Clostridium difficile Infection (CDI): Surveillance and Diagnosis
Dale N. Gerding, MD

Slide 1
Clostridium difficile Infection (CDI): Surveillance and Diagnosis
Gerding:
Thank you so much, Cliff. As you can tell, this epidemiology is really evolving as we now start to perhaps see additional factors coming out of the community and also, of course, the relationship to animal strains.
I'm going to pick it up now and provide perhaps some caution about the interpretation of both laboratory tests and also the difficulties of trying to do surveillance.

Slide 2
Disclosures
My disclosures are here. I have relationships as a consultant for a number of companies. Also have patents in the use of non-toxigenic *C. diff* and the Department of Veterans Affairs never wants me to represent them and I don't.

And then I won't talk about treatment, but in the course of the presentation, I'm sure metronidazole, rifaximin, nitazoxanide will be mentioned, if not by me, by Stu Johnson, and those are not approved by the FDA at this time.

Slide 3
Four Major *C. difficile* Infection (CDI) Clinical Problems
But if you can imagine *C. difficile* pressure, as Cliff described it, coming, say, from a non-toxigenic strain, where you actually were seeing all kinds of patients in the hospital with a preventive strain, you might imagine that you could use *C. difficile* pressure as a way to actually protect patients, if this becomes an effective approach.

The big four clinical problems that I think we faced are the inability to prevent this disease in high-risk settings, especially the hospital, but also long-term care, as you heard Cliff say; lack of a sensitive and rapid diagnostic test for *C. diff* infection is clearly a major problem, and I'll talk a little bit about that; and the absence of a treatment that will prevent recurrence of *C. diff*; and inability to treat effectively fulminant *C. diff*, are both treatment problems.

I'm going to talk about 1 and 2 and Stu Johnson will probably have a lot to say about 3 and 4.

Slide 4
Annual VHA Discharges with *Clostridium difficile*
And this is the rates in VA hospitals, which particularly are showing rates by discharge, per 1,000 discharge. And you can see that rate now is up at around 10. I did talk to Steve Kralovic, who's at the meeting from Cincinnati VA, who prepared these data, and he told me that the rates appear to be flattening in the VA system. That will be the first indication that we might be seeing a peaking of the current epidemic. You noticed Cliff's data did not suggest that that was the case in hospitals in general. So we'll await the formal publication of the latest VA data.

Slide 5
CDI Surveillance Issues
There are problems with *C. difficile* surveillance definitions and how to go about it. There's no *C. difficile* infection surveillance system currently in effect right now. And as you know, we struggle to try to figure out what is going on in the Unites States in terms of the frequency of this disease and we are really stretching to use data that's coming from ICD-9 coding. We had at least two presentations at this meeting today, indicating just how insensitive ICD-9 coding is when trying to diagnose hospital-acquired infections. And so I think this is really posing a significant problem.

I'm hoping that in the future we'll have more hospitals actually submitting real infection control data, so that we'll have a better handle on what the rates are.

The *C. diff* infection case definitions have not received any kind of formal endorsement, including the ones published in ICHE [*Infection Control and Healthcare Epidemiology*] last year. They are more or less best concepts right now of how to go about doing this. And we have no means of systematically doing any kind of molecular surveillance for *C. diff* because of the problems of so few institutions doing culturing, as well as few laboratories that do molecular typing, if you do do the culturing. And furthermore, there's no generally accepted typing system available. So that's why you see this convoluted naming of the organism, BI/NAP1/027. Those are at least three different typing systems currently in effect for *C. diff*. So we have a ways to go, but I think we're much farther ahead than we were, say, 5 years ago.

Slide 6
Healthcare Facility CDI Surveillance
So for healthcare facilities, *C. diff* infection surveillance, the first point to take home I think is please do *C. diff* infection surveillance. There are still a lot of hospitals out there that appear not to be surveying for the frequency of *C. diff* infection in their institutions.

I think every acute healthcare institution should do it and certainly many of our long-term care facilities, especially those that are, quote, acute long-term care, where they're more or less step-down units from the hospital.

I think this would give you an idea of the burden of *C. diff* infection in your facility and, if nothing else, give you a benchmark on which to compare yourself to other facilities, and a baseline on which to determine if you're actually having an effect on the *C. difficile* infection rates.

