Preventing Health Care-Associated Infection: Development of a Clinical Prediction
Rule for Clostridium difficile Infection.

by

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Dedication

To the patients that have suffered from

Clostridium difficile infection.

Acknowledgements

"Man's mind, once stretched by a new idea, never regains its original dimensions."
-Oliver Wendell Holmes, US author & physician (1809 - 1894).

The University of Michigan has given me the most well-rounded, challenging and thorough education I could have ever imagined. Not only did it give me the opportunity to "stretch my mind beyond its original dimensions," but I have had the great pleasure to meet some of the smartest, talented, and interesting faculty and staff from across the entire campus. I would like to start out by acknowledging my Co-Chairs, Dr. Bonnie Metzger and Dr. Richard Redman, both of whom have been there for me through every phase of my doctoral education and who are deserving of my deepest, heartfelt gratitude. Dr. Metzger has given me unfailing support, generous amounts of her time and has both challenged and inspired me when I needed it the most. It is fitting that the quote above was a part of her official electronic signature block as Dr. Metzger has changed the way I will think about nursing-- forever. As for Dr. Redman, he is an exemplar of an extraordinary nursing leader. Under his tutelage, I have had the opportunity to learn and grow both personally and professionally. I credit both of them as key forces in helping me to achieve success.

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Abstract

Introduction: The incidence of *Clostridium difficile* infection has been steadily rising, growing in virulence, and demonstrating an increase in the severity and morbidity of the disease. A clinical prediction rule (risk score), applied early in, or prior to, hospitalization is a strategy to identify vulnerable patients, target preventative interventions, improve outcomes for *Clostridium difficile* infection, and translate evidence into clinical practice. Objectives: The purpose of this research was to develop and validate a clinical prediction rule for the risk of *Clostridium difficile* infection. Methods: Between August 2007 and June 2009, preoperative variables and positive *Clostridium difficile* assays were collected for adult patients admitted for surgical colectomy from 24 hospitals in Michigan. After performing univariate analysis of 36 preoperative patient risk factors, significant variables associated with *Clostridium difficile* infection at a p value $\leq .15$ were advanced into a binary logistic regression model. The regression coefficients of this model were translated into a weighted scoring system to develop the clinical prediction rule. The Receiver operating characteristic curve analysis evaluated the predictive accuracy of the score. Results: 2274 patients underwent colectomy and fulfilled inclusion criteria. A total of 55 patients (2.4% overall) developed *Clostridium difficile* infection. Mechanical ventilation ($p=.012$) and a history of a transient ischemic attack ($p=.042$) were independently associated with *Clostridium difficile* infection. A clinical prediction rule, including the variables from the final model, demonstrated a larger score with an increased patient risk ($p \leq .01$). The area under the

receiver operating characteristic curve was 0.628 (95% CI .550 -.706). <u>Conclusions:</u>
Pulmonary and neurological morbidities emerged as significant preoperative predictive
variables of *Clostridium difficile* infection in this cohort. In contrast to previous studies,
bowel preparation, with and without antibiotics, was not associated with an increased risk
of CDI. Findings from this study suggest pathogen-directed interventions, such as a
clinical prediction rule to quantify the risk factors of *Clostridium difficile* infection, may
offer a promising adjunctive strategy to reduce infection and protect vulnerable patient
populations.

Chapter I

Introduction

The 2000 Institute of Medicine report, "To Err is Human "(Institute of Medicine, 2000), galvanized a national effort to reduce medical errors and put the pressure on healthcare organizations to improve patient safety (Yokoe & Classen, 2008). Nearly a decade later, patient safety is a top priority at the local, national and global level (Pittet & Donaldson, 2005). Although the transformation to a safer patient environment has advanced significantly, the challenges of moving healthcare closer to a state of flawlessness is still well beyond the reach of most hospitals (Sprague, 2009). The patient safety movement, which has been progressive, but slow, is now summoning greater government involvement, oversight and mandates.

In 2008, the Centers for Medicare and Medicaid Services (CMS) began implementing its landmark decision to restrict reimbursing hospitals for the cost of preventable patient injury and infection (Centers for Medicare and Medicaid Services, 2009). This decision is intended to save the government billions of dollars, drive patient safety initiatives and spur healthcare reform to address medical errors. The widespread impact of this decision will likely have marginal financial repercussions on the relatively rare medical errors such as operating on the wrong limb or infusing incompatible blood (Fuhrmans, 2008). However, the decision to impose financial penalty on the more commonplace patient injuries such as pressure ulcers, falls and health care-associated

infection is already shifting the traditional view of hospital complications from that of an inevitable consequence of hospitalization to that of an entirely preventable event.

This could have an especially profound impact on the various preventable hospital infections generically termed health care-associated infection (HAI). Although accounts in the popular press frequently emphasize medication errors, patient falls or surgical errors in the discussion of patient safety, an HAI is the most common adverse event a patient will encounter during hospitalization (Gasink & Lautenback, 2008; Haley, Culver, White, Morgan, & Emori, 1985). HAI is the cause of an estimated 2 million infections and 100,000 deaths annually (Klevens, et al., 2007) which translates into approximately 5-10% of all hospitalized patients (Weinstein, 1998). This prevalence has led experts to predict HAI will be one of the primary medical and public health problems in the United States in the near future (Nelson, K. E. & Williams, 2007). This prediction is also due, at least in part, to the steady increase in the aging population, the ability of modern medicine to continue to devise technologies that prolong life and the emergence of dangerous pathogens resistant to traditional antimicrobial treatment (Nelson, K. E. & Williams, 2007; Yokoe & Classen, 2008).

The financial consequences associated with HAI are considerable. The United States Department of Health and Human Services (HHS) report that the cost of HAIs are as much as $20 billion dollars annually (Klevens, et al., 2007). Other more recent estimates, adjusted for inflation, and taking into account the resources required in order to prevent infection, placed the price tag between 5.7 billion and 6.8 billion in direct patient costs (Scott, 2009). Even this conservative estimate of the direct medical costs of HAI rival the annual cost of treating stroke (6.7 million), diabetes with complications (4.5

million) and chronic obstructive lung disease (4.2 million) (Levit, Stranges, Ryan, & Elixhauser, 2008). Thus, preventing HAI is clearly a fiscal strategy deserving of adequate investment and resources.

Less often described but of equal importance is the human cost of HAI. The indirect costs (lost wages, unpaid leave) and the intangible costs (emotional distress, disfigurement, and pain) (Scott, 2009) generate a human cost that may be difficult to measure, but can exact a significant human toll - a toll that no patient wants to pay, to which no clinician will knowingly want to contribute and to which no hospital wants to be deemed an accessory. It is clear that strategies to eradicate infection summed up in the phase "chasing zero" (Cardinal Health, 2008) is the only appropriate goal if a true culture of patient safety is to be achieved (Sprague, 2009).

This research is the foundation for the investigation of a clinical prediction rule as a novel strategy to reduce the impact of unnecessary HAI. It opens with a review of the current strategies used to prevent and control HAI currently in practice and then discusses the definition, methodology and application of clinical prediction rules as a potential effective adjunct to these strategies. To contextualize the investigative strategy, a conceptual framework of HAI risk is proposed and a working model presented. Chapter II focuses on one of the most serious offending HAI organisms, *Clostridium difficile* (*C. difficile*) which recently passed methicillin-resistant *Staphylococcus aureus* (MRSA) as the most common HAI in the United States (Dubberke, et al., 2008; McDonald, Owings, & Jernigan D., 2006) and therefore has both timely and practical significance as a focus. Chapter III defines the research methods and procedures followed by the presentation of the results (in Chapter IV). The closing chapter discusses the research findings and the

clinical implications for practice and future research in order to help abolish HAI caused by *C. difficile* – one of the most common, problematic, and avoidable adverse outcomes patients are likely to have during the course of their hospitalization

Health Care-Associated Infections: Defined

An HAI is an infection that afflicts a patient while receiving treatment in a health care environment (Horan, Andrus, & Dudeck, 2008). Sometimes referred to as nosocomial infections or hospital-acquired infections, HAI is the broader, more appropriate term to reflect the changing patterns in healthcare delivery where patients may receive care in outpatient surgical centers, ambulatory clinics, and long term care facilities, not only hospital centers (Burke, 2003; Siegel, Rhinehart, Jackson, Chiarello, & Healthcare Infection Control Practices Advisory Committee, 2007). The most significant HAIs are attributed to the specific organisms of MRSA and *C. difficile* and those associated with devices or procedures such as central line-associated bloodstream infections (CLABSI), ventilator- associated pneumonia (VAP), catheter-associated urinary tract infection (CAUTI) and surgical site infection (SSI) (Sprague, 2009).

Key factors in the cause of HAI. Despite the national attention on HAIs in the United States, the incidence of HAI continues to plague most hospital organizations. This may be due in part to better reporting and detection, but this alone is insufficient to explain the problem. One possible explanation is that the over-prescribing of antibiotics has caused a generation of multidrug-resistant organisms (MDROs) or "superbugs" that have evolved a resistance to the standard antimicrobial treatment. The number of such organisms has risen sharply over the last decade and organisms are even harder to detect and treat (Gasink & Lautenback, 2008; Tenover, 2001). Described as the microscopic

illustration of the dictum "What doesn't kill you makes you stronger," (Sprague, 2009, p. 4), pathogens that evolve from resistance to antibiotics thrive and persist during traditional antimicrobial treatment regimes. The growth in MDROs comes at a time when the development of new antimicrobial agents targeting these organisms, has decreased by about 56% (Gasink & Lautenback, 2008; Spellberg, Powers, Brass, Miller, & Edwards, 2004).

Being that the most rapidly rising segment of the population in the United States are those 85 years of age and older (Fried, 2003), and those are more likely to have a compromised immune system due to underlying diseases (Nelson, K. E. & Williams, 2007), this subset of the population is especially vulnerable to an adverse outcome of HAI. To illustrate, a recent study investigating the prevalence of *C. difficile* infection found that among the elderly the risk of infection was as much as 20-fold higher than among adult patients under the age of 45 (McDonald, et al., 2006). Clearly, the disproportionate impact of HAI on the older segment of the population will continue to be an area of concern.

