TRANSCRIPT
*Clostridium difficile* Infection*:*
Tracking a Virulent Pathogen
Fort Lauderdale, Florida
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**Dr. Stuart Johnson (Slide 1: *Clostridium difficile* Infection):**
Good morning, everyone, I am Dr. Stuart Johnson. I'm professor of medicine at Loyola University Medical Center and the Hines VA Hospital in Chicago. It's my pleasure to introduce you, welcome you to the continuing medical education satellite symposium, *The Impact of Clostridium difficile: Tracking a Virulent Pathogen.*

I'd like to thank the joint sponsors of this symposium, Robert Michael Educational Institute and Postgraduate Institute for Medicine. I'd also like to thank ViroPharma Incorporated for providing an educational grant for this program.

I'd like to also take the opportunity to point out that there are brochures available on your tables for CE certified lecture series entitled ***Clostridium difficile* Infection: Strategic Approaches for a Better Outcome.** So this is what it looks like. I'm told it's also referred to as "CDopoly." This is a lecture that you can request to hold at your institution. It is intended to assist clinicians in understanding the changing paradigm for diagnosing and managing patients with CDI, and information for scheduling the lecture at your institution is included in the brochure.

Now I'd like to discuss today's program. It will consist of four segments.

**Slide 2: *C. difficile*: Changing Epidemiology**
First, I'll give an overview discussing the changing epidemiology of *C. difficile*. Next, Dr. Dale Gerding will discuss *Clostridium difficile* testing. Then Ciarán Kelly will discuss *Clostridium difficile* infection treatment strategies, and then, finally, Dr. Keith Kaye will review prevention and control methods for *C. difficile.* Lastly, we'll take your questions.

**Slide 3: Dr. Johnson: Disclosures**
Please refer to your workbook for the learning objectives for this program, as well as for full disclosure information, so we don't have to repeat that. To receive CE credit for this program, you must complete the activity Evaluation form located at the back of your program.

**Slide 4: Overview**
Then at this time I'd like to begin the first presentation, *C. difficile: Changing Epidemiology*. In this segment I'd like to ask a series of questions, and then at the end, I'll answer them the best I can. The first question might be, is the incidence of hospital-acquired *Clostridium difficile* infection, aka CDI, still increasing? Two, what is the current status of the BI/NAP1/027 epidemic? Is there a community-acquired CDI epidemic? And are there clinically important strains that have emerged? Are there new risk groups? And then finally, are there new reservoirs or sources of infection?

**Slide 5: Discharges With CDI as Any Diagnosis**
So, this slide here shows you the changing incidence of *C. difficile* as reflected by discharge diagnosis from acute care hospitals in the United States, non-federal institutions. And as you're probably aware, since the year 2001, there's been a dramatic increase in the rates of *C. difficile* infection, whether it's the first diagnosis listed at discharge or as one of many diagnoses on the bottom line.

The last year that we have data for this suggests that maybe this slope is decreasing, if you will, maybe leveling off. And that's still yet to be determined.

**Slide 6: CDI-Related Mortality**
However, in addition to increased incidence, we've also seen an increase of CDI-related mortality. These are data based on listings on US death certificates from 1999 to year 2004.

Again, if you look at the age-adjusted mortality rate per million population, you can see that age is a major factor here, particularly for those patients over the age of 75. A very high rate of mortality.

**Slide 7: VA Hospital Discharges, CDI Diagnosis**
These are data that have been presented in a meeting, at the SHEA meeting, this spring by Dr. Kralovic. These are data from the VA hospital system looking at, again, discharge diagnosis where *C. difficile* was listed. And the slope of the curve appears to have changed significantly in two points. Again, between 2000 and 2001, you see the same increase that we saw in the other slide. But at the end of 2005, the slope decreased. So this is like the first real evidence that the incidence of *C. difficile* may be peaking, if you will, or have peaked.

**Slide 8: CDI Mortality Rates Parallel Age**
These are data from Vivian Loo in Quebec where the rates and mortality increase in parallel with patient age. And, again, you can see the data is similar to the US discharge data or the mortality data. The attributed mortality really increases once a patient is over 71 years old.

**Slide 9: Emergence of Epidemic BI/NAP1 Strain**
Coincident with this increase in rates that we've seen across the United States and Canada, there's been this emergence of this epidemic strain that's been referred to by various typing techniques as BI/NAP1 or 027. It was the predominant strain in eight US hospital outbreaks in 7 states that was reported by Cliff McDonald at the end of 2005.

Now this strain has a variety of characteristics. Just pay attention to toxinotype III, because I'll talk about another emerging strain that's a different toxinotype, if you will. In addition to toxin A and B, it has a different toxin called binary toxin. And then the deletion in what's been shown to be one of the negative regulators of toxin production, *tcdC*.

Most dramatically, this outbreak occurred in the Quebec area, Montreal, between 2003 and 2004. There were over 12 hospitals that reported increased rates and severity of CDI. And, in fact, it's been estimated that 2000 people died directly attributable to *C. difficile* infection in that city in those 2 years.

A task force was formed. Public reporting became mandatory for CDI, and the same predominant strain that was responsible for the outbreaks in the US hospitals was found in the Montreal outbreaks.

**Slide 10: States Reporting BI/NAP1 Strain**
These are the current states of the spread of the epidemic strain in the United States. It was confirmed by the CDC. Now, you can see there are several states that are missing here, but most of these states we do not have good data for. No isolates were submitted or specimens were submitted for testing. So this is really prevalent throughout the United States, and you'll see in Canada as well.

**Slide 11: Prevalence of BI/NAP1 Strain, Canada**
These are data on prevalence of the outbreak strain in Canada as of 2005, and these are the percent of isolates that were typed from each province here. You can see that Quebec here had the predominant number of isolates due to the epidemic strain with almost 80%, and much lower in some of the western provinces.

**Slide 12: Prevalence of BI/NAP1 Strain, Europe**
This outbreak has spread to Europe. If you just pay attention to the stars—the stars represent outbreaks, the dots represent sporadic cases. But this is really kind of centered in the United Kingdom, northern France, the Netherlands, and Germany, and you don't see any real outbreaks—I guess there was one outbreak here in Finland, but mostly in northern Europe.

**Slide 13: *C. difficile* Isolates in North America**
These are data from clinical isolates that were submitted to our laboratory as part of a large phase III multicenter study comparing vancomycin, metronidazole, and a toxin-binding polymer. And what I'd like to point out is just the incidence or the prevalence of the epidemic BI strain here in North America and Europe and then Australia. It was 36% of the isolates across the study from North America were the epidemic BI strain. Much lower in Europe. However, if you looked at those three countries—the United Kingdom, the Netherlands, and Belgium—this accounted for about 33% of the isolates there. So very similar to what was seen in North America.

And Australia they did not see it. It was a very small sample size, but it was not seen in Australia. And then this REA type BK, you will see it only comprised 9% of the North America isolates, 18% of the Europe isolates, and was seen in one case in Australia. But I'll point that out because this is another strain that's been emerging, if you will, and is of particular interest.

**Slide 14: Epidemiologic Risk Factors**
So if you look at the epidemiologic risk factors, or the major risk factors that we know for CDI,

antibiotic exposure surely is one of the major risk factors, hospitalization, and advanced age. And the reason that these are risk factors is likely due to the fact that antibiotics make a patient susceptible to *C. difficile* acquisition. Hospitalization is a surrogate for exposure to the spores, and then advanced age may represent waning immunity.

Now, if you look at the newly reported risk factors, you can see there are cases that have been reported where no antibiotics were listed. So what is it that makes these patients particularly susceptible? We don't know for sure, but inflammatory bowel disease is one potential reason that maybe they are susceptible. Community-onset cases—there are other reservoirs probably for *C. difficile* spores, and so their exposures are different. And then peripartum women are one risk group that has been reported previously or recently and may somehow relate to immunity as well.

**Slide 15: Community-Onset CDI, North Carolina**
So this is one study of community-onset *C. difficile* infection at a VA center in North Carolina where they looked at the predisposing risk factors among cases and controls. And what shows up here, not surprisingly, as significant factors, would be, first of all, antibiotics or antimicrobials, inflammatory bowel disease was significant, as well as outpatient visits. So, again, even in the setting of community-onset disease, there seems to be some kind of link with hospitalization or healthcare institutions.

Proton pump inhibitor use in this study was not significant. And, again, this is somewhat of a controversial risk factor. If it is a risk factor, it's clearly less important than antibiotics.

**Slide 16: From Discharge to Positive Assay**
These are data from the Hines VA Hospital in the Chicago area, where Heidi Chang was a medical student at the time, looked at all cases of CDI that were diagnosed in patients that presented in the clinic setting or in the emergency room. So these were people that came to our institution with *C. difficile* infection. We actually had intended to study community-acquired CDI, but as you can see the vast majority of cases had recently been in the hospital. And these are data of the number of patients compared to their previous hospitalizations. So, 70% of the patients that presented in our community setting had actually been recently hospitalized. And not only hospitalized, but their other risk factor, antibiotics, had occurred primarily in the previous hospitalization—either exclusively in this hatch bar or both in the previous hospital and as outpatients.

Then if you look over here, there's a smaller group that appeared 61 to 100 days after they'd been discharged, and they were more likely to have antibiotics only as outpatients and probably represent a true community-onset *C. difficile* infection or community associated. So, again, in our setting, even though we see community-onset cases, the vast majority of these cases have been recently hospitalized.

**Slide 17: Timing of Community-Onset CDI**
These data were repeated in a much larger study in North Carolina with several institutions where they saw the same phenomena—that there was a big cluster of cases that occurred where

they had been hospitalized recently. But you can see beyond that there was a number of cases, in fact many cases here are greater than 52 days after previous hospitalization that showed up, really had no association with previous hospitalization and probably had community-onset disease, or true community-associated disease was more common in this area.

**Slide 18: *C. difficile* in the Environment**
So if you don't need to be hospitalized to be exposed to *C. difficile*, what are some potential reservoirs in the environment? This was a study where they looked at a variety of different sources: river water, swimming pools, lake water, sea water, soil, tap water, dog feces, cat feces, home environments, raw vegetables. So even being a vegetarian doesn't protect you necessarily. Farm animals—but no fish guts. So you're free to be exposed to fish guts, if you will.

This organism is not unlike *Clostridium perfringens*, and the spores can be found in a variety of different environmental sites if you look very carefully.

