

LETTERS TO THE EDITOR

***Clostridium difficile*—To Test or Not to Test?
Response to Kundrapu et al**

To the Editor—While the laboratory diagnosis of *Clostridium difficile* infection (CDI) has been a subject of much discussion in recent years, the exact criteria to decide which specimens to test are less debated. Kundrapu et al¹ call for laboratories using stand-alone nucleic acid amplification tests for *C. difficile* testing to reduce testing of specimens that fail to meet clinical criteria, specifically patients with diarrhea without recent antibiotic exposure. In their study, a patient did not meet clinical criteria for testing if they had <3 unformed stools within 24 hours. We caution against this approach because it may delay implementation of infection prevention and control precautions. In addition, the potential for confusion exists between the criteria for laboratory testing of a diarrheal specimen and the definition of a clinical case of CDI.

The guidelines from the American Society for Microbiology² recommend that toxigenic *C. difficile* testing be limited to patients with ≥ 3 unformed stool specimens in a 24-hour period unless ileus is suspected. This recommendation contrasts with other international CDI guidelines, and the reasoning behind this difference is unclear. European guidelines recommend testing unformed stool of patients with potential infective diarrhea and negative tests for common enteropathogens, irrespective of a number of factors, including antibiotic use.³ Irish⁴ and UK⁵ guidelines recommend testing all diarrheal specimens as early as possible if an infectious cause is suspected rather than waiting until 3 episodes of diarrhea have occurred. This approach allows early implementation of appropriate infection prevention and control precautions as delays may increase the risk of *C. difficile* transmission. Likewise, the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) guidelines⁶ (also cited by Kundrapu et al¹) recommend testing for *C. difficile* or its toxins on diarrheal (unformed) stool only, unless ileus is suspected. The usual presentation of CDI is defined in IDSA/SHEA guidelines as ≥ 3 episodes of diarrhea within 24 hours; however, they do not specify that stool specimens are *not* to be tested unless the patient has at least 3 unformed stools.

Assuming that stool specimens meet the necessary requirements for laboratory testing (ie, unformed), we are not convinced that the laboratory is the appropriate place to decide whether specimens be tested for *C. difficile*. Notably, of the patients defined as ‘not meeting clinical criteria for testing,’ a significant proportion (37%) had received antibiotics within the previous 90 days,¹ which is a risk factor for CDI and should have prompted testing. As with many infections,

CDI should be diagnosed on clinical grounds with laboratory results supporting the diagnosis, and not vice versa.⁷ We are concerned that implementation of the authors’ proposal to reduce testing in patients not meeting clinical criteria for CDI may have a detrimental effect on efforts to control the dissemination of *C. difficile* spores in the hospital environment. While the use of the clinical definition is useful to provide a standardized definition for reporting, this definition is more suitable for standardized surveillance purposes than for laboratory processing. A significant limitation of this study, as acknowledged by the authors, is the absence of *C. difficile* toxin testing. Had the diagnostic testing included an assay for *C. difficile*, it would have added certainty to the decision to exclude these patients as CDI cases and more validity to their strict use of this case definition.^{8,9}

We agree that details of the patient’s clinical presentation are needed for accurate interpretation of CDI laboratory results; however, we suggest that this be done after the laboratory has tested the (unformed) stool specimen. Because *C. difficile* laboratory results are used not only to manage patients with CDI but also to minimize *C. difficile* transmission risk, we argue that delaying specimen acquisition until the patient has had ≥ 3 episodes of diarrhea in 24 hours increases the risk of *C. difficile* transmission. If strategies are required to reduce inappropriate laboratory testing, clinician engagement and education are key to ensuring correct patient selection based on clinical assessment. We suggest that stool specimens be sent to the laboratory when CDI is clinically suspected, regardless of the number of episodes of diarrhea, and we suggest that clinical correlation be required between the patient’s symptoms and laboratory results. As well as improving laboratory efficiency, this approach minimizes cross infection by promoting early implementation of infection prevention and control precautions; it also prevents inappropriate treatment of asymptomatic carriers.

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Response to Prior and Fitzpatrick

To the Editor—Many laboratories in the United States use nucleic acid amplification tests (NAATs) for the diagnosis of *Clostridium difficile* infection (CDI). Although NAATs have excellent sensitivity, there is increasing concern that asymptomatic carriers of toxigenic *C. difficile* with unformed stool due to other causes (eg, laxatives) are often diagnosed with CDI, resulting in unnecessary treatment and inflation of CDI rates.^{1–5} One strategy to address this concern has been to restrict testing to patients with 3 or more unformed stools within 24 hours.⁵ Alternatively, a common approach in Europe is not to restrict testing but to use a 2- or 3-step testing

algorithm in which results of stool toxin testing and clinical assessments are used to guide management for patients with positive initial screening assays for *C. difficile*. In this approach, a positive toxin assay indicates CDI and a negative toxin assay suggests an asymptomatic carrier who may contribute to transmission as a fecal excretor.⁶ Fecal excretors are isolated but are not routinely treated or reported as CDI cases.

As noted by Prior and Fitzpatrick,⁷ the European CDI testing approach has some advantages. Testing after a single unformed stool facilitates rapid diagnosis, and fecal excretors are isolated but not exposed to unnecessary CDI treatment. We share the concern of Prior and Fitzpatrick regarding the potential for transmission by fecal excretors. We demonstrated that antibiotic-exposed patients not meeting criteria for CDI (ie, <3 unformed stools within 24 hours) were as likely to have skin and/or environmental contamination as CDI patients meeting criteria for testing.¹ Similarly, Biswas et al⁸ demonstrated that fecal excretors frequently shed spores.

It is possible that the European approach to CDI testing may begin to replace stand-alone NAAT testing in the United States, as has been advocated by Polage et al.³ However, some caveats to this approach deserve further study. First, our findings suggest that a subset of fecal excretors may present a relatively low risk for transmission. Specifically, none of 17 patients with an alternative explanation for diarrhea (eg, laxatives) and no antibiotic exposure in the past 90 days had skin and/or environmental shedding (see Figure 1 of Kundrapu et al¹). In the absence of antibiotic exposure, the microbiota of these carriers may be sufficiently intact to maintain *C. difficile* colonization at low levels that are less likely to be associated with shedding. Based on these results, we recommended that facilities using NAATs for CDI testing could reduce testing in this subset of patients because isolation of those with positive CDI tests might provide limited infection prevention benefits while subjecting patients to isolation. Because our study was relatively small and included only 1 center, additional studies are needed to confirm our findings. Second, although Prior and Fitzpatrick suggest that toxin testing adds certainty to decision making, further studies are needed to clarify whether the presence or absence of toxin truly provides certainty in distinguishing colonization from infection. In previous studies, asymptomatic carriers, including those who have recently completed successful CDI treatment, often have had detectable toxin in stool.^{2,9,10} Thus, unnecessary treatment may be prescribed for carriers if a positive toxin assay is deemed sufficient evidence to diagnose CDI in the absence of clinically significant diarrhea.

Third, the recommendation that the clinical presentation should be assessed after lab results are available is reasonable but will require education. In practice, clinicians often reflexively treat positive tests. For example, Buckel et al⁴ found that 100% of asymptomatic patients testing positive for toxin genes by NAAT were treated for CDI despite a stewardship intervention that included education plus