Another major cause in the rise of HAI, is unintentional exposure to the pathogen in the health care environment (Nelson, K. E. & Williams, 2007). The transmission of pathogens is aided by the exposure of contaminated equipment, the proximity of uninfected patients to colonized patients and the likelihood that a health care worker did not adhere to prescribed hand hygiene policies. This cause is especially important in light of the rise of the sophistication of health care monitoring and the increased use of indwelling catheters and other medical devices (Nelson, K. E. & Williams, 2007). Furthermore, in a health care industry that is operating in an era of constrained resources

and manpower, the environment may be further compromised and vulnerable patients further exposed to unintended transmission of pathogens (Nelson, K. E. & Williams, 2007).

Hospital practices to prevent HAI. At the organizational level, hospital-based infection control, prevention and surveillance programs have been at the epicenter of efforts to control, detect and monitor HAIs (Yokoe & Classen, 2008). The cornerstone of these programs is the enforcement and monitoring of basic hygiene, the first line of defense against HAI. This includes decontaminating surfaces that an infected person may have contaminated, cleaning of supplies and equipment for re-use by other patients and the most important of hygiene practices, decontamination of the hands. A comprehensive compendium of evidence-based recommendations for hand hygiene is published by the Centers for Disease Control and Prevention's federal advisory board, the Healthcare Infection Control Practices Advisory Committee (HICPAC) (Boyce & Pittet, 2002). Despite this relatively simple intervention, adherence to hand hygiene standards is typically low (Larson, 1988) and although the addition of alcohol-based hand hygiene has helped to improve adherence (less time to perform, less skin irritation, convenient) (Boyce, Kelliher, & Vallande, 2000), sustained improvements are still difficult to achieve (Gasink & Lautenback, 2008). The next line of defense for HAI is the initiation of barrier precautions and/or isolation precautions (Siegel, et al., 2007). Tiered precautions, based on the offending infection and organism, are detailed and specific and range on a scale from routine standard precautions to the most heightened precaution, isolation.

Another preventive measure is the implementation of antimicrobial stewardship programs. The objective of these programs is the reduction of unnecessary antimicrobial

use (Owens, Donskey, Gaynes, Loo, & Muto, 2008). This is significant because emerging evidence has revealed the duration of antimicrobial use and the concomitant use of multiple antimicrobials to confound the risk for developing HAI (Owens, et al., 2008). Although additional research is needed regarding the specific strategies for the prevention and containment of MDROs (Dellit, et al., 2007), the practice of effective antimicrobial stewardship programs, in concert with environmental control strategies, is regarded as critical for the reduction of HAI (Dubberke, et al., 2008; Fowler, et al., 2007; Gerding, Muto, & Owens Jr., 2008).

The idea of leveraging technology in the fight against infection began over 20 years ago in an effort to devise "clinical triggers" to enhance the detection and surveillance of infection (Burke, 2003; Burke, Classen, Pestotnik, Evans, & Stevens, 1991; Evans, et al., 1992) For instance, the HELP (Health Evaluation through Logical Processing) hospital information system was used to automate the surveillance and analysis of hospital-acquired infections, provide reminders for prophylactic antibiotic administration and identify patients at high risk for nosocomial infection (Burke, et al., 1991). Now more sophisticated technology such as the MedMined, Inc. (Cardinal Health, 2009) and TheraDoc (Theradoc Inc., 2009) are enabling hospital clinicians to analyze data from patients more rapidly than ever before. These and other electronic surveillance systems can detect overuse or misuse of antibiotics, prescribing histories and identify infection "clusters" within hospitals and units. Although promising new strategies for the prevention and surveillance of infection, they still fall short as a mechanism for identifying at-risk patients for unit level interventions.

Some of the most successful accounts of reducing HAI implemented a multifaceted, multidisciplinary and multimodal intervention approach. For example, the implementation of several evidenced-based interventions simultaneously "bundled" together in the effort to decease CLABSI demonstrated a substantial reduction in overall CLABSI rates (Pronovost, et al., 2006). The implementation of similar approaches is underway to reduce SSI and VAP (Institute for Healthcare Improvement, 2009). Checklists are gaining momentum as means to implement "bundles" and combine healthcare worker education in tandem with simple and easy to follow multidisciplinary detection, surveillance and control procedures (Abbett, et al., 2009). Others have reported state-wide collaborative efforts as a means to monitor, trend and recommend practice-based solutions (Share, et al., 2011). These strategies underscore the basic but innovative approaches of challenging the existing clinical practices to fight HAI.

The overall strategy on how to best implement the interventions is just as important as the intervention itself. For example, infection control interventions that are tailored to a specific organism, such as *C. difficile*, are called pathogen-directed or (vertical) interventions (Jernigan, 2011; Wenzel & Edmond, 2010). These interventions are designed to prevent transmission of the specific pathogen causing the infection. In contrast, the non-pathogen directed, or the horizontal intervention approach, attempts to reduce the rates of all infections, from all pathogens, simultaneously (Harris, 2011; Wenzel & Edmond, 2010). The advantages and disadvantages of both infection control approaches is a topic of recent debate (Harris, 2011; Jernigan, 2011; Wenzel & Edmond, 2010). Advocates for the pathogen-directed approach argue the epidemiological characteristics of the organism must drive the interventions (Jernigan, 2011). For

example, rapid screening and decolonizing of nasal carriers of *Staphylococcus aureus* on admission, has reported excellent success in the reduction of surgical site infections (Bode, et al., 2010). Proponents of the non-pathogen directed approaches cite similar success rates using horizontal interventions with similar success rates at a significant cost savings (Harris, 2011; Wenzel, Bearman, & Edmond, 2008; Wenzel & Edmond, 2010). Although effective horizontal successes have been reported in relation to CDI infection (Abbett, et al., 2009), the magnitude and scope of the escalating CDI epidemic may prove to sufficiently challenge the current views of the horizontal infection intervention position.

Despite whether or not the infection control strategy is implemented as a horizontal or vertical, the escalation of HAI continues to emerge as a serious medical and public health threat (Nelson, K. E. & Williams, 2007). Long considered an inevitable part of hospitalization, HAI is now recognized as preventable, and therefore avoidable. A rapidly growing elderly population, the emergence of new virulent pathogens, and the concern over resistance to traditional antibiotic regimens have elevated HAI prevention to a high priority on a national level (Yokoe & Classen, 2008). Unfortunately, the incidence of HAI continues to grow (Burke, 2003) and the financial and human costs of HAI continue to mount (Scott, 2009). The government's decision to withhold Medicare reimbursement for hospitals due to preventable patient injury and infection (Centers for Medicare and Medicaid Services, 2009) underscores the gravity of the problem and the "top-down" strategy necessary to address its prevalence.

Although not currently available for clinical implementation, a clinical prediction rule to identify those at the greatest risk for HAI, may be a cost-effective,

nontechnological, and nonpharmaceutical approach to translate evidence-based research into clinical bedside practice. Since nurses provide round-the-clock, direct patient care, they are uniquely positioned to prevent the HAI at the point of impact – the bedside. And since the foundation of nursing practice is built upon a strong assessment, a logical extension of this practice would be to strengthen the assessment ability of nurses to detect those patients most vulnerable for the risk of HAI. The addition of a clinical prediction rule CPR could move the nursing process "upstream," so that environmental challenges can be modified and /or individual defenses strengthened. The following section provides more detail on clinical prediction rules and their clinical application to HAI.

Clinical Prediction Rules

Tools and models to predict clinical sequela have proliferated with the efforts to translate research evidence into clinical practice and the growth of an increasingly rich scientific base (Beattie & Nelson, 2006). These tools, broadly termed *clinical decision rules* or *clinical prediction rules*, are defined as research-based tools where clinically relevant patient characteristics are quantified into numeric indices as a predictor of a specific disease, as a clinical necessity for treatment or for diagnostic testing (Beattie & Nelson, 2006; Randolf, Guyatt, Calvin, Dolg, & Richardson, 1998; Reilly & Evans, 2006; Shapiro, 2005; Toll, Janssen, Vergouwe, & Moons, 2008). Clinical prediction rules differ from clinical pathways or treatment algorithms in both the strict methodology of their development and the adherence to rigorous statistical testing (Shapiro, 2005). The number of published articles discussing prediction rules has more than doubled in the last decade (Toll, et al., 2008) reflecting the ability of clinical prediction rules to bring the most relevant evidence-based practice to clinical bedside care (Jervis & McGinn, 2008).

Types of clinical prediction rules. The term "clinical prediction rule" is used interchangeably in the literature with the terms: (1) clinical decision rule (Shapiro & Driever, 2004) (2) prognostic score (Steyerberg, et al., 2008b), (3) scoring system (Scholz, Bäsler, Saur, Burchardi, & Felder, 2004; Schurink, et al., 2004), (4) risk index (Kheterpal, et al., 2009), (5) risk score (Ferro, et al., 2009), (6) severity score (Omachi, Yelin, Katz, Blanc, & Eisner, 2008) or tool (Woo, et al., 2009). The concomitant use of the term clinical decision rule with clinical prediction rule has recently come under increased scrutiny in the literature because the two terms have distinctly different outcomes; decision rules recommend diagnostic care or treatment where as prediction rules provide prognostic probability (Beattie & Nelson, 2006; Reilly & Evans, 2006). For example, the Ottawa Ankle Rule is a clinical decision rule to guide decisions of emergency department physicians regarding the necessity of radiographs for patients with ankle fractures (Shapiro & Driever, 2004). In contrast, the Braden Scale for Pressure Ulcer Risk (Bergstrom, Braden, Laguzza, & Holman, 1987) predicts a patient's risk for developing a pressure ulcer, not a direct treatment recommendation. For the purposes of this dissertation, the term clinical prediction rule (CPR) has been selected since it is the most widespread, descriptive and accurate term to investigate the risk of HAI (Ingui & Rogers, 2001).

Clinical prediction rules are used routinely in clinical practice to identify patients at high risk for falls (Hendrich, 1989, 2007; Morse, 2006; Morse, Morse, & Tylko, 1989), pressure ulcers (Bergstrom, et al., 1987), and severity of disease (known as the Acute Physiology and Chronic Health Evaluation (APACHE) score) (Knaus, Draper, Wagner, & Zimmerman, 1985). The prognostic utility and operational effectiveness of the

aforementioned prediction rules have been demonstrated to reduce cost, enhance patient safety (Hendrich, 2007; Morse, 2006) and standardize comparisons among and within health care organizations (Knaus, et al., 1985).

