Impact of Cell Cytotoxicity Neutralization Assay in Patients with Suspected *C. difficile* Infection

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Purpose/Background: *Clostridium difficile* remains a major public health threat causing at least 220,000 infections and 12,800 deaths annually, resulting in an estimated $6.3 billion of healthcare associated costs. Antimicrobial stewardship programs have demonstrated success in combating *C. difficile*, primarily through optimizing antibiotic utilization. However, several studies have been published indicating there is a high level of inappropriate CDI testing, indicating that more diagnostic stewardship is warranted in this population. The 2018 IDSA guidelines on the management of *C. difficile* infections (CDI) in adults recommends a multistep diagnostic algorithm utilizing a combination of GDH antigen, PCR (polymerase chain reaction), and stool toxin tests. Choice of diagnostic testing is institution dependent as there is no clear guidance regarding the optimal testing algorithm. Many institutions have adopted the use of PCR following indeterminate GDH antigen and toxin AB enzyme immunoassay (EIA) testing due to its ability to yield rapid results despite limitations in detecting an active infection. Cell cytotoxicity neutralization assay (CCNA) is considered the gold standard for CDI diagnosis, due to its ability to detect active CDI; however, it is less commonly used as a reflex testing method due to prolonged turnaround time. In July 2020, our large community health system updated its *C. difficile* stool testing to include cell cytotoxicity neutralization assay (CCNA) in in place of PCR testing for patients with an indeterminate GDH antigen and toxin enzyme immunoassay result. Currently, there are no studies that compare the impact of PCR and CCNA on patient outcomes in a hospitalized setting.

Objective: To evaluate the impact of cell cytotoxicity neutralization assay in patients with suspected CDI.

Methods: This retrospective cohort study was conducted at a community health system. A report was utilized to identify patients with *C.difficile* stool testing ordered between July 2019 through July 2021. Patients were included if their GDH antigen and toxin AB EIA was indeterminate. If patients had a repeat positive result following the first index positive event, they were excluded from secondary outcomes. The primary endpoint was *C. difficile* test positivity rate. Secondary endpoints included CDI therapy initiation, CDI therapy continuation after final result, treatment failure, recurrent CDI, 30-day emergency department (ED) visit for CDI symptoms after first reported indeterminate result, and 30-day readmission secondary to CDI after first reported indeterminate result.

Results: The study included 518 patients (279 in the PCR arm and 239 in the CCNA arm). The mean age was 61 years old, 40.5% of patients were male, and 20.4% had a previous medical history of CDI. The mean total hospital length of stay was 7.8 days in the PCR arm and 9.7 days in the CCNA arm and the mean time from initial *C.difficile* test order to final result was 0.3 days in the PCR arm and 4.5 days in the CCNA arm. Final results were reported following discharge in 7% of the PCR and 61% of the CCNA arm. *C. difficile* test positivity rates were significantly lower in the CCNA arm (PCR 66.7%; CCNA 20.9%, $p < 0.0001$). Of those who tested positive for *C. difficile*, significantly more patients were initiated on CDI therapy in the PCR arm (PCR 96%; CCNA 84%; $p=0.0046$), recurrent CDI occurred more frequently in the PCR arm (PCR 5; CCNA 0), and there was no difference in treatment failure. Of those who tested negative for *C. difficile,* significantly more patients in the CCNA were initiated on CDI therapy (PCR 9%; CCNA 33%, $p < 0.0001$) and significantly more patients in the CCNA arm also continued therapy following negative result (PCR 1%; CCNA 11%; $p=0.0018$). There were no differences in the rates of readmission or ED visits.

Conclusion*: C. difficile* testing positivity rates were significantly reduced following the transition from PCR to CCNA stool testing. Despite the prolonged turnaround time associated with CCNA testing, there were no significant differences in patient outcomes.