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Impact of toxigenic *Clostridium difficile* polymerase chain reaction testing on the clinical microbiology laboratory and inpatient epidemiology ☆

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ABSTRACT

Conversion from *Clostridium difficile* toxin A/B EIA to *tcdB* polymerase chain reaction for diagnosis of *C. difficile* infection (CDI) resulted in significant decreases in laboratory testing volume and largely unchanged *C. difficile* toxin detection rates. Decreases in healthcare-associated CDI rates ($P \leq 0.05$) reflected a clinical practice benefit of this conversion.

Clostridium difficile is the most common etiology of hospital- and antimicrobial-associated diarrhea (Johnson and Gerding, 1998; Wilkins and Lyerly, 2003). These conditions can result in implementation of contact precautions upon diagnosis which can accelerate healthcare costs due to increased utilization of personal protective equipment, additional antimicrobial therapy, and ancillary housekeeping services (Dubberke et al., 2008). While reports have revealed no deleterious effect of contact precautions on healthcare worker contact with patients (Klein et al., 1989) and on patient satisfaction (Gasink et al., 2008), past analyses have been limited by study design or nonstandardized collection of data (Morgan et al., 2009). Conversely, in matched cohort designs, Evans et al. (2003) determined that both frequency of healthcare worker/patient encounters and time per encounter were less with patients in contact precautions than in noncontact precaution patients. Stelfox et al. (2003) reported that preventable adverse effects such as falls and pressure ulcers were more common within patients in contact precautions. Tarzi et al. (2001) demonstrated that rehabilitation patients in contact precautions exhibited increased depression and anxiety than patients not in contact precautions. Two of these studies (Tarzi et al., 2001; Stelfox et al., 2003) also reported decreased patient satisfaction with care.

C. difficile toxin B (*tcdB*) polymerase chain reaction (PCR) is a highly specific, highly sensitive detection method when compared to toxin A/B enzyme immunoassay (EIA) (Kvach et al., 2010; Munson et al., 2011; Novak-Weekley et al., 2010; Quinn et al., 2010). Improved clinical diagnostics, in the context of appropriate clinical criteria (Cohen et al., 2010), assist in focusing testing on those patients possessing a higher probability of *C. difficile* infection (CDI) (Peterson and Robicsek, 2009). Moreover, specificity indices of these diagnostics should allow for more appropriate utilization of contact precautions. We present data from a multi-facility healthcare system that document the impact of *C. difficile tcdB* PCR on laboratory workload, inpatient target detection rates, and healthcare-associated CDI rates.

Wheaton Franciscan Healthcare encompasses 5 Milwaukee (Wisconsin) inpatient healthcare facilities. Three of these facilities were selected for this study on the basis of significant patient census and testing volume. Hospitals A, B, and C have licensure for 166, 538, and 260 beds, respectively. The 20-month interval of *C. difficile* toxin A/B EIA testing that directly preceded commencement of *C. difficile tcdB* PCR was reviewed, as well as the first 20 months of PCR testing. This investigation was approved by the Wheaton Franciscan Healthcare Institutional Review Board. Parameters included testing volume, frequency of positive result, and monthly inpatient census. Frequency of healthcare-associated CDI was calculated on the basis of

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recommendations published by the Society for Healthcare Epidemiology of America (McDonald et al., 2007). In brief, cases of healthcare-associated CDI were defined as patients with CDI symptom onset >48 h after inpatient admission. With respect to the current review, a diarrheal testing episode was defined as 1 day for the EIA testing interval on the basis of past recommendations (Thomson, 2007) and laboratory policy that allowed for replicate testing per 24-h interval. The diarrheal testing episode was lengthened to 1 week for *tcdB* PCR on the basis of recommendation revisions (Cohen et al., 2010; Baron and Thomson, 2011) and changes to laboratory policy.

ProSpecT® *C. difficile* Toxin A/B Microplate assay (EIA; Remel, Lenexa, KS, USA) was performed during the 20-month interval of November 2008 through June 2010 on nonformed stool per manufacturer specifications. BD GeneOhm™ Cdiff assay (*tcdB* PCR; BD Diagnostics, Ste-Foy, Quebec, Canada) was performed from July 2010 through February 2012 on nonformed stool using previously published modifications (Munson et al., 2011). For both intervals, all testing was performed at Wheaton Franciscan Laboratory, a free-standing microbiology laboratory that is centrally located with respect to the 3 inpatient facilities. The significance test of proportions (2-proportion *Z* ratio) determined whether changes in detection rate and testing frequency were significant (Triola, 1992). The *t* test for independent samples determined whether monthly changes in census and healthcare-associated CDI rates were significant.