Methodology of development. Clinical prediction rules help guide and organize information, they are considered a special type of decision support tool (Shapiro 2004). And, because they are developed using strict methodological standards, rather than expert panels, they are designed to guide practice in a variety of settings and patient populations (Shapiro 2004). The literature distinguishes three phases of clinical rule development in order to achieve satisfactory clinical validation: (1) development, (2) external validation and (3) clinical impact (Toll, et al., 2008). Each phase provides a foundation for the next. For example, the first phase is considered critical for successful rule development since a carefully constructed, theoretically driven tool will help insure its internal validity (Shapiro, 2006). Internal validity, in turn, will help ensure adequate external validity (Polit & Hungler, 1999; Shapiro, 2006). Accurate clinical prediction depends on sequential testing of all three phases of prediction research to ensure the validity (internal and external), accuracy (calibration and discrimination) and necessary clinical impact analysis for successful implementation (McGinn, et al., 2000; Toll, et al., 2008).

The methodology employed to develop, validate and test a clinical prediction rule is rigorous and specific to each phase of development. During the initial phase of development, statistical analysis reveals which predictive values are the most robust and which can be eliminated from the rule without losing any predictive ability (McGinn, et al., 2000). Typically these derivations are accomplished through logistical regression,

however, depending on the clinical situation, analysis may also include discriminate analysis, recursive partitioning analysis or neural networks (McGinn, et al., 2000). Although the use of univariate analysis can also be employed (McGinn, et al., 2000), only one predictor variable can be compared with the outcome, therefore limiting the full predictive ability of the rule.

The validation phase is testing for the clinical accuracy of the clinical predictive tool and therefore, the population selected for validation should be different than the one used for rule derivation (Toll, et al., 2008). Ideally, this validation should be conducted prospectively in a different population (Beattie and Shapiro 2006). Two kinds of analysis should accompany validation studies: measures of accuracy (sensitivity, specificity and predictive values) and measures of agreement between raters (two examples being the kappa statistic or correlation coefficient (Shapiro, 2005). Finally, during the last phase, the clinical prediction rule should be examined in relation to the full impact of how the clinical prediction rule will affect the outcome to include the change in behavior of the clinicians and the cost-benefit analysis (Toll, et al., 2008).

Unfortunately, despite the abundance of published articles on clinical prediction rules, few actually achieve the necessary statistical rigor and clinical impact analysis necessary for the precision of implementation in the clinical environment (Reilly & Evans, 2006). The degree of specificity and sensitivity inherent within the predictive model are imperative constructs to achieve in order to successfully and accurately predict, stratify or eliminate risk (Reilly & Evans, 2006). Clinicians are cautioned against adoption of predictive variables that have not achieved these necessary evidentiary

standards (Reilly & Evans, 2006). In a systematic review of four general medical journals, only half of the clinical prediction rules and clinical decision rules analyzed (21 out of 41) met the criteria at a level of validation that could confidently be applied to clinical practice environments (Reilly & Evans, 2006).

Clinical application for HAI. Provided that the prediction rule has undergone the necessary methodological testing, statistical rigor and clinical impact analysis, prediction rules have the potential to systematically improve patient outcomes. An accurate rule will improve patient care, streamline inconsistencies, demonstrate cost effectiveness and be practical to implement at the bedside (Shapiro, 2006). Given the resources, expense and escalation of HAI, it is not surprising that two clinical prediction rules were located in the literature for this purpose. Over the last decade, The National Nosocomial Infection Surveillance System Basic Surgical Site Infection Risk Index (NNIS SSI) has been applied as a strategy to reduce surgical wound infections and also serves to establish benchmarks for the prediction and comparison of surgical infection rates across hospitals (Bundy, Gonzalez, Barnard, Hardy, & DuPont, 2006; Emori, et al., 1991). The Clinical Pulmonary Infection Score (CPIS) is used to enhance the ability to predict the diagnosis of VAP in patients suspected of an infection (Kherallah, 2004; Pugin, et al., 1991). Both have significant shortcomings (Ercole, Starling, Chianca, & Carneiro, 2007; Fartoukh, et al., 2003; Gaynes, et al., 2001); however, their contribution to advancing the science and pursuit of innovative strategies to prevent HAI is undisputable.

There are several recent reports of clinical prediction rules that have attempted to quantify different aspects of the HAI caused by *C. difficile*. The majority of CPR's in the literature have focused on predicting the severity and morbidity of CDI (Belmares, Gerding, Tillotson, & Johnson, 2008; Bhangu, Bhangu, Nightingale, & Michael, 2010; Velazquez-Gomez, et al., 2008; Zar, Bakkanagari, Moorthi, & Davis, 2007). This type of CPR was developed to help categorize a patients CDI status in order to choose the most effective therapeutic approach. For example, the ATLAS severity score (based on a index of a patients age, temperature, leukocytosis, albumin and systemic concomitant antibiotics) helps physicians determine the best antibiotic treatment for patients based on whether or not they have mild, moderate or severe infection (Miller, 2011). If a patient was categorized as having severe disease, vancomycin would be the treatment of choice, whereas, a patient categorized as having mild disease may benefit from metronidazole (Zar, et al., 2007).

CPR's that aim to utilize the methodology further 'upstream' to prevent CDI infection have received much less attention. These CPR's are focused on the time before a patient gets an infection, not in response to the infection. Kyne et al. (2002) was the first to describe how stratifying patients by a modified Horn's Index (a measure of underlying disease severity), could predict CDI in elderly, hospitalized patients on antibiotics (Kyne, Sougioultzis, McFarland, & Kelly, 2002). A sequential two-predictor scoring system (antibiotic use and Horn's Index), identified 56% of CDI cases. A later study using similar methodology, developed a CPR for recurrence of CDI (not initial infection) adding age and serum antitoxin A that predicted recurrent CDI with an accuracy of 69.2% (Hu, et al., 2008). Garey et al. (2008) developed a more

comprehensive CPR based on two intrinsic (age, hemodialysis) and two extrinsic (non surgical admission and length of ICU stay) risk factors of disease (Garey, et al., 2008). Although the index demonstrated good discrimination (area under the ROC: 0.713-0.712), it is limited in its ability to be applied on admission to the hospital because of its reliance on length of stay as a predictive variable since this is collected either at discharge or during hospitalization.

In an innovative attempt to expand the use of a CPR already well integrated into practice, an adapted version of the Waterloo Risk Assessment for Pressure Ulcers was applied to an inpatient population as a measure to assess a patient's risk for CDI (Tanner, Khan, Anthony, & Paton, 2009). It was hypothesized that the same subset of patients identified as high risk for pressure ulcers, could also be considered high risk for CDI. Utilizing an existing CPR already well integrated into practice, could prove an efficient use of resources, time and talent. Although a small observation study and lacking in statistical rigor, the results suggested moderate success in validating the tool and predicting CDI (Tanner, et al., 2009). More importantly, this research brings together two unlikely, albeit important, nursing priorities, preventing pressure ulcers and reducing infection. Adapting an existing CPR's for use in a broader capacity could prove to be a resourceful method to increase efficient and decreasing adverse events. This may be especially useful in patient areas where the standard infection prevention and control interventions are not working.

With the move to electronic records and data collection, clinical prediction rules have been integrated into computerized clinical information systems as a strategy to detect patterns of related infection, monitor antimicrobial management and provide the

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most up-to-date evidence-based practices (Bakken, et al., 2007; Cardinal Health, 2009; Shapiro, 2006; Theradoc Inc., 2009). By leveraging the use of a collected repository of data, a series of computerized patterns can formulate electronic alerts much like the commercial process employs computer screening alerts to scan for credit card fraud. Although the medical informatics literature provides evidence of computer-assisted models for infection surveillance (Brossette, et al., 2006; Cardinal Health, 2009; Evans, et al., 1992; Theradoc Inc., 2009), the effectiveness for predicting at-risk patients for early clinical intervention at the point-of-care, not via infection control or administrative channels, is yet unclear.

Pitfalls. The overall goal of a clinical decision rule is to improve patient outcomes through a change in clinical practice. However, clinical prediction rules are designed to augment and strengthen clinical acumen, not serve as a replacement for it. Claims that clinical expertise and simple intuition trump the objective measures of clinical prediction rules may be true to some extent (Randolf, et al., 1998). Some studies have indeed found the intuition of experienced clinicians was just as good, if not better, for clinical prediction of mortality (Brannen, Godfrey, & Goetter, 1989; Kruse, Thill-Baharozian, & Carlson, 1988; Scholz, et al., 2004). However, in this time of constrained resources, a busy unit may lack an expert clinician; thus, a method to standardize assessment of a patient's unique risk is a complement to, not a replacement for the clinical judgment and decision making necessary for quality patient care.

In addition, the overall feasibility and efficacy of a clinical prediction rule requires the sustained and coordinated ability to change the course of clinical outcomes.

For example, the knowledge of a high score on the Braden Scale for Pressure Sore Risk (Braden & Bergstrom, 1988) is clinically ineffective unless nursing interventions are implemented in conjunction with the score to avert the pressure ulcer. Therefore, clinical prediction rules rarely stand alone. Their ability to enhance the discrimination of an assessment requires the implementation of concurrent interventions or treatments (Morse, 2006).

Nursing implications. In the continued quest to reduce HAI, clinical prediction rules are a potential strategy nurses could easily implement into the workflow to focus care, standardize assessments and guide nursing interventions. Translating the risk of HAI into a quantifiable standardized score, via a clinical prediction rule, would provide a nurse-driven strategy to modify the environment for an individual patient's risk. Interventions such as cohorting of patients, determining optimal bed locations, allocation of private bed space, standing nursing orders for laboratory specimens or isolation, and coordinating increased staffing requirements are all nonpharmaceutical, nontechnological interventions that are well within a nursing scope of practice. If applied on admission, a clinical prediction rule could identify those patients at highest risk for HAI and enable nurses to intervene on behalf of those patients deemed most vulnerable.

Conceptual Framework

The fundamental components of the epidemiologic triad of infection are the *pathogen* (agent), the *exposure* and the *host defense* (Nelson, K. E. & Williams, 2007). The interaction of these three components serves as the conceptual framework for modeling the transmission of infectious disease (Nelson, K. E. & Williams, 2007). The *pathogen* component includes the virus, bacteria, parasite or fungi that are potentially

infectious to the host. The *pathogen* must be sufficiently virulent to gain access to the host in sufficient quantity and have the ability to replicate (Relman & Falkow, 2000). The ability of the *pathogen* to replicate and proliferate on or within the host distinguishes it from other pathogens that do not cause disease (Relman & Falkow, 2000). The *pathogen* gains access to the host via *exposure*, the second component. Exposure encompasses the environmental factors that modulate the amount and circumstances of how the *agent* gains entry into the host. For example, environmental exposure may occur when health care providers practice poor hand hygiene or inadequate disinfection of medical equipment surfaces. The *exposure* component includes all the "extrinsic" factors relative to infection risk (Collins, 2008). The third component, *host defense*, signifies the ability of the host to resist or fight the insult. The host defenses comprise the "intrinsic" factors of infection risk (Collins, 2008). Infection ensues when a patient's host defenses lack the capacity to resist the exposure (Parsons & Krau, 2006) or when the host's normal defenses are lowered with treatments or drugs that render them more vulnerable to the invasion of a pathogen. The "chain of infection" puts into motion the series of physiological events that transpire when a pathogen successfully gains access to the host, replicates and the host response is overwhelmed, insufficient or blunted (Parsons & Krau, 2006).

