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The Effects of Implementing Best Practice on Clostridium Difficile Infection Treatment

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THE EFFECTS OF IMPLEMENTING BEST PRACTICE ON *CLOSTRIDIUM DIFFICILE* INFECTION TREATMENT

by

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DEDICATION

To my mother for teaching me the value of hard work and perseverance and my husband for years of unwavering support, encouragement, and love.

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ABSTRACT

For many years the number of *Clostridium difficile* infections (CDI) has steadily risen. This common cause of antibiotic-associated diarrhea can have variable clinical presentations ranging from mild diarrhea to severe cases complicated by the development of pseudomembranous colitis, electrolyte abnormalities, dehydration, sepsis, and even death. The resistant nature of the spores produced by the bacteria and the emergence of hypervirulent strains have made treatment challenging. Previous studies have demonstrated clinician non-adherence to CDI clinical treatment guidelines may result in poor patient outcomes. This evidence-based practice project was implemented at a 311 bed academic medical center in the Midwest. The project development, implementation, and evaluation was guided by the Iowa Model Revised: Evidence-Based Practice to Promote Excellence in Health Care. Pre-post analysis was used to determine the effect of clinician utilization of an evidence-based CDI treatment order set on clinical cure rate (resolution of diarrhea and no longer requiring treatment for CDI), 30-day disease recurrence, and 30-day readmission rates for CDI. Treatment guideline adherence was 35% in pre-implementation group and 48.9% in post-implementation group (p= 0.113). Guideline adherence did not have a statistically significant effect on recurrence rates (12.3% vs 14.8%, p = 0.425) or clinical cure rates (15.8% vs 23.9%, p = 0.241). The rate of 30-day readmission was higher among the guideline treatment adherent group (7% vs 1.1%, p = 0.078). However, this finding was not statistically significant. Clinician order set utilization increased the rate of guideline adherence versus clinicians that did not use the order set in the post-implementation group (83.3% vs 43.6%, p = 0.096). Although this is a promising result, the small sample size was not adequate enough to demonstrate statistical significance. Further studies are needed to determine the impact of clinician treatment guideline adherence on patient outcomes.

Keywords: *Clostridium difficile* infection, evidence-based practice, adherence, outcomes

CHAPTER 1

INTRODUCTION

Clostridium difficile infections (CDI) are costly, potentially fatal, and becoming increasingly more common in the United States. Nearly half a million people in the United States were diagnosed with a *Clostridium difficile* infection in 2011 (Centers for Disease Control and Prevention, 2015). Approximately 83,000 of those people developed at least one recurrence of CDI, and 29,000 died within 30 days of the initial diagnosis (CDC, 2015). In 1993, CDI led to 85,700 hospitalizations in the United States (Agency for Healthcare Research and Quality, 2012). In 2009, the number increased to an alarming 336,600 hospitalizations (AHRQ, 2012). Over this 16 year period, CDI associated hospitalizations increased nearly four-fold (AHRQ, 2012). The average cost for a CDI hospital stay in 2009 was $24,400 with an aggregate cost of $8.2 billion (AHRQ, 2012; Reveles, Lee, Boyd, & Frei, 2014). Hospital stays that involved CDI as a secondary diagnosis were more than twice as long than those with a primary diagnosis of CDI (16.0 days versus 6.9 days) and costs were more than three times higher respectively ($31,500 versus $10,100) (AHRQ, 2012). Patients with CDI hospitalizations in 2009 were also more severely ill. An estimated 9.1% of all CDI hospital cases were fatal compared to less than 2% for all other inpatient hospitalizations (AHRQ, 2012). A study in Canada demonstrated patients with hospital acquired CDI had an increased median length of stay by six days compared to those who did not acquire the infection during their hospitalizations (Forster, Taljaard, Oake, Wilson, Roth, van Walraven, 2012).

The increased incidence and cost of CDI has not gone unnoticed by the United States government healthcare agencies, such as the Centers for Medicare and Medicaid Services (CMS). Under the Affordable Care Act (ACA), hospitals are incurring financial penalties for several hospital acquired conditions (HAC), as well as excessive readmissions for certain conditions. CDI will be added to the HAC measure scoring system for FY 2017 (CMS, 2015). It

is critical to understand the characteristics of CDI, the associated risks factors, and develop strategies to treat, prevent and, control this growing potentially life-threatening and costly infection.

Background

Clostridium difficile is an anaerobic, endospore-forming, gram positive rod-shaped bacterium found most commonly in soil and other inanimate surfaces, but it can also occur as a part of the flora of the human gut (Singh, & Kappar, 2010; Rineh, Kelso, Vatansever, Tegos, & Hamblin, 2014). As a pathogen, *C. difficile* produces toxin A and B which can result in extensive microscopic and gross intestinal disease (CDC, 2015). Furthermore, these microorganisms are particularly likely to be the cause of antibiotic-associated diarrhea (AAD) and can occur in any individual treated with antibiotics in any setting. *C. difficile* is easily transmitted between persons via an oral-fecal route or from an inanimate objects to persons (Rineh et al., 2014). It has been estimated CDI accounts for one-fourth of AAD which represents approximately three million cases per year (Rineh et al., 2014). Transmission-based precautions are utilized in healthcare facilities to reduce the spread of the spores. Unfortunately, donning gloves and gowns may be seen as cumbersome and time-consuming leading to poor compliance to such precautions in the clinical setting.

In *C. difficile* infections, toxins are present in an individual's colon and manifests as an inflammatory and/or immune response to the pathogen. Individuals infected with *C. difficile* may develop a variety of clinical signs and symptoms ranging from mild diarrhea and abdominal cramps to severe presentations involving the development of septicemia (CDC, 2015). In addition, other life-threatening complications may include: toxic megacolon, dehydration, electrolyte abnormalities, bowel perforation, acute kidney injury, and other forms of organ failure (CDC, 2015; Rineh et al., 2014). It has been estimated that 2 to 8% of patients with CDI will develop the potentially life-threatening complication, pseudomembranous colitis (van der Wilden et al., 2014). Salvage therapies, such as surgical interventions for complicated cases have

associated with poor outcomes with mortality ranging from 35 to 80% (Surawicz et al., 2013). However, early operative management of this complication has been associated with improved survival (Surawicz et al., 2013).

Persons at risk for CDI include those with antibiotic exposure, gastric acid suppressant use, gastrointestinal surgeries, lengthy stays in healthcare settings, a severe underlying illness, immunosuppression, and advanced age (CDC, 2015; Barletta, El-Ibiary, Davis, Nguyen, & Raney, 2013). CDI are generally treated with antibiotics, such as metronidazole and vancomycin. However, treatment has become more challenging with the emergence of vancomycin resistance enterococcus (VRE) and the emergence of a more virulent strain of *Clostridium difficile*, type B1, North America Pulsed Field type 1 (NAP1), or PCR ribotype also known as B1/NAP/027 (CDC, 2015; Kenneley, 2014; Louie et al., 2011; Cornely, Crook, Esposito, Poirier, Somero, & Gorbach, 2012; O'Horo, Jindai, & Safdar, 2014). The strain is believed to be more virulent than historical strains due to its binary toxin or ability to produce both toxin A and B (CDC, 2015). Recent successful treatment approaches have also included fecal microbiota transplantation. Another treatment, fidaxomicin, has also been noted to decrease disease recurrence compared to vancomycin (Cornely, et. al, 2012; Louie et al., 2011; Lancaster & Matthews, 2012; Scott, 2013). Due to limited treatment options, emphasis must also be placed on preventive strategies to reduce CDI. Those efforts include wiser use of antibiotics, avoidance or cautious use of gastric acid suppressants, utilization of contact and enteric precautions, hand hygiene with soap and water, using dedicated medical equipment when possible, and implementation of cleaning and disinfection protocols and policies (CDC, 2015; Surawicz et al., 2013; Cohen et al., 2010).

Impact of Health Policy on CDI. In 2001, the Institute of Medicine (IOM) developed their landmark report, *Crossing the Quality Chasm: A New Health System for the 21st Century,* in order to address the healthcare challenges the United States was and still is facing. The IOM cited several concerns within the healthcare system that prompted change including:

inconsistency in care, patient harm, technology advances, failure to translate knowledge into practice, changing healthcare needs, and lack of organization and coordination (IOM, 2001). The intent of their publication was to improve the delivery of care by fostering innovation (IOM, 2001). The IOM suggested six aims for improvement, ten rules for redesign, and three approaches to change. The six aims included care that is 1) safe; 2) effective; 3) patient-centered; 4) timely; 5) efficient; and 6) equitable (IOM, 2001). The ten rules for redesign focused on the following principles: a continuous healing relationship, customized care based on patient needs and values, patient as the source of control, knowledge sharing with freely flowing information, decision making based on evidence, safety, transparency, anticipation of needs, decreased waste, and cooperation among clinicians (IOM, 2001). The recommended approaches included redesigning health professional training, modifying health professional regulations and accreditation, and use a liability system to support change while retaining accountability (IOM, 2001).

Fifteen years after the release of the IOM recommendations to improve the health system in the United States, we continue to face challenges in delivering efficient, effective, and equitable care. In response, the Patient Protection and Affordable Care Act was enacted in 2010 with the intent to provide affordable, quality healthcare to all Americans (U.S. Department of Health and Human Services, 2015.). Under this law, provisions have continued to be developed to further improve the quality and efficiency of healthcare delivery. The Hospital Readmission Reduction Program (HRRP) was added under the Affordable Care Act in 2012 (CMS, 2015). Under this program hospitals can incur financial penalties for excessive readmissions within 30 days of discharge for specified conditions. Initially those conditions included: acute myocardial infarction, heart failure, and pneumonia (CMS, 2015). Despite the attempts to improve health delivery, health expenditures in the United States exceeded $2.9 trillion or $9,255 per capita in 2013 (CDC, 2015). This represented 17.4% of the United States' gross domestic product (GDP) (CDC, 2015). In 2014, the CMS ruled to expand the HRRP to

include additional conditions for fiscal year (FY) 2015. Those additional conditions include: chronic obstructive pulmonary disease (COPD), elective total hip arthroplasty (THA), and total knee arthroplasty (TKA) (CMS, 2015).

Although CDI is not currently a condition included under HRRP, this will soon change. Under the ACA, the Hospital Acquired Condition (HAC) Reduction Program was developed in effort to reduce hospital acquired conditions, such as catheter associated urinary tract infections (CAUTI) and central line associated bloodstream infections (CLABSI) (Medicare.gov, 2015). Since FY 2015, the Secretary of the Department of Health and Human Services has been required to reduce payments to hospitals that perform poorly with regard to HAC prevention (Medicare.gov, 2015). Starting in 2016, surgical site infections (colon surgery and abdominal hysterectomy) have been added to HAC measures (Medicare.gov, 2015). In 2017, methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* infection (CDI) will also be added to the quality measures under HAC reimbursement policy (Medicare.gov, 2015). The addition of CDI to this legislation will present a particular challenge to advanced practice providers and other clinicians who, despite their best efforts to rapidly identify and treat individuals with this condition, face an evolving pathogen that is becoming more common, more dangerous, and more resistant to standard antibiotic treatment.

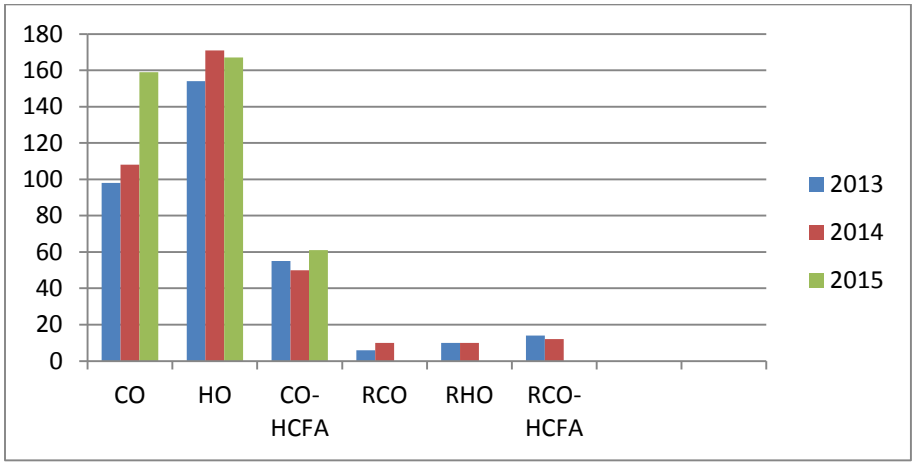
Statement of Problem

Data from the Literature Supporting the Need for the Project

Despite efforts to improve CDI prevention and treatment strategies, the cases of CDI have continued to rise over the last decade. CDI discharges accounted for 5.6 per 1,000 in 2001 compared to 11.1 per 1,000 discharges in 2010 (Chopra, Neelakanta, Dombecki, Awali, Sharma, Kaye, & Patel, 2015). The CDC (2015) reported nearly half a million people in the United States developed CDI in 2011. Approximately 29,000 patients died within 30 days of the initial diagnosis of CDI (CDC, 2015). Fifteen thousand of those cases were directly attributed to CDI (CD, 2015). One study compared CDI readmissions with all-cause readmissions in seven

tertiary care hospitals and found CDI discharges returned back to the healthcare system nearly twice as frequently as all-cause discharges (30.1% vs. 14.1%) (Chopra, Neelakanta, Dombecki, Awali, Sharma, Kaye, & Patel, 2015). Among the CDI readmission group, 22.2% were admitted for any reason and 7.8% were readmitted with the primary diagnosis of CDI (Chopra, Neelakanta, Dombecki, Awali, Sharma, Kaye, & Patel, 2015). It was projected that rates of CDI hospitalizations would continue to increase between 2011 and 2012 from 12.5 per 1,000 non-maternal, adult discharges to 12.8 per 1,000 (Steriner, Barrett, & Terrel, 2012). The potential fatal and costly complications associated with CDI and reimbursement reductions for hospital onset CDI were additional factors supporting the need for the project.

Data from the clinical agency supporting the need for the project. The clinical agency selected for the evidence-based project has had an increase in the cases of CDI for the last three consective years. There were 337 cases in 2013, 361 cases in 2014, and 387 cases in 2015 (Y. Wung, personal communication, January 21, 2016). See Figure 1.1. Recurrent community onset, recurrent hospital onset, and recurrent community onset-healthcare facility onset data for 2015 were not available from the clinical agency.



CO- community onset; HO- hospital onset; CO-HCFA- community onset-healthcare facility onset; RCO- recurrent community onset; RHO- recurrent hospital onset; RCO-HCFA- recurrent community onset-healthcare facility onset

Figure 1.1 Cases of *Clostridium difficile* Infections at Clinical Agency

Purpose of the EBP project

The purpose of this evidence-based practice project was to determine the effect of clinician adherence to an evidence-based treatment order set for *Clostridium difficile* infection (CDI) on clinical cure rate (resolution of diarrhea and no longer requiring treatment for CDI), 30-day disease recurrence, and 30-day readmissions for CDI.

Significance of the Project

CDIs have increased an alarming rate over the last decade. Despite efforts directed at both disease prevention and treatment, they continue to be a significant healthcare challenge. CDIs have been associated with longer and more costly hospitalizations. Patient clinical courses may be complicated by electrolyte abnormalities, renal failure, toxic megacolon, septicemia, and even death. The increased incidence and cost of CDI has not gone unnoticed by government healthcare agencies, CMS. Under the ACA, hospitals are incurring financial penalties for hospital acquired conditions. CDI will be added to the HAC measure scoring system for FY 2017. Clinicians and healthcare systems have an opportunity to improve both prevention and treatment strategies to combat this potentially fatal and costly problem. Incorporation of an evidence-based order set for CDI may be a promising solution in improving clinician adherence to treatment guidelines, improving clinical cure rates, and reducing disease recurrence and CDI 30-day readmissions.