Site-specific *C. difficile* testing volume decreased by 32.5–53.9% following implementation of *tcdB* PCR (Table 1). Mean testing frequency per diarrheal episode significantly decreased at all 3 hospitals ($P < 0.0001$). These data are analogous to findings from Catanzaro and Cirone (2012). In addition, a significant decrease in the percentage of episodes managed with 2 or more tests was observed at all 3 hospitals ($P < 0.0002$). A reduction in testing volume did not adversely affect rates of detection. Hospital A experienced a significant increase in *C. difficile* detection (Table 1). Hospital B and C detection rates were unchanged post-conversion ($P \geq 0.07$).

All 3 hospitals experienced significant reductions in healthcare-associated CDI upon introduction of molecular diagnostics ($P \leq 0.05$; Fig. 1). Healthcare-associated CDI rates were not impacted by fluctuations in patient census, as hospitals A and B had a consistent census during the entire audit ($P \geq 0.10$; Table 1) and hospital C experienced a monthly census increase during the PCR interval ($P = 0.0003$).

With the incidence of CDI more than doubling since 2000 (Zilberberg et al., 2008), and increased mortality rates and virulence associated with some strains (McDonald et al., 2005; Warny et al., 2005), implementation of accurate and reliable laboratory testing is essential for diagnosis of CDI and patient management (McDonald et al., 2012). Our data suggest that *tcdB* PCR was able to meet this clinical need in a metropolitan healthcare setting. EIA data from multiple facilities (Table 1) demonstrated a past clinical practice of multi-specimen submission within a 24-h period for laboratory diagnosis of CDI. In contrast, a shift to single-specimen submission (1 component of specimen acceptability guidelines; Cohen et al., 2010) was observed during the PCR interval ($P < 0.0002$), resulting in decreased workload for the laboratory. Increased accuracy of *tcdB* PCR (Kvach et al., 2010; Munson et al., 2011; Novak-Weekley et al., 2010; Quinn et al., 2010) obviates the need for repeat testing. In further support, an investigation of repeat toxigenic *C. difficile* PCR analysis by Aichinger et al. (2008) reported that just 2% of patients had an initially negative result that reverted to positive.

In conjunction with monitoring testing volumes, *C. difficile* detection rates were determined for the 20 months pre- and post-conversion. Despite overall decreases in testing volume, 2 facilities showed no significant change in the rate of positive *C. difficile* results, while the third facility demonstrated a significant increase in detection rate. Furthermore, increased *tcdB* PCR detection at hospital A was not paired with increased census; an increased hospital C census did not procure elevated *tcdB* PCR detection (Table 1). In our experience (Munson et al., 2011), the predictive value of a positive *C. difficile* toxin EIA result was only 45.3% concomitant to evaluation of *tcdB* PCR adjudicated by toxigenic culture. This parameter increased to 94.7% with *tcdB* PCR (Munson et al., 2011). These data predict a significant reduction of false-positive results via PCR testing. Taken together with improved *tcdB* PCR sensitivity (Kvach et al., 2010; Munson et al., 2011; Novak-Weekley et al., 2010; Quinn et al., 2010), it was not surprising that CDI rates were largely unchanged at hospitals B and C. Moreover, a hypothetical increased CDI rate over the PCR interval could have been the result of increased utilization of the more-sensitive assay. However, this phenomenon was not observed at any of the hospitals.

Data from Fig. 1 reveal significant decreases in healthcare-associated CDI at all 3 inpatient facilities upon conversion to *tcdB* PCR. In a single community hospital, Catanzaro and Cirone (2012) also

Table 1
Comparison of *Clostridium difficile* laboratory requisition and detection data, plus mean inpatient census figures, for hospital A, hospital B, and hospital C between consecutive 20-month intervals of *C. difficile* toxin A/B enzyme immunoassay testing and *C. difficile tcdB* PCR analysis.

Parameter	*C. difficile* Toxin A/B EIA	*C. difficile tcdB* PCR	*P* value
Hospital A			
Monthly census (mean inpatient days)	1812.8	1748.2	0.17
Monthly testing volume (mean)	57.0	31.9[a]	
Tests per episode (mean)	1.145	1.072	<0.0001
Percentage of episodes with ≥2 tests	13.7	7.1	<0.0002
Percentage detection	13.4	18.2	0.007
Hospital B			
Monthly census (mean inpatient days)	5787.7	5575.5	0.10
Monthly testing volume (mean)	85.4	39.4[b]	
Tests per episode (mean)	1.152	1.023	<0.0001
Percentage of episodes with ≥2 tests	14.7	2.3	<0.0002
Percentage detection	12.1	13.2	0.42
Hospital C			
Monthly census (mean inpatient days)	3025.5	3294.8	0.0003
Monthly testing volume (mean)	76.8	51.8[c]	
Tests per episode (mean)	1.121	1.049	<0.0001
Percentage of episodes with ≥2 tests	11.8	4.9	<0.0002
Percentage detection	12.8	15.3	0.07

[a] A reduction of 44.1% in mean monthly testing volume.
[b] A reduction of 53.9% in mean monthly testing volume.
[c] A reduction of 32.5% in mean monthly testing volume.