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Letter to the Editor

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Clostridioides difficile Treatment Guided by Polymerase Chain Reaction Stool Testing Does not Alter Outcomes for Patients With Inflammatory Bowel Disease

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To the Editor

The management of *Clostridioides difficile* (*C. difficile*) infection (CDI) for patients with inflammatory bowel disease (IBD) is an ongoing challenge. CDI complicating IBD has been shown to be associated with worse outcomes including hospitalization, colectomy and death. The recent American Gastroenterological Association clinical practice review of IBD and CDI provides a comprehensive update of the factors leading to CDI with IBD, and standards of care for treatment [1]. More recently changes in recommendations for CDI treatment in the general population have been made, advancing fidaxomicin as the preferred first-line treatment, though there is not yet an updated guideline for those with IBD [2].

The essential first step to effective treatment of CDI is to make an accurate diagnosis. While this may seem simple enough, it is understood that testing with the rapid and popular high-sensitivity nucleic acid amplification test (NAAT), also known as polymerase chain reaction (PCR), may in fact over-diagnose CDI, i.e., a positive PCR may reflect *C. difficile* colonization rather than true infection. This potential for PCR over-diagnosing CDI has been observed in the general population, leading to recent guideline recommendations for a stepwise diagnostic approach [3, 4]. The guidelines recommend first-line testing with a high-sensitivity glutamate dehydrogenase (GDH) assay. A positive finding is followed by a more specific test directly for *C. difficile* toxin. Utilizing this strategy, a PCR test is only employed as an arbiter to rule in CDI for those cases with discordant results, i.e., a positive GDH with negative toxin assay.

Only recently however has real world clinical evidence emerged demonstrating a superiority of a test and treat strategy directed by toxin-positive assay over PCR testing for suspected CDI in the IBD population. Gupta et al in a study of 92 IBD patients (61% Crohn's disease), of whom 28 (30%) where toxin-positive, found that 82% of toxin-positive patients responded to antibiotics directed against CDI compared to only 25% of toxin-negative PCR-positive patients ($P < 0.001$), and that only 21 % of toxin-positive patients required IBD therapy escalation compared to 63% of toxin-negative PCR-positive patients ($P < 0.001$) [5].

While Gupta et al's work supports a toxin-positive result as the preferred modality of diagnosing CDI in the IBD population, it does not exclude the possibility that first-line PCR testing may still have some value and impact outcomes in the IBD population. Though guidelines clearly advocate against first-line PCR testing, this modality remains popular, widely available, and may in fact be the only test available at some institutions [6]. As such, we investigated whether patients with IBD treated for CDI based on a positive PCR had different outcomes compared to those with a negative PCR. We analyzed all outpatients 18 years and older within our health system over the last 14 years with IBD and outpatient *C. difficile* PCR testing with at least 1 year of documented office follow-up. *C. difficile* PCR-positive patients were matched 1:1 to PCR-negative patients by age, IBD type, disease extent, disease duration, and IBD therapy. Our primary outcomes compared PCR-positive and -negative patients by escalation of IBD treatment and time to escalation within 1 year following *C. difficile* testing. Escalations were defined as an addition/change of medications, increase in dose/frequency of current therapy, or surgery.

Of 168 IBD patients who were *C. difficile* PCR-positive, 46 patients met inclusion criteria. Seventy percent of patients were treated with vancomycin, and the rest with metronidazole or fidaxomicin. From 2,321 IBD patients who were *C. difficile* PCR-negative, 46 matches were identified. *C. difficile* PCR-positive patients were older than *C. difficile* PCR-negative patients, but had similar disease duration (Table 1). At 1-year

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Table 1. Patient Demographics and Outcomes

Demographics	PCR-positive	PCR-negative	P-value
Total cases	46	46	
Age (years)			< 0.0021*
Mean (SD)	45.8 (20.8)	43.8 (19.8)	
Range	20 - 92	18 - 85	
IBD duration in years			< 0.7451*
Mean (SD)	7.9 (5.9)	7.5 (7.1)	
Range	0 - 26.0	0.1 - 37.0	
Ulcerative colitis, N (%)	28 (60.9)	28 (60.9)	
Total IBD therapy escalation at 1 year, N (%)	30 (65.2)	26 (56.5)	< 0.3458**
Addition of biologic therapy or change of biologic therapy at 1 year, N (%)	18 (39.1)	12 (26.1)	0.1088**

