2000**

Again, the only FDA-indicated drug for this at the present time is vancomycin. But as you can see, in the randomized, comparative trials, looking at vancomycin and metronidazole prior to the year 2000, metronidazole appeared to stack up very nicely against vancomycin and appeared to be in the—not inferior, if you will, by these studies. The cure rates of 94% to 95% for metronidazole and 94% to 100% for vancomycin. Relapse rates were comparable, maybe a little under-represented here, but about 15% to 16%. Then the time to resolution was similar, about 3 days mean.

**Slide 6**
**SHEA Position Paper on CDI: Treatment Recommendations 1995**

The SHEA [Society for Healthcare Epidemiology of America] position paper that came out in 1995 had the following recommendations as regards to treatment. If clinically appropriate, discontinuation of the offending antimicrobial was recommended. If CDAD, at the time was called, is suspected, 20% to 25% of patients were thought to respond just to simple discontinuation of the precipitating antibiotic. Metronidazole or vancomycin for 10 days was

recommended as effective treatment. Metronidazole was less expensive and may be preferable to avoid the issues of vancomycin resistance that was the concern in other nosocomial enteric bacterial species. Then for patients that have a first recurrence of diarrhea following treatment of CDAD, retreatment in the same manner as for the initial episode was recommended.

Now we had really no evidence, other than our clinical experience at the time, but since then Jacques Pépin has looked at that answer and we actually do have some clinical evidence to support that last recommendation.

**Slide 7**
**Recent Observational Reports of CDI Treatment Response Rates to Metronidazole**
What's gone on more recently? Those of you in the trenches who see and treat patients with *C. difficile* disease I think will recognize this and understand this. That the response to metronidazole does not seem to be as predictable as it was in the past. Now these studies are done and conducted in a different manner. These were retrospective studies, if you will, but they were fairly consistent in that the rate of response was 62% to 78%. So clearly much less than what you'd like as a predictable response to treatment.

**Slide 8**
**Response Time for Treatment of CDI with Metronidazole or Vancomycin**
Part of the answer may be shown here, data that Mark Wilcox reported in 1995 actually. If you look at the response time to treatment for CDI with metronidazole in yellow or vancomycin in the blue, you can see that by day 7, virtually all the patients treated with vancomycin had responded. But yet there's this tail, if you will, of slow response to metronidazole. Several patients responded, but took longer to respond. And most of the studies that have looked at response have used day 5 or day 6 as far as whether success or cure has been achieved. So this may explain some of the lower rates of response.

**Slide 9**
**Response Time for "Slow MTR Responders"**
Jaime Belmares in our hospital did a retrospective study and this is just looking at those slow responders. So those groups of patients that didn't respond by day 6. You can see that most of those patients will eventually respond by 14 days, even though some of them respond even much later than that.

Unfortunately, in this day and age of increasing rates and increasing severity, this may not be the most optimal drug. We have data now from two randomized, placebo-controlled trials for CDI that would suggest that vancomycin and metronidazole may not stack up.

**Slide 10**
**Recent Prospective, Randomized, Placebo-Controlled Treatment Trials for CDI**
Now the first study here was reported last year at CID [*Clinical Infectious Diseases*] by Fred Zar et al. It was a double-blinded study of 172 patients who were randomized to those two regimens, and 150 completed the study. This was all one center. It took about 5 years to complete. It ended up, I think 2004, if I remember right.

**Slide 11**
**Recent RCTs for CDI (Cure/Success Rates)**
More recently has been presented in abstract form, the tolevamer or the Genzyme study. This was a double-blinded, multicenter, randomized comparative trial of tolevamer, which is a toxin-binding agent, versus vancomycin and versus metronidazole. Now this was a multicenter study and really has a lot of power in it. And 543 patients were available for full analysis and 471 patients were available for per protocol analysis.