**Slide 19: Timelines for CDI Exposure**
This was the timeline for definitions proposed by the CDC, the working group on *C. difficile* epidemiology. What's proposed here is that we define patients with hospital-onset, healthcare facility–associated disease is those cases that occur 48 hours after admission during their hospitalization. And then if you have the ability to do so, it's also, I think, helpful and instructive to look at cases that occur shortly after discharge. These would be community-onset but healthcare facility–associated. Beyond 4 weeks after their previous hospitalization, this would be an indeterminant and not clearly associated with the hospital, and then beyond 8 weeks, these would be the community-associated *C. difficile*–associated disease.

**Slide 20: Severe CDI in Peripartum Women**
The cases of severe CDI in peripartum women have been reported by a couple different investigators, and some of these cases are quite dramatic. These are just two that are shown here. One was a 20-year-old that had preterm labor, had watery diarrhea, significant—10 bowel movements per day—apparently had no antibiotics or recent hospitalization. And this patient had a fairly severe case and required a colectomy but survived.

Another 31-year-old that you can see here, it was 14 weeks' gestation with twins. She had 3 weeks of watery diarrhea, had antibiotics, but it seemed to be somewhat trivial from the trimethoprim-sulfa 3 months previously. She was admitted to the ICU with a dilated colon, poor response to metronidazole and vancomycin, was readmitted with shock 3 days later and had a spontaneous abortion. Then, unfortunately, the patient died. However, if you look at overall, I think that peripartum cases are not very common. This review by Kevin Garey et al. found 24 cases, and most of them had otherwise typical risk factors. Most of them had been associated with antibiotic use, and most of them had been at the hospital. The unusual part of this, of course, is their age.

**Slide 21: Transmission: Food-Producing Animals**
So what about other potential sources for *C. difficile* transmission? The one area that is of particular interest is food-producing animals, and previous studies have suggested that *C. difficile*

isolates from humans and animals were of different lineage. There's been at least one study where patients and their pets were looked at, and they seemed to have no relationship. You could find *C. difficile* in the feces of their pets, but they were not related to the isolates in the cases in the patients. However, it's been increasingly recognized that food animals—this *C. difficile* is either a pathogen or sometimes a commensal, and *C. difficile* strains that have been responsible for human disease have been found to contaminate retail meats.

**Slide 22: Toxinotype V Strains Humans, Animals**
We collaborated with the CDC in this one study looking at, again, toxinotype V strains. This was the REA type BK that I showed you on the earlier slide—different than the epidemic BI/NAP1/027 strains. But we collaborated with the CDC and Glen Songer at University of Arizona. We compared 15 human and 33 animal isolates. They were all compared by REA typing and pulsed field typing. They belonged to what we refer to as a BK group and NAP7/NAP8.

Fifty percent of the human isolates, however, came from community-associated cases. And from our experience we would expect maybe 20% or less, in most hospital surveys, coming right from the community, if you will. So they seem to be enriched in the community, these isolates. And there was a suggestion of increase in these cases over the time period that the study was done.

**Slide 23: Toxinotype V Infection (Netherlands)**
Ed Kuijper and his group at the Netherlands reported this last fall. Again, these were these toxinotype V isolates defined by ribotyping as 078, looking at over 1600 isolates from 2005 to 2008 that were analyzed by PCR and toxinotyping. What he did is he looked at the risk factors or the epidemiologic associations with these cases, and if you compare the toxinotype III, which is the North American epidemic strain 027/BI/NAP1 compared to this toxinotype V, you can see that overall frequency was less than it was for the epidemic toxinotype III strain. However, over the time period, the number of isolates due to toxinotype III decreased, where they increased for toxinotype V.

And more interestingly, I think here, was that healthcare facility outbreaks, 14 outbreaks were associated with this epidemic BI/NAP1/027 strain, whereas only one healthcare facility outbreak was associated with this toxinotype V—so, very similar to what we see in the North America studies. This toxinotype III strain is associated with outbreaks in healthcare facilities, where these tend to be more community associated, if you will. Age, not terribly different, a little higher in the toxinotype III cases. And then, again, community-associated cases were enriched in the toxinotype V cases.

**Slide 24: Minimum Spanning Tree Analysis**
They also used another sophisticated molecular genetic testing that may give more information as far as the genetic relationship. All of these strains were related by MLVA testing. However, there were four clonal groups, defined as A, B, C, and D, where they were very, very closely associated—only one or two genetic differences by this testing technique. And as highlighted by the red arrows, the pig isolates lined up right with the human isolates. So they were really indistinguishable from the animal isolates. They're very, very closely related.

So this is not proof that *C. difficile* is foodborne related, but it is suspicious that there is a connection here between animal isolates and human isolates for this particular strain.

**Slide 25: Conclusions**
So, in conclusion for this section, is hospital-acquired CDI still increasing? Yes, but it may be slowing, and this is data that is still coming out. So what is the current status of the BI/NAP1/027 epidemic? It remains as the most prevalent strain in the United States, and, again, highly associated with hospital-acquired cases.

Is there a community-acquired CDI epidemic? I can say probably no, but the community cases will continue to occur. Are there other clinically important strains that have emerged? We talked about toxinotype V.

And then, are there new risk groups? I would say maybe. Peripartum women in particular are a group that I think still needs further study. And then finally, are there new reservoirs? Again, foodborne transmission is tantalizing but has not been proven.

**Slide 26: CDI Testing: The Shortcomings?**
So, I would like to now move on, and Dr. Gerding will begin his presentation [*CDI Testing: What are the Current Shortcomings and How Can We Improve Testing?*]. Dr. Gerding is a professor of medicine at Loyola University, Stritch School of Medicine, and the associate chief of staff for research and development at the Hines VA. So it's my pleasure to introduce Dale.

**Dr. Dale Gerding (Slide 27: Disclosures):**
Thank you, Stu, and good morning. Wow, you guys get up early for these meetings! The first question I wanted to ask everyone is, how many of you know what lab tests for *C. diff* your hospital does? Could you name the test? Just put your hand up if you can. So the take-home message from this talk is going to be: find out what test your lab was doing because it's probably going to change its test system very soon, and some of the new testing is very likely to increase the sensitivity of *C. difficile* detection. You may see your hospital rates change, and it may be related to testing. So, get to know your lab, go talk to them, find out what they're doing, and if they're going to change, be sure they let you know about it—because I think it's potentially going to affect our rates in hospitals because the new testing hopefully is going to be much more sensitive and specific.

**Slide 28: Four Major CDI Clinical Problems**
So, we have had four problems with *C. diff*. You're well aware of the first one, which are inability to prevent *C. diff* in high-risk settings. The second one, which is our lack of a sensitive and rapid diagnostic test, is the subject of this talk. And we still don't have the answer for that. But we have had very poor treatments that would prevent the recurrence of *C. difficile*—we're pretty good at treating the disease initially. And finally, we really have not got good treatments for fulminant or extremely severe cases of *C. diff*.

**Slide 29: Key Points To Be Covered**
So the focus of this presentation will be on the detection of *C. difficile*, either the organism or its toxin. So the points to be covered, the history of testing for *C. difficile*, the standard reference tests, there have been two traditionally. One is to do a cell cytotoxin test to detect toxin in the stool directly. The second reference test is to culture the stool, isolate the organism, and show that it makes toxin. So those two reference tests I'll compare. I'll look at test sensitivity, specificity, and also a very important third factor, which is the turnaround time to get a result from the laboratory.

I'm going to talk a little bit about the two-step glutamate dehydrogenase, or GDH test. And whether that's the answer, your laboratory may be using that protocol. And then—how many of you have seen orders for "*C. diff* toxin times three"? Oh boy! So we're going to talk a little bit about, can you bludgeon a test and eventually get the answer you want out of it by just keeping on doing it? Which is really what that's all about. And unfortunately it is, and I hope I can prove to you that that is *not* the thing to do.

Finally, there's a new test coming. This is the one that probably will improve sensitivity. It's called real-time polymerase chain reaction, or PCR. And we'll talk a little bit about what its role is and how it might affect testing.

**Slide 30: Before We Begin CDI Testing**
So before you begin testing for *C. difficile*, it's very important to look at the patient. You really need a reason to send the test. Tests should not just be sent because somebody feels like it. The patient should have diarrhea, watery, or unformed stools. The laboratory should act as the gatekeeper for those specimens so that when they get what in the laboratory is referred to as "rattlers"—rattlers make noise when you shake the stool container. Those should not be tested for *C. diff*. And the patient should meet minimum clinical criteria for diarrhea—that is, have at least three loose or unformed stools in a 24-hour period.

**Slide 31: History of CDI Diagnosis**
So, what's the history of testing? Well, it turns out that the cell cytotoxin assay was developed roughly at the same time that the organism was discovered as the cause of *C. difficile* infection. Because the first thing that was discovered was the toxin in the stool. Nobody knew where it was coming from, but it was very clear that it affected the cells. So the cell cytotoxicity assay was developed in Boston by Chang in 1978.

Shortly thereafter, the culture method was also published by Lance George in 1979. And he developed a selective media so that we could isolate *C. diff* from stool and suppress all of the other competing bacteria.

Then it was shortly thereafter in 1983 that the first enzyme immunoassay for toxin A was developed. This is really the technology that we've been using now for about the last 25 years, and it was developed for the detection of toxin A. Because toxin A, when you put it into hamster models, produced disease alone, whereas when you put toxin B into the hamster, it did not

produce disease alone. Therefore, toxin A was thought to be the most important toxin. We now know that that's also incorrect. And unfortunately, we used the toxin A test for probably 10 or 15 years until we realized that there were strains around that could cause disease that don't make toxin A.

The latex test was the glutamate dehydrogenase test originally developed as a test for toxin. But the people who developed it mistakenly identified the protein as toxin A, when indeed it was something else. It was this glutamate dehydrogenase. And that test, the latex test, historically, was very poor with sensitivity and also very poor in terms of specificity. However, the test has now been put into a new format and is now referred to as the common antigen test, and you may find that that is being used in your institution as well.

**Slide 32: History of CDI Diagnosis**

So the PCR, the polymerase chain reaction, which actually amplifies the genes of these organisms, has been around a long time. In 1993, Kato working at CDC, who is now in Japan, published on this test, and it has never come out commercially until just the past year. So we now have that test, and we probably will have a second commercial test available soon. And that's what I think you need to be aware of in terms of changing testing in case your lab—which, by the way, if you're doing MRSA screening, then your lab is probably using PCR right now. Those same instruments can then be adapted to test for *C. difficile* as well. So labs are very interested in this because they're now getting used to the PCR technology.

