UNIVERSITY OF CALIFORNIA SAN DIEGO

# Switching to a 2-step Diagnostic Testing of *C. difficile* in a Large Academic Institution: Colonization Versus Infection

A Thesis submitted in partial satisfaction of the requirements
for the degree Master of Public Health

in

Epidemiology

by

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The Thesis of Kathia Nunez is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

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# DEDICATION

This thesis is dedicated to my parents, who have been my greatest support since the initiation of my academic journey. With their unwavering encouragement and commitment to my education, they have been a true source of light in my success.

A special recognition to my mother who I owe my deepest love, gratitude, and respect. Thank you for always working hard as a single mother to ensure my happiness and success. This work stands as a testament to your sacrifices and unending support.

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LIST OF ABBREVIATIONS

| | |
|---|---|
| CDI | *Clostridioides difficile* infection |
| HAI | Hospital Acquired Infection |
| HO-CDI | Hospital-onset *Clostridioides difficile* infection |
| PCR | Polymerase Chain Reaction |
| EIA | Enzyme Immunoassay |
| SHEA. | Society for Healthcare Epidemiology of America |
| IDSA | Infectious Diseases Society of America |
| QI | Quality Improvement |
| UCSD | University of California San Diego |
| BPA | Best Practice Alerts |
| ELISA | Enzyme Linked Immunoassay |
| ACQUIRE | Aligning and Coordinating Quality Improvement, Research, and Evaluation |
| MRN | Medical Record Number |
| EMR | Electronic Medical Record |
| tcdB | toxin B gene |
| FDA | Food & Drug Administration |
| CDC | Center for Disease Control and Prevention |
| NHSN | National Healthcare Safety Network |
| PO | *Per os* (by mouth) |
| IV | Intravenous |
| mg | milligrams |

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## VITA

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## FIELD OF STUDY

Major Field: Epidemiology
Studies in Infectious Disease
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ABSTRACT OF THE THESIS

Switching to a 2-step Diagnostic Testing of *C. difficile* in a Large Academic Institution: Colonization Versus Infection

by

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Master of Public Health, Epidemiology

University of California San Diego, 2024

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**Background:** It is clinically important to distinguish *C.difficile* colonization from active infection, yet diagnostic methods are not standardized.. A two-step algorithm test is recommended to improve the

accuracy CDI detection compared to traditional one-step testing, but clinical assessment and decision to treat CDI continues to vary across clinical settings.

**Objective:** Understand the impact of the transition from a one-step to a two-step method for CDI on diagnostic accuracy, treatment decisions, patient outcomes and reporting.

**Methods:** Two UC San Diego Health (UCSDH) in-patient populations were studied. In Phase 1 (July 1st, 2022, to August 31st, 2023), the two-step method with reflex toxin EIA testing was piloted in the Hematology-Oncology unit and 44 Polymerase Chain Reaction positive (PCR+) patients underwent toxin Enzyme Immunoassay (EIA) testing. In Phase 2 (December 1st, 2023, to April 30th, 2024), the two-step method was implemented house-wide and 157 PCR+ patients were tested for the toxin. Patient charts were reviewed using EPIC to collect data on patient demographics, isolation precautions, treatment, CDI complications, mortality and isolation costs. Statistical analyses were used to compare the outcomes of PCR+EIA- (colonized) to the PCR+EIA+ (active infection) patients in Phase 2 compared to Phase 1.

**Results:** In Phase 1, the duration of isolation in the colonized group (8.53 days) was similar to that of the active infection group (8.75 days). In addition, duration of CDI antibiotics was not statistically different in the colonized vs. active infection group: 11.5 vs. 11.1 days. In Phase 2, providers discontinued CDI precautions in the colonized compared with the active infection group, leading to reduced isolation days: 1.92 vs 8.98 days. Treatment was given only to 9 (12%) colonized compared to all 86 with active infection.

**Conclusion:** The implementation of the two-step method resulted in a change in provider behavior leading to a reduction of CDI precaution orders, treatments and cost in Phase 2.

**Keywords:** CDI, C.difficile, Colonization, Two-step diagnostic method, Antibiotic Stewardship

# INTRODUCTION

*Clostridioides difficile* infection (CDI) is a common healthcare-associated infection (HAI) in the U.S, resulting in approximately 70,000 hospital-onset CDI (HO-CDI) infections each year.[1] Although rates of HO-CDI are decreasing, it remains a public health concern leading to almost 13,000 deaths per year and billions in healthcare costs.[2,3] Despite this, disagreement in the accuracy of clinical diagnostic methods for CDI continue to be well-recognized barriers present in healthcare leading to overtreatment, increased isolation and treatment for colonized patients, emphasizing a need for improved diagnostic methods for CDI.

CDI is caused by an overgrowth of the spore-forming bacteria *C.difficile*, which can secrete pathogenic toxins A and B as a result of gut microbiome disruption from antibiotic exposure.[3] While it primarily affects hospitalized populations, CDI can also be observed in community settings.[3] Patients suspected of acquiring *C.difficile* will exhibit new onset diarrhea, or three or more unformed stools within twenty-four hours.[4] Other clinical symptoms include stomach tenderness, fever, and nausea which can lead to severe complications such as dehydration, colitis, sepsis and even death.[5]

Diagnosing CDI is complex because *C.difficile* is often a colonizer before being associated with an actual infection. This means that a patient can be absent of clinical disease, but still colonized by the bacterium.[2,5] Colonized patients are asymptomatic because the toxin, although present, is not expressed. Infection can eventually develop if the gut microbiome is disrupted due to increased antibiotic exposure allowing for toxin expression.[3] One study highlighted that colonization was a significant risk factor for CDI and found that 29% of CDI cases were linked to asymptomatic patients.[6] Patients are considered infected when they present clinical symptoms for CDI and test positive for *C.difficile* toxins.[7]

CDI is typically diagnosed using one or more stool toxin tests to determine if the sample contains the toxigenic strain.[8] These tests can include molecular techniques like nucleic acid amplification tests, known to have great sensitivity in detecting strains that harbor the toxin, regardless of whether the toxin is

secreted.[9] Polymerase chain reaction (PCR) tests are the most commonly used molecular tests, but they do not differentiate between colonization and infection.[7,9] Therefore, if a patient is colonized with the bacterium, the PCR diagnostic tests will report it as a positive result, leading to a higher likelihood of falsely classifying colonization with CDI infection.[7,10] Alternatively, enzyme immunoassay (EIA) toxin tests do not detect the *C.difficile* bacterium itself, [9,11] rather the toxin producing strains; toxins A and B.[7]

Guidelines from the CDC, The Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) recommend a multistep algorithm involving an initial molecular test like PCR followed by an EIA to accurately distinguish colonization from active infection.[4] Implementing a two-step diagnostic algorithm aims to improve the accuracy of CDI diagnosis, reduce isolation precautions and unnecessary treatment, and ultimately lower healthcare costs.