If you look at the first column, the overall response between vancomycin and metronidazole, they were fairly consistent. About 90% overall, vanco being 97% and metronidazole 84%. If you look at the severe category, and I'll tell you what the definition for severe was in a minute, you can see that the differences between vancomycin and metronidazole appeared, whereas 97% of patients defined as severe in the study responded, only 76% responded to metronidazole. And this was significant.

If you look at the tolevamer study, the tolevamer agent, however, was very disappointing and only 47% of patients overall responded to this. It was very disappointing to us that were looking for another agent. Certainly for the company. So it did not stack up against vancomycin or metronidazole. However, overall, vancomycin and metronidazole were very similar. They were not statistically different.

But again, if you look at their description of severe cases, 85% responded to vancomycin, where only 65 responded to metronidazole.

**Slide 12**
**Recent RCTs for CDI (Relapse/Recurrence Rates)**
If you look at recurrences, in the Zar study there were 10% overall and looked to be very similar between metronidazole and vancomycin, and this did not appear to be different among the severe cases.

However, if you look at the tolevamer study, the one good thing about tolevamer is a very low recurrence rate. So if this drug were as effective as vancomycin or metronidazole, they would have had a very nice option. There may still be a role for this drug in the future, but not as primary therapy against vancomycin or metronidazole.

**Slide 13**
**Recent RCTs for CDI (Definition of "Severe")**
The definition, however, is —really ad hoc definitions for both studies. We really don't know exactly what constitutes a severe case right away. But for purposes of this study they used, in the Zar study, age—I'm not sure that's severity illness per se, but certainly an indicator by itself for outcome. Temperature. Albumin. White count greater than 15,000. Pseudomembranes on endoscopy. Or treatment in the ICU [intensive care unit]. So either pseudomembranes or admission to the ICU would have made that a severe case by itself.

If you look at the tolevamer study, the criteria for severe disease were greater or equal to 10 bowel movements per day. Or a white count of greater than 20,000. Or severe abdominal pain.

So we still do not have a perfect or an ideal predictor of either severe disease or treatment outcome. But ideally, we would have a validated score that was attainable at the time of clinical presentation and would predict such complications as toxic megacolon, sepsis, or death.

**Slide 14**
**Markers of Severe CDI Vs. Predictors of Treatment Outcome**
However, factors that may indicate complicated course are listed below. Certainly age has been a consistent factor in most studies that have looked at this, and may relate to senescence of the immune response. Leukocytosis clearly is a marker and probably represents severity of the colonic inflammation. Then serum creatinine may also be a marker. This may reflect diarrhea or severity of diarrhea, but potentially also the underlying renal dysfunction.

So at this point I think if you have a patient who clinically looks to be severe, that vancomycin would be the initial drug of choice. Not to start with metronidazole and then switch to vancomycin if they don't do well. But if you have a patient who looks to be severe to begin with, this is the drug that we should probably start with, based on the current available evidence.

**Slide 15**
**Investigational Treatment Agents for CDI**
The investigational agents that are listed here, that are not indicated yet for *C. difficile* disease, some of them haven't reached Phase III study, but you can see the tolevamer product by Genzyme, ramoplanin by Oscient, which I'm not sure what is going to happen with that drug. OPT-80 by Optimer is a drug right now undergoing two extensive Phase III studies; we'll be very interested to know what the results are there. Rifaximin by Salix, there was an early patient study that I show the numbers there, there is a Phase III study that's ongoing right now. Nitazoxanide has a study that was compared against metronidazole. Then Medarex and Acambis have two different immune strategies, but we do not have any data to show you here.

**Slide 16**
**RCT of Tolevamer (6 and 3 grams) Vs. Vancomycin**
So these were the data from the Phase II study of tolevamer. This was the study that looked to be very promising for toxin-binding agent. This was comparing 3 grams or 6 grams of this toxin-binding polymer versus vancomycin, and there appeared to be a dose response. However, as I mentioned, in the formal Phase III study this was not comparable to vancomycin or metronidazole.

