Hospital Cost Savings Using Ultrasensitive Single Molecule Counting for Detection of *Clostridium difficile* Toxins A and B

Akash Bijlani[1], Joel Estis[2], Johanna Sandlund[2]

[1]Strategy Access Solutions, San Carlos, California; [2]Singulex, Alameda, California

Background

- Enzyme immunoassays (EIAs) for *Clostridioides difficile* (formerly *Clostridium difficile*) toxins have low sensitivity and lead to missed cases of *C. difficile* infection (CDI).[1]
- With the introduction of nucleic acid amplification tests (NAATs), which cannot differentiate between colonized individuals and CDI patients, the CDI incidence at many institutions has increased.[2]
- CDI has become the most common cause of health care-associated infections in the U.S. and the yearly excess healthcare costs related to CDI are estimated to be as much as $4.8 billion.[3]
- The Singulex Clarity® C. diff toxins A/B assay, in development for the Singulex Clarity system and using Single Molecule Counting technology, was designed to provide a highly sensitive and specific rapid assay for *C. difficile* toxins A and B in stool.

Aims

The aim of this study was to understand the cost savings, in a U.S. context, of the Singulex Clarity C. diff toxins A/B assay compared to the following four current CDI laboratory testing methods:

1) NAAT alone
2) Glutamate dehydrogenase (GDH) EIA and toxin EIA
3) Multistep algorithm: GDH-and-toxin EIA followed by NAAT
4) Multistep algorithm: NAAT followed by toxin EIA if NAAT positive

Methods

Singulex Clarity C. diff toxins A/B assay

The Singulex Clarity C. diff toxins A/B assay measures *C. difficile* toxins A and B in stool on the Singulex Clarity system, an automated, *in vitro* diagnostic platform. The system is based upon a paramagnetic microparticle-based immunoassay powered by Single Molecule Counting technology that uses single-photon fluorescence detection for analyte quantitation. The quantitative limits of detection for TcdA and TcdB has been shown to be 0.8 and 0.3 pg/mL in buffer, and 2.0 and 0.7 pg/mL in stool, respectively. The instrument automatically performs the immunoassay with a 1:1 mixture of paramagnetic microparticles pre-coated with either toxin A or B monoclonal antibodies (capture reagent) and toxin-specific antibodies labeled with the fluorophore, Alexa Fluor 647 (detection reagent). The Singulex Clarity software interpolates the data, using the florescent signal, into a combined toxin A/B concentration reported in units of pg/mL stool. The total turnaround time is 32 min and the system can process 1–48 samples in an assay run.

Diagnostic Performance

Specificity and sensitivity data for this study was based on fresh samples from 897 subjects with suspected CDI who were tested at two sites with the Singulex Clarity assay, PCR (Xpert® *C. difficile* or Xpert® *C. difficile/Epi*), and EIA (C. Diff Quik Chek Complete®) for detection of GDH and toxins A+B. The performance of the assays and multistep algorithms were evaluated against cell cytotoxicity neutralization assay (Microbiology Specialists, Inc.).

Health Economic Cost-Savings Model

A U.S.-based economic model to describe the annual hospital cost savings utilized:

- Previously published cost data, which were updated to 2017 values using the United States Department of Labor Bureau of Labor Statistics (BLS) medical care database.[4]
- Cost calculations based on the average number of admissions per U.S. registered hospital = 5,363.[5]
- 2018 American Hospital Association data (April 1, 2017-March 31, 2018) including hospital gross revenue and discharges.
- National annual rate of CDI stays per 1,000 adult, non-maternal discharges = 14.2/1,000.[6]
- Differences in sensitivity, specificity, and associated clinical outcomes of the Clarity assay compared to NAAT, GDH-and-toxin EIA, and multistep algorithms (GDH-and-toxin EIA followed by NAAT, and NAAT followed by toxin EIA if NAAT positive).

Key cost-saving measures included decreases in 1) preemptive isolation, 2) missed cases, 3) additional length of stay (LOS), 4) medication cost, 5) CDI hospital readmissions, and 6) Centers for Medicare and Medicaid Services (CMS) penalties.

Results

Table 1. CDI Assay Sensitivity and Specificity

CDI Testing Method	Sensitivity	Specificity
Singulex Clarity C. diff Toxins A/B	91%	93%
NAAT alone	96%	80%[18]
GDH EIA and toxin EIA (Quik Chek Complete)	88%	87%
Multistep algorithm: GDH EIA and toxin EIA (Quik Chek Complete) → NAAT	96%	80%[18]
Multistep algorithm: NAAT → Toxin EIA if NAAT positive	88%	87%

Note: Akbari et al 2015 noted that NAAT increased CDI detection by 34-67% increase while there was no increase in actual CDI prevalence.[17] Given this, we assumed there was an increase in the false positive rate (FPR). Based on Polage et al 2015[18], the NAAT FPR = 55.3%. Compared to CCNA, NAAT specificity was 87%, but since FPR = 1.0-Specificity (1.0-.87=.13), we assumed FPR was 55.3%, therefore, the new FPR = .13 * 1.553 = 0.20. Therefore, specificity is 1.0-.20=0.80 (80%).

