Study shows popular molecular tests

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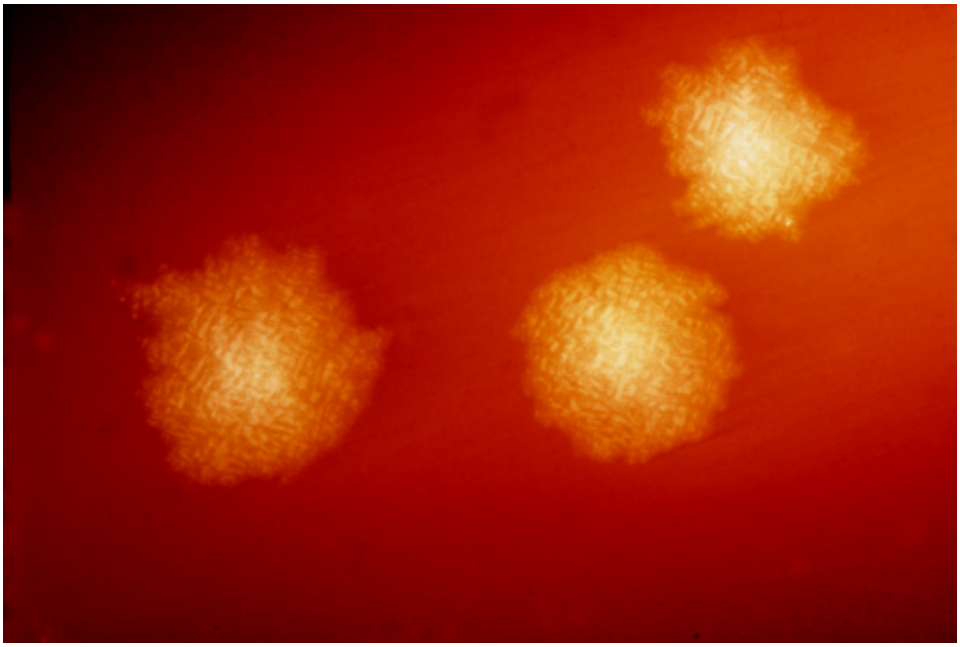

This photograph depicts Clostridium difficile colonies after 48hrs growth on a blood agar plate; Magnified 4.8X. C. difficile, an anaerobic gram-positive rod, is the most frequently identified cause of antibiotic-associated diarrhea (AAD). It accounts for approximately 15–25% of all episodes of AAD. Credit: CDC

Clostridium difficile is a common cause of infection and diarrhea in hospitalized patients, but a new study by UC Davis pathologists suggests that many patients are mistakenly diagnosed and do not need antibiotic treatment. As a result, patients are likely being over-diagnosed and over-treated, adding to concerns about antibiotic resistance, damage to the "good" bacteria that live in people's intestines, and increased health-care

costs.

"It all depends on the type of test doctors use to diagnose patients," said Christopher R. Polage, associate professor of pathology and infectious diseases at UC Davis Medical Center and first author of the study. "Molecular tests are great at detecting *C. difficile* DNA in the laboratory but probably over diagnose a lot of patients in hospitals, if doctors assume that everyone with a positive result needs treatment."

On Sept. 8 Polage and colleagues reported results of a two-year study in *JAMA Internal Medicine* that examined clinical outcomes in patients with conflicting results by common tests used to diagnose *C. difficile* infection in the U.S. For the study, researchers evaluated 1,416 hospitalized patients tested for *C. difficile* at UC Davis, tracking the outcomes and severity of infection according to the results of toxin tests versus molecular tests such as PCR.

The surprising conclusion of the study was that newer molecular tests, which have been adopted by nearly half of U.S. hospitals over the last six years, are unable to distinguish infected patients who need treatment from patients who are colonized with the bacteria and do fine without treatment.

"Over the past several years there has been a movement nationally and around the world to change test methods for *C. difficile* diagnosis from traditional toxin tests to newer, molecular tests," Polage said. "This has been driven by concern that patients with infections were being missed, but very few studies looked at clinical outcomes to see if these concerns were justified."

In the study, patients diagnosed with *C. difficile* using a traditional toxin test had more severe disease, a longer duration of symptoms and greater risk of bad outcomes, validating their need for treatment. In comparison,

patients who were positive by the new molecular test but negative by the traditional toxin test had milder symptoms and outcomes that were similar to patients without *C. difficile*, even without treatment.

"This finding caused us to question whether these patients really had a *C. difficile* infection or needed treatment at all," he said.

Polage noted that a large number of patients in acute-care facilities and hospitals are colonized with *C. difficile* without having an active infection and don't need treatment. Because colonized patients can be five to 10 times more common than those with symptomatic infection, he emphasized how important it is to use the test methods that can make this distinction.

"The reality is that diarrhea has many causes in hospitalized patients and sometimes patients with *C. difficile* colonization have diarrhea that has nothing to do *C. difficile*," he said. So, if you only detect DNA or the presence of the organism, you haven't necessarily proven that the organism is what's causing those symptoms. Yet, doctors routinely assume that all patients with positive molecular test results are infected and treat everyone with antibiotics, even when they might be better off left alone."

Treating patients for a *C. difficile* infection with antibiotics when they don't necessarily have an active infection contributes to antibiotic resistance and upsets the normal balance of bacteria in the intestines. It may even prolong diarrheal symptoms and increase the likelihood of transmission, he said.

"The more antibiotics we give, the more collateral damage we do to the microbiome, wiping out lots of beneficial bacteria that don't need to be treated. In addition, if we give antibiotics when they're not needed, we potentially perpetuate the cycle of *C. difficile* spread and infection."

Polage conducted the study because he wanted to know if the extra patients detected by molecular tests had clinically significant symptoms or any of the negative outcomes traditionally associated with *C. difficile* infection. After a five-year historical study showed no complications among patients with negative toxin tests, he decided to evaluate outcomes prospectively to determine if one type of test was a better predictor of clinical disease and outcome.

"We found that virtually all of the bad, negative outcomes occurred in the patients with positive toxin tests," Polage said. "This suggests that we should really focus on toxin-positive patients for treatment. There may be room for trying to improve the sensitivity of toxin tests and look for additional tests to help identify patients at greatest risk for bad outcomes. Apart from this, we need to understand that most toxin-negative patients don't need treatment and may not even be infected."

Data from the National Healthcare Safety Network (NHSN), an arm of the Centers for Disease Control and Prevention that tracks hospital-acquired conditions, suggest that 40 to 45 percent of NHSN-reporting hospitals currently use molecular tests, either alone or in combination with other tests. Polage says that this translates to almost half of facilities in the U.S. potentially over diagnosing patients.

He said that hospitals that made the switch to molecular tests experienced a dramatic increase in the number of patients they reported with positive *C. difficile* infection. Many noticed an immediate doubling in the number of these patients, adding to concerns that they would be penalized for using a more sensitive test relative to other facilities.

"Our data suggest that these hospitals were really over-reporting *C. difficile*, over diagnosing these patients, and that these patients probably didn't have Clostridium difficile infection," he said. "So, some of the reporting differences between hospitals may be an artifact of testing

rather than a real difference in *C. difficile* infections."

Polage recommends that physicians and laboratories move in a direction of defining *C. difficile* disease based on the detection of toxins and limit molecular tests to screening, similar to Europe and the United Kingdom.

Provided by UC Davis