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Relationship Between Clostridium difficile Testing Method, Antibiotic Treatment, and Clinical Symptoms

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This is to certify that the doctoral study by

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has been found to be complete and satisfactory in all respects,
and that any and all revisions required by
the review committee have been made.

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Walden University
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Abstract

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MBA-HCM, University of Phoenix, 2007

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Doctoral Study Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Public Health

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Abstract

Clostridium difficile (*C. difficile*) infection is a leading cause of morbidity and mortality in the United States, making the infection a top public health priority. Early and accurate identification of disease is a critical factor in successful management, including clinical symptomology. The testing methods for *C. difficile* have improved in efficiency and sensitivity, which potentially causes over- or underprescribing behavior. Guided by the symbolic theory, the purpose of this study was to examine the association between *C. difficile* testing method by case year (2015 and 2018) and antibiotic treatment with the potential moderation of clinical symptoms. The secondary correlational analysis included patients admitted to a large suburban hospital with a positive test for *C. difficile* in 2015 and 2018 ($N = 509$). The relationship between the study predictor (case year), dependent variable (antibiotic treatment), and moderator (symptom) was analyzed using binomial logistic regression. Antibiotics showed a significant association with the case year ($OR = 1.889$) and no significant moderation with the addition of symptoms ($OR = 1.303$). Health care providers may find these findings useful in standardizing treatment of *C. difficile* through the implementation of additions to clinical algorithms, resulting in positive social change. Increased education, and policy, through antibiotic-resistant organism reduction, increased antimicrobial stewardship, and increased patient safety, may have social implications.

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Dedication

First, I would like to dedicate this project to my mother, Jackie, without whom I could not have spent the hours necessary to accomplish my goal. I thank her for being the other parent for my kiddos and for helping me work through the frustration, happiness, and chaos of this journey. I also want to thank my children, Isabelle and Leo, who have had to deal with my half presence or nonpresence on more than one occasion over the last 3 years. My twin sister, Ann, who has been my constant confidante and competitor, making me strive for that next goal. Thanks to my brother-in-law, Mike, who has stepped in repeatedly with taking the kiddos to allow for quiet time.

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Section 1: Foundation of the Study and Literature Review

Clostridium difficile (*C. difficile*) is a spore-forming bacillus that is acquired through orally ingesting the organism in the environment (Jump, 2013). The human intestinal system protects most people from the organism colonizing (Lawley & Walker, 2013). Individuals who have had exposure to antibiotics such as Vancomycin are at risk for *C. difficile* infection due to the changes in the microbiota in the intestines producing symptomatic diarrhea (Isaac et al., 2017). The incidence of *C. difficile* in the United States among patients at least 1 year of age was 130 per 100,000 or 15,512 cases in 2017 (Centers for Disease Control and Prevention [CDC], 2018). More than 50% (7,973) were hospital-associated due to a positive test at least 4 days after admission to a health care facility (CDC, 2019c, 2019d, 2020). The method used to identify *C. difficile* includes different testing methods with the result guiding, in part, the patient's course of treatment (McDonald et al., 2018). Diagnostic stewardship is critical to the management, identification, and appropriate treatment of *C. difficile* infection (Rock et al., 2018).

Background

Nucleic Acid Amplification Test

The nucleic acid amplification test (NAAT) is a sensitive and rapid test used to determine the presence or absence of *C. difficile* in a stool sample (Truong et al., 2017). The NAAT alone cannot distinguish between toxin negative and toxin positive *C. difficile* (Truong et al., 2017). The guidelines for testing indicate that NAAT is sufficient for diagnosis, but only in the presence of symptoms such as three or more liquid stools within 24 hours or fever or an increase in serum creatinine (McDonald et al., 2018). The

NAAT is not appropriate if other reasons for diarrhea have not been ruled out, such as the use of laxatives or recent colon surgery (McDonald et al., 2018). The use of the NAAT preliminarily identifies the possibility of *C. difficile* as one cause of diarrhea. However, it does not provide enough clinical evidence because the confirmatory toxin is not able to be identified with the NAAT (Quest Diagnostics, 2017).

Two-Step Testing

The two-step testing method was developed to identify stool specimens that were toxin negative and required further testing to rule out potential causes for diarrhea other than *C. difficile* (McDonald et al., 2018; Truong et al., 2017). The two-step method includes an antigen (glutamate dehydrogenase [GDH]) test and a toxin test to identify the presence of toxigenic *C. difficile* (Quest Diagnostics, 2017). If both tests are positive, then the sample is considered positive for toxigenic *C. difficile*, and the physician should treat accordingly (Quest Diagnostics, 2017). If the GDH is positive and the toxin is negative, then a tiebreaker (NAAT) must be completed to confirm the result (Quest Diagnostics, 2017). The result of the tiebreaker is used for treatment and determines the most effective patient treatment strategy (Quest Diagnostics, 2017) . If the GDH and toxin are negative, then the result is negative (Quest Diagnostics, 2017). The result used for treatment and reporting is the final answer from either the NAAT or the toxin from the two-step method.

Reasons for Change

The reasons for the change from a two-step algorithm to a single NAAT are twofold. First is the consideration of turnaround time for receiving results. The result of a

NAAT is available in less than an hour, while the two-step takes longer due to the increased number of steps involved to obtain accurate results (Quest Diagnostics, 2017). The other consideration is that the sensitivity is slightly less with the two-step versus the NAAT. The change from a single NAAT to the two-step is not due to concerns related to the capabilities of the testing procedures, but rather to the need to identify toxin-negative samples for discerning appropriate treatment methods. The NAAT cannot classify toxin status but can identify the presence or absence of *C. difficile* (Quest Diagnostics, 2017). The only scientific evidence-based method to isolate the presence of toxin is to use a toxin assay (Theiss, Balla, Ross, Francis, & Wojewoda, C.T, 2018)