The biggest drivers across the key cost-saving measures were:

1) Decreased additional LOS due to improved specificity and true CDI diagnosis.
2) Reduced oral vancomycin prescribed for CDI-negative cases.

The annual mean cost savings — by adding the cost reduction across all cost-savings measures — ranged from $150,000–$317,000 per institution. This was dependent on the current CDI lab test(s) utilization and whether the hospital was penalized by the hospital-acquired conditions (HAC) reduction program or value-based purchasing (VBP). The largest cost savings benefit was observed when comparing the Singulex Clarity assay with NAAT alone and the multistep algorithm of GDH-and-toxin EIA followed by NAAT.

Table 2. Annual Mean Cost Savings per Institution if an Institution Switches from One Current CDI Laboratory Testing Method to Clarity. Based on National AHA Average Number of Admissions per Institution.

CDI Testing Method	Not Penalized by HAC or VBP	Penalized by HAC	Penalized by VBP	Penalized by HAC & VBP
NAAT alone	$233,000	$289,000	$261,000	$317,000
GDH EIA and toxin EIA (Quik Chek Complete)	$150,000	$206,000	$177,000	$233,000
Multistep algorithm: GDH EIA and toxin EIA (Quik Chek Complete) → NAAT	$233,000	$289,000	$261,000	$317,000
Multistep algorithm: NAAT → Toxin EIA if NAAT positive	$150,000	$206,000	$177,000	$233,000

Conclusions

- Singulex Clarity C. diff toxins A/B assay may offer hospital an opportunity to: 1) decrease additional LOS due to improved specificity and true CDI diagnosis; 2) improve patient access, especially for those hospitals with bed capacity issues; 3) save pharmacy cost by reducing oral vancomycin prescribed for CDI-negative cases.
- The NAAT false positive rate (FPR) has a direct impact on NAAT specificity and the multistep algorithm of GDH EIA and toxin EIA (Quik Chek Complete) followed by NAAT. Additional real world evidence studies are needed to further distill the NAAT FPR.
- Cost savings may vary based on an institution's yearly admissions, discharges, gross revenue, and current CDI laboratory testing method.
- With high sensitivity, specificity, and a rapid turnaround time compared to current CDI laboratory testing methods, use of the Singulex Clarity C. diff toxins A/B assay may result in hospital cost savings.

Figure 1. Key Cost-Savings Measures

Key Cost-Savings Measures

Decreases in preemptive isolation cost

- Per test cost included current isolation room, labor, and material costs
- NAAT: $126[7]
- GDH EIA and toxin EIA: $80[7]
- GDH EIA and toxin EIA followed by NAAT: $172[7]
- NAAT followed by toxin EIA if NAAT positive: $172[7]
- Assumptions: 10% of CDI patients will have preemptive isolation, 50% reduction in patients needing preemptive isolation, and hospital utilizes 20% NAAT, 20% GDH EIA and toxin EIA, 40% GDH EIA and toxin EIA followed by NAAT, and 20% NAAT followed by toxin EIA if NAAT positive

Decreases in missed cases

- Based on differences in sensitivities of Singulex vs vs four testing methods
- Sensitivity differences:
  - NAAT: -5%
  - GDH EIA and toxin EIA: 3%
  - GDH EIA and toxin EIA followed by NAAT: -5%
  - NAAT followed by toxin EIA if NAAT positive: 3%
- Missed cases add 7 days of length of stay (LOS)[8]
- Assumed that only 22.5% of those missed cases would return to the hospital within 30 days
- 37% of CDI cases utilize ICU beds; 63% of CDI cases utilize general ward beds[8]
- Blended per night LOS cost: $2,972[9]
- Total LOS cost per patient: $20,804

Decreases in additional LOS due to improved specificity and true CDI diagnosis

- CDI increases LOS by 5.7 days[8]
- Based on differences in specificities of Singulex vs four testing methods
- Specificity differences:
  - NAAT: 13%
  - GDH EIA and toxin EIA: 6%
  - GDH EIA and toxin EIA followed by NAAT: 13%
  - NAAT followed by toxin EIA if NAAT positive: 6%
- Blended per night LOS cost: $2,972[9]
- Total LOS cost per patient: $16,940