Multiple studies have shown that a two-step testing strategy improves the accuracy of CDI diagnosis and reduces the likelihood of false positives (i.e colonized patients) without increasing harm. One study found that almost all patients with a positive toxin immunoassay resulted in CDI related complications or deaths, regardless of whether they tested negative or positive in the PCR test.[12] Patients who tested negative in the toxin immunoassay test, even if their PCR test result was positive, had outcomes comparable to patients without *C. difficile*.[12] This strongly suggests that most patients with a negative toxin test result and positive PCR test are suspected of being colonized and do not need treatment for CDI.[12] This study demonstrates the importance of not relying on a single molecular PCR test to accurately diagnose CDI, but to also include a toxin immunoassay as a confirmatory step to decrease overdiagnosis, over treatment, unnecessary isolation, and increased healthcare costs.[12]

Even with the implementation of a two-step algorithm, clinical assessment, and decision to treat for CDI continues to vary across clinical settings. This is emphasized in one study in an academic medical center where almost 80% of patients who tested positive with the PCR test and negative with the toxin immunoassay test (TOX-) still received treatment for CDI after clinical assessment of patient symptoms.[9] An explanation for this behavior was likely due to patients with a PCR+/TOX- have possible risk factors

for CDI and providers often treat these results as true CDI cases instead of colonization.[9] This highlights the need to evaluate whether a negative toxin result would actually prompt healthcare providers to stop or continue CDI specific treatment and *C. difficile* infection prevention precautions in other clinical settings.

Given the limited information available on the effect that a two-step algorithm has in clinical settings and whether this affects treatment decision making among physicians, we designed a retrospective, observational quality improvement (QI) project to evaluate the effect of switching from a one-step PCR test to a two-step PCR and EIA diagnostic testing method for hospital onset *C. difficile* at UCSD Health. The decision to conduct this project is grounded in the existing body of evidence supporting the impact that a two-step diagnostic approach for *C. difficile* has on hospital populations in identifying patients who have clinical disease that requires treatment and isolation precautions (positive PCR and positive EIA) and distinguishing them from those who are colonized (positive PCR and negative EIA) and at high risk of developing CDI if antimicrobial stewardship measures are not followed. Our aim was to understand the impact of this transition on diagnostic accuracy, treatment decisions, patient outcomes and reporting of HO-CDI at UC San Diego Health. Specifically, if changing from a one-step testing method to a two-step influenced provider treatment decision making. Additionally, we were interested in identifying how the two-step method affected hospital costs and if there was a relationship between colonization, CDI and patient zip codes.

## Chapter 1 METHODS

*Background*

In 2010, University of California San Diego Health switched to a PCR-based test to diagnose CDI. In 2017, diagnostic stewardship interventions such as Best Practice Advisory (BPA) alerts and nursing education on the definition of diarrhea were introduced, leading to a reduction in overall CDI testing and repeat testing within 7 days. However, diagnoses of HO-CDI increased, due to the PCR assay's high sensitivity, mainly due to an increase in the proportion of colonizations, which led to excess isolation precautions and treatment.

In 2021, a two-step testing method was piloted in the bone marrow transplant units. If the initial PCR test was positive for the CDI toxin genes, an enzyme-linked immunoassay (EIA) was performed to confirm the presence of the toxin. In November 2023, the two-step method pilot testing was subsequently implemented hospital wide across UCSD Health (UCSDH).

*Study Design*

This retrospective quality improvement project evaluated the effect of switching to a CDI two-step diagnostic method by comparing the differences in treatment decisions and outcomes between the PCR positive (colonized) and the two step positive (infected) populations. This study was considered exempt from IRB oversight and granted approval by the University of California San Diego the Aligning and Coordinating Quality Improvement, Research, and Evaluation (ACQUIRE) Committee.

*Setting and Population*

This project's focus consisted of two different hospital populations representing two different phases in the study. Phase 1 was conducted between July 1, 2022 and August 31, 2023 in adult patients admitted to the Hematology-Oncology floors at the La Jolla Jacobs Medical Center (JMC 5 and 6). A total of 371 tests were sent for *C.difficile* two-step testing: of 69 PCR +, 44 were sent for confirmatory EIA testing.

After the pilot test was completed successfully, the two-step testing algorithm was implemented hospital-wide. This included UCSD Health campuses in La Jolla and Hillcrest, excluding East Campus, where a total of 1,302 *C.difficile* tests were administered. This population comprised 157 adult patients who tested positive in the two-step method from December 1, 2023 to April 30, 2024. During this phase, the presentation of the test results were different compared to how the results were presented to the clinicians in Phase 1. In Phase 1, both PCR and EIA results could be marked "positive" or "negative," and there was no "Abnormal" indication. In Phase 2, the UCSDH lab changed the presentation of the algorithm, showing only one result, with only EIA+ results being called "positive" and clearly marked "Abnormal."

*Data Collection*

Data were extracted from medical records for all patients in both phases. A list of patient identifiers, such as their medical record numbers (MRN) and admission dates for all relevant hospital encounters from when the patient got tested for *C.difficile* during the two study periods were used to access patient info. Medical information that was collected included patient demographic information, zip code of residence, type of hospital service, reason for hospital admission, the date *C.difficile* testing was performed, *C.difficile* testing results, information on isolation precautions, *C.difficile* risk factors such as, treatment types, treatment duration, incidences of relapse, and mortality rate.

All clinical data information was retrieved from the UC Health Electronic Medical Record (EMR) database, EPIC. Demographic information was collected for each patient who had c.diff tests ordered during the study period.. Patient's visit report and discharge summary were used to collect information on a patient's admitting service, reason for admission, information on *C.difficile* infection, treatment type and duration, secondary maintenance treatment, evidence of needing a higher level of care due to *C.difficile*, medication list at discharge, and date of mortality for deceased patients.

*C.difficile* results were confirmed by retrieving data from the Stool studies section under laboratory results. This provided information on the date of *C.difficile* testing, the date the results came back positive, and if there was evidence that the patient had a relapse episode after the initial positive test result. Information on isolation precautions - such as the type of precautions used, the date they were initiated, and date of discontinuation - was also collected from the isolation overview section.

To confirm the specific treatment type the patient was prescribed after *C.difficile* testing, a thorough assessment of the patient's timeline of fever and antibiotic dosage was conducted. This was also used to count the number of days the patient was on the treatment during hospital stay. To confirm the accuracy of this information, find evidence of secondary maintenance, and discover if the patient had risk factors for CDI, a review of the patient's medication list history was performed. Additional confirmation of medical information was done by examining the patient's progress notes written and attested by their main attending physicians and infectious disease attendings.

*C.difficile Laboratory Testing*

Phase 1: *C.difficile* Toxin, PCR + *C. difficile* Toxin EIA

In Phase 1, a select number of patients that tested positive for PCR, an FDA-approved assay used for the qualitative detection of the *C.difficile* toxin B gene (tcdB), received an additional FDA approved EIA test (EIA), which is a rapid enzyme-linked immunoassay test used to detect toxins A and B produced by *C.difficile*. This was used as a confirmatory step to determine if the actual *C. difficile* toxins, aside from the tcdB gene, were produced and detected in the fecal specimen of the patient, distinguishing them from colonization or active infection status.

