C. difficile near-patient testing versus centralized laboratory testing: a cluster randomized study

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Background and Significance:

Antimicrobial resistance (AMR) has been designated as a major priority by the World Health Organization (WHO), Centers for Disease Control and Prevention (CDC) and the Public Health Agency of Canada (PHAC). PHAC has identified *Clostridium difficile* infection (CDI) as a Tier 1 AMR priority pathogen. CDI occurs directly as a consequence of antibiotic use and falls under the clinical syndrome of antibiotic-associated diarrhea (AAD). It is the most common cause of infectious diarrhea among hospitalized patients in developed countries like Canada (Skidmore, 1993). The economic cost of CDI in the United States is estimated at USD 5.4 billion, close to 87% of which occurs in healthcare settings (Desai et al., 2016). CDI epidemics in the last two decades have resulted in significant morbidity and mortality especially in the elderly (Miller et al., 2010). In particular, the emergence and dissemination of a hypervirulent strain (North American Pulsotype (NAP) 1) has resulted in hospital outbreaks and increased mortality in the elderly (Loo et al., 2005). NAP 1 carries genetic resistance to commonly used antibiotics for pneumonia and may have spread due to the overuse of certain classes of antibiotics that select for this strain (McDonald et al., 2005; Pillai et al., 2010). As CDI is strongly associated with previous antibiotic use, antimicrobial stewardship is believed to have a role in preventing and terminating CDI outbreaks.

Diagnostic methodology has evolved rapidly in the last decade. The European Society of Clinical Microbiology and Infectious Diseases recently provided recommendations on diagnostic testing for CDI but questions remain (Crobach et al., 2009). Early testing approaches relied on detection of the toxin using a neutralization assay (TNA). In this approach, stool supernatants are evaluated for the presence of toxin by plaque formation on lawns of mammalian cells. The presence of CDI toxin was confirmed by the ability of anti-toxin to neutralize CDI toxin effects. The method took 3 to 4 days to complete and required a cell culture facility no longer commonplace in diagnostic laboratories. TNA was soon replaced by enzyme immune assays (EIA) that do not require cell culture and could be performed in 2-3 hours. However, as the epidemic of NAP 1 swept through North American and Europe it became very clear that the EIA lacked sensitivity and missed cases, prompting physicians to repeat testing. EIAs were advantageous in terms of ease of use, turnaround time, and cost. Toxin antigen detection could also be performed using rapid diagnostic tests (RDT) such as lateral flow assays. However, EIA and RDT both suffered a lack of sensitivity and, in some cases, specificity (Novak-Weekley et al., 2010). With the NAP 1 epidemic, molecular assays were emphasized with their increased sensitivity. These nucleic acid amplification tests (NAATs) are able to detect very low levels of bacteria and have emerged as the predominant test in the last five years (Gould et al., 2013). However, NAATs are costly and so clinical microbiologists have developed a two-step algorithm in which an EIA or RDT is first used to screen stools for the presence of glutamate dehydrogenase (GDH) antigen derived from *C. difficile*. The GDH antigen test is very sensitive (> 95%) and negatives could be reported right away, only requiring GDH-positive toxin negative specimens by EIA or RDT to be confirmed by NAAT. At CLS, the two-step algorithm is performed for a population of close to 1.5 million people at an offsite Diagnostic and Scientific Centre (DSC). The use of a testing centre, however, undermines to some extent the advantages of the

rapid testing methodologies developed in recent years, because of increased transportation and processing time.

A key issue in many settings, including ours, is that testing falls into a separate budget from the treatment of patients with CDI infections. This has the potential to distort the decision of whether to run a test and, if so, what sort of test. The distortions are of two types. First, the hospital may decide to order more tests than is optimal, since the tests are perceived as "free" from the perspective of decision-makers. At the same time, the diagnostic facility may choose low-cost, slow diagnostics, because the costs associated with delays in test results are borne by the hospital. This is a classic case of silos in health care costs inefficiently distorting policy decisions, with potentially negative results for both patient health and costs.

Many institutions follow the clinical practice guidelines provided by the Infectious Diseases Society of America for the management of *C. difficile* (Cohen et al., 2010). As part of routine Infection Prevention and Control (IPC) management, patients with acute diarrhea of unknown cause are pre-emptively placed in private rooms with additional contact precautions, which mandate the use of gowns and gloves for healthcare workers. This is also known as patient isolation. Investigation for gastrointestinal pathogens is typically initiated and the duration of patient isolation depends largely on the result of microbiological testing. When severe or complicated CDI is suspected, patients are initiated on empiric treatment as soon as the diagnosis is suspected. Generally, oral metronidazole is used for mild-to-moderate CDI and oral vancomycin for severe CDI. Among hospitalized patients with acute diarrhea, initiation of pre-emptive management for CDI is common. With requested CDI screening, 85% are negative on GDG screen and 89% are negative post PCR confirmation.

