Kentucky Antimicrobial Stewardship Innovation Consortium

Educational Pearl

C. difficile Colonization Conundrum

Clostridioides difficile infection (CDI) is a bacterial infection of the colon that arises from gut dysbiosis allowing *C. difficile* to proliferate, germinate, and produce toxin. Using a combination of stools tests is recommended in CDI diagnosis.[1,2] Often patients will test positive for *C. difficile* by polymerase chain reaction (PCR) but negative with a toxin test (e.g. enzyme immunoassay (EIA)). Are these patients just colonized or do they have CDI and require treatment?

How should *C. difficile* PCR (+)/Toxin EIA (–) be interpreted?

C. difficile PCR (+)/Toxin EIA (–) can represent either colonization OR actual CDI that requires treatment. PCR testing is able to detect the presence of viable or non-viable *C. difficile* organism; however, disease is due to *C. difficile* toxin.[3] Therefore, PCR is often paired with a toxin test. Toxin EIA has low sensitivity meaning there are frequent false negatives. Toxin can degrade at room temperature after 2 hours, and clinically significant toxin concentrations may be below the threshold for detection by toxin EIA.[2, 4, 5] Therefore, clinical correlation with patient presentation is needed to interpret discordant PCR and Toxin EIA results.

What is the evidence for management of patients with *C. difficile* PCR (+)/Toxin EIA (–) results?

No randomized controlled trials have compared treatment vs no treatment in patients that are *C. difficile* PCR (+)/Toxin EIA (–). Available data is conflicting and likely limited by confounding. In one meta-analysis, 30-day mortality was lower among PCR (+)/Toxin EIA (–) patients that were treated (5%) when compared to those that were not (12.7%) (Risk difference -7.45%; 95% CI -12.29 to -2.60). However, 60-day recurrence was not significantly different in those treated (11.6%) and not treated (7.0%) (Risk difference 5.25%; 95% CI -1.71 to 12.22).[6] In a quasi-experimental study using a unique PCR cycle threshold-based toxin test, untreated and treated patients had similar 30-day all-cause mortality suggesting that withholding antibiotics for select patients with discordant results was safe.[7]

How should patients with *C. difficile* PCR (+)/Toxin EIA (–) be managed?

The patient should be reviewed for CDI risk factors (e.g., advanced age, immunocompromise, recent antibiotic use), clinical signs of CDI (e.g., elevated WBC, elevated serum creatinine), and alternative explanations for diarrhea (e.g., laxatives, tube feeds). In stable patients whom are able to have the alternative explanation discontinued (e.g. laxatives), monitoring for resolution of diarrhea without CDI treatment may be reasonable. In patients whom are not able to have the alternative explanation discontinued (e.g. tube feeds), monitoring for progression without CDI treatment may be reasonable. If diarrhea persists or clinical signs of CDI appear or worsen, CDI treatment is warranted. Risk stratification should be employed when selecting patients to be monitored off CDI treatment. Monitoring off CDI treatment may not be appropriate for critically ill or frail patients who have risk factors and clinical signs likely attributable to CDI, despite the presence of alternative explanations.

Key Takeaway: Patients with *C. difficile* PCR (+)/Toxin EIA (–) may be colonized with *C. difficile* **OR** have *C. difficile* infection and require treatment. Clinical correlation is needed to diagnosis CDI. Monitoring off CDI treatment may be reasonable in select patients.

References:

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