So, in the next box, clinical outbreaks of *C. difficile* due to what are called A−/B+ organisms—they don't make toxin A, but they do make toxin B—were discovered. They were completely missed by this toxin A test. And it turned out there were multiple outbreaks; although this strain has never become very common. It's still only about a 2% or 3% frequency. But basically once that was discovered, that was the end of the toxin A test, so it's pretty gone by the wayside.

Then O'Connor published a paper about the insensitivity of the enzyme immunoassays. It's interesting that that took almost 20 years to get into the literature. And then the superior sensitivity of toxigenic culture versus the cell cytotoxin assay was published by Delmee, showing that even though so-called gold standard cell cytotoxin tests have been around a long time, it is not nearly as sensitive as trying to culture for the organism and testing the organism for toxins.

**Slide 33: Toxigenic Culture vs Cell Cytotoxin**

So here's the Delmee paper. Delmee was using culture in their laboratory in Belgium, and they had over 1000 liquid unformed stools that were culture-positive for *C. diff.* Now, when you culture, not everything you get is going to be toxigenic *C. diff* because circulating in our hospitals are a lot of non-toxigenic organisms—probably as many as 40%. So 77% of those isolated stools were toxigenic *C. diff,* and 23% were nontoxigenic.

So then they did the cell cytotoxin assay on the stools of those patients that had the toxin-positive *C. diff*, and the sensitivity of the cell cytotoxin assay in their lab was only 56%. Surprisingly low, I think, because most people would have predicted that would be about 80%.

And then they did the opposite, which is to look at the stools that were cell cytotoxin-positive to see how many of them actually grew *C. diff*, and only five of them did not grow. So that, compared to the cell cytotoxin test, the culture was 99% sensitive, whereas the cell cytotoxin test was only 56% sensitive compared to culture and testing for toxin. Now, the problem with both these tests is they're extremely slow. They're too slow for most laboratories in today's rapidly moving hospital environment.

**Slide 34: Interpreting Cell Cytotoxicity Assay**
For those of you who wonder about cell cytotoxin assays and what they look like, this is a typical cell layer. The cells are attached to each other. When toxin is present, they round up and turn into little balls like this. You can prove that this is due to a *C. difficile* toxin by using a neutralization step, which is an antibody that's specific for these toxins. So cell cytotoxicity is still being used, still a good reference test, but generally slow for our current needs.

**Slide 35: 86-Year-Old Man With Pneumonia**
So I've put into the talk an old case that's probably at least 10 years old. Typical hospital patient, 86 years old, comes into the hospital with community-acquired pneumonia, gets ceftriaxone, and gets switched over to an oral fluoroquinolone. By day 4 he's doing great, normal temp, preparing to discharge, develops loose stools. Abdominal cramping, 6 to 8 watery bowel movements a day, no blood in the stool. Three stool specimens are submitted to the laboratory, and they all come up negative by this enzyme immunoassay for toxin A. This is very similar to a case that Stu Johnson described in our hospital, which unfortunately led to the death of this patient because nobody really paid attention to the test and decided that maybe the test was wrong. And we refer to this repeatedly as what's called "the tyranny of the test result." Some physicians and healthcare providers cannot ignore the result of a test, so if the test is negative, they believe the patient doesn't have disease. And if the test is positive, they believe the patient has the disease. And yet none of these tests are perfect in terms of identifying those patients.

**Slide 36: Pseudomembranes on Endoscopy**So this patient underwent endoscopy. And you can see that he has pseudomembranes. This is how pseudomembranes look through the sigmoidoscope or colonoscope. You see these large white patches on the interior of the colon. This is a good specificity test, but not a very good way sensitivity wise to detect the disease, because it's positive only in about half the patients who have *C. difficile* infection.

**Slide 37: Diagnosis: Pseudomembranous Colitis**
So the question is, in a patient with pseudomembranous colitis, why is this EIA toxin A test negative three times? And the answers are, the test is only 50% to 70% sensitive. Some strains of *C. diff* do not make toxin A. It's not the best test, but laboratories like it because it's fast and less labor intensive than other tests and relatively inexpensive. Or is it all of the above? All of the above. If you're a good test taker, you can always figure out these answers. But indeed that is correct, all of these are correct, and all of the above is the answer.

**Slide 38: 4 Toxin  EIA Tests vs Cell Cytotoxin**
This is just an example of some of these comparative test results. So if you take a cell cytotoxin

assay and you say its sensitivity is 98%—and remember, this is much lower sensitivity than doing culture, then these toxin A tests are only about 50%, these two right here. And as a result of that, testing has changed to detect both toxin A and B. You see then you can raise the sensitivity up to around 80%. So these are the tests that are currently highly likely to be used in your hospital.

**Slide 39: Method of Laboratory CDI Diagnosis**
So when you go to the laboratory, you might ask, "Are you doing an enzyme immunoassay for A and B?" Because that very likely will be the answer, because when this was surveyed in the past, and this is several years ago, the vast majority of laboratories are indeed doing that kind of test.

The next most common test is—the answer that I got when I asked the question, is "I don't know." So even among—these were primarily epidemiologists and infectious disease physicians answering this question did not know what test their laboratory was using. Relatively few laboratories are still using the enzyme immunoassay. For toxin A, I would say that's zero now. And very few are also using the cell cytotoxin assay, because it's also labor intensive and also somewhat slow.

**Slide 40: *Clostridium difficile* Diagnostic Tests**
So the diagnostic testing that we have, endoscopy—very specific for pseudomembranes but very insensitive. Culture—very sensitive and not so specific, because you have to test for toxin when you're doing culturing. The cell cytotoxin assay—reasonable sensitivity and very good specificity. Enzyme immunoassays for toxin A are relatively less sensitive, and enzyme immunoassays for A and B improve that sensitivity. Then we have the glutamate dehydrogenase test as done as a latex-type test and then as an enzyme immunoassay. And when the enzyme immunoassay technology was used, sensitivity improved markedly. As a result, the two-test strategy has been developed.

**Slide 41: Two-Step Testing Using GDH-EIA**
The two-test strategy is done in the following way: use this GDH common antigen test as your first step in the laboratory. And the idea here is to get a screening test in with very high sensitivity and identify all the negatives immediately. Now, this test is not specific enough to say that it's toxigenic *C. diff*, and all you can say is that we need to do further testing to make sure it is *C. diff*. But you can probably eliminate 80% to 90% of your test specimens by doing this test if the sensitivity is indeed as high as it has been claimed in some studies.

The remaining stools then undergo cell cytotoxin testing and negative assays, which are more than 99% predictive of the cell cytotoxicity being negative in at least one study, would suggest that this is a very reasonable way to go. It saves a lot of workload in the lab, saves a lot of cost to labs, but it's still very slow, and it's slow because the cell cytotoxin test takes a couple of days to report back the results.

**Slide 42: Sensitivity: GDH, Toxigenic Culture**
So some advantages to this for the laboratory—it's still not clear if this is a good strategy because the GDH has now been tested against toxigenic culture, which is the most sensitive test

we have. And what was thought at one time to be at least 90% to 100% sensitivity is really more in the 84% to 87% sensitivity range. And the question is, is that good enough to be used as a screening test in laboratories? A more recent test just found that the Triage® GDH test was only 76% sensitive, which really would not be sensitive enough to use as a screening test.

**Slide 43: Can Low Sensitivity Be Overcome?**
Now, here's the slide about trying to bludgeon the test result that you want by sending more specimens, and this is courtesy of Lance Peterson who gave this presentation at ICAAC last year. If you do 1000 tests, and your prevalence in the population for positive tests is 10%—which is close in hospitals, generally around 10% to 15%—and the sensitivity of your test as it is with the enzyme immunoassay is 73%, and the specificity is 97.6%, which is quite good, you do your first 1000 tests. The true positives that you pick up, which would be 100, you'll pick 73% of them up, or 73 positive tests, but your false positives will be 24 tests. So the 2.4% will turn up as false positives. You will fail to detect 27 patients who really have the disease, and you'll have 903 patients left who are still negative. So now you take stool two, and you submit another specimen. Now, with your 73% detection positivity, you pick up 18 patients. But now because of the specificity issues, you now have 22 false positives. So now you've picked up 40 positives, but over half of them are actually false positives. If you continue this, it only gets worse because the number left in the population that are undetected keeps going down, and the number that you are picking up as a result of the poor specificity also keeps going up. Hence, you are detecting more false positives than you are true positives. So this is really not an effective strategy to deal with poor sensitivity of tests.

**Slide 44: Comparison of Real-Time PCR**
Now, what might you do that could improve sensitivity? Real-time PCR now is something that's being looked at very carefully and is now available commercially. So if you use a culture, so-called cytotoxic culture, you culture the organism and test for toxin, use that as your reference test. Then real-time PCR detected 93% of those cases with a fairly high specificity of 97%.

The toxin A/B enzyme immunoassay was pretty good. It was 73%, and it's actually pretty close to cell cytotoxin, which was 77% in this study. But this sensitivity is what is making people interested in this test, plus its rapid turnaround.

**Slide 45: Real-Time PCR vs Toxigenic Culture**
And the test that's currently on the market in the US, the BD GeneOhm™ test, was compared in a recent meeting at ICAAC-IDSA. And sensitivities, again, ran in this 92% to 94% range, with specificities up in the 98% range. So it looks like these may be potentially single test methodologies that will be sufficiently sensitive to pick up *C. difficile* considerably more frequently than our current test methodology does.

**Slide 46: Real-Time PCR vs Toxigenic Culture**
So real-time PCR can be used to detect the toxin genes of *C. diff.* It's usually targeting the toxin B gene to avoid missing the toxin A−/B+ strains, and this is done on a stool specimen. Real-time PCR can also be used to detect specific genetic markers, such as the epidemic BI/NAP1/027 strain. So you would not only be able to say I've got *C. diff* in this patient, but I've got the

BI/NAP1 strain. Now what we think eventually will happen is some other strain will become more common than the BI/NAP1/027 strain. But for now, at least this may, epidemiologically, be very helpful for you. So you have three new *C. diff* cases on a ward, you actually will be able to say, yes, they're all the epidemic strain or they're all not the epidemic strain. So you'll have some information that may be helping you epidemiologically. Recently, we've had an outbreak of eight cases on a long-term care unit. We got the isolates, got them into our research lab. About two weeks later, we were able to type them all, and everyone of them was the epidemic BI/NAP1 strain. But you could have known that the same day that you were isolating the specimen from stool if you were using this technology.

**Slide 47: Unresolved CDI Diagnosis Issues**
So to wrap it up, unresolved *C. difficile* diagnosis issues. We still have low sensitivity of most current tests that are in use, with the exception perhaps of the real-time PCR. We have slow turnaround of our most sensitive tests, that is, the cell cytotoxicity or the culture. The use of the two-step method with the GDH enzyme immunoassay still has slow turnaround for the positive test, and it may not be a sufficiently sensitive screening methodology.

