Characterizing Hospital-Associated *Clostridioides difficile* Infection: A Retrospective Descriptive Review and Bed Tracing Analysis

by

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Bachelor of Science, West Virginia University, 2022

Submitted to the Graduate Faculty of the

Department of Infectious Diseases and Microbiology

School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Public Health

University of Pittsburgh

2024

UNIVERSITY OF PITTSBURGH

SCHOOL OF PUBLIC HEALTH

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April 2, 2024

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Abstract

Description of problem: *Clostridioides difficile* is a common hospital-associated infection that is defined as an urgent threat to public health by the CDC (CDC, 2019). Risk of *C. difficile* infection (CDI) is highest in elderly and immunocompromised individuals, as well as those with recent antibiotic exposure and frequent or prolonged hospitalization. This essay aims to analyze an increase in hospital-associated CDI (HA-CDI) cases in an urban, acute care hospital from June 2022 – August 2023.

Aims: 1) Characterize and describe HA-CDI patients to identify trends, exposures, and risk factors among these patients. 2) Analyze the movement of HA-CDI patients to determine if shared environments or exposure to other infected patients may have contributed to transmission in the hospital setting.

Methods: Data was collected from the electronic health records of HA-CDI patients during the study period, including risk factors, testing, demographics, and admissions information. Variables were assessed for their frequency and significance among these patients. Contact tracing was performed to determine if shared environments may have contributed to transmission and identify plausible exposures between patients.

Results: This study included 48 patients with 50 reported cases of HA-CDI. Antibiotics were the most common risk factor exposure (88.0%). Patients were found to be younger but with more severe comorbidities than expected. There was a significant relationship identified between

enteric tube insertion and toxin positivity. Contact tracing revealed that 83.3% of patients had at least one plausible exposure to another HA-CDI patient on the same unit preceding infection. Shared rooms were not implicated as common sources of transmission.

Conclusions: Hand hygiene, adherence to transmission-based precautions, and thorough cleaning practices are vital to the prevention of HA-CDI. Adherence to testing protocol may reduce unnecessary CDI testing. The significant relationship between enteric tubes and toxin positivity requires further study but may highlight a risk of infection during tube insertion or manipulation.

Public Health Significance: Findings from this study will inform infection prevention practices at the facility of study. Understanding HA-CDI risk factors specific to this facility allows for identification of at-risk patients and the implementation of targeted interventions to reduce the incidence of CDI and HA-CDI.

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Preface

I would like to acknowledge and thank my essay committee, Dr. David Givens, Dr. Mohamed Yassin, and Barbara Hildebrand, for their continued support throughout this project. I would especially like to thank my essay advisor, Dr. Mohamed Yassin, for his guidance, encouragement, and unwavering willingness to teach.

I would like to express my appreciation for the Infection Prevention team at UPMC Magee-Womens Hospital for welcoming me into their facility, taking me under their wing, and helping me to gain important infection prevention skills and knowledge. Specifically, thank you to Barbara Hildebrand, without whom this project would not have been possible.

Lastly, I would like to thank and recognize my family for their support throughout my academic career. Their encouragement to pursue my passion has been, and continues to be, a driving force in my education and career. Without their support I would not be where I am today. A very special thank you to my dog, Stella, for her countless hours keeping me company while I study, write, and work. She has been by my side since I was nineteen – at the beginning of the COVID-19 pandemic, lockdowns, and virtual learning. She was with me as I completed my undergraduate degree, and now, as I complete my master's degree and begin my career. The value of her friendship and companionship cannot be overstated.

1.0 Introduction

Clostridioides difficile is a potentially life-threatening bacterial infection of the large intestine which most often causes watery diarrhea, nausea, cramping, and fever (Mada & Alam, 2023). Infections range in severity and can be fatal, especially in elderly or immunocompromised patients. *C. difficile* is a common hospital-associated infection, with nearly a quarter million infections in hospitalized patients and nearly thirteen thousand attributed deaths in 2017 (CDC, 2019). Additionally, *C. difficile* infections (CDI) are frequently acquired in the community, but reporting is limited in these cases and determining exact prevalence of CDI is difficult. Overall, it is estimated that *C. difficile* is responsible for upwards of half a million infections every year. CDI is associated with significant cost, with an estimated one billion dollars in attributable healthcare costs in 2017.

In 2013, the CDC released the first Antibiotic Resistance Threats report with the goal of providing an overview of antibiotic resistance trends in the United States (CDC, 2013). Although *C. difficile* is not considered an antibiotic resistant organism, infections are driven by the same factors that drive antibiotic resistance and, therefore, was included in the report. In 2013, and again in 2019, *C. difficile* was classified as an urgent threat, indicating that it is a public health hazard that requires urgent and aggressive action (CDC, 2013, 2019).

The purpose of this essay is to analyze and describe a series of hospital-associated *Clostridioides difficile* infection (HA-CDI) cases that occurred over a 15-month period at an urban, acute care, teaching hospital. This essay has two primary aims that will be addressed throughout. The first aim is to characterize and describe the patients diagnosed with CDI, who were identified and reported as hospital-associated infections, with the purpose of identifying trends, exposures,

and risk factors among these patients. The second aim is to analyze the movement of patients with HA-CDI, before and after infection, to determine if shared environments or exposure to other infected patients may have contributed to transmission in the hospital setting. This essay will provide insights into common risk factor exposures among HA-CDI patients and determine if environmental contamination may have played a role in facility-based transmission, with the goal of informing future infection prevention initiatives at the facility of study.

1.1 About *Clostridioides difficile*

1.1.1 Microbiology and Epidemiology

C. difficile is a gram-positive, spore-forming, toxin-producing, obligate anaerobic bacteria that infects the large intestine of susceptible humans (Smits et al., 2016). The pathogenicity of *C. difficile* is primarily driven by the production of two toxins, TcdA and TcdB. These toxins induce morphological changes and apoptosis of host intestinal epithelial cells, ultimately leading to severe gastrointestinal symptoms, such as diarrhea and colitis (Bella et al., 2016; Smits et al., 2016). Approximately 40 percent of *C. difficile* strains isolated from hospitals are nontoxigenic and considered harmless to patients (Bowling, 2018).

As an obligate anaerobe, vegetative *C. difficile* bacteria are not suited to survive outside of the host gastrointestinal tract. Transmission of and infection with *C. difficile* is mediated by spores, which are released from an infectious host, germinate in the colon of a susceptible and exposed person, and form vegetative, toxin-producing bacteria (Paredes-Sabja et al., 2014; Zhu et al., 2018). *C. difficile* spores easily contaminate the environment and can survive on surfaces for up to

five months in the absence of appropriate cleaning and disinfection practices (Bowling, 2018; Srinivasa et al., 2019). Spores are inherently resistant to antibiotics, non-bleach disinfectant chemicals, and alcohol-based hand sanitizers (Smits et al., 2016; Zhu et al., 2018).

Acquisition of CDI can occur both in the hospital setting and in the community. Recent research indicates that approximately 40 percent of infections are considered to be community-associated, occurring in individuals with no recent history of hospitalization, while the remaining 60 percent of CDI cases are hospital-associated (Mada & Alam, 2023). However, a much smaller proportion of patients, 24.2 percent, experience onset of disease during the hospitalization in which they are infected with *C. difficile* (Bowling, 2018). In hospitals, rates of CDI vary widely over time and across facilities, which highlights the need for facility-specific surveillance programs.

Mortality associated with non-toxin variant strains of *C. difficile* is generally low, ranging from 0.6 percent to 3.5 percent (O'Connor et al., 2009). Mortality rates increase with patient age and presence of comorbidities, which are further addressed in a subsequent section. Although associated mortality is relatively low, patients who have a primary infection with *C. difficile* are highly likely to have a recurrent infection at some point in their life, with an approximate recurrence rate of 25 percent. In patients who have had one recurrence, approximately 40 percent to 65 percent will have multiple recurrences (Feuerstadt et al., 2021). This recurrence risk increases the probability of additional cost, clinical complications, and transmission of infection to others over a patient's lifetime, making the prevention of initial infection even more important.

1.1.2 Clinical Presentation of *C. difficile* Infection

The most common symptom of CDI is unformed, watery or mucoid diarrhea with high frequency – as few as three and as many as 20 bowel movements per day (Bowling, 2018). Clinical

manifestations of CDI vary greatly across patients, ranging from asymptomatic colonization or mild diarrhea, to severe disease presenting with toxic megacolon, bowel perforation and sepsis (Smits et al., 2016). Additional common symptoms include abdominal pain or cramping, occurring in 22 percent of CDI patients, and fever, occurring in 28 percent of CDI patients (Bowling, 2018). On laboratory examination, approximately 50 percent of patients present with leukocytosis and 26 percent with occult fecal blood (Bowling, 2018).

1.1.3 *C. difficile* Testing and Diagnosis

Diagnostic testing for CDI is only indicated for symptomatic patients, as to avoid identification of colonized individuals as true infections. Colonization with *C. difficile* is common, with one to three percent of adults and up to 20 percent of hospitalized patients of all ages asymptomatically carrying the bacteria in their stool (Bowling, 2018). Generally, the presence of three or more unexplained, unformed, or watery stools in 24-hours is adequate to initiate testing (Bowling, 2018). Other explanations for diarrhea, such as the use of laxatives, tube feeding, or patient diagnosis with other diarrhea-inducing infections or conditions, should be explored before testing is initiated (Smits et al., 2016).

At the facility of study, testing guidelines require that the patient have three or more unformed stools within 24 hours, not related to the use of laxatives, enemas, bowel prep, or tube feeding, as these treatments have diarrhea as a known side effect. Additionally, the patient must have at least one additional indication for testing, such as elevated white blood cell count (WBC) within 24 hours of diarrhea onset, abdominal tenderness, cramping, or distention, fever, antibiotic use within the previous 60 days, recent chemotherapy or immunosuppression, or history of CDI (UPMC, 2023).

The Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) recommends the use of multi-step diagnostic testing for CDI, which includes a stool toxin test used in conjunction with other enzyme testing or PCR (McDonald et al., 2018). Typically, these testing algorithms target at least two of three common *C. difficile* markers in a stool sample:

- *C. difficile* toxins, TcdA and TcdB
- Glutamate dehydrogenase (GDH), an enzyme and common antigen present in all isolates of *C. difficile*
- Toxin genes, which determine if the bacteria present are toxigenic, even if toxin was not detected in the sample

Since GDH is present in both toxigenic and nontoxic strains of *C. difficile*, the addition of toxin testing and correlation to patient symptoms is key to determining proper treatment. When the toxin is not detected in the stool, toxin gene testing via PCR can be used to determine if the bacteria present are toxigenic or nontoxigenic.

CDI is largely considered to be a toxin-mediated disease, as it is the toxin that damages the cells of the intestinal epithelium and ultimately causes the symptoms of CDI (Bella et al., 2016; Polage et al., 2015). Patients who test toxin-negative but test positive for toxigenic *C. difficile* via PCR often have less severe symptoms, shorter duration of diarrhea, and low rates of CDI-related complications when compared to toxin-positive patients (Polage et al., 2015). In these patients, a negative toxin test may indicate colonization with toxigenic *C. difficile* and may not require treatment. In this case, correlation to symptoms, knowledge of patient risk factors for CDI, and identification of other plausible causes of diarrhea is key to preventing unnecessary antibiotic therapy.

The facility of study employs a multi-step testing algorithm, as recommended by SHEA and IDSA (UPMC, 2023). The testing occurs in two sequential steps: 1) Enzyme immunoassay (EIA) for GDH and toxins TcdA and TcdB, then 2) PCR testing for toxin-producing genes. If conflicting results are found in the first step, PCR will be performed. The reported result and interpretation of each possible test result is available in Table 1.

Table 1. Interpretation of *C. difficile* Multi-Step Testing Algorithm Results.

Test Result			Reported Result	Interpretation
EIA: GDH	**EIA: Toxin A/B**	**PCR: Toxin gene**		
Negative	Negative	Not performed	Negative	Negative for *C. difficile.*
Negative	Positive	Not performed	Indeterminate	Rare result. Retest specimen.
Positive	Positive	Not performed	Positive	Free toxin and toxigenic *C. difficile* are present.
Positive	Negative	Positive	Positive	Positive for toxigenic *C. difficile*, no free toxin present. Clinical correlation required.
Positive	Negative	Negative	Negative	Negative for free toxins and toxigenic *C. difficile*.

Note. Adapted from *C. difficile Testing Frequently Asked Questions* by UPMC, 2023.

1.2 *Clostridioides difficile* as a Hospital-Associated Infection

CDI is one of the most common hospital-associated infections in the United States and is the leading cause of antibiotic-associated diarrhea (CDC, 2023c). *C. difficile* spreads exceptionally well in the hospital environment, primarily due to shared environments, equipment, and staff, as well as the congregation of patients, many of whom have several risk factors for CDI.