Treatment Methods

Treatment of *C. difficile* depends on the level of the disease present and the status of a recurrent or initial episode of *C. difficile* (McDonald et al., 2018). Patients without symptoms of *C. difficile*, such as increased diarrhea (more than three episodes in 24 hours), increase in white blood cells, fever, abdominal pain, or ileus, should not be treated (McDonald et al., 2018). Testing results should not be used without the clinical collaboration of symptomology (McDonald et al., 2018). If the patient's clinical symptoms (with or without testing confirmation) are suspicious for *C. difficile*, then the patient should be started on an antibiotic (McDonald et al., 2018). The regimen should include vancomycin or fidaxomicin unless both are unavailable; then metronidazole is suitable for the first episode of nonsevere *C. difficile* (McDonald et al., 2018). Patients with recurrent *C. difficile* should be started immediately on vancomycin or fidaxomicin, and patients with fulminant *C. difficile* regardless of the number of episodes should be

started on vancomycin (McDonald et al., 2018). The inappropriate use of antibiotics for *C. difficile* is simultaneously related to current accepted clinical testing and treatment practices, and a lack of knowledge regarding patient outcomes over the long run when antibiotics are prescribed unnecessarily to treat a suspected diagnosis of *C. difficile*.

Problem Statement

Antibiotic resistance, recurrent *C. difficile*, and prolonged hospitalization are potential outcomes for patients identified with *C. difficile* in the hospital (CDC, 2019b); Rock et al., 2018). Patients with a positive *C. difficile* test result without clinical symptomology are at risk for inappropriate administration of antibiotics (Rock et al., 2018). The Centers for Medicare and Medicaid Services instituted a requirement in 2013 for all acute care facilities to report all laboratory-identified *C. difficile* to assist in holding administrators accountable through financial incentives for *C. difficile* infection avoidance (Medicare Program Hospital Inpatient Prospective Payment Systems for Acute Care Hospitals, 2017). Although patients are identified with a positive result of *C. difficile*, physicians are strongly encouraged to confirm the infectious status through toxin confirmation along with the presence of symptoms before prescribing treatment (Ooijevaar et al., 2018).

One reason for the inappropriate treatment of *C. difficile* is the misclassification of the presence of nontoxigenic *C. difficile* as an indication of infection (Ooijevaar et al., 2018). The identification of *C. difficile* using the NAAT from both symptomatic and asymptomatic patients is similar (Truong et al., 2017). A testing algorithm, including both the NAAT and toxin confirmation testing, is another useful option for health care

facilities to consider when identifying and attempting to distinguish between *C. difficile* infection and colonization to guide appropriate treatment decisions (Truong et al., 2017). Research is clear about the potential for the different testing methods to identify the presence of toxigenic *C. difficile* and the reason for using each type based on the needs of each facility (Ooijevaar et al., 2018). Many facilities have moved to the NAAT from a cost perspective resulting in faster available results with standard guidelines for antibiotic treatment (Amado, Bekker, Moshgriz, Keiser, & Siegel, 2016). However, the effect of a change from a single NAAT to a two-step algorithmic testing method with a moderating effect of patient symptomology upon antibiotic treatment is not well defined based on available literature.

Purpose of the Study

The purpose of this study was to examine the effect of changing from the NAAT to a two-step algorithm for the identification of *C. difficile* and the resultant prescribed treatment for hospitalized patients with a modifying presence of symptoms. A quantitative approach was used to address the gap regarding the relationship between the testing year (2015 and 2018), antibiotic prescribing (yes or no), and recognized patient symptomology (yes or no). The secondary de-identified patient data set, which included the testing year, results, and antibiotics prescribed, was examined for differences. The study was unique because it addressed moving from a specific testing method (NAAT) conducted during 2015 to a two-step method that included toxin identification during 2018 (see Ooijevaar et al., 2018) along with the prescribing patterns, test results, and recognized symptomology cues (see McDonald et al., 2018).

Research Questions and Hypotheses

RQ1: Is there a statistically significant association between the testing period (2015 and 2018) and antibiotic treatment (yes or no)?

H_o1: There is not a statistically significant association between the testing period (2015 and 2018) and antibiotic treatment (yes or no).

H_a1: There is a statistically significant association between the testing period (2015 and 2018) and antibiotic treatment (yes or no).

RQ2: Does the presence of a recognized symptom (yes or no) moderate the relationship between the testing period (2015 and 2018) and antibiotic treatment (yes or no)?

H_o2: The presence of a recognized symptom does not moderate the relationship between the testing period (2015 and 2018) and antibiotic treatment (yes or no).

H_a2: The presence of a recognized symptom moderates the relationship between the testing period (2015 and 2018) and antibiotic treatment (yes or no).

Theoretical Framework

The framework applicable to this study was the symbolic interaction theory (see Goffman, 1967; Rose, 1962). The social interaction between the actor (physician) and the world (the hospital) is the primary focus that guides the interaction or treatment of the patient (see Goffman, 1967). The theory contains the following assumptions: (a) Humans interact in both physical and symbolic environments, (b) a person's response to a symbolic communication is ascribed from learned behavior or meaning from others, and

(c) a person's experience is used to assign meaning to the behavior of others (see Goffman, 1967; Rose, 1962).

C. difficile infection diagnosis requires a physician to complete a complex decision-making process. The interactions or weighing by the physician of the particular tool used for testing, the patient's symptoms, and the need to treat are interrelated (see Bobenchik, 2019). The physician's decision to prescribe treatment is related to the outcome of the testing and the accepted behavior through symbolic interactions among physician peers within the facility. The present study focused on the interaction of the testing method and the physician's decision to treat. The research questions were related to the theory in examining whether an association of symptoms is present as indicated when using NAAT alone when testing for *C. difficile* to determine the need for treatment.

Nature of the Study

The nature of the study was quantitative with a correlational design including secondary data from electronic medical records. The data set included records from January 1, 2015, through December 31, 2015, and January 1, 2018, through December 31, 2018, from a large suburban health care facility with over 500 beds. All patients who tested for *C. difficile* at the acute care facility with a positive result were included in the analysis. The patient population under study included all ages and service status such as intensive care or medical ward. The predictor variable was the case year (2015 or 2018). The dependent variable was the treatment being prescribed (yes or no). The mediator variable was whether a recognized symptom of *C. difficile* was present (yes or no). Binary logistic regression was used for both research questions to determine association.