And the big questions that remain are, is the sensitivity of real-time PCR sufficiently high to displace enzyme immunoassays for toxin and the GDH test? And finally, is gene detection, which is what these PCR tests are doing, equivalent to toxin detection for the diagnosis of *C. diff* infection? And I think we're going to have to wait until the test is used more before we get those answered.

Thank you very much.

**Dr. Stuart Johnson (Slide 48: CDI—Treatment Strategies):**
Thank you, Dale. Next, Dr. Ciarán Kelly will present *Clostridium difficile Infection: Treatment Strategies.* Dr. Kelly is an associate professor of medicine at Harvard Medical School and the director of gastroenterology fellowship training at Beth Israel Deaconess Medical Center, and the chief of the Herrman L. Blumgart Internal Medicine firm in Boston, Massachusetts.

**Dr. Ciarán Kelly (Slide 49: Disclosures):**
Thank you. Good morning. I hope you're still awake or have begun to waken up. Either way, it's a pleasure to speak with you, and I've been given the task of talking about treatment of *Clostridium difficile* infection.

**Slide 50: CDI: Treatment Strategies**
So, if I was giving this talk in, I guess 1980, I would talk about metronidazole and vancomycin. And I'm mainly going to be talking about metronidazole and vancomycin, unfortunately. With the challenges we've heard about, how the epidemiology of *C. diff* is changing, and in particular increasing numbers of cases. Unfortunately, our management strategies have not quite kept in pace.

I will be talking a little bit about some more subtle ways that we're perhaps changing the ways

that we use metronidazole and vancomycin, and in particular, about using vancomycin in severe disease. And then I'll finish with hopefully some good news about some newer treatment approaches—some that unfortunately don't seem to be the answer, but a couple that actually hold some promise, although they're not yet FDA approved. And I should say at the very beginning, the only FDA-approved agent for *C. diff* is vancomycin. So everything else that I talk about, including metronidazole, are not FDA approved.

**Slide 51: *C. difficile* Diarrhea Treatment**
Metronidazole and vancomycin, if we look at the literature, at least up until 2005 as it was published, we can see on the right of this slide in red are failure rates and in light blue are recurrence rates in controlled clinical trials treating *Clostridium difficile* infection. And for vancomycin, although there have been variations from study to study, the overall results have been fairly consistent over the last couple of decades. And if you do the math, you find that the failure rate in the literature was only 4%, but the recurrence rate is fairly consistently around 20% or so.

With metronidazole, the situation is actually quite different. If you look at the literature up until 2000 and look at the reported studies before 2000, the recurrence rates and failure rates were identical to those of vancomycin, and there really was no evidence that vancomycin was better or metronidazole was worse. But the studies since 2000 have been quite different, and they have suggested increasing failure rates with metronidazole, although the recurrence rates do not appear to have changed remarkably. So that the combined literature, up until 2005 at least, for metronidazole were very similar recurrence rates to vanco, but beginning to show increased failure rates compared to vancomycin.

**Slide 52: Vancomycin vs. Metronidazole**
And the trial that really was, I think, pivotal in providing evidence that vancomycin is better than metronidazole in a subset of patients with *C. difficile* infection was published by Zar and colleagues in 2007. So we had believed, I think many of us for many years, that vancomycin had an edge on metronidazole. But we were never able to point to data, because the data, as I've just shown you, indicated that they were equivalent.

This study, however, approached it in a different way. It was a prospective, randomized controlled trial comparing vancomycin at a standard dose of 125 QID for 10 days to metronidazole at what arguably is a relatively low dose of 250 QID. But nonetheless, a dose that's sometimes used.

What was different about this study was that they stratified for disease severity. Now, how do you do that? And this is something we'll come back to. We actually don't know exactly the best way to identify somebody who's going to have or already has severe disease, but the way that they approach it in this study was to say that anyone with two or more points had severe disease. And you earned a point by being over 60 years of age, which in my *C. diff* population is almost everybody, and you saw the data on that. It's predominantly an illness of the elderly. So you have to have at least one of these additional features. You have to have a fever, low albumin, or a high white blood cell count.

Alternatively, you earned two points straight if you were known to have pseudomembranous colitis or if you were in the intensive care unit. So, having stratified by disease severity and randomized to metronidazole and vanco, this is what they found.

So if we look at mild to moderate, so these are patients with a score of 0 or 1, you can see that the response rates to vancomycin and metronidazole were similar. Metronidazole numerically was slightly more likely to have a treatment failure, 10% failures, and vancomycin only 2%, but that difference was not statistically significant.

In those with severe disease, however, the difference was numerically greater, 97% responding to vanco, 76% to metronidazole, and that difference did reach statistical significance. So this is the first evidence that vancomycin is more likely to be effective in treating patients with *C. diff*, specifically those with severe disease.

**Slide 53: Treatment of a First Episode of CDI**
So that has changed our approach to managing *Clostridium difficile* infection. Mild *Clostridium difficile* infection—the approach is, stop the antibiotic that caused the disease if you can. Request one of the stool toxin assays that Dr. Gerding has just been speaking about, and see how the patient does. And some patients, a substantial proportion of patients, will improve and will not need metronidazole or vancomycin. Although I will say that, at least in our hospital, previously about 10% of our patients when we looked at this 10 years ago, 10% of our patients were managed conservatively by stopping the antibiotic and following the course of the disease. And when we looked at it more recently, 0% of our patients were managed conservatively. Everybody was put on metronidazole or vancomycin.

If a patient has moderate symptoms, or if you stop the antibiotic and their symptoms persist, or if you can't stop the antibiotic that caused the disease, then we would treat with metronidazole. A dose that's often recommended now is 500 TID, so a little bit higher than the dose that was used in the Zar study.

Then if the patient has severe disease, now I think there's a firm recommendation that vancomycin be used as a first-line agent in patients with severe disease, and that's something that's relatively new. There was sort of a soft recommendation previously. And I think the recommendation is becoming more clear and more definite that patients with severe disease are more likely to fail metronidazole and therefore should be treated with vanco first line.

**Slide 54: Markers of Severe CDI**
So that brings up the question, well, then how do we identify patients with severe disease to make this clinical decision, as regards whether to treat with vanco or treat with metronidazole? On the left I've listed some, not all, but some of the parameters that have been looked at and have been used or shown to indicate severe disease. High number of bowel movements, and elevated white count has been a consistent performer in terms of identifying severe disease. In other words, a number of studies have independently indicated that a high white count is an indicator of severe disease, and a very high white count is an indicator of fatal outcomes or

colectomy. So that's a very useful parameter if it's present. The absence of an elevated white count doesn't exclude severe disease, but if you have a patient with *C. diff* and a white count that's rising above 15 or above 20, that's something certainly to take note of. A rising creatinine has also been identified, as well as low albumin. CT findings as shown here, and so on.

So there's a long list of potential indicators, but really the only one that's been demonstrated prospectively and published is the Zar study, and those are the indicators that I had shown earlier. There's another study that also showed similar data that I'll show later, but that's not yet published.

**Slide 55: Colonic Distention**
Talking about fulminant disease, which I'm going to talk about the management of in a moment, I just wanted to alert you to the phenomenon of patients presenting with severe *C. difficile* infection who may have very little or no diarrhea. And this is a diagnostic trap. These patients will often present with abdominal distention and discomfort but have very little diarrhea because they have an ileus and/or are developing toxic megacolon. The absence of diarrhea or the fact that there's minimal diarrhea often means that the diagnosis of *C. diff* is missed or delayed until the illness progresses even further. So somebody with *C. diff* colitis who has very little diarrhea is equivalent to what we used to talk about patients with ulcerative colitis whose diarrhea resolved as they got sicker—toxic megacolon requiring surgery. And the same occurs in *C. diff* infection.

This is an elderly patient who underwent hip surgery and 4 days postoperatively developed abdominal distention and mild discomfort. It was felt to be Ogilvie's syndrome or pseudo-obstruction, he was taking narcotics. The following day, he was hypotensive and had fulminant *C. diff*, went to surgery, and unfortunately died. This is a situation where we heard about the poor sensitivity but high specificity of colonoscopy finding pseudomembranous colitis. The patient presenting with an acute abdomen type picture where there's a question as regard to whether or not this may be pseudomembranous colitis versus some other intra-abdominal catastrophe, such as ischemic colitis, perforated diverticulum, et cetera.

This is one situation where sigmoidoscopy can be very useful in providing an immediate diagnosis. So in a patient like this, if you see these classical pseudomembranes, then medically you know exactly what the diagnosis is and you can define or decide upon the medical or surgical management accordingly.

**Slide 56: Management of Fulminant CDI**
In patients with fulminant *C. diff*, which refers to *C. diff* where the clinical course is rapidly progressive, like the patient I just described, or refractory where a patient has severe *C. diff* that is not responding to treatment with either metronidazole or vancomycin. The recommendation is to use a higher dose of vancomycin orally. This recommendation really is not evidence-based. It's based on opinion, so it's not as firm a recommendation as the recommendation to use 125 QID in severe disease. This recommendation to use a higher dose in fulminant or refractory disease is based on opinion, as I said, and not really based on data. I can't show you data to say that these patients are more likely to respond to the higher dose, but it's something that I would

nonetheless do.

If the patients with severe disease, fulminant disease, have an ileus—which is not uncommon—then there's a problem of course with giving oral vancomycin. And in that situation we can use the intravenous route. Metronidazole given orally is almost completely absorbed in the upper small intestine and then re-excreted or secreted across the inflamed colon into the colonic lumen, so giving intravenous metronidazole will result in the same form of re-excretion into the colon. And in this way you can get around the problem of an ileus. Most of us though, in this situation, would like if at all possible to get vancomycin in there as well. And we'll do that any way we can. If the patient can take some PO, then let them take some liquid, oral vancomycin. Or it could be given via nasogastric tube, or it can even be given by enema—sort of, basically, any way we can get it in there.

Certainly this is a situation where an early surgical consultation is important to try to make the very difficult decisions about surgery in these patients. These are typically elderly, high-risk patients with multiple comorbidities who aren't fit for a haircut let alone a colectomy. It's a difficult decision, but colectomy can be lifesaving. So it's important to get your surgical colleagues involved at an early stage.