Phase 2: Clostridioides (Clostridium) difficile Testing Algorithm, S

In Phase 2, all patients developing diarrhea suspicious of *C.difficile* infection received the official testing algorithm, S, which included the PCR assay for the detection of tcdB gene, immediately followed by the enzyme-linked immunoassay (EIA) for the detection of toxins A and B.

*Patient Outcomes*

Colonization vs Active Infection

Based on the clinical guidelines for diagnosing CDI by the CDC [13] and studies that have used PCR and EIA diagnostic methods,[12,14] patients who tested PCR positive and EIA negative (PCR+/EIA-) were considered to be colonized by the bacterium and categorized as colonizations. Patients who tested PCR positive and EIA positive (PCR+/EIA+) were considered active infections and categorized as true cases of CDI.

Changes in Isolation Precautions

Following UCSDH's and The National Healthcare Safety Network (NHSN) protocols, enhanced precautions for *C.difficile* requiring isolation, contact and hand hygiene using soap and water were initiated immediately after a *C.difficile* infection was suspected and a test was sent.[13] Changes in precautions were noted if providers followed UCSDH's protocol and Infection Prevention and Clinical Epidemiology (IPCE) recommendations to discontinue precautions once laboratory results confirmed that a patient was only colonized (PCR+/EIA-) with *C.difficile* and not infected.

CDI Treatment & Duration

Based on recommendations by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA), Fidaxomicin (200 mg) and PO Vancomycin (125 mg) for 10-14 days, or an IV Flagyl (Metronidazole, 500 mg) as an alternative, are the antibiotics recommended for CDI.[15] Our project compared the preferred types of treatments prescribed to patients that were colonized vs those with the active infection, treatment duration, and the reasons for treatment discontinuation.

Secondary Maintenance

For patients with a history of CDI, secondary prophylaxis was prescribed at discharge for the management of recurrent CDI. In accordance with IDSA and SHEA, patients who received the following regimens as outpatients in addition to standard CDI treatment were considered to have received secondary maintenance: Fidaxomicin (200 mg) given twice daily for 10 days, a prolonged tapered/pulsed PO vancomycin (125 mg) regimen, and/or a single treatment of intravenous (IV) Bezlotoxumab infusion as an outpatient procedure.[15]

Higher level of care

Patients needing higher level of care were those who experienced CDI complications requiring admission to an intensive care unit (ICU) due to fulminant CDI or septic shock, surgery for toxic megacolon, intestinal perforation, or refractory colitis.[13]

First CDI Episode After Colonization/Relapse

Following NHSN guidelines, an actual relapse episode occurred if a patient who tested positive using the two-step method and had a known active infection (PCR+/EIA+) experienced another confirmed CDI episode that occurred more than 14 days and less than or equal to 56 days after the initial CDI event.[13] Patients suspected of being colonized who tested PCR+ only were considered to have experienced their first CDI episode if they tested positive in the two step within the NHSN timeframe.

Mortality

Based on NHSN guidelines, CDI is reported as a contributor to any mortality outcome that occurred within the 30 days a patient started experiencing CDI symptoms and during their current hospital admission.[13] For our project, we indicated the number of patients who died less than 6 months after discharge and up to one year after discharge.

Zip codes:

San Diego county identified 39 health equity zip codes using the Healthy Places Index Health Equity Quartile (HEQ) census tract.[16] This index measures how social, economic and environmental factors affect the health of residents across San Diego County to assess health equity.[16] Using this information, a thorough analysis was done to identify patients in our project who live in areas belonging to these 39 health equity zip codes. A distribution analysis was done to provide a quantitative measure of the distribution of patients who live in areas belonging to the 39 zip codes.

Costs of Isolation Precautions and Cost Avoidance:

The costs of isolation precautions for Phases 1 and 2 were calculated by referencing a systematic analysis by the Canadian Journal of Infection Control that broke down the daily costs of contact precautions and found that the estimated daily cost of contact precautions was $153.[17] Leveraging this value, we calculated the total cost of isolation precautions in Phase 1 by taking the number of colonized patients and multiplying them by the mean number of days this group was on isolation precautions and $153. Following the same methodology, the colonized patients in Phase 2 were multiplied by their mean number of isolation days, multiplied by $153 to calculate the total cost spent on precautions for this group.

To calculate the total cost avoidance in Phase 2 compared to Phase 1, we multiplied the number of colonized patients in this phase by their mean number of isolation days and $153. We then calculated how much this group would have spent on precautions by multiplying the number of colonized patients by the mean number of isolation days in the group with the active infection and $153. The products of the two calculations were then subtracted to calculate the estimated total cost avoidance.

*Statistical Analyses*

All statistical analyses were done using R and R studio statistical software version 2022.12.0+353. A positivity rate was calculated to determine the percentage of PCR tests that were positive during Phase 1. In Phase 1, 44 patients were analyzed with no exclusions. There were 160 patients in Phase 2, but after excluding three duplicate patients with more than one *C.difficile* episode, 157 were analyzed. Duplicate data were handled by choosing the most recent episode.

To compare colonized patients to true CDI cases, descriptive analytical methods were employed to tabulate counts and percentages for patient demographics and outcome frequencies. Secondary analysis involved calculating the cost effectiveness of the reduction in isolation precautions in Phase 2 compared to Phase 1. A distribution analysis was performed as a tertiary analysis to determine if there may be an association between colonization, active infection and patient zip codes.

*Data Normalization*

To account for the differences in populations, time periods, and hospital department sizes in each phase, we normalized our raw data by patient days and hospital admissions to calculate standardized PCR positivity, colonization and known active infection rates using the NHSN's guidelines on CDI data analysis.[13]

For Phase 1, the PCR positivity rate was calculated by dividing the number of positive PCR tests by the number of patient days recorded in the Hematology-Oncology unit during July 1$^{st}$, 2022, to 31$^{st}$ 2023 multiplied by 10,000 patient days **(Figure 1)**. Additionally, the colonization rate and known active infection rate were each normalized by dividing the number of patients that were colonized and had the active infection, by the number of patient days in the Phase 1 period, multiplied by 10,000 patient days. (**Figure 1)**. Lastly, the normalization of the positivity rate, colonization rate, and known active infection rate by hospital admissions were performed by dividing the number of positive PCR tests, number of colonized patients, and the number of patients with the active infection, by the number of hospital

admissions recorded in the Hematology-Oncology unit during Phase 1, multiplied by 1,000 hospital admissions. **(Figure 2)**. Similarly, the raw data in Phase 2 was normalized using the same methodology, adjusting for the difference in time period for this phase. **(Figures 3-4)**

$$\text{PCR Positivity Rate} = \frac{\text{Number of Positive PCR Tests}}{\text{Number of Patient days during July 1st, 2022-August 31st, 2023}} \times 10{,}000 \text{ Patient Days}$$

$$\text{Colonization Rate} = \frac{\text{Number of PCR+/EIA- Patients}}{\text{Number of Patient days during July 1st, 2022-August 31st, 2023}} \times 10{,}000 \text{ Patient Days}$$

$$\text{Known Active Infection Rate} = \frac{\text{Number of PCR+/EIA+}}{\text{Number of Patient days during July 1st, 2022-August 31st, 2023}} \times 10{,}000 \text{ Patient Days}$$