If Medicare in the future decides to make this a target for non-reimbursement, I think this is going to become incredibly important obviously.

The other important point for surveillance is to try to use the laboratory because the laboratory obviously determines who has a positive test. And if they can report results to the infection control professionals in the hospital promptly, that should be more effective in getting patients isolated quickly and also getting them on therapy. And there is a poster at this meeting indicating

exactly that, that if the lab calls, that the patient gets treatment instituted considerably more promptly.

The rate calculation currently recommended is that you use 10,000 patient days as your denominator. That is a number that I don't have a good intuitive feel for. I've always used discharges and those are good for acute care settings, but as you know, not very good for use in long-term care. So please use a denominator of 10,000 patient days as you do your determinations of your rates.

Slide 7
Community CDI Surveillance
For community surveillance, you heard Cliff talk about a couple of studies and I'll show you some additional data on that. Disease in persons with no overnight stay in an inpatient healthcare facility for at least 3 months prior to symptom onset is the current definition. And you will see studies where as long as 1 year has been used for inpatient stay in patients in order to call them community-associated. But I think 3 months is probably a reasonable time period.

And the denominator for community-associated *C. diff* infection is per 100,000 person years. And that, of course, may not be a number that you have readily available to you in your institution. However, it appears that the Connecticut data looked very much like earlier data, both from the Boston area and from Philadelphia. And the data from North Carolina obviously are looking much, much higher, as Cliff pointed out, around 20, 25 per 100,000 population.

So it's possible that we are seeing differences by region, certainly that's the way MRSA [methicillin-resistant *Staphylococcus aureus*] in the community began, with marked increases in certain parts of the country that eventually were confirmed elsewhere. It remains to be seen if that's going to be the case with *C.diff.*

Slide 8
CDI Outbreaks and Epidemics
So unfortunately, we don't even know how to define an epidemic or an outbreak with *C. diff* and just what constitutes an outbreak. And we don't know what a hyperepidemic—endemic—rate is.

An outbreak as suggested can be defined as an increase in rates greater than what is expected. I'm not sure what we should expect. Hyperendemic rate can be defined as persistently high rates compared with historic rates or with similar healthcare facilities, so it would obviously make it necessary for us to compare rates by institutions. And when the rates are high, it's important to try to identify high-risk locations within your facility that you might target for intervention. And usually when we find a high rate, it's usually coming from one or two sites within the institution, often a site where patients are being treated for bone marrow transplant, cancer chemotherapy, hematology units. In our institution, when we first noticed this, it happened to be coming from a general and vascular surgery service.

The general guidance that I've used is kind of a mental benchmark, based on 10 years of data in one institution, was that when rates were below five per 1,000 discharges, we felt that we were doing a pretty good job. When they rose to the five to 10 per 1,000 discharge rate, we felt we

needed to be very concerned. And if they exceeded 10 per 1,000 discharges, those rates were not acceptable.

Now depending on your length-of-stay data, these numbers would have to be adjusted per 10,000 patient days obviously. And if you have a 10-day length of stay, which almost no one in the US does, but many Canadian hospitals appear to have length of stay of about 10 days, then the two numbers are exactly the same. So five per 1,000 discharges is five per 10,000 patient days.

If your length of stay is only 5 days, as many US hospitals are very close to now, then obviously a rate of five per 1,000 discharges is now 10 per 10,000 patient days. So the shorter your length of stay, the higher your rate per 10,000 patient days goes in this game.

On the other hand, if you have really short lengths of stay, the chance that you'll pick up *C. diff* in the hospital goes down also. So that it does benefit you to have a short length of stay, but the difficulties that we have identifying these postdischarge cases.

Slide 9
Surveillance Definitions
These surveillance definitions come from the paper published in *Infection Control and Hospital Epidemiology* by Cliff McDonald. And in many ways he should be presenting this. But we had many discussions about these definitions. I'm not sure they're really fine-tuned optimally as yet. But the *C. diff* infection definition, and you notice that we're increasingly using CDI rather than CDAD, and that's not to further confuse things, it's because there's been criticism of the term CDAD from any number of sources. And so as the guideline writing committee has gone forward, they have decided to adopt a different terminology, "*C. difficile* infection." So we hope that won't cause any additional concerns or confusion.