We've reported the use of IVIG in this circumstance, but I will say that the data do certainly not strongly support its use. It's used as a form of passive immunotherapy because it contains neutralizing antitoxin, but really there are not good data to support its use. It's a sort of a desperate measure. In a recent study in Canada, a number of parameters were identified to indicate those patients most likely to require colectomy or who would die without colectomy. And those were, again, a high and rising white count again appeared, as did a rise in creatinine, incipient and organ failure, basically in the form of renal failure, as well as a high lactate.

**Slide 57: Recurrent CDI**

We've talked about already the problem of increasing incidence of *C. diff*, which is the single greatest problem we face. The second problem about poor treatments for refractory *C. diff*. And I want to now turn onto a third problem, which is the problem of recurrent *C. diff.*

And as I showed you in the very first data slide, this affects at least 20% of patients, historically, treated with metronidazole or vancomycin. And in fact, the more recent studies have tended to show recurrence rates more in the order of 25% to even 30%. So it's 20% to 30% of patients will have a recurrence.

I use this when treating patients to warn them to say that there's a 1-in-4 to 1-in-5 chance that when you stop metronidazole or vancomycin, this illness may return. And it's important that you know that, I mean the patient knows that, so that if that happens they'll quickly seek retreatment, re-diagnosis, and retreatment, rather than neglect it and end up being readmitted to hospital. So I think it's important that patients know, are forewarned about the most common complication of *C. diff* infection. If a patient's had one recurrence, their likelihood of having a second one is doubled. And if they've already had two or more, they have a greater than 50% chance of having subsequent recurrences. So these are a self-selected group.

So why do patients recur? Well, it's not a problem of antibiotic resistance. Antibiotic resistance to vancomycin is essentially not described, and metronidazole is very unusual and really thankfully as yet has not become a significant clinical problem.

What's more likely happening is that the treatment for their *C. diff* infection in the form of metronidazole or vancomycin is recapitulating the very situation that resulted in *C. diff* infection in the first place. In other words, continued antibiotic treatment prevents the normal colonic microflora from re-growing. And so, once the patient stops metronidazole or vanco, if they're re-exposed or if there are lingering organisms, then the infection will occur again. So very often these are new infections. In fact, in some studies where they've looked at strains causing first and second and third infections, the strain causing the recurrence can be quite different, distinct from, separate from the strain causing the first episode. So many of these are new infections.

We've shown, and I'll show you some data in a few moments, that the immune response of the host is important in determining whether or not recurrence occurs, and this is now being used in new therapeutic strategies against *C. diff* and *C. diff* recurrence.

**Slide 58: Treating a First Recurrence of CDI**
So if this slide looks familiar, it's because it's exactly the same as the slide I showed earlier about the treatment of a first episode. This is a treatment of a first recurrence, and most of us don't differentiate between treating a first episode and treating the first recurrence. We have the same approach. It's dependent upon disease severity. So mild disease, moderate, and severe. If a patient has a mild recurrence and you can manage without antibiotic therapy, then they won't have subsequent recurrences. They will be cured, because their normal colonic microflora will take over. That's a very good treatment, but unfortunately most patients just aren't suited to a conservative approach with recurrence. And then whether you chose metronidazole or vancomycin is really dependent on the same parameters as if it were a first episode.

**Slide 59: Approach to Treating Recurrent CDI**
If you then go onto a second or third or subsequent episode of recurrent *C. difficile* infection, how do we approach this? Well, for a second recurrence, what I use is a prolonged tapering and pulse dose regimen of oral vancomycin. An example is shown here—this is the first tapering and pulse dose regimen that was described in 1985 by Tedesco and colleagues. And it may not be any better than your recipe, but I have grave respect for my elders, and this is the oldest and so this is the one I use.

**Slide 60: Treatment of Multiply Recurrent CDI**
And there are some data, albeit not conclusive, to indicate that it might be a good approach. These are the results of a study, which was not a randomized controlled trial. Instead, this is actually part of a different study that was looking at *Saccharomyces boulardii* but where they looked at the placebo group who didn't receive the active agent and asked, what types of treatments did the treating physician give the patient with multiple recurrences of *C. diff*, and what were the outcomes? How many patients had subsequent recurrences?

You can see here, if we look at the very bottom, there were a total of 163 patients with multiple episodes of *C. diff* infection being treated for a recurrence, and you can see here that the overall recurrence rate in this group was 45%. These were not first episodes or first recurrence, these were multiple-recurrence patients.

And you can see here the percent recurrence rates in the different groupings. The only groupings that have significantly lower recurrence rates were those individuals that received tapering doses of vancomycin, starting with a higher and working to a lower, or those with pulse dosing. In other words, the regimen incorporated on-days and off-days, where vancomycin was given and then not given for a day or two, was given or not.

**Slide 61: Approach to Treating Recurrent CDI**

And if we go back to the last slide, you'll see that this particular regimen has both of those elements. There's a tapering dose, and then there's an every other day and every third day, which is the pulse part. So based on this, this is what I recommend and use for a second recurrence. If that too fails, then currently what I'm using is an approach that was spearheaded by Stu Johnson beside me and which I've also used in some patients. And that is, treating the episode with vancomycin, and then when that vancomycin treatment has been effective and has reached its end, to follow that with a course of rifaximin. The theory there is that rifaximin, although its efficacy in treating *C. diff* primarily is unclear, may have a better selectivity for *C. difficile* and may allow some reconstitution of the more normal flora. Therefore, when you stop rifaximin, your likelihood of a recurrence may be somewhat lower than if you've just stopped vancomycin. So in this regimen, 400 twice a day for 14 days, for example. In fact, a number of different dosage regimens have been used, but that's the dosage that I've been using.

Beyond that, there be dragons, because really we're sort of outside of any area where there are control studies or even large case series to guide us. IVIG has been used for multiple recurrences of *C. diff*. Probiotics have been used, and fecal transplantation have been used. But there aren't control trials to support any of those approaches, and so it really becomes a personal preference.

**Slide 62: PMC at Colostomy Site**

This is a segue slide. You've seen a couple of pictures of pseudomembranous colitis already, and usually you see it in a pathology specimen, like I showed, or in a colonoscopy picture like myself and Dr. Gerding showed. This is an unusual one—a bedside diagnosis. One of my fellows called me one day very excitedly that I had to come up and see this. This was a woman who'd had a sigmoid resection for diverticulitis and had a colostomy formed and was readmitted with increased colostomy output. And when Andy Bedford opened the colostomy bag, he was able to see that the patient, on the stoma, had very obvious pseudomembranes and was able to make a bedside diagnosis of pseudomembranous colitis.

**Slide 63: CDI: Unmet Medical Needs**

So we've been talking about unmet medical needs in *C. difficile* infection, and I think we've talked already about all of these. But let's look at the concept of cure of *C. difficile* infection. I've already shown you that 4% to 13% of patients don't respond to therapy, depending on

whether we're looking at studies of metronidazole or vancomycin. We know that a proportion of patients die, and in some of the outbreaks, it's been 7% or even more. And we know that more than 20% have recurrence. So when you add those numbers together, we could say that the first treatment cures fewer than 75% of patients, and more than 25% of patients are not cured by the treatment.

**Slide 64: New Treatment Approaches for CDI**
So, what's available? Dr. Gerding rightly criticized this slide as having far too many arrows, and I agree with him. There are. There are four too many arrows on the slide. This goes through sort of how disease is caused. Usually, but not always, antibiotic therapy changes the colonic microflora, and then if exposure occurs usually, but not always in hospital, colonization occurs. If the *C. diff* is a toxin producer, it produces toxins. If there's a memory immune response, then the individual becomes a symptomless carrier and doesn't get disease. But if there isn't a memory immune response, they will develop diarrhea. If during that episode they develop a primary immune response, they will not develop recurrence. But if they fail to do so, they're susceptible to recurrent disease. So, lots of places we can intervene.

Probiotics seem very promising because they appear to address the basic underlying problem with *C. diff* infection of altered colonization resistance. Antibiotics we've been using for a long time. Toxin binders have been used as a non-antibiotic approach and have shown some promise. And then, of course, there's active and passive immunotherapy. I'm very quickly going to show you some data on each of those approaches.

**Slide 65: *S. boulardii* for Prevention of CDI**
The first is probiotics, which I would say have been promising and then disappointing, and I think the story with *S. boulardii* is fairly typical. There are two studies here. In the first study, *S. boulardii* was compared to placebo following a course of treatment with vancomycin or metronidazole and looking at recurrence rates. With a first episode of *C. diff* infection, the recurrence rate was about 20% to 25% and did not really differ much between *S. boulardii* and placebo. However, in this study, which was published in *JAMA* in '94, *S. boulardii* did appear to protect against recurrence in those with a prior history of recurrence who had a very high recurrence rate with placebo and a significantly lower rate with *S. boulardii.* Unfortunately, when the same agent was studied in a very similar protocol some years later, and this was published in *Clinical Infectious Disease* in 2000, the recurrence rates with placebo and *S. boulardii* were almost identical. So it seems that *S. boulardii* worked between 1994 and 2000 and then unfortunately stopped working.

**Slide 66: New Antimicrobial Agents for CDI**
Antibiotics—there are a lot of antibiotics that have been looked at for *C. diff* infection. I guess the new kid on the block that's causing a stir is OPT-80. In this study with OPT-80—I'll just go straight to the graph.

**Slide 67: OPT-80 in CDI**
Looking at treatment failure, OPT-80 had 8% failures compared to 10% with vancomycin, so this is not statistically significant. So, not inferior to vancomycin in terms of response. But in

recurrence rates, recurrence rates with vanco were 24%, and they were substantially lower, 13%, with OPT-80. So it suggests that this agent, which also may be more selective, may be associated with lower recurrence rates than vancomycin. This is a phase III study—a second phase III study is ongoing and nearing completion. So this is a possibility that this may prove to be effective and perhaps be associated with lower recurrence rates, so we're waiting further data on this agent with anticipation.

**Slide 68: Tolevamer for CDI Therapy**
Unfortunately, the toxin binder—this is a picture of toxins being bound by tolevamer, which is an agent designed to bind *C. diff* toxins.

**Slide 69: Tolevamer for CDI Therapy**
And unfortunately, in this phase III study, tolevamer, which is shown in blue, was inferior to either vanco or metronidazole. Basically, it did not work very well, so that's been a disappointment to us, that this non-antibiotic approach unfortunately does not appear to be effective. Interestingly though, in this particular study in severe disease, the difference in response rates between metronidazole and vancomycin is, again, repeated as it was in the Zar study.