*Continuous factors (age and IBD duration) compared using the paired *t*-test. **Categorical factors (IBD therapy escalation, addition/change in biologic) compared using McNemar's test. No comparison carried out for ulcerative colitis, as there were no discordant pairs. PCR: polymerase chain reaction; IBD: inflammatory bowel disease; SD: standard deviation.

follow-up, there was no difference between the two groups with regard to overall escalation of IBD treatment, or addition/change of biologic therapy. There was also no significant difference of time to escalation of IBD treatment within 1 year between groups at any time point (P < 0.7319) (Fig. 1).

Our results show that the diagnosis and treatment of CDI by a stand-alone PCR-directed strategy did not impact the clinical course in a cohort of IBD patients. In this regard, our findings add to those of Gupta et al by demonstrating that PCR testing as a guide to CDI therapy is not just inferior to toxin, but may perhaps be of no use whatsoever. It suggests that PCR-positive testing for *C. difficile* in the setting of IBD overwhelmingly represents patients with colonization rather than infection, making the use of toxin testing critical to distinguish between the two. Our observation of similar rates of escalation of IBD therapy between the *C. difficile* PCR-positive and PCR-negative IBD patients lends further real-world data to support the current stepwise testing guidelines. In accordance with these results, institutions should routinely offer stepwise GDH *C. difficile* testing and redirect requests away

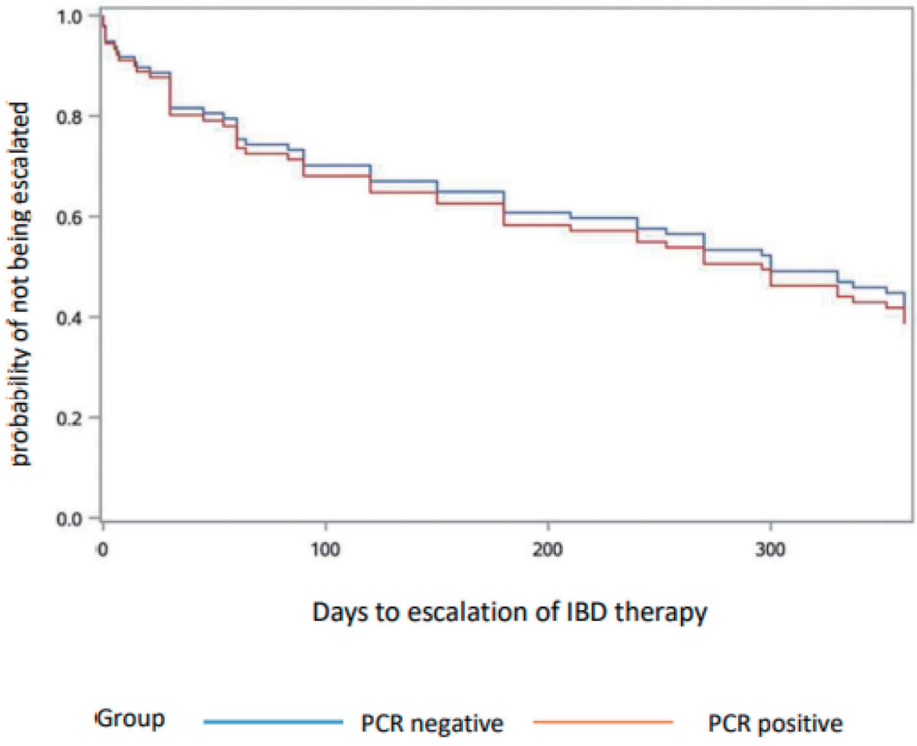

Figure 1. Escalation of IBD therapy. PCR: polymerase chain reaction; IBD: inflammatory bowel disease.

from PCR stool assays for those patients with IBD.

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Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Requirement for informed consent was waived by IRB approval.

Author Contributions

Conceptualization: CC and KS. Methodology: CC, KS, and NK. Formal analysis: CC, KS, and NK. Data curation: CC, KC, and YU. Project administration: CC. Visualization: CC, KS, NK, and AS. Writing-original draft: CC. Writing-review and editing: KS and AS. Approval of final manuscript: all authors.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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