Significance

According to the World Health Organization (2020), "patient safety is the absence of preventable harm to a patient during the process of health care and reduction of risk of unnecessary harm associated with health care to an acceptable minimum" (Patient safety section, para. 1). Health-care-associated *C. difficile* harmed almost 224,000 hospitalized patients in 2017 (CDC, 2019b). Correct identification of the disease is necessary to ensure proper treatment (Bobenchik, 2019). The emergence of antibiotic-resistant *C. difficile* is on the rise (CDC, 2018). The outcome of this study may increase awareness and knowledge surrounding the appropriateness of treatment based on the two-step testing results versus the treatments currently prescribed for NAAT results. Knowledge regarding appropriate treatment requires precise results to determine the difference between colonization and infection (Bobenchik, 2019). Testing methods and treatment guidelines have been addressed in multiple research outcomes and scientific societal guidelines (Bobenchik, 2019; Cho, Pardi, & Khanna., 2020; Crowell et al., 2017; McDonald et al., 2018). However, the effect of a change from the NAAT to two-step testing methods on prescribing patterns is not apparent (Ooijevaar et al., 2018; Truong et al., 2017). The original contribution of this research was in two areas. First was the review of following a counterintuitive path that requires two steps versus one step. Second was the contribution to the physicians with documentation to identify patterns of prescribing behavior among the population.

Positive Social Impact

The identification of how prescribing patterns changed or did not change after the implementation of two-step testing was one way to inform professional practice and to identify appropriate or inappropriate antibiotic use. Inappropriate antibiotic use leads to infections with antibiotic-resistant organisms, such as vancomycin-resistant enterococcus (Isaac et al., 2017). One potential social outcome of the study was to increase awareness among health care providers regarding the effect of treatment for *C. difficile* clinical practice and the resultant impact on the antibiotic resistance problem that is prevalent in the United States (see Colman, Krockow, Chattoe-Brown, & Tarrant, 2019; McCullough, Rathbone, Parekh, Hoffmann, & Del Mar, 2015). If inappropriate antibiotic use is identified, hospital administrations and medical staff may review the results to determine better treatment algorithms.

The physicians who practice at the study facility are part of the same primary group servicing multiple other facilities in the region. Sharing the clinical outcomes data from this study with local physicians, local hospital infectious disease departments, and local hospital administrators may improve testing and treatment outcomes within the local community. Also, there is a possibility that the results may be generalized to other populations, and that antibiotic-resistant cases may be minimized.

The identification and correction of inappropriately prescribed antibiotics may positively affect patients, administrators, and providers. The benefits of decreasing the overuse and misuse of antibiotics can positively affect everyone, including patients and providers. For instance, patients who have nonmultidrug infections are less costly than

patients who have multidrug-resistant infections (Chen & Fu, 2018). One of the primary causes of *C. difficile* infection is the use of antibiotics; therefore, by reducing inappropriate antibiotic use regardless of the prescription reason, the overall burden of *C. difficile* may be reduced. In 2019, there were more than 2.8 million antibiotic-resistant infections worldwide (CDC, 2019a).

Finally, *C. difficile* was responsible for 14,000 deaths and more than 200,000 infections in 2019, making the organism one of the top priorities for prevention and control (CDC, 2019a). The ability to treat appropriately requires specific knowledge for identifying the disease under scrutiny (CDC, 2019c). The contribution of this doctoral project may be a local change in identifying the patterns of application or prescribing of antibiotic use for *C. difficile*, which may lead to a decrease in antibiotic use. The decrease in antibiotic use may lead to a reduction in multidrug-resistant organisms that expose staff and patients to an increased risk of infection (CDC, 2019c).

Literature Search Strategy

The doctoral project included a search for relevant literature from multiple databases. The search included CINAHL, Medline, PsycInfo, ScienceDirect, ProQuest, and Embase databases for peer-reviewed scholarly journal articles published during or after 2017. The initial search terms of *c-diff* or *Clostridium difficile* or *C diff* or *c diff* or *c. diff* or *CDI* and *test* or *testing* and *symptoms* or *signs* or *characteristics* or *presentation* or *symptomatology* resulted in 625 nonduplicative results. The search results were narrowed using the search terms *toxic* or *toxicity* or *toxigenic* or *toxin*, which resulted in 593

nonduplicative results. A final narrowing was conducted to include articles that met specific inclusion criteria.

The inclusion criteria for the literature review included (a) relevance to the health care industry, (b) English language articles, (c) relevance to *C. difficile* testing or treatment, and (d) relevance to antibiotic use. Seminal works from as early as 1962 related to the symbolic interaction theory were included in the study. Also, the literature review included six books and multiple internet-based subject-matter expert sources such as the CDC. The final literature review included 104 articles.

Literature Review

Unnecessary antibiotic use contributes to the increased prevalence of diarrheal episodes with longer episodic time frames and increased subsequent complications (Cho, et al., 2020). Patients with *C. difficile* are more likely to have taken third-generation cephalosporins for 3 or more days than those who do not have *C. difficile* (Lee et al., 2019). The cause of *C. difficile* is unknown. However, the recognition of the symptoms that leads to testing has been well researched (Hematyar et al., 2020; Truong et al., 2017).

Symptoms

Symptoms of *C. difficile* include diarrhea with abdominal cramps, fever, increased serum creatinine, and increased white blood cell count in any combination (McDonald et al., 2018; Rock et al., 2018). Confirmation of the symptoms, along with a positive *C. difficile* test, is critical to the management of *C. difficile* (Cho et al., 2020; Crowell et al., 2017; Ooijevaar et al., 2018). The definition endorsed by health care facilities for diarrhea is three or more episodes of liquid stool that takes the shape of the

container, and fever is a temperature above 100.4 Fahrenheit (CDC, 2020; Quest Diagnostics, 2017). Abdominal cramps are subjective, and white blood cell count above the patient's normal levels are considered symptomatic (McDonald et al., 2018; Rock et al., 2018). Although symptomatic carriers are more readily identified, consideration must be given to asymptomatic carriers who may develop the disease with symptoms during hospitalization (Kagan et al., 2017).