CHAPTER 2

THEORETICAL FRAMEWORK AND REVIEW OF LITERATURE

The theory and evidence-based practice (EBP) model used as the framework to develop this evidence-based project were the epidemiological triangle and The Iowa Model Revised: Evidence-Based Practice to Promote Excellence in Health Care, respectively. The epidemiological triangle provides an understanding of the fundamentals of epidemiology. It is essential to understand the basic components of the epidemiological triangle to develop effective strategies to diagnose, treat, control, and prevent CDI. An EBP model, such as the Iowa Model, offers to guide the user(s) through the process of incorporation of the best evidence into clinical practice.

Theoretical Framework: The Epidemiological Triangle

Under additions to the ACA, hospitals will begin facing greater financial penalties for excessive readmission rates and hospital acquired conditions such as CDI. Clinicians and healthcare systems need to develop effective approaches to prevent excessive readmissions and hospital acquired conditions to avoid such penalties. Failure to take meaningful action will inevitably lead to increased complications, mortality, and potential financial devastation that can effect healthcare system viability. CDI is a growing threat that requires effective prevention and treatment strategies.

Description of theoretical framework. The epidemiological triangle is the theoretical framework used to illustrate the interaction of the key components of communicable diseases. Those components include the infectious agent, the host, and the environment (Bonita, Beaglehole, & Kjellström, 2006) (see Figure 2.1). The mechanism by which those components interact and the factors that determine disease and infection development are explained by the theoretical framework.

The first part of the epidemiological triangle is the *infectious agent* or a microorganism that is capable of causing disease or infection. *Infection* is the state in which an infectious agent

enters the host, develops, multiples, and causes the host to develop an inflammatory response to the pathogen. The likelihood a microorganism will cause infection within a host is known as its *pathogenicity*. The degree of disease severity caused by the pathogen is known as *virulence*. Pathogens can be carried through the environment through a variety of reservoirs, including humans, animals, and inanimate surfaces, which become the source by which the host initially acquires the pathogen from the environment. In infectious disease epidemiology, a *carrier* is a person or animal that has the pathogen, but is clinically asymptomatic. These carriers, potentially health care providers or visitors, often become important sources of health care associated infections (Bonita, Beaglehole, & Kjellström, 2006).

The second component of the epidemiological triangle is the *environment.* This component includes transmission or the mode in which the agent is transferred to the host. There two main modes of transmission: direct and indirect. *Direct transmission* is the immediate transfer of the infectious agent from an infected host or reservoir to a host. Direct transmission may include kissing, touching, sexual intercourse, childbirth, medical instrumentation, coughing, sneezing, blood transfusion, or placental transfer. *Indirect transmission* is categorized as vehicle-borne, vector-borne, or airborne. *Vehicle-borne transmission* may include contaminated food or water, towels, or equipment. *Vector-borne transmission* can occur by way of insects or animals. Airborne *transmission (long distances)* can occur through dust and droplets. *Parenteral transmission* occurs by injection with contaminated needles (Bonita, Beaglehole, & Kjellström, 2006).

The third component of the triangle is the *host* or the person or animal that is suitable for the infectious agent to multiple. The points of entry into the host may be the skin, mucous membranes, the respiratory tract, and gastrointestinal tract. The host response to the infectious agent may range from clinically asymptomatic to severe illness or death. The environment is a crucial element to the development of communicable diseases. Several environmental factors such as sanitation, temperature, air quality and water quality can affect any component of the

epidemiological triangle (Bonita, Beaglehole, & Kjellström, 2006). Hospitals and other health care facilities provide care for patients with a variety of infectious diseases and various states immunocompetence, and health care providers and visitors can serve as potential carriers of a multitude of pathogens that can be transferred to those patients and cause infection. Medical treatments and devices also pose a risk to patients. Medical devices, such as, indwelling urinary catheters and central venous catheters are potential portals for infections. Additionally, certain medications are capable of immunosuppression or disruption of human normal flora. Appropriate and mindful use of invasive, indwelling medical devices, wise medication prescribing practices, and utilization of precautions to reduce pathogenic transmission are fundamental aspects of preventing hospital acquired infections.

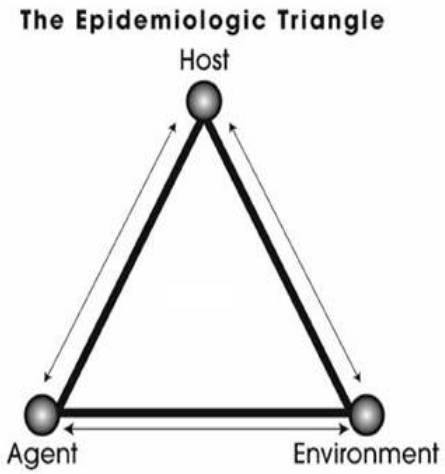


Figure 2.1 The Epidemiological Triangle

Application of theoretical framework to EBP project. *Clostridium difficile* is a spore-forming bacterium that is spread by indirect transmission or more specifically by an oral-fecal route. Disruption of normal gut microbiota from antibiotic use and direct ingestion of the spores are the two modes by which CDI develops. Inanimate objects or *fomites* such as commodes, faucets, and medical equipment can contain spores on their surface and can be transferred from the hands of others that have been in contact with contaminated surfaces. Furthermore,

the spores can persist on inanimate surfaces for more than 12 months and have demonstrated resistance to many disinfectants (Rineh et al., 2014). A peptidoglycan cortex and several layers of a protein coating allow the spores to survive in harsh environmental conditions, including some disinfectant methods (Rineh et al., 2014). Although the pathogenesis of CDI is not fully understood, certain mechanisms have been identified as key factors in the immune and inflammatory responses the bacteria elicits from the host.

C. difficile pathogenecity is reliant upon the effect of at least one of two major toxins, A and B. Although several strains have been identified, about 10 % account for a virulent strain known as B1/NAP/027. This strain has been noted to produce high levels of both toxins A and B (Rineh et al., 2014). This characteristic has made development of an effective treatment challenging. The hypervirulent toxin B has demonstrated broader tropism and cytotoxicity *in vivo* and is more hydrophobic at higher pH levels compared to historical strains. These factors permit a more rapid cell entry and the ability to cause a more severe form of illness (Rineh et al., 2014). Binary toxins are then capable of triggering microtubule protrusions in the gastrointestinal epithelial cells and lead to colonization (Rineh et al., 2014). The binary toxins have two main mechanisms of action. The first mechanism is the enzymatic action of glucosyltransferases that lead to disruption of the cytoskeleton and tight junctions, cell rounding, detachment from the cell membrane, and cell death (Rineh et al., 2014). Detachment from the cell membrane in the intestinal wall causes the formation of a pseudomembrane between the detached layer and the basement membrane, which becomes the primary site for *C. difficile* biofilm formation. The second mechanism involves triggering pro inflammatory mediators and cytokines that causes injury by disrupting the protective barrier of the intestinal epithelial lining causing cellular death (Rineh et al., 2014; Peniche et al., 2013; Barriò et al., 2014).

Bile salts have been also identified as one of the important determinants in spore germination and inhibition (Rineh et al, 2014; Peniche, Savidge, & Dann, 2013; Barriò et al., 2014). Primary bile salts (i.e. cholate and taurocholate) have been noted to be stimulators of

spore germination while secondary bile salts (i.e. deoxycholate and chenodeoxycholate) have been found to inhibit germination and spore growth (Rineh et al, 2014; Peniche, Savidge, & Dann, 2013).

Collectively these responses initiate fluid accumulation, edema, increased mucosal permeability, mast cell degradation, epithelial cell death, and changes in neutrophil recruitment (Barriò et al., 2014). Complications, such as megacolon, electrolyte derangements, and septicemia can then ensue.

The two main antibiotics used to treat CDI include vancomycin and metronidazole. Vancomycin, a glycopeptide, inhibits cell wall synthesis. Metronidazole, a nitroimidazole, causes loss of helical DNA structure by breaking the DNA strand and inhibiting protein synthesis leading to cell death. Although they can reduce the number of viable *C. difficile* bacteria, they do not have the capability to inhibit toxin and spore formation. Eradication of spores in feces has proven difficult and their presence has been implicated in 20 to 25% of recurrent cases of CDI after treatment (Rineh et al., 2014). Fidaxomicin, a macrocylic antibiotic, has been noted to reduce disease recurrence up to 45% (Rineh et al., 2014). The mechanism of action is bactericidal, as it inhibits protein synthesis and causes cell death. It additionally has minimal systemic absorption with high fecal concentrations (Lexicomp, 2015). However, current treatment with fidaxomicin is cost prohibitive (Scott, 2013). Development of novel therapies aimed directed at spore and toxin development and proliferation is fundamental. Until more effective treatments are developed, focus on prevention and control strategies will be crucial to reduce the growing number of CDI cases. Although this EBP project specifically addresses treatment of CDI it will be used in conjunction with prevention and control measures that are currently being utilized. Identification of risk factors and minimizing modifiable risks factors will also prove to be important clinician considerations.

It is crucial to have an understanding of the components of the epidemiological triangle (the infectious agent, transmission, and the host), as well as their interactions with the

environment. Knowledge of each of these components is necessary in order to develop effective interventions to prevent, control, and treat infections. Failure to identify the unique characteristics of each component will inevitably lead to unsuccessful preventive strategies and treatment interventions. CDI is no exception.

Strengths and limitations of theoretical framework for the EBP project. The strength of the framework is its simplicity. It provides the user a fundamental understanding of the components of infection and communicable diseases. Additionally, the concept can be easily applied to understanding the basic components of a multitude of infectious diseases. The epidemiological triangle provides a simple framework for understanding the components of *C. difficile* pathogenicity, effect on the host, its transmission, and how it replicates.

Despite the clear and concise nature of the epidemiological triangle, it is not specific to one infection or disease. While this can be a potential strength of the framework, it could also serve as a limitation as it provides little guidance in terms of understanding the specific pathogenesis, effective treatments, and potential sequelae of untreated infections. Each infectious agent, transmission process, host, and environment is unique. Therefore, interventions directed at the components of the epidemiological triangle need to be specific to the uniqueness of the infection causing pathogen(s).

EBP Model of Implementation

Under the ACA, hospitals are being held accountable for excessive readmissions and hospital acquired conditions. Failure of hospital systems to respond appropriately to the changes under the ACA could potentially lead to financial instability and threaten organizational viability. In 2017, CDI will be among the hospital acquired conditions for which hospitals will incur financial penalties. With the rates of CDI more the doubling over the last decade, hospitals need to begin developing strategies aimed at prevention and treatment. Clinicians need to find, critique, synthesis, and apply best evidence to current practices in CDI prevention and treatment. The process continues with implementation of practice changes and evaluation.

Finding and evaluating research and new evidence is constantly evolving. It is essential to search, evaluate, and apply best evidence to current practices to provide effective and efficient care. The Iowa Model Revised: Evidence-Based Practice to Promote Excellence in Health Care reflects the dynamic nature of healthcare and can be instrumental in incorporation best evidence into practice (Buckwalter et al., 2015).

Description of the EBP Model and Application to EBP Project

The Iowa Model of Research-Based Practice to Promote Quality Care was developed in 1994 by Linda Titler and colleagues and first implemented at the University of Iowa Hospitals and Clinics to guide nurses and other healthcare professionals to utilize research findings to improve patient care (Titler et al., 2001). The initial version was an algorithm based upon identification of triggers to improve clinical practice through research utilization. Triggers were categorized as either problem focused or knowledge focused. The problem focused triggers included risk management data, quality assessment, quality improvement, identification of a clinical problem, total quality management or continuous quality improvement (Titler et al., 2001). Knowledge focused triggers included national agencies or national organizational standards and guidelines, philosophies of care, questions from institutional standards committee, and new information in the literature. After a trigger was identified the relevant research was assembled, critiqued, and evaluated for practice. If sufficient research existed, outcomes to be achieved would be established. A nursing or multidisciplinary practice would be developed, and implemented as a practice change on a pilot. An evaluation process would follow examining the outcomes. Modifications to the practice change or intervention were made if necessary. The change would be implemented into practice if it was deemed appropriate for adoption. Outcomes would continue to be monitored after adoption into practice. The results would then be disseminated to patient and family, staff, and fiscal department. The utility of the original model was well demonstrated as evidenced by the numerous requests for use in publications, clinical research programs, clinical practice, and academic courses (Titler et al.,

2001). The authors of the model were also awarded the Sigma Theta Tau International Research Award in 1997 (Titler et al., 2001). Several helpful components of the model were noted to be helpful including: the ease of use, decision making points, emphasis on pilot testing, and evaluation of change (Titler et al., 2001).

Despite the acceptance of the original model, changes in healthcare and user feedback prompted revisions. The revised model, released in 2001, included the addition of feedback loops to illustrate the ongoing process of research utilization, new terminology, and more decision points (Titler et al., 2001). Healthcare system changes, such as incentives for research-based practice, increased market competiveness, and the need for efficient and cost effective practices also incited model revisions (Titler et al., 2001). One of the fundamental changes of the original model was a name change to The Iowa Model of Evidence-Based Practice to Promote Quality Care. The name change reflected the evolution of utilization of *research based* to *evidence-based practice* (Titler et al., 2001). The term evidence-based practice was more reflective of nursing practice as it incorporated research based information, clinical expertise, and patient preferences (Schmidt & Brown, p. 4, 2015). Research refers to the systematic search for new knowledge. Although research is utilized in the nursing profession, it does not reflect or include the aspects of clinical expertise and patient preferences. In the revised model, process improvement data, internal/external benchmarking data, and financial data were added under the problem focused triggers (Titler et al., 2001). The addition of new research or other literature was included under knowledge focused triggers (Titler et al., 2001). Determining if the topic was a priority for the organization was an action step added beneath the triggers on the algorithm. The first feedback loop was included after this decision point. If the topic was not deemed an organizational priority then the algorithm directed the user back to the triggers. If the topic was determined to be a priority then the next action step was to assemble a team. The team assembles, critiques, and synthesizes relevant research and other literature. If sufficient research supports a change, the practice change was piloted. This involved selecting

outcomes to achieve, collecting baseline data, designing evidence-based guidelines, implementation of the change, evaluation of the process and outcomes, and any necessary modifications. If sufficient research did not support a change then a feedback loop directed the user to seek other types of evidence including: case reports, expert opinion, scientific principles, and theory. An additional choice for this feedback loop was to conduct new research. After considering other sources of evidence or conducting new research the feedback loop directs the user to pilot the practice change. After the practice change was piloted, a decision point calls for the user(s) to determine if the change was appropriate for adoption into practice. If the change was adopted then monitoring and analysis of structure, process, and outcome data was conducted. The following action step calls for dissemination then continued back to the beginning of the algorithm to problem- and knowledge-based triggers. If a change is piloted but not appropriate to adopt into practice then the feedback loop directs the user to continue to evaluate the quality of care and new knowledge and then return again to the beginning of the algorithm. This incorporation of the feedback loops and actions steps reflected the dynamic and cyclic nature of clinical inquiry, searching for evidence, appraisal and synthesis of evidence, and the process of piloting a practice change, evaluation, adoption, and dissemination (Titler et al., 2001).

The model was again revised and renamed The Iowa Model Revised: Evidence-Based Practice to Promote Excellence in Health Care. The finalized version was under review at the time of this project (Buckwalter et al., 2015).The first step in the latest revised version is to identify triggering issues or opportunities. These include: 1) clinical and patient identified issues; 2) organization, state, and national initiatives; 3) data/new evidence; 4) accrediting organization requirements/regulations; and 5) philosophy of care. The rise in CDI prevalence, evidence of poor outcomes associated with guideline discordant treatment, and changes in penalties for hospital acquired conditions were the triggering issues that prompted this project.

The second step is to state the question or purpose. For this project, the purpose was to determine the effect of clinician adherence to an evidence-based order set for CDI treatment on clinical cure rates, 30-day disease recurrence, and 30-day readmissions for CDI.

The third step or the first decision point is to determine if the topic is a priority. The topic of CDI treatment and adherence to current guidelines was determined to be an organizational priority as it would potentially improve clinical cure rates, as well as reduce disease recurrence and readmissions for CDI. As a result patient outcomes would potentially improve and the hospital could potentially avoid costly financial penalties for hospital acquired CDI and readmissions. After several meetings and presentations, a multidisciplinary group of stakeholders determined the project was an organizational priority. If the topic was not considered a priority, the feedback loop would direct the user to consider other triggers. Since the topic was determined to be an organizational priority, the next fourth step was the development of a team. For this EBP project, the team consisted of a nurse practitioner/nursing doctoral student, a gastroenterologist, an internist, and clinical pharmacist.