**Slide 70: Human Monoclonal Anti-Toxin A and B**
Then, finally, talking about immune approaches, I'm going to actually quickly go to this slide which talks about another new interesting approach using human monoclonal antibodies directly against toxins A and B, and they're infused. Here you can see that they remain in the blood for about a month, about 28 days. In the phase II study, which hasn't been published but has been reported, 200 patients were randomized either to receive standard of care vancomycin/metronidazole or standard of care plus the monoclonal antibody infusions. The recurrence rate in those individuals who were infused with the monoclonal antibodies was 70% lower than in the placebo group. So it does seem that this passive immunization approach is capable of preventing recurrent disease and potentially could also be capable of preventing primary disease, although it would probably turn out to be a very expensive intervention.

**Slide 71: Toxoid Vaccine Induces High Response**
Then, finally, what is perhaps the most obvious approach in terms of immune treatment, vaccinations. So, on the left are studies that we've reported looking at individuals who are symptomless carriers of *C. diff* who have significantly higher antibody levels than those who develop disease. And here is a second study where we looked at patients with a single episode of *C. diff* versus recurrence. After their episodes, those with a single episode showed an antibody increase. Those with recurrence failed to increase and were at risk for recurrent disease. So this indicates that the immune response may be important in determining whether somebody develops symptomatic disease or recurrent disease. On the right, these are immune responses in response to a toxoid vaccine, which contains inactivated toxins A and B. And you can see, this is a healthy volunteer study. You can see here very brisk immune responses. And at the end of vaccination, the median antibody level in these volunteers was about 150 compared to antibody levels of 3 or 4 in those protected, it seems, during natural infection. So the vaccine is promising. The development process for the vaccine has been quite slow, but it has, after a hiatus, begun

again, and a phase II study in recurrent disease has just resumed in the United Kingdom.

**Slide 72: New Treatment Approaches for CDI**
So, as I say, sort of the big new thing is vancomycin in severe disease, but there is hope on the horizon that either immune-based therapies or perhaps new antibiotics or new probiotics may be effective in helping us to combat this difficult pathogen.

**Slide 73: The Difficult *Clostridium***
Thank you.

**Dr. Stuart Johnson:**
Thank you, Dr. Kelly.

**Slide 74: CDI Prevention & Infection Control**
Our final presenter, Dr. Keith Kaye, will now discuss *Clostridium difficile: Prevention and Infection Control.* Dr. Kaye is a professor of medicine at Wayne State University and the corporate director of infection prevention, epidemiology, and antimicrobial stewardship at the Detroit Medical Center in Detroit, Michigan.

**Dr. Keith Kaye:**
Thank you very much. First, we'll say it's an honor to be here lecturing to you guys so early in the morning. It's also an honor to be on this panel. I don't know if you guys know, but this really is a dream team of *Clostridium difficile* expertise. So I've learned a lot.

**Slide 75: Dr. Kaye: Disclosures**
And now I get to preach to the choir. I can talk about how important infection control is, because I really think you can talk about MRSA and VRE and you can argue about contact precautions, but clearly barrier precautions, hand hygiene, are absolutely critical for the control of *C. diff*, particularly in closed institutional settings.

**Slide 76: Impact of CDI**
*Clostridium difficile* is a very important pathogen—the most common cause of infectious diarrhea that's acquired in the hospital. More than a quarter million cases yearly in the US. And basically among patients who receive antibiotics—which in some studies are 50% of patients who are hospitalized—of that group, anywhere from 3% to almost 30% will develop CDI or *C. difficile* infection.

Attributable mortality is quite high. On the low end, you're talking about 2% to 6%. But in some cases, particularly in high-risk groups, whether these are transplant, immunocompromised, or very sick ICU patients, mortality ranges can reach almost 30%.

*Clostridium difficile* is really a different type pathogen. When we're used to our typical bacteria or in some cases viruses, *C. diff* really is unique. We've heard about the diagnostic challenges. I think the fact that it's a spore-former really is a driving force for some of the challenges that this bug poses to infection prevention and control.

Again, I will demonstrate in this talk how the spore-former can get all over the place in the environment, whether it's the bedrail, the carpet, the drapes, the patient, the healthcare provider, it really is almost ubiquitous, as Dr. Johnson was describing in his first talk. Again, not only symptomatic patients, but there are asymptomatic colonized patients who can serve as reservoirs, something that we don't usually think about, but certainly in outbreak settings is something to consider. And, again, these spores that are formed, we know that typical germicide, typical quats will not kill these spores. We're reaching more and more for bleach. If you like the smell of bleach, you're in luck. There are a few people who actually say it reminds them of cleanliness. I don't know too many men who say they like the smell of bleach, but occasionally I have met some people who like the smell.

**Slide 77: Impact of CDI: Economic Burden**
Economic burden. Again, we're not going to belabor this. Excess costs, I think on the low end, you're talking about CDI leading to about $2500 in hospital costs. But I think more realistically, we're talking, in many cases, that you can push $5000 to $10,000 of attributable cost at least.

Again, if you look in the outpatient setting, that's where you get to the more $5000 to $10,000 in attributable costs. Three days of excess hospitalization, about a 20% attributable readmission over 100 days. Mortality rate over 180 days, about 6%, which is fairly high. And also an association between *C. diff* infection and not going home but rather going to a long-term care facility or rehab.

So we've heard that diagnosis and the treatment are really suboptimal. I think we've come a long way, but really we're still talking about fairly high failure rates and fairly low sensitivity for many of the tests we're using in our labs. So I'd say, more so than any other nosocomial pathogen, prevention is really critical with this bug, and we can really have an impact on prevention. It's not rocket science.

**Slide 78: Prevention & Infection Control**
We have our basic tenets of infection control. There are some curveballs and unique aspects to these basic tenets, but again we're talking hand hygiene, we're talking prompt and in some cases pre-emptive isolation and contact precautions. You may not bank on that toxin test coming back to make your decision. You might just be—if someone has clinical indicators for severe *C. diff*, or even for mild to moderate, you might presumptively isolate, particularly in settings of outbreaks or high endemic rates.

Environmental disinfection, we'll look at some of the data that's really pushed us more towards a bleach-based environmental disinfection. And finally, I think more so than any other hospital-acquired pathogen, *C. diff* is really where the nexus of antimicrobial stewardship and infection control meet. I think this really can be a win–win if you can have a two-pronged attack with your antibiotic stewardship colleagues.

**Slide 79: Pathogenesis of CDI**
This is one of my favorite slides that I think I've gotten from Stuart and Dale over the years.

Basically, this is sort of a happy/slouchy patient who comes in the hospital. So really the hospital exposure is critical, and it's a combination of hospital plus antibiotics. The patient gets bombarded with potential colonizing *C. diff* strains that either get asymptomatically colonized with a non-toxin producing *C. diff* bug, or they get a toxin-producing *C. diff* infection. They're bent over and unhappy and grumpy and having diarrhea.

So basically, we really, once they're in the hospital, that's the major risk factor. Remember, community-acquired cases are getting a lot of press, but still most of this is happening in institutional settings. We really have the opportunity to prevent the hit, the acquisition of *C. diff* exposure, minimizing antimicrobial exposures and trying to prevent that horizontal transmission to the patient, primarily through our hands and our equipment.

**Slide 80: Hand Hygiene**
This is a slide that depicts the effect of different hand-hygiene approaches on eradicating *C. diff* from the hands of healthcare workers. Essentially, on the Y axis we have a decrease in colony-forming units. And here we have warm water, cold water—these are with soap. Here we have warm water and antibacterial soap. Here we have an alcohol hand wipe. So, again, you have the wiping motion. And here's just the alcohol hand rub. Bottom line is, soap and water definitely decrease the counts on the hands more effectively. Whether or not you're using an antibacterial or just soap doesn't seem to make a huge difference. When you use an alcohol hand wipe, you do have a reduction here that's significantly above zero, and the reason is not that alcohol is killing the spores, but actually you're wiping them off. And with soap and water, I always say the soap and water doesn't kill the spores either, but you're washing them off your hands. So, again, the wipe has a little bit of effect. And just a hand rub itself really is not sporicidal and you don't see a significant effect.

**Slide 81: Alcohol-Based Rubs and CDI Incidence**
This is some scientific data that really supports the reason why we like to selectively use soap and water for *C. diff.* When alcohol products and hand-hygiene products, I'll say, were first making their blitz really nationally, I'd say in the early 2000s is when we were seeing really an exponential increase in the number of hospitals that were rolling out hand-hygiene products. I remember going to meetings and nationally, we're saying, are you seeing increased *C. diff*? Yes. Are you? Yes. And basically what we were seeing was the NAP1 strain was starting to spread nationally. Stuart showed some of the data on the states reporting positive cases. We're starting to see spread, and that coincided with the time that alcohol hand rubs were coming into the hospital.

I think the bottom line is, we know that alcohol is not preferred for hand hygiene in cases of *C. diff*. John Boyce has a nice paper here where he demonstrated that, when he looked at the percent of episodes with hand hygiene with soap and water, in pink here, in 2001, 90% of hand hygiene was using soap and water. And then at his institution that switched drastically to the alcohol-based hand rubs, over 80%. Yet he showed during that time period that *C. diff* infection actually decreased.

So I think there are a lot of advantages to the alcohol-based products. But, again, for typical bacteria and for ease and convenience and access, I think these are important products. But really for *C. diff* infection, we do want to sort of focus and target soap and water whenever possible, and I think it's worth trying to deliver that double-faceted message to healthcare providers. Sometimes I'm just thrilled if they do *anything* to wash their hands. So hand hygiene in general is great. *(applause)*

**Slide 82: Skin Contamination**
In terms of skin contamination, these are patients who have *C. difficile* infection, 27 different patients. And the bottom line is, the big areas of colonization seem to be the abdomen and groin, but certainly hands, forearms, chests. Remember, diarrhea spreads pathogens all over the place. So these are all over the patient, and we're going to look in a minute, these are all over the environment as well.

**Slide 83: Asymptomatic Carrier Transmission**
This is really a wonderful study. This is from Riggs et al. and Curtis Donskey from Cleveland, who did a *Clinical Infectious Disease* paper in 2007. What they did is they went to a long-term care facility during a *C. diff* outbreak, and essentially they cultured stool for the presence—they identified *C. diff* spores and the presence of *C. diff* in symptomatic individuals with *C. diff,* and then asymptomatic carriers—so people who had toxigenic *C. diff* but were not symptomatic. And then they had a group of patients who they couldn't find *C. diff* in their stool, but what they did with these individuals is they compared patients with infection, asymptomatic carriers, and non-carriers, and they cultured any part of their skin and the groin and chest, abdomen.