**Slide 17**
**RCT of Nitazoxanide Vs. Metronidazole**
Nitazoxanide has been compared to metronidazole in a randomized study by Dan Musher et al. And in this study the response to metronidazole was 82% with 29% recurrence rate. Nitazoxanide had a very similar response rate of 89% and recurrence rate of about 21%. So this, although it's not indicated yet for *C. difficile* disease, appears to be similar, at least in this study, to metronidazole. It's not clear to me yet if they're going to seek a formal indication for this. They'd need to study it against vancomycin.

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**Severe, Complicated CDI**
So what I call here is severe, complicated CDI, is what we really hate to see, but these are patients with very, very severe outcome or severe disease, and may paradoxically occur without the presence of diarrhea. In one series, 37% of the patients with severe, complicated *C. difficile* infection had no diarrhea. It may mimic other acute abdominal syndromes.

CT [computed tomography] scan findings that are suggestive would be a thick colonic wall, presence of ascites, and dilatation.

Empiric medical treatment includes oral and rectal instillation of vancomycin with intravenous metronidazole. The role of other adjunctive therapies is also unclear. We don't have any good evidence to support this, but basically in someone who is looking to go down the tubes, so to speak, may require colectomy. Some of the things that can be done would be to give vancomycin by NG [nasogastric] tube. But certainly if they had a complete ileus, you might try to give it by a rectal tube in order to get some effective drug at the site of action. Colectomy, however, may be performed. Exactly when to do that is tricky.

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**Dilated Colon**
This is just the typical patient, of someone with a very dilated colon. Patient was toxic, in addition to toxic megacolon.

**Slide 20**
**CT Findings of Severe Disease**
These are typical CT scan findings of severe disease, showing a very thick colonic wall. The white arrow up in the corner shows ascites.

**Slide 21**
**Vancomycin Administration When the Oral Route is Compromised**
These are the data for vancomycin administration when the oral route is compromised. We've recommended—again, anecdotal evidence for this—of giving the intravenous form of vancomycin by rectal instillation: 500 milligrams of the IV formulation in 100 mL of normal saline, and using a Foley catheter. Now these bowel management systems, and I'll show you a picture in the next slide, have also been used, it can be used, for this particular purpose. Other people have inserted a long tube into the small intestine to give the vancomycin. Then one study talked about colonic decompression, followed by guidewire positioning of a fenestrated tube and giving vancomycin by a perfusion type of route.

**Slide 22**
**Bowel Management Systems**
This is just a picture of one of these bowel management systems. They're used fairly frequently in our intensive care unit. But again, maybe another route for administering vancomycin.

**Slide 23**
**Surgery for Severe, Complicated CDI**

Surgery for severe, complicated CDI. A total abdominal colectomy with end ileostomy is the procedure of choice. So certainly not just a decompression or a segmental resection, but if the surgery is determined necessary, the whole colon should come out. The mortality is still high after the procedure and exactly when to undergo the procedure is not clear. Certainly if the physician has experience with this, it's helpful. What I usually recommend is you have someone who has a hint of severe disease to begin with, let the surgeon see the patient initially and follow them with you.

Hypotension requiring vasopressors is a bad prognosis, so you'd like to pick them up before that. Lactate greater than 5 millimoles per liter would indicate a postoperative mortality of greater than 75% in one study. So should be done before that. And one little clinical pearl might be a rapidly increasing white blood cell count. This is often a very ominous sign.

**Slide 24**
**Recurrent CDI**
Recurrent *C. difficile* infection. Again, we don't have great clinical evidence for what to do. But it is a very common problem. Recurrent diarrhea after resolution of initial episode is seen in about 20% of patients. However, if you have a subsequent episode, your risk for another episode may rise to even 45% or higher.

Antibiotic resistance after treatment with metronidazole or vancomycin has not been reported and you can reliably treat patients with their first episode with the same agent.

Many empiric regimens have been advocated for these multiple recurrences. But repeated, prolonged courses of metronidazole are cautioned against because of risk of neurotoxicity. I've seen more than one patient who's been referred to me, who had such severe neuropathy that they can't even walk. Where people have just put them on metronidazole and sent them to the nursing home per se. So be very cautious about that.