1.2.1 Transmission in the Healthcare Setting

C. difficile transmission occurs primarily via the fecal-oral route. Spores are released from a symptomatic or asymptomatic patient, which are then ingested or otherwise introduced to the gastrointestinal tract of a susceptible patient, such as via insertion of a nasogastric tube (Smits et al., 2016; Wijarnpreecha et al., 2016). Spores can be spread between patients by unclean hands and equipment, as well as due to lapses in environmental cleaning between discharges and admissions, which results in patient exposure to a contaminated room. However, ingestion of spores does not always result in infection and is highly dependent on a number of patient risk factors (Martin et al., 2016). Although risk factors for CDI are known, it is difficult to establish a temporal relationship between exposure to the risk factor, spore exposure, and onset of symptoms.

A challenge to managing CDI in hospital settings is the variability of the *C. difficile* incubation and infectious period. The incubation period of *C. difficile* varies greatly, and likely depends significantly on host susceptibility and characteristics of the causative strain (Martin et al., 2016). In a study of CDI in the hospital setting, most incubation periods ranged from a few days to four weeks, with some longer than three months (Walker et al., 2012). It is largely unknown if and when a patient may be contagious preceding symptom onset.

Additionally, a significant proportion of *C. difficile* infections are asymptomatic but may be a source of transmission. A 2013 study from UPMC found that approximately a quarter of HA-CDI cases reported in their facility were highly genetically related to isolates from asymptomatic carriers (Curry et al., 2013). In that same study, nearly half of patients remained positive for *C. difficile* after treatment, confirming that patients with asymptomatic infection, even those who have been treated, can be contagious and contribute to infection rates in a facility.

1.2.2 Prevention and Control

Prevention and control measures are generally directed at reducing the risk of transmission. These measures include the use of contact precautions when interacting with the patient or their environment, handwashing with soap and water, and environmental cleaning and disinfection practices (Bowling, 2018). Transmission of *C. difficile* spores occurs primarily via contaminated hands of healthcare workers. Spores can severely contaminate the hospital environment and can be isolated from beds, walls, floors, and various other surfaces throughout the environment of care (Srinivasa et al., 2019). *C. difficile* has been cultured in nearly half of all hospital rooms previously occupied by a CDI patient and is one of the most frequently recovered pathogens from hospital floors. Spores can then collect on the hands during patient care or interaction with the environment. In cases where hand hygiene and contact isolation procedures are not followed closely, spores can be spread from unclean hands to surfaces outside of the infected patient's room and then easily transmitted to susceptible patients. To reduce spore contamination of equipment and the environment, thorough cleaning and disinfection with a bleach-based or other EPA-approved sporicidal chemical is paramount.

There is ongoing debate regarding the duration of CDI patient contact isolation since, despite symptom resolution and treatment, patients can shed spores in their stool for weeks to months and may serve as a source of infection in the facility (Banach et al., 2018). Additionally, the patient environment may remain highly contaminated with bacterial spores until terminal cleaning can be performed, further increasing the risk of transmission if contact precautions are ceased prematurely (Bowling, 2018). The current recommendations from the Society for Healthcare Epidemiology indicate that contact precautions should be used in patients with CDI for at least 48 hours after the resolution of diarrhea, but that the use of contact precautions should be

extended for the duration of hospitalization if a facility is experiencing elevated rates of CDI (Banach et al., 2018). Some facilities may choose to continue isolation for the duration of stay regardless of infection rates (Curry et al., 2013).

Additional prevention measures aim to reduce the risk of illness if transmission does occur, such as minimizing exposure to high-risk antibiotics and emphasizing the importance of antimicrobial stewardship (Bowling, 2018).

1.2.3 NHSN Reporting Standards and Definitions

The CDC's National Healthcare Safety Network (NHSN) is a healthcare-associated infection tracking system, widely implemented across the United States. NHSN provides facilities with data collection and reporting capabilities to allow for the identification of infection prevention problems, benchmark progress, and comply with reporting mandates, with the ultimate goal of reducing and eliminating hospital-associated infections (CDC, 2023b). Reporting to NHSN is required for hospitals to maintain funding and receive reimbursements from the Centers for Medicare and Medicaid Services. As part of the NHSN data collection standards, they provide facilities with definitions of infections to facilitate accurate reporting.

According to NHSN diagnostic criteria, a *C. difficile* infection is defined by a positive test for toxin-producing *C. difficile* on an unformed stool sample or the patient must have evidence of pseudomembranous colitis on gross anatomic or histopathologic exam (CDC, 2023a).

An infection is reportable as a hospital-associated infection if the date of sample collection is on or after the third calendar day of hospitalization, where admission is calendar day one (CDC, 2024). The date of infection is the day that a stool sample was collected for testing. The inpatient location where the patient was assigned when the positive sample was collected is considered the

location of attribution. If the patient is transferred on that same day, the location of attribution is the first location of the patient on that day. If the patient is retested and tests positive again within 14 days, the second positive test will not be reported as an HAI.

1.3 Patient Risk Factors for Hospital-associated *Clostridioides difficile* Infection

Several risk factors are associated with increased risk of HA-CDI. Prolonged or repeat hospitalization can significantly increase the risk of CDI (Smits et al., 2016). Additionally, several medications, treatments, comorbidities, and personal factors have been associated with increased risk of CDI or undesirable outcomes of infection.

1.3.1 Antibiotics

The use of antibiotics, particularly in the 60 days preceding infection, is considered to be the most significant risk factor for CDI when hospitalized (Bowling, 2018). The greatest risk is associated with penicillins, third- and fourth-generation cephalosporins, fluoroquinolones, and clindamycin, however, most antibiotics carry some degree of risk (Mada & Alam, 2023). Additional factors that increase the risk of CDI associated with antibiotic use is the number of antibiotics administered, dose, and duration of therapy (Smits et al., 2016). The disruptive effect of antibiotics on the intestinal microbiome can persist for weeks or months following treatment, leaving patients susceptible to infection. Antibiotic use is a prevalent risk factor, particularly in the hospitalized population, with approximately 65 percent of patients in acute care settings receiving antibiotic therapy (Goodman et al., 2020).

1.3.2 Proton Pump Inhibitors

Proton pump inhibitor (PPI) medications are widely accessible over-the-counter and frequently prescribed to reduce the production of gastric acid to treat peptic ulcer disease or gastroesophageal reflux (Smits et al., 2016). Gastric acid inhibits the germination of *C. difficile* spores in the gastrointestinal tract and serves as a protective mechanism for patients who have ingested spores (Patil & Blankenship, 2013). The use of PPI medications has been commonly associated with CDI and, although the exact role of PPI treatment in CDI is not well understood, it is thought that the use of acid reducing drugs may limit the protective nature of gastric acid. A meta-analysis found that the use of PPI medications doubled the risk of infection (Deshpande et al., 2012).

1.3.3 Opioids

Opioid medications are known to have a significant impact on the gastrointestinal system such as reduced motility and decreased intestinal secretions, often resulting in constipation and other unfavorable symptoms (Mora et al., 2012). In the setting of reduced motility, the gastrointestinal environment becomes increasingly favorable for bacterial growth. A study by Mora et al found that, in patients who were also receiving broad-spectrum antibiotics, patients with moderate and high usage of opioids developed CDI at significantly higher rates than patients with low or no opioid use. Additionally, there is evidence that reduced bowel motility caused by opioids may reduce the effectiveness of CDI treatment. Patients receiving opioids during CDI treatment are at a significantly increased risk of experiencing a relapse with the same organism, likely due to delayed bowel movements and ineffective elimination of the infection (Marsh et al., 2020).

1.3.4 Antidepressants

New, limited data indicates that certain antidepressant medications may increase the risk for CDI. A 2009 study aiming to examine the association between PPI and CDI incidentally found a significant association between antidepressant exposure and CDI (Dalton et al., 2009). However, at the time, it was believed that this association was likely related to the poor attention to self-care that is found in patients with psychiatric illnesses and not a result of the medications themselves. A recent publication aiming to directly assess the association between antidepressants and HA-CDI found that the risk of HA-CDI is significantly higher in patients who take certain antidepressants, specifically trazadone, nortriptyline, and mirtazapine (Boustany et al., 2023).

1.3.5 Nasogastric Tubes and Enteral Nutrition

Enteral tube feeding is frequently used in patients with a contraindication for oral intake and has been associated with an increased risk of CDI, with one meta-analysis reporting a 1.81-fold increased risk of *C. difficile*-associated diarrhea in patients who had a nasogastric tube inserted for enteral feeding or treatment of an intestinal obstruction (Wijarnpreecha et al., 2018). Although not clear, the association between nasogastric tubes, enteral nutrition, and CDI could be explained by several factors, including introduction of *C. difficile* spores during insertion or manipulation of enteric tubes, potentially contaminated formula and instruments, and the disruptive nature of formula used for enteric feeding, which lacks dietary fiber and contributes to lower acidity of the colonic fluid, which may be associated with increased survival and toxin production of *C. difficile* (O'Keefe, 2010; Wijarnpreecha et al., 2018). Additionally, patients requiring enteral nutrition are

typically very ill, at high risk for complications, and more often on antibiotic therapy, further increasing their risk of CDI (O'Keefe, 2010).

1.3.6 Age and Long-Term Care

Older individuals, particularly those 65 and older, are at an increased risk for HA-CDI. It is estimated that two-thirds of all HA-CDI cases occur in patients age 65 years or older (CDC, 2013). The risk of CDI in the elderly is driven by several factors including the prevalence of admission to long-term care facilities, severity of underlying illness and comorbidities, immunosenescence and immunosuppression, other medications, and prior hospitalization (Asempa & Nicolau, 2017).

Residents of long-term care facilities are at a particularly elevated risk for CDI due to frequent antibiotic exposure, vulnerability due to age and general health, congregate living conditions conducive to the spread of infection, and high rates of *C. difficile* colonization among long-term care facility residents (Jump & Donskey, 2015). Additionally, transmission may occur between long-term care facilities and hospitals via patients who are infected in the hospital and transitioned to long-term care, or patients who are infected in long-term care and then hospitalized, posing a risk of transmission in both types of facilities.

1.3.7 Comorbidities

Certain medical conditions are associated with an increased risk of CDI or poor outcomes, such as diabetes, chronic kidney disease, immunodeficiency, malignancy, as well as inflammatory bowel and other gastrointestinal diseases (Gupta et al., 2021; Leffler & Lamont, 2015). Increased

risk related to these conditions may be related to the condition itself, required treatments, or increased exposure to hospitals and healthcare environments.

1.4 Public Health Significance

CDI is one of the most commonly reported hospital-associated infections in the United States. The prevention and control of CDI in the hospital setting is vital to limiting the spread of *C. difficile* in hospitals and in the community, improving patient safety and quality of care, and reducing the incidence of hospital-associated infections. Hospitals play a central role in our communities and preventing the spread of *C. difficile* in every facility is vital to the ongoing health and safety of hospitalized patients, long-term care facility residents, and the community. Using facility-specific findings related to HA-CDI patient characteristics, risk-factors, and hospital-based transmission will guide targeted interventions and aid in the development of effective prevention initiatives.

1.5 Aim of Study

This study aims to: 1) Characterize and describe the patients diagnosed with HA-CDI to identify trends, exposures, and risk factors among these patients. 2) Analyze the movement of patients with HA-CDI, before and after infection, to determine if shared environments or exposure to other infected patients may have contributed to transmission in the hospital setting, via a bed and contact tracing investigation

2.0 Methods

This project was approved by the Institutional Review Board of the University of Pittsburgh Medical Center as a Quality Improvement Project (ID number: 4576) on November 3, 2023. This study does not include or release patient identifiers or confidential health information.

2.1 Study Site Characteristics and Inclusion Criteria

This study took place at a mid-sized, urban, acute care, teaching hospital. While primarily focused on gynecologic and obstetric services, this hospital provides full inpatient and outpatient services to men and women, including an emergency room and 14-bed intensive care unit.

Patients included in the study population were all inpatients at the acute care hospital of study that were diagnosed with CDI and reported as a hospital-associated infection from June 2022 through August 2023. No patients with HA-CDI were excluded.

2.2 Data Collection

Patient clinical data was collected via review of Electronic Health Records. Each patient was deidentified to conceal protected health information and identifiers were stored separately from clinical data. Data collected includes demographics, admissions information, symptoms, *C. difficile* test results and orders, medications and treatments, comorbidities, infection with other MDROs or previous CDI, and room locations during hospitalization and previous admissions.