The fifth step was to assemble, appraise, and synthesize the body of evidence. This involved conducting a systematic search followed by weighing quality, quantity, consistency, and risk. Since sufficient evidence was identified by the user, a practice change was designed and piloted as the sixth step in the model. The seventh step was designing and piloting the practice change and included: 1) engaging patients and verifying preferences; 2) considering resources, constraints, and approval; 3) developing a localized protocol; 4) creating an evaluation plan; 5) collecting baseline data; 6) developing and implementing the plan; 7) preparing clinicians and materials; 8) promoting adoption; and 9) collecting post-pilot data. If evidence was found to be insufficient, a feedback loop directs the user to conduct research.

In step eight, the user will determine if the change is appropriate for adoption. If it is deemed inappropriate, then a feedback loop guides the user to consider alternatives, and then redesign the practice change. If the change is determined to be appropriate, the user will move

to step nine or integrate or sustain the practice change. This step includes identifying and engaging key personnel, hardwire change into system, monitor key indicators through quality improvement, and reinfuse as needed.

The next step is dissemination of the results. After this step the user is directed by a feedback loop to step one again, identifying trigger issues and opportunities (Buckwalter et al., 2015).

Strengths and limitations of the Iowa Model for the EBP project. The strengths of the model include the emphasis of the ongoing, dynamic nature of incorporation of best evidence into practice, clinical inquiry through identification of problem and knowledge focused triggers, determination of organizational priorities, evidence appraisal and synthesis, piloting changes prior to adoption into practice, and dissemination of findings. The revised version of the model incorporates feedback loops and action steps that reflect the continuum of incorporation of best evidence into clinical practice. An additional strength of the model is the revisions are responsive and reflective of current changes in health care.

Limitations of the model may include lack of relevance in an organization or among individual users that fail to recognize the importance of clinical inquiry and incorporation of best evidence into practice. The model does not address organizations that may lack financial and human resources and effective leaders needed to develop multidisciplinary teams to develops and implement evidence-based practice changes. However, the most recent version in review now prompts the user to consider resources and constraints.

Literature Search

Identification of Sources Examined for Relevant Evidence

The American College of Gastroenterology (ACG) released an online publication *The Guidelines for Diagnosis, Treatment, and Prevention of Clostridium difficile Infections* in 2013. The guidelines were developed to provide recommendations for the diagnosis and management of CDI and prevention and control strategies. The authors considered it as a supplement to the

2010 Society of Hospital Epidemiologists of America (SHEA)/ Infectious Disease Society of America (ISDA) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines and an evidence-based review. In addition to well outlined recommendations, a summary and strength of recommendations was also provided. The GRADE system was utilized for evidence appraisal. SHEA/IDSA released a peer reviewed clinical practice guideline for the diagnosis, management, and prevention of CDI in 2010. The guideline was developed with the intent to serve as a systematic statement to assist healthcare providers to make clinical decisions regarding CDI.

Search engines. A search for additional evidence was conducted using the Cumulative Index to Nursing and Allied Health (CINAHL), ProQuest, The Joanna Briggs Search Institute (JBI), the Cochrane Library, and Medline/National Center for Biotechnology Information (NCBI). A librarian from Valparaiso University was consulted and assisted with the evidence search.

Keywords. The keywords included medical subject headings (MeSH terms) in addition to quotations, Boolean terms, and truncation. The final combination of terms included “clostridium difficile” AND manage* OR therap* OR guideline* or treat*. For JBI “clostridium difficile” was used. For the Cochrane Library MeSH term “clostridium difficile” and drug therapy were used.

Inclusion and exclusion criteria. Inclusion criteria included: 1) publications from 2010 to 2015; 2) adult subjects; 3) publications written in English; and 4) scholarly journals. Exclusion criteria included: 1) publications prior to 2010; 2) non-adult subjects; 3) animal subjects; 4) non-scholarly or unpublished articles; 5) non-English articles; and 6) duplicate articles.

The search of CINAHL using the above combination of terms, inclusion criteria, and exclusion criteria yielded 69 articles. The ProQuest database search yielded 66 articles. JBI yielded 28, Cochrane Library 4 articles, and Medline 28 articles. After hand searching the results, the following were deemed to relevant, non-duplicate articles: 13 of the 69 CINAHL articles, 9 or 66 articles from ProQuest, JBI 2 of 28 articles, Cochrane Library 1 of 4 articles, and

Medline 3 of 28 articles. The final yield of relevant, non-duplicate articles was 21 (see Table 2.1).

Table 2.1

Literature Search Strategies

Database	Search terms	Limiters	Hits	Included
CINAHL	"clostridium difficile" AND manage* OR therap* OR guideline* OR treat*	2010 to 2015 English All adults Scholarly journals	251 251 73 69	8
ProQuest	"clostridium difficile" AND manage* OR therap* OR guideline* OR treat*	2010 to 2015 English All adults Scholarly journals	133 133 66 66	7
JBI	"clostridium difficile"	2010 to 2015	28	2
Cochrane	"clostridium difficile" and drug therapy	2010 to 2015	4	1
Medline	"clostridium difficile" AND manage* OR therap* OR guideline* OR treat*	2010 to 2015 English Humans Add adherence OR readmit* Clinical journals	4377 1870 1283 1048 206 28	3

Levels of Evidence and Appraisal of Relevant Evidence

The Melnyk Hierarchy of Evidence (Schmidt & Brown, 2015) was utilized to categorize the level of evidence. The final 21 articles included 5 systematic reviews (level I), 4 evidence-based practice guidelines (level I), 2 randomized control trials (level II), 1 cohort study (level IV), 3 case control studies (level IV), 2 systematic reviews of descriptive studies (level V), 1

descriptive study (level VI), 2 interventional studies (level VI), and 1 observational study (level VI) See Table 2.3.

The articles were appraised using the Critical Appraisal Skills Programme (CASP) which addresses three categories: validity, results, and usefulness. CASP offers tools specific to reviews, trials, and case control studies. Each tool offers 10 to 11 questions that address each of the above categories. Each question has a set of hints that allow the user to answer each screening question. After reading and critiquing each article, a numeric rating was given to each appraised article using an adapted version of the CASP tool, (Kline, 2015). With the adapted version, each screening question has a value of 2 points. A numeric rating of 0 to 7 is poor, 8 to 14 is fair, and 15 to 22 is excellent (Kline, 2015). CASP does not have a specific tool to appraise clinical guidelines. Therefore, a comprehensive tool from www.evidence-based-medicine.co.uk was used. The tool was adapted from the St. George's Health Care Evaluation Unite *Appraisal Instrument for Clinical Guidelines*, the Leicestershire *Evidence Based Guidelines Checklist*, and the *Agency for Health Care Policy and Research Guidelines*. The guideline evaluation checklist is a series of questions that fall under 15 categories that are used to assess validity of clinical guidelines. The categories include: 1) responsibility for the guideline; 2) objectives; 3) guideline development group; 4) identification and interpretation of evidence; 5) formulation of recommendations; 6) likely costs and benefits; 7) peer review; 8) updating; 9) other guidelines; 10) overall assessment of the development process;11) applicability; 12) clarity; 13) guideline dissemination and implementation 14) national guidelines only and 15) monitoring of guidelines/clinical audit (www.evidence-based-medicine.co.uk, 2015.). After reading and critiquing each clinical guideline, a rating of either poor, fair, good, or excellent was assigned based on utilization of this tool. See Table 2.3 for the literature summary.

Table 2.2.

Levels of Evidence

Level of Evidence	Type of evidence	Number of articles
I	Systematic reviews Meta-analysis EBP guidelines	5 systematic reviews 4 EBP guidelines
II	Randomized control trials	2 randomized control trials
III	Controlled trials without Randomization	0
IV	Cohort studies or Case control studies	1 cohort study 3 case control studies
V	Evidence form systematic reviews of descriptive or qualitative studies	2 evidence from systematic reviews of descriptive studies
VI	Evidence from single descriptive or qualitative studies	1 descriptive study 2 interventional studies 1 observational study
VII	Evidence from the opinion of authorities and/or reports of expert committees	0

Table 2.3

Levels and Appraisal of Relevant Evidence

Citation	Measures	Levels of Evidence
Bagdasarian, Rao, & Malani, (2015)	Review included: diagnosing, testing, and treating CDI	Level I 15 excellent
Barletta, El-Ibiary, Davis, Nguyen, & Raney, (2013)	PPI use and duration and development nosocomial CDI	Level IV 18 excellent
Brown & Seifert, (2014)	Complication rates for patients who received guideline-concordant therapy	Level IV 18 excellent

	and guideline-discordant therapy	
Cohen et al., (2010)	Strength of recommend-ations and quality of evidence was graded using an adapted tool from the Canadian Task Force on Periodic Health Examination	Level I excellent
Cornely et. al, (2012)	Clinical cure with fidaxomicin versus vancomycin	Level II 18 excellent
Jardin, Palmer, Shah, Le, Beyda, Jiang, & Garey, (2013)	Use of oral vancomycin for severe CDI before and after policy implementation Refractory disease in severe CDI before and after policy implementation	Level IV 14 fair
Jury, Tomas, Kundrapu, Sitzlar, & Donskey, (2013)	Metronidazole for severe CDI Positive test not acted upon Time from test to positive test results Time from positive test to treatment Non- adherent treatment Inappropriate use of empirical CDI treatment	Level VI 10 fair
Khanna, Aronson, Kammer, Baddour, & Pardi, (2012)	Gastric acid suppression and disease severity	Level IV 16 excellent
Khanna & Pardi, (2012)	CDI treatment effectiveness	Level I 14 fair
Lancaster & Matthews, (2012)	Phase III prospective, randomized, double-blind, multicenter study compared fidaxomicin with oral vancomycin for the treatment of mild to moderate CDI (Louie, et. al)	Level I 16 excellent

	End points- clinical cure rates, global cure rates, rate of recurrence and time of diarrhea resolution Phase III randomized, non-inferiority trial compared fidaxomicin to oral vancomycin for CDI treatment (Crook et. al) Endpoints- clinical cure, CDI recurrence, and global cure Phase III clinical trial evaluating the role of concomitant antibiotics with fidaxomicin compared to oral vancomycin (Mullane, et. al) Endpoint- does concomitant use of antibiotics change overall clinical outcomes	
Louie et. al, (2011)	Clinical cure rate and global cure rate	Level II 20 excellent
McEllistrem, McGraw, Sahud, Chan- Tompkins, Goswami, & Bhanot, (2014)	Adherence to clinical guidelines for CDI treatment	Level VI 18 excellent
Mulherin, Hutchinson, Thomas, Hansen, & Childress, (2014)	Concordance of the ATLAS scoring system with IDSA/SHEA severity staging for CDI severity Sensitivity, specificity, positive predictive value, and negative predictive value of ATLAS scoring system Clinical characteristics associated with CDI severity	Level VI 16 excellent
Nelson et. al, (2011)	Symptomatic cure, bacteriologic cure, and risk of relapse	Level I 16 excellent

O'Horo, Jindal, Kunzer, & Safdar, (2014)	Clinical cure of recurrent CDI	Level I 16 excellent
Ritter & Petri, (2013)	Rate of recurrent CDI	Level V 10 fair
Scott, (2013)	Clinical cure rate, recurrence, and global cure	Level V 18 excellent
Surawicz et. al, (2013)	GRADE system	Level I excellent
Van Nispen tot Pannerden, Verbon, & Kuipers, (2011)	Treatment options for recurrent CDI	Level V 12 fair
Xue, (2014)	Efficacy of antibiotic therapy for CDI	Level I fair
Xue, (2014)	Efficacy of antimicrobial therapy for recurrent CDI	Level I fair

Table 2.3

Levels and Appraisal of Relevant Evidence continued

Purpose/ Aim	Sample/ Setting/ Eligibility Criteria	Design	Results/ Findings
Review best practice evidence for diagnosis and treatment of CDI	116 articles Studies related to CDI diagnosis and treatment from 1978 to 2014 Excluded studies- non English, animal studies and studies including children	Systematic review	Best tests included multiple step algorithms using PCR or single step PCR on liquid stool Multistep- sensitivity 0.68-1.00 specificity 0.92-1.00; Single step-sensitivity 0.94-0.97 Vancomycin and metronidazole are first line therapies for most patients Treatment failures have been noted with metronidazole in severe or complicated cases

			Clinical success rate for severe CDI metronidazole 66.3% vancomycin 78.5% Newer -therapy fidaxomicin is similar to vancomycin but lower recurrence rates fidaxomicin 15.4% vancomycin 25.3% Fecal microbiota transplant response rates 83-94% for recurrent CDI
Examine the relationship between PPI use and nosocomial CDI and determine if length of use increases risk of CDI	*n* = 201 (67 with CDI, 134 matched controls) Two affiliated hospitals Inclusion criteria-18 years or older, LOS of at least 72 hours, acquired CDI within 48 hours of admission Exclusion criteria-community acquired CDI within 90 days Matched controls-met inclusion and exclusion criteria, matched in a 1:2 ratio	Retrospective case-control	Patients with PPI use were more likely to develop nosocomial CDI (76% vs 39%; *p* <.001) Patients with longer duration of PPI use was a risk factor for nosocomial CDI (OR 1.14; 95% CI, 1.02-1.27: *p* =.018)
Determine if 2010 ISDA treatment guideline	*n* = 180 420 bed tertiary care referral	Retrospective case-control	51.7% received guideline concordant therapy

concordant therapy for CDI reduces the rates of compli-cations	county teaching hospital Inclusion criteria- 18 years or older, treated for CDI during their hospital stay		Patients receiving guideline concordant therapy had fewer complications (17.2% vs. 35.6%, *p* = .0007) Patients with severe and complicated CDI received guideline-concordant therapy less often than patients with mild disease (19.7% vs. 35.3%, and 81.2% respectively, *p* <0.001)
Improve the diagnosis and management of CDI in adult patients	Literature review and analysis Literature search- PubMed, English language, 1994 to 2009, terms "*Clostridium difficile*", "epidemiology", "treatment" and "infection control" Reviewed by SHEA Board of Directors and IDSA Standards and Practice Committee	Clinical guideline	Mild to moderate CDI- leukocytosis 15,000 or lower and serum creatinine less than 1.5 times premorbid level Severe CDI- leukocytosis greater than 15,000 and serum creatinine equal to or greater than 1.5 times higher than premorbid level Severe, complicated CDI- severe criteria in addition to hypotension, shock, ileus, or megacolon Discontinue inciting antimicrobials as soon as possible (A-II) Initiate empirical therapy as soon as severe or complicated CDI is suspected (C-III) Avoid use of anti-peristaltic agents if possible (C-III) Metronidazole 500 mg tid 10-14 days for initial mild to moderate CDI (A-I) Vancomycin 125 mg qid for 10-14 days for initial severe CDI (B-I) vancomycin 500 mg qid and per rectum 500 mg in 100 mL normal saline every 6 hours if ileus is present with or without IV metronidazole 500 mg every 8 hours for severe, complicated CDI (C-III) First recurrence mild to moderate CDI, same regimen as initial episode (A-II) Do not use metronidazole beyond first recurrence (C-III)