But you should have an unformed or watery stool, three or more per day for 1 to 2 days. And usually 1 day is going to have to be sufficient simply because no one wants to wait 2 days to see how long the diarrhea is going to last before intervening in most institutions. And then combine that with a *C. diff* toxin test or a test for the toxigenic organism in the stool, or evidence of pseudomembranous colitis, either by endoscopy, by surgery, autopsy or histopathology.

And recurrent *C. diff* is an episode that meets the definition of *C. diff* within 8 weeks of the end of a successful treatment or spontaneous resolution of *C. diff* infection.

And severe *C. diff* infection really does not have precise definitions right now, but things that are usually included would be need for a colectomy, death of the patient, toxic megacolon or need to care for the patient in an intensive care unit setting because of a *C. difficile* infection. However, I think those definitions also need refinement considerably.

Slide 10
CDI Surveillance Terminology
The terminology for *C. diff* infection. Healthcare facility onset or HO is one abbreviation that probably technically should be HCFO, is healthcare facility onset of symptoms. Healthcare facility-associated, on the other hand, would be that the *C. diff* infection episode is attributed to

that healthcare facility. Community onset means that the symptoms occur in the community. Community-associated means that the episode is attributed to the community. And there is now a quite large indeterminate period of time when it appears to be impossible for us to attribute either the episode to the healthcare facility or to the community.

Slide 11
Recommendations for Surveillance of *Clostridium difficile* Infection
Cliff has kindly loaned me this slide, which outlines the issues of the problems of trying to define this. And the key area here to begin with, when someone comes in the hospital at admission, is the first 48 hours, shown there in green, and during that period a number of definitions might apply. For example, if the patient comes in in 48 hours and has onset of diarrhea, then it could be community-onset healthcare facility–associated if the patient was discharged from a healthcare facility within the previous 4 weeks. So this would mean somebody coming out of the hospital, going home, having onset of diarrhea, either shortly before or within the first 48 hours of coming back in the hospital. So that would be community onset, but healthcare facility–associated.

Then you get to the blue area shown on the line there of the 4- to 12-week period, which is indeterminate disease. So if the patient's diarrhea comes on in the first 2 days of admission, but has been out of the hospital in that 4- to 12-week window, we don't know what to call that and that doesn't help things very much, so we're going to have to get that resolved at some point.

And finally, if you have community-associated *C. difficile* infection, this patient whose onset is within the first 48 hours, would be termed a community-associated infection, if they had been more than 12 weeks from discharge from the hospital previously.

Then if the patient develops diarrhea after that 48 hour window, then they're healthcare onset, healthcare facility–associated, while they're in the hospital up to the time of discharge.

Big problem, of course, is when you get to the yellow area, the 4 weeks that are supposed to be attributed to the previous discharge and the patient doesn't come back in, how are we going to find those people? And of course, that is a major undertaking.

Slide 12
Within 48 h to 72 h of admission?
Another interesting problem is we always have this 48- to 72-hour period of admission. And one way to look at that is to allow at least two complete 24-hour days from admission. So in this example here, patient admitted any time on Monday, just to have an arbitrary admission day, would then have Tuesday and Wednesday as two full 24-hour days before they would have exhausted the 48-hour time period. And so beginning just after midnight on Thursday would be the start of your hospital-associated infection, healthcare onset, healthcare facility–associated infection. This is one way at least of dealing with that question of 48 to 72 hours.

Slide 13
Days from Hospital Discharge to Diagnosis for Community-Onset CDI
Now what are the data for this business about following patients out 4 weeks after discharge? Well, they come from—at least one part of the data comes from this paper by Chang et al. This is

using VA data from the Hines VA. The purpose of this paper initially was to try to identify risk factors around community-associated *C. difficile*. And when we searched for all of the cases that had occurred as outpatients, we found that, as you can see in this graph, most of them are clustered very tightly right at the first 30 days postdischarge. And you can see that most of the patients have either had their antibiotic exposure as inpatients and outpatients in the clear bars, or as in the crosshatch bars, exposed to antibiotics as an inpatient. There was only, I think, one patient there that was exposed only to antibiotics as an outpatient.