The space created when these components intersect and overlap formulates the "risk" of infection prediction; the larger the area of intersection and overlap, the greater the likelihood a patient will develop an infection (risk). (See Figure 1.1) Although expert clinicians can frequently identify patients at high risk for infection, rarely is an expert clinician available round-the-clock. Furthermore, a patient that may be deemed at high

risk for HAI does not usually receive infection prevention interventions beyond standard protocol. Whether or not any additional interventions (in terms of resources and manpower) would protect a vulnerable patient from an HAI infection is arguable. However, quantifying a patient's risk for infection upon initial assessment is undeniably a potential opportunity to reduce infection risk and a prospect that as of yet, remains unexplored for considerations in nursing care.

Figure 1.1. Conceptual Model of Infection Risk Prediction
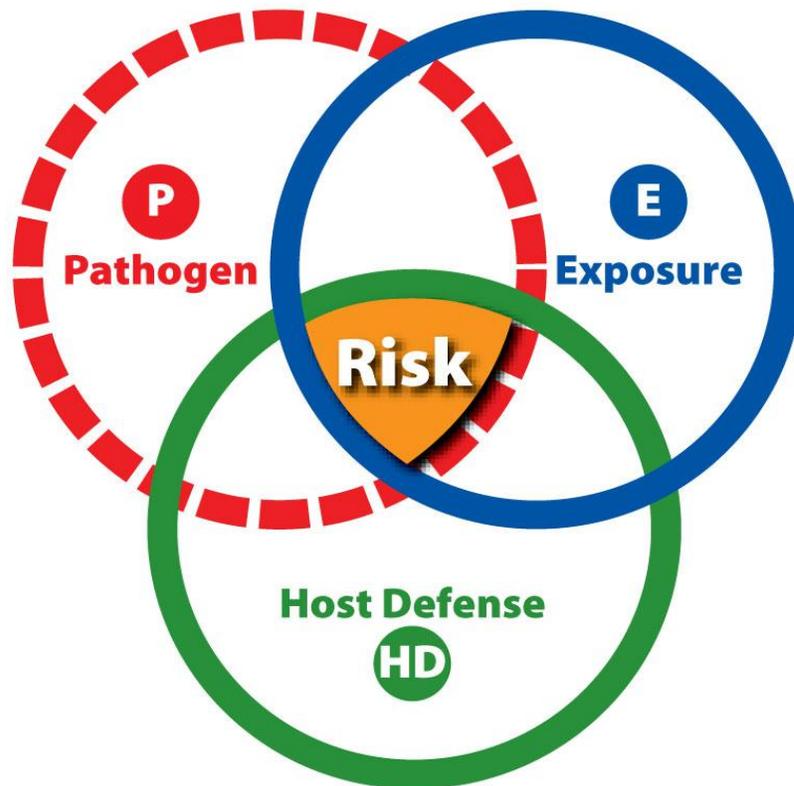
Translation of the intersection of the three components (pathogen, exposure and host) that comprise the "risk" of CDI into a quantifiable score via a clinical prediction rule could be a mechanism to integrate a patient's initial assessment data into a useful tool for bedside clinical practice. This is especially critical in combating the escalation of

HAI, where the traditional approach of reducing exposures appears insufficient and the modes of effective treatment are diminishing. As depicted in Figure 1.2, a clinical prediction rule that includes the unique behavior of the pathogen, the specific characteristics of exposure and the vulnerabilities of the host, could be systematically translated into levels of low, medium and high risk infection scores. A high score, indicating a high risk patient, would serve to drive interventions to modify the hospital environment in order to maximize individual patient outcomes early in, or prior to their hospitalization.

Figure 1.2. Conceptual Model of Infection Risk Prediction Stratified by Risk Level.
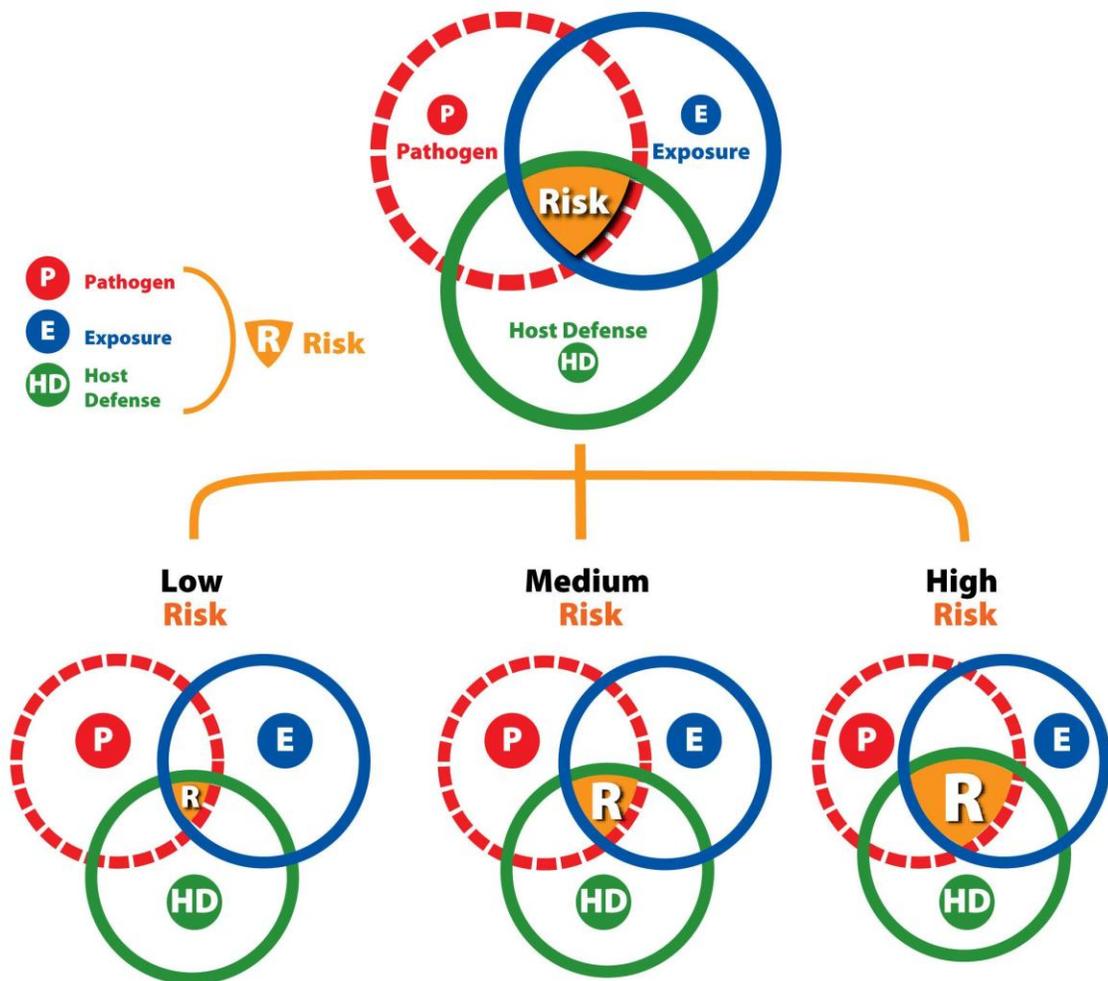
Since the term *risk* is frequently used synonymously with the term *vulnerable* in the literature, a clarification of the two terms is necessary at this point. (Jacobs, 2000). The term *risk* infers that the probability or likelihood of the event occurring portends an adverse or dangerous outcome. The term *vulnerability* is derived from the Latin word *vulnerabilis,* "wounded or likely to injure" (Purdy, 2004, p. 83) and is defined in terms of individual characteristics (not group or population measures) that render a patient susceptible to, exposed to, or unprotected from infection (Purdy, 2004). In other words, whereas vulnerability addresses the underlying factors predisposing an individual to infection, risk addresses the immediate probability of acquiring an infection. Therefore, in this context, a patient's individual vulnerability is regarded as a necessary condition of risk but not a sufficient component in and of itself to predict it; environmental and systems components may also contribute to risk. The integration of both risk (intersection of circles) and vulnerability (within the host defenses) are captured in this framework and therefore provide a broad and comprehensive underpinning for the conceptual structure of a clinical prediction rule for HAI.

In the next chapter, the focus of HAI is refined to one of the most serious offending organisms, *C. difficile*. *C. difficile* recently surpassed MRSA as the most common nosocomial pathogen in hospitals within the United States (Dubberke, et al., 2008) and therefore has both timely and practical significance as a chosen focus area for clinical prediction rule development.

Chapter II

Background and Significance

The Health care- Associated Infection of *Clostridium difficile*

Clinical Presentation and Treatment.

The clinical manifestations of CDI can range the full spectrum of infection from asymptomatic to life threatening (Giannasca & Warney, 2004; Pelleschi, 2008). Mild forms of infections are characterized by frequent, nonbloody diarrhea and associated symptoms of fever, nausea, vomiting, and abdominal cramping which may progress to worsening symptoms of abdominal pain and colitis requiring aggressive medical management. Fulminant disease develops in three to eight percent of CDI patients and is characterized by severe ileus megacolon, perforation, hypertension requiring vasopressor support or refractory septicemia (Jaber, Olafsson, Fung, & Reeves, 2008).

Antimicrobial use almost always precedes CDI (McDonald, 2008). Treatment with certain antibiotics is thought to suppress the normal host line of defense of indigenous colonic microflora and promote *C. difficile* pathogen proliferation. Thus, the current first line treatment option has been discontinuation of putative offending antimicrobial agents (Kelly, 2009). In some patients, and in the absence of all other antimicrobial treatment, discontinuation alone may cause the infection to subside (Kelly, 2009; Nelson, R., 2007). Depending on the severity of the illness, a CDI specific,

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stratified antimicrobial treatment regime is now recommended (Kelly, 2009).

