Improving *C difficile* Infection (CDI) Diagnosis, Reporting, and Treatment: A UC Team Science Approach

Background: The Infection Prevention programs across the UC medical centers have joined together to address the enlarging local and national problem of overdiagnosis and misattribution of *C difficile* infection (CDI) by overly sensitive and inappropriate diagnostic testing. UC Davis (Polage/Cohen - JAMA Internal Medicine, PMID: 26348734) has done seminal work showing that current tests (PCR and other testing strategies) do not correlate well with clinical disease and that community onset CDI is often misclassified as hospital-acquired by delayed testing. Impact of these issues has been:

- Overly sensitive genomic tests (PCR) have dramatically increased CDI rates and antibiotic treatment.
- One in five CDI cases reported as hospital-acquired is actually present on admission
- High rates of publicly reported CDI at UC medical centers with Value Based Purchasing financial penalties

Goal: 1) to reduce misclassification of community-onset CDI cases as hospital-acquired disease, and
2) to validate a novel testing strategy to increase the accuracy of laboratory reporting for true CDI

Specific Aims

Aim 1 – Validate use of rectal swabs for CDI diagnosis in patients with diarrhea for whom a stool specimen is difficult to obtain. This will prevent late stool specimens from being classified as hospital-acquired by CDC criteria.

Aim 2 – Validate a quantitative PCR cycle time threshold for optimizing diagnosis to report clinically meaningful CDI disease. UC Davis has shown that low burden PCR detection is not correlated with benefit from CDI treatment.

Research Plan

Aim 1 - We will conduct a two-center prospective cohort study to evaluate a) perirectal swabs (UC Davis) and b) rectal swabs (UC Irvine) as alternatives to traditional loose stool samples for CDI diagnosis in hospitalized patients. Concurrent swabs and loose stool samples submitted for CDI diagnosis will be tested by genomic (PCR) and toxin (enzyme immunoassay (EIA) with glutamate dehydrogenase (GDH)) methods to validate same-test performance characteristics (sensitivity, specificity) relative to loose stool. We will use the gold standard of loose stool testing, but will also evaluate performance characteristics compared to a standard where either loose stool or swab is positive. If validated to be similar, swabs will be operationally adopted as an alternative collection method to prevent misclassifying 10-15% of CDI as hospital-acquired due to delays in loose stool collection (accidental flushing, mixed with urine, dehydration) for symptoms present on admission.

Aim 2 – We will conduct a multi-center (UCD, UCI, UCSD, UCSF) prospective cohort study evaluating the sensitivity and specificity of a variety of *C difficile* testing strategies. Specifically, we will evaluate a novel PCR strategy using a cycle time threshold that is more indicative of higher *C difficile* burden along with three FDA-approved *C difficile* testing strategies: traditional PCR, EIA, and a common 2-step strategy involving EIA/GDH→PCR for negative samples). These tests will be compared to a clinical gold standard of expected improvement with or without therapy. This is a critical improvement over prior studies that have assumed PCR as the gold standard to detect disease – a faulty assumption as rising evidence suggests that it captures a substantial amount of asymptomatic carriage.

Clinical improvement will be defined by prospectively collected symptoms (resolution of diarrhea to < 3 loose stools per day within 1 week of therapy) and clinical elements from the electronic health record. Lack of improvement will be defined by continued diarrhea, or attributable colectomy, ICU transfer, or death. Analysis will involve multivariable logistic regression using expected clinical outcome based upon test results (expected/unexpected) as the dependent variable and using test type, virulence factors (027/BI/NAP1 strain type), CDI and non-CDI antibiotic treatment, and laxatives/ stool softeners as independent variables. If PCR cycle time performs well, we will retrospectively evaluate the performance of cycle time in the swab analysis performed in Aim 1.

Impact and Plans for Extramural Funding:

Results will ***directly impact*** the way the UC medical centers operationalize *C difficile* testing. It will provide much needed evidence to change national guidance for testing and reporting to be more aligned with clinical outcomes**.** These data will provide foundational data to apply for an AHRQ RO1 to conduct a cluster-randomized trial of CDI testing strategies.

Investigators:

UC Davis	UC Irvine	UC San Diego	UC San Francisco
Christopher Polage, MD MAS	Susan Huang, MD MPH **(PI)**	Francesca Torriani, MD	Catherine Liu, MD
Stuart Cohen, MD	Shruti Gohil, MD MPH	Shira Abeles, MD	Lynn Ramirez, MD