			Second or third recurrence of CDI, use pulse dose or tapered vancomycin (B-III) No recommendations regarding recurrent CDI in patients who require continued antimicrobial therapy for underlying infections (C-III)
Compare the efficacy and safety of fidaxomicin versus vancomycin for the treatment of CDI	*n* = 509 (252 assigned to fidaxomicin, 257 vancomycin) Multicenter in U.S., Canada, and Europe Inclusion criteria-CDI, 16 years of age or older, no more than one previous episode of CDI in the 3 months prior Exclusion criteria-negative *C. difficile* toxin, <3 bowel movements in 24 hours, concomitant treatment for CDI, clinical failures, protocol violation, cured with < 8 days treatment	Double-blind, randomized, non-inferiority trial	Clinical cure with fidaxomicin versus vancomycin (90.6% vs. 97.5% CI -4.3%) Non inferiority for clinical cure (87.7% vs 86.8%) receiving concomitant antibiotics for other infections cure rate was higher with fidaxomicin (90.2% vs. 73.3%; *p* = 0.031) Treatment emergent adverse events (7.6% vs. 6.5%)
Compare CDI treatment patterns and patient outcomes before and after Implement-ation of a severity-	*n* = 256 144 before policy implementation 112 after implementation Single tertiary teaching hospital Inclusion criteria-positive *C. difficile*	Cohort study	Use of oral vancomycin for severe CDI increased significantly following implementation of the policy 14% (*n*= 8) to 91% (*n* = 48) Refractory disease in patients with severe CDI decreased significantly from 37% to 15% following policy implementation

based CDI treatment policy	stool toxin, age 18 years of age or older Exclusion criteria- received antibiotics for CDI other than metro-nidazole or vancomycin, more than one recurrence of CDI		
Determine if a CDI stewardship initiative would result in more prompt CDI therapy and adherence to treatment recommend-ations	Baseline *n* = 48, early intervention *n* = 52, late intervention *n* = 46 VA center and adjacent LTCF Inclusion and exclusion criteria not given	Interventional study	Metronidazole prescribed for severe disease- baseline vs. early intervention vs. later intervention 6% vs. 0% (*p* =0.03) vs. 0% (*p* = 1.00) Positive test not acted upon 5% vs. 0% (*p* = .02) vs. 0% (*p* = .06) Time from test to positive results median hours 23 vs. 13 (*p* = .002) vs. 12 (*p* = .003) Time from positive test to treatment median hours 4 vs. 1 (*p* = .007) vs. 1 (*p* = .004) Non-adherent treatment dose or duration 8% vs. 0% (*p* = .002) vs. 0% (*p* = .006) Inappropriate use of empirical CDI treatment 18% vs. 9% (*p* = .07) vs. 2% (*p* <.0001)
Evaluate the association between acid suppression and CDI outcomes	*n*= 385 county residents Inclusion criteria- CDI inpatient and outpatient	Case control study	36.4% acid suppression (23.4% PPI, 13.5 % H2 blocker, 0.5% both) Patients taking acid suppression medications were older (69 vs. 56 years,

	exclusion criteria-recurrent CDI		*p* = <0.001) and more likely to have severe disease (34.2% vs. 23.6%, *p* = .03) and severe, complicated disease (4.4% vs. 2.6%, p = .006)
Review epidemio-logy, traditional and novel risk factors, and advance-ments in treatment of CDI	Review of current literature	Systematic review	1991-2002 in Quebec 9.6% CDI treatment failure rate with metronidazole then rose to 26% in a 2003-2004 outbreak; Houston study 22% failure rate Lack of initial response with metronidazole is associated with increased mortality Oral vancomycin is superior to metronidazole in patients with severe CDI (cure rate 97% vs. 76%) Metronidazole is recommended in patient first or first recurrent CDI. Change to oral vancomycin if no improvement in 72-96 hours Fidaxomicin similar response rates to oral vancomycin but fewer recurrences (15.4% vs. 25.3%, *p* = .005) Fidaxomicin had lower recurrence rates in hypervirulent strains compared to oral vancomycin (7.8% vs. 25.5%, *p* <.001) Patients receiving systematic antibiotics concurrent with CDI treatment had better cure rate with fidaxomicin compared to oral vancomycin (90% vs. 79.4%, *p* = 0.48) Overall success rate for fecal microbiota transplant is 92% No RCTs for recurrent disease first recurrence in mild to moderate CDI oral metronidazole for 14 days was recommended Second recurrence, 6-7 week tapering oral vancomycin regimen was recommended

			Rifaximin, IVIG and vaccines are alternative treatments
Review published literature on fidaxomicin for CDI treatment	Literature search of MEDLINE, EMBASE, and BIOSIS 1975 to 2011 Search terms- *fidaxomicin, tiacumicin B, PAR-101, OPT-80, Clostridium,* diarrhea, and pseudo-membranous colitis. Additional articles were obtained from reference lists of publications, meeting abstracts, and correspondence with the manufacturer No grading method was used for evidence appraisal	Systematic review	Louie et. al Clinical cure rate 92.1% (fidaxomicin) vs. 89.9% (vancomycin) (97.5% CI each arm, -2.6), *p* value not given Global cure rate 74.6% (fidaxomicin) vs. 64.1% (vancomycin) (*p* = 0.006) Rate of recurrence 15.4% (fidaxomicin) vs. 25.3% (vancomycin) (95% CI, -16.6 to -2.9; p = 0.005) Resolution of diarrhea 58 hours (fidaxomicin) vs. 78 hours (vancomycin) *p* value not given Crook et. al Clinical cure rate 87.7% (fidaxomicin) vs. 86.8% (vancomycin) (1 sided 97.5% CI, -4.9) *p* value not given rate of recurrence 12.7% (fidaxomicin) vs. 26.9% (vancomycin) (97.5% CI, -21.4 to -6.8; *p* value <0.001) Global cure rate 76.6% (fidaxomicin) vs. 63.4% (vancomycin) (97.5% CI, 5.2-20.9; *p* = 0.001) Mullane et. al Clinical cure without concomitant antibiotics 84.4%% vs. 92.6%% did not receive a concomitant antibiotic (95% CI, 3.0%-13.9%; *p* = <0.001) Global cure rate without concomitant antibiotics 74.7% vs. 65.8% (95% CI, 2.54%-15.4%; *p* = 0.005) Clinical cure rate with fidaxomicin with concomitant antibiotics 90.0% vs. 79.4% with vancomycin and concomitant antibiotics (95% CI, 0.23%-20.3%; *p* -0.004)

			Global cure rate with concomitant antibiotics 72.7% with fidaxomicin vs. 59.4% with vancomycin (95% CI, 2.1%-24.1%, *p* = 0.02)
Compare efficacy of fidaxomicin vs. vancomycin for CDI	*n*= 548 Multicenter study Inclusion criteria-16 years of age or older, CDI Exclusion criteria-life threatening or fulminant CDI, toxic megacolon, previous fidaxomicin exposure, history of ulcerative colitis or Crohn's disease, more than one recurrence of CDI in 3 months	Prospective double blind, parallel-group trial	Clinical cure mITT (modified intent to treat) 88.2% (fidaxomicin) vs. 85.8% (vancomycin) (97.5% CI of -3.1%) *p* value not given Rate of recurrence mITT 15.4% (fidaxomicin) vs. 25.3% (vancomycin) (95% CI -16.6 to -2.9; *p* = 0.005) Rate of recurrence for non virulent strains *C. difficile* 7.8% (fidaxomicin) vs. 25.5% (vancomycin) (95% CI, -27.5 to -7.9, *p* = <0.001) Rate of recurrence strain B1/NAP/027 24.4% (fidaxomicin) vs. 23.6% (vancomycin) (*p* = 0.93) Global cure mITT 74.6% (fidaxomicin) vs. 64.1% (vancomycin) (95% CI, 3.1 to 17.7, *p* = 0.006) Median time to resolution of diarrhea 58 hours (fidaxomicin) vs. 78 hours (vancomycin)
Usefulness of a computer-ized decision support tree for CDI treatment	*n*= 78 661 bed acute tertiary care teaching hospital Inclusion criteria-CDI, non-pregnant, ages 18-89 years, treatment with metronidazole, oral vancomycin or combination of metronidazole and oral vancomycin Exclusion criteria-history of CDI in	Retro-spective observational study	61.5% of patients received CDI treatment non adherent to SHEA/IDSA 2010 guidelines for CDI. For mild to moderate disease, 85.7% received recommended treatment. For severe disease, no patients (0/43) received recommended treatment (*p* <0.01). 17.9% of patients received concurrent oral metronidazole and vancomycin (not a currently recommended therapy)

	past 1 year, antibiotics for CDI < 5 days, sequential use of metronidazole and vancomycin, receipt of IV metronidazole or vancomycin enemas		
Evaluate concordance of the ATLAS scoring system with IDSA/ SHEA severity staging for CDI severity	*n*= 64 350 bed community hospital Inclusion criteria-CDI, age 19 years of age or older Exclusion criteria-pregnancy, other sources of intra-abdominal infection, hyper-sensitivity to metronidazole or vancomycin, treatment with oral vancomycin or oral or IV metronidazole within 14 days prior to CDI diagnosis	Retrospective study	Bivariate analyses showed moderate agreement between the ATLAS scoring system and SHEA/IDSA severity staging for CDI Sensitivity of ATLAS in predicting CDI severity 58.3% to 87.5%; specificity 67.5% to 87.5%
Investigate the efficacy of antibiotic therapy for CDI, deter-mine the most effective therapy, and deter-mine the need for stopping causative	15 articles Literature search MEDLINE 1966-2010, EMBASE 1980-2010, Cochrane Central Database of Controlled Trials, and the Cochrane IBD Review Group	Systematic review	Symptomatic cure No differences were found among metronidazole vs. vancomycin 3 studies, N = 335 (79% vs. 71%; CI 95% 0.81-1.03; p = 0.14) Studies also compared bacitracin vs. vancomycin; rifaximin vs. vancomycin; nitazoxanide vs. vancomycin; fusidic acid vs. vancomycin; teicoplanin vs. vancomycin

anti-biotics during therapy	Specialized Trials Registry Search terms- "pseudomem-branous colitis and randomized trial", "*Clostridium difficile* and randomized trial", "antibiotic associated diarrhea and randomized trial"		No statistically significant differences were found between them Bacteriologic cure 1 study, *n*= 59 teicoplanin vs. vancomycin (82% vs. 45%; RR 1.82; 95% CI1.19-2.78; *p* = 0.006) Two studies, *n*= 163 no statistical difference between metronidazole and vancomycin (45% vs. 53%; RR 0.85; 95% CI 0.62-1.17; *p* = 0.33) No statistically significant difference between vancomycin and fusidic acid Relapse Two studies, *n*= 104 no statistically significant differences were noted between bacitracin and vancomycin; teicoplanin and vancomycin; fusidic acid and vancomycin; nitazoxanide and vancomycin; metronidazole and nitazoxanide; metronidazole and metronidazole plus rifampin; metronidazole and teicoplanin; metronidazole and fusidic acid; teicoplanin and fusidic acid
Review of literature for recurrent CDI management	64 articles Literature search- MEDLINE, CINAHL, EMBASE, and the Cochrane Database No publication date or language restrictions search terms- not given	Systematic review	Vancomycin 10 studies, 6 high quality Initial cure rate 20-100%, sustained cure rates 49-100% pulsing and tapering doses has weak evidence Vancomycin with metronidazole comparator 3 high quality studies Using sustained response, vancomycin was as efficacious as metronidazole RR 1.08, 95% CI, 0.85-1.35, p =0.53 Vancomycin with fidaxomicin comparator

			fidaxomicin appeared slightly more efficacious RR 1.86, 95% CI1.04-3.31, *p* = 0.04 Evidence supporting the use of vancomycin is moderate, dosing and duration are variable Metronidazole one study concluded metronidazole was non inferior to vancomycin in first relapse two studies favored vancomycin
Review current literature for new treatment options for CDI and relapse	Literature review	Narrative review	Metronidazole and vancomycin Cure rate 90% for metronidazole vs. 98% for vancomycin) Fidaxomicin and vancomycin Crook et. al Clinical cure rate 87.7% (fidaxomicin) vs. 86.8% (vancomycin) (1 sided 97.5% CI, -4.9) *p* value not given rate of recurrence 12.7% (fidaxomicin) vs. 26.9% (vancomycin) (97.5% CI, -21.4 to -6.8; *p* value <0.001) Global cure rate 76.6% (fidaxomicin) vs. 63.4% (vancomycin) (97.5% CI, 5.2-20.9; *p* = 0.001) Wenisch et al Oral metronidazole, IV metronidazole, and vancomycin IV metronidazole 38.1% mortality, oral metronidazole 7.4% mortality, vancomycin 9.5% mortality 30 day mortality IV metronidazole RR 4.3 compared to oral vancomycin (95% CI 1.92-10, *p* <0.001)
Use of fidaxomicin for CDI	Review of two RCTs	Review of RCTs	OPT 80-003 trial Clinical cure mITT 88.2% (fidaxomicin) vs. 85.8% (vancomycin)

			(97.5% CI -3.1) Recurrence mITT 15.4% (fidaxomicin) vs. 25.3% (vancomycin) Global cure rate mITT 74.6% (fidaxomicin) vs. 64.1% (vancomycin) OPT-80-004 trial Clinical cure mITT 87.7% (fidaxomicin) vs. 86.8% (vancomycin) Recurrence mITT 12.7% (fidaxomicin) vs. 26.9% (vancomycin) Global cure rate mITT 76.6% (fidaxomicin) vs. 63.4% (vancomycin)
Provide recomm-endations for the diagnosis and management of CDI as well as prevent-ion and control of outbreaks	Literature review	Clinical guideline	Empiric treatment for suspected CDI (strong recommendation, moderate quality evidence) Discontinue inciting antimicrobial agent if able (strong recommendation, high quality evidence) Mild to moderate CDI metronidazole 500 mg tid for 10-14 days (strong recommendation, high quality evidence) Severe CDI vancomycin 125 mg qid for 10 days (conditional recommendation, moderate quality evidence) Failure to respond to metronidazole in 5-7 days, consider switching to vancomycin at standard dosing (strong recommendation, moderate quality evidence)- mild to moderate CDI in pregnant women or patients with intolerance to metronidazole vancomycin with standard dosing (strong recommendation, high quality evidence)

			CDI in patients with segment of colon not able to be reached by oral antibiotics (i.e. Hartman's pouch, ileostomy) vancomycin via enema added to above treatments until condition improves (conditional recommendation, low quality evidence) Avoid or limit use of anti peristaltic agents (strong recommendation, low quality evidence) Severe, complicated CDI without abdominal distention vancomycin 125 mg qid plus IV metronidazole 500 mg every 8 hours (strong recommendation, low quality evidence) Surgical consultation for complicated CDI (hypotension requiring vasopressors, sepsis, organ dysfunction, mental status changes, white blood cell count >50,000, lactate equal to greater than 5, failure to improve with medical therapy after 5 days (strong recommendation, moderate quality evidence) First recurrence mild to moderate CDI same treatment as initial episode Severe initial recurrence use vancomycin Second recurrence pulsed vancomycin (conditional recommendation, low quality evidence) Third recurrence after pulsed vancomcyin consider fecal microbiota transplant (conditional recommendation, moderate quality evidence)
Treatment options for recurrent CDI	Review of literature	Narrative review	First episode mild to moderate CDI stop antimicrobials if possible, metronidazole 500 mg tid for 10-14 days or vancomycin 125 mg qid for 10-

			14 days or if unable to take oral medications IV metronidazole 500 mg every 8 hours for 10-14 days consider fidaxomicin 200 mg bid First episode severe disease vancomycin 500 mg qid for 10-14 days or if unable to take oral medication IV metronidazole 500 mg every 8 hours for 10-14 days and vancomycin 500 mg qid via nasogastric tube or enema First recurrence similar to first episode consider fidaxomicin 200 mg bid or rifaximin 200-400 mg bid for 10-14 days *Saccharomyces boulardii* 500 mg for 21-28 days Second recurrence mild disease vancomycin 125 mg qid for 10-14 days with consider tapering after initial treatment, fidaxomicin 200 mg bid or rifaximin 200-400mg for 10-14 days or *Saccharomyces boulardii* 500 mg for 21-28 days Second recurrence, severe disease Vancomycin 500 mg qid 10-14 days or if not able to take oral medication then IV metronidazole 500 every 8 hours AND vancomycin 500 mg qid via nasogastric tube or enema Third or more recurrence consider fecal microbiota transplant or monoclonal antibodies or immune-globulins Life threatening CDI surgical consultation and consideration of colectomy
Best evidence regarding safety and efficacy of antibiotic therapy for CDI	Literature review	Clinical guideline	Rate of initial cure vancomycin vs. metronidazole (79% vs. 66%, $p = 0.22$) No difference in mean duration of diarrhea related to CDI or toxin clearance vancomycin vs. metronidazole (2.4 to 3.2 days), (60% vs. 74%, respectively)

