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Letter

Evaluation of the microbiological diagnostic algorithm for *Clostridioides difficile* infection and associated clinical factors in a tertiary care hospital

Evaluación del algoritmo diagnóstico microbiológico de la infección por *Clostridioides difficile* y de los factores clínicos asociados en un hospital de atención terciaria

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Sir,

We would like to share the results of a retrospective observational study evaluating the microbiological diagnostic algorithm for *Clostridioides difficile* infection (CDI) implemented at the Hospital Clínico Universitario Virgen de la Arrixaca (HCUVA) during 2024. This study was motivated by an institutional need to assess the impact of a newly implemented diagnostic algorithm aimed at improving case detection and infection control, compared with the previous algorithm, which relied mainly on toxin detection and had shown limited sensitivity in routine clinical practice. Our aim was to assess its diagnostic performance, CDI prevalence, recurrence rates, and associated clinical factors.

A total of 2,699 diagnostic requests from 1,965 patients were analyzed. The diagnostic algorithm initially included an immunochromatographic test (ICT) for GDH and toxins A/B (TECHLAB® *C. DIFF QUIK CHEK COMPLETE®*) and a toxigenic culture (CHROMID® *C. difficile*, bioMérieux). PCR testing (BD MAX™ Cdiff, Becton Dickinson) was added in cases with high clinical suspicion—defined as the presence of clinically significant diarrhea (≥3 unformed stools within 24 h) together with epidemiological or clinical risk factors for CDI (recent antibiotic exposure, recent hospitalization, immunosuppression)—and a negative ICT, or when discordant ICT results were observed (GDH positive/toxin negative), following national recommendations. In these scenarios, PCR was preferred over culture for rapid clinical decision-making, while culture was maintained for epidemiological purposes and for cases with low initial clinical suspicion [1,2].

The overall prevalence of CDI was 7% (188/2,699). ICT enabled diagnosis in 38.3% of cases (n=72). PCR proved decisive in 46.3% (n=87) of specimens with discordant ICT results, and in 7.5% (n=14) of cases with negative ICT but strong clinical suspicion, in which PCR was subsequently requested by the clinician after reviewing the negative ICT result. Notably, culture alone was responsible for diagnosing 8% of cases (n=15),

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primarily among patients with low suspicion, in whom PCR was not initially performed. Importantly, 40% of these culture-positive/ICT-negative cases originated from the Emergency Department, followed by Internal Medicine, the Pediatric Emergency Unit, and the Infectious Diseases Unit (13.3% each). All culture-positive cases included in the analysis were clinically significant, presenting with compatible signs and symptoms, and were individually evaluated by an expert infectious disease specialist in order to distinguish true infection from asymptomatic colonisation.

Among the 407 patients who underwent multiple diagnostic requests, recurrence was defined as the reappearance of compatible clinical symptoms within 8 weeks after resolution of the initial episode, together with a positive microbiological test [3]. Thirty-four patients experienced recurrence (8.3%), leading to a total of 50 recurrence episodes. Thus, the 8.3% figure refers to the proportion of patients with recurrence, while the recurrence rate calculated per episode is higher when using the total number of episodes as the denominator. In our institution, all cases with laboratory detection of *Clostridioides difficile* are systematically reviewed by the Infectious Diseases Unit as part of the antimicrobial stewardship programme, to avoid inappropriate treatment of colonised patients. We believe this expert evaluation may have contributed to the relatively low recurrence rate observed. Of these episodes, 82.4% occurred within 50 days of the initial diagnosis, consistent with persistent spore-mediated intestinal recurrence rather than reinfection with new spores from the environment. Furthermore, 35.3% of recurrent patients had two or more episodes. The average interval between recurrences was 36.8 ± 47.1 days.

Regarding hospitalization, 64.8% of CDI patients had stays of fewer than 20 days, but 10.1% had prolonged stays exceeding 40 days, reflecting clinical complexity or delayed diagnosis in some cases.

Diagnostic test requests primarily originated from the Internal Medicine and Emergency Departments (both 19%), followed by Gastroenterology and Oncology (10% each). In the 166 patients with complete clinical records, 59.6% had received prior antibiotic therapy, which was the main predisposing factor identified. Diarrhea was the most frequent presenting symptom, reported in 90% of cases. Regarding therapeutic management, oral vancomycin was the most frequently prescribed treatment (53.7%), followed by fidaxomicin (41.5%). A small subset of patients received metronidazole, typically in mild cases.

The most relevant finding was the diagnostic value of culture, which, in addition to being the only method that enables strain isolation for epidemiological investigations and outbreak analysis, proved essential in ICT-negative cases with low clinical suspicion. Delays in diagnosis of up to 5 days led to postponed antibiotic therapy and the lack of appropriate infection control measures, reinforcing the need to review the diagnostic approach in specific clinical contexts. In fact, 40% of those cases originated from the Emergency Department. Based on this finding, we have modified our diagnostic algorithm: all ICT-negative samples from these settings are now re-evaluated to determine whether they meet criteria for inclusion in the high clinical suspicion category. This adjustment reflects the fact that requesting clinicians cannot specify diagnostic methods such as PCR when ordering CDI testing on fecal specimens; the algorithm is initiated with ICT, and the decision to include PCR is made by the microbiologist, who must therefore exercise careful clinical judgment.

Our findings are consistent with previously published studies from other tertiary care hospitals, which have reported improved diagnostic yield when combining GDH/toxin screening with PCR confirmation, particularly in discordant or clinically high-risk cases [4].

This study has several limitations, including those inherent to its retrospective design, the absence of inferential statistical analysis, and incomplete clinical information, as only 166 patients had fully documented clinical records. These limitations may restrict the generalisability of our findings.

In conclusion, our analysis highlights the added value of PCR in cases with negative ICT and high clinical suspicion, as well as in discordant ICT results (GDH-positive, toxin-negative), where the superior sensitivity of PCR enables the detection of toxin genes even when toxin expression is low. The availability of *C. difficile* culture in our tertiary care setting—despite its labor-intensive nature and the requirement for specific media—allowed for delayed diagnosis in 8% of cases. These findings support the need to systematically reassess clinical risk in ICT-negative requests and led to a revision of our diagnostic algorithm, which initially relies on dual ICT for simultaneous GDH and toxin detection. We believe these observations may be relevant for other institutions using similar diagnostic pathways without access to culture and that may not yet recognise the diagnostic value that PCR adds in such scenarios.

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Conflict of interest

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AI statement

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