**Figure 1**: Normalization by Patient-Days for Phase 1

$$\text{PCR Positivity Rate} = \frac{\text{Number of Positive PCR Tests}}{\text{Number of Hospital Admissions during July 1st, 2022-August 31st, 2023}} \times 1{,}000 \text{ Hospital Admissions}$$

$$\text{Colonization Rate} = \frac{\text{Number of PCR+/EIA- Patients}}{\text{Number of Hospital Admissions during July 1st, 2022-August 31st, 2023}} \times 1{,}000 \text{ Hospital Admissions}$$

$$\text{Known Active Infection Rate} = \frac{\text{Number of PCR+/EIA+ Patients}}{\text{Number of Hospital Admissions during July 1st, 2022-August 31st, 2023}} \times 1{,}000 \text{ Hospital Admissions}$$

**Figure 2:** Normalization by Hospital Admissions for Phase 1

$$\text{Colonization Rate} = \frac{\text{Number of PCR+/EIA- Patients}}{\text{Number of Patient days during December 1st, 2023-April 30th, 2024}} \times 10{,}000 \text{ Patient Days}$$

$$\text{Known Active Infection Rate} = \frac{\text{Number of PCR+/EIA+ Patients}}{\text{Number of Patient days during December 1st, 2023- April 30th, 2024}} \times 10{,}000 \text{ Patient Days}$$

**Figure 3:** Normalization by Patient-Days for Phase 2

$$\text{Colonization Rate} = \frac{\text{Number of PCR+/EIA- Patients}}{\text{Number of Hospital Admissions during December 1st, 2023-April 30th, 2024}} \times 1{,}000 \text{ Hospital Admissions}$$

$$\text{Known Active Infection Rate} = \frac{\text{Number of PCR+/EIA+ Patients}}{\text{Number of Hospital Admissions during December 1st, 2023-April 30th, 2024}} \times 1{,}000 \text{ Hospital Admissions}$$

**Figure 4:** Normalization by Hospital Admissions for Phase 2

Chapter 2 RESULTS

*Sample Characteristics*

The final study sample included 201 patients for Phases 1 and 2: 44 in Phase 1 and 157 in Phase 2, after removing duplicates. **Table 1** shows demographic characteristics and outcomes for colonized and active CDI patients during Phase 1 (July 2022 to August 2023). The mean age was 57 and 64 years, respectively. Forty-five percent of patients identified as female, and 54.5% as male, while half (50%) identified as being white.

In Phase 1, 10 of the 44 patients lived in zip codes falling under the 39 San Diego County Health Equity zip codes: 8 were colonized and lived in the areas of National City, Encanto, Jamul, and Spring Valley. Two were known active infections and lived in Oceanside. **(Table 2)**

**Table 3** shows demographic characteristics and outcomes for colonized and active infection patients during Phase 2 (December 2023 - April 2024). The mean age was 56 and 60 years of age, respectively. Forty-eight percent identified as male and 51.6% as female. Forty-two percent identified as white, while 29.3% as Mexican.

In Phase 2, 51 of the 157 patients analyzed lived in zip codes falling under the 39 San Diego County Health Equity zip codes: 27 were colonized and 24 had known active infections. Thirteen of the colonized patients lived in areas of Chula Vista. **(Table 4)**

**Table 1:** Descriptive Statistics, Diagnostic Test, Number of Patients that Tested PCR+/EIA+, or PCR+/EIA-, and Outcomes for *C.difficile* for Phase 1: July 1st 2022 to August 31st 2023

| | | **Two-Step Diagnostic Algorithm** | |
|---|---|---|---|
| **Outcome** | | **PCR+/EIA- No. (%)** | **PCR+/EIA+ No. (%)** |
| **N** | 44 | 32 (72.7%) | 12 (27.3%) |
| **Age** | Mean ± SD | 57.2 ±1 8.5 | 64.2 ± 15.2 |

**Table 1:** Descriptive Statistics, Diagnostic Test, Number of Patients that Tested PCR+/EIA+, or PCR+/EIA-, and Outcomes for *C.difficile* for Phase 1: July 1st 2022 to August 31st 2023 (Continued)

| | | Two-Step Diagnostic Algorithm | |
|---|---|---|---|
| **Outcome** | | **PCR+/EIA- No. (%)** | **PCR+/EIA+ No. (%)** |
| **Sex** | Female | 16 (50.0%) | 4 (33.3%) |
| | Male | 16 (50.0%) | 8 (66.7%) |
| **Race/Ethnicity** | White | 14 (43.8%) | 8 (66.7%) |
| | White/other Hispanic or Latin American | 1 (8.33%) | 2 (16.7%) |
| | Mixed race/Mexican | 9 (28.2%) | 1 (8.33%) |
| | Black/African American | 3 (9.4%) | 0 |
| | Asian | 1 (3.13 %) | 0 |
| | Other | 4 (12.5%) | 1(8.33%) |
| **Admitting Service** | | | |
| | BMT Service | 20 (62.5%) | 5 (41.7%) |
| | Hospital Medicine | 11 (34.4%) | 4 (33.3%) |
| | Hospital Medicine, BMT | 0 | 2 (16.7%) |
| | GIP Hospice, BMT service | 0 | 1 (8.33%) |
| | Surgical Oncology | 1(8.33%) | 0 |
| **Isolation Precautions** | *C.difficile*/Spore | 30 (93.8%) | 11 (91.7%) |
| | *C.difficile*/Contact | 1 (3.1%) | 1 (8.30%) |
| | Contact | 1 (3.1%) | 0 |
| **Changes in Precautions** | Precautions Continued | 26 (81.3%) | 12 (100%) |
| | Precautions Discontinued | 6 (18.7%) | 0 |
| **Duration of Isolation Precautions** | Mean ± SD | 8.53 ± 6.59 | 8.75 ± 6.18 |
| **Treatment for CDI** | PO Vancomycin | 19 (59.4%) | 8 (66.7%) |
| | PO Vancomycin, IV Flagyl | 3 (9.38%) | 2 (16.7%) |
| | PO Fidaxomicin | 1 (3.13%) | 1 (8.33%) |
| | PO Vancomycin, Fidaxomicin | 7 (21.9%) | N/A |
| | IV Flagyl, PO Vancomycin | 1 (3.13%) | N/A |
| | IV metronidazole therapy and vancomycin enemas, PO Vancomycin | N/A | 1 (8.33%) |
| | None | 1 (3.13%) | 0 |
| **Duration of CDI Treatment** | Mean ± SD | 11.5 ± 5.07 | 11.1 ± 6.00 |