			Only one study concluded statistically significant difference of CDI recurrence with fidaxomicin and vancomycin (p = 0.05) No antimicrobial therapy is superior to others for treatment of initial cure for mild CDI Fidaxomicin may cause less recurrence than vancomycin
Determine the best evidence regarding efficacy and safety of anti-microbial therapy for recurrent CDI	Literature review	Clinical guideline	First recurrence same therapy as initial episode Moderate CDI metronidazole 500 mg every 8 hours for 10-14 days Severe CDI vancomycin 125 mg every 6 hours for 10-14 days Second recurrence vancomycin course with taper. 125 mg every 6 hours for 10-14 days followed by 125 mg every 12 hours for 7 days, followed by 125 mg every 24 hours for 7 days, followed by 125 mg every 48-72 hours for 2-8 weeks Vancomycin as effective as metronidazole (RR = 1.08, 95% CI, 0.85-1.35, p = 0.53) Fidaxomicin is slightly more efficacious than vancomycin (RR 1.86, 95% CI, 1.04-3.31, p = 0.04) Metronidazole is not recommended for repeat course given possible neurotoxicity

Construct the EBP

Synthesis of Critically Appraised Literature

The appraised literature is described using categories of disease severity and defined as mild to moderate, severe, severe/complicated, and recurrence. The American College of Gastroenterology (ACG) defines mild to moderate disease as diarrhea plus any additional signs or symptoms not meeting severe or severe, complicated criteria (Surawicz et al., 2013). Severe disease is defined as serum albumin <3gm/dL plus a white blood count of ≥15,000 cell/mm or abdominal tenderness (Surawicz et al., 2013). Severe, complicated disease is defined as admission to intensive care unit for CDI, hypotension with or without required use of vasopressors, fever ≥38.5°C, ileus or significant abdominal distention, mental status changes, white blood cells ≥ 35,000 cell/mm, serum lactate >2.2 mmol/L, or end organ failure (Surawicz, et al., 2013). The SHEA/IDSA guidelines define mild to moderate disease as white blood cell count of 15,000 cells/µL or lower with a serum creatinine level less than 1.5 times the premorbid level (Cohen et al., 2010). Severe disease is defined as leukocytosis of 15,000 cells/µL or higher with a serum creatinine level greater than 1.5 times the premorbid level (Cohen et al., 2010). Severe, complicated disease includes the criteria for severe disease in addition to hypotension, shock, ileus, or megacolon.

Mild to moderate CDI. The ACG guidelines recommend discontinuation of inciting antimicrobials, avoiding or limiting use of anti-peristaltic agents if possible for any severity of CDI, and initiation of empiric therapy until the presence of CDI can be confirmed (Surawiz et al., 2013). The ACG guidelines recommend metronidazole 500 mg orally three times per day for 10 days (Surawicz et al., 2013). If no clinical improvement is noted within 5 to 7 days, consideration should be given to changing to vancomycin 125 mg orally four times per day for 10 days. If a patient is intolerant or allergic to metronidazole or if a woman is pregnant or breastfeeding, vancomycin with the above standard dosing should be utilized (Surawicz et al.,2013). First trimester exposure to metronidazole is not recommended as there is concern it can cross the

placenta. Case reports have described facial anomalies with maternal metronizadole exposures (Surawicz et al., 2013). Metronidazole and its active metabolites have been found in breast milk and the plasma of breastfeeding infants (Surawicz et al., 2013).

The SHEA/IDSA offer the same recommendations with exception of the addition giving metronidazole 500 mg orally three times up 14 days for mild to moderate disease (Cohen et al., 2010). The ACG guidelines recommend 10 days for the length of treatment for mild to moderate disease (Surawicz et al., 2013). A systematic review conducted by Bagdasarian et al. (2015) also recommends metronidazole 500 mg orally three times a day for 10 to 14 days for mild to moderate CDI. Metronidazole by intravenous route is not recommended as monotherapy (Bagdasarian et al., 2015). A study by Johnson et al. (2014) showed a lower clinical success rate for metronidazole versus vancomycin.

A systematic review by O'Horo et al., 2014 found moderate-strength evidence that treatment with either oral vancomycin or oral metronidazole has consistent efficacy for clinical cure. A systematic review by Khanna & Pardi (2012) also showed evidence metronidazole has similar efficacy to vancomycin as a treatment for mild to moderate CDI. A systematic review by Van Nispen tot Pannerden, C.F., Verbon, A., & Kuipers, E.J. (2011) suggested stopping inciting antimicrobials, metronidazole 500 mg orally three times per day for 10 to14 days or vancomycin 125 mg orally four times a day for 10 to14 days or metronidazole 500 mg intravenous three times a day if the oral route could not be given. Consideration to monotherapy with fidaxomicin 200 mg orally twice daily was also suggested.

Severe CDI. The ACG clinical treatment guidelines recommend use of vancomycin 125 mg orally four times per day for 10 days (Surawicz et al., 2013). The SHEA/IDSA guidelines recommend provide the same recommendation for severe CDI with the course of treatment can be between 10 and 14 days (Cohen et al., 2010).

A retrospective, non-interventional study by Bass et al., 2012 showed no difference in clinical cure between monotherapy with oral vancomycin versus combination therapy of oral

vancomycin with oral metronidazole (57.1% vs.65.1%, p = 0.49). However, the sample size was small (*n* =78) and several limitations were noted by the investigators. Those included: incomplete medical records, potential unaccounted differences in the clinician's decision to prescribe monotherapy versus combination therapy, practice changes over the span of the study, and changed therapy within the first 72 hours (Bass et al. (2013).

In a systematic review by Khanna & Pardi (2012) oral vancomycin was found to be superior over metronidazole for clinical cure rate in severe CDI (97% vs. 76%). A systematic review by Bagdasarian et al. (2015) found the same results. An additional study found higher treatment failure with metronidazole compared to vancomycin (22.4% vs. 14.2%, *p* = .002).

A systematic review by Van Nispen tot Pannerden et al (2011) suggested vancomycin 500 mg orally four times per day for 10-14 days or metronidazole 500 mg intravenous every 8 hours if oral route is not possible and vancomycin 500 mg four times per day via nasogastric tube or enema. If patients have a segment of the colon that cannot be reached by oral medication due an ileus or surgical alteration, consideration should be given to adding vancomycin enemas to the above therapies (Surawicz et al., 2013).

Severe, complicated CDI. The ACG guidelines recommend vancomycin 125 mg orally four times per day plus intravenous metronidazole 500 mg three times per day in patients with severe, complicated CDI without the presence of abdominal distention (Surawicz et al, 2013). In cases complicated by an ileus or megacolon and/or significant abdominal distention, it is recommended to use vancomycin 500 mg orally four times per day and per rectum 500 mg in 500 mL of solution four times per time plus intravenous metronidazole 500 mg three times per day. Surgical consultation for possible colectomy should be considered in patients presenting with hypotension requiring vasopressors, clinical signs of sepsis, organ dysfunction, mental status changes, white blood cell count ≥50,000 cell/μL, lactate ≥5 mmol/L, or failure to improve with medical therapy after 5 days (Surawicz et al., 2013). The SHEA/IDSA guidelines recommend oral vancomycin 500 mg orally four times per day (and per rectum 500 mg in 100

mL normal saline every 6 hours if an ileus if present) with or without intravenous metronidazole 500 mg three times per day for severe CDI (Cohen et al., 2010). Additionally, a colectomy is recommended for severely ill patients. Cases with a serum lactate ≥5 mmol/L and a white blood cell count ≥50,000 µL have been associated with increased perioperative mortality (Cohen et al., 2010).

A systematic review by Bagdasarian et al (2015) showed oral vancomycin 125 mg is non- inferior to higher doses for the treatment of severe CDI. However, expert opinion favors higher doses in both severe and severe/complicated disease. The review also showed support for the use of rectal vancomycin as an adjunct therapy. The review also revealed treatment failures have also been noted in patients that received intravenous metronidazole as monotherapy (Bagdasarian et al., 2015).

Recurrent CDI. After treatment for an initial episode of CDI, the chance of recurrence is 10 to 20% (McFarland et al., 2009; Surawicz et al., 2013). After one recurrence, the chance of developing further recurrences is 40 to 60%. The ACG guidelines recommend using the same regimen as the initial episode for the first recurrence of CDI. However, if the first recurrence is a severe presentation then vancomycin is recommended. For a second recurrence, a pulsed vancomycin regimen should be used. Fecal transplantation should also be considered (Surawicz et al., 2013). The SHEA/ISDA guidelines recommend the same management for recurrent CDI (Cohen et al., 2010).

A JBI review (Xue, 2014) suggest the following tapering vancomycin regimen: 125 mg every 6 hours for 10 to14 days, 125 mg every 12 hours for 7 days, 125 mg every 24 hours for 7 days, and 125 mg every 48-72 hours for 2 to 8 weeks. In a systematic review (Bagdasarian et al., 2015), pulsed vancomycin was recommended for subsequent recurrent CDI as cited in McFarland et al., (2009). Tapering and pulsed courses of vancomycin were associated with significantly fewer recurrences (31%; $p = .01$ and 14.3%; $p = .02$) (McFarland et al., 2009).

A systematic review by Van Nispen tot Pannerden et al. (2011) also recommended repeating the same regimen as the first episode of CDI. For a second recurrence of mild disease, fidaxomicin or rifaximin or *S. boulardii* were suggested. However, there is a risk of fungemia associated with *S. boulardii* use in patients with central venous catheters and immunosuppressed patients (Van Nispen tot Pannerden et al., 2011). For a second recurrence of mild disease, the same systematic review suggested vancomycin 125 mg orally four times per day for 10 to 14 days followed by tapering, fidaxomicin 200 mg twice daily for 10 to14 days, or rifaximin 200 to 400 mg twice daily for 10 to14 days, or *S. boulardii* 500 mg twice daily for 21 to 28 days (Van Nispen tot Pannerden et al., 2011). For a second occurrence with severe disease, vancomycin 500 mg orally four times per day for 10 to14 days or metronidazole 500 mg intravenous (if oral route is not possible) and vancomycin 500 mg four times per day via nasogastric tube or enema were recommended according to the systematic review by Van Nispen tot Pannerden et al (2011). Additionally, consideration to fecal transplant, monoclonal antibodies, or immunoglobulins were recommended for third and subsequent recurrences (Van Nispen tot Pannerden et al.,2011).

Duration of therapy. Although it is a common practice to prescribe treatment for 10 to 14 days, the ACG guidelines suggests there is no evidence to support the efficacy of extending treatment beyond 10 days in mild to moderate cases of CDI (Surawicz et al., 2013). Additionally, there is also no evidence to support use of extending CDI treatment beyond 10 days for persons on simultaneous antimicrobial therapy for other infections (Surawicz et al., 2013).

Gastric acid suppression. A case control study by Khanna, Aronson, Kammer, Baddour, & Pardi (2012) showed patients on gastric acid suppression therapy were significantly older (69 vs. 56, p <.001), more likely to have severe disease (34.2% vs. 23.6%, p = .03), and severe, complicated disease (4.4% vs. 2.6%, p =.006) than patients not receiving gastric acid suppression therapy. There was no association found between treatment failure or recurrent disease development and gastric acid suppression use. After adjusting for age and co-

morbidities, patients on gastric suppression therapy were not more likely to experience severe disease, severe/ complicated disease, treatment failure, or recurrent infection (Khanna et al., 2012).

A retrospective case control study conducted by Barletta, E-Ibiary, Davis, Nguyen, & Ramey (2013) showed hospitalized patients who developed CDI were more likely to have been on a proton pump inhibitor (PPI) (76% vs. 39%; p <.001) and had a longer duration of therapy (median range 5 days [0-20] vs. 0 days [0-11]; p <.001). A longer duration of PPI therapy was found to be associated with CDI. In 2012, the Food and Drug Administration's Adverse Reporting System released a warning to the public PPI use may increase the risk of *Clostridium difficile* associated diarrhea (CDAD). The FDA cited most studies demonstrated a 1.4 to 2.75 higher risk for CDAD for persons using PPIs compared to those that did not use PPIs. However, many of the subjects had other risks factors including antibiotic use, older age, and co-morbid conditions (Estes, 2012).

The SHEA/IDSA and ACG guidelines both suggest limiting or avoiding the use of anti-peristaltic agents as they may obscure symptoms and trigger the development of complicated disease. ACG guidelines suggest the use of anti-peristaltic agents in the presence of CDI must include concomitant CDI treatment (Surawicz et al., 2013).

Fidaxomicin. Fidaxomicin was approved by the FDA for treatment of CDI in 2011. A treatment specifically for CDI had not been approved by the FDA for nearly twenty years prior to this approval. Studies have showed promise for its use particularly in regards recurrence rates. However, cost remains a factor that may be hindering its use. An academic medical center pharmacist provided the following retail costs for 10 day treatment: vancomycin 125 mg orally four times a day $1392.00, metronidazole 500 mg orally three times per day $37.84, and fidaxomicin 200 mg orally twice daily $3,927.12 (T. Shelton, personal communication, June 30, 2015).

A double blind, randomized control trial RCT comparing the safety and efficacy of fidaxomicin and vancomycin for the treatment of CDI, which showed non-inferiority of fidaxomicin for clinical cure rate (87.7% vs.86.8%). In patients receiving antibiotics for other infections cure rate was higher with fidaxomicin (90.2% vs. 73.3%; $p = 0.031$). Treatment emergent adverse events were not significantly different for fidaxomicin and vancomycin (7.6% vs. 6.5%) (Cornley et al., 2012).

Scott (2013) conducted a review of two RCTs, the OPT 80-003 trial and OPT-80-004 trial. The OPT 80-003 trial revealed a similar clinical cure rate between fidaxomicin and vancomycin mITT 88.2% vs. 85.8%. Recurrence rate was lower in the fidaxomicin group (mITT 15.4% vs. 25.3%). Global cure rate were also higher among the fidaxomicin group (mITT 74.6% vs. 64.1%). In the OPT-80-004 trial results were similar compared fidaxomicin and vancomycin including: clinical cure (mITT 87.7% vs. 86.8%), recurrence (mITT 12.7% vs. 26.9%), and global cure rate (mITT 76.6% vs. 63.4%).

Another RCT conducted by Louie et al. (2011) also the compared the efficacy of fidaxomicin and vancomycin in treatment of CDI. The clinical cure rates for fidaxomicin were non-inferior (mITT 88.2% vs. 85.8% respectively). Significantly fewer patients in the fidaxomicin group developed recurrence (mITT 15.4% vs. 25.3%, $p = 0.005$).

The ACG guideline did not include fidaxomicin as a current treatment recommendation. They did state at the time of its FDA approval for CDI treatment in 2011, only 2 RCTs had demonstrated non-inferiority to vancomycin. The ACG guideline authors noted several limitations to these studies including: neither trial was over 90 days, no differences in minimal inhibitory concentrations (MIC) between B1/NAP/027 and non-B1/NAP/027, both have similar activity against gram positive stool bacteria, and surveillance testing in the fidaxomicin arm already had revealed the evolution of a *C. difficile* strain with elevated MIC concentration to fidaxomicin due to mutation in the RNA polymerase B. They additionally cite resistance to vancomycin in vitro has not been observed, and cost of fidaxomicin is significantly higher than

fidaxomicin. They concluded by advising clinicians should consider fidaxomicin use with caution until more post marketing clinical trials are conducted (Surawicz et al., 2013).

The 2010 SHEA/ISDA did not include any recommendations regarding the use of fidaxomicin in CDI. However, it did not receive FDA approval for use in CDI until May 2011.

Guideline concordant treatment and patient outcomes. A study by McEllistrom et al. (2014) demonstrated of 78 treatment cases in a 661 bed acute tertiary care teaching hospital examined 78 cases of CDI and the rendered treatment to determine the potential usefulness of a computerized decision support pathway to guideline CDI treatment. Sixty-one percent of patients received CDI treatment non adherent to SHEA/IDSA 2010 guidelines for CDI. For mild to moderate disease, 85.7% received guideline concordant treatment. However, no patients with severe disease (0/43) received recommended treatment (p <0.01). Nearly 18 % of patients with severe disease received guideline discordant treatment of concurrent oral metronidazole and vancomycin.