2.3 Data Analysis

2.3.1 Age-Comorbidity Score

In order to compare patients based on their overall health at the time of hospitalization and infection, the Charlson Comorbidity Index was used to quantify patient health and risk of mortality (Charlson et al., 1987). The Charlson Comorbidity Index provides a set of comorbid conditions for which there is an increased risk of associated mortality. Each condition is assigned a weighted score from one to six based on mortality risk and severity. Scores are also assigned for patient age, adding one point for every decade over the age of 40 (Charlson et al., 1987, 1994). Total age-comorbidity scores for each patient are used to estimated relative risk of mortality and ten-year survival. The estimated relative risk of death for each one-point increase in age-comorbidity score is 1.45 (99% CI: 1.25 – 1.68). As such, patients with an age-comorbidity score of zero have a 1.00 estimated relative risk of death, correlating to a predicted ten-year survival of 99 percent, while patients with a score of five have a 6.38 (99% CI: 3.07 – 13.24) estimated relative risk of death, correlating to a predicted ten-year survival rate of 21 percent. Scores greater than five were associated with low rates of long-term survival. A full list of conditions included in the calculation of age-comorbidity score for this study are available in Appendix A, Table 14.

Using the dataset calculator published in 2022 by Prommik et al, ICD-10 codes of patient problems and diagnoses addressed during hospitalization, as well as relevant medical history or conditions noted in clinical charting, were used to calculate each patients' age-comorbidity score (Charlson et al., 1987, 1994; Prommik et al., 2022).

2.3.2 Facility-Wide HA-CDI

Age-comorbidity score was used to stratify and compare frequency of patient exposure to risk factors and symptoms. Comparisons were also made based on age, toxin positivity, and exposures to certain risk factors or treatments. In order to determine the significance of relationships between variables, when appropriate, the Chi-Square Test of Independence was used, in which a p-value less than 0.05 signified significance. Results of Chi-Squared Tests are only included if the finding was statistically significant.

Due to variation between number of patients, infections, and admissions, some variables are assessed with different sample sizes. Variables and their sample size are displayed in Table 2.

Table 2. Sample Size by Variable.

Sample Size	Variable
n = 48	Patient Based Variables Age Sex Race Ethnicity Comorbidities and Age-Comorbidity Score
n = 49	Admission/Hospitalization Based Variables Route of admission Living arrangement before hospitalization Inpatient Medications Home Medications
n = 50	Infection Based Variables Test Results Symptoms Medication or risk-factor exposure preceding infection/positive test

2.3.3 Bed and Contact Tracing

Data used in the bed tracing analysis was collected from electronic health records to track patient movement throughout the facility, before and after infection, to determine if shared rooms or environments may have contributed to infection. Patient room numbers and units were deidentified. Units are identified by M, and A through F. Room locations from previous hospitalizations at the facility of study, within three months from time of admission, were also included to determine if exposure may have occurred during a previous admission. Tracing data included inpatient rooms only, and did not include operating rooms, procedure rooms, triage, or rooms within the emergency department.

Consistent with the findings and methods of Walker et al (Walker et al., 2012), possible exposures were identified when two HA-CDI patients were both housed on the same unit, and the first case of HA-CDI was identified before the second case. In order to determine plausible sources of transmission, a maximum infectious period of eight weeks from date of infection and a maximum incubation period of 12 weeks from earliest known, possible exposure was used. Potential exposures that occurred outside of these windows were considered not to be plausible. Punitive incubation periods for each patient's exposure(s) were calculated from earliest possible date of exposure to patient date of infection.

Exposures were classified into two groups: direct and indirect. Direct exposures are those in which both patients were on the unit at the same time. Indirect exposures are those in which the first HA-CDI patient had left the unit before the second patient arrived but was still a plausible source of transmission.

In order to determine the most plausible exposure for each patient, preference was given to exposures with the shortest exposing patient infectious period, assuming that patients are more

infectious earlier in the course of illness. If a patient had more than one exposure with the same infectious period, preference was given to exposures closer in proximity based on room location at time of exposure.

For patients with more than one infection during the period of study, only their first infection was included in analysis for their own potential exposures. All infections and room locations, for all infections, are included as potential sources of exposure for other patients.

3.0 Results

A total of 50 HA-CDIs affected 48 patients during 49 hospitalizations. Two patients experienced recurrent infections within the study period. One patient had a primary and recurrent infection during the same hospitalization, while the other patient had a primary infection and recurrent infection during two separate hospitalizations. During the period of study, an average of three (SD: 2) infections occurred per month, ranging from one to seven (Figure 1). On average, reported date of infection occurred on hospitalization day eight (SD: 8.1, Median: 5), ranging from days two to 50.

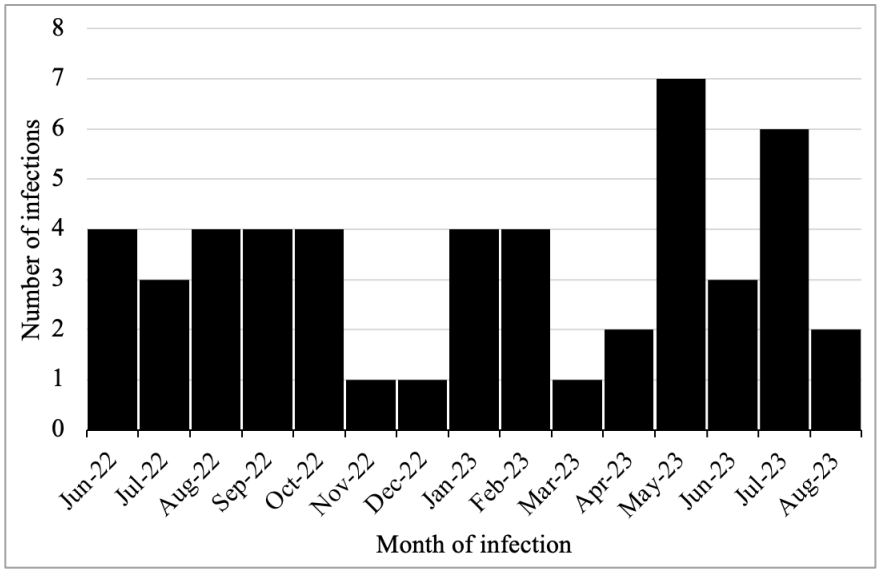

Figure 1. HA-CDI Incidence by Month.

3.1 Facility-Wide HA-CDI

3.1.1 Patient Demographics, Admission, and Comorbidities

The average age of HA-CDI patients was 64, ranging from 29 to 85 years (SD: 14.3). The majority of patients were white, female, and non-Hispanic or Latino (Table 3).

Most patients had been living at home before admission, with less than a quarter of patients living in a long-term care facility or having lived in a long-term care facility at any point in the previous thirty days. Patients were primarily admitted through the emergency department or transferred from an outside hospital. Eight patients were hospitalized as a direct, planned admission, primarily for surgery or gynecologic oncology care. Three patients were internal transfer admissions, as they were discharged from an acute care unit and directly admitted into the transitional care unit or vice versa, within the facility of study (Table 4).

A substantial number of patients had a recent hospitalization preceding infection. Of 49 total admissions during which HA-CDI was identified, 38 (77.6%) of those were preceded by at least one night's stay at the facility of study or an outside hospital in the three months before admission. Overall, 40 (81.6%) admissions were preceded by recent hospitalization or long-term care admission.

Table 3. Patient Demographics.

Age at Admission	Count (n = 48)	%
20-29	1	2.1
30-39	4	8.3
40-49	0	0.0
50-59	6	12.5
60-69	18	37.5
70-79	15	31.3
80+	4	8.3
Sex		
Male	4	8.3
Female	44	91.7
Race		
White	38	79.2
Black or African American	6	12.5
Asian	1	2.1
Other	1	2.1
Not Specified	2	4.2
Ethnicity		
Non-Hispanic/Latino	42	87.5
Not Specified	5	10.4
Declined	1	2.1

Table 4. Patient Admissions.

Living arrangement before hospitalization	Count (n = 49)	%
Home	41	83.7
Long-term care *(in last 30 days)*	8	16.3
Route of Admission		
Emergency Department	19	38.8
Transfer from outside hospital	19	38.8
Direct/Planned	8	16.3
Internal Transfer, *Acute care to/from Transitional Care Unit*	3	6.1

Based on past medical history, admission data, and problems addressed during hospitalization, patients were assessed for various comorbidities, including advanced age, according to the Charlson Comorbidity Index (Charlson et al., 1987). The most common comorbidities across all HA-CDI patients were rheumatic or connective tissue diseases, chronic

pulmonary diseases, metastatic solid tumors, and congestive heart failure (Table 5). HA-CDI patients, on average, had notably high age-comorbidity index scores, indicating high risk of all-cause mortality. The average age-comorbidity score for these patients was six, ranging from zero to 17 (SD: 3.7) (Table 6).

Table 5. Charlson Comorbidity Index - Frequency of Patient Comorbidities.

Disease / Condition	Count (n = 48)	%
Myocardial Infarction	8	16.7
Congestive Heart Failure	10	20.8
Peripheral Vascular Disease	5	10.4
Cerebrovascular Conditions	9	18.8
Dementia	1	2.1
Chronic Pulmonary Diseases	14	29.2
Rheumatic / Connective Tissue Diseases	21	43.8
Peptic Ulcer Disease	4	8.3
Mild Liver Disease	5	10.4
Diabetes without complications	5	10.4
Diabetes with complications	4	8.3
Hemi- or Paraplegia	5	10.4
Moderate/Severe Renal Disease	4	8.3
Any Malignancy	6	12.5
Moderate Severe Liver Disease	0	0.0
Metastatic Solid Tumor	10	20.8
AIDS	0	0.0

*Patients may have multiple comorbid conditions.

Table 6. Frequency of Age-Comorbidity Scores Among HA-CDI Patients.

Charlson Age-Comorbidity Index Score	Count (n = 48)	%
0	3	6.3
1-2	5	10.4
3-4	9	18.8
5-6	10	20.8
7-8	9	18.8
>8	12	25.0

3.1.2 CDI Testing Results and Symptoms

Across 50 confirmed HA-CDI cases, 25 were PCR and toxin positive, and 25 were PCR positive and toxin negative. Forty-six (92.0%) had a record of three or more unformed stools in 24 hours, noted either in clinical charting or *C. difficile* test order. Thirty (60.0%) patients presented with elevated WBC counts and eight (16.0%) patients presented with fever within 24 hours of diarrhea onset and subsequent testing. Six (12.0%) patients presented with elevated WBC count in combination with fever, while 18 (36.0%) patients presented with neither.

Record of three or more unformed stools and fever in combination with elevated WBC were slightly higher in patients who tested positive for *C. difficile* toxin. Rates of elevated WBC was slightly higher in those who tested toxin-negative. Prevalence of fever alone, and no fever or elevated WBC were the same between both patient groups (Table 7). Differences in symptoms between toxin-negative and toxin-positive patients were not found to be statistically significant.

Table 7. Symptom Prevalence Between CDI Test Result Groups.

Symptom	PCR + / Toxin -		PCR + / Toxin +	
	Count (n=25)	%	Count (n=25)	%
Record of 3+ unformed stools in 24hrs	21	84.0	25	100.0
Elevated WBC only *(>10K within 24hrs of positive test)*	13	52.0	11	44.0
Fever only *(>38℃ within 24hrs of positive test)*	1	4.0	1	4.0
Elevated WBC and fever	2	8.0	4	16.0
No elevated WBC or fever	9	36.0	9	36.0

Patients with low age-comorbidity scores had higher rates of toxin positivity when compared to patients with higher scores, although differences in toxin positivity between groups was not found to be statistically significant (Table 8). Patients with lower scores were also more likely to present with fever. Patients with higher age-comorbidity scores were more likely to have

to have been tested without clear record of three or more unformed stools in 24 hours. Rates of elevated WBC counts were similar between groups, but slightly higher in those with high age-comorbidity scores (Table 9). Differences in test results, symptoms and clinical presentation between age-comorbidity score groups were found not to be statistically significant.

Table 8. CDI Test Results Between Age-Comorbidity Score Groups.

Charleson Age-Comorbidity Score	PCR + / Toxin -		PCR + / Toxin +	
	Count	%	Count	%
0	1	33.3	2	66.7
1-2	1	20.0	4	80.0
3-4	4	40.0	6	60.0
5-6	6	60.0	4	40.0
7-8	7	70.0	3	30.0
>8	6	50.0	6	50.0

Table 9. Symptoms Between Age-Comorbidity Score Groups.