Testing

Testing methodologies include one or two tests to confirm the presence and toxigenic status of the patient's sample. The specimen quality (liquid only) is vital for two reasons. If the NAAT is used, part of the process is to ensure only appropriate liquid diarrheal specimens are tested because the test detects regardless of the sample type (Goret et al., 2018). If an NAAT is used and the sample is not meeting diarrheal criteria, then treatment may be instituted on asymptomatic patients (Goret et al., 2018). The issue becomes whether the sample is toxigenic and whether the sample is indicative of a patient with a current symptomatic disease (Kagan et al., 2017). One way to combat the carrier status problem is to use a two-step approach that combines the NAAT with the GDH to determine the status (Davis et al., 2019; Mawer et al., 2019). Implementation of a two-step process identifies those patients who have true toxigenic *C. difficile* and, if symptomatic, require treatment (Davis et al., 2019).

Treatments and Outcomes

The outcome for patients with *C. difficile* is dependent on the severity of the disease, the treatment, and associated risk factors including presence (Fisher & Halalau,

2018; Gateau, Couturier, Coia, & Barbut, 2018; Novotný et al., 2018). The treatments per the Infectious Disease Society of America guidelines are separated by the first episode, first recurrence, or subsequent recurrences along with nonsevere, severe, or fulminant (McDonald et al., 2018). The categorizations are standard among research experts (Cho et al., 2020; Crowell et al., 2017). Patients who are undertreated for *C. difficile* are at equal risk for mortality compared to those who are overtreated or appropriately treated (Crowell et al., 2017). Length of stay at a facility is a risk factor for increased *C. difficile* infection (Zhang et al., 2016). Length of stay remained static for inappropriately treated patients in the study by Crowell et al. (2017). However, a significant length of stay decrease was seen in appropriately treated patients (Crowell et al., 2017). Reductions in hospital-onset laboratory identified *C. difficile* cases have been recognized with a two-step method (Block et al., 2018). However, an equal decrease has not been found in antibiotic prescribing (Albert, Ross, Calfee, & Simon, 2018; Davis et al., 2019). Although case counts have decreased, subsequent use of antibiotics has not decreased, which has led to poor outcomes up to and including death (Patel et al., 2017).

Research indicated that testing methods have improved in efficiency and accuracy (Amado et al., 2016; Bai et al., 2017; Block et al., 2018; Brukner et al., 2019; Chang et al., 2019; Kamboj et al., 2018; Paitan et al., 2017). The agreement among scientists and professional organizations is well documented regarding the clinical manifestations of infection (McDonald et al., 2018; Ooijevaar et al., 2018; Reinink et al., 2017). Also, treatment algorithms are documented based on the disease level (Ooijevaar et al., 2018; Origüen et al., 2018; Simeunovic et al., 2017; Theiss et al., 2018; Truong et al., 2017). A

gap exists in the research related to whether the existence of clinical symptoms moderates the administration of antibiotic treatment based on a positive result between a two-step method or an NAAT that may or may not have been appropriately collected.

Definitions

Dependent variable: Antibiotic treatment referred to the administration or initiation of antibiotics used for *C. difficile* treatment. The antibiotics included vancomycin, metronidazole, and fidaxomicin. The administration or continuation of any of these antibiotics after testing counted as treatment (see Cho et al., 2020; Crowell et al., 2017; Giancola, Williams, & Gentry, 2018; Ooijevaar et al., 2018).

GDH: Glutamate dehydrogenase, which is a species-specific test used for rapid diagnostic testing for *C. difficile* (Quest Diagnostics, 2017). Most commonly used in conjunction with toxin assays to determine presence and toxin status together (Quest Diagnostics, 2017).

Moderating variable: Symptoms referred to temperature, white blood cell count, or serum creatinine level. Temperature over 100.4, serum creatinine over 1.3 mg/dL, and white blood cell count over 15×10^9/L counted as symptoms and were marked as yes (see Bauer et al., 2012). Any other values in those lab values were counted as nonsymptomatic or no. The lab value or vital sign must have been within 24 hours before or after the test for *C. difficile* was conducted.

NAAT: The nucleic acid amplification test, which is a rapid diagnostic test that is used to detect *C. difficile* toxin genes (Quest Diagnostics, 2017).

Predictor variable: Testing period for January 1 to December 31, 2015, and January 1 to December 31, 2018. All records during this time from patients with an admission who were tested for *C. difficile* and a positive result were included.

Two-step method: The rapid diagnostic method used to detect toxigenic *C. difficile* in stool specimens combining the toxin assay and clostridium-specific gene detection with a second test performed if the results are mismatched (Johansson, Karlsson, & Norén, 2016; Quest Diagnostics, 2017). The GDH and toxin testing result as positive or negative for both the toxin and the *C. difficile* presence. If the GDH is negative and the toxin is positive, then the result is positive. If the GDH is positive but the toxin is negative, then another test is run as a tiebreaker (Quest Diagnostics, 2017).

Assumptions

I assumed that the collection of the specimens was done only if the patient required testing. Second, I assumed that the nursing staff accurately documented the temperatures. I also assumed that the knowledge regarding the testing varied by provider, and testing was conducted only when appropriate based on the clinician's understanding. Finally, I assumed that the application of the serum creatinine or white blood cell changes were attributed to the probable or possible *C. difficile* infection and not attributed to other infectious processes, if present.

Scope and Limitations

The data set for the analysis was restricted to 2 years (2015 and 2018) in which a positive test result was obtained. The reasons for limiting the scope were related to the methodology of the project. The elimination of negative results focused the population on

the cases related to the research question of positive case outcomes (see Creswell & Creswell, 2017). Also, all extra variables were excluded from the data set, including only those that were used in the analysis. Restriction of the antibiotics for treatment to only three types (vancomycin, metradionazole, and fidaxomicin) ensured that only antibiotics associated with treatment for *C. difficile* were included. In other words, the elimination of other antibiotics helped to lower the level of dilution of the results (see Creswell & Creswell, 2017).