A study by Jardin et al. (2013) examined the treatment patterns and outcomes for severe CDI pre- and post- implementation of a severity-based *Clostridium difficile* infection treatment policy. Use of oral vancomycin for severe CDI increased significantly following implementation of the policy (14 % to 91%, p <0.0001), and refractory disease in patients with severe CDI decreased significantly from 37% to 15% (p = 0.0035) following policy implementation.

Another study by Jury et al. (2013) found a *Clostridium difficile* stewardship initiative improved adherence to practice guidelines and improved timeliness of treatment initiation. The number of patients prescribed metronidazole for severe disease decreased from 6% to 0. Median time from a positive test to treatment was reduced by 10 hours. 23 vs. 13 (p = .002) vs. 12 (p = .003).

A study by Brown & Seifert (2014) found CDI therapy concordant with the 2010 SHEA/IDSA guidelines had better outcomes. The 51.7% of patients that received guideline concordant therapy developed fewer complications (17.2% vs. 35.6%, p = .0007). Patients with

severe and complicated CDI were found to have received guideline-concordant therapy less often than patients with mild disease (19.7% vs. 35.3%, and 81.2% respectively, p <0.001).

A summation of the CDI pharmacological management recommendations based on disease severity have been extracted from two major clinical guidelines, the ACG and SHEA/IDSA. The recommendations include treatment for mild to moderate disease, severe disease, severe/complicated disease, and recurrent disease. Clinical definitions for each disease severity are also based on recommendations from those two major clinical guidelines.

Table 2.4

Recommendation for Treatment and Disease Severity Definitions

Disease severity	ACG guidelines	SHEA/IDSA guidelines
mild to moderate disease	mild – presence of diarrhea only moderate- diarrhea with other symptoms not meeting severe disease criteria metronidazole 500 mg orally three times per day for 10 days if unable to take metronidazole, vancomycin 125 mg orally four times per day for 10 days if no clinical improvement is noted within 5 to 7 days, consideration should be given to changing to vancomycin 125 mg orally four times per day for 10 days	WBC ≤15,000 OR serum creatinine < 1.5 times premorbid level metronidazole 500 mg orally three times per day for 10 to 14 days
severe disease	serum albumin <3 g/dL and one of the following: WBC ≥15,000 OR abdominal tenderness	WBC ≥15,000 OR serum creatinine >1.5 times premorbid level

	vancomycin 125 mg orally four times per day for 10 days	vancomycin 125 mg orally four times per day for 10 to 14 days
severe/complicated disease	intensive care unit admission OR hypotension with or without required use of vasopressors OR fever ≥38.5° OR ileus OR megacolon OR significant abdominal distention OR mental status changes OR WBC≥35,000 OR WBC <2,000 OR serum lactate >2.2 mmol/L OR evidence of end organ failure vancomycin 500 mg orally four times per day AND metronidazole 500 mg intravenous three times per day AND vancomycin 500 mg in 500 mL of saline per rectum four times per time PLUS consider surgical consultation for possible colectomy	hypotension, shock, ileus, or megacolon vancomycin 500 mg orally four times per day AND metronidazole 500 mg three times per day AND rectal instillation of vancomycin if a complete ileus is present
first recurrence, mild to moderate disease	recurrence- within 8 weeks of treatment completion same regimen as initial treatment	same regimen as initial treatment
first recurrence, severe disease	vancomycin 125 mg orally four times per day for 10 days	vancomycin 125 mg orally four times per day for 10 to 14 days

second recurrence	vancomycin 125 mg orally four times per day for 10 days followed by 125 mg pulsed every 3 days for ten doses	vancomycin tapered regimen: 125 mg every 6 hours for 10-14 days, 125 mg every 12 hours for 7 days, 125 mg every 24 hours for 7 days, and 125 mg every 48-72 for 2 to 8 weeks
≥ 3 recurrences	consider fecal microbiota transplant	consider fecal transplant OR consider nitazoxamide OR intravenous immunoglobulins 150-400 mg/kg

*Discontinuation of inciting antibiotics should be stopped if possible and gastric acid suppression should be stopped or limited if possible

Answering the Clinical Question

What is the effect of clinician adherence to an evidence-based *Clostridium difficile infection* (CDI) order set on clinical cure rate (resolution of diarrhea and no longer requiring treatment for CDI), 30-day disease recurrence, and 30-day readmission rates for CDI?

The EBP recommendations were based upon the ACG and SHEA/IDSA guidelines and supplemented with expert opinions. The recommendations drawn from the literature were utilized to develop a pharmacological evidence-based order set for CDI treatment. See Table 2.5. Although the are several other therapies that have been utilized for the treatment of CDI, the focus of this project is on pharmacological management supported by the two current major guidelines from ACG and SHEA/IDSA. Expert opinions from a gastroenterologist, an internist, and a clinical pharmacist were elicited and incorporated into the order set. Fidaxomicin was not included in the order set as it is a non-formulary drug at the clinical agency, and current policies do not allow inclusion of non-formulary drugs on order sets. See appendix A.

The development and implementation provided clinicians with an accessible tool that defined disease and provided recommended treatment. The primary outcome were to determine

the effects of clinician adherence to an evidence-based treatment order set on clinical cure rate, 30-day disease recurrence, and 30-day readmissions for CDI.

CHAPTER 3

IMPLEMENTATION OF PRACTICE CHANGE

Hospital systems are currently facing potential financial penalties for hospital acquired infections, such as catheter associated urinary tract infections (CAUTI) and central line associated blood stream infections (CLABSI) in order to improve patient outcomes and reduce healthcare expenditures. In the next few years, CDI will be included in the Center for Medicare and Medicaid's HAC Reduction Program. Therefore, it is crucial to implement evidence-based practices to provide the best care for CDI to achieve clinical cure, reduce the development of associated complications, and prevent disease recurrence. This is especially important with the emergence of hypervirulent strains of *C. difficile* and increased risk for recurrent disease. Implementation of an evidence-based practice order set for the treatment of CDI can be a potential solution to improve clinician adherence to current clinical guidelines. Therefore, improvement in clinical cure rates, reduction in disease recurrence, reduction in readmission rates for CDI, and prevention of associated complications could potentially be achieved. This chapter describes the proposed project methods to answer the following the clinical question: What is effect of clinician adherence to an evidence-based *Clostridium difficile* infection (CDI) treatment order set on clinical cure rate (resolution of diarrhea and no longer requiring treatment), 30-day disease recurrence, and 30-day readmission rates for CDI?

Participants and Setting

Participants in the retrospective pre-implementation phase of this project included a convenience sample of 100 adult, non-critical care inpatients who met the eligibility criteria at a Midwestern academic medical center during the 3-month period of time prior to project implementation (n = 100). The participants in the prospective post-implementation phase

included a convenience sample of 45 adult, non-critical care inpatients (*n* = 100). Eligibility criteria included patients with a stool assay confirmed CDI, age 18 years or older, and inpatient status in a non-critical care areas. Exclusion criteria included non-English speaking patients, and persons not able to provide informed consent or consent by proxy.

The academic medical center is part of a large and comprehensive health care system. The health care system is comprised of 18 hospitals, as well as urgent care centers, and multiple outpatient facilities throughout a Midwestern state. The combined hospitals have a total of 3,098 staffed patient beds and 29,395 team members. Six of those hospitals have achieved and maintained Magnet Designation, a national honorary recognition for nursing excellence bestowed by the American Nurses Credentialing Center. Fewer than 400 hospitals nationwide have achieved this highly regarded designation (IU Health, 2015).

The academic medical center is comprised of two not-for-profit hospitals that have a total of 1,371 beds and combined admit 55,379 patients annually. The facility selected for the EBP project implementation has a 311 bed capacity. The academic medical center has been nationally recognized in *The U.S. News Best Hospitals* for 18 consecutive years. This is a national ranking achieved by the top 3% of U.S. hospitals. Additionally, the health care system has a partnership with one of the largest, well known, and prestigious medical schools in the Midwest (IU Health, 2015).

The mission of the healthcare system is to improve the health of our patients and community through innovation and excellence in care, education, research and service. The proposed evidence-based project is congruent to that mission of excellence (IU Health, 2015).

Outcomes

The primary outcome of interest was clinician adherence to an evidence-based treatment order set for CDI treatment. Secondary outcomes of interest included: achievement of clinical cure defined as resolution of symptoms and not requiring further treatment for CDI, 30-day disease recurrence, and 30-day readmission rates for CDI.

Intervention and Planning

The CDI treatment order set was based on two national guidelines from ACG and SHEA/IDSA and supplemented with other high level evidence from RCTs and systematic reviews. The order set included severity-based pharmacological treatments, as well as clinical definitions for each disease severity. The disease severities included mild to moderate, severe, severe/complicated, as well as recurrence. The order set was be reviewed by three health care professionals (a gastroenterologist, an internist, and a clinical pharmacist) associated with the healthcare system prior to implementation. The feedback from the reviewers was incorporated into the order set. The finalized order set was presented to the academic medical center informatics review board for approval. Prior to implementation, clinicians were provided with information about the order set using a multimodal educational approach, including: email notifications, newsletter articles, posters, and face-to-face discussions. It was initially planned for *C. difficile* positive stool assays to trigger a computer-based alert and message referring the clinician to utilize the CDI order set. Due to time restrictions associated with implementing the project and concern for alert fatigue, this was not feasible. Alert fatigue is a phenomenon that occurs when healthcare workers' exposure to numerous alerts, ranging from physiological monitoring alarms to drug-drug interactions notifications with computerized physician order entry, can lead to desensitization and failure to respond to such alerts over time. This can potentially lead to unintended patient harm. Wise utilization of computer-based alerts may help to minimize such unintentional consequence of clinicians and other healthcare workers ignoring the alerts (Embi & Leonard, 2012). Clinicians and other healthcare workers at the clinical agency currently receive computer-based alert for tobacco cessation, infectious disease (i.e. VRE, MRSA), behavioral care contracts, narcotic agreement contracts, and NPO status >72 hours.

Recruiting participants

After obtaining Institutional Review Board (IRB) approval, retrospective data were collected from a convenience sample of 100 previous patients meeting eligibility criteria. These data were supplied by the infection prevention team at the project implementation site in a de-identified form, so the IRB waived the need to obtain informed consent from participants in the retrospective sample.

The prospective sample was recruited using a sentinel event reporting system within the electronic health record that identified all positive *C. difficile* stool assays during the post-implementation period. The principal investigator or research assistant approached each patient meeting inclusion criteria to explain the purpose, potential risk, potential benefit, and procedures of the study, and to invite eligible and interested patients to enroll in the study.

Data Collection

Retrospective and prospective data included: participant demographic information, where the patient was admitted from, nursing unit, primary team, consulting team, risk factors for CDI, disease severity, clinician guideline adherence, order set adherence (post-implementation group only), clinical cure rate, discharge location, 30- day disease recurrence, and 30-day readmission rate for CDI. Retrospective data were collected for participants admitted between April 2015 and July 2015, and prospective data were collected from November 2015 to February 2016. Data for each participant were recorded on hard-copy case report forms and promptly entered into a password-protected spread sheet database that was only accessible by the principal investigator and faculty advisor.

Analysis

The full data analysis plan is described in Table 3.1. Briefly, characteristics of the retrospective and prospective samples were analyzed using descriptive statistics (mean and standard deviation for age in years, percent in each category for all categorical variables) and compared using Student's *t*-test for age in years and either the Chi-square test of independence

or Fisher's exact test for categorical variables. The level of significance for comparing these sample characteristics was set at 0.05.

Retrospective and prospective data were pooled to answer the primary PICOT question for this project. The primary project outcomes (i.e. cure rate, 30-day recurrence of CDI, 30-day readmission for CDI) were compared between those with complete treatment adherence to those with incomplete treatment adherence using either the chi-square test of independence or Fisher's exact test with a level of significance equal to 0.05.

Table 3.1

Data Analysis Plan

Variables	Statistical analysis
Age (years)	mean, standard deviation *t*-test for baseline-to-post comparisons
Sex	% male, % female Chi-square test for baseline-to-post comparisons
Race	% White, % African-American, % American Indian or Alaskan Native, % Asian, % Native Hawaiian or Pacific Islander, % Other, % Not identified Fisher's exact test for baseline-to-post comparisons
Location prior to admission	% clinic, % home, % emergency department, % another hospital, % short term rehab/extended care facility, % deceased, % other

	Fisher's exact test for baseline-to-post comparisons
Primary medical team	% internal medicine, % bone marrow transplant, % general surgery, % transplant surgery, % hepatology, %urology, % pulmonary, % plastic surgery, % hematology/oncology, % renal transplant Fisher's exact test for baseline-to-post comparisons
Consulting team and effect on clinical cure rate, 30-day recurrence, and 30-day readmission for CDI	% infectious disease, % gastroenterology, % both Fisher's exact test for baseline-to-post comparisons
Disease severity	% mild to moderate, % severe, % severe/complicated, % unknown, recurrent mild to moderate, % recurrent severe or % severe/complicated, % second recurrence, third or more recurrence Fisher's exact test for baseline-to-post comparisons
Risk factors for CDI	% immunosuppression, % antimicrobial therapy, % healthcare facility, % gastric acid suppression, % history of CDI Chi-square test for baseline-to-post comparisons

Clinician adherence to treatment guideline	% yes, % no (orders must have been adherent to current clinical guidelines) Chi-square test for baseline-to-post comparisons
Clinician order set use	% yes, % no Fisher's exact test for post-implementation analysis
Over treatment Under treatment	% yes, % no %yes, % no Chi-square test for baseline-to-post comparisons
Clinical cure prior to discharge (resolution of diarrhea and no longer requiring treatment for CDI)	% yes, % no Chi-square test for baseline-to-post comparisons
30-day readmission for CDI	% yes, % no Chi-square test for baseline-to-post comparisons
Effect of clinician guideline adherence on clinical cure rate	Chi-square test of independence for comparison between adherent and non-adherent groups
Effect of clinician guideline adherence on 30-day disease recurrence	Fisher's exact test for comparison between adherent and non-adherent groups
Effect of clinician guideline adherence on 30- day readmissions for CDI	Fisher's exact test for comparison between adherent and non-adherent groups

Protection of Human Subjects

Prior to seeking IRB approval to conduct the study, a required computer-based course on protecting human subjects was completed by the PI. IRB approval was received from Valparaiso University. The clinical agency IRB policy required students not associated with their university affiliate to obtain IRB only from their affiliated university. However, the proposed study was presented to the academic center's nursing research committee. Informed consent was obtained from each participant or from a legally authorized representative. If informed consent was obtained from a legal representative, a legal documentation stating the right serve as the legal representative of the participant was obtained and kept with the informed consent. Once data collection began, the patient health information was stored in a locked filing cabinet accessible only to the primary investigator. Any computer based records were password protected to ensure privacy of the subjects. Due to the number of participants to consent, IRB approval was made to include the utilization of research assistants to obtain consent was requested and granted.

CHAPTER 4

FINDINGS

The purpose of this evidence-based project was to determine the effect of adherence to an evidence-based CDI treatment order set on clinical cure rates, 30-day disease recurrence, and 30-day readmissions for CDI. A computer-based order set for CDI treatment was developed and implemented for clinician utilization. The aim was to determine if clinician adherence improved patient outcomes.

Size

Baseline data were collected from a pre-implementation group consisting of a convenience sample of 100 inpatient adults diagnosed with stool assay confirmed CDI at a Midwestern academic center from April 2015 to July 2015 (n = 100). Post-implementation data was gathered from a convenience sample of 47 (n = 47) at the same academic medical center from November 2015 to February 2015. Two patients were still hospitalized at the end of the study period and therefore were excluded from the post-implementation group leaving a post-implementation sample of 45 (n = 45).

