Overdiagnosis of *C. difficile* with a Multiplex PCR Panel

Vaneet Arora, MD, MPH1,3; Donna R. Burgess, RPH1,2; Katie L. Wallace, PharmD, BCPS1,2; Sarah E. Cotner, PharmD, BCPS1,2; Julie A. Ribes, MD, PhD1,3; Derek Forster, MD1,3

1. University of Kentucky HealthCare2. University of Kentucky College of Pharmacy3. University of Kentucky College of Medicine, Lexington, KY

ABSTRACT (revised)

**Background:** While advantageous by casting a wider diagnostic net, multiplex panels can be problematic if the pretest probability is low. A significant increase in reported *Clostridium difficile* infections (CDI) was noted at our institution following introduction of a multiplex comprehensive GI (CGI) Panel which includes an analytic for *C. difficile*. Due to these concerns, the *C. difficile* analytic result was suppressed when results were reported and providers were advised to order a standalone C. difficile PCR (CDPCR) test if CDI was a concern. The objective of this study was to investigate concerns of false positive *C. difficile* results from the CGI Panel.

**Methods:** *C. difficile* diagnostic practices were prospectively evaluated from April to August 2017. Patient charts were reviewed in response to a positive *C. difficile* analytic on the CGI Panel. CDPCR results were reviewed if ordered. If not ordered, chart review and discussion with the provider was conducted to investigate clinical suspicion for CDI. The results were analyzed to examine the performance of the *C. difficile* analytic on the CGI Panel.

**Results:** Overall, a total of 1611 CGI Panels were performed with *C. difficile* being detected in 157 specimens. A sub analysis was performed on 123 positive specimens for whom complete data was available. A CDPCR was performed in 89 (65%) of these specimens. Among those, only 44 (50%) were CDPCR positive, 23 (28%) were CDPCR negative (likely a false positive CGI result), and 14 (17%) were rejected because of specimen consistency. For the remaining 43 *C. difficile* positive CGI Panel specimens that did not have an accompanying CDPCR, 7 were in children below 2 years of age. Direct provider discussion occurred in the remaining 36 cases. Providers declined CDPCR testing in 24 of those cases due to a lack of clinical concern. The introduction of the CGI Panel for *C. difficile* led to over diagnosis of CDI with a false positive rate of 27.5%. This could have significant consequences for clinical care and the reporting of hospital acquired infections.

**Background / Objectives**

- Using nucleic acid amplification testing for the diagnosis of *C. difficile* may lead to overdiagnosis
- Diagnostic stewardship strategies targeted for *C. difficile* (i.e. indication based testing and not performing tests on formed stools) are more difficult to implement with the CGI Panel
- The introduction of the CGI Panel at our institution was temporally associated with an increased number of reported *C. difficile* infections (Fig. 1)
- There was a concern that the increased number of CDI positive tests may have been a reflection of increased and inappropriate testing, and not of true clinical disease

**Methods**

- Beginning in April 2017, the *C. difficile* analytic result on the CGI Panel was no longer reported and providers were advised to order the stand alone *C. difficile* PCR (CDPCR) test if they had a clinical concern for CDI
- From April 2017 – August 2017, *C. difficile* diagnostic practices were prospectively reviewed in response to a positive *C. difficile* analytic on the CGI Panel
  - If a CDPCR was ordered, results were reviewed
  - If a CDPCR was not ordered, the medical director for Infection Prevention and Control (IPAC) contacted providers who ordered the CGI Panel to discuss the case and advised to order the CDPCR if it was to be clinically indicated
- The data was collected and analyzed as part of a microbiology quality assurance project to assess the performance of the *C. difficile* analytic on the CGI Panel and to assess the safety of removing this result from reporting into the medical record

**Results**

- 157 CGI Panels had a positive *C. difficile* analytic result (Fig. 2)
- 123 cases for which complete data was available were included in this review
  - 80 (65%) had a concomitant CDPCR order
  - 36 (29.3%) did not have a concomitant order and were referred to the IPAC medical director for review and provider discussion
  - 7 (5.7%) were positive in patients < 2 yrs of age and thus CD PCR was not indicated
- Among the 80 cases that were CGI Panel *C. difficile* analytic positive and an order for the stand alone CDPCR was entered (Fig. 3)
  - 44 (55%) were CDPCR positive
  - 22 (27.5%) were CDPCR negative (likely false positives)
  - 14 (17.5%) were not tested by CDPCR because of receipt of formed stools in the laboratory
- Among the 36 cases that were CGI Panel *C. difficile* analytic positive but did not have an order for a stand alone CDPCR test
  - 24 (66.7%) did not have a clinical indication for CDPCR testing based on discussion with the provider
  - 7 (20%) of cases had a CDPCR ordered and all were positive
  - 5 (13.8%) of cases were discharged and follow up was unavailable
- Overall, 67 (54.9%) *C. difficile* analytic positive CGI Panel cases were either negative by CDPCR stand alone testing or CDPCR testing was not indicated (Fig-4)
  - 24 cases were determined to be not clinically indicated for CDPCR testing following direct provider communication
  - 22 were tested and were CDPCR negative
  - 14 were not tested by CDPCR because the stool was formed
  - 7 occurred in patients < 2 yrs of age (testing not generally indicated)

**Conclusions**

- We found a 27.5% false positive rate for the *C. difficile* analytic on the CGI Panel when tested by a stand alone CDPCR test
- Overall, we found that 54.5% of the positive *C. difficile* analytic CGI Panel cases were either negative by stand alone testing or CDPCR testing was not indicated
- The use of a multiplex PCR platform (such as the CGI Panel) for *C. difficile* diagnostics may lead to an increase in the number of CDI cases which has a significant impact on the clinical management of patients as well as on CDI reporting

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