**Table 1:** Descriptive Statistics, Diagnostic Test, Number of Patients that Tested PCR+/EIA+, or PCR+/EIA-, and Outcomes for *C.difficile* for Phase 1: July 1st 2022 to August 31st 2023 (Continued)

| | | **Two-Step Diagnostic Algorithm** | |
|---|---|---|---|
| **Outcome** | | **PCR+/EIA- No. (%)** | **PCR+/EIA+ No. (%)** |
| **Discharged with CDI Treatment** | Yes | 14 (43.8%) | 8 (66.7%) |
| | No | 18 (56.3%) | 4 (33.3%) |
| **Treatment Stopped due to Colonization Status** | Yes | 2 (6.25%) | 0 |
| | No | 30 (93.7%) | 12 (100%) |
| **Secondary Maintenance/Taper** | Yes | N/A | N/A |
| | No | 32 (100%) | 12 (100%) |
| **Higher Level of Care Needed (ICU)** | Yes | 1 (3.13%) | 1 (8.33%) |
| | No | 31 (96.9%) | 11 (91.7%) |
| **First CDI Episode After Colonization/Relapse** | No | N/A | N/A |
| **Mortality** | *<6 months follow up after discharge* | | |
| | Alive | 22 (68.8%) | 7 (58.3%) |
| | Died | 10 (31.3%) | 4 (33.3%) |
| | *1 year follow up after discharge* | | |
| | Died | N/A | 1 (8.33%) |
| **CDI Risk factors** | Antibiotic use | 7 (21.9%) | 1 (8.33%) |
| | Age, Antibiotics, PPI | 3 (9.38%) | 5 (41.7%) |
| | Age, PPI | 3 (9.38%) | 0 |
| | Age | 1 (3.13%) | 1 (8.33%) |
| | Age, Antibiotics | 1 (3.13%) | 1 (8.33%) |
| | Age, Antibiotics, PPI, H2B | 1 (3.13%) | 1 (8.33%) |
| | Antibiotics, H2B | 2 (6.25%) | 0 |
| | Antibiotics, PPI | 3 (9.38%) | 0 |
| | PPI | 2 (6.25%) | 1 |
| | Prior *C.difficile* episodes | 4 (9.38%) | 2 |
| | N/A | 3 (12.5%) | 0 |
| | Antibiotics, PPI, H2B | 1 (3.13%) | 0 |
| | Other | 1 (3.13%) | 0 |

Note: PCR, Polymerase Chain Reaction test; EIA, Enzyme Immunoassay test; +, positive; -, negative. SD, Standard Deviation; CDI, *C.difficile* infection; PO, Per os; IV, Intravenous; N/A, not any; ICU,

Intensive Care Unit; BMT, Bone Marrow Transplant; GIP, General Inpatient; PPI, Proton Pump Inhibitors; H2B; Hydrogen 2 Betablockers. PCR tests were performed first on all patients. EIA test was done only on patients that tested PCR+ first.

**Table 2:** Patient Health Equity Zip code distribution for Phase 1

| Health Equity Zip code | City | Colonized | Known Infection | Frequency Total |
|---|---|---|---|---|
| 91950 | National City | 2 | 0 | 2 |
| 92114 | Encanto | 2 | 0 | 2 |
| 92058 | Oceanside | 0 | 2 | 2 |
| 91935 | Jamul | 1 | 0 | 1 |
| 91977 | Spring Valley | 1 | 0 | 1 |
| 91910 | Chula Vista | 1 | 0 | 1 |
| 92105 | City Heights | 1 | 0 | 1 |

**Table 3:** Descriptive Statistics, Diagnostic Test, Number of Patients that Tested Positive in the Two Step Algorithm, S, and Outcomes for *C.difficile* for Phase 2: December 1st 2023 to April 30th 2024

| Outcome | | Two-Step Diagnostic Algorithm, S | Two-Step Diagnostic Algorithm, S |
|---|---|---|---|
| | | PCR+/EIA- No. (%) | PCR+/EIA+ No. (%) |
| **N** | 157 | 71 (100%) | 86 (100%) |
| **Age** | Mean ± SD | 55.9 ± 18.6 | 60.0 ± 15.8 |
| | Median | 55.0 | 60.5 |
| | Min-Max | 20-95 | 24-88 |
| **Sex** | Male (%) | 29 (40.8%) | 47 (54.6%) |
| | Female (%) | 42 (59.2%) | 39 (45.3%) |

**Table 3:** Descriptive Statistics, Diagnostic Test, Number of Patients that Tested Positive in the Two Step Algorithm, S, and Outcomes for *C.difficile* for Phase 2: December 1st 2023 to April 30th 2024 (continued)

| Outcome | | Two-Step Diagnostic Algorithm, S | Two-Step Diagnostic Algorithm, S |
|---|---|---|---|
| | | PCR+/EIA- No. (%) | PCR+/EIA+ No. (%) |
| **Race/Ethnicity** | White | 28 (39.4%) | 38 (44.2%) |
| | Mixed race/Mexican | 24 (33.8%) | 22 (25.6%) |
| | Black/African | 3 (4.23%) | 9 (10.5%) |
| | American | 5 (7.04%) | 8 (9.30%) |
| | Other, not Hispanic | 8 (11.3%) | 3 (3.49%) |
| | Asian | 3 (4.23%) | 3 (3.49%) |
| | White/other Hispanic or Latin American | 0 | 2 (2.32%) |
| | White or Mixed race/Middle Eastern | 0 | 1 (1.16 %) |
| | American Indian or Alaska Native | 0 | 0 |
| ***C.difficile* Precautions** | Yes | 13 (18.3%) | 83 (96.5%) |
| | No | 58 (81.7%) | 3 (%) |
| **Changes in Precautions** | Precautions Continued | 0 | 79 (91.9%) |
| | Precautions Discontinued | 13 (18.3%) | 5 (5.81%) |
| | No Precautions | 58 (81.7%) | 2 (2.33%) |
| **Duration of Isolation Precautions** | Mean ± SD | 1.92 ± 1.04 | 8.98 ± 7.00 |
| **Treatment for CDI** | No Treatment | 62 (87.3%) | 0 |
| | PO Vancomycin | 7 (9.86%) | 52 (60.5%) |
| | Fidaxomicin | 2 (2.82%) | 11 (12.8%) |
| | PO Vancomycin, IV Flagyl | 0 | 7 (8.14%) |
| | PO Vancomycin + Fidaxomicin | 0 | 6 (6.98%) |
| | NGT Vancomycin | 0 | 4 (4.65%) |
| | NGT Vancomycin, IV Flagyl | 0 | 1 (1.16%) |
| | PO Vancomycin, IV Flagyl, Fidaxomicin | 0 | 2 (2.33%) |
| | Other | 0 | 2 (2.33%) |
| | Fidaxomicin + IV Flagyl | 0 | 1 (1.16%) |