Then you notice the marked fall-off going out to the next 30-day period, where there are almost no cases. Then some 100 days out, we found just a few additional cases. In that case found some additional patients who were exposed to antibiotics in the outpatient setting.

What we found was that 85% of all the patients in the community were within 30 days of a hospital discharge. I think that was at least an initial cut at trying to associate those with their prior hospitalization.

Slide 14
Community-Onset CDI Relative to Previous Discharge, North Carolina, 2005

Now this slide also comes courtesy of Cliff McDonald at CDC. These are the data of Kutty in the North Carolina experience. You can see they're quite different from what I just showed you. They show in yellow the first 4 weeks, where again the majority of these cases are coming up, identified in the community again. Then the 5 to 12-week period, where they begin to fall off, is somewhat longer than the period that we followed them. But then you see this remarkable number of cases coming from the community in the final bar on the far right, showing that there were 184 (48%) of these patients who had more than 1 year since discharge from the hospital. So there are a tremendous number of patients who were apparently truly community-associated here, compared to the numbers that we found in our experience.

Our experience was that there were very few of these patients being diagnosed in the community. This experience is that, as Cliff pointed out, about 20% of the cases were looking like they were truly community.

So it appears that the data are still somewhat mixed. Erik Dubberke in St. Louis found similar things to what we found at Hines in Chicago. But in Atlanta they appeared to also be finding increased community cases. Are we all looking the same way? It's still not clear. Or is this true geographic differences?

Slide 15
Correlation Between Monthly Rates of CO-HCFA Cases of *Clostridium difficile* Infection (CDI) and Rates of HO-HCFA Cases, by Hospital
Now one of the things that was useful in this particular study was to show that if you had a high rate of healthcare onset, healthcare facility–associated cases, then you also had a high rate of community-onset healthcare facility-associated, which would make sense. You have a lot of cases in the hospital, you're going to get a lot of cases in that 30-day window right after discharge. You can see that these two diagnoses correlate. But you could not guarantee that the

ranking or the number of cases per hospital would be the same if you did not count the healthcare facility–associated, but community-onset cases in your tabulating of cases.

Slide 16
Differences in Ranking of Hospitals if HCFO-HCFA Only is Counted Vs. HCFO-HCFA Plus CO-HCFA are Counted
So on the top of this graph [A] you see the ranking of the hospitals by number of cases when you used only healthcare-onset, healthcare facility–associated. Those would be the ones that just occurred during the period from 48 hours after admission to discharge.

Then you see in the lower graph [B] that if you count the onset of the cases in the 30-day or 4-week window after discharge, that it changes the ranking. So 1 and 2 changed positions, 3 and 4 changed positions, and 5 and 6 changed positions in the ranking.

So there apparently is not a complete one-to-one relationship of having more cases diagnosed in the hospital and more cases in the community, but rather if you look at both of them, putting them together can change the ranking in terms of numbers of cases from one hospital to another. This is a problem that we're going to have to address and I don't think we've resolved it as yet.

Slide 17
Unresolved Surveillance Questions
So the unresolved surveillance questions, and there are quite a few. What are the criteria for a *C. diff* infection outbreak? Are we ever going to get mandatory national reporting of *C. diff* infection rates? And if so, if it comes state by state, how are we going to do this in a way that will identify the important numbers of cases and also be able to allow us to compare institutions? Should surveillance of these cases include documentation of diarrhea in the patients or should we just use a laboratory test? Can we use the surrogate of the laboratory insisting on a watery or unformed stool for doing the test, as evidence that the patient has diarrhea? If you don't do that, you have to determine whether the patient has really had three or more stools per day of diarrhea in the hospital; that is going to take a tremendous amount of time. Because you have to go to the ward usually, frequently not in the chart, and you have to ask somebody who knows what's going on with the patient. Even then you may not be able to get the information.

I think the current recommendation is to identify healthcare facility onset and associated *C. diff* cases for rate calculations, at minimum. I think that's reasonable. Then how to conduct surveillance for these community-onset healthcare facility-associated cases that are frequently lost to follow-up after discharge from the healthcare facility, remains to be determined. It's easy if you can just identify them if they're readmitted, but that's going to be the minority of cases. If they're treated as an outpatient in a physician's office, we may have no evidence of that case going on.