One limitation of the study may have been the implementation of a strict rejection process for inappropriate specimens that were not in place at either time. Because the study focused on one facility, a limitation was potentially present for generalizing the results to other facilities without further research. Based on these restrictions and limitations, the conclusions of the study cannot be generalized to all health care facilities or all comparisons of testing methods.

Summary

C. difficile is a significant societal issue because over- or undertreatment of the disease impacts the overall morbidity and mortality of the population. The difference in testing methods was concerning due to the subsequent treatment based on the results. If the results are not correlated with the symptoms, then the patient may be inappropriately treated. The trends of hospital-onset *C. difficile* continue to decrease without the alignment of reducing antibiotic use (CDC, 2019b, 2018). One gap in the research was whether antibiotic treatment prescribed based on the case year via a positive test result was modified by the presence of recognized symptoms. Recognizing differences in

testing and the presence of symptoms may help with initiatives to mitigate inappropriate antibiotic prescriptions, which endangers the public health.

Section 2: Research Design and Data Collection

The de-identified patient data records were collected on December 3 and 4, 2019, through the electronic medical record system as a special request from corporate clinical analytics. The secondary medical record set included the predictor variable of the case year, which also indicated the testing method as only one method was used during each case year. The record also included the dependent variable of antibiotic treatment and the moderating variable of symptoms present. The rationale for using the data was that the information available through the patient data records would provide an adequate sample that was representative of the population and would provide the necessary data points necessary for answering the research questions.

Population

The target population for the study included all patients who tested positive for *C. difficile* in 2015 or 2018 ($N = 509$).

Sample Size Determination

Although the sample size was determined based on tests conducted for *C. difficile*, a power analysis was performed using G-Power software (see Faul, Erdfelder, Buchner, and Lang., 2009). I assumed a two-tail test, an odds ratio of 2.25, an alpha of 0.05, and a minimum statistical power of 0.95. A null hypothesis probability of the dependent variable being equal to 1 if the independent variable was equal to 1 of 0.40 produced a minimum sample size of 325. The accurate a priori power analysis included an alpha level of .05 to reduce type I error, and power level of .95 to reduce type II error. The

effect size of 60% inappropriately treating was calculated based on the average for over or under treating (see Crowell et al., 2017).

The data were accessed by contacting the clinical analytics team via the clinical services group director of infection prevention with the authority to request and share the data. The information included the test being conducted with a positive result on any patient for the case years of 2015 and 2018 and for the specified facility. The data were sent in an Excel file from the clinical services group infection prevention director.

Method of Data Collection

The data were collected by the clinical analytics team based on a positive result for *C. difficile* presence during calendar years 2015 and 2018. The data were extracted from electronic medical records. The standard confidentiality agreement that is signed each year by every staff member was maintained via the approval process for access to the documents through the Clinical Analytics Group. Reliability evidence was considered with the ability to reconstruct the data set and analysis (see Stewart & Hitchcock, 2016).

One internal validity consideration was that historical context might have included other events that affected the outcomes during each case year. Another internal validity concern was maturation due to the possibility of changing patient types and prescribers during the different range of collections (see Stewart & Hitchcock, 2016). External validity concerns included the generalizability of the outcomes to different settings and treatment variations, which may be related to the timing of testing or results (see Stewart & Hitchcock, 2016).

Variables

The main variables used in the analysis were clinical symptoms, case year, and antibiotic treatment. Each variable was introduced into the data analysis model as the predictor, dependent, or moderating variable. Table 1 lists all relevant variables examined in this analysis, followed by subsections describing the variables in detail.

Table 1

All Variable Definitions and Coding

Variable name	Type of measurement	Definition	Use	Variable codes
Case year	Nominal	Year of test	Predictor	2015 or 2018
Length of stay	Ratio	Length of stay for admission during which the test was performed	Demographic	0-635
Collect_location	Nominal	Location of test collection	Demographic	Adult ER=1; adult inpatient=2; adult outpatient=3; pediatric ER=4; pediatric inpatient=5
Symptom	Nominal	Presence of temperature, WBC, or serum creatinine above the standard threshold	Moderator	Yes or no
Abx_administered	Nominal	At least one of the c.diff antibiotics prescribed or continued after testing.	Dependent	Yes or no
Know_Exp_Abx	Nominal	Known exposure to antibiotics within 30 days before testing	Independent	Yes or no
Onset	Nominal	NHSN categorization of the organism onset	Independent	Hospital onset=1; community onset=2

Predictor Variable

The predictor variable was the test case year. The case year was dependent on the date of the *C. difficile* test. No calculation or modifications were made to this variable. The case year 2015 corresponded to the two-step method fully implemented, and the case year 2018 corresponded to the NAAT only.

Dependent Variable

The dependent variable antibiotic treatment was the administration of *C. difficile* targeted antibiotics, including vancomycin, metronidazole, and fidaxomicin (see Cho et al., 2020; Crowell et al., 2017; McDonald et al., 2018). Based on medication administration records for each patient, the date and time of antibiotic administration were documented. Any administration of the targeted antibiotics was coded as "yes" for the dependent variable indicating that the patient received antibiotic therapy after testing or that antibiotic therapy continued after testing if already started before testing. If no targeted antibiotic was administered after testing, then the antibiotic administration variable was coded as "no."

Moderator

The moderator variable symptoms included temperature, serum creatinine, and white blood cell count. The temperature threshold to indicate a clinical symptom was greater than 100.4 Fahrenheit. The temperature of 100.5 or more was coded as "yes" for symptoms. Serum creatinine level above 1.3 mg/dl was coded as "yes" for a clinical symptom. Finally, white blood cell counts above 15×10^9/L were coded as "yes." Fever,

liver abnormality, and leukocytosis (increased white blood cell count) are indicative of *C. difficile* infection (Bauer et al., 2012; McDonald et al., 2018).