**Table 3:** Descriptive Statistics, Diagnostic Test, Number of Patients that Tested Positive in the Two Step Algorithm, S, and Outcomes for *C.difficile* for Phase 2: December 1st 2023 to April 30th 2024 (continued)

| Outcome | | Two-Step Diagnostic Algorithm, S | Two-Step Diagnostic Algorithm, S |
|---|---|---|---|
| | | PCR+/EIA- No. (%) | PCR+/EIA+ No. (%) |
| **Duration of CDI Treatment** | Mean ± SD | N/A | 13.7 ± 5.81 |
| **Discharged with CDI Treatment** | Yes | N/A | 70 (80.5%) |
| | No | N/A | 17 (19.5%) |
| **Secondary Maintenance** | No | 70 (98.6%) | 69 (80.2%) |
| | Yes | 1 (1.41%) | 17 (19.8%) |
| **Secondary Maintenance Taper (n=17)** | Prolonged PO Vancomycin | N/A | 6 (35.3%) |
| | NGT Vancomycin Taper | N/A | 4 (23.5%) |
| | Bezlotuximab Infusion | N/A | 3 (3.45%) |
| | PO Vancomycin + Bezlotuximab Infusion | N/A | 3 (3.45%) |
| | PO Vancomycin Taper | N/A | 1 (5.88%) |
| **First CDI Episode After Colonization/Relapse** | No | 68 (95.8 %) | 78 (90.7%) |
| | Yes | 3 (4.23 %) | 8 (9.30%) |

**Table 3:** Descriptive Statistics, Diagnostic Test, Number of Patients that Tested Positive in the Two Step Algorithm, S, and Outcomes for *C.difficile* for Phase 2: December 1st 2023 to April 30th 2024 (continued)

| Outcome | | Two-Step Diagnostic Algorithm, S | Two-Step Diagnostic Algorithm, S |
|---|---|---|---|
| | | PCR+/EIA- No. (%) | PCR+/EIA+ No. (%) |
| **CDI Risk Factors** | Antibiotics, PPI | 6 (8.45%) | 17 (19.8%) |
| | Antibiotics | 25 (35.2%) | 14 (16.3%) |
| | Antibiotics, age | 6 (8.45%) | 13 (15.1%) |
| | History of CDI episodes | 0 | 12 (14.0%) |
| | Antibiotics, age, PPI | 1(1.41%) | 11 (12.8%) |
| | No risk factors | 13 (18.3%) | 7 (8.14%) |
| | Age | 10 (14.1%) | 4 (4.65%) |
| | History of Colonization (PCR+ only) episodes | 3 (4.23%) | 3 (3.49%) |
| | Age, PPI | 3 (4.23%) | 2 (2.33%) |
| | PPI | 2 (2.82%) | 2 (2.33%) |
| | Antibiotics, H2B | 0 | 1 (1.16%) |
| | PPI, H2B | 1 (1.41%) | 0 |
| | Antibiotics, PPI, h2b | 1 (1.41%) | 0 |
| **Higher Level of Care Needed (ICU)** | No | 71 (100%) | 75 (87.2%) |
| | Yes | 0 | 11 (12.8%) |
| **Mortality** | | | |
| | *<6 months follow up after discharge* | | |
| | Alive | 58 (81.7%) | 70 (81.4%) |
| | Died | 13 (18.3%) | 16 (18.6%) |
| | *1 year follow up after discharge* | | |
| | Died | N/A | N/A |
| **Admitting Service** | Hospital Medicine | 42 (59.2%) | 38 (44.2%) |
| | BMT | 10 (14.1%) | 12 (14.0%) |
| | General Surgery | 4 (5.63%) | 10 (11.6%) |
| | Cardiology/Cardiac Surgery | 4 (5.63%) | 7 (8.14%) |
| | Family Medicine | 2 (2.82%) | 5 (5.81%) |
| | Pulmonary Medicine | 4 (5.63%) | 4 (4.65%) |

**Table 3:** Descriptive Statistics, Diagnostic Test, Number of Patients that Tested Positive in the Two Step Algorithm, S, and Outcomes for *C.difficile* for Phase 2: December 1st 2023 to April 30th 2024 (continued)

| Outcome | | Two-Step Diagnostic Algorithm, S | Two-Step Diagnostic Algorithm, S |
|---|---|---|---|
| | | PCR+/EIA- No. (%) | PCR+/EIA+ No. (%) |
| | Emergency Medicine | 1 (1.41%) | 3 (3.49%) |
| | Surgical Oncology | 0 | 2 (2.33%) |
| | Anesthesiology | 0 | 2 (2.33%) |
| | Colon + Rectal Surgery | 1 (1.41%) | 1 (1.16%) |
| | Neurology/Neurosurgery | 2 (2.82%) | 1(1.16 %) |
| | Gynecology Oncology | 0 | 1(1.16 %) |
| | Psychiatry | 1 (1.41%) | 0 |

Note: PCR, Polymerase Chain Reaction test; EIA, Enzyme Immunoassay test; +, positive; -, negative. SD, Standard Deviation; CDI, *C.difficile* infection; PO, Per os; IV, Intravenous; N/A, not any; ICU, Intensive Care Unit; BMT, Bone Marrow Transplant; GIP, General Inpatient; PPI, Proton Pump Inhibitors; H2B; Hydrogen 2 Betablockers. PCR tests were performed first on all patients. EIA test was done only on patients that tested PCR+ first.

**Table 4:** Patient Health Equity Zip code distribution for Phase 2

| Health Equity Zip code | City | Colonized | Known Infection | Frequency Total |
|---|---|---|---|---|
| 91910/91911 | Chula Vista | 6 | 3 | 13 |
| 91950 | National City | 3 | 4 | 7 |
| 92113 | Logan Heights | 2 | 3 | 5 |
| 92102 | Golden Hill | 3 | 2 | 5 |
| 92114 | Encanto | 2 | 0 | 2 |
| 92154 | Otay Mesa | 3 | 1 | 4 |
| 91935 | Jamul | 0 | 1 | 1 |
| 92173 | San Ysidro | 1 | 2 | 3 |
| 92105 | City Heights | 1 | 2 | 3 |
| 91977 | Spring Valley | 1 | 0 | 1 |
| 92027 | Escondido | 1 | 1 | 2 |
| 91963 | Campo | 0 | 1 | 1 |
| 92083 | Vista | 0 | 1 | 1 |
| 92020 | El Cajon | 0 | 1 | 1 |
| 91905 | Boulevard | 0 | 1 | 1 |
| 92536 | Aguanga (RIVERSIDE) | 1 | 0 | 1 |

*Phase 1: PCR and EIA Positivity Rate*

During Phase 1, a total of 6134 tests were administered. **Table 5** shows that 371 stool tests were sent to UCSD Health laboratories for *C.difficile* testing. Of those, 69 tests were PCR positive (18.6%).

Forty-four (63.8%) of the PCR positive tests were sent for the additional EIA toxin testing, while 25 (36.2%) were not. The review of the medical record did not provide a reason for not performing the EIA. Of the 44 tests that underwent PCR and EIA testing, 32 (73%) patients were colonized (PCR+EIA-) and 12 (27.3%) had an active *C.difficile* infection (PCR+EIA+) (**Table 6)**.