The intervention of interest is implementing a new RDT to Near Patient Testing (NPT); screening for CDI to be performed at the hospital rapid response laboratory (RRL) instead of the DSC. Techlab Inc. offers a lateral flow assay (C. DIFF QUIK CHEK COMPLETE® test) that detects both GDH and Toxin simultaneously and further simplifies the testing algorithm. As prescribed in the two-step algorithm, GDH and Toxin negatives will be reported out immediately as negative for CDI, while positive or discrepant results will be confirmed at the DSC using NAAT. The vast majority of requests for CDI testing are negative thus allowing a majority of results to be reported immediately to patient wards without NAAT confirmation at the DSC.

Study Objectives:

Calgary presents a unique opportunity to examine the effect of decentralizing CDI testing to Near Patient Testing. While it is not possible to perfectly duplicate the testing technology (described earlier) at NPT and the central laboratory, it is possible to provide equivalent testing. In a pilot study, we tested 20 stool samples by our current CLS centralized testing algorithm and anticipated NPT algorithm. Both algorithms rely on a two-step approach, namely GDH screen and molecular confirmation for toxin although the platforms are different. We had 100% concordance in the final result (presence of toxin) between the two algorithms. Further confirmation of this assumption (equivalence in performance) will be completed with a larger sample size prior to finalization of the NPT algorithm.

We will conduct a two-period, two-intervention, cluster randomized crossover (CRXO) design study at Foothills Hospital. Each cluster (ward) will receive each of the two interventions in a separate 6-month period of time leading to two "cluster-periods" with associated "wash-in" and "wash-out" periods attached. The interventions are RDT using NPT for CDI, and testing for CDI using centralized testing at the DSC.

This study in a cross-sectional CRXO in that, each cluster-period consists of different individuals (patients). The order in which the interventions are delivered to each cluster (ward) is randomized to control for potential period effects. Within Foothills Hospital there are 40 wards which will be observed over a 12-month period. Each ward is randomly assigned to administer one of the two interventions for the first 6-month period (Period 1). In the second 6-month period (Period 2), the ward will administer the other intervention. Within each ward (cluster) there are two cluster-periods. Study outcomes during Period 1 and Period 2 intervention will be compared in both arms (NPT and centralized laboratory testing).

NPT testing can deliver results within several hours, while typically off-site testing takes one to two day. If NPT and the off-site testing deliver identical test results as our pilot data suggest, we can follow the clinical outcomes for each arm without the confounder of differences in test performance. As a contingency, if variation in test performance characteristics is found, analysis of patient outcomes will take this into consideration.

For patients without CDI, the antibiotics, and in many cases, the isolation, are unnecessary. NPT testing has the potential to avoid this unnecessary use of antibiotics and to avoid costly isolation procedures for the day+ that standard testing requires. It also enables a better-directed diagnostic process for the cause of diarrhea. For patients who are positive for CDI, the earlier test result will influence downstream events such as initiation of antibiotic therapy, resolution of disease, hospitalization days, and other clinical outcomes.

We hypothesize that NPT for CDI will result in reduced patient isolation days in the hospital, decreased morbidity and mortality, reduced unnecessary antibiotic use and overall reduced costs to the health care system, including both hospital and laboratory.

Previous data has indicated that the mean number of patients a ward is 39/month (SD=43) for a total of 1578 patients in a 6-month period and the mean number of negative patients is 33/month (SD=34) for a total of 1300 negative pts in a 6-mnth period The inclusion criteria will be diarrhea in adult patients admitted to four acute care hospitals in the Calgary region being tested for CDI. Outpatients and patients in the emergency room will be excluded.

Our primary endpoint is to examine the differential effect of NPT on the duration of contact precautions (i.e. patient isolation days). Secondary outcomes will compare turn-around times from specimen submission to result, days of hospitalization, the number of days of antibiotic therapy, the incidence of CDI, severe CDI, and in-hospital mortality. A comprehensive economic evaluation will be performed to determine the cost of testing, patient isolation, and hospitalization for all patients in the control and treatment arms.

Methods:

Contact precautions (i.e. patient isolation) due to CDI will be defined as an order by healthcare workers for contact precautions within the 7-day infection window of a CDI diagnosis. The length of time on contact precautions will be defined as the calendar date contact precautions are completed or patient discharge date minus the calendar date contact precautions are ordered. Data on contact precautions will be extracted from the clinical patient management system in Calgary, known as Sunrise Clinical Manager (SCM). It is used extensively in all Calgary acute care facilities and emergency departments. These data include patient identifiers (e.g. patient health number, names, date of birth), start and stop dates of isolation, facility, and patient care unit where isolation order was placed, and reason for isolation (e.g. CDI, diarrhea). These data will be linked to the specimen results tested for CDI by the patient's Personal Health Number (PHN). Turn-around times from specimen submission to result will be provided by Calgary Laboratory Services. Days of hospitalization will be defined as the difference between the admission and discharge date. The specimen results will be linked to the Discharge Abstract Database using the patient's PHN to determine during which acute care encounter the specimen was collected and the admission/discharge dates of that encounter. Antibiotic therapy will be defined as the administration of antibiotics initiated on the day of and up to 48 hours after specimen collection for CDI testing. Total days of antibiotic therapy during the acute care encounter will be defined as the calendar date antibiotic therapy is completed minus the calendar date antibiotic therapy is ordered. The data will be extracted from SCM.