And what you can see is, not surprisingly, asymptomatic carriers and patients with *C. diff*—essentially you could detect this in 60% to 80% of combined skin samples. But interestingly even the non-carriers, when it wasn't in their stool, up to 20% of these individuals still had it on their skin. So what this is indicating is, either these people were carriers before or previous patients in the environment there, had *C. diff*, or healthcare workers or providers were spreading these *C. diff* pathogens to these patients. So this was really surprising to me.

Then, in the environmental specimens here, you can see in the *C. diff* patients, up to 80% combined environmental. They had one or more environmental specimen that was positive. You can see the call buttons, bedrails, tables, telephones. Asymptomatic carriers they found at least one positive in 60%. Then the non-carriers, where they did not have *C. diff* in their stool, about 20% to 30% of environmental—they had found at least one environmental surface positive in 20% to 30% of patients. This was a little eye-opening. I think things could be a lot worse. *C. diff* is all over the place. And I think, due to some immune responses and host factors, we're not seeing as much infection as we could be. So, again, infection prevention, even if our rates are low, we probably could be doing an even better job.

**Slide 84: Environmental Disinfection**
So, again, environmental disinfection—the bottom line is, if you have a *C. diff* case, and I would say you probably need to be thinking if your endemic rates are fairly high, even if you have a

toxin-negative case but there's a high index of suspicion, you have the antibiotics, the hospitalization, the leukocytosis, definitely your clinical definition for diarrhea, you really should think about cleaning the surfaces with a bleach solution, the 1:10 dilution of concentrated sodium hypochlorite. I will show a little data on vaporized hydrogen peroxide. I think most of us are using bleach.

I think the day is going to come where we're going to be routinely using this for cleaning throughout hospitals. I think with norovirus, I think with *C. diff* becoming a persistent problem, and with new and emerging pathogens—unless you can sort of guarantee that you're going to be hitting all those rooms that had *C. diff* consistently and you have a process that works, the easier way is probably to just switch out. I'm not saying that that is necessary. That's certainly not the recommendations, but I worry in a big institution, when I was at Duke and now at the DMC, I worry about missing some of those pockets. In some ways, it might just be easier, I think, to swap out. But basically you need the bleach to kill the spores. And good data has shown that if patients who were discharged who had *C. diff* in an individual room, if quat is used there, that patients coming into that room next will be at an increased risk for subsequent *C. diff* because this persists in the environment.

**Slide 85: Hypochlorite in Highly Endemic Ward**
This is a quasi-experimental time series study from Mayfield et al. where essentially they looked at high rates of CDAD infection per 1000 patient days. They then switched to an intervention where they used their sodium hypochlorite concentrated solution. They dropped their *C. diff* rate and then they stopped their intervention, went back to their standard disinfectant, and you can see their rates came back up.

**Slide 86: Efficacy of Hydrogen Peroxide**
Hydrogen peroxide vaporized to clean patient rooms. This is new technology. It's been used in Britain. It's also been used in the Department of Defense for emerging infections, anthrax spores, et cetera. This is very effective. Hydrogen peroxide is very effective at sterilizing the environment. It also will sterilize *you* if you go in. I mean, it's lethal. So there are some healthcare worker issues, safety issues, and I think room turnover time is one of the factors here. I think in rapid situations you can have room turnover to about 4 hours. I think when the technology gets even better, and we're talking more like 30 minutes to an hour, I think this is very promising. Certainly this can be part of a rotation in ICU or in an emergency room, but you're going to have a room that's out of commission for hours while you're disinfecting the room or sterilizing the room, and you also need to put tape up in all the crevices. You have to have the process *down*. But I do think this is promising technology.

**Slide 87: Antimicrobial Stewardship**
Antimicrobial stewardship, we've got to give a shout out to the antibiotic stewards. Basically clindamycin is one of the stereotypical risk factors for *C. difficile* infection. This is a study here where you can see their baseline *C. diff* infection rates were about 3 patients per year. Basically had an increase, a unique strain that was clinda resistant. They restricted clinda, and they dropped their rates down.

**Slide 88: Fluoroquinolone Class Effect**
This is a very complicated, busy slide. Probably Dale was not happy with this slide either as this is quite busy. Bottom line is, the fluoroquinolones here–remember, the NAP1 strains are fluoroquinolone resistant. So fluoroquinolones really are coming out as an independent risk factor for the NAP1 or epidemic strain. This has emerged as an important risk factor, and, historically, fluoroquinolones were not as important.

This study tried to show that this is your overall respiratory fluoroquinolone prescription rate, which is quite stable. This was a levo hospital, shown here in green. They switched out to moxi and, coincident with their switch, you can see levo dropped off, moxi went up. They had a bump in their *C. diff* rates. And I think they switched back to levo here. You can see levo came up, and I think if you squint hard and take a deep breath, you might say that the rates are starting to come back down. The conclusion here was that the fluoroquinolones as a class, particularly the respiratory fluoroquinolones, are important risk factors for *C. diff*.

**Slide 89: Fluoroquinolone Class Effect**
Another study from Muto et al. from *ICHE, Infection Control and Hospital Epi*, showed an independent risk factor here with levofloxacin. There have been studies showing both levofloxacin and moxifloxacin as independent risk factors for *C. diff*. It seems mostly to be due to NAP1 strain or epidemic strain. This really is a class effect for the fluoroquinolones.

**Slide 90: Antimicrobial Stewardship**
This is yet another study showing, again, over time we have on the Y axis the incidence of CDAD per 1000 patient days. So, *C. diff*–associated diarrhea. X axis here, we have time going from 2003 to 2005. And on this axis, we essentially have targeted antibiotic use per 1000 patient days. You can see the targeted antimicrobials were fluoroquinolones, cephalosporins, clindamycin, and macrolides. What you can see is in yellow here, as the antibiotic use dropped, that was coincident here with *C. difficile*, the rates of *C. diff* coming down significantly over time as well.

Now, remember, whenever there's a focus in restricting antibiotics, there's usually a hyped-up intensified infection control approach. So to separate and say independent effects of antibiotics versus infection control, I'd say it's very hard to say how much of an effect antibiotics have versus infection control, but there's plenty of room for happy successes in joint ventures here with *C. diff*.

**Slide 91: CDI Bundle: Pittsburgh**
The CDI bundle. We're very bundle-driven now. I think IHI and Keystone have had losses, successes with bundles. There's now a *C. diff* bundle. The one out of Pittsburgh, again, puts together some nice basic things educating, sort of explaining the spore issue, explaining some of the testing issues. And clinical signs and symptoms are important. Again, early case finding, the presumptive isolation that patients with febrile diarrhea, particularly who have been in the hospital and antibiotic exposed.

Expanded infection control measures. In some cases, they've used contact precautions for the duration of hospitalization. We'll cover the guidelines in a minute. This isn't officially in the guidelines, but in some very high-risk settings, I know at Troy Medical Center, Karmanos, our cancer hospital, we do the *C. diff* patients there, part of the modified bundle include prolonged contact precautions. That was associated with a decreased spread. Soap and water as opposed to alcohol. Again, the sodium hypochlorite for environmental cleaning, which I think is really important. They also had a special team focused on *C. difficile*, because they had a particular problem with *C. difficile.* And also antimicrobial management. They put some enhanced restrictions on problem antibiotics like cephalosporins, clindamycin, and levofloxacin.

Again, a quasi-experimental time series–type analysis. You can see over time, the rates of *C. diff* coming down coincident with implementation of this bundle.

**Slide 92: CDI Bundle: Quebec**
Also, Quebec, they had a very similar bundle here. They also included dedicated equipment, which I think is really important. I think stethoscopes, blood pressure cuffs—these are things that, if they're shared between patients with *C. diff*, you're almost certainly going to be spreading the bug around the unit. So, again, early case finding very important. Again, you can see the combination of antibiotic stewardship hand in hand with infection control.

**Slide 93: SHEA/IDSA Practice Recommendations**
The SHEA practice recommendations, these were part of the compendium that came out earlier in the year.

**Slide 94: Guidelines: Contact Precautions**
Some basic things, you can see, we talked about the contact precautions, single-patient room whenever possible. I'd say this is probably more important for *C. diff* than any other sort of bacterial-type bug that we try to prevent the spread of is single room and avoiding shared bathrooms as well. Contact precautions for the duration of illness. Some say for 48 hours after the resolution of symptoms to continue as well. These are the official recommendations. And asymptomatic colonized patients, we shouldn't actively seek these patients out. Attempts to decolonization are not useful. Again, the diarrhea, the symptoms are what makes this highly infectious. So if you find people, you shouldn't be testing these people anyway. But if you have asymptomatically colonized people who are toxin-positive, they don't need contact precautions. But, again, in outbreak settings or when you have persistent—you're looking for reservoirs, these are times when you might want to seek out this group, but not routinely or in standard practice.

**Slide 95: Guidelines: Decontamination**
Environmental decontamination, we're talking about a terminal cleaning or horizontal cleaning with the bleach solutions, the concentrated hypochlorite, 1:10 dilution of sodium. You can see the various patient care equipment, frequently touched surfaces, room furnishings. And by the way, for the hydrogen peroxide, for some of the shared equipment what some hospitals are doing are dedicating one room where they'll zap all the IV poles and wheelchairs periodically, whether it's weekly or monthly. And apparently, I was told yesterday that there are sort of traveling

services who will come to your hospital and do routine sort of hydrogen peroxide disinfection. So, some of the shared equipment this might be—you obviously can't do it after every patient use, but it might be, once in a while you might want to sort of sterilize those equipment. This is an interesting approach. Again, dedicated equipment again is an important part of the recommendations.

**Slide 96: Guidelines: Laboratory Testing**
Lab testing, I think Dr. Gerding sort of hit this home. If patients, if they have "rattlers," as Dr. Gerding said, or if they really don't really meet the case definition for diarrhea, we really shouldn't be looking for this. If you do even a very specific test in a low-risk population, you're going to get a lot of false positives. And, again, do *not* do tests of cure. Toxin can persist. Patients are better, that's fine. I don't care if the nursing home says they want to see a negative toxin, it is not clinically indicated. These are diagnostic tests to help make the diagnosis, but really you monitor symptoms and response to therapy.

**Slide 97: Guidelines: Education, Alert Systems**
Education, we're not going to hit on that much more except to think about environmental services here. They're really important in using the bleach solution. And if you help them understand why it's important and really try to involve them and let them know how important they are in limiting the spread of this problem pathogen. Education of family members, patients, why they're on contact precautions, is this a risk to their family, et cetera. This is all useful information.

Laboratory-based alert system rapidly notifying infection prevention and control when a positive *C. diff* or if there's a confirmatory test being done and something is screen positive, you might want to be notified at that time, and setting up either an automated method for that or direct communication with the lab is very useful.