If you have electronic medical records that are both outpatient and inpatient, they can be extremely helpful obviously in picking up the diagnostic test in the laboratory. If your healthcare facility's laboratory is a reference lab for outpatients, that can be extremely helpful as well. But this is going to be difficult and I think we're going to have to look at creative ways to identify these cases.

Slide 18
An 86-Year-Old Man with Pneumonia
Okay, and then finally we really have got problems with diagnosis. This is a case that's reminiscent of several we've seen. A typical 86 year old, community-acquired pneumonia, gets treated with antibiotics, looking good, fever down. Starts to develop loose stools, abdominal cramping and he has six to eight watery bowel movements a day, there's no blood in the stool. And the three specimens go to the laboratory. They're all negative by enzyme immunoassay for toxin A and the question is how come? This guy should have *C. diff*, right? Everybody in this room would say he's got it.

Slide 19
Pseudomembranous Colitis
But this happens. And fortunately most of the time these patients get treated. And in this case the patient eventually got scoped and did have pseudomembranous colitis, as you can see here.

Slide 20
The Patient Has Pseudomembranous Colitis
And the question is why are we not picking these patients up? This is a few years ago when the toxin A enzyme immunoassay was being used. The answer is that we've proposed here, the test is only 60% to 70% sensitive. Some strains of *C. diff* that cause CDI do not make toxin A, therefore would not be picked up by that test. Or is it just that it's not a great test, but laboratories like it because it's more rapid and less labor-intensive than other tests.

Any thoughts? Or is it all those things? Everybody want to vote for all four? Yeah, it's all those things.

Slide 21
Four Toxin EIA Tests Vs. Cell Cytotoxin
This just is one illustration from a paper by O'Connor, just showing in blue there the toxin A test results of around 50% sensitivity. That's compared to cell cytotoxin, which is not even the most sensitive test. The toxin A/B assay, you can see, is sensitive up to about 80% there, compared to cell cytotoxin.

Slide 22
Cell Cytotoxicity Assay Interpretation
This is the cell cytotoxin assay. It's extremely time-consuming to do because you have to look at the cell lines for the cytotoxic cell rounding effect on the right, and you have to do a neutralization step with antibody against the toxin to prove that it's due to *C. diff*. It takes about 2 days to get the results back.

Slide 23
***Clostridium difficile* Diagnostic Tests**
So among the tests that we have, sensitivity is lowest for endoscopy. It's highest for culture, especially if you do it for a cytotoxic strain. And cell cytotoxin would probably be the third most

sensitive test. And enzyme immunoassays for toxin A and B are superior to toxin A, as you can see.

Then the two tests that have in the past been used extensively, the glutamate dehydrogenase test, done with a latex formulation, latex agglutination, that test had a very low sensitivity and a very low specificity. But now that test has been put into enzyme immunoassay formation and now it appears to have very good sensitivity, although its specificity continues to be fairly low. It can be used as a nice screening test. That is potentially where we're headed with testing.

Slide 24
Stool *C. difficile* Toxin and Culture Results in a Period of Toxin A EIA Testing and After Changing to a Toxin A/B EIA

Now Stu has put together some data on the use of the new—new at the time—toxin A/B testing in a hospital that was doing culturing backup. Very few opportunities to do this. But this was done at Northwestern Hospital in Chicago and the first line you can see, that the toxin-positive and culture-positive specimens went from 25% up to 45% when the toxin A/B assay was put in. However, the toxin positive/culture negative, the last line in that table, went from 16% to 27%, meaning that we were picking up probably some additional false-positives when using the toxin A/B test. One of the things under the second bullet point that he emphasized was that this was more common in stools that were bloody or in patients who had a history of inflammatory bowel disease, where the rate was 27% for these presumably false-positives, compared to only 4% in patients who did not have either blood in their stool or inflammatory bowel disease.

Slide 25
Two-Step Testing Using GDH-EIA
Now in the recently published data from Connecticut on community-associated *C. diff*, 23% of the patients in that study had bloody diarrhea. A question, they were using a toxin enzyme immunoassay like this, so the question becomes, are we picking up some false-positives with testing. It's probably low level, but it could be contributing to some of these more unusual cases that are being detected now. We need to do a better study of this with better backup, as well as additional culturing for other pathogens in these patients.