Metronidizole is the first-line primary option for mild to moderate CDI (Cinti, Washer, &

Chenoweth, 2007). However, in patients with severe disease, vanocmycin has been

associated with higher cure rates than standard metronidizole treatment (Nelson, R.,

2007). Reliance on one of these two antibiotics remains one of the few effective weapons

of choice against CDI (Kelly, 2009). Further complicating the sufficiency of current

treatment options is the rate of recurrence which has been reported to be as high as 20%

(Aslam, Hamill, & Musher, 2005).

In CDI refractory to conventional therapy, intravenous immunoglobin, higher

doses of vancomycin, intracolonic administration of vancomycin and donor stool

infusions are all documented treatments (Calfee, 2008). When options for medical

management are exhausted, an emergency surgical colectomy is considered an

alternative, but risky, option (Jaber, et al., 2008). Mortality associated with colectomy,

although high, is reportedly better than sustained unsuccessful CDI medical management

(Johnson, 2008; Lamontage, et al., 2007).

Given the challenges of treating CDI, specifically recurrent CDI, alternative

treatment measures to prevent the disease are being fully explored. One potential

preventive treatment measure against CDI that has received widespread attention is the

use of probiotics (such as *Lactobacillus casei*, *Streptococcus thermophilus*, and

Lactobacillus bulgars) (Hickson, et al., 2007). Probiotics are hypothesized to enhance

the normal intestinal microflora whereby they can effectively bolster the host's normal

defenses against *C. difficile* colonization (Hickson, et al., 2007). However, a recent

comprehensive scientific review of the use of probiotics for the prevention of CDI

concluded there was a dearth of strong evidence to recommend the clinical use of probiotic therapy for the prevention of CDI (Surawicz, 2008).

Active immune response, via vaccination, is emerging as another alternative treatment for the prevention of CDI. Passive protection from disease is acquired by a majority of patients when the body generates antibodies to toxin A after exposure to *C. difficile* (Louie, Peppe, Watt, & et al., 2006; Pelleschi, 2008). The inability of the body's ability to acquire the antibodies to toxin A has been associated with an increased severity of disease and relapse (Giannasca & Warney, 2004) suggesting an innate or acquired immune response may play a more important role than expected (Kuijper, Coignard, & Tull, 2006). Theoretically, vaccination with inactivated and purified A & B toxins would provoke the stimulation of antibodies that would bind and dispose of the potent toxins responsible for CDI. Although still at the preliminary stages of research, larger scale trials are necessary to establish vaccination as an effective alternative to antimicrobial therapy (Giannasca & Warney, 2004).

Pathogen and Pathogenesis.

The dramatic increase of the incidence of *C. difficile* and its transformation into a more dangerous pathogen is primarily associated with the hypervirulent strain identified as NAP1/BI/027 toxinotype III. The complicated nomenclature was derived from the different typing systems used for identification of the *C. difficile* strain, namely, NAP1 using pulsed-field gel electrophoresis (PFGE) pattern, BI using restriction endonuclease analysis (REA), toxinotype III by polymerase chain reaction (PCR) characterization of the pathogenicity locus, and 027 by PCR ribotyping (McDonald, et al., 2005). Prior to

2000, the NAP1/B1/027 toxinotype III strain accounted for less than 1% of isolates of *C difficile* in the United States. Now, however, the NAP1/B1/027 toxinotype III (designated NAP1 from this point forward) strain is the predominant strain in many hospitals across the nation and has been detected in over 10 European countries (McDonald, 2008).

The pathogenicity of *C. difficile* is largely attributed to two potent toxins: toxin A (Tsd A) a 308-kDa enterotoxin, and toxin B (Tcd B) a 270-kDa cytotoxin (Kuijper, et al., 2006). Tsd A and Tsd B are both large single-chain proteins that are located on an area of the genome known as the pathogenicity locus (PaLoc) (Kuijper, et al., 2006; Voth & Ballard, 2005). Tsd A has long been considered the most important toxin to mediate diarrhea (Kuijper, et al., 2006), as it signals the release of inflammatory mediators which alter the cell wall junctions, increase cell permeability, and promote fluid secretion (Voth & Ballard, 2005). The role of Tsd B is less understood, but is implicated in the disruption the epithelial integrity of cells in the colon (Voth & Ballard, 2005). In the NAP1 isolate, Tsd A and Tsd B production is sixteen times and twenty-three times, respectively, greater than that of other *C. difficile* hospital-acquired strains (Warny, et al., 2005). This production of increased toxin concentration has emerged as the primary explanation for the increased virulence of the NAP1 strain (Warny, et al., 2005).

Apart from Tsd A and Tsd B, two other factors may also be contributing to the increase in the virulence of *C. difficile*. Recently, a newly discovered binary toxin (an actin-specific ADP-ribosyltransferase), has been suggested as an additional virulence marker for *C. difficile*. Although the role of the binary toxin still remains largely unknown (Kuijper, et al., 2006), an increased prevalence of the binary toxin was isolated

from lethal outbreaks of CDI suggesting the binary toxin in the NAP1 strain may contribute to the severity of CDI (McDonald, et al., 2005). Another distinguishing molecular characteristic of the NAP is an 18-base pair (bp) deletion in gene *tcdC*, a negative regulator of the production of Tsd A and Tsd B (McDonald, et al., 2005). It is hypothesized that a *tcdC* gene mutation disrupts the normal regulatory feedback mechanism and promotes increased toxin production (McDonald, et al., 2005).

Based on virulence alone, it is unlikely that an uncommon strain of *C. difficle* could escalate to epidemic proportions (Blossom & McDonald, 2007). Other variables, such as overuse of antibiotics and the emergence of antimicrobial resistance have been considered possible contributing factors in the dramatic rise of CDI. Antibiotic treatment has long been considered a prerequisite for CDI since it disturbs the colonic microflora and allows the organism to proliferate in the lower intestine however, the emergence of the new antimicrobial resistance is attributed to the NAP1 strain. The comparison of historical NAP1 isolates prior to 2001, with NAP1 isolates from recent outbreaks after 2001, demonstrated a significant increase in the number of isolates resistant to fluoroquinolones (levofloxacin, gatifloxacin and moxifloxacin). It appears the widespread use of antibiotics may have provided enough of a selective advantage for the NAP1 *C. difficile* strain to proliferate and further contribute to the emergence of CDI (McDonald, et al., 2005).

Detection & Surveillance.

A significant barrier to the detection, identification and surveillance of CDI at the hospital level is complicated by the lack of a sensitive and rapid diagnostic test for CDI

(Gerding, et al., 2008). The most widely used diagnostic test is the enzyme-linked immunosorbant assay (EIA) test for toxin A or toxins A and B. EIA's provide efficient testing turnaround in about 2 hours but they lack sensitivity (60-95%) (Blossom & McDonald, 2007), potentially underestimating the population with true disease. Tissue cytotoxic assay is more specific but requires additional technical expertise and 48 hours for a definitive result (Blossom & McDonald, 2007). The slow turnaround time prevents quick intervention to isolate, treat, and prevent person-to-person spread of the disease. While the traditional stool culture measures have fallen out of favor recently due to their inability to detect toxic from non-toxic producing strains (Blossom & McDonald, 2007), this has disabled a critical aspect of epidemiological surveillance, the ability to determine the offending strains (Blossom & McDonald, 2007). Two and three step processes have been proposed to increase timeliness and preserve accuracy for the short-term and have recently been adopted at major U.S. centers, including the University of Michigan Health System (Dr. Laraine Washer, personal communication, February 19, 2009). In the future, the availability of real-time PCR testing has the potential to provide the most accurate, rapid and sensitive testing option (Gerding, 2008).

Community-Acquired vs. Hospital-Acquired CDI.

Although the incidence and severity of community-acquired CDI is rising in tandem with hospital-acquired CDI (McDonald, 2008), the strains and the risk factors that characterized a community-acquired CDI are markedly different. In the community setting, antibiotic use has been found to be a predisposing factor in only half of the cases of CDI, which is in stark contrast to CDI in the hospital where antibiotic use is almost always precedent to CDI (McDonald, 2008). Furthermore, the surveillance of *C. difficile*

strains in the community was heterogeneous with only16% of the strains identified as

NAP 1 and a various array of toxinotypes. It is worth mentioning that the rising, albeit

different, presentation of community-acquired CDI versus the health care -acquired CDI,

have shown a growth of toxinotype V, the primary toxinotype associated with *C. difficile*

in calves and pigs (Jhung, et al., 2008; McDonald, 2008). A possible animal-to-human

transmission through retail meat in community-acquired CDI is an emerging hypothesis,

but is yet unsubstantiated (Jhung, et al., 2008; McDonald, 2008).

Exposure: The Transmission of CDI in Hospitals.

Exposure to *C. difficile* from inadequate personal hygiene, insufficient

disinfection of surfaces and nonadherence to barrier precautions are considered important

and significant contributors to the spread of the disease in the hospital environment

(Boyce, 2007; Cohen, et al., 2010). Since *C. difficile* can reside in a spore-form, where it

is resistant to the bactericidal effects of alcohol and standard disinfectants unlike the

common HAIs such as S*taphylococcus aureus* or *Escherichia coli*, alternative hygiene

measures to reduce CDI are central to combating the spread of *C. difficile* contamination

(Dubberke, et al., 2008). Hand hygiene with alcohol-based hand sanitizers is ineffective

against spores and therefore cannot be substituted for the traditional practice of hand

hygiene with soap and water (Dubberke, et al., 2008). Although the escalation in the

rates of CDI has also been attributed to the progressive increase in the use of alcohol-

based hand sanitizers, evidence suggest the increased use of alcohol-based hand sanitizers

to be unrelated (Boyce, Ligi, Kohan, Dumigan, & Havill, 2006a).