Demographic and Additional Variables

Other data points were available for descriptive analysis, including collect locations to define the geographical location within the facility. Length of stay or the time from admitting to the collection was used to define the onset of the case per National Healthcare Safety Network criteria (see CDC, 2020). Community onset included cases identified within the first 3 days of admission, and the rest were hospital-onset cases (see CDC, 2020). The length of stay was a continuous variable. Finally, known exposure to antibiotics within 30 days before the case identification indicated the significant risk for the development of *C. difficile* infection (Lee et al., 2019).

Statistical Design

IBM SPSS Statistics Version 25 was used for the data analysis of this study. The data set was downloaded in Excel and cleaned in IBM SPSS Statistics Version 25. The file was provided in an Excel format containing 509 records. Each record was thoroughly reviewed for missing data or inconsistencies. No data records had missing information. Variables not needed in the analysis were removed from the data set.

Binary logistic regression was chosen for statistical analysis, including variables from both research questions. Binary logistic regression assumptions were met with a dichotomous dependent variable (antibiotic treatment), nominal independent variables (case year and symptoms), and independence of observations (see Lund Research Ltd., 2018). Frequency tables were included for descriptive analysis of additional variables

(length of stay, known exposure to antibiotics, and onset). In the binary logistic regression, the probability cut value of 0.5 was used to determine the appropriate classification (see Lund Research Ltd., 2018). The Wald test was used to identify variables that had a significant effect at or above a *p* value of 0.5.

Research Questions

RQ1: Is there a statistically significant association between the testing period (2015 and 2018) and antibiotic treatment (yes or no)?

H_o1: There is not a statistically significant association between the testing period (2015 and 2018) and antibiotic treatment (yes or no).

H_a1: There is a statistically significant association between the testing period (2015 and 2018) and antibiotic treatment (yes or no).

RQ2: Does the presence of a recognized symptom (yes or no) moderate the relationship between the testing period (2015 and 2018) and antibiotic treatment (yes or no)?

H_o2: The presence of a recognized symptom does not moderate the relationship between the testing period (2015 and 2018) and antibiotic treatment (yes or no).

H_a2: The presence of a recognized symptom moderates the relationship between the testing period (2015 and 2018) and antibiotic treatment (yes or no).

Threats to Validity

Historical internal validity was addressed by confirming the process change dates for the *C. difficile* testing processes and policies (see Stewart & Hitchcock, 2016). The laboratory department and infection prevention department personnel who are

responsible for changes to the *C. difficile* testing processes confirmed no other historical changes occurred during the two study years. Although no changes occurred in the process, the medical staff and patients were continuously changing. New staff learning the processes can lead to errors. However, the same continuous education was given throughout each case year. No correction for this issue was available.

External validity consideration for the timing of testing and resultant antibiotic prescriptions must be considered for generalization because an inpatient facility has staff 24 hours a day to result and prescribe where other facilities may not (see Stewart & Hitchcock, 2016). This leads to a generalizing issue based on the location where testing takes place because the current project was set only for an inpatient acute care facility. The findings may not be applicable to long-term care facilities or outpatient settings.

Ethical Considerations

A facility-based institutional review board application was completed and approved before study implementation. Data access to the secondary data set required permission via an email from the clinical services group infection prevention director, who requested the data on my behalf. Confidentiality, honesty, and integrity in all data gathering, storage, and use were consistently maintained even though the data set was a secondary data set that did require primary subject contact. All data will be kept secured via password protection for at least 5 years.

Summary

Section 2 included the details regarding the study methodology. The assessment included the statistical testing plan for the case year predicting the antibiotic treatment.

The influence of a *C. difficile* symptom presence was assessed. Also, the onset categorization, collect location, and length of stay were included in the assessment. Validity, reliability, and ethical considerations were reviewed. The study results are presented in Section 3.

Section 3: Results and Findings

I examined the influence of symptoms indicative of *C. difficile* among two different case years in which a different testing method was employed each year. The antibiotic-prescribing behavior of the physician was the dependent or outcome variable. The study addressed the relationship between testing period, antibiotic treatment, and presence of symptoms indicative of *C. difficile* infection. This section includes the quantitative analysis, results, and interpretation of the results.

Data Collection of Secondary Data Set

The data included in this study originated from electronic medical records from a large suburban health care facility with over 500 beds. A single data set included the two years selected for analysis, 2015 and 2018. Discrepancy concerns included possible missing data values, incorrect reporting of values, or potential bias. Bias was minimized through the inclusion of objective variables based on test results. No missing data values were identified in the data set. The potential for incorrect reporting, although not eliminated, was minimized because the methods for reporting the test results, symptoms, and descriptive values are standardized throughout the hospital based on standard policy and procedure. The data set review included quality and validity assurance with no issues identified.

Descriptive Statistics

The demographic population included a total sample size of 509 patients with the inclusion of both 2015 and 2018 cases. The G*Power analysis resulted in a minimum sample size of 325 with odds ratio = 2.25, alpha = 0.05, power = 0.95, and

implementation of a priori. Table 2 includes results of the analysis conducted for the length of stay to obtain mean, median, standard error of deviation, minimum, and maximum values. Table 3 includes the results of the analysis for frequency and test for proportions as the remainder of the variables were categorical and discrete in nature. No data values were excluded.

Table 2

Descriptive Analysis for Length of Stay

Case year	Mean	Median	Standard error	Minimum	Maximum
2015	22.31	11.00	2.675	0	635
2018	19.37	10.00	2.414	0	201

Table 3

Descriptive Analysis for Categorical Variables

Variable	Category	Case Year 2015		Case Year 2018	
		Frequency	Percentage	Frequency	Percentage
Collect location	Adult ER	23	6.6	17	10.4
	Adult inpatient	276	79.8	123	75.5
	Adult outpatient	0	0	12	7.4
	Pediatric ER	11	3.2	7	4.3
	Pediatric inpatient	36	10.4	4	2.5
Symptom	Yes	190	54.9	109	66.9
Abx_administered	Yes	287	82.9	147	90.2
Know_Exp_Abx	Yes	212	61.3	124	76.1
Onset	Hospital onset	151	43.6	80	49.1
	Community onset	195	56.4	83	50.9

Analysis of Hypothesis

Research Question 1

RQ1: Is there a statistically significant association between the testing period (2015 and 2018) and antibiotic treatment (yes or no)?