Characteristics

Age, gender, race, length of stay, location prior to admission, and disease severity did not differ significantly between the retrospective and prospective samples. Risk factors for the development of CDI were also similar between the pre- and post-implementation groups with exception of antimicrobial therapy (60% vs. 77.8%, p = 0.037) and recent healthcare facility stay (17% vs. 40%, p = 0.003). See Table 4.1.

Twenty-two percent of participants in the retrospective sample experienced clinical cure, compared to eight percent in the prospective sample. This difference was not statistically significant (p = 0.562). There was also a statistically nonsignificant difference between the retrospective and prospective samples with regard to CDI recurrence or CDI re-admissions (p = 0.425 and 0.096, respectively).

The effect of gastroenterology and infectious disease consultation on outcomes was also analyzed. The highest level of adherence was observed when either the gastroenterology or infectious disease service was consulted (50%). If neither of these services were consulted, adherence was 36.5%. If both of these services were consulted, adherence was only 25%. However, these differences were not statistically significant ($p = 0.434$). There was also not enough evidence to conclude that the clinical cure rate was better when consulting gastroenterology or infectious disease specialists ($p = 0.504$). The 30-day recurrence rate was 21.4% when consulting gastroenterology and 8.3% rate when consulting infectious disease. When consulting both, the recurrence rate was 25%, and when consulting neither, the recurrence rate was 11.9%. There was not enough evidence to conclude consulting either team improved recurrence rates ($p = 0.628$). There were only five 30 day readmissions for CDI; therefore, the effect of consultation could not be answered with any confidence.

Table 4.1

Characteristics of Pre- and Post-Implementation Groups

Characteristics	Pre-implementation (n = 100)	Post-implementation (n = 45)	p
Age (years) [a]	54.8 (16.1)	53.2 (16.8)	0.594
Gender (%)[b]			
Male	53 (53.0)	25 (55.6)	0.775
Female	47 (47.0)	20 (44.4)	
Race (%)[c]			0.824
Black	16 (16.0)	8 (17.8)	
White	82 (82.0)	36 (80.0)	
Hispanic	1 (1.0)	1 (2.2)	
Unknown	1 (1.0)	0 (0.0)	
Length of stay (days) [d]	7 (4-19)	1 (6-21)	0.155
Admitted from (%)[c]			0.399
Clinic	11 (11.0)	4 (8.9)	
Home	32 (32.0)	10 (22.2)	
Emergency department	13 (13.0)	5 (11.1)	
Other hospital	32 (32.0)	23 (51.1)	
Short/long term care	3 (3.0)	0 (0.0)	
Unknown	9 (9.0)	3 (6.7)	

Risks (%)[b]			
Immunosuppression	53 (53.0)	29 (64.4)	0.198
Antimicrobial use	60 (60.0)	35 (77.8)	0.037
Recent healthcare facility	17 (17.0)	18 (40.0)	0.003
Gastric acid suppression	75 (75.0)	36 (80.0)	0.511
History of CDI	28 (28.0)	10 (22.2)	0.464
Disease severity (%)[c]			0.271
Mild to moderate	35 (35.0)	22 (48.9)	
Severe	13 (13.0)	4 (8.9)	
Severe/complicated	23 (23.0)	11 (24.4)	
1st recurrence mild to moderate	3 (3.0)	2 (4.4)	
1st recurrence severe	8 (8.0)	1 (2.2)	
2nd recurrence	6 (6.0)	0 (0)	
3rd or more recurrence	12 (12.0)	4 (8.9)	
Asymptomatic	0 (0.0)	1 (2.2)	

[a]Reported as mean (SD), p-value from two-sample t test.
[b]Reported as count (%), p-value from chi-square test.
[c]Reported as count (%), p-value from Fisher's exact test.
[d]Reported as mean, p-value from Wilcoxon sum test

Clinician characteristics

Pre- and post-implementation characteristics of the primary and consulting teams were similar. See Table 4.2.

Table 4.2

Pre- and Post-Implementation Clinicians

Primary team (%)[c]			0.657
Internal medicine	38 (38.0)	17 (37.8)	
Bone marrow transplant	7 (7.0)	3 (6.7)	
General surgery	10 (10.0)	4 (8.9)	
Transplant surgery	11 (11.0)	6 (13.3)	
Hepatology	4 (4.0)	5 (11.1)	
Urology	10 (10.0)	3 (6.7)	
Pulmonary	1 (1.0)	2 (4.4)	
Hematology/oncology	11 (11.0)	2 (4.4)	
Renal transplant	6 (6.0)	3 (6.7)	
Plastic surgery	2 (2.0)	0 (0.0)	
Consultants (%)[c]			0.705
Gastroenterology	19 (19.0)	9 (20.0)	
Infectious disease	8 (8.0)	4 (8.9)	
Both	4 (4.0)	0 (0.0)	
Neither	69 (69.0)	32 (71.1)	

[a]Reported as mean (SD), p-value from two-sample t test.
[b]Reported as count (%), p-value from chi-square test.
[c]Reported as count (%), p-value from Fisher's exact test.
[d]Reported as mean, p-value from Wilcoxon sum test

Treatment measures

A Chi-square test and the Fisher's exact test were used to determine the effect evidence-based guideline treatment order adherence on clinical cure rates, 30-day recurrence rates, and 30- day readmissions for CDI in the pre- and post-implementation groups.

Outcomes

The overall rate of guideline adherence was 39.3% (pre- vs post-: 35% vs 48.9%, p = 0.113). When guideline adherence was not met, 17.9% (pre- vs post-: 18 vs 17.8%) was over-treatment and 41.4% (pre- vs post-: 45% vs 33.3%) was under treatment. The effect of guideline adherence on achievement of clinical cure rate (resolution of diarrhea and no longer requiring treatment) was 15.8% adherent group vs 23.9% non-adherent (p = 0.241). The effect of guideline adherence on 30-day recurrence rates was 12.3% adherent group vs 14.8% non-adherent group (p = 0.425).The effect of guideline adherence on 30-day readmission rates was 7.0% among the guideline adherent group versus 1.1% among the non-adherent group (p = 0.078).

Table 4.3

Treatment Guideline Adherence

		Adherent	Over treatment	Under treatment	None	Total
Frequency	Pre-	35	18	45	2	100
Percent		24.14	12.41	31.03	1.38	68.97
Row Percent		35.00	18.00	45.00	2.00	
Collective percent		61.40	69.23	75.00	100.00	
	Post-	22	8	15	0	45
		15.17	5.52	10.34	0.00	31.03
		48.99	17.78	33.33	0.00	
		38.60	30.77	25.00	0.00	
	Total	57	26	60	2	145
		39.31	17.93	41.38	1.38	100.00

Table 4.4

Guideline Adherence Effect on Clinical Cure Rate

	Adherence	Clinical cure				
		Yes	No	Unknown	Not applicable	Total
Frequency	Yes	9	47	1	0	57
Percent		6.21	32.41	0.69	0.00	39.31
Row Percent		15.79	82.46	1.75	0.00	
Collective percent		30.00	45.19	25.00	0.00	
	No	21	57	3	7	88
		14.48	39.31	2.07	4.83	60.69
		23.86	64.77	3.41	7.95	
		70.00	54.81	75.00	100.00	
	Total	30	104	4	7	145
		20.69	71.72	2.76	4.83	100.00

Table 4.5

Guideline Adherence Effect on 30-day Recurrence Rates

	Adherence	Recurrence			
		Yes	No	Deceased	Total
Frequency	Yes	7	47	3	57
Percent		4.83	32.41	2.07	39.31
Row Percent		12.28	82.46	5.26	
Collective percent		35.00	38.84	75.00	
	No	13	74	1	88
		8.97	51.03	0.69	60.69
		14.77	84.09	1.14	
		65.00	61.16	25.00	
	Total	20	121	4	145
		13.79	83.45	2.76	100.00

Table 4.6

Guideline Adherence Effect on 30-day Readmission for CDI

	Adherence	30-day readmission for CDI		
		Yes	No	Total
Frequency	Yes	4	53	57
Percent		2.76	36.55	39.31
Row Percent		7.02	92.98	
Collective percent		80.00	37.86	
	No	1	87	88
		0.69	60.00	60.69
		1.14	98.86	
		20.00	62.14	
	Total	5	140	145
		3.45	96.55	100.00

CHAPTER 5

DISCUSSION

The purpose of this evidence-based project was to determine the effect of clinician adherence to *Clostridium difficile* infection treatment guidelines on clinical cure rates, 30-day disease recurrence, and 30-day readmissions for CDI. The following section includes a discussion of the findings, applicability of the theoretical and evidence-based practice framework, study strengths and weakness, and clinical implications.

Explanation of findings

Adherence to the CDI severity-based treatment guidelines did not significantly improve clinical cure rates, 30-day recurrence rates, or 30-day readmission rates for CDI. In fact, the clinical cure rate and 30-day readmission rates for CDI tended to be worse in those with complete guideline adherence. Because these results were not statistically significant, they could have occurred due to chance alone. However, these paradoxical findings require further investigation to explore factors that could be useful in predicting which patients will benefit from guideline adherence and which ones may not. One way to approach this would be to collaborate with a nurse scientist and/or biostatistician to develop regression models that can be used to explore the effects of various predictors, including interaction effects, on each outcome. While this approach is beyond the scope of this project, another approach may be to collaborate with clinicians or use clinical experience to identify variables that may have had an impact on the outcomes of interest.

Forty-five of the eighty-five of CDI cases were included in the prospective sample. Forty patients were not included for various reasons. Twenty-one patients were discharged prior to the investigator being able to obtain IRB required written consent for participation. The principal investigator (PI) was at the academic medical center three days a week. Therefore, there were several patients discharged prior to the PI returning to the academic medical center resulting in missed recruitment opportunities. Two patients were excluded from the study as they were still

hospitalized at the time the study ended. Therefore, data on clinical cure, 30-day recurrence, and 30-day readmission rates could not be obtained in those two cases. To reduce the number of lost recruitment opportunities three research assistants (2 nurse practitioners and 1 physician) were added after IRB approval was received. Two cases were disease recurrence readmissions and were ineligible due to previous recruitment. Ten patients had some degree of altered mental status making informed consent unattainable. Two were intensive care patients and therefore were excluded due to failure to meet eligibility criteria. Two patients refused participation. One patient refused participation citing previous participation in multiple studies and several recent hospitalizations. The other patient was not able to fully comprehend the purpose of the study and his family declined participation on his behalf. One patient had a positive *C. difficile* stool assay without symptoms and was considered colonized. In the post-implementation group, 47% of patients that were diagnosed with CDI were not included in the study. Patients that were not consented due to altered mental status, may have more severe presentations of this disease. On the other hand, some of the patients that were discharged prior to being consented may have had shorter length of stays and less severe disease. Therefore, the post-implementation sample (n = 45) may not have been a true representation of the patients diagnosed with CDI at the clinical agency during the post-implementation period.

Treatment variability and experience of the prescribers may also have accounted for outcome differences. At the academic medical center, residents and fellows begin new rotations in July. Post-implementation data were collected after a new group of residents started rotations as opposed to the retrospective sample that received care from more experienced medical residents and fellows. Therefore, the prospective sample may have received less treatment from less experience clinicians.

There also may have been a greater number of patients with post-discharge follow up outside of the academic medical center health care system. Since the clinical agency is a tertiary care center it is common for patients to receive post-discharge care at other health care

systems. Therefore, there may have been unaccounted for cases of disease recurrence and/or readmission for CDI.

There also may have been confounding factors between the pre- and post-implementation groups that results in outcome variability. Those factors may have included co-morbidities, acuity levels, re-admissions to other hospitals, patient noncompliance non-adherence with treatment, and failure to correctly use appropriate CDI transmission-based precautions. Since participants were not randomly assigned to either the “adherent” or “non-adherent” groups, and these variables were not measured in this project, it cannot be assumed or verified that the confounding factors listed above were evenly distributed between participant groups.

An additional explanation for outcome variability may have been in the informatics design of the order set. Other computer-based order sets at the clinical agency leave all of the order options visible once a treatment option has been selected and initiated. For example, if a clinician selected metronidazole 500 mg orally three times a day for ten days under the mild to moderate disease recommendations, then all of the other treatment options would no longer be visible. If the patient did not respond to the initial treatment with 5 to 7 days or if the patient development a higher disease severity from initial presentation it would have been appropriate to escalate the treatment. However, those other treatment options would no longer have been visible to the clinician without initiating a new CDI order set. With the CDI order set, once a treatment option is selected all the other options “drop off” and are no longer visible. Therefore, clinicians who used the order set were unable to use the same order set to modify the CDI treatment plan. They would have had to initiate a new CDI order set for the patient if the disease severity changed, which is not how order sets are traditionally used in the implementation site. This may have hindered clinicians escalating treatment in participants who did not respond to the initial treatment or for those patients that developed a worsening severity of disease.

The results of this study varied from previous studies examining the effect of guideline adherence on patient outcomes that identified a statistically significant positive effect of clinician guideline adherence on patient outcomes. One retrospective study at a 420 bed tertiary care center examined the effect of treatment variation on the development of CDI related complications including recurrence, any surgical procedure to cure CDI, toxic megacolon, and 30-day mortality (Brown & Seifert, 2014). Length of stay and achievement of clinical cure rates were also examined. Only 51.7% of prescribers were followed the 2010 SHEA/IDSA treatment guidelines (Brown & Seifert, 2014). The patients who received guideline-adherent treatment had fewer complications than those patients who received guideline non-adherent treatment (17.2% vs 56.3%, p = <.0012) (Brown & Seifert, 2014). The difference was mainly due to a reduction in mortality (5.4% vs 21.8%, p = .0012) and infection recurrence (14% vs 35.6%, p = .007) (Brown & Seifert, 2014). Patients who presented with severe and severe complicated disease received guideline adherent treatment significantly less often than with mild disease which was consistent with the findings of this EBP study (Brown & Seifert, 2014). Study design may account for some of the outcome difference. This study was retrospective, had a larger sample (n = 180), included intensive care patients, and a more diverse racial composition that may or may not account for outcome differences. There were also no cases of CDI related mortality in this study that may have impacted outcome differences. The investigators acknowledged that there may have been unaccounted for treatment failures as there were no formal follow ups with patients upon discharge (Brown & Seifert, 2014).

Three identified studies examining the effect of guideline adherent treatment on patient outcomes all demonstrated a significant rate of clinician non-adherence which was consistent with this study. The three studies had pre-intervention guideline non-adherence rates ranging from 51.7% to 89.0% (Brown & Seifert, 2014; Jardin et al., 2013; Mc Ellistrom et al., 2014). Another study demonstrated improvement in refractory disease after implementation of a severity-based treatment policy (37 % to 15%, p = 0.035) (Jardin, et al., 2013). Again, the

sample size was larger (n = 144). Additionally, the outcome difference may have been related to the mandatory nature of the treatment policy change. Utilization of the guideline- adherent order set in this study was voluntary for clinicians.

Theoretical framework

The epidemiological triangle was the theoretical framework used to illustrate the interaction of the key components of communicable diseases, in this case *Clostridium difficile* infections. The components as it applied to the study included: *Clostridium difficile* (the infectious agent), patient (the host), and the academic medical center (the environment). Preventing and treating CDI is dependent upon understanding the components of epidemiology including pathogenicity, sporulation, transmission, and impact of the bacterial toxins on the gastrointestional tract will continue to be important factors in treating CDI, preventing associated complications, preventing transmission, and reducing disease recurrence. The order set contained treatment targeted at eliminating *Clostridium difficile* bacteria causing an infection based upon disease severity. The intent of the order set was to influence and guide clinicians to use evidence-based treatment. Identifying risk factors for the development of CDI assisted the clinicians in eliminating or reducing modifiable risks factors when feasible. For example, reducing or eliminating gastric acid suppression use. However, factors such as age could not be modified. Additionally, the order set prompted the utilization of enteric precautions. This intervention was aimed at reducing person-to person transmission through the use of protective wear (gowns and gloves), proper handwashing with soap and water, and dedicated equipment (disposable thermometer and stethoscope). Once enteric precautions were initiated, a sign was placed on the patient hospital door to alert persons entering the room of the guidelines to be followed before, during and after entry. The framework also helped to understand the effect of treatment on the host or outcomes such as cure, recurrence, and treatment failures. Although the framework provides a basic understanding of communicable diseases and interactions with the environment and host, it is not specific to CDI. Despite the applicability of the framework, it

was lacking generalizability as each infectious agent, host, and environment has unique features that cannot be accounted for by the epidemiological triangle.