**Slide 25**
**Treatment of First Recurrence of CDI**
Treatment of the first recurrent episode. These are data that I mentioned from Jacques Pépin, that would bolster our recommendation from that earlier SHEA position paper. But in this study, 47% recurrence rate was documented. This was in the setting of a multiple hospital outbreak in Quebec, due to this new epidemic BI/NAP1/027 strain. Metronidazole was not inferior to vancomycin in this study for treatment of the first recurrence. Treatment of the first recurrence with a different agent made no difference in outcome. So if you were treated with metronidazole first and then were treated with vancomycin, that did not seem to make a difference as far as outcome went.

However, complications were seen in about 11% at the first recurrence rate. So this was something that was a little bit unusual to us. We usually considered recurrence as a problem, but more manageable issue, not necessarily complicated with shock or colectomy, perforation. But this clearly was seen in this study.

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**Recent Reports of Treatment for Recurrent CDI**
Recent reports of treatment for recurrent CDI would include tapering/pulsed vancomycin regimens, probiotic approaches as I show here, immunologic approaches, fecal transplantation, and this rifaximin chaser, that I use out of desperation. I'll show you a little bit more with that.

**Slide 27**
**Recurrent CDI in 163 Cases**
Again, there's not a lot of great data for tapering or pulsing vancomycin, but this is probably the first thing that should be done. If someone's had a couple of recurrences already, there probably are more data with this technique than others. In this one retrospective study, comparing different approaches to patients in the placebo arm, if you will, of the *Saccharomyces* study, it appeared that tapering or pulse dosing was better than medium dose vancomycin.

So I don't know if I put the regimen on here, but one regimen that has been used empirically would be to taper the regimen rather quickly from four times a day of vancomycin to twice a day for a week, then once a day for a week, and every other day—this is the pulse form—for a week or so, and then every third day. So it may be the pulse part of this is more important. But if you have seen patients with multiple recurrences, think of this as a first measure.

**Slide 28**
**Treatment of Recurrent CDI with *S. boulardii***
These are the data for *Saccharomyces boulardii*. This is the one probiotic approach that has been looked at in a more rigorous manner. This is basically a subset of a larger study, but given that caveat, what they saw, that if you gave *Saccharomyces* at a gram per day for 28 days, with vancomycin for the first 10 days, you got 15 out of 18 responders, whereas if you gave placebo for 28 days with vancomycin the first 10 days, and again this was the high dose of vancomycin, the old 500 milligrams four times a day, they only saw 7 out of 14 responses. The *P* value here is .05, so it did not quite reach statistical significance. But anecdotally this has been helpful for some patients.

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**Treatment of Recurrent CDI by Fecal Transplantation**
Now I have a growing population of multiple recurrences in my clinical practice. Let me go back. This is not my study. This is the ever lovely, somewhat aesthetically challenging, fecal transplantation. This is the study by Johannes Aas and Johan Bakken in Duluth, where they reported their experience with 18 patients. The specimens were obtained from their spouses for the most part and were delivered by an NG tube, following vancomycin regimen and then omeprazole. What they did was they prepared the specimen, as they described in their methods, as fresh, less than 6 hours, 30 grams or about 2 centimeters per cube volume, and then added 50 milliliters of normal saline. Homogenized in a blender. And then filtered through a paper coffee filter, if you will. So it sounds like you could do it in your kitchen.

But this was very, very effective for most of these patients. Only 1 of 16 survivors had a single subsequent recurrence. Now the implication here is that two died, but from other causes.

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**Interruption of Recurrent CDI by Serial Therapy with Vancomycin and Rifaximin**
This is the study that I reported last year. Again, I'll say that this was an uncontrolled study, I did not specifically treat patients with rifaximin, but this was done out of a sense of frustration, of getting people over the hump, if you will, from these multiple recurrences. There were eight women in the study. The mean age was 72, and had a mean number of episodes of 5.8 or almost six episodes before we went to this approach.