Charleson Age-Comorbidity Score	Record of 3+ unformed stools in 24hrs	
	Count	%
0	3	100.0
1-2	5	100.0
3-4	10	100.0
5-6	10	100.0
7-8	8	80.0
>8	10	83.3
	Elevated WBC *(>10K within 24hrs of positive test)*	
	Count	%
0	2	66.7
1-2	3	60.0
3-4	5	50.0
5-6	9	90.0
7-8	5	50.0
>8	6	50.0
	Fever *(>38℃ within 24hrs of positive test)*	

	Count	%
0	2	66.7
1-2	1	20.0
3-4	2	20.0
5-6	1	10.0
7-8	0	0.0
>8	2	16.7

3.1.3 Medications and Treatments

Antibiotics were the most frequently prescribed inpatient medication preceding HA-CDI in the study population. Thirty-six patients (75.0%) received antibiotics during their hospitalization before their date of infection. One patient with two hospitalizations during the period of study received antibiotics during their first hospitalization but not the second. One patient with two infections during the same hospitalization received antibiotics preceding the first and second infection. On average, among patients who received antibiotic treatment, two different antibiotics were prescribed over the course of hospitalization before infection, ranging from one to five. The most frequently prescribed antibiotics across all hospitalizations were piperacillin-tazobactam, ceftriaxone, and vancomycin (Table 10).

Table 10. Frequency of Inpatient Antibiotic Use Across All Hospitalizations, Preceding HA-CDI Diagnosis.

Antibiotic	Count (N=49)	%
Penicillins		
Amoxicillin-Clavulanate	4	8.2
Ampicillin-Sulbactam	5	10.2
Piperacillin-Tazobactam	20	40.8
Cephalosporins		
Cefazolin *(1st generation)*	3	6.1
Cefoxitin *(2nd generation)*	5	10.2
Cefuroxime *(2nd generation)*	5	10.2
Ceftriaxone *(3rd generation)*	10	20.4

Cefepime *(4th generation)*	5	10.2
Fluoroquinolones		
Levofloxacin	1	2.0
Other Antibiotics		
Clindamycin	1	2.0
Vancomycin	10	20.4
Metronidazole	4	8.2
Azithromycin	3	6.1
Meropenem	3	6.1
Linezolid	1	2.0
Daptomycin	1	2.0

Patients had additional exposure to antibiotics outside of their inpatient stay at the facility of study. Antibiotics were the most reported home medication, medication received at an outside hospital prior to patient transport, or medication given at a recent prior hospitalization. Twenty-five (51.0%) patients were taking home antibiotic treatment or were recently exposed to inpatient antibiotics prior to their hospitalization in which they acquired a CDI. The antibiotics that patients were most frequently exposed to prior to hospitalization were piperacillin-tazobactam (18.4%), vancomycin (14.3%), and ceftriaxone (12.0%).

Overall, of the 50 HA-CDI cases, 44 (88%) infections were preceded by the use of any antibiotic and 39 were preceded by the use of an antibiotic that is considered high-risk for CDI. HA-CDI patients were most frequently exposed to penicillins or penicillins and cephalosporins before their infection (Table 11). Eleven infections were not preceded by the use of high-risk antibiotics. Of those, five were preceded by exposure to first- and second- generation cephalosporins but no other antibiotics and six did not have exposure to antibiotics of any class. Rates of high-risk antibiotic exposure (80% versus 76%) and exposure to any antibiotics (88% versus 88%) were nearly identical between toxin-positive and toxin-negative patients.

Table 11. High-Risk Antibiotic Exposure Preceding HA-CDI.

Antibiotic	Count (n = 50)	%
Cephalosporins only *(3rd & 4th Gen.)*	5	10.0
Fluoroquinolones only	2	4.0
Penicillins only	20	40.0
Clindamycin only	1	2.0
Cephalosporins *(3rd & 4th Gen.)* & Penicillins	9	18.0
Cephalosporins *(3rd & 4th Gen.)* & Clindamycin	1	2.0
Cephalosporins *(3rd & 4th Gen.)* & Fluoroquinolones	1	2.0
No high-risk antibiotics	11	22.0

Additional inpatient medications of interest included certain antidepressants, opioids, and proton pump inhibitors. Eight admissions of infection (16.3%) included antidepressant medications mirtazapine or trazadone, 30 admissions (61.2%) included opioid medications, and 31 admissions (63.3%) included proton pump inhibitors. One patient received all these medications twice, across two hospitalizations and preceding two infections.

For all infections, between inpatient and home medications, nine (18.0%) infections had recent or current exposure to antidepressants mirtazapine or trazadone, 35 (70.0%) infections had recent exposure to opioids, and 36 (72.0%) had exposure to proton pump inhibitors.

Fourteen patients (29.2%) had a nasogastric or orogastric tube inserted before their date of primary infection, with an average of 4.7 days (SD: 3.5) between tube insert and date of infection, ranging from one to 11 days. Notably, 71.4 percent of patients who had enteric tubing inserted before their primary infection tested toxin-positive. In this case, there was a significant relationship between these variables; those with recent enteric tube insertion preceding primary infection were more likely to test toxin-positive than those without an enteric tube ($X^2(1, N=48) = 4.378$, $p = 0.036$). All tubes were inserted at the facility of study except for one, which was inserted at an outside hospital prior to patient transport.

3.1.4 Age as a Risk Factor for HA-CDI

There were significant differences between the clinical presentation and medical history of HA-CDI patients above and below 65 years of age (Table 12). Half of all HA-CDI cases occurred in patients aged 65 or older. Patients younger than 65 were more likely to present with fever and had higher rates of toxin positivity. They were also more likely to have a recent nasogastric or orogastric tube insertion, receive tube feeding, and have recent exposure to high-risk antibiotics, antibiotics of any class, antidepressants, and opioids. Patients over the age of 65 were more likely to have recent admission to long-term care facilities but had equal or lower rates of exposure to other risk factors when compared to younger patients. None of these differences were found to be statistically significant.

Table 12. Symptoms and Risk Factor Exposure by Age.

Symptom, Test Result, or Risk Factor Exposure	Age < 65		Age 65+	
	Count (n=25)	%	Count (n=25)	%
Elevated WBC *(>10K within 24hrs of positive test)*	15	60.0	15	60.0
Fever *(>38℃ within 24hrs of positive test)*	8	32.0	0	0.0
PCR + / Toxin +	14	56.0	11	44.0
NGT inserted before infection	9	36.0	5	20.0
High-risk antibiotics	21	84.0	18	72.0
Any antibiotics	23	92.0	21	84.0
Antidepressants	5	20.0	4	16.0
Opioids	20	80.0	15	60.0
Proton pump inhibitors	18	72.0	18	72.0
History of long-term care	2	8.0	6	*25.0
Recent hospitalization	19	76.0	19	*79.2

Note: (*) n=24 due to one patient who had two infections during one admission.

3.1.5 Additional Demographic Factors and HA-CDI

The patient population was comprised of 44 (91.7%) females and four (8.3%) males. Of the two recurrent infections during the study period, one occurred in a female patient during one admission, and one occurred in a male patient during two separate admissions.

Although male patients were slightly older on average (69 [SD: 9.0] vs. 64 [SD: 12.1]), average age-comorbidity score was slightly higher among female patients than male patients (6.1 [SD: 3.8] vs. 5.3 [SD: 2.6]), however, both were within one standard deviation. Female patients had slightly higher rates of toxin positivity, elevated WBC, and fever, as well as recent long-term care admission, insertion of enteric tubes, testing without a clear record of 3 or more unformed stools, and laxatives when tested. Male patients had higher rates of exposure to all medications studied, including antibiotics, antidepressants, opioids, and proton pump inhibitors.

The overwhelming majority of HA-CDI patients were White, with a total of 38 White patients, six Black or African American patients, one Asian patient, and three patients with an unspecified race. Rates of risk-factors, exposures, symptoms, and toxin positivity were not notably different between racial groups. Average age-comorbidity score was significantly higher among Black patients than White patients (8.3 [SD: 4.8] vs. 5.8 [SD: 3.3]), however, this difference is primarily attributed to one Black patient with a severely high age-comorbidity score of 17. When that outlier was removed, the average age-comorbidity score among Black patients was 6.6 (SD: 2.7), much closer to that of White patients and the overall HA-CDI patient population. All patients identified as non-Hispanic or Latino, except for six who were not specified or declined. Due to the low number of male patients or patients who identified as a racial or ethnic minority, statistical analysis yielded invalid results.

3.1.6 Previous CDI and MDROs

Ten patients were identified as having a current or previous infection with a multi-drug resistant organism in addition to *C. difficile*. These infections were diagnosed during hospitalization, or the patient was under transmission-based precautions based on a previous diagnosis. MDROs identified include MRSA, drug-resistant Klebsiella, ESBL-producing bacteria, VRE, and drug-resistant Acinetobacter. Of these patients, half tested toxin-positive.

One patient had been previously hospitalized with a CDI nearly a decade before admission during the period of study. This patient (age-comorbidity score: 5) experienced a second infection nearly a week into their admission, following inpatient exposure to several high-risk antibiotics and other medications.

Two patients had a primary and recurrent CDI within the period of study. One patient (age-comorbidity score: 8) had a recurrent infection 38 days after their primary infection during the same hospitalization. The patient was treated after diagnosis of their primary infection with incomplete resolution of symptoms, leading to retesting and, ultimately, a second positive test. A second patient (age-comorbidity score: 3) had a recurrent infection 44 days after their primary infection during a second hospitalization. During and after the first hospitalization, the patient was taking a high-risk antibiotic, as well as several other medications associated with an increased risk of CDI.

3.1.7 Review of Adherence to Testing Protocol

Of the 50 *C. difficile* tests ordered, 29 (58.0%) included responses to a clinical decision support prompt. This prompt asks providers to confirm the presence of three or more unformed

stools without the use of bowel preps, laxatives, or tube feeds, along with one additional indication for testing such as elevated WBC count, abdominal pain, fever, immunosuppression, history of CDI, or exposure to antibiotics within 60 days. Although the clinical decision support prompt is supposed to appear for all providers ordering a test for *C. difficile*, it is unclear if the question was prompted for all ordering individuals or if the prompt was bypassed.

Four (8.0%) patients had no clear record of three or more unformed stools in 24 hours, either in *C. difficile* testing orders or in clinical notes. Of those, three had explicit record of fewer than three unformed stools in clinical notes and one had no explicit record in clinical notes and no indication in *C. difficile* testing order. None of these patients' testing orders included a response to the clinical decision support prompt.

Twenty-three (46.0%) patients were prescribed laxatives, either PRN or scheduled, on the day before and day of *C. difficile* test collection. Only 13 (56.5%) of these patients' testing orders included a response to the clinical decision support prompt. Of those patients receiving laxatives, ten (43.5%) tested toxin positive and 13 (56.5%) tested positive via PCR only.

Of the 14 patients who had a nasogastric tube inserted before their date of infection, five (35.7%) were receiving tube feeds on the day of or day before sample collection. Of those, three (60.0%) tested toxin positive.

For seven (14.0%) patients, there was a delay in testing which may have contributed to the infection being reported as an HAI. In three cases, diarrhea was reported on admission, *C. difficile* testing was noted and bowel movements continued through day two, but collection of a sample for testing was delayed until day three or later. In two cases, diarrhea was noted on admission and day two, testing for *C. difficile* was noted midday on day two, but a sample was not collected until day three. Two patients developed diarrhea late on day two and a sample was not collected until day

three. Five (71.4%) of these patients' testing orders included a response to the clinical decision support prompt.

3.2 Bed and Contact Tracing

HA-CDI cases were attributed to seven units on, M and A through F, on four floors. The greatest number of infections occurred on unit F, a surgical oncology unit. The fewest number of infections occurred on unit M, a maternity unit (Figure 2).

