For *C. difficile*, lab assessment alone is not enough

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May 2017—Toxigenic *Clostridium difficile* can be isolated in about one-third of hospital rooms in which there is no patient with *C. diff* infection, and the same is seen in the community. A study published in 2014 found that 32 percent of the samples obtained from 30 houses in Houston were culture-positive for toxigenic *C. diff.* And *C. diff* was isolated from 83 percent of the houses (Alam MJ, et al. *Anaerobe.* 2014;27:31–33).

Dr. Dubberke

Although associated with hospitals and the most common cause of health-care-associated infections, toxigenic *C. diff* is a ubiquitous organism, and infection is far more than a positive test, said Erik R. Dubberke, MD, MSPH, associate professor of medicine, Division of Infectious Diseases, Washington University School of Medicine, St. Louis. He recently co-presented a webinar hosted by CAP TODAY and sponsored by BioFire, "*Clostridium difficile* in the Community Setting: Epidemiology and Diagnostic Implications." (His co-presenter, Ferric C. Fang, MD, talked about the approaches to *C. diff* diagnosis, page 48.)

"We are constantly exposed to *C. difficile*," Dr. Dubberke told his listeners. "We periodically pick it up and then we clear it in the absence of an antibiotic exposure. It's been cultured from soil, it's been cultured from water, including drinking water. It's been cultured from food purchased at a supermarket. It's also been cultured from household pets."

"Even in the hospital setting," he added, "there are 10 times more asymptomatically colonized people than people with *C. difficile* infection. Presumably this ratio of asymptomatic to symptomatic is even greater in the community."

Data from the CDC Emerging Infections Program show an estimated 450,000-plus cases of *C. difficile* infection—with more than 29,000 associated deaths—in the United States each year. More than 150,000 of those cases represent community-onset disease, defined as disease in those with no inpatient health care exposure in the prior three months.

Why might it be that *C. diff* infection is more prevalent in the community than previously thought? One explanation is that the trends in the community are probably reflecting those seen in the hospital, "because the primary reservoir for *C. difficile* is in the community," Dr. Dubberke noted. "So if we're seeing increases in the hospital, it should not be surprising there might be increases in the community as well."

Better surveillance can explain higher prevalence in the community than previously thought. Dr. Dubberke pointed to the CDC community-based EIP, in which every case of *C. diff* infection in the surveillance areas was publicly reportable.

Increasing awareness of *C. difficile* infection is another explanation, as is decreasing length of stay in the hospital. Half of hospitalized patients never have the opportunity to develop hospital-onset infection because they're discharged in fewer than three days. "Many of them have been exposed to antibiotics. They go home. They may be exposed to toxigenic *C. difficile* in their home, but they're still at risk because they had received antibiotics in the hospital and are then diagnosed with community-onset *C. difficile* infection."

The risk factors for community-associated *C. difficile* infection include gastric-acid suppression treatment (a correlation "not entirely clear," Dr. Dubberke said) and exposure to infants ("asymptomatic colonization among infants is nearly universal"). The most common risk factor, of course, is antibiotic exposure. But "any alteration of the microbiome could potentially be permissive to *C. difficile* colonization, and there are surely alterations that can occur in the absence of an antibiotic exposure. So it's not entirely surprising we're seeing less *C. difficile* infection with an antibiotic exposure in the community."

Recall bias is another way to explain why fewer antibiotic exposures are being seen. "I not infrequently come across patients where I know they were prescribed an antibiotic in the outpatient setting, I know they picked up the antibiotic from the pharmacy, but then the patient is unaware they took an antibiotic," he said. "Conversely, about one in 10 people who are taking an antibiotic in the community are taking a leftover antibiotic. If you're assessing antibiotic exposure based off prescribing data, you're going to miss these people."

All of this is important to be aware of when interpreting *C. diff* diagnostic assays, Dr. Dubberke said. "Most of us, including myself, were not taught properly in regards to the *C. difficile* diagnostic literature. And that's because *C. difficile* infection is a clinical diagnosis," he said. "To have *C. difficile* infection, you need someone with appropriate signs and symptoms of C. difficile infection, and then you have a positive test for *C. difficile*."

Yet before 2011, few *C. difficile* assay comparisons included clinical data. "So all you know is you've got poop in the lab and it's either positive for *C. difficile* or negative for *C. difficile*. So what these assay evaluations are doing is looking at detection of *C. difficile*, not diagnosis of *C. difficile* infection. Therefore, it's important to remember that as many as 15 percent of patients are colonized with toxigenic C. difficile on admission to the hospital." There are other reasons for diarrhea. "And so the concern arose that the enhanced sensitivity for *C. difficile* detection could decrease the specificity of these assays for *C. difficile* infection."