The mean time between recurrence episodes was a week and a half. What we did basically was after they finished a course—and in this setting all of them had been on vancomycin of 10 to 14 days, where they were completely asymptomatic—we stopped the vancomycin cold. We didn't taper or pulse it, but we gave rifaximin at a dose of 400 milligrams twice a day for 2 weeks. And then we followed them carefully. Seven of the eight patients had no further diarrhea recurrences; however, one patient had a symptomatic recurrence 10 days after stopping the rifaximin and then responded to a second course without a subsequent recurrence.

**Slide 31**
**Timeline**
Now I'd like to show this timeline because it's somewhat instructive on a number of levels, if you will. But if you see on the top, CD -plus, this is the indication of their stool cytotoxin testing, and results, and then at the end where we did culture. If you look at the bottom of the line you see the treatment regimens. So the first episode was treated with metronidazole. A week and a half later the CD toxin was negative, but clearly had symptoms that were similar to her first episode and we treated her with metronidazole. The third episode, the cytotoxin testing was positive, was treated with vancomycin and responded quite nicely again. However, had a fourth episode and at this time the toxin test was negative, but was exactly like her other episodes, so we took the stool specimen, brought it to our research laboratory, cultured it and indeed was 4-plus culture–positive. She responded to vancomycin. We stopped the vanco, put her on rifaximin. I saw her in clinic—at that one time point where you see the negative toxin, negative culture assay, and she was fine, had no symptoms whatsoever. I went out of town for 2 to 3 days and she had a big incontinent episode and called Chris Schriever, the clinical pharmacist at Loyola, and my colleague said well, just put her back on rifaximin. I'm not sure I would have done that, but it was done. The patient responded quite nicely and never had another recurrence.

Now I saw her about 2, 3 weeks later in clinic and at that time her stool specimen was still toxin-positive and 4-plus culture, but had no symptoms whatsoever.

So the point here is that we do not recommend this in a nonstudy situation, meaning do not get test-of-cure cultures or toxin specimens, because some people will still be toxin-positive, but not symptomatic. That clearly is the desired result. We think eventually that this will go away.

**Slide 32**
**Stool Cultures**
But we had these two stool specimens available and we cultured them, as I mentioned, and we were able to type them by restriction and nucleus analysis. These are the REA patterns that are shown here. And they were virtually identical. We would call these identical. It's a little light at the top, but all these bands were identical from the pre-rifaximin isolate to the post-rifaximin

isolate. However, we looked at the susceptibility of these isolates *in vitro* to rifaximin and whereas the initial isolate was exquisitely susceptible at .0078 mic per mL, posttreatment with rifaximin the isolate had an MIC [minimal inhibitory concentrations] of greater than 256 mics per mL. Now remember that this patient responded and we only have the posttreatment isolate available, but this is a little bit of caution about this particular drug, that we have seen these high MICs develop.

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**Subsequent Clinical Experience with Serial Therapy: the "Rifaximin Chaser" Protocol for Recurrent CDI**
Now my subsequent experience with this rifaximin chaser is shown here. This is not published, but I looked at these data a month ago. I've only treated five patients since that report. I was basically waiting for a randomized, placebo-controlled trial of this approach, but this has been delayed for a variety of reasons. However, I've treated five patients, four of them women, again, very similar to our original experience, mean age of 73, previous episodes again 5 and a half, and all had failed the tapering and pulse vancomycin regimens. So they're really tough patients, difficult to resolve.

What I did is restarted the vancomycin at four times a day until they were asymptomatic. Then discontinued that and gave them the rifaximin and that same regimen. Three of these five patients had no further diarrhea recurrences and we followed them at least for two and a half months. The MIC of the *C. difficile* isolate to rifaximin from one of the failures was greater than 256, very similar to the experience with the other patient that we reported. However, the isolate from the other failure that we saw in the study was fully susceptible. So I don't know exactly why she failed.