**Slide 98: Guidelines: Reporting**
In terms of reporting internally, basically compliance with hand hygiene, compliance with contact precautions, external reporting. In states where this is a reportable disease—obviously for reimbursement issues this is a rising important issue and will be more and more important as time moves on. Obviously there are going to be requirements at the state and national level for external reporting.

**Slide 99: Guidelines: Surveillance**
And surveillance rate, it's a number of cases in your population that you're performing surveillance on. Your denominator is the patient days in that population who you're doing surveillance on. Again, if you're doing house-wide, then it will be house-wide patient days and house-wide number of cases. You multiply your ratio of cases over patient days by 10,000. So essentially, you have cases per 10,000 patient days.

**Slide 100: Summary**
So the bottom line is, *C. difficile* is great job security for us. It's persistent. It's a tough pathogen. It's a spore-former—very challenging and very hardy. This really requires multidisciplinary

groups to effectively control the spread of this pathogen. We're talking infection prevention, we're talking antibiotic stewardship, we're talking nursing, environmental services, administration. It really takes a multidisciplinary approach. And we really can make a difference, probably more so than any other pathogen in the hospital. We can make a huge difference in controlling this bug and preventing harm to our patients.

So thank you very much, I'll turn it back over to Stuart.

**Dr. Stuart Johnson (Slide 101: Question-and-Answer Session):**
Thank you, Dr. Kaye. We do have a couple minutes for questions. I think we're running close to time. It was supposed to end at 7:45. So we'll open it up for questions, but I'm probably going to have to cut it out soon. I think we have to get you out of here. But I'll be glad to stick around, I'm sure the others will, for a few minutes if you have other questions. Go ahead.

**Audience:**
In Montreal at one of the hospitals I work in, we've set up a cohort for *C. difficile*–positive patients. One of the questions, what we do presently is, after 72 hours without symptoms, we remove them from the cohort and put them in other areas of the hospital. My concern, and what we're finding at some point, is that we're simply spreading it around. Is there any indication for how long, if we're going to set up a cohort, how long they should stay in that cohort? Should there possibly be a step-down unit? Or is there a possibility for continuing to keep them on some type of precautions throughout the hospitalization?

**Dr. Stuart Johnson:**
Keith, do you want to talk about cohorting?

**Audience:**
Like a cohort unit that we have and then when we remove them from the cohort, are we then possibly just spreading *C. difficile* elsewhere, it's a control issue?

**Dr. Kaye:**
Once again, the primary risk for infection and spread is associated with the symptoms and the diarrhea. So I think by keeping them in that cohort when they are no longer symptomatic, particularly when they come off therapy, might be risk of re-infection. If you are worried about potential continued spread, we know these patients can have positive contamination. One tack might be to remove them from the cohort but try to restrict their activity in common areas. Obviously you don't want to limit physical therapy, but you might want to restrict activity maybe in some of the higher-risk common areas. That might be a compromise. But I would base removing them from the cohort after 48 or 72 hours after symptoms. I think that's a good approach.

**Audience:**
Unfortunately they have reoccurrence elsewhere too, which is also a problem.

**Audience:**
I'm in a facility where, believe it or not, we have *not* switched to soap and water or cleaning with the bleach solution, and there's a lot of controversy within our group about that. You had mentioned being a facility with an endemic rate. To help in my proposal to move ahead with this, what would you consider that endemic rate to be?

**Dr. Kaye:**
I think the question is about an endemic rate for *C. diff*, what's high and what isn't. That's a great question. I think one of the things that I'd like to see at the CDC is some benchmarks put out there for situations such as yours. Now I don't think that there are published benchmarks for what are acceptable rates of *C. diff* or what a 50th percentile are, or 25th. I would basically, if you don't have external benchmarks, I probably would benchmark against yourself over time. Show variation in units. Try to find out what the higher units are, and see if your rates have been going up. But I would say—I don't know, I'll ask the others here. Do you guys have any ideas of any benchmarks that are out there for hospitals?

**Dr. Gerding:**
I have my own internal benchmark, and it's based on 1000 discharges. It's less than 5 is a reasonably low rate; 5 to 10 is one that you need to be very concerned about. And if you're over 10, you definitely have got a problem. So if you're in a low-risk environment, you probably do not have to employ hand washing or bleach. In fact, bleach probably is not effective in a low-rate environment. It does not, at least in Mayfield's study, did not lower rates further on already low rate wards. So I think knowing your rate is very valuable in terms of knowing what kinds of interventions you need to take.

**Audience:**
In your rate, are you including just those that you're counting as acquired within your hospital, or all that are coming into the hospital? Because that number is very different.

**Dr. Gerding:**
Right, nosocomial rates. So healthcare-associated rates.

**Audience:**
I'm from the Netherlands and I'm wondering, it's about decontamination. I was traveling through a lot of countries and I saw that it didn't use the wash out disinfectors, but they are emptying, cleaning, and disinfect the bedpans highly contagious with feces by hands and spreading it all over. And I talked with a lot of people about this, but they said, well, this is not a problem. But we know it's only 50% cleaned after cleaning manual, and the hands are not always washed. So what's your opinion about that, not having bedpan washers or washing disinfectors?

**Dr. Johnson:**
That's a good question. Have you run into that?

**Dr. Kaye:**
Obviously, we need to clean the bedpans. You probably want to do it in controlled areas. I guess if people are washing these by hand, they want to make sure that they absolutely decontaminate themselves after they're done because they don't want to be moving these around the hospital. You're right, patients with *C. diff*, that's where you're going to have the highest concentration of spores. So, ideally, you probably wouldn't want—you want to be doing this only in a dirty area, preferably not near other patient care items. So it does sound like a bad situation. You probably would want to dedicate a very dirty area to adequately clean these.

**Audience:**
Thank you.

**Audience:**
Hi, I'm Georgine from Ft. Myers, Florida, and I had a couple questions. Now that half the room's empty, I just wondered how many of the ICPs here, IPs are collecting healthcare-onset rates for CD right now? So a pretty good amount. Do you all recommend that we include the toxic megacolon and pseudomembranous cases when we're collecting CD rates?

Because I was trying to use the SHEA guidelines, and of course there's some room for interpretation. Because what I've been collecting is total facility CDI-positive stool samples by the toxic immunoassay, and then also collecting the rates of healthcare-onset, healthcare facility–associated, just to have those two. But should we be including the toxic and pseudomembranous colitis? I can only grab those by discharge diagnosis.

**Dr. Kaye:**
I think ideally capturing *C. diff* rates, even for toxin–negative cases that are pseudomembrane-positive and stratifying out the adverse outcomes, the colectomy and the deaths, I think would be wonderful. Again, this is going to be for mostly internal use. But I think that showing the severe bad outcomes and also finding additional cases that might only be present by diagnostic criteria other than toxin testing makes a lot of sense.

**Audience:**
Another case for getting MedMined™ or something. Okay. Actually, if you've got these negative *C. diff* stool samples and you're looking at diarrhea, do you see practitioners just starting the treatment? Because I've even had one of my ID doctors say if it looks like it, I just start it. I don't even get a stool. What's your feeling? Is that antibiotic overuse? Is that good antibiotic stewardship? What do you think about that?

**Dr. Johnson:**
I think I'll direct that to Ciarán.

**Dr. Kelly:**
I think that's an important clinical question, and especially when you look at the data that Dr. Gerding showed us as regards the relatively poor sensitivities of the tests that most of us are

using. I would say that clinical concern for the diagnosis *does* override a negative test result. I'm not advocating that everybody with antibiotic-associated diarrhea be treated with metronidazole or vanco. Of course I'm not advocating that. But if you've got a patient in whom you've a very high clinical index or suspicion, then I think treatment should be initiated even before you get the test result back. And if it comes back negative, then you can re-evaluate, but you may well decide to continue treatment.

**Audience:**
Great! One last question. My pharmacist in the ICU was kind of saying probiotics and antibiotics at the [same] time kind of cancel each other out. And I know you did mention probiotics. Is there any place—I can see there might be a place for their use, but statistically it didn't look like it made a huge difference. What about patients that have been treated, has there been any work after patients have been treated for *C. diff* put on probiotics? Has there been any kind of data on that?

**Dr. Kelly:**
I think there are good data that probiotics are effective in reducing the incidence of simple antibiotic-associated diarrhea, and for that reason they're often used in conjunction with antibiotics. However, the data to indicate that they can protect against *C. difficile*–associated diarrhea are much more varied, with some studies showing positive and others studies showing no. So I think we don't know whether any probiotic as yet can protect against *C. diff*. But they can protect against simple antibiotic-associated diarrhea.

**Audience:**
Thank you so much. It was a great presentation. I got a lot out of it. Thanks.

**Dr. Johnson:**
Maybe one more question, and then we can answer some of the others individually.

**Audience:**
I have the question about children. I'm seeing some cases in the [children] less than 6 months. And I know that it's really kind of fuzzy information, but if they have definite symptoms and then are being treated, how do you address those cases as far as counting them in our nosocomials?

**Dr. Gerding:**
The problem there is that huge numbers of children under the age of 1 [year] have *C. difficile* in the stool and also toxin. And of course if they have diarrhea and somebody tests them, then you will come up with a positive test. But in the past, this has been looked at carefully, and if you use a control group who don't have diarrhea and you test them, you find the same rate of *C. diff* in those groups. So my view is that most of that diarrhea in those under 1-year-old children is not due to *C. diff*, even if *C. diff* is found in the stool.

But your question is, what do you do about counting them in terms of your hospital rates? That's an interesting question, because I think they shouldn't be counted, but I think we need more data

on those kids frankly. There are a few of them that are appearing to actually have *C. diff* diarrhea, but the majority I think are false-positive tests in those kids and that the diarrhea is probably due to something else. Sometimes we identify another pathogen and sometimes we don't.

**Audience:**
So, you're saying actually under 1 year as opposed to 6 months?

**Dr. Gerding:**
Yeah, I think you probably shouldn't be counting the under 1–year-olds as having *C. diff* diarrhea. That's my personal view, but I think you'll get differences of opinion depending on which pediatricians you talk to about those patients.

**Audience:**
Thank you.

**Dr. Johnson:**
Thank you very much for your attention this morning. We hope you found this information will be useful in your practice. Please do not forget to complete the activity Evaluation form and turn it into the meeting attendants so that you can receive your CME credit. I would also like to remind you to take one of the brochures that we left on the table to schedule a CDI lecture in your institution.

Thank you again for joining us, and enjoy the rest of your time here at the APIC 2009 Annual Conference.

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