H_o1: There is not a statistically significant association between the testing period (2015 and 2018) and antibiotic treatment (yes or no).

H_a1: There is a statistically significant association between the testing period (2015 and 2018) and antibiotic treatment (yes or no).

Binomial logistic regression was performed to determine whether a relationship existed between the testing period and antibiotic treatment. The logistic regression model was statistically significant, $\chi2(1) = 4.91$, $p < .05$. The model explained 1.7% (Nagelkerke R2) of the variance in antibiotic treatment and correctly classified 85.3% of cases. Sensitivity was 100%, and specificity was 0%. The predictor variable case year was statistically significant and shown to contribute to the model with the year 2015 set as the reference (see Table 4). Patients in the case year 2018 had 1.889 times higher odds of having antibiotic treatment than patients in the case year 2015. The unstandardized Beta weight for the predictor variable 2018: B = [0.636], Wald = [4.506], $p = .034$. In 2018, the odds ratio increased by 89% [Exp (B) = 1.889, 95% CI (1.050, 3.397)] for antibiotic treatment.

Table 4

Binary Logistic Regression: Case Year

Variables	B	Wald	Exp(B)	95% C.I for EXP(B)		Sig
				Lower	Upper	
Case year	.636	4.506	1.889	1.050	3.397	.034

Research Question 2

RQ2: Does the presence of a recognized symptom (yes or no) moderate the relationship between the testing period (2015 and 2018) and antibiotic treatment (yes or no)?

H_o2: The presence of a recognized symptom does not moderate the relationship between the testing period (2015 and 2018) and antibiotic treatment (yes or no).

H_a2: The presence of a recognized symptom moderates the relationship between the testing period (2015 and 2018) and antibiotic treatment (yes or no).

Binomial logistic regression was performed to determine whether the relationship between the testing period and antibiotic treatment was moderated by the presence of symptoms. The logistic regression model was statistically significant, $\chi 2(2) = 5.998$, $p <$ .05. The model explained 2.1% (Nagelkerke R2) of the variance in antibiotic treatment and correctly classified 85.3% of cases. Sensitivity was 100%, and specificity was 0%. The predictor variable case year was statistically significant (see Table 5) with "2015" set as the reference, and was not statistically significant with "No" set as the reference. Patients in the case year 2018 had 1.831 times higher odds of having antibiotic treatment than patients in the case year 2015 with the symptom moderating at 1.303 higher odds ratio. The adjusted unstandardized Beta weight for the predictor variable 2018: B = [0.605], Wald = [4.032], p = .045. In 2018, the odds ratio increased by 83% [Exp (B) = 1.831, 95% CI (1.015, 3.304)] for antibiotic treatment when accounting for the Symptom moderator (see Table 5).

Table 5

Binary Logistic Regression: Case Year With Symptom Moderator Adjusted

Variables	B	Wald	Exp(B)	95% C.I for EXP(B)		Sig
				Lower	Upper	
Case year	.605	4.032	1.831	1.015	3.304	.045
Symptom	.265	1.093	1.303	.793	2.140	.296

Summary

Before statistical analysis, all variables were validated and recoded. Descriptive summaries with frequency and percentage were completed for all categorical variables. Binary logistic regression was conducted for the two research questions. The alternative hypothesis was accepted with statistical significance for the case year and antibiotic treatment association. Therefore, there was a significant association between the case year and antibiotic treatment. However, for the second research question, the null hypothesis was accepted because no statistically significant association between case year and antibiotic treatment with the moderating effect of the symptom presence existed. The key findings, social change implications, and application to professional practice are presented in Section 4.

Section 4: Application to Professional Practice and Implications for Social Change

The aim of the study was to determine whether an association exists between the type of *C. difficile* testing based on case year and antibiotic treatment in a large hospital population. The secondary aim was to determine whether the presence of known *C. difficile* symptoms moderated the relationship between case year and antibiotic treatment. Death related to *C. difficile* incidence in the United States equaled approximately 70 per 1,000 infections in 2019 (14,000 deaths / 200,000 infections) (CDC, 2019a). The study findings indicated whether a significant relationship exists between testing type based on case year, antibiotic treatment and presence of *C. difficile* symptoms.

Key Findings

Case Year and Antibiotic Treatment

The case year was aligned with the type of test that was conducted on the group. The NAAT was conducted in 2015, and GDH with Toxin was conducted in 2018. The total case counts decreased by 51%; there were 346 cases in 2015 and 169 cases in 2018. The decrease in testing from NAAT to GDH with Toxin is congruent with the literature related to the efficiency of turnaround time (see Davis et al., 2019). The antibiotic treatment percentage decreased by 8% from 90% in 2015 to 82% in 2018. The combination of a large decrease in case counts with minimal decrease in antibiotic treatment is congruent with current literature (see Albert et al., 2018; Davis et al., 2019). The odds ratio of antibiotic treatment for *C. difficile* was 1.889 times higher in 2018 compared to 2015. The results increase the discipline clarity that GDH with Toxin testing compared with NAAT was associated with higher antibiotic treatment odds.

Case Year, Antibiotic Treatment, and Symptoms

The presence of at least one clinical symptom (white blood cell count increase, fever, or serum creatinine increase) increased by 12% from 2015 (54.9%) to 2018 (66.9%). The increase indicates that the physicians may have been focusing more on the agreed-upon criteria for testing, as evidenced in the literature (see Bauer et al., 2012; McDonald et al., 2018). The addition of a moderator of clinical symptoms to the relationship of case year and antibiotic treatment did not result in a statistically significant association. The odds of the existence of the moderator (symptoms) with antibiotic treatment was 30%. However, the addition of the moderator had only a 6% change in odds for the case year and antibiotic treatment relationship with a resultant 83% higher odds of antibiotic treatment in 2018 compared to 2015. Therefore, the presence of one or more symptoms known to be clinically relevant did not affect the testing type and antibiotic treatment relationship.

