Comparison of testing approaches for *Clostridium difficile* infection at a large community hospital

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Abstract

Multiple diagnostic approaches are available for *Clostridium difficile* infection (CDI); current guidelines support two-step testing (2ST) as the preferred approach. We retrospectively evaluated the impact of switching from toxin enzyme immunoassay (EIA) to 2ST, and then to polymerase chain reaction (PCR), on CDI rates, test utilization and CDI treatment at a 900-bed tertiary care community teaching hospital. All inpatients tested for CDI between December 2008 and February 2011 were included. A positive toxin EIA or PCR was diagnostic of CDI; 2ST was performed using glutamate dehydrogenase EIA, followed by PCR if positive. Repeat tests within 8 weeks on the same patient were considered part of the same testing episode. Data were collected electronically and studied in aggregate from 9725 unique inpatients tested for CDI, representing 20 836 individual tests. PCR detected 41% more patients with CDI than toxin EIA ($p < 0.0001$), and 15% more than 2ST (p 0.02), corresponding to higher hospital-onset and community-onset CDI rates. The number of CDI tests performed per patient decreased by 48% with PCR ($p < 0.0001$) compared with toxin EIA. For patients with CDI, time to the first positive test result was shortest with PCR. For patients without CDI, a negative PCR, but not 2ST, was associated with 22% fewer CDI treatment days, compared with toxin EIA ($p < 0.0001$). Compared with both toxin EIA and 2ST, PCR detected more CDI patients faster and with less frequent testing, and negative PCR results were associated with less empirical CDI treatment.

Keywords: Clostridium difficile, infection, nosocomial, PCR, testing algorithm, two-step testing
Original Submission: 3 December 2012; **Revised Submission:** 12 February 2013; **Accepted:** 13 February 2013
Editor: F. Allerberger
Article published online: 4 March 2013
Clin Microbiol Infect 2014; **20:** 65–69
10.1111/1469-0691.12198

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These data were previously presented as an oral abstract presentation at the 49th Annual Meeting of the Infectious Diseases Society of America in Boston, 21 October 2011, Oral Abstract Session 86 (#753).

Introduction

Clostridium difficile infection (CDI) incidence and severity have reached historic levels, yet optimal testing approaches remain unclear and pose a barrier to timely and reliable diagnosis [1–3]. Current Infectious Diseases Society of America guidelines endorse two-step testing (2ST) over toxin enzyme immunoassay (EIA) for the diagnosis of *C. difficile* infection [4]. However, despite its poor sensitivity [2,5], toxin EIA remains the primary diagnostic test for most hospitals because it is inexpensive, simple to perform and yields quick results [1].

The effect of more sensitive CDI testing methods on clinical treatment decisions, laboratory resource utilization, infection control practices and publicly-reported CDI rates is not well described. Although polymerase chain reaction (PCR) testing is regarded as highly sensitive and specific for CDI [6], guidelines have cited a need for more data prior to fully embracing PCR over 2ST [4]. For quality improvement purposes, we switched from toxin EIA to 2ST, and then to exclusive PCR testing. We describe the impact of these testing changes on CDI rates, test utilization and clinical treatment.

Methods

Cedars-Sinai Medical Center is a 900-bed acute tertiary care community teaching hospital in Los Angeles, California. All inpatients tested for CDI between December 2008 and February 2011 were included. A CDI episode was defined as a patient with a positive toxin EIA or PCR. Testing for CDI was performed at the discretion of the attending physician; no chart review was conducted to assess for CDI symptoms, and testing was not restricted to unformed stool specimens. All repeat CDI tests performed for the same patient within 8 weeks of the initial test were attributed to the same CDI testing episode. Community-onset (CO) CDI was defined as a patient with a positive CDI test within the first 3 days of admission; we did not distinguish community-onset, healthcare facility-associated CDI as defined by IDSA guidelines [4]. All CDI patients testing positive after hospital day 3 were considered to have hospital-onset (HO) CDI.