Several studies have reinforced the necessity for rigorous environmental decontamination of rooms of patients with CDI. Similar to the ineffectiveness of alcohol-based hand sanitizers, *C. difficile* spores can also resist the bactericidal effects of alcohol and most hospital disinfectants. In an effort to eradicate *C. difficile* spores, some of which can persist on hard surfaces for prolonged periods (Gerding, et al., 2008), terminal cleaning of hospital rooms require the use of sodium hypochlorite (household bleach) diluted 1:10 (McMullen, et al., 2007). Special attention must also be given to "high touch" contaminated surfaces such as the nursing call light, bed side rails, intravenous pumps and bedside tables (Dubberke et al., 2008)

The importance of the environmental exposure is underscored by a recent investigation demonstrating that the risk of CDI increased with the number of patients with CDI on a unit or ward, termed the "*Clostridium difficile*-associated disease pressure" or CDAD pressure (Dubberke, et al., 2007b). In fact, the investigators found *C. difficile* colonization pressure to be one of the strongest independent risk factors for CDI (Dubberke, et al., 2007b). The ability to predict an increased risk of CDI when hospitalized patients are in close proximity to CDI patients is an important implication for the prevention and control of endemic CDI (Dubberke, et al., 2007b; McDonald, 2008). Similarly, the risk of CDI was increased when a patient was assigned to a room where a prior occupant had been diagnosed with CDI or adjacent to it (Howitt, et al., 2008; Shaughnessy, et al., 2011). Even after controlling for established CDI risk factors (severity of illness, exposure to PPI and antibiotic use), the acquisition of CDI infection was significantly associated ($p=.002$) with a higher rate of CDI infection (Shaughnessy, et al., 2011).

Another recent study demonstrated a greater risk of CDI when the exposure factors of a previous recent hospitalization or a transfer from another hospital were present (Kyne, et al., 2002; Southern, et al., 2010). Similarly, a higher risk of CDI was also associated with a greater length of stay (LOS) and hospitalization in a medical center (versus community hospital) (Bliss, et al., 1998; Garey, et al., 2008; Zerey, et al., 2007). These findings clearly suggest that the environmental exposure to *C. difficile* has contributed to the rise in the incidence of CDI and therefore, interventions to reduce CDI must encompass a broad range of early, proactive and comprehensive environmental control strategies. See Table 2.1 for a synopsis of the CDI risk factors related to the conceptual construct of *Exposure.* See Appendix A for a summary of the research studies cited for this evidence.

Table 2.1

Summary of CDI Risk Factors Associated with Exposure

Risk Factor	Reference
Type of hospital (medical center, community)	(Zerey, et al., 2007)
Hospital room assignment	(Howitt, et al., 2008; Shaughnessy, et al., 2011)
Recent hospitalization/ Prior Operation/ER visits	(Kyne, et al., 2002; Oake, et al., 2010; Southern, et al., 2010)
Length of stay	(Bliss, et al., 1998; Garey, et al., 2008; Zerey, et al., 2007)
Transfer –in from another facility	(Kyne, et al., 2002)
C. difficile colonization pressure	(Dubberke, et al., 2007a; Dubberke, et al., 2007b)
Insufficient disinfection of surfaces	(McMullen, et al., 2007)

Host Defense in CDI: Patient Characteristics and Treatment-Related Variables.

Not all patients that are exposed to *C. difficile* develop CDI (Kelly, 2009). Why some patients can escape *C. difficile* exposure unscathed, while for others it is lethal, underscores the complex pathogenesis of CDI and the importance of the host health and immune status. The variables affecting host resilience to CDI can be separated into two main categories: (1) patient characteristics, and (2) treatment-related variables that render the host more vulnerable to colonization.

Patient characteristics. The two classic patient characteristics associated with an increased risk of CDI are age and severity of illness. The increased risk of CDI and advanced age has been demonstrated repeatedly (Crabtree, et al., 2007; Dubberke, et al., 2007b; Garey, et al., 2008; Kyne, et al., 2002; Metzger, et al., 2010; Rodrigues, Brady, Rodrigues, Graham, & Gibb, 2010; Zerey, et al., 2007) and recently confirmed in subsets of surgical patients (Crabtree, et al., 2007; Zerey, et al., 2007). The association between CDI and advanced age has been attributed to a declining humoral and innate immune response although there is little evidence to suggest that older patients have a less developed immune response to the *C. difficile* toxins than their younger counterparts (Pepin, et al., 2005).

Severity of illness has been identified as a risk factor for CDI in several studies, although different measures of illness severity were described (Dubberke, et al., 2007b; Kyne, et al., 2002; Metzger, et al., 2010; Peled, et al., 2007; Pepin, et al., 2005; Vesta, Wells, Gentry, & Stipek, 2005) and often, severity of illness was used as a surrogate to

predict patient mortality (Ang, Heyes, Morrison, & Carr, 2008; Bhangu, et al., 2010; Velazquez-Gomez, et al., 2008) rather than as predictive factor for disease. As one would expect, the risk factors of age and severity of illness were found to be frequently related to each other and therefore have been confounding variables in the investigation of CDI (Pepin, et al., 2005).

Because the epidemiology of *C. difficile* has recently changed into a more virulent and deadly pathogen, there is only limited evidence to fully understand the how age and severity of illness contribute to CDI risk. However, more sensitive factors of host vulnerability have started to emerge in recent research investigations. For example, CDI has been associated with diabetes (Rodrigues, et al., 2010) cardiovascular disease (Lesperance, Causey, Spencer, & Steele, 2011; Rodrigues, et al., 2010), cancer (Dubberke, et al., 2007b; Rodrigues, et al., 2010) pulmonary disease (Dubberke,, et al., 2007b; Rodrigues, et al., 2010), obesity (Lesperance, et al., 2011) malnutrition (Lesperance, et al., 2011) , anemia (Rodrigues, et al., 2010), and renal disease (Eddi, et al., 2010; Garey, et al., 2008; Kyne, et al., 2002). Specific markers for underlying risk included leukocytosis and hypoalbuminemia (Dubberke, et al., 2007b; Peled, et al., 2007). Functional status, a measure of a patient's independence in daily activities, was also identified as a risk factor for CDI (Peled, et al., 2007) and implicated as a risk factor in recurrent (not primary, CDI) because of its association with stroke (Cadena, et al., 2010). As these recent studies suggest, identifying and understanding the intrinsic factors of the host may be particularly important in preventing CDI especially in vulnerable patient populations.

Although the variables of race and gender are routinely analyzed in research studies, neither has been associated with CDI. Only two studies have demonstrated either race or gender as significant risk factors for CDI after multivariate analysis (Crabtree, et al., 2007; Lesperance, et al., 2011). Lesperance et al, (2011) identified race as a statistically significant risk factor for CDI when compared with their nondiseased controls but race was analyzed as a dichotomous variable (Caucasian vs. non-Caucasian) which may have decreased the variability in the sample population. Similarly, the risk of the female gender, identified as a risk factor in a study by Crabtree et al (2007) lacked collaboration in other surgical cohorts (Metzger, et al., 2010; Southern, et al., 2010). Therefore, whether or not race or gender significantly contribute to a patient's risk of CDI is unclear and requires additional inquiry. See Table 2.2 for a synopsis of the CDI risk factors related to the conceptual construct of *Host* vulnerability. See Appendix A for a summary of the research studies cited for this evidence.

Table 2.2

Summary of CDI Risk Factors Associated With Host Vulnerability

Risk Factor	Reference
Age	(Crabtree, et al., 2007; Dubberke, et al., 2007b; Garey, et al., 2008; Kyne, et al., 2002; Metzger, et al., 2010; Rodrigues, et al., 2010; Zerey, et al., 2007)
Female sex	(Crabtree, et al., 2007)
Race	(Lesperance, et al., 2011)
Severity of Illness	Horn's Index (Kyne, et al., 2002; Peled, et al., 2007; Vesta, et al., 2005) APACHE (Dubberke, et al., 2007b; Metzger, et al., 2010) Charlston Comorbidity Index (Pepin, et al., 2005)
Diabetes	(Rodrigues, et al., 2010)

Cardiovascular disease	(Lesperance, et al., 2011; Rodrigues, et al., 2010)
Cancer	(Dubberke, et al., 2007b; Rodrigues, et al., 2010)
Pulmonary disease	(Dubberke, et al., 2007b; Rodrigues, et al., 2010)
Obesity	(Lesperance, et al., 2011)
Malnutrition	(Lesperance, et al., 2011)
Anemia	(Rodrigues, et al., 2010)
Renal disease	(Eddi, et al., 2010; Garey, et al., 2008; Kyne, et al., 2002)
Leukocytosis	(Dubberke, et al., 2007b; Peled, et al., 2007)
Hypoalbuminemia	(Dubberke, et al., 2007b; Peled, et al., 2007)
Functional Status	(Peled, et al., 2007)

Treatment-related variables. Treatment-related variables associated with increasing the risk of CDI include the use of antimicrobial therapy (Aslam & Musher, 2006; Davey, et al., 2009; Owens, et al., 2008), gastric acid suppression (proton pump inhibitors and H_2-receptor antagonists) (Dial, Alrasadi, Manoukian, Huang, & Menzies, 2004; Dubberke, et al., 2007b; Peled, et al., 2007), tube feeding (Bliss, et al., 1998) blood product transfusions (Crabtree, et al., 2007) and gastrointestinal surgery (Howitt, et al., 2008; Rodrigues, et al., 2010; Zerey, et al., 2007). Specific to surgical patients, the use of mechanical bowel preparation (with antibiotics) has also been implicated in CDI risk (Wren, Ahmed, Jamal, & Safadi, 2005).

As discussed previously, the treatment-related variable that poses the greatest risk for CDI is antimicrobial therapy (Calfee, 2008; Davey, et al., 2009; McDonald, et al., 2005; Owens, et al., 2008). While all classes of antimicrobial therapy have been implicated in CDI, clindamycin, third-generation cephalosporins and pencillins are

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considered the greatest offenders (Owens, et al., 2008). Recently, the use of fluoroquinolones has also been identified as a risk factor for CDI, however, this finding was attributed to antimicrobial resistance among the NAP1 strain (McDonald, et al., 2005). In addition to the type of antibiotic, emerging evidence has also implicated the duration of antimicrobial use and the concomitant use of multiple antimicrobials to confound the risk for developing CDI (Owens, et al., 2008). Thus, the implementation of antimicrobial stewardship programs, in concert with environmental control strategies, are regarded as critical for the reduction of CDI (Davey, et al., 2009; Dubberke, et al., 2008; Fowler, et al., 2007; Gerding, et al., 2008).