Decreases in medication cost due to improved specificity

- 10-day oral vancomycin cost: $1,596[10]
- Based on differences in specificities of Singulex vs four testing methods
- Specificity differences:
  - NAAT: 13%
  - GDH EIA and toxin EIA: 6%
  - GDH EIA and toxin EIA followed by NAAT: 13%
  - NAAT followed by toxin EIA if NAAT positive: 6%

Decreases in hospital CDI readmissions

- Readmission cost: $9,039[11]
- 22.5% of CDI cases are readmitted[11]
- 20% estimated decrease in readmissions[12]

Improved CDI diagnosis translates to improved CDI scores and decreases in CMS penalty dollars attributable to CDI

- Average admissions per U.S. hospital: 6,353[13]
- National average Medicare patient population: 40.9%[14]
- Average inpatient Medicare reimbursement: $12,694[14]
- CMS penalty percentages:
  - Hospital acquired conditions (HAC): 1%[15]
  - Value based purchasing (VBP): 2%[16]
- Annual HAC and VBP penalties attributable to CDI:
  - HAC: 17%[15]
  - VBP: 4%[16]

References

1. Burnham CA, Dubberke ER, Kociolek LK, et al. *Clostridium difficile* – diagnostic and clinical challenges. Clin Chem 2016;62(2):31.
2. Gould CV, Edwards JR, Cohen J, et al. Effect of nucleic acid amplification testing on population-based incidence rates of *Clostridium difficile* infections. Clin Infect Dis 2013;58(9):1304-1307.
3. Lessa FC, Mu Y, Bamberg WM, et al. Burden of *Clostridium difficile* infection in the United States. N Engl J Med 2015;372(9):825-834.
4. United States Department of Labor. Bureau of Labor Statistics. Databases, Tables & Calculators by Subject. Medical Care. https://data.bls.gov/timeseries/CUUR0000SAM?output_view=data Accessed August 15, 2018.
5. American Hospital Association (AHA). Fast Facts on U.S. Hospitals, 2018. https://www.aha.org/statistics/fast-facts-us-hospitals. Accessed August 15, 2018.
6. Barrett ML, Owens PL. *Clostridium Difficile* Hospitalizations, 2011-2015. ONLINE. August 18, 2018. U.S. Agency for Healthcare Research and Quality. Available: www.hcup-us.ahrq.gov/reports.jsp.
7. Schroeder LF, Robilotti E, Peterson LR, et al. Economic evaluation of laboratory testing strategies for hospital-acquired *Clostridium difficile* infection. J Clin Microbiol 2014;52(2):489-496.
8. Magee G, Strauss ME, Thomas SM, et al. Impact of *Clostridium difficile*-associated diarrhea on acute care length of stay, hospital costs, and readmission: a multicenter retrospective study of inpatients, 2009-2011. American Journal of Infection Control 2015;(43):1148-1153.
9. Halpern NA, Pastores SM. Critical care medicine in the United States 2000-2005: an analysis of bed numbers, occupancy rates, payer mix, and costs. Crit Care Med 2010;38(1):65-71.
10. Cruz MP. Fidaxomicin (dificid), a novel oral macrocyclic antibacterial agent for the treatment of *Clostridium difficile* associated diarrhea in adults. P T 2012;37(5):278-281.
11. Desphande A, Pant C, Olyaee M, et al. Hospital readmissions related to *Clostridium difficile* infection in the United States. Am J Infect Control 2018;46(3):346-347.
12. Longtin Y, Trottier S, Brochu G, et al. Impact of the type of diagnostic assay on *Clostridium difficile* infection and complication reates in a mandatory reporting program. CID 2013;56(1):67-73.
13. American Hospital Association (AHA). Fast Facts on U.S. Hospitals, 2018. https://www.aha.org/statistics/fast-facts-us-hospitals. Accessed August 15, 2018.
14. Becker's Hospital Review. 60 things to know about the hospital industry 2016. https://www.beckershospitalreview.com/lists/50-things-to-know-about-the-hospital-industry-2016.html. Accessed August 15, 2018.
15. Centers for Medicare & Medicaid Services (CMS). Hospital-acquired condition reduction program fiscal year 2018 fact sheet.
16. Centers for Medicare & Medicaid Services (CMS). Medicare Learning Network (MLN) Booklet. Hospital Value-Based Purchasing. September 2017.
17. Akbari M, Vodonos A, Silva G, et al. The impact of PCR on *Clostridium difficile* detection and clinical outcomes. J Med Microbiol 2015;64(9):1082-1086.
18. Polage CR, Gyorke CE, Kennedy MA, et al. Overdiagnosis of *Clostridium difficile* infection in the molecular test era. JAMA Intern Med 2015;175(11):1792-1801.