So the two-step test uses the GDH [glutamate dehydrogenase] enzyme immunoassay. This has been pioneered by the people at Johns Hopkins, who have used this as initial screening test. If it's negative, it eliminates about 80% to 90% of all the specimens that the laboratory has submitted to it. You can report those as negative. Now the positives, you need to do a confirmatory test and they were doing cell cytotoxicity and that seemed to be working fine, except that it's kind of slow to get the cell cytotoxin assay back, still takes a couple of days. They had good negative, greater than 99% predictive value of a negative GDH assay when compared to cell cytotoxicity. So that appears to be one effective strategy for at least getting the negatives identified very quickly. It did save work and it saved costs to the laboratory. But the return of the positive test still is slow. The issues here are sensitivity, specificity, and turnaround time, because everybody wants the information quickly.

Slide 26

Comparison of RT-PCR to Three Standard *C. difficile* Detection Tests in Patients with ≥ 3 Loose Stools/Day

So one way to improve rapidity and sensitivity might be to do real-time PCR. This paper was just published recently by Lance Peterson and colleagues again in Chicago. They did culture for a toxin-positive organism as their basic baseline gold standard. That was set at 100% sensitivity. Real-time PCR then was at 93%. The toxin A/B assay was at 73%, so about 20% lower. This would approximate a test that would really meet all the needs of being, assuming it was done every day, rapid, sensitive, and specificity could even be fine-tuned to amplify particular genes that might be associated with epidemic strains and things of that type. So if this can be developed as an everyday test in laboratories and hold these kinds of numbers, then I think that may be very promising for the future in terms of the speed, sensitivity, and specificity we're looking for.

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Method of Laboratory CDI Diagnosis

Currently laboratories do the EIA [enzyme immunoassay] for toxin A and B primarily. I'm sure most of your laboratories are the same way. In this particular survey, the next most frequent test was the "I'm not sure" test, which is probably fairly accurate for many institutions.

And a number are still using the EIA for toxin A, but the EIA for toxin A now I think is out of manufacture. So that isn't used much.

And you can see relatively few labs, in the light blue, use the cell cytotoxin assay, which is labor-intensive and somewhat slow. But a really good sensitive test.

Slide 28

Relative Sensitivity of *C. difficile* Tests

So the relative sensitivity of testing right now, and you can see in orange there, the current most common test is about number 4 on the list. The culture with toxin confirmation done in relatively few laboratories. The GDH for EIA, though, appears to be very sensitive. The RT-PCR, based on one study, would fit somewhere between GDH and cell cytotoxin. Then toxin A/B assay. Then the toxin A assay. Then the latex test. And then endoscopy, which is only about 50% sensitive for *C. diff* diarrhea, but is 100% sensitive for pseudomembranous colitis.

Slide 29

Unresolved CDI Diagnosis Issues

So unresolved diagnostic issues. We have low sensitivity of most of our current tests. And unfortunately, the ones that are most sensitive are the slowest turnaround. So cell cytotoxin testing and culture for toxigenic strain are both 24- to 48-, 72-hour tests.

Use of a two-step GDH-EIA will result in rapid reporting of the negative test, but it still leaves you a slow turnaround on the positive test results.

And question being raised I think by the data that Stu has gathered is do toxin A/B EIA results have false-positives and to what extent are they false-positive? Can the sensitivity of PCR, which is now still experimental (there are no approved PCR tests available), can it be increased to be as sensitive as culture and even more specific?

So those are the unresolved questions and I think we have a long way to go, but it looks like there may be promise in the area of PCR. But if we want to do what we'd really like to do, which is molecular epidemiology, we still need to get cultures on these organisms unless we can become so sophisticated that we can amplify by PCR from stool all the various characteristics that we want to know about the organisms. Thank you very much.

The final presentation will be by my colleague, Stuart Johnson, who is Associate Professor of Infectious Diseases at Loyola University and works with me in our combined research laboratory at the Hines VA. Stu's going to talk about the very important issues of the changing and evolving treatment of *C. diff*.