Evidence-Based Practice Framework

The Iowa Model Revised: Evidence-Based Practice to Promote Excellence in Health Care was the evidence-based practice framework used to guide the development of this study. The framework was an effective model as its steps of the algorithm correlated with the process necessary to implement a practice change at the clinical agency. The model was modified as several obstacles during the change implementation required revision or involvement of other clinical agency stakeholders that were not previously identified. The clinical agency also required order set revisions to comply with institutional policies. An example was the inclusion of fidaxomicin on the initially proposed order set under disease recurrence. The request to include it on the order set was declined due to clinical agency policy against the use of non-formulary medications, such as fidaxomicin, on order sets. A suggestion was made to add a statement to the order set advising the users of the non-formulary medication status and requirement for an infectious disease consultation to order this particular medication. Unfortunately, making this addition to the order set was rejected. It was felt that this would potentially increase unwarranted use of this costly medication. It is unlikely that modifications to the model would be required for future use as they were primarily necessary due to the investigator's lack of familiarity of the clinical agency process to implement practice changes. However, the model can easily be adapted to meet the need of the user.

Strengths and weaknesses

The study incorporated current evidence from literature and included a multidisciplinary team for order set development, content review, and implementation. The order set is an easily accessible, disease-severity based treatment tool for clinicians. Although previous studies have implemented treatment stewardships, use of an order set was a novel approach to CDI treatment at the clinical agency. As far as it is known, an order set specifically directed at CDI

treatment had not previously been developed or implemented at the clinical agency. Despite the availability of the order set, only 13% of clinicians utilized the order set. This could be potentially explained by several factors including: lack of order set awareness, clinician confidence in personal CDI treatment knowledge, avoidance due to belief that order sets do not allow for treatment individualization, lack of awareness of clinical agency treatment variability among clinicians, and non-mandatory use status. Although multimodal education was used prior to order set release, the education period was limited to two weeks prior to the start of the implementation period due to delays in final approval of the order set. A longer education period prior to the order set release may have proven beneficial as it would allowed for more opportunities to reach out to more clinicians and medical students. The multimodal educational approach included: email notifications to department chiefs and chief residents, medical newsletter notification, information technology newsletter notification, posters, and face-to-face education. In retrospect, sending out email notifications to all clinicians and medical students would have been a better choice to ensure more clinicians and medical students received personal notification of the order set release. In person in-services or computer-based presentations prior to the order set release may have been useful for increasing clinician awareness to the increased number of cases of CDI at the academic medical center over the last three years, clinician treatment variability, upcoming financial penalty changes for hospital acquired CDI, and the possible association between guideline non-adherent treatment and poor patient outcomes. Short questionnaires could have also been used to test clinician knowledge of current CDI treatment guidelines and assist in the recognition of any knowledge deficits related to CDI treatment. Initially a computer-based message alerting clinicians of a positive stool study and a reminder to utilize the order set was suggested. Permission to implement such a message was declined to due to concern about alert fatigue.

Another limitation may have included avoidance of order set use among some clinicians as they may feel it fails to address the need to individualize treatment in special cases. This

issue was brought forth by one of the key stakeholders. However, as with every order set at the clinical agency a written disclaimer states that the recommendations in the order set serve as a guide and are not to replace clinical judgement. Additionally, the orders could be easily modified by clinicians. For example, a longer treatment period can be changed to meet the needs of individualize patients. One of the above mentioned studies successfully implemented a policy change that directed clinicians to utilize guidelines for treatment. The study demonstrated positive patient outcomes associated with guideline adherence. Given the initial stakeholder resistance to voluntary utilization of a guideline-based order set, significant resistance would probably make a mandatory policy change unlikely.

Generalizability to patients outside of the clinical agency was also a possible limitation as the patient population at the academic medical center have numerous risk factors for CDI (i.e. immunosuppression, antimicrobial use, recent health care facility stay, gastric acid suppression, and history of CDI) that may not be seen to the same extent in smaller hospitals.

Despite the identified limitations, this study enforced there are improvements to be made both in the treatment and prevention of CDI. This study has brought attention to the need for the clinical agency and stakeholders to strengthen efforts to improvement strategies directed at both prevention and treatment.

Implications for the future

***Practice*.** In response to the growing number of HAI, a government-based program was established to reduce payments to hospitals with poor HAI prevention performance. Currently, CAUTI, CLABSI, and surgical site infections (colon and abdominal hysterectomy) are quality measures tracked under the program. In 2017, MRSA and CDI will be added to the list of quality measures. Health care systems that fail to respond to the growing number of CDI will be at risk for financial penalties and reduced reimbursement. Reducing risk factors associated with CDI has proven challenging. Those risk factors include immunosuppression, antimicrobial therapy, recent health care facility stay, gastric acid suppression, and history of CDI. Although the

purpose of this study focused on treatment, implementing preventive measures will also be instrumental in reducing the incidence of CDI. Treatment goals need to be aimed at using evidence-based practices to successfully treat CDI and reduce future recurrence. Post-implementation data indicated few clinicians are using recommended treatment for CDI, especially for severe and severe complicated disease. These more severe cases may develop potentially fatal complications, such as pseudomembranous colitis or sepsis. Dissemination of the findings can be utilized to encourage incorporation of current evidence into clinical practice. It has also been demonstrated that preventive efforts such as reducing modifiable risk factors (i.e. gastric acid suppression and antimicrobial therapy) may potentially reduce disease recurrence. Implementing a treatment policy as with one of the previously mentioned studies would likely improve clinician guideline adherence. The findings will be disseminated at the clinical agency to determine if the set will be extended beyond the pilot study period. It will also be suggested for the clinical agency to develop a multidisciplinary team aimed at both treatment and prevention strategies.

***Theory*.** Utilization of theoretical framework, such as the Iowa Model, will prove invaluable for future efforts in the prevention and treatment of CDI. The model offers a systematic approach to identifying problems, prioritizing problems, searching for and synthesizing best evidence in literature, developing and implementing changes, evaluating implemented practice change, and determining if the proposed change will be adopted into practice. The model has been revised twice times since the original model was released. The changes have been in response to changes in the health care industry and used feedback. This demonstrates the responsiveness and adaptability to the dynamic nature of health care. It is likely the model will continued to be revised in response to changes in healthcare.

***Research*.** Future longitudinal, multicenter studies should be conducted to determine the long-term effect of treatment stewardships on clinical cure rates, 30-day disease recurrence, and 30-day readmission rates for CDI. Future studies should also be designed to account for

confounding factors that may impact patient outcomes. Future studies should also consider follow-up patient phone calls to determine a more accurate account of disease recurrences and readmissions. As previously mentioned, there were patients transferred from other hospitals for their treatment. Post discharge care may have been at local health care systems limiting an accurate accounts of disease recurrence and 30-day readmissions for CDI.

If the order set is adopted into practice at the clinical agency, efforts must be made to conduct interval literature reviews to identify any new evidence related to CDI treatment and determine if it should be incorporated in order to reflect best practice.

***Education*.** Although patient education was not an intended focus of this study, only 20% of patients in both the pre- and post-implementation groups received CDI-specific discharge instructions. In the post-implementation group, the failure to provide CDI specific instructions did not appear to have a negative effect on 30-day disease recurrence (22.2% received instructions vs 5.6% did not receive instructions, $p = 0.173$) or 30-day readmission rates (22.2% received instructions vs 8.3% did not receive instructions, $p = 0.258$). Failure to provide CDI specific discharge instructions (i.e. risk factors, transmission, and hand washing) to patients and their families may contribute to disease recurrence and transmission to others although this study did not demonstrate any negative effect on patient outcomes. An explanation for this finding may have been clinician failure to document CDI specific instructions provided at the time of discharge. Additionally, clinician education regarding CDI treatment must be continued, as well as the potential impact of inappropriate treatment of CDI. This includes complications associated with CDI and the potential financial impact on healthcare systems for hospital-acquired CDI.

The study has showed a significant number of patients did not receive guideline adherent treatment. The long term implications on patient outcomes has yet to be fully demonstrated. Treating patients with a mild to moderate disease may lead to unnecessary utilization of vancomycin and increased risk for development of vancomycin resistant

enterococcus (VRE). Unwarranted use of vancomycin also creates an unnecessary expense as the cost is higher than metronidazole. Additionally, patients with severe or severe/complicated disease may develop CDI related complications (i.e. pseudomembranous colitis) due to failure to appropriately treat with a combination of metronidazole and an appropriate dose of vancomycin. Inclusion of fidaxomicin for recurrent disease may have also reduced the number of recurrences. Despite the cost of fidaxomicin and its non-formulary status at the clinical agency, utilization may have decreased recurrence and proven less costly than the expense and potential complications associated with disease recurrence, as well as the possible need for the potentially more costly treatment option, fecal microbiota transplant.

Conclusions

CDI is a continued health care issue that can result in a number of disease-associated complications. Successfully reducing the incidence of CDI must include interventions aimed at both prevention and treatment. This study has demonstrated there is still work to be done in making improvements to both preventing and treating this growing problem. In addition to the possible physical complications associated with CDI, there may also be a significant financial impact on healthcare systems. It has previously been demonstrated that CDI has been associated with increased length of stay (LOS). In addition, impending reimbursement changes for HAI may have a potentially devastating effect on health care systems as CDI will be added the list of HAI that will result in potential financial penalties beginning in 2017. Efforts aimed at disease prevention, such as enteric isolation precautions for suspected and confirmed CDI cases, responsible use of antibiotic and gastric acid suppression, and patient education should also be encouraged. Failure to incorporate evidence-based practice for CDI treatment and prevention may have potentially devastating physical and financial consequences. This study also demonstrated doctoral-prepared advanced practice nurses have the ability and commitment to develop, implement, and evaluate clinical practice changes to improve patient outcomes through incorporation of evidence-based practice. References

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Melissa A. Craig

Mrs. Craig graduated from Indiana University with the degree of Associate of Science in Nursing in 1996. She worked in a medical surgical setting while continuing her education. She returned to Indiana University and completed the degree of Bachelor of Science in Nursing in 2006. The same year she was inducted into the Alpha Chapter of Sigma Theta Tau International. She continued on to graduate school while working in an interventional radiology setting. Upon completing the degree of Master of Science in Nursing in 2010 from Indiana University, she was awarded the Suzy Rader award for her dedication to the profession of nursing, colleagues, and family. In addition, she was presented with an academic achievement award. After receiving certification as adult nurse practitioner through the American Nurses Credentialing Center in 2010, she practiced in a preoperative clinic until taking her current position in 2011 as a nurse practitioner in an internal medicine setting at an academic medical center. Her professional interests include hepatology, improving communication processes in healthcare, and nursing education. Upon completing the degree of Doctorate of Nursing Practice at Valparaiso University, she will continue in her current practice and pursue a teaching position in undergraduate nursing.

ACRONYM LIST

AAD: antibiotic-associated diarrhea

ACA: Affordable Care Act

ACG: American College of Gastroenterology

AHRQ: Agency for Healthcare Research and Quality

CASP: Critical Appraisal Skills Programme

CDC: Centers for Disease Control and Prevention

CDI: *Clostridium difficile* infection

CINAHL: Cumulative Index to Nursing and Allied Health

CMS: Centers for Medicare and Medicaid Services

EBP: Evidence-Based Practice

HAC: hospital acquired conditions

HAI: hospital acquired infections

HRRP: Hospital Readmission Reduction Program

IOM: Institute of Medicine

JBI: The Joanna Briggs Search Institute

NCBI: Medline/National Center for Biotechnology Information (NCBI)

PI: principal investigator

SHEA/IDSA: Society of Hospital Epidemiologists of America/ Infectious Disease Society of America

VRE: vancomycin resistance enterococcus

Appendix A. Clostridium difficile Infection Order Set

***Clostridium difficile* Infection**
The person initiating entry should write legibly, date the form (using Mo / Day / Yr), enter time, sign, and indicate their title.
Until signed, these are for general information and reference only. They should not be relied on as advice for a particular patient or situation or as a substitute for the independent professional judgment of the physician.

Date	Time	Physician Orders
		Labs ☐ serum creatinine daily collection routine, results routine x 2 days ☐ serum albumin daily collection routine, results routine x 2 days ☐ CBC with differential daily collection routine, results routine x 2 days ☐ venous lactate x 1 collection routine, results routine
		Medications ****Discontinue inciting antibiotics if possible** ****Discontinue or limit gastric suppressant medications (i.e. H2 blockers, PPIs) if possible** **Duration can be modified by the clinician to individualize treatment **Mild to Moderate Disease** ****WBC count less than 15,000 OR serum creatinine less than 1.5 times baseline AND absence of severe disease criteria** ☐ metroNIDAZOLE 500 mg Q8H for 10 days ☐ PO (DEF) ☐ Feeding Tube ****For ALLERGY / intolerance to metroNIDAZOLE OR** **No clinical improvement in 5-7 days on metroNIDAZOLE OR** **Pregnant / breastfeeding OR** **History of inflammatory bowel disease** ☐ vancomycin 125 mg Q6H, oral susp. for 10 days ☐ PO (DEF) ☐ Feeding Tube **Severe Disease** ****Serum albumin less than 3 gm/dL AND one of the following: serum creatinine greater than 1.5 times baseline OR abdominal tenderness OR WBC greater than or equal to 15,000** ☐ vancomycin 125 mg orally Q6H for 10 days ☐ PO (DEF) ☐ Feeding Tube

Date	Time	Physician Orders
		Severe Complicated Disease ****Intensive care unit admission for *Clostridium difficile* infection OR hypotension with or without required vasopressors OR fever greater than or equal to 38.5 OR ileus OR megacolon OR significant abdominal distention OR mental status changes OR WBC greater than or equal to 35,000 OR WBC less than or equal to 2,000 OR serum lactate greater than 2.2 OR evidence of end organ damage** ☐ vancomycin 500 mg Q6H for 10 days ☐ PO (DEF) ☐ Feeding Tube **AND** ☐ metroNIDAZOLE 500 mg IVPB Q8H for 10 days **AND** ***IF ILEUS is present or suspected OR if there is a history of Hartman's pouch, ileostomy, or colon diversion.** ☐ vancomycin 500 mg in 500 mL 0.9% sodium chloride per rectum Q6H **Consider surgical consultation for all severe complicated cases
		Recurrent Infection Treatment **Recurrence defined as an episode that occurs 8 weeks after a previous episode that involved resolution of symptoms **First Recurrence of mild to moderate disease: Repeat initial regimen** ☐ metroNIDAZOLE 500 mg orally Q8H for 10 days ☐ PO (DEF) ☐ Feeding Tube **OR** ☐ vancomycin 125 mg Q6H for 10 days ☐ PO (DEF) ☐ Feeding Tube **First Recurrence of severe or severe complicated disease** ☐ vancomycin 125 mg Q6H for 10 days ☐ PO (DEF) ☐ Feeding Tube **Second Recurrence** ☐ vancomycin 125 mg Q6H for 10 days, ☐ PO (DEF) ☐ Feeding Tube **THEN** ☐ vancomycin 125 mg Q12H for 7 days ☐ PO (DEF) ☐ Feeding Tube **THEN** ☐ vancomycin 125 mg orally Q24H for 7 days ☐ PO (DEF) ☐ Feeding Tube **THEN** ***May choose a duration of up to 2-8 weeks***

Date	Time	Physician Orders
		☐ vancomycin 125 mg Q48H for 2 weeks ☐ PO (DEF) ☐ Feeding Tube *****For reoccurrence and treatment failure CONSIDER infectious disease and GI consultation** **Third and Subsequent recurrences** *****consider fecal microbiota transplant**
		Consults **Note: Ordering provider must call service for consult*** ☐ medical service consult : gastroenterology ☐ medical service consult : surgical ☐ medical service consult : infectious disease ☐ Social work consult – if vancomycin therapy needed upon discharge