Known Exposure to Antibiotics and Length of Stay

Two risks of developing *C. difficile* infection are known exposure to antibiotics and length of stay in a facility (Lee et al., 2019; Zhang et al., 2016). The length of stay for patients with positive *C. difficile* results in 2015 averaged 22.31 days and decreased to 19.37 days in 2018. The mean length of stay was at the top of the acceptable average range for *C. difficile* infection and slightly under in 2018 (Zhang et al., 2016). Crowell et al. (2017) suggested that one possible reason for the decrease may be that the antibiotic treatment may have been appropriately applied. Patients taking third-generation cephalosporins within 3 days before the positive test increased by approximately 15%

from 2015 (61.3%) to 2018 (76.1%). Both case years of *C. difficile* infections showed rates of previous exposure to antibiotics above 50%, which aligns with the research (Lee et al., 2019).

Collect Location and Onset

The collect location was included as a demographic variable to address validity concerns (see Stewart & Hitchcock, 2016). The collect location includes the general age of the patient (pediatric versus adult) and inpatient or outpatient. The highest number of samples collected in 2015 equaled 79.8% in an adult inpatient location and decreased by 4.3% in 2018. Pediatric inpatient specimens were second highest in 2015 with 10.4% and 2.5% in 2018. The total pediatric location samples equaled 13.6% in 2015 and half the amount in 2018 at 6.7%. The total adult location samples were higher by 8% in 2018 (93.3%) compared to 2015 (86.4%). Combined outpatient or ER samples were double the amount in 2018 (22.1%) compared to 2015 (9.8%). Finally, overall inpatient samples showed a difference of 27.7% between 2015 (90.2%) and 2018 (77.9%).

The collection location is one of the criteria used to determine the onset category of community-onset or hospital-onset. The hospital-onset rate of *C. difficile* infections in the United States in 2017 was approximately 50% (CDC, 2019a, 2019b, 2020). The hospital-onset rate in 2015 was 6.4% below the 2017 U.S. rate and was less than 1% below the rate in 2018, indicating that the hospital rates are in line with the existing literature (CDC, 2019a, 2019b, 2020). Facility administrators are financially incentivized to have the lowest possible count of hospital-onset cases, and the percentage is moving in

the wrong direction (Medicare Program Hospital Inpatient Prospective Payment Systems for Acute Care Hospitals, 2017).

Alignment With the Theoretical Framework

The symbolic interaction theory refers to patient treatment as a result of interactions between the physician (actor) and the hospital (world; Goffman, 1967). The interactions between the physician, patient, and test findings initiate the decision-making process as part of symbolic interaction theory (Bobenchik, 2019; Goffman, 1967; Rose, 1962). Physicians require ample knowledge regarding the application of test results, clinical manifestation of illness, and appropriate treatment options that come from multiple different interactions (CDC, 2019c). The physician considers the presence of symptoms, test results, and antibiotic treatment options while weighing the potential of over- or undertreating, which may lead to outcomes that cause harm or even death (Crowell et al., 2017; Patel et al., 2017).

Limitations of the Study

The generalizability of the data was a limitation. The data were limited to a single acute care facility with more than 500 beds in a suburban location. Another limitation related to the location was the availability of services such as physician call, pharmacy interaction, and size of the physician group. The differences in size, services, and type of facility limited the generalizability of the data (see Stewart & Hitchcock, 2016). The results are not generalizable to different size facilities or types (e.g., rehabilitation, long-term care facilities, or outpatient settings). The validity and reliability of data were reviewed for accuracy before use.

Recommendations

This study focused on the moderating effect of recognized symptoms on the relationship of a change from NAAT to GDH/Toxin testing and antibiotic treatments. The study findings indicated that the presence of symptoms did not significantly affect the treatment being applied. Research exists related to appropriate treatment of *C. difficile* based on the level of disease severity (McDonald et al., 2018). Further study of the choices of antibiotic treatment based on the level of severity of illness with the identified change in the testing method should be conducted. The additional research will provide the opportunity to explore the association between testing methods, antibiotic treatment, and severity of illness. An investigation into different facility sizes and types may help to expand the generalizability of the current findings. Facilities of similar size and type may apply the epidemiological findings from this study.

Implications for Professional Practice and Social Change

The study finding that symptoms did not moderate the antibiotic treatment prescribing patterns indicates a potential antimicrobial stewardship concern. The potential for increased severity in illness or antibiotic-resistant organisms stems from inappropriate antibiotic use (Isaac et al., 2016). Successful treatment of *C. difficile* infection requires multiple interactions (communicative, symbolic, physical) between the physician, patient, and other medical staff leading to learned behavioral outcomes in the form of diagnosis and treatment led by the physician (Bobenchik, 2019; Goffman, 1967; Rose, 1962).

One professional practice recommendation is to include the severity of illness with documented symptoms as criteria for antibiotic therapy. The physician group has the

potential to agree upon an approved treatment algorithm. The treatment algorithm also addresses the community level. Many of the physicians work in multiple facilities, which allows for the physician's experience to spread the policy through interactions. Organizationally, continued appropriate testing with the presence of clinical symptoms, as found in the current study, supports the financial incentives by lowering the hospital-onset cases (see Medicare Program Hospital Inpatient Prospective Payment Systems for Acute Care Hospitals, 2017). Finally, the societal impact is in the potential reduction in global antibiotic-resistant organisms, *C. difficile* infection, and *C. difficile* death in the United States (see CDC, 2019c; Colman et al., 2019; Isaac et al., 2017; McCullough et al., 2015).

Conclusion

An examination of the association between testing method (case year), antibiotic treatment post testing, and the presence of symptoms indicated that the presence of symptoms (or lack of symptoms) did not change the relationship between testing method and treatment for *C. difficile* positive patients. *C. difficile* has the potential for mortality if not identified correctly and not treated in a timely or appropriate manner. Overtreatment and undertreatment of *C. difficile* are crucial for physicians to monitor. The addition of an improved algorithm with clinical symptoms and severity of illness defined may help physicians protect patients from unintended harm. The implementation of the improved algorithm and policy across the organization for the medical staff and clinical staff may promote improved quality, patient outcomes, and overall health management.

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