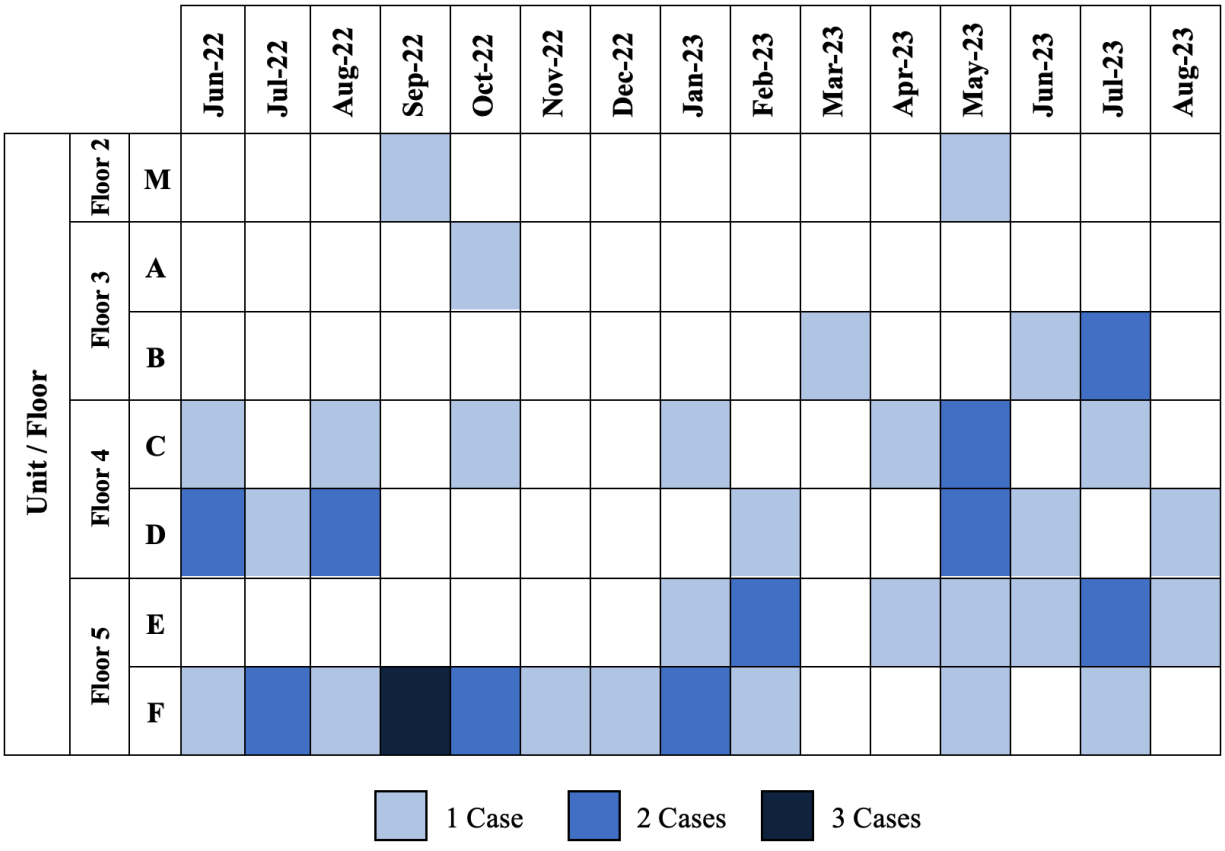

Figure 2. Infections by Location of Attribution by Month.

Days between infections varied widely. Facility-wide, HA-CDI infections occurred an average of 8.9 days apart, ranging from zero to 25 days (SD: 6.6). On unit M, which had two attributed HA-CDI cases, infections occurred 226 days apart. Unit A had only one attributed HA-CDI case and days between infections could not be calculated. Days between infections for units B through F are displayed in Table 13.

Table 13. Days Between Infections by Location of Attribution.

	Days Between Infections		
Unit	Average	Median	Range
B	45.0	15.0	11 – 109
C	54.1	50.0	1 – 95
D	46.9	37.0	3 – 192
E	28.3	28.5	13 – 43
F	26.7	22.0	4 – 87

Of the 48 primary HA-CDI cases that occurred during the period of study, 40 (83.3%) had at least one plausible direct or indirect exposure preceding their first positive test. Two recurrent infections during the period of study have been excluded. Three of the eight patients with no plausible exposure were the first three HA-CDI identified in the period of study, for which there was no or limited data available for potential exposures.

There was a total of 23 plausible, direct exposures. Seventeen patients had at least one direct exposure, five of which had multiple direct exposures. Thirteen direct exposures occurred during the admission in which the exposed patient was diagnosed with CDI. Eleven direct exposures occurred during a previous admission.

Indirect exposures, up to eight weeks after the exposing patients date of infection, occurred often. There was a total of 105 plausible, indirect exposures of 36 patients identified. Twenty-six indirect exposures of 15 patients occurred within two weeks of the exposing patient's date of

infection. An additional 21 patients had at least one indirect exposure up to the maximum infectious period of the exposing patient.

Each patient's most plausible exposure was established into an infection network. The network revealed six clusters of transmission, displayed in Figure 3. In an effort to connect as many clusters as possible, additional plausible exposures were explored beyond the most plausible exposure allowing for the identification of two separate transmission pathways over the period of study, Cluster A and Cluster B. No plausible connections were identified between the two pathways. A cluster map of all plausible exposures is available in Appendix A, Figure 5. The results of bed and contact tracing may not indicate true transmission pathways and require further genomic study to determine the relatedness of cases.

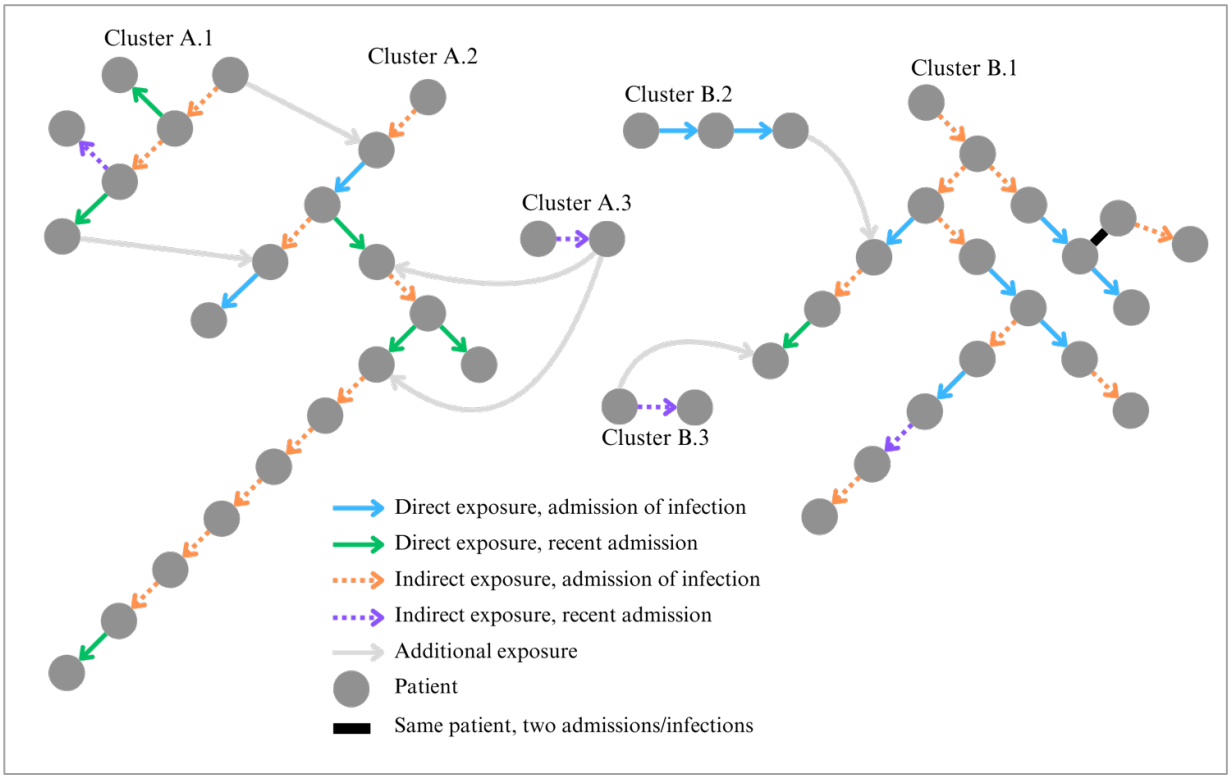

Figure 3. Most Plausible Exposures and Transmission Pathways.

Note. Arrows point from the exposing patient to the exposed patient. The proximity of circles does not represent the proximity of patient location or a measure of time.

Incubation periods were calculated for all most plausible exposures. Incubation periods for direct exposures ranged from one to 82 days (median, 5; average, 19.1; SD, 25.1). Incubation periods for indirect exposures ranged from one to 50 days (median 5; average 7.7; SD, 10.2). All but eight (20%) most plausible exposures occurred on the same unit that was identified as the exposed patient's location of attribution. Ten (25%) most plausible exposures occurred in directly neighboring rooms, with the exposing patient housed across the hall or next door to the exposed patient.

Nine rooms were implicated as the location of attribution for more than one patient. Eight rooms had two infections, while one room had three infections accounting for ten potential exposures related to occupation of a contaminated room. However, only one potential exposure was deemed plausible. All other exposures occurred beyond the maximum eight-week infectious period and all patients had at least one other plausible exposure. Although these exposures were not deemed plausible by measure of patient infectious period, five exposures occurred within the maximum *C. difficile* spore environmental survival period of five months from exposing patient discharge. This indicates that infection due to environmental contamination from the previous patient was possible in these cases. Across all plausible exposures, only three indirect exposures occurred in the same room, however, in two of those cases, the room where the patient was exposed was not the same room that was implicated as that patient's location of attribution.

CDI patients moved rooms often during the period of study. Across 49 admissions where a patient was identified with HA-CDI, sixteen (32.7%) patients were transferred at some point following their positive test. Thirteen patients were transferred once, two were transferred twice,

and one was transferred three times, for a total of twenty transfers. Sixteen transfers were to a different unit and four transfers were to a different room on the same unit. Figure 4 shows HA-CDI patient movement between units following CDI diagnosis. Medical necessity was obvious for many of the unit transfers, as thirteen (81.3%) unit transfers occurred between the ICU and other medical units, while room transfers less often had clear necessity. Appendix A, Figure 6 shows a full timeline of all HA-CDI patient room locations, before and after date of infection, across the 15-month study period.

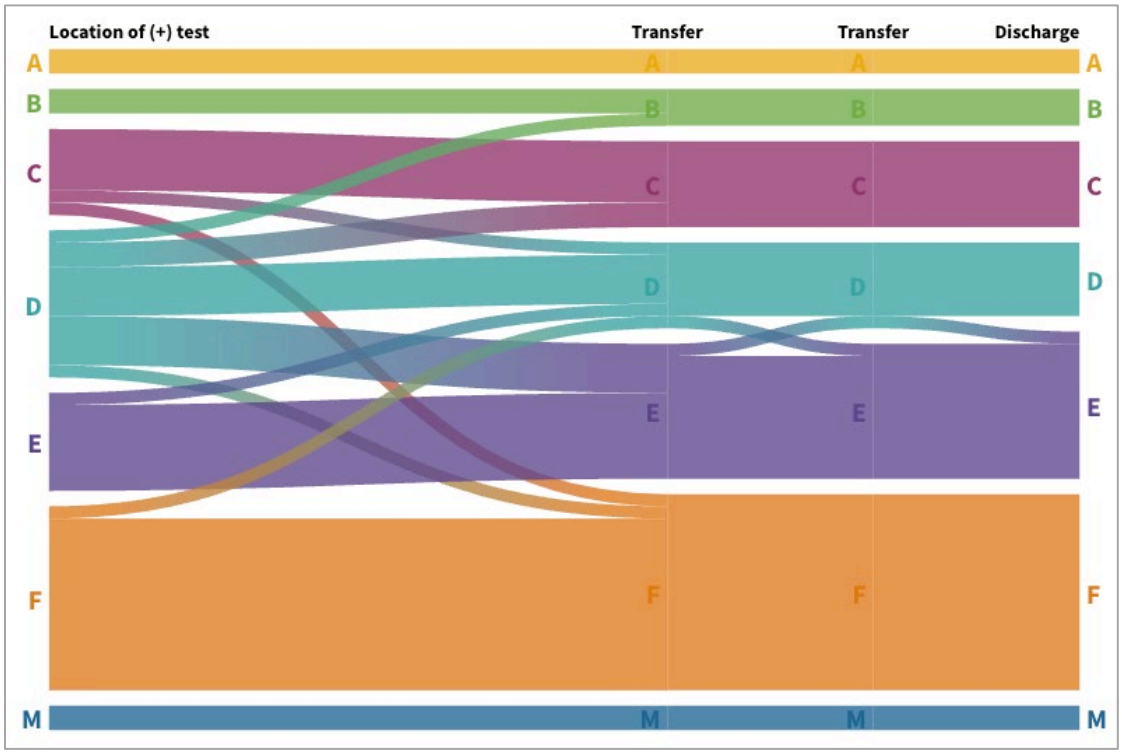

Figure 4. Patient Transfers Following CDI Diagnosis.

Note. This figure is not time-bound and shows all HA-CDI patient transfers that occurred during the period of study, after diagnosis with CDI.

Regardless of medical necessity, CDI patients who were transferred after diagnosis frequently exposed patients on more than one unit. Of the thirteen patients who were transferred

to a different unit following their date of infection, eleven (84.6%) were identified as a plausible exposure to at least one patient on at least one unit outside of the unit on which they were diagnosed with CDI. Three patients who only had a room transfer and were not transferred to other units were not identified as exposing patients.