However, failures in this study were recognized very early, within 3 days of completion, or in one patient was during rifaximin administration. So they show up very soon in my experience.

It still is an option, but we would like to see this in a randomized study to have a little more confidence about this particular approach.

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**Mechanism of Action**
So it begs the question, of how does this work or why does it work? One of the thoughts might be that there's more efficient eradication of the remaining *C. difficile* organisms. Maybe better drug delivery to luminal reservoirs. Or relative sparing of the normal fecal flora. I think this latter part is likely the mechanism, but clearly needs to be studied.

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**Positive Stool Cultures in 30 Asymptomatic *C. difficile* Carriers after 10 Days of Treatment with Vancomycin, Metronidazole, or Placebo**
Just want to mention a study what we've done a long time ago. These were not symptomatic patients, these were not recurrent patients, but these were asymptomatic patients that we found on the ward in the Minneapolis VA. The idea here was that we were going to try to eradicate *C.*

*difficile*, the colonization state or the carrier state, if you will. It was a naive approach, I guess, but this is what we found.

We found that at day 10 of treatment with vancomycin, that only one of the 10 were culture positive, whereas seven of the 10 that we gave metronidazole, were still culture positive. Very similar to the eight of 10 of the placebo patients. Again, we looked at the concentration of these drugs in the stool and we could find essentially no metronidazole in the stool on day 10. These were asymptomatic patients. And vancomycin, we predictably found very high concentrations of this drug because it's not absorbed. However, if you look at day 70, patients who were treated with vancomycin were much more likely to be positive again than if we'd given them nothing. If you look down, six of nine of the vancomycin patients versus two of the 10 placebo patients were culture positive. So it would have been better just to leave them alone, is the bottom line. In fact, one of those patients who we gave vancomycin became symptomatic, so we probably did harm.

The reason to do this, we thought might be to eradicate the carrier state when we moved from an old institution to a new institution and maybe get a leg up on the epidemiology in the new hospital. But this clearly was not helpful.

But again, shows vancomycin, while it's very effective at eradicating the organism, has this problem of recurrences. Exactly why that is is not clear.

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**Changes in *B. fragilis* grp Counts During Treatment of *C. difficile* Diarrhea with OPT-80**
This was a study done by Tom Louie, in a subset of patients that were studied in the early OPT-80 study. This is this new drug that's non-absorbed and has been studied for *C. difficile* disease. But what you can see here are the mean counts of *Bacteroides fragilis* before and after treatment. And these are three different doses of the Optimer's versus 125 milligrams of vancomycin. And you can see that by day 10 of treatment, the *Bacteroides* counts dropped significantly in the patients who were treated with vancomycin. So it's not something you'd normally predict. Vancomycin is usually thought of as an anti–gram-positive agent, but at least in the concentrations in the stool, this appears to affect *Bacteroides* counts significantly. So is just one issue, I think, with vancomycin, and maybe the reason is for recurrences.

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**Summary**
So in summary, metronidazole is effective treatment for mild and moderate *C. difficile* infection. However, vancomycin is superior to metronidazole in patients with severe disease. Early surgical consultation is recommended for patients with severe, complicated *C. difficile* infection. Treatment of the first recurrent episode should be based on criteria used for the initial episode. Treatment of patients with multiple recurrences is empiric, but tapering/pulsed dosing of vancomycin regimens are a reasonable and safe option.

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**Unanswered Questions**

The unanswered questions in regards to treatment would include how should severe *C. difficile* infection be defined? We're still looking for a good scoring system, if you will, or tool to define these patients. What factors predict complications or response to treatment? Should treatment for CDI be continued if the offending antibiotic cannot be discontinued? Such as in the case of osteomyelitis or endocarditis. We do not have any data to give a recommendation in that regard. And what is the optimal management of severe, complicated CDI? And will bowel flora–sparing regimens, if they can be defined, decrease *C. difficile* infection recurrences?

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**Acknowledgments**

**Slide 40**
**The End**