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1 **Reply to Comment Letter**

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5

6 **To the Editor**

7 In a Letter to the Editor, Tenover *et al* suggest that on-label testing with nucleic acid amplification tests
8 (NAATs) for the diagnosis of *Clostridioides difficile* infection (CDI) is discussed, to put toxin testing in
9 perspective. The authors argue that guidelines from the Infectious Diseases Society of American- Society
10 for Healthcare Epidemiology of America (IDSA-SHEA)(1), the American Society for Microbiology (ASM)
11 (2), and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) (3), “all make it
12 clear that NAATs play an essential role in the laboratory diagnosis of CDI.” This statement is potentially
13 misleading. Firstly, the ESCMID guidelines state that “using NAAT as a stand-alone test and relying on
14 clinical symptoms to discern patients with CDI from asymptomatic carriers is not an optimal approach:
15 patients colonized by a toxigenic *C. difficile* strain may very well develop diarrhea due to other causes
16 (3).” Secondly, the systematic review from ASM evaluated performance compared to detection of *C.*
17 *difficile* organism/toxin/toxin and not clinical diagnosis (2). However, this systematic review somewhat
18 disingenuously evaluated only testing methods and algorithms including NAAT, and excluded key studies
19 that have demonstrated the clinical value of toxin based testing (4, 5). Tenover *et al* claim that ASM
20 guidelines “endorses a role for stand-alone NAATs for CDI,” while the ASM authors state that the use of
21 NAAT alone is recommended best practice “for the detection of the *C. difficile* toxin gene or organism
22 (2).” The two statements are certainly not synonymous. Thirdly, the IDSA-SHEA guidelines do

23 recommend that NAAT can be used alone, but only when there are pre-agreed institutional criteria for
24 patient stool submission (weak recommendation, low quality of evidence). These guidelines also clearly
25 recommend an algorithm approach to CDI diagnosis that includes toxin testing. The clinical criteria,
26 unexplained and new-onset ≥ 3 unformed stools in 24 hours in patients not receiving laxatives, are
27 discussed in the guidelines: “some of these conditions and interventions associated with diarrhea in
28 their own right, [...], have been shown to have increased risk of CDI. So, in practice it is difficult to
29 exclude the possibility of CDI on clinical grounds alone in a patient with new-onset or worsened diarrhea
30 (1).”

31

32 Tenover *et al* agree that using NAAT for the diagnosis of CDI leads to overdiagnosis, but only if the
33 clinical criteria for testing are not met. The authors further argue that any diagnostic *C. difficile* assay can
34 be positive in asymptomatic carriers. In a recent study, it was shown that the proportion of CDI
35 overdiagnosis was over three times higher in NAAT+/toxin- than in NAAT+/toxin+ patients when an
36 ultrasensitive toxin assays was used for CDI diagnosis, in an institution where rigorous stool-submission
37 criteria were recently successfully set in place (6, 7). CDI is a toxin-mediated disease and, although it has
38 been known for decades that toxin-producing strains can be present in asymptomatic carriers (8, 9),
39 presence of toxins better correlate with disease *and* outcome than presence of toxin genes (4–6).
40 Hospital-onset diarrhea is a common condition and importantly a recent large study showed that the
41 majority (85%) have multiple possible causes (median 3; IQR 2-5) (10). Thus, reliance on NAAT alone for
42 the diagnosis of CDI will still lead to overdiagnosis even if clinical criteria are used to guide who/when to
43 test.

44 A number of NAAT qualities are highlighted in the Letter: speed, sensitivity, high negative predictive
45 value, and cost-effectiveness when used appropriately (although the latter can be debated). The authors

46 have, rightfully so, left out high clinical specificity and high positive predictive value, both critical
47 components of any diagnostic test. Surprisingly, Tenover *et al* close their Letter with the statement “we
48 simply note that three recent guidelines support the value of NAATs for diagnosing CDI, while none
49 indicate a role of ‘ultrasensitive’ toxin tests.” Notably, however, an ultrasensitive toxin test was not
50 commercially available at the time of publication of these guidelines, making such a recommendation
51 impossible.

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