Eight patients had no identified exposures during the period of study, three of whom were the first three CDI patients identified during the period of study, and therefore had limited exposure data. Of the remaining five patients, three had an indirect exposure to another HA-CDI patient beyond the plausible infectious period, but within the maximum spore environmental survival period. Two patients had no exposures at any time. The two patients with no identified exposure at the facility of study had been recently hospitalized at another facility.

4.0 Discussion

Risk factors for *C. difficile* are well described in the literature, including patient age, history of contact with the medical system, as well as several medications, treatments, and conditions. However, characterization of *C. difficile* in a specific medical facility may provide valuable insights to increase the accuracy and effectiveness of interventions to prevent infection.

In this study, half of all HA-CDI patients were age 65 or older, with an average patient age of 64. The proportion of patients older than 65 is lower than that typically reported, as two-thirds of all reported HA-CDI cases and upwards of 80 percent of all CDI cases occur in people aged 65 and older (Asempa & Nicolau, 2017; CDC, 2013). It is unknown whether this difference reflects the overall patient population at this facility, but this may indicate an increased risk of HA-CDI in younger individuals in this facility.

Although patients were younger than expected, age-comorbidity index scores were unexpectedly high, with an average age-comorbidity index of six. When compared to one study of 182 patients, analyzing comorbidities among those with recurrent CDI, the patient population of this study had a 36.5 percent higher mean age-comorbidity index score, despite similar average age and the presumption that those with recurrent CDI may have significant comorbidities beyond those found in patients with only a primary infection (Berenson et al., 2023). Compared to a second study of 200 HA-CDI patients, aimed at describing incidence and outcomes of HA-CDI at a major healthcare center in the US, the patient population of this study had a 5.1 percent higher mean age-comorbidity score, also with a similar average patient age (Karaoui et al., 2020). These differences may reflect high rates of comorbidities among HA-CDI patients overall, even when compared to

those with recurrent CDI, but may also reflect notably high rates of comorbidities among HA-CDI patients in this facility.

The high number of infections in female patients and differences between male and female HA-CDI patients, especially increased rates of toxin positivity, elevated WBC, fever, recent long-term care admission, and enteric tube insertion, may be explained by the types of inpatient care provided at this facility. The unit most impacted by HA-CDI at this facility, unit F, is a surgical oncology unit which primarily provides gynecologic oncology services to female patients. All patients in this study with malignancy as a contributing factor to their age-comorbidity score were female. Chemotherapy and other immunosuppressive treatments for cancer are a known risk-factor for CDI (Neemann & Freifeld, 2017). Additionally, oncology patients often have several other risk factors for CDI, including frequent or prolonged hospitalization, antibiotic exposure, advanced age, and use of feeding tubes.

The most frequent risk-factor exposure among HA-CDI patients was antibiotics, with 75 percent of patients receiving inpatient antibiotics during admission, preceding infection. Overall, 88 percent of patients were exposed to high-risk antibiotics, penicillins, third- and fourth-generation cephalosporins, fluoroquinolones, and clindamycin, and 78 percent were exposed to any antibiotic, as a reported home medication or inpatient, preceding their infection. While these levels of overall antibiotic exposure do not differ notably from what is reported in the literature among HA-CDI patients, antimicrobial stewardship remains to be a powerful tool in the prevention and control of *C. difficile* in the hospital setting (Brown et al., 2015; Pakyz et al., 2014). Interestingly, in a multi-level study analyzing patient- and facility-specific risk factors for HA-CDI, one of the most prominent antibiotics preceding infection was piperacillin-tazobactam (Pakyz et al., 2014). This antibiotic was noted as the most frequently prescribed inpatient antibiotic

in this study, with 40.8 percent (n=49) of patients receiving the antibiotic during their admission, preceding infection. Piperacillin-tazobactam, a penicillin and beta-lactamase inhibitor combination, is associated with a significant reduction in the diversity of the gut microbiome, which can leave patients at significant risk of CDI and other intestinal bacterial infections (Peto et al., 2024; Smits et al., 2016).

Delays in CDI testing may have contributed to inflated rates of HA-CDI in this facility. In this study, up to 14 percent of reported HA-CDI cases may have been avoidable with prompt and timely testing. In these cases, diarrhea was reported before day three of admission, when CDI becomes reportable as a hospital-associated infection, but testing was not completed until the infection was reportable (CDC, 2024). Although sample collection may have been difficult given the variability in timing of bowel movements, availability of nursing staff for collection, or diarrhea that began late on day two, many infections reported at HA-CDI were likely community-associated CDI that was identified and diagnosed late. In patients with contraindications for testing, such as fewer than three bouts of diarrhea in 24 hours, consistent use of the clinical decision support prompt should be considered to guide appropriate testing practices and reduce unnecessary testing.

Additionally, laxatives were frequently prescribed to patients who were subsequently tested for *C. difficile*, with 46 percent of patients having an open prescription for at least one laxative within the 24 hours preceding sample collection. *C. difficile* testing in patients taking laxatives is common in many facilities, with some studies suggesting that as few as 9.8 percent and as many as 44 percent of patients tested for CDI having received laxatives within the 24 hours before sample collection (Bilinskaya et al., 2018; Carter & Malani, 2019). Testing patients for CDI when there is another potential cause for diarrhea increases the risk of identifying patients

colonized with *C. difficile* as true infections, leading to unnecessary antibiotic treatment and increased reporting of hospital-associated infections to regulatory bodies (Carter & Malani, 2019; Polage et al., 2015). Of the patients who received laxatives, 43.5 percent tested positive for toxin, compared to patients who did not receive laxatives, of which 55.6 percent tested positive for toxin. Although this difference was not found to be statistically significant, it may still be an indicator of the identification of patients who are colonized with *C. difficile* and experiencing laxative-related diarrhea.

Testing negative for *C. difficile* toxin but positive by PCR is considered by some to indicate colonization with the bacteria and not true infection. This aligns with reported findings in the literature that toxin-positive patients are more likely to have unfavorable symptoms, such as fever and elevated WBC (Polage et al., 2015). Overall, in this study sample, half of HA-CDI patients were toxin positive, but symptom trends among those toxin-positive and -negative were not consistent. While those who tested toxin-positive were more likely to have record of three or more unformed stools, potentially indicating more severe diarrhea in these patients, as well as fever in combination with elevated WBC, those who tested toxin-negative had slightly higher rates of elevated WBC alone. Both groups had the same rate of fever alone and no fever or elevated WBC. However, these differences were not statistically significant. Exposure to antibiotics, which have been associated with increased risk of toxin-positivity, did not appear to increase the risk of toxin positivity in this study. Interestingly, those with lower age-comorbidity scores had higher rates of toxin positivity when compared to their counterparts with higher age-comorbidity scores, once again indicating that the at-risk population for HA-CDI in this facility may be younger and healthier than expected based on risk-factors reported in the literature. Of note, nasogastric tube insertion was found to be associated with a significantly increased risk of toxin positivity (X^2(1,

N=48) = 4.378, p = 0.036), which may indicate higher rates of true infection in these patients. High rates of toxin-positivity in these patients may be related to comorbidities and other treatments, or be an indicator of infection related to enteric tube insertion or manipulation.

The bed and contact tracing analysis revealed high rates of potential transmission between HA-CDI patients in this facility. In this study, 83.3 percent of patients had a plausible exposure to an infected patient preceding their CDI diagnosis. While genomic data is not available to validate epidemiologic findings, there is evidence of unit-based transmission based on punitive direct and indirect exposures alone. Although shared rooms were not necessarily implicated as a source of transmission in this study, several rooms were identified as the location of attribution for more than one patient. One room housed three HA-CDI patients at their time of diagnosis and preceding their infection. The second patient was admitted 52 days after the discharge of the first patient, and the third patient was admitted 136 days after the discharge of the second patient. Although these exposures occurred weeks or months apart, they both are within the maximum environmental survival period of *C. difficile* spores and may suggest lapses in terminal cleaning between patients, however, other routes of exposure are more likely (Srinivasa et al., 2019). Nearly all identified plausible exposures occurred in patients in directly neighboring or nearby rooms. The proximity of most exposures and cases on units may indicate lapses in hand hygiene, transmission-based precautions, and cleaning of equipment, floors, and shared spaces. These findings highlight the need for continued staff education on prevention and control measures and their importance for patient safety.

Additionally, bed and contact tracing revealed two clusters of transmission with seemingly no connection. While there were no connections between the clusters based on unit-based exposure, several patients in each cluster were hospitalized at the same time or shortly after the

discharge of at least one HA-CDI patient on the other cluster, who was housed on a different unit. This may indicate transmission between units by the movement of staff and equipment, unrecognized exposure in other treatment areas, or potential transmission from an unidentified or asymptomatic patient with CDI (Curry et al., 2013). Although transmission between units beyond patient transfers could not be assessed, it is possible that transmission occurred both between and within units.

4.1 Limitations

Several limitations were identified throughout this study. Firstly, as a descriptive study with no control group, there were limitations on data analysis. Comparisons were not able to be made against the general patient population at the facility of study and could only be made against findings reported in the literature. Therefore, it was not possible to determine if common characteristics or risk factors identified in HA-CDI patients differed significantly from patients at the facility of study that did not have HA-CDI. Additionally, this was a single center study with a small sample size, increasing the risk that any findings occurred by chance and are not significant.

This study was retrospective and relied on clinical chart review, making it highly reliant on thorough clinical chart reporting by clinical staff and accurate data collection. Although every effort was taken to ensure thorough data collection, there is an increased likelihood that at least some findings are related to inaccurate or incomplete clinical charting, or inaccurate data collection, and not due to true clinical or epidemiological findings.

Bed and contact tracing was limited by several unique factors. Firstly, although records of patient movement within the facility was readily available and accurate, it was not possible to

assess the movement of healthcare staff or equipment between patient rooms. This limited the scope of exposure assessment related to contaminated hands, equipment, or the environment beyond individual rooms, all of which are a known source of C. *difficile* spore contamination and transmission (Martin et al., 2016; Srinivasa et al., 2019). Secondly, data was not available for exposures that may have occurred at an outside facility or during an admission prior to the period of study. Thirdly, identification of plausible exposures through epidemiologic tracing does not necessarily indicate true exposure or transmission. Without the use of genomic data to assess the relatedness of infections, this study is unable to further validate or quantify nosocomial transmission (García-Fernández et al., 2019).

Overall, medical necessity of testing, treatments, or other clinical decisions could not be assessed. Clinical charting offers limited information related to specific medical decisions involved in each patient's care, especially exposure to risk factors, *C. difficile* testing, or other variables studied. Identification of areas for potential quality improvement related to HA-CDI in this study do not necessarily indicate lapses in judgement, lack of adherence to or knowledge of protocol, or reduced care quality.

4.2 Future Directions

Further studies are required to validate the findings of this study, especially to assess these findings in comparison to the greater patient population or community-acquired CDI patients in this facility. Comparison against a control group is vital to assess if the patient characteristics, risk factors, and exposures identified among HA-CDI patients in this study are significant. The most significant finding in this study, the association between enteric tube insertion and toxin positivity,

requires further study to determine causality. Additionally, genomic analysis of *C. difficile* bacteria isolated from each HA-CDI patient is valuable to determining the genetic relatedness of each infection, and verifying if punitive, plausible transmissions identified in this study are true transmissions. Finally, the findings from this and future studies may aid in the development of infection prevention and antimicrobial stewardship measures or criteria to identify patients who may be at an increased risk for HA-CDI to limit further exposure to medications or treatments that may further increase the risk of CDI.

5.0 Conclusions

This study identified several patient- and facility-specific factors that may have contributed to HA-CDI cases, as well as several findings that diverge from that presented in the literature. On average, HA-CDI patients were found to be younger and with more severe comorbidities than expected. The HA-CDI patient population at this facility had a lower proportion of patients over the age of 65 than is reported by the CDC and a higher average age-comorbidity score than that reported in studies of HA-CDI and recurrent CDI patients (Berenson et al., 2023; CDC, 2013; Karaoui et al., 2020). Patients had notable exposure to antibiotics preceding infection, particularly piperacillin-tazobactam. Findings highlighted a significant association between enteric tube insertion and toxin positivity, which may be indicative of other comorbidities and risk-factors in these patients or lapses in adherence to infection prevention protocol during tube insertion and manipulation, and requires further investigation (O'Keefe, 2010; Wijarnpreecha et al., 2018). Overwhelmingly, HA-CDI patients were female. It is unknown if demographic differences represent the general patient population of this facility, or if high infection rates in female patients represents increased risk among the oncology patient population.