There is a recent and accumulating body of research associating an increased risk of CDI with the use of gastric ulcer suppressors, specifically, a proton pump inhibitor (PPI) (Cunningham & Dial, 2008; Dubberke, et al., 2008). This association seems plausible considering PPIs reduce gastric acid secretion and therefore hinder the key defense mechanism the host has to fight against intestinal infection. Although several convincing studies suggests an association between PPI and CDI in hospitalized patients (Aseeri, Schroeder, Kramer, & Zackula, 2008; Cadle, Mansouri, Logan, Kudva, & Musher, 2007; Dial, et al., 2004; Peled, et al., 2007), there is also evidence to the contrary (Beaulieu, Williamson, Pichette, & Lachaine, 2007; Lowe, Mamdani, Kopp, Low, & Juurlink, 2006; Pepin, et al., 2005). Additional evidence is required to elucidate the role of proton pump inhibitors in CDI, divorced from the impact of the confounding variables such as age and severity of illness, before the causation of CDI from PPIs can be determined.

Three important risk factors for CDI that are commonplace in routine nursing care are the manipulation and delivery of tube feedings and patient bathing. The use of tube feedings has been independently associated with a higher rate of CDI (Bliss, et al., 1998) but the evidence is limited and the etiology remains unclear. The higher rate of CDI has been attributed to the contamination of the tube feeding apparatus during routine care or even the lack of fiber in the nutritional supplement (Bliss, et al., 1998). Bed baths, part of the daily routine of a hospitalized patient, decreases the colonization of pathogens on a patient's skin. However, in CDI, the concentration may be more efficient and improved when the patient is given the opportunity to shower. Much like the physical act of hand washing, the effectiveness of the cleansing action of the shower water has been found to decrease the burden of spores on the skin of patients with CDI (Jury, Guerrero, Burant, Cadnum, & Donskey, 2011). This may be especially useful for patients with fecal incontinence since stool releases a heavy burden of spores into the hospital environment.

Among surgical patients, those who undergo colectomy are at the highest risk for CDI (Howitt, et al., 2008; Rodrigues, et al., 2010; Zerey, et al., 2007). This is primarily attributed to the additional physical disruption of the indigenous colonic microflora (Zerey, et al., 2007). Traditionally, bowel preparation with oral antibiotic prophylaxis has been the standard of care for colon and rectal surgery (Zmora, et al., 2003) because it rids the intestines of bulk stool and reduces the residual live bacteria during the surgical procedure. Recently, this common practice has been implicated as a possible antecedent to CDI because of the eradication of the normally protective microflora (Wren, et al., 2005).

Wren et al. (2005) concluded the addition of oral antibiotics to mechanical bowel preparation significantly increased the rate of CDI. Although limited by a retrospective case-controlled design, there is little other available research comparing the impact of bowel preparation regimens and the risk of CDI. Therefore, the use of bowel preparation, both with and without antibiotics, has become a topic of debate among traditionalists who cite prolonged experience and success of the practice and empiricists who cite adverse outcomes per randomized trial evidence (Espin-Basany, et al., 2005; Lewis, 2002; Slim, Vicaut, Launay-Savary, Contant, & Chipponi, 2009). Whether or not bowel preparation contributes to the risk of CDI has timely importance for patients undergoing colectomy surgery since the rate and virulence of CDI continues to climb in this population (Zerey, et al., 2007).

Also unique to the surgical patient population is the association of CDI and blood product transfusions. Although the evidence is limited (Crabtree, et al., 2007), the use of blood transfusions has been implicated in other HAI's (Campbell, et al., 2008). Additional investigations may help to clarify whether or not the use of blood transfusions are a unique risk factor in CDI or a surrogate for other factors such as severity of illness or immunosuppression. See Table 2.3 for a synopsis of the CDI risk factors related to the conceptual construct of host factors that were *Treatment-related.* See Appendix A for a summary of the research studies cited for this evidence.

Table 2.3

Summary of Treatment-related Risk Factors for CDI

<u>**Risk Factor**</u>	<u>**Reference**</u>
Antibiotics	(Davey, et al., 2009)
Gastric acid suppression	(Dubberke, et al., 2007b; Peled, et al., 2007)
Tube feeding	(Bliss, et al., 1998)
Blood product transfusions	(Crabtree, et al., 2007)
Gastrointestinal surgery	(Howitt, et al., 2008; Rodrigues, et al., 2010; Zerey, et al., 2007)
Mechanical bowel preparation with antibiotics	(Wren, et al., 2005)

Summary

Now the most common HAI (McDonald, et al., 2006), the incidence of CDI is rising dramatically while the treatment options are narrowing. The problem may be due, at least in part to a hypervirulent strain of *C. difficile* which is more severe and deadly (McDonald, et al., 2005). Compounding the problem is the disproportionate burden of infection CDI has on the elderly (McDonald, et al., 2006). Effective efforts to curb the escalation of CDI are focused on decreasing the exposure of the organism by enhanced personal hygiene, improved disinfection of surfaces and adherence to barrier precautions. Parallel efforts are also underway to maximize the host resistance by reducing treatment-related modulators such as antimicrobial stewardship programs (Dubberke, et al., 2008).

Despite efforts to mitigate the epidemic of this virulent infection, the rate of CDI continues to escalate without evidence of a peak or plateau (Gerding, 2008). Identification of risk factors that predispose a patient to CDI will be critical in providing clues as to where preventive interventions should be targeted and how resources should be expended. Because the epidemiological changes in *C. difficile* are of a relatively new

science, there is limited high-quality evidence per randomized trials to support unilateral changes in practice. However, evidence is beginning to accumulate which can help clinicians to better understand the host, exposure, and treatment-related variables that contribute to the risk of CDI.

Knowledge of these risk factors is especially important for vulnerable patient populations or locations in the hospital that that have unacceptably high rates of CDI. In these instances, a clinical prediction rule for quantifying the risk of infection would enable healthcare providers to anticipate infection, and not simply react to its sequela. Valid and reliable screening tools to identify patients for infection risk are not standard procedures in most hospitals and even though risk screening for infection using computer-assisted predictors has been discussed in the literature, its purpose has been primarily surveillance and administrative rather than an assessment tool at the bedside. A clinical prediction rule, applied by nurses, early in, or prior to, hospitalization is a strategy to protect vulnerable patients, target preventative interventions, improve outcomes for CDI, and a method to translate evidence into clinical practice

Chapter III

Methodology

Epidemiologic data suggest that the burden of CDI is increasing among surgical patients, especially among patients having intestinal tract resections or colectomies (Zerey, et al., 2007). Colectomy patients are almost twice as likely to acquire CDI as patients having other surgical procedures (Zerey, et al., 2007). This investigation seeks to identify the unique risk factors predictive of CDI in a cohort of non-emergent colectomy surgical patients using data collected as part of the Michigan Surgical Quality Collaborative (MSQC). Results of this study are intended to serve as a beginning step, in a series of studies, in the development of a clinical prediction rule for CDI in this vulnerable patient population. A clinical prediction rule specific for initial onset of CDI in surgical patients is without precedence in the published literature and has received only limited attention in other patient populations (Hu, et al., 2008; Kyne, et al., 2002).

Aims

The aims of this study were to:

1) Determine the significant univariate associations between the preoperative risk factors of patients with CDI and without CDI.

2) Integrate the most robust variables associated with CDI in the postoperative colectomy patient into a clinical prediction rule model.

3) Evaluate the predictive accuracy of the CDI prediction rule.

Research Design and Methods

Using a retrospective, cohort design, this research examined the predictive variables associated with CDI and constructed a model to determine a prognostic estimation of risk based on statistical derivation (Aim One and Aim Two). Evaluation of the model (Aim Three) evaluated the predictive rule's external validity and clinical impact. Institutional Review Board approval was obtained from the University of Michigan Institutional Review Board-Medical (HUM00033887).

Setting

The data collected as part of MSQC Project comprised the cohort population for this investigation. The MSQC, headquartered in Ann Arbor, Michigan, is an organization commissioned to measure and improve the quality of care through regional collaboration. A coalition of 24 teaching and community hospitals across the state of Michigan are currently enrolled in the MSQC which is funded, in part, by Blue Cross Blue Shield of Michigan and the Blue Care Network (Michigan Quality Surgical Collaborative, 2009). The Colectomy Project, a special subset of the larger MSQC initiative, was started in 2007 to better understand best practices in various areas of colon surgery, a high-volume, high-risk procedure. This unique initiative, augmenting the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP), collects perioperative patient characteristics, intraoperative processes of care and postoperative outcomes from general and vascular surgery patients. Dr. Darrel A. Campbell, Jr. MD, a pioneer of the MSQC initiatives, is the Program Director of the MSQC, and one of the principle forces behind the development and implementation of the ACS NSQIP in non-VA hospitals (Campbell, et al., 2008; Fink, et al., 2002).

Sample

All adult patients (18 years and older) enrolled into the MSQC Colectomy Project between August 15, 2007 and June 30, 2009 were eligible for the extant study. Because there is a great deal of variation in the different types of operations performed on the colon, MSQC data collection was targeted to a very specific subset of Current Procedural Terminology Modification (CPT) codes, referred to as the colon "bucket" (Michigan Quality Surgical Collaborative, 2009) (See Table 3.1.).

Table 3.1

The Four CPT Codes included for the MSQC Colectomy Project

CPT Code	Definition
44140	Open colectomy, partial with anastomosis
44160	Open colectomy, partial with removal of terminal ileum with ileocolostomy
44204	Laparoscopic colectomy, partial with anastomosis
44205	Laparoscopic colectomy with removal of terminal ileum with ileocolstomy

By January 2010, an estimated 1800 total nonemergent colectomy patients had been accrued into the Colectomy Project, Fifty-four of those patients (three percent) are anticipated to be diagnosed with CDI postoperatively. Three percent falls on the lower end of the range of between two and seven percent given in the current literature (Wren, et al., 2005). This is likely due to the strict definition of CDI (including only diagnostic validation of *C. difficile*) and the restriction of the sample to only those patients undergoing emergent (versus nonemergent) colectomy procedures. The sample was

restricted to only nonemergent colectomy procedures in order to narrow the compounding preoperative variables associated with emergent colectomy such as immunosuppression and disease severity (Yoo, Mulkeen, Frattini, Longo, & Cha, 2006).

Power analysis was conducted using NQuery software to determine the adequacy of the sample size to provide 80% power for the logistic regression analyses used to meet Aim Two with alpha of .05, two-tailed. For Aim two, seven predictors were to be used to predict CDI in logistic regression. A medium size effect was sought, i.e., an odds ratio of 2.0 in logistic regression (Cohen, J., 1988). NQuery software indicated that a sample size of 552 would provide 80% power for logistic regression assuming a squared multiple correlation of the key predictor with other predictors was 0.2 and an overall rate of infection of 2%. This sample size is less than the estimated available sample size of 1800 so power will be over 80% for analysis of Aim Two. The power analysis focuses on Aim Two as this aim addresses the test of the full (multivariate) prediction model.