Between December 2008 and November 2009, patients were tested for CDI with toxin A/B EIA (Meridian Bioscience Inc, Cincinnati, OH, USA), and physicians commonly ordered three tests per diarrhoeal episode. From December 2009 to April 2010, CDI testing changed to 2ST. This consisted of an initial test with glutamate dehydrogenase (GDH) EIA (Alere Inc, Waltham, MA, USA); positive tests were confirmed with molecular testing for *tcdB* by PCR (GeneXpert®; Cepheid, Sunnyvale, CA, USA). Results of GDH EIA and PCR (if performed) were reported simultaneously, and laboratory reporting of positive GDH EIA results directed clinicians to refer to PCR results for diagnosis. Physician education regarding CDI testing changes was provided through grand rounds, written communication and other educational forums, and repeat testing for the same diarrhoeal episode was discouraged. Beginning May 2010, PCR was used exclusively, and repeat CDI tests within 1 week were cancelled by the laboratory per hospital policy.

Admission dates, CDI test results, demographic information, antibiotic usage and colectomy procedures were electronically collected and studied in aggregate for each testing period. Inpatient days were calculated, excluding neonates. CDI treatment days were calculated as the number of days on metronidazole (oral or intravenous) or oral vancomycin within 15 days of the initial CDI test collection. Antibiotic usage data were available from August 2009. No clinical chart review was performed. All statistical calculations (chi-squared, *t*-tests, Wilcoxon rank sum and Kruskal–Wallis tests) were performed using SAS v9.2. This study was reviewed by our institutional review board and exempted from requiring informed consent.

Results

A total of 9725 unique patient testing episodes, accounting for 20 836 individual *C. difficile* tests, occurred for inpatients during the study period; 36 PCR results were excluded due to indeterminate results (inhibitory substances). Patient demographics, overall length-of-stay and the number of unique patients tested per day were no different across the three testing periods (Table 1).

Patients with CDI

With toxin EIA testing, 14.2% of unique patients tested for CDI had a positive test result. This proportion increased to 17.5% with 2ST (23.2% increase, p 0.001). With PCR, 20.0% of unique patients tested were positive, representing a 41.1% increase compared with toxin EIA (p <0.0001) and a 14.6% increase compared with 2ST (p 0.02).

The increased 2ST and PCR test sensitivity was associated with differences in both HO and CO CDI rates. Compared with a HO CDI rate of 12.88 cases per 10 000 patient days with toxin EIA, rates were higher with both 2ST (14.23 per 10 000 patient days, 10.6% increase, p 0.28) and PCR (15.63 per 10 000 patient days, 21.4% increase, p 0.01), though the

TABLE 1. Comparison of patient demographics, *C. difficile* infection rates, testing characteristics and outcomes between three *C. difficile* diagnostic testing approaches

Diagnostic test	Toxin EIA	2ST	PCR	p value
#Unique patients tested for CDI	4205	1916	3604	
Average age (years)	62.2	61.9	61.0	NS
% Female	51.6	51.3	51.5	NS
Average hospital LOS (days)	15.6	16.2	15.3	NS
Average # unique patients tested/day	11.6	11.9	12.1	NS
Average # CDI tests performed/patient	2.70	n/a	1.39	<0.01
% Patients with only one CDI test	19.9	n/a	72.8	<0.01
% Patients with CDI	14.2	17.5	20.0	≤ 0.02[a]
HO CDI cases per 10 000 patient days	12.88	14.23	15.63	0.01[b]
CO CDI cases per 1000 admissions	4.73	6.76	8.42	≤ 0.03[a]
Patients with CDI (*n*)	597	335	722	
Hours to first positive result (median)[c]	32.3	26.5	17.0	≤ 0.01[a]
LOS after CDI diagnosis (average days)	12.2	11.8	10.1	NS
Colectomies per 100 CDI cases	0.83	0.57	0.72	NS
Patients without CDI (*n*)	3608	1581	2882	
Average # CDI treatment days	2.12	2.02	1.65	≤ 0.01[d]
% Receiving ≥ 4 days of CDI treatment	25.0	22.8	18.7	≤ 0.01[d]

EIA, enzyme immunoassay; 2ST, two-step testing; PCR, polymerase chain reaction; NS, not statistically significant (p >0.05); CDI, *Clostridium difficile* infection; LOS, length of stay; HO, hospital onset; CO, community onset; GDH, glutamate dehydrogenase; n/a, not applicable.
[a]Significant difference observed between all groups (toxin EIA vs. 2ST, 2ST vs. PCR, and toxin EIA vs. PCR).
[b]Significant difference between toxin EIA and PCR only; p >0.05 for toxin EIA vs. 2ST, and 2ST vs. PCR.
[c]Measured from the time of first specimen collection.
[d]Significant difference between 2ST vs. PCR and toxin EIA vs. PCR only; p >0.05 for toxin EIA vs. 2ST.