*Phase 1: Data Normalization*

Over the Phase 1 period (July 1st, 2022, to August 31st 2023), a total of 175,303 patient-days were recorded in the Hematology-Oncology Units. After normalizing the raw data from Phase 1 by patient-days, it was found that the PCR positivity rate was 3.94 PCR tests per 10,000 patients. There were 1.83 colonized cases per 10,000 patient-days for the rate of colonization, and 0.68 known active infections per 10,000 patient-days.

Similarly, a total of 4,454 hospital admissions were recorded for Phase 1. After normalizing by hospital admissions, it was observed that there were 7.18 colonized cases per 1,000 hospital admissions and 2.69 known active infections per 1,000 hospital admissions.

**Table 5 :** PCR Positivity Rate in Phase 1; July 1st, 2022-August 31st 2023

| **Total number of tests sent for *C.difficile*** | **Number of Positive PCR Tests No.** | **PCR Positive Rate (%)** | **PCR Tests Sent for EIA No.** | **Rate of PCR tests sent for EIA (%)** |
|---|---|---|---|---|
| 371 | 69 | 18.6% | 44 | 63.8% |

Note: PCR, Polymerase Chain Reaction test; EIA, Enzyme Immunoassay test; +, positive; -, negative; PCR Positivity Rate, (Number of Positive PCR Tests / Total Number of PCR Tests sent for *C.difficile*) × 100; Rate of PCR tests sent for EIA, (PCR Tests Sent for EIA / Number of Positive PCR Tests) x 100.

**Table 6:** Colonized vs Active Infection (Phase 1)

| **Status after *C.difficile* Testing** N=44 | **Colonized, No. (%)** | **Known Active Infections, No. (%)** |
|---|---|---|
| | 32 (72.7%) | 12 (27.3%) |

Note: Colonized; PCR+/EIA- ; Active Infection, PCR+/EIA+.

*Phase 2: PCR and EIA Positivity Rate*

During the Phase 2 study period, a total of 1302 tests were administered. 157 (12.1%) stool tests resulted positive for PCR (**Table 7)**. Of those, 71 (45.2%) were PCR+ and 86 (54.8%) tests were both PCR and EIA positive **(Table 8)**.

*Phase 2: Data Normalization*

In Phase 2, there were a total of 835,969 patient days recorded during December 1st, 2023, to April 30th, 2024, hospital-wide. After normalizing, it was found that there were approximately 0.85 colonized cases per 10,000 patient-days and 1.03 active infections per 10,000 patient-days.

Furthermore, there were 14,454 hospital admissions accounted for during this phase resulting in 4.91 colonized cases per 1,000 hospital admissions, and 5.95 known active infections per 1,000 hospital admissions after normalization.

**Table 7:** PCR & EIA Positivity Rate in Phase 2; December 1st, 2023, to April 30th, 2024

| **Total number of tests sent for *C.difficile*** | **Number of Positive PCR Tests** | **PCR Positive Rate (%)** | **Number of PCR+/EIA+ tests** | **Rate of EIA+ Tests (%)** |
|---|---|---|---|---|
| 1302 | 157 | 12.1% | 86 | 6.61% |

Note: PCR, Polymerase Chain Reaction test; EIA, Enzyme Immunoassay test; +, positive; -, negative; PCR Positivity Rate, (Number of Positive PCR Tests / Total Number of Tests sent for *C.diffcile*) × 100; Rate of EIA+ tests, (Number of PCR+/EIA+ tests/Total number of tests sent for *C.difficile*) x 100.

**Table 8:** Colonized vs Active Infection Status for Phase 2; December 1st, 2023, to April 30th, 2024

| **Status after *C.difficile* Testing** N=157 | **PCR+/EIA- (colonized) No. (%)** | **PCR+/EIA+ (active infection) No. (%)** |
|---|---|---|
| | 71 (45.2%) | 86 (54.8%) |

Note: Colonized; PCR+/EIA- ; Active Infection, PCR+/EIA+.

*Patient Outcomes for Phases 1 and 2*

Changes in Isolation Precautions

Of the 32 colonized patients (PCR+/EIA-) in Phase 1, six had their isolation precautions stopped after their EIA test result came back negative. Of the 12 patients with known active infections (PCR+/EIA+), none had their precautions discontinued. **(Table 1).**

In Phase 2, 58 colonized patients were not placed on CDI precautions, while 13 patients had their precautions discontinued once the two-step test resulted PCR+/EIA- **(Table 3)**. For the group with active infection, 79 had their precautions continued while five had their precautions discontinued. Two patients were not placed on CDI precautions due to short hospital stay. **(Table 3)**

Duration of Isolation Precautions

In Phase 1, colonized patients were placed in isolation for 8.53 days on average while patients with the active infection were isolated for 8.75 days. In Phase 2, colonized patients were isolated for a duration of 1.92 days and those with the active infection were isolated for 8.98 days.

Treatment for CDI and Duration of Treatment:

Oral vancomycin was most often used for CDI treatment (61.4%) in Phase 1 and was prescribed for approximately 11 days for both colonized and active infection patients. **(Table 1).** In Phase 2, 87.3% of colonized patients did not receive treatment for CDI, while all patients with active infection were treated; of those, 60.5% were prescribed PO Vancomycin for almost 14 days. **(Table 3).**

Discontinuation of Treatment

In Phase 1, likely due to their immunocompromised state, 30 of 32 colonized patients had treatment continued despite colonization status. Treatment was discontinued in only two of 32 colonized patients, who also had their isolation precautions stopped. None of the patients with active infection had their treatment stopped. **(Table 1).**

First CDI episode after Colonization/Relapse & Higher level of Care Needed

In Phase 1, none of the 32 colonized patients developed an infection and none of the 12 infected patients experienced relapse. Two patients (one PCR+/EIA- and one PCR+/EIA+) needed higher level of

care and were admitted into the ICU. **(Table 1 ).** ICU admittance was attributed to septic shock in the setting of *E. coli* bacteremia in the colonized patient. In the actively infected patient, ICU admittance was attributed to sepsis syndrome in the setting of severe CDI pancolitis and previous *C.difficile* episodes.

In Phase 2, the Two-Step Algorithm, S was associated with eight episodes of relapse for patients with known active infections (PCR+/EIA+). Three patients experienced their first CDI episode after being colonized with *C.difficile* (PCR+/EIA-). **(Table 3)** For patients with relapsed CDI in the PCR+/EIA+ group, only one patient had previously tested PCR+/EIA- in Phase 1. Eleven patients with active infection were admitted to the ICU. Of these, six were due to complications related to fulminant CDI, while the other five were attributed to complications related to other medical issues **(Table 3)**.