We will also account for the severity of CDI. The epidemiological definition for severe CDI is that primarily proposed by Cohen *et al*. This definition has been used by infectious disease specialists in Alberta to guide the management and treatment of patients with CDI. Patients with severe CDI will have leukocytosis with a white blood cell (WBC) count >15,000 cells/µL OR an elevated serum creatinine (i.e. 200 µmol/L or greater). The inpatient laboratory results that will be considered to meet the definition for severe CDI will be those collected within a 7-day infection window around the date the laboratory tested positive for *C. difficile*. The presence of either measure meeting the criteria within the defined infection window will qualify as meeting the definition of severe CDI. If either criterion is measured more than once during the infection window, the highest value will be used to represent the severity of CDI. The laboratory values will be provided by Calgary Laboratory Services and linked to the positive *C. difficile* test results. In-hospital, all-cause mortality will be defined as death occurring during the acute care encounter where specimens were collected for *C. difficile* testing.

We predict that, given the large number of patients and randomized study design, matching of patients by age, gender, and co-morbidities is not required. Potential hurdles in the study model are logistical challenges associated with building a testing and reporting system for a hospital on a 24hrs/7 days per week basis. The strength of the proposal lies in the scale and nature of the study which seeks to establish the medical and economic benefit of NPT versus centralized testing. The results could dramatically influence public health policy in this country and seek to bridge traditional silos, namely the laboratory and hospital budgets. Data on costs will be furnished by our partners at Calgary Laboratory Services and Alberta Health Services (Infection Prevention and Control).

Data Analysis:

In order to make the data generalizable to other settings, an appropriate econometric methodology to assess the impact of the impact of the NPT testing through multivariate regression is required. For example, consider the following potential model:

$$y_i = \beta_0 + \beta_1 POCT_i + \beta_2 Z_i + \beta_3 H_i + \beta_4 T_i + u_i$$

where y_i is the outcome variable of interest (such as the hours that a patient spends in isolation or the days of hospitalization); $POCT_i$ is a dummy variable indicating whether the patient had a NPT test; Z_i is a vector of individual-specific variables, including age, gender, CDI status and severity, and the like; H_i is a set of dummies indicating ward; T_i is a set of dummies indicating season or month; and u_i is an individual-specific error term. This approach allows us to identify the effect of NPT testing independent of patient, ward and season. In addition, the NPTT dummy can be interacted with other variables to see whether the impact of NPT testing is higher for certain types of patients

Beyond evaluating the relative merits of NPT versus centralized testing, studies will also look at the microbiology of CDI in this study. Specifically, we will conduct several laboratory methods to examine antibiotic resistance and genetic variation in CDI. For example, whole genome sequencing of cultured CDI isolates may inform us about the transmission of specific strains in our setting. Indeed, certain strains and states of gut dysbiosis may result in increased morbidity and mortality (Shahinas et al., 2012). We will look at the microbiome of patients in this study to determine if dysbiosis contributes to adverse clinical outcomes. We will also correlate the strain types with the results of testing to determine if genetic variation affects test performance. Cultured toxin-producing CDI isolates will serve as a gold standard to evaluate test performance.

Originality of the proposal:

It is our view that in the clinical laboratory arena NPT for CDI (described earlier) as a technology has already matured to a stage that translation of this technology into the clinical domain is now needed. As described previously, several formats including lateral flow are currently available through major diagnostic companies. The Infectious Diseases Society of America (IDSA) has recently recommended that rapid diagnostic testing can enhance antimicrobial stewardship by promoting appropriate antibiotic use for respiratory infections (Barlam et al., 2016). However, the recommendation is listed as “weak” with “low-quality evidence”.

This proposal directly aims to improve the evidence base for rapid diagnostic testing in this case for CDI. We will harness innovative new diagnostic tools in collaboration with industry partners to perform a cluster randomized clinical trial. We aim to demonstrate the clinical and economic impact of NPT for CDI, a major cause of morbidity and mortality in our hospitals. Previous

attempts to assess the impact of NPT for CDI have focused on intensive care unit and have been relatively small in sample size (Goldenberg et al., 2014). The innovation lies in the application of a cluster randomized trial model to NPT bridging the clinical laboratory and infection control domains in the hospital to assess the clinical and economic impact. We will leverage the existing infrastructure of one of the largest centralized laboratories in Canada namely Calgary Laboratory Services (Alberta Health Services) which provides testing to a population of 1.5 million people in Southern Alberta. The experimental arm will enable the use of NPT testing in the hospital. The total number of enrolled patients ($n \approx 3000$) will be one of the largest prospective analyses of NPT according to our reading of the literature. The large number of patients will permit a rigorous statistical evaluation of the significance of NPT technology for a key AMR organism. We believe this model can be expanded to other PHAC high priority Tier 1 antibiotic resistant organisms where NPT technology can be evaluated in a second phase.