In addition to patient-specific findings, there were several identified avenues for quality improvement and infection prevention. Firstly, to reduce the number of HA-CDI cases that may have been more appropriately classified as community-acquired, it is important to continue to encourage testing as soon as possible in the first two days of admission, particularly when a patient reports diarrhea on admission. Secondly, to guarantee the appropriateness of testing at the onset of diarrhea, ensure that samples are not collected when other diarrhea inducing medications or conditions are present, particularly laxative medications, or that the impact of diarrhea inducing

medications are adequately assessed before testing is ordered. Additionally, ensuring that all tests are accompanied by a response to the clinical decision support prompt may improve testing appropriateness. Finally, due to findings that indicate probable facility-based transmission without the indication of shared rooms as a source, the infection prevention team should continue to advocate for and empower health care workers and staff to perform adequate hand hygiene, adhere to transmission-based precautions, and clean shared equipment between uses.

The implications of this study primarily include recommendations for interventions that may reduce the incidence of HA-CDI in this facility by identifying at-risk patients, recognizing medications and treatments which may increase risk of infection, improving testing protocol adherence and timely testing, and preventing transmission of *C. difficile* in the facility. Developing targeted interventions using facility-specific data may increase the effectiveness of prevention and control initiatives to aid in the reduction of HA-CDI.

Appendix A

Table 14. Age-Comorbidity Index Qualifying Conditions and Score.

Charleson Comorbidity Index Comorbid Condition	Qualifying Diagnoses or Conditions
1 POINT	
Myocardial Infarction	• History of one or more MI(s)
Congestive Heart Failure	• Any heart failure • Exertional or paroxysmal nocturnal dyspnea
Peripheral Vascular Disease	• Peripheral vascular disease • Peripheral Artery disease • Intermittent claudication or those who had a bypass for arterial insufficiency • Gangrene • Acute arterial insufficiency • Untreated thoracic or abdominal aneurysm (6 cm or more)
Cerebrovascular Disease	• History of a cerebrovascular accident with minor or no residua and transient ischemic attacks • Transient Ischemic attack (TIA) & stroke • Aneurysms • Arteriovenous malformations (AVM) • Arteriovenous fistula (AVF) • Cerebral cavernous malformations (CCM) • Carotid-Cavernous Fistula • Carotid Stenosis
Dementia	• Chronic cognitive deficits
Chronic Pulmonary Disease	• COPD • Chronic bronchitis • Chronic Hypercarbic Respiratory Failure
Rheumatic or Connective Tissue Diseases *Those identified in the study population*	• Systemic lupus erythematous • Fibromyalgia • Polymyositis • Mixed connective tissue disease • Polymyalgia rheumatica • Rheumatoid arthritis • Ehlers Danlos Syndrome • Multiple Sclerosis
Peptic Ulcer Disease	• Required treatment for ulcer disease, including those who have bled from ulcers
Mild Liver Disease	• Cirrhosis without portal hypertension or chronic hepatitis • Untreated hepatitis w/o cirrhosis
Diabetes	• Treated with insulin or oral hypoglycemics, but not diet alone *Diet Controlled = 0 Points*

2 POINTS	
Hemi- or Paraplegia	• Dense hemiplegia or paraplegia, whether it occurred as a result of a cerebrovascular accident or other condition • One sided weakness post CVA
Moderate or Severe Renal Disease	• Dialysis • History of kidney transplant • Uremia • Moderate: Serum creatinine >3 mg% *Transient/acute increases in creatinine not counted*
Uncontrolled Diabetes	• Diabetes with Organ Damage • Retinopathy, neuropathy, or nephropathy • Kidney failure or dialysis
Any Malignant Tumor	• Non-metastatic cancers
Leukemia	• Acute and chronic myelogenous leukemia • Acute and chronic lymphocytic leukemia • Polycythemia vera
Lymphoma	• Hodgkin's • Lymphosarcoma • Waldenstrom's macroglobulinemia • Myeloma • Other lymphomas
3 POINTS	
Moderate or Severe Liver Disease	• Cirrhosis • Portal hypertension • History of variceal bleeding • Moderate: cirrhosis with portal hypertension, but without bleeding
6 POINTS	
Metastatic Solid Tumor	• Designated stage 4 or explicitly stated metastases of solid tumor to other organ(s)
AIDS	• AIDS diagnosis

Note. Adapted from *A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation*. Charlson et al., 1987.

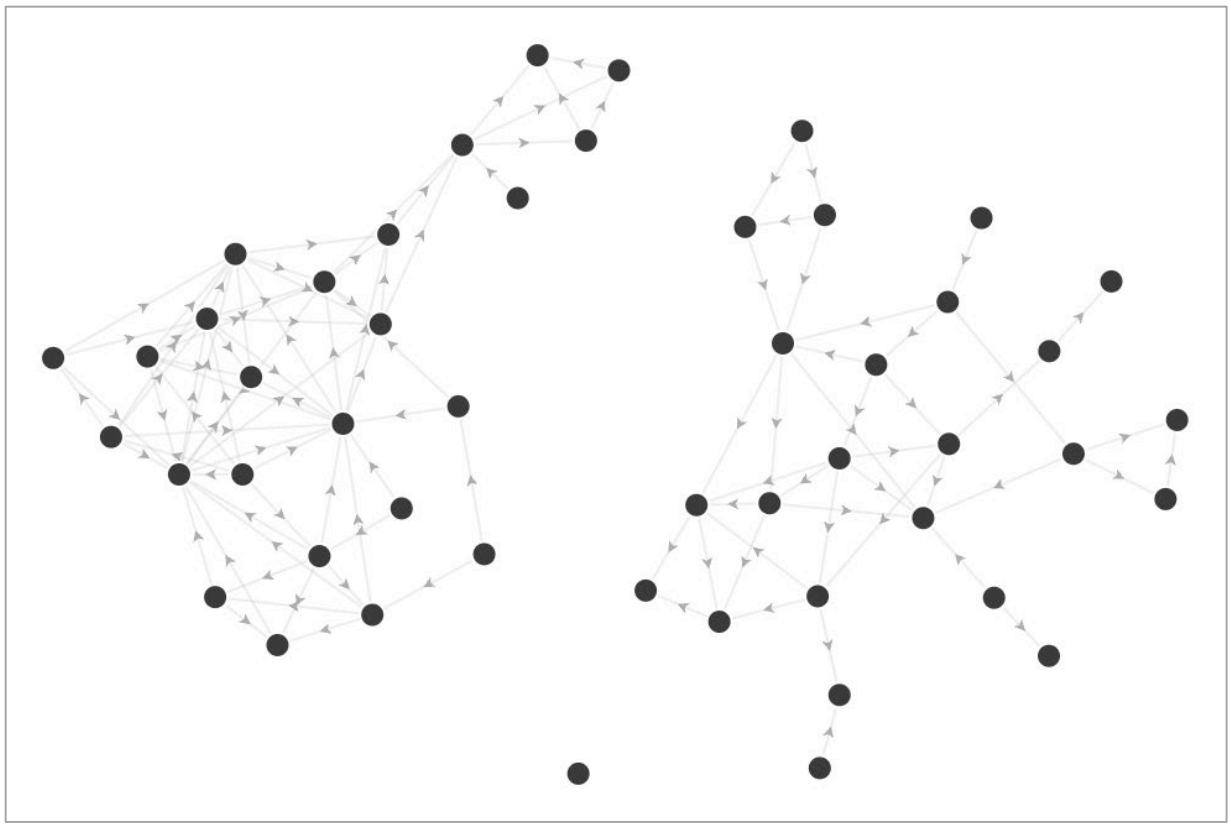

Figure 5. Exposure Network of All Plausible Exposures.

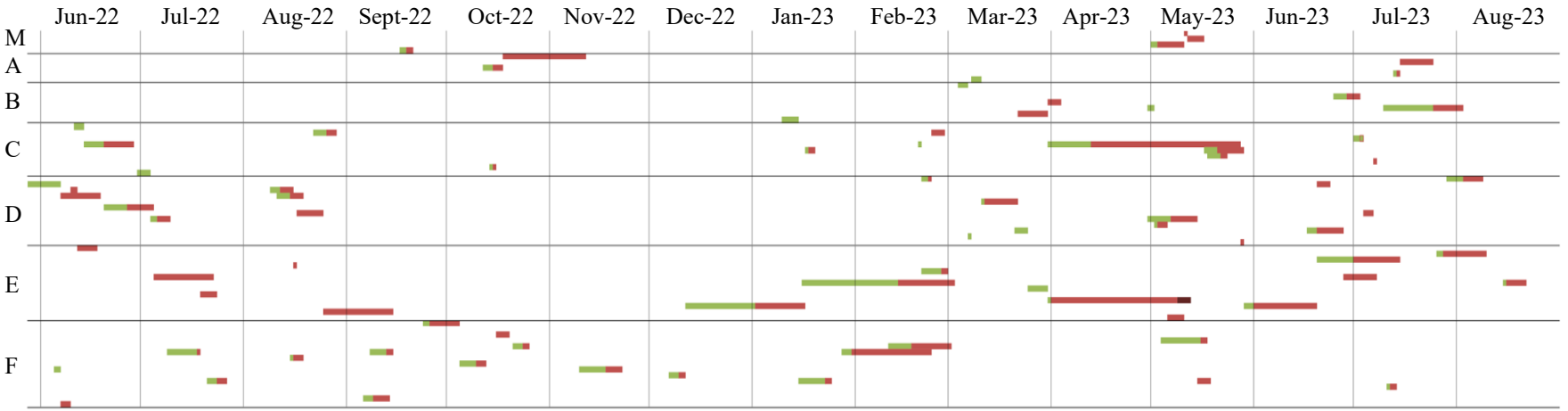

Figure 6. Timeline and Locations of All HA-CDI Cases.

Note. This timeline displays HA-CDI patient hospitalizations over time and throughout the facility of study. Colored space indicates that a room was occupied by a HA-CDI patient during that time during their admission of infection. Green indicates room occupation prior to date of infection. Red indicates room occupation on or after date of infection. Dark red indicates room occupation by the same patient during the same hospitalization after a second positive test. Specific dates and room locations have been removed. Deidentified units are labelled, and rooms locations occur in sequential order, although not every room location in the facility is included.

Bibliography

Asempa, T. E., & Nicolau, D. P. (2017). Clostridium difficile infection in the elderly: An update on management. *Clinical Interventions in Aging*, *12*, 1799–1809. https://doi.org/10.2147/CIA.S149089

Banach, D. B., Bearman, G., Barnden, M., Hanrahan, J. A., Leekha, S., Morgan, D. J., Murthy, R., Munoz-Price, L. S., Sullivan, K. V., Popovich, K. J., & Wiemken, T. L. (2018). Duration of Contact Precautions for Acute-Care Settings. *Infection Control & Hospital Epidemiology*, *39*(2), 127–144. https://doi.org/10.1017/ice.2017.245

Bella, S. D., Ascenzi, P., Siarakas, S., Petrosillo, N., & Masi, A. di. (2016). Clostridium difficile Toxins A and B: Insights into Pathogenic Properties and Extraintestinal Effects. *Toxins*, *8*(5). https://doi.org/10.3390/toxins8050134

Berenson, C. S., Lashner, B., Korman, L. Y., Hohmann, E., Deshpande, A., Louie, T. J., Sims, M., Pardi, D., Kraft, C. S., Wang, E. E. L., Cohen, S. H., Feuerstadt, P., Oneto, C., Misra, B., Pullman, J., De, A., Memisoglu, A., Lombardi, D. A., Hasson, B. R., … Lee, C. H. (2023). Prevalence of Comorbid Factors in Patients With Recurrent Clostridioides difficile Infection in ECOSPOR III, a Randomized Trial of an Oral Microbiota–Based Therapeutic. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, *77*(11), 1504–1510. https://doi.org/10.1093/cid/ciad448

Bilinskaya, A., Goodlet, K. J., & Nailor, M. D. (2018). Evaluation of a best practice alert to reduce unnecessary Clostridium difficile testing following receipt of a laxative. *Diagnostic Microbiology and Infectious Disease*, *92*(1), 50–55. https://doi.org/10.1016/j.diagmicrobio.2018.04.009

Boustany, A., Onwuzo, S., Zeid, H. K. A., Almomani, A., & Asaad, I. (2023). Antidepressant Medications are Associated with Increased Risk of Hospital-Acquired Clostridioides difficile Infection: A Population-Based Study. *Arquivos de Gastroenterologia*, *60*(3), 309–314. https://doi.org/10.1590/s0004-2803.230302023-21

Bowling, J. E. (2018). *Clostridium difficile Infection and Pseudomembranous Colitis*. APIC Text. https://text.apic.org/toc/healthcare-associated-pathogens-and-diseases/clostridium-difficile-infection-and-pseudomembranous-colitis

Brown, K., Valenta, K., Fisman, D., Simor, A., & Daneman, N. (2015). Hospital Ward Antibiotic Prescribing and the Risks of Clostridium difficile Infection. *JAMA Internal Medicine*, *175*(4), 626–633. https://doi.org/10.1001/jamainternmed.2014.8273

Carter, K. A., & Malani, A. N. (2019). Laxative use and testing for *Clostridium difficile* in hospitalized adults: An opportunity to improve diagnostic stewardship. *American Journal of Infection Control*, *47*(2), 170–174. https://doi.org/10.1016/j.ajic.2018.08.008

CDC. (2013). *Antibiotic resistance threats in the United States, 2013*. Centers for Disease Control and Prevention (U.S.). https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf

CDC. (2019). *Antibiotic resistance threats in the United States, 2019*. Centers for Disease Control and Prevention (U.S.). https://doi.org/10.15620/cdc:82532

CDC. (2023a). *2023 NHSN Gastrointestinal System Infection (GI) Checklist*.