Secondary Maintenance:

In Phase 1, none of the patients in the colonized or active infection group received any sort of secondary maintenance for CDI. Of the 157 patients assessed during the second phase, 22 received secondary maintenance from the PCR+/EIA+ group. Ten of these patients were prescribed secondary maintenance due to a history of confirmed CDI events or previous colonization episodes. Only one of these ten patients experienced CDI relapse two months after their initial CDI event, despite receiving secondary maintenance. Secondary maintenance tapers ranged from prolonged PO Vancomycin regimens, PO or NGT Vancomycin tapers, one-time Bezlotuximab infusions as outpatients, or both PO Vancomycin + Bezlotuximab Infusion.

Mortality:

Mortality was not associated with *C.difficile* in either phase. In Phase 1, 14 (31.8%) patients died less than six months after discharge, and one died one year after discharge. In Phase 2, 29 (18.5%) patients died less than six months after discharge.

Isolation Precautions Costs for Colonized Patients & Cost Avoidance:

During Phase 1, the mean duration of isolation in the 32 colonized patients was 8.53 days, **(Table 1)** resulting in an estimated total cost of $41,762.88. In Phase 2, only 13 of 71 (12.7%) patients were placed on CDI precautions. Of this population, the mean duration of isolation was 1.92 days, resulting in an estimated $3,818.88 spent on precautions.

## Chapter 3 DISCUSSION

Our study aimed to evaluate the impact of the transition from a one-step to a two-step diagnostic method for *C.difficile* on diagnostic accuracy, treatment decisions, patient outcomes and reporting of HO-CDI at UC San Diego Health. After comparing isolation precautions and treatment decisions between both phases, our study suggests that, in Phase 1, medical providers continued to treat PCR+/EIA- patients as active infections despite the negative EIA toxin result. These results are highlighted in **Table 1** where the duration of isolation days in the colonized group (8.53 days) is similar to that of the actively infected group (8.75 days). Additionally, medical providers maintained a standard treatment plan for CDI by prescribing PO vancomycin to the colonized group for 11 days[15] . This was attributed to the concern that the distinction between colonization and infection was uncertain and that this severely immunocompromised population could experience severe complications and outcomes, even though colonized. This suggests that providers assumed the safest option was to treat the colonized group as infected during Phase 1.

Similarly, another retrospective observational study performing a multisite analysis on the implementation of a two-step method involving a nucleic acid amplification test (NAAT) followed by a toxin assay across 36 laboratories at CDC Emerging Infections Programs (EIP), found that 71.5% of NAAT+/Toxin- patients received treatment for CDI.[18] Additional studies have also noted similar challenges in distinguishing colonization vs active infection and its effect on decision making, resulting in treating colonized patients as infectious.[9,19, 20]

In Phase 2, the two-step method results prompted providers to change their behaviors and follow NHSN and IPCE protocols to stop isolation and treatment if the EIA test came back negative.[13] We believe that this is an important observation, since Phase 2 included both general and immunocompromised patients. This suggests that, in this phase, immunocompromised status did not influence most treatment decisions in colonized patients. A possible justification for this shift is that, unlike in Phase 1, where the two-step was a new diagnostic method for providers at UCSDH, in Phase 2,

providers had already been exposed to the two-step method without experiencing negative outcomes. Another possible explanation could be because of the difference in the presentation of the two-step results in Phase 2 compared to Phase 1. In Phase 2, if the EIA was positive, results were clearly marked abnormal, supporting the discontinuation of precautions and treatment. Previous studies found similar results with significant associations between colonization status and a reduction in CDI treatment.[21, 22]

Lastly, our cost analysis suggests that there was a significant cost reduction in isolation precautions in Phase 2 compared to Phase 1. During Phase 1, the mean duration of isolation for the 32 patients assumed to be colonized was 8.53 days, **(Table 1)** resulting in a total estimated cost of $41,762.88. In Phase 2, 58 of 71 colonized patients were not placed on any CDI precautions. In the Phase 2 population, mean duration of isolation for colonized patients was 1.92 days, amounting to an estimated $3,818.88 in isolation precautions in colonized patients instead of $20,856.96 if all 71 colonized patients had been isolated for 1.92 days.

Additionally, if we had interpreted the PCR+/EIA-'s as active infections instead of colonizations, then we would have placed these patients on isolation precautions for 8.98 days **(Table 3).** This suggests that an estimated $97,549.74 would have been spent in isolation precautions.

Considering the daily costs of isolation including donning and doffing using the breakdown costs of contact precautions[17], the implementation of the two-step diagnostic method suggests that it resulted in a cost avoidance of an estimated $76,692.78.

We hypothesize that the avoided isolation precautions also resulted in increased patient and family satisfaction, given that studies have shown that extended contact precautions are associated with decreased patient satisfaction [23,24], and increased symptoms of depression and anxiety.[25]

This is the first quality improvement project at UCSD Health that analyzed the impact of a two-step algorithm for *C.difficile*. Normalization by patient-days and hospital admissions were performed to account for the differences in populations, time periods, and hospital department sizes among each phase to produce standardized results. Given that this is an observational retrospective project, ethical considerations were not hindered because our analysis involved a review of patient charts to identify past

medical histories/outcomes and did not include human subjects for the purpose of research. Lastly, the methodology used could assist other institutions in reproducing similar studies.

The study's limitations included reliance on patient chart reviews from the electronic medical record EPIC to obtain our data, creating the possibility of misinterpreting a patient's information. All patient info from both phases was abstracted by a graduate student with no medical background alongside two medical doctors, potentially creating inconstancies and inaccuracies in the data. Also, the way in which each UCSDH provider recalls and records information for their patient may be inconsistent. The duration of Phase 2 was only five months compared to the 13-months analyzed in Phase 1, creating a difference in sample sizes. Furthermore, our population in Phase 1 consisted of immunocompromised patients compared to Phase 2, which included the entire UCSDH population. While normalization was employed to account for these differences, these limit the comparability between our phases. Our study population is not representative of a wider ethnic population due to its small sample size, with the majority of our patients identifying as White or Mexican. In addition, this project focuses on the effect of a two-step diagnostic method for the detection of *C.difficile* at UCSD Health only and did not consider other health institutions, limiting the generalizability of our findings. Another limitation in our study was the use of estimated costs derived from a Canadian study[17] instead of UCSDH or California specific isolation costs. Lastly, our project aimed to identify if there were notable changes in the way providers treated colonized patients compared to patients with CDI after the implementation of the two-step method, but we do not infer a causal relationship between the two-step and change in provider behavior or treatment decision making.

In conclusion, our findings suggest that the implementation of the two-step method for *C.difficile* led to a change in CDI isolation precautions and treatment in Phase 2, where it was implemented hospital-wide, compared to pilot testing in Phase 1 that was limited to the immunocompromised ward, leading to a reduction in isolation costs. Ultimately, we did not identify severe outcomes, infections or relapses in Phase 2, and therefore conclude that the two-step method is safe even in the immunocompromised populations. Our results suggest that the two-step method helped avoid unnecessary isolation and

exposure to antibiotics thereby strengthening antibiotic stewardship efforts. To address gaps in literature, future research should explore the longitudinal effects of the two-step method over a longer study period with a more representative study sample to identify further changes in provider behavior and highlighting the effect of false positives on hospital costs, patient outcomes and satisfaction.

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