The fact that not all toxin-detection assays are equal is not entirely appreciated, Dr. Dubberke said. "The first toxin EIAs that were available detected only toxin A. And these assays were commercially available until just a few years ago, despite knowing for two decades that some strains of *C. difficile* only produced toxin B and can cause the same spectrum of illness as *C. difficile* isolates that produce both toxins A and B. So you need to make sure you have an assay that detects both A and B—but in addition, even among those assays, not all assays are equal."

When considering factors that affect assay performance, one must think about not only the assay's sensitivity and specificity but also the prevalence of disease in the population. "The two big things that will decrease the positive predictive value are decreasing prevalence of disease as well as decreasing specificity of the assay. And when it comes to *C. difficile* diagnostics, we need to remember there are also a lot of asymptomatic carriers of *C. difficile*. So when interpreting an assay, if you have a PCR-based assay, you need to remember that PCR-based assays are going to be more likely to detect the asympto-matic carriage than toxin detection. Toxin-detection assays do detect asymptomatic carriage, but not nearly to the same degree as PCR-based assays."

When PCR-based assays became commercially available, his laboratory performed its own assay comparison study. "We did something unique here at the time in that we prospectively interviewed all patients who had a stool specimen that we're going to include in our assay comparison. So we interview the patient, we examine the patient, and review the medical rec-ords to see what medications they were on. And we did this while we were blinded to the result of the *C. difficile* assay that was done by the clinical lab," he said. "We wanted to look at what happens when we include this clinical information in the gold standard comparator." As it turned out, including clinically significant diarrhea in the gold standard had no impact on the sensitivity of the assays evaluated.

"And so we found the PCRs that have a sensitivity of 99 percent plus, but actually we also had toxin EIA that had very good sensitivity as well," he said. When they included the clinical information, they found the specificity of the PCR assays decreased from 98 percent to 89 percent. "So, again, that 98 percent is consistent with what historically had been found when you don't include clinical information. But with a decrease in specificity to 89 percent, we found that the positive predictive value of the PCRs we were evaluating was only 60 percent." Thus,

four of 10 positive results would be false-positive results because the patient was asymptomatically carrying *C. difficile*. In addition, the study found no *C. diff* infection-related complications in PCR-positive, toxin-negative patients, and no correlation between the start of empirical treatment for *C. diff* infection and ultimate diagnosis of *C. diff* infection.

Based on the findings, Dr. Dubberke and his laboratory colleagues continued using their toxin EIA, the Techlab Tox AB II. "We're still using it today," he said. "And we've been following our results closely and we know for a fact we have very few false-negative EIAs. I'm unaware, in the last five years plus, of having an adverse outcome related to a false-negative EIA. We have great confidence."

With asymptomatic colonization so common and PCR assays so sensitive, Dr. Dubberke advises considering several things upon finding that a multiplex PCR is positive for *C. difficile* on a person in the community with no health care exposure. One is that the *C. difficile* infection prevalence among people with at least one hospitalization is 1.2 percent, while the prevalence among those with no hospitalizations is 0.5 percent. Another is that, in his words, "Looking at only those people who have not had a hospitalization, the CDI prevalence among those who have a known antibiotic exposure is 0.23 percent. But the CDI prevalence among those without a known antibiotic exposure is 10-fold lower at 0.023 percent. So, again, an antibiotic exposure makes it much more likely that a multiplex PCR positive for *C. difficile* represents *C. difficile* infection versus someone who did not have a known antibiotic exposure."

Age is an important factor. Since *C. diff* colonization is so common among infants, guidelines recommend against testing for it in children under age two. If the infant is tested, however, and the result is positive, other etiologies for the diarrhea have to be considered. Even older children have higher colonization compared with adults. Studies have found that children in the community under age five and with diarrhea are just as likely to test positive for *C. diff* as children in the community without diarrhea. So in his view, "If you have a child less than five years of age with a positive test for *C. difficile*, regardless of the test—if it's a toxin assay, if it's a PCR—you still need to consider the possibility that it might be something else causing the diarrhea."

For a positive test to represent C. diff infection, symptoms such as diarrhea, abdominal pain and cramping, and nausea should be present and persistent. "If they're improved or improving, then it's probably not *C. difficile* infection that needs to be treated," he said. Vomiting and blood in the stool are uncommon signs of CDI and, if present, make it less likely the patient has C. diff infection. If the multiplex PCR is positive for other organisms—especially if there's an epidemiologically important link to that organism, such as travel or norovirus season—it's probably that other organism, not *C. difficile*, causing the symptoms.

Response to treatment is a further consideration. If symptoms resolve before the results are back, Dr. Dubberke recommends against starting *C. diff* treatment, given that about 20 percent of CDI cases resolve without it—and that treatment puts patients at higher risk for recurrence. "If their symptoms resolve by the time you know the test is positive, best just to leave well enough alone," he said.
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