CDC. (2023b, April 26). *About NHSN*. https://www.cdc.gov/nhsn/about-nhsn/index.html

CDC. (2023c, June 28). *Clostridioides difficile Infection (CDI) Tracking*. https://www.cdc.gov/hai/eip/cdiff-tracking.html

CDC. (2024). *Identifying Healthcare-associated Infections (HAI) for NHSN Surviellance*. CDC.

Charlson, M., Pompei, P., Ales, K. L., & MacKenzie, C. R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *Journal of Chronic Diseases*, *40*(5), 373–383. https://doi.org/10.1016/0021-9681(87)90171-8

Charlson, M., Szatrowski, T. P., Peterson, J., & Gold, J. (1994). Validation of a combined comorbidity index. *Journal of Clinical Epidemiology*, *47*(11), 1245–1251. https://doi.org/10.1016/0895-4356(94)90129-5

Curry, S. R., Muto, C. A., Schlackman, J. L., Pasculle, A. W., Shutt, K. A., Marsh, J. W., & Harrison, L. H. (2013). Use of Multilocus Variable Number of Tandem Repeats Analysis Genotyping to Determine the Role of Asymptomatic Carriers in Clostridium difficile Transmission. *Clinical Infectious Diseases*, *57*(8), 1094–1102. https://doi.org/10.1093/cid/cit475

Dalton, B. R., Lye-Maccannell, T., Henderson, E. A., Maccannell, D. R., & Louie, T. J. (2009). Proton pump inhibitors increase significantly the risk of Clostridium difficile infection in a low-endemicity, non-outbreak hospital setting. *Alimentary Pharmacology & Therapeutics*, *29*(6), 626–634. https://doi.org/10.1111/j.1365-2036.2008.03924.x

Deshpande, A., Pant, C., Pasupuleti, V., Rolston, D. D. K., Jain, A., Deshpande, N., Thota, P., Sferra, T. J., & Hernandez, A. V. (2012). Association Between Proton Pump Inhibitor Therapy and Clostridium difficile Infection in a Meta-Analysis. *Clinical Gastroenterology and Hepatology*, *10*(3), 225–233. https://doi.org/10.1016/j.cgh.2011.09.030

Feuerstadt, P., Boules, M., Stong, L., Dahdal, D. N., Sacks, N. C., Lang, K., & Nelson, W. W. (2021). Clinical complications in patients with primary and recurrent Clostridioides

difficile infection: A real-world data analysis. *SAGE Open Medicine*, *9*. https://doi.org/10.1177/2050312120986733

García-Fernández, S., Frentrup, M., Steglich, M., Gonzaga, A., Cobo, M., López-Fresneña, N., Cobo, J., Morosini, M.-I., Cantón, R., del Campo, R., & Nübel, U. (2019). Whole-genome sequencing reveals nosocomial Clostridioides difficile transmission and a previously unsuspected epidemic scenario. *Scientific Reports*, *9*(1), 6959. https://doi.org/10.1038/s41598-019-43464-4

Goodman, K. E., Cosgrove, S. E., Pineles, L., Magder, L. S., Anderson, D. J., Dodds Ashley, E., Polk, R. E., Quan, H., Trick, W. E., Woeltje, K. F., Leekha, S., & Harris, A. D. (2020). Significant Regional Differences in Antibiotic Use Across 576 US Hospitals and 11 701 326 Adult Admissions, 2016–2017. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, *73*(2), 213–222. https://doi.org/10.1093/cid/ciaa570

Gupta, A., Savanti, F. N. U., Singh, B., Sachdev, P., Raj, D., Garg, I., Aruwani, S. K., Shaukat, F., Gupta, A., Savanti, F. N. U., Singh, B., Sachdev, P., Raj, D., Garg, I., Aruwani, S. K., & Shaukat, F. (2021). Risk Factors Associated With Clostridium difficile-Associated Diarrhea. *Cureus*, *13*(9). https://doi.org/10.7759/cureus.18115

Jump, R. L. P., & Donskey, C. J. (2015). Clostridium difficile in the Long-Term Care Facility: Prevention and Management. *Current Geriatrics Reports*, *4*(1), 60–69. https://doi.org/10.1007/s13670-014-0108-3

Karaoui, W. R., Rustam, L. B. O., Bou Daher, H., Rimmani, H. H., Rasheed, S. S., Matar, G. M., Mahfouz, R., Araj, G. F., Zahreddine, N., Kanj, S. S., Berger, F. K., Gärtner, B., El Sabbagh, R., & Sharara, A. I. (2020). Incidence, outcome, and risk factors for recurrence of nosocomial *Clostridioides difficile* infection in adults: A prospective cohort study. *Journal of Infection and Public Health*, *13*(4), 485–490. https://doi.org/10.1016/j.jiph.2019.11.005

Leffler, D. A., & Lamont, J. T. (2015). Clostridium difficile Infection. *New England Journal of Medicine*, *372*(16), 1539–1548. https://doi.org/10.1056/NEJMra1403772

Mada, P. K., & Alam, M. U. (2023). *Clostridioides difficile Infection*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK431054/

Marsh, J. W., Arora, R., Schlackman, J. L., Shutt, K. A., Curry, S. R., & Harrison, L. H. (2020). Association of Relapse of Clostridium difficile Disease with BI/NAP1/027. *Journal of Clinical Microbiology*, *50*(12), 4078–4082. https://doi.org/10.1128/jcm.02291-12

Martin, J. S. H., Monaghan, T. M., & Wilcox, M. H. (2016). Clostridium difficile infection: Epidemiology, diagnosis and understanding transmission. *Nature Reviews Gastroenterology & Hepatology*, *13*(4), Article 4. https://doi.org/10.1038/nrgastro.2016.25

McDonald, L. C., Gerding, D. N., Johnson, S., Bakken, J. S., Carroll, K. C., Coffin, S. E., Dubberke, E. R., Garey, K. W., Gould, C. V., Kelly, C., Loo, V., Shaklee Sammons, J., Sandora, T. J., & Wilcox, M. H. (2018). Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clinical Infectious Diseases*, *66*(7), e1–e48. https://doi.org/10.1093/cid/cix1085

Mora, A. L., Salazar, M., Pablo-Caeiro, J., Frost, C. P., Yadav, Y., DuPont, H. L., & Garey, K. W. (2012). Moderate to High Use of Opioid Analgesics Are Associated With an Increased Risk of Clostridium difficile Infection. *The American Journal of the Medical Sciences*, *343*(4), 277–280. https://doi.org/10.1097/MAJ.0b013e31822f42eb

Neemann, K., & Freifeld, A. (2017). Clostridium difficile–Associated Diarrhea in the Oncology Patient. *Journal of Oncology Practice*, *13*(1), 25–30. https://doi.org/10.1200/JOP.2016.018614

O'Connor, J. R., Johnson, S., & Gerding, D. N. (2009). Clostridium difficile infection caused by the epidemic BI/NAP1/027 strain. *Gastroenterology*, *136*(6), 1913–1924. https://doi.org/10.1053/j.gastro.2009.02.073

O'Keefe, S. J. (2010). Tube feeding, the microbiota, and Clostridium difficile infection. *World Journal of Gastroenterology : WJG*, *16*(2), 139–142. https://doi.org/10.3748/wjg.v16.i2.139

Pakyz, A. L., Jawahar, R., Wang, Q., & Harpe, S. E. (2014). Medication risk factors associated with healthcare-associated Clostridium difficile infection: A multilevel model case–control study among 64 US academic medical centres. *Journal of Antimicrobial Chemotherapy*, *69*(4), 1127–1131. https://doi.org/10.1093/jac/dkt489

Paredes-Sabja, D., Shen, A., & Sorg, J. A. (2014). Clostridium difficile spore biology: Sporulation, germination, and spore structural proteins. *Trends in Microbiology*, *22*(7), 406–416. https://doi.org/10.1016/j.tim.2014.04.003

Patil, R., & Blankenship, L. (2013). Proton Pump Inhibitors and Clostridium Difficile Infection: Are We Propagating an Already Rapidly Growing Healthcare Problem? *Gastroenterology Research*, *6*(5), 171–173. https://doi.org/10.4021/gr575w

Peto, L., Fawcett, N., Kamfose, M. M., Scarborough, C., Peniket, A., Danby, R., Peto, T. E., Crook, D. W., Llewelyn, M. J., & Walker, A. S. (2024). *The impact of different antimicrobial exposures on the gut microbiome in the ARMORD observational study* (p. 2024.03.06.24303874). medRxiv. https://doi.org/10.1101/2024.03.06.24303874

Polage, C. R., Gyorke, C. E., Kennedy, M. A., Leslie, J. L., Chin, D. L., Wang, S., Nguyen, H. H., Huang, B., Tang, Y.-W., Lee, L. W., Kim, K., Taylor, S., Romano, P. S., Panacek, E. A., Goodell, P. B., Solnick, J. V., & Cohen, S. H. (2015). Overdiagnosis of Clostridium

difficile Infection in the Molecular Test Era. *JAMA Internal Medicine*, *175*(11), 1792–1801. https://doi.org/10.1001/jamainternmed.2015.4114

Prommik, P., Tootsi, K., Saluse, T., Strauss, E., Kolk, H., & Märtson, A. (2022). Simple Excel and ICD-10 based dataset calculator for the Charlson and Elixhauser comorbidity indices. *BMC Medical Research Methodology*, *22*(1), 4. https://doi.org/10.1186/s12874-021-01492-7

Smits, W. K., Lyras, D., Lacy, D. B., Wilcox, M. H., & Kuijper, E. J. (2016). Clostridium difficile infection. *Nature Reviews Disease Primers*, *2*(1), 16020. https://doi.org/10.1038/nrdp.2016.20

Srinivasa, V. R., Hariri, R., Frank, L. R., Kingsley, L., Magee, E., Pokrywka, M., & Yassin, M. H. (2019). Hospital-associated Clostridium difficile infection and reservoirs within the hospital environment. *American Journal of Infection Control*, *47*(7), 780–785. https://doi.org/10.1016/j.ajic.2018.12.013

UPMC. (2023). *C. difficile Testing Frequently Asked Questions*. UPMC.

Walker, A. S., Eyre, D. W., Wyllie, D. H., Dingle, K. E., Harding, R. M., O'Connor, L., Griffiths, D., Vaughan, A., Finney, J., Wilcox, M. H., Crook, D. W., & Peto, T. E. A. (2012). Characterisation of Clostridium difficile Hospital Ward–Based Transmission Using Extensive Epidemiological Data and Molecular Typing. *PLOS Medicine*, *9*(2), e1001172. https://doi.org/10.1371/journal.pmed.1001172

Wijarnpreecha, K., Sornprom, S., Thongprayoon, C., Phatharacharukul, P., & Cheungpasitporn, W. (2018). Nasogastric tube and outcomes of Clostridium difficile infection: A systematic review and meta-analysis. *Journal of Evidence-Based Medicine*, *11*(1), 40–45. https://doi.org/10.1111/jebm.12288

Wijarnpreecha, K., Sornprom, S., Thongprayoon, C., Phatharacharukul, P., Cheungpasitporn, W., & Nakkala, K. (2016). The risk of Clostridium difficile associated diarrhea in nasogastric tube insertion: A systematic review and meta-analysis. *Digestive and Liver Disease*, *48*(5), 468–472. https://doi.org/10.1016/j.dld.2016.01.012

Zhu, D., Sorg, J. A., & Sun, X. (2018). Clostridioides difficile Biology: Sporulation, Germination, and Corresponding Therapies for C. difficile Infection. *Frontiers in Cellular and Infection Microbiology*, *8*. https://www.frontiersin.org/articles/10.3389/fcimb.2018.00029