Data Source

The ACS NSQIP is a national outcome-based, risk-adjusted, peer-controlled program for the reporting and measuring of quality surgical care and patient outcomes (Khuri, 2005). The proprietary program currently includes 234 hospitals across the United States (American College of Surgeons National Surgical Quality Improvement Program, 2009). At each participating hospital, a specially trained, dedicated surgical clinical reviewer, prospectively collects preoperative, intraoperative, and 30-day surgical outcome data for major surgical operations. The clearly defined and standardized data collection methodology is routinely validated through scheduled site visits, conference calls and meetings. All eligible surgical operations are included at lower volume

hospitals. However, in order to reduce sampling error, only the first 36 cases of an 8 day cycle (alternating different days of the week each cycle) are collected for high volume institutions (Khuri, 2005).

The data abstracted for this study included both the ACS NSQIP and MSQC data. The ACS NSQIP contains over 135 variables for each surgical patient (ACS NSQIP,2010) and the MSQC Colectomy Project data, which is collected by the same surgical clinical reviewer, contains an additional data field that incorporates 25 specific elements of interest to colorectal surgeons and the outcomes of the colectomy patient (See Appendix B). The MSQC Colectomy Project data fields are not designed to stand alone; ACS NSQIP data is collected in conjunction with the MSQC Colectomy Project under the same patient identifier.

The MSQC dataset will provide the treatment-related variables of mechanical bowel prep, mechanical bowel prep with antibiotics and the outcome variable of CDI. All other variables will be ascertained as part of the larger ACS NSQIP data elements.

Measures

Dependent Variable. The presence of infection with the *C. difficile* organism was the outcome measure. In order to be considered a CDI, the presence of *C. difficile* had to be verified by laboratory detection of the toxin in the stool or by a positive stool culture. Empirical treatment alone was insufficient to verify infection. See Appendix C for MSQC operational definition.

Independent Variables. The risk predictive factors were theoretically derived from the literature review and classified via the three foundational components of the

epidemiological triad of the infection conceptual model. The risk factors were then

matched to variables included within both the ACS NSQID and MSQC data elements.

They are summarized below within each construct of the model, *Host, Treatment-related*

and *Exposure*.

Host.

As summarized in Table 3.2, a total of seven patient characteristics, twenty

preoperative cormorbid conditions and two laboratory variables were selected for

analysis.   Two variables were used as a proxy for risk factors that were not available in

the database : (1) American Society of Anesthesiologists (ASA) Physical Status

classification as a proxy for severity of illness and (2) the hematocrit level as a proxy for

anemia. The American Society of Anesthesiologists (ASA) Physical Status classification

is a measure of a patients physical status prior to surgery (American Society of

Anestheologists, 2011). It was developed in 1941 as a measure to classify and grade

patients in relation to their physical status prior to surgery (Lema, 2002). Since then, the

ASA classification system has been used, mostly by disciplines outside of anesthesia, as a

measure to classify patients into severity levels and estimate their risk of morbidity and

mortality (Davenport, Bowe, Henderson, Khuri, & Mentzer, 2006; Lema, 2002). As an

indicator of anemia, the hematocrit level was used as a proxy. The hematocrit level is a

test of the level of red blood cells and is a routine screening for anemia (Guyton & Hall,

2006).

In order to capture the most relevant patient information, one variable was

constructed from the original data elements and two others reduced from categorical

measures to dichotomous outcomes. The constructed variable, body mass index (BMI), was calculated taking the data elements of height and weight. The data element for *functional status* was reduced from a categorical variable (independent, partially dependent and totally dependent) to a dichotomous variable (independent/ non-independent) since less than three patients populated the total dependent category. The data element for *dsypnea* was collapsed to a dichotomous variable (none/moderate exertion and at rest) for the same reasons.

Table 3.2

Independent Variables for Host

Independent Variable	In Data Set?	Type	Definition †
Patient Characteristics			
1. Age	YES	Continuous	Chronological age
2. BMI	YES	Continuous	Calculated by dividing the body weight by the square of the height
3. Gender	YES	Dichotomous	Male or Female
4. Race and Ethnicity	YES	Categorical Dichotomous	Race as reported by patient (White, Black or African American, American Indian, Native Hawaiian or Pacific Islander, Asian). Ethnicity is reported as Hispanic or Latino, (Yes/No).
5. Smoking	YES	Dichotomous	Smoked cigarettes in the year prior to surgery
6. ASA Physical Status Classification (proxy for severity of illness)	YES	Categorical	**ASA 1** -Normal healthy patient **ASA 2** -Patient with mild systemic disease **ASA 3** -Patient with severe systemic disease **ASA 4** -Patient with severe systemic disease that is a constant threat to life **ASA 5** -Moribund patient who is not expected to survive without the operation. **ASA 6** not in dataset
7. Functional status - prior to surgery - prior to current illness	YES	Dichotomous	Level of self-care for activities of daily living demonstrated by the patient prior to surgery and prior to current illness. **Independent:** The patient does not require assistance from another person for any activities of daily living. **Partially dependent or totally dependent:** The patient requires some assistance or total assistance from another person for activities of daily living
Comorbidities			
Pulmonary			
1. Dyspnea	YES	Dichotomous	Difficult, painful, or labored breathing.

2. Ventilator dependent	YES	Dichotomous	Requiring ventilator-assisted respiration at any time during the 48 hours preceding surgery.
3. COPD	YES	Dichotomous	History of COPD such as emphysema and chronic bronchitis.
Cardiovascular			
4. History of CHF	YES	Dichotomous	History of CHF within the previous 30 days.
5. MI (within 6 months)	YES	Dichotomous	History of Q wave or a Q wave myocardial infarct in the six months.
6. Cardiac surgery (previous)	YES	Dichotomous	Any major cardiac surgical procedure (performed either as an 'off-pump' repair or utilizing cardiopulmonary bypass).
7. Angina	YES	Dichotomous	Chest pain or discomfort within one month prior to surgery.
8. Hypertension	YES	Dichotomous	Systolic blood pressure > 140 mmHg or a diastolic blood pressure > 90 mmHg or requires an antihypertensive treatment.
Central Nervous System			
9. Impaired sensorium	YES	Dichotomous	Acutely confused and/or delirious but responds to verbal and/or mild tactile stimulation within 48 hours prior to surgery
10. CVA with neurological deficit)	YES	Dichotomous	History of a cerebrovascular accident (embolic, thrombotic, or hemorrhagic) with persistent residual motor, sensory, or cognitive dysfunction
11. CVA (without neurological deficit)	YES	Dichotomous	History of a cerebrovascular accident (embolic, thrombotic, or hemorrhagic) with neurologic deficit(s) lasting at least 30 minutes, but no current residual neurologic dysfunction or deficit.
12. Hemiplegia	YES	Dichotomous	Sustained acute or chronic neuromuscular injury resulting in total or partial paralysis or paresis (weakness) of one side of the body (not a single limb).
13. TIA	YES	Dichotomous	Reports focal neurologic deficits of sudden onset and brief duration (usually <30 minutes) that usually reflects dysfunction in a cerebral vascular distribution.
Renal			
14. Acute renal failure	YES	Dichotomous	The clinical condition associated with increase in BUN level and creatinine of above 3 mg/dl.
15. Dialysis	YES	Dichotomous	Acute or chronic renal failure requiring treatment with peritoneal dialysis, hemodialysis, hemofiltration, hemodiafiltration, or ultrafiltration within 2 weeks prior to surgery.
Other			
16. Diabetes	YES	Dichotomous	Requires daily dosages of exogenous parenteral insulin or an oral hypoglycemic agent to prevent a hyperglycemia/metabolic acidosis.
17. Disseminated Cancer	YES	Dichotomous	Cancer that has spread to one site or more sites or who has multiple metastases.
18. Chemotherapy	YES	Dichotomous	Chemotherapy treatment for cancer in the 30 days prior to surgery.

19. Radiotherapy	YES	Dichotomous	Radiotherapy treatment for cancer in the 90 days prior to surgery.
20. Weight loss >10%"	YES	Dichotomous	Greater than 10% decrease in body weight in the six month interval immediately preceding surgery.
Laboratory			
21.WBC count	YES	Continuous	Pre-operative WBC
22. Hematocrit (proxy for anemia)	YES	Continuous	Pre-operative hematocrit

† Definitions are abbreviated from the ACS NSQIP variable data element descriptions (American College of Surgeons National Surgical Quality Improvement Program, 2010).
BMI = Body Mass Index; ASA= American Society of Anesthesiologists COPD= Chronic Obstructive Pulmonary Disease CHF= Congestive Heart Failure; MI =Myocardial infarction; CVA =cerebrovascular accident; TIA =transient ischemic attack; WBC =White blood cells; BUN= Blood urea nitrogen.

Treatment-related.

Since patients undergoing colectomy comprise the cohort of the population, this risk factor was already included within the cohort, however, the CPT codes for whether or not the patient received a laparoscopic or open procedure were retained for analysis since laparoscopic surgery has been associated with lower morbidity (Masoomi, et al., 2011). Unfortunately, variables of whether or not patients received acid suppression medications, preoperative antibiotics and whether or not the patient was being tube fed, were not available in the data set and a sufficient proxy was unavailable. (See Table 3.3)

Table 3.3

Independent Variables Treatment-related

Independent Variable	**In Data Set?**	**Type**	**Definition**
1. Blood Transfusions	YES	Dichotomous	Greater than 4 units of whole blood/packed red cells transfused during the 72 hours prior to surgery.†
2. Mechanical Bowel prep	YES	Categorical	Included patients that received :** - Magnesium citrate - Fleet Phospho-soda - Fleet enema(s) - Polyethylene glycol (PEG), electrolyte solutions (GoLYTELY, etc), - Other, specified prep - Other, unknown type - Information unavailable
3. Mechanical Bowel Prep with Antibiotics	YES	Dichotomous	Evidence of oral antibiotics with bowel preparation in medical record.**
4. **CPT codes**	YES	Categorical	The CPT code of the principal operative procedure: **44140** - Open colectomy, partial with

			anastomosis
			44160 - Open colectomy, partial with removal of terminal ileum with ileocolostomy
			44204- Laparoscopic colectomy, partial with anastomosis
			44205 - Laparoscopic colectomy with removal of terminal ileum with ileocolstomy

† Definition is abbreviated from the ACS NSQIP variable data element descriptions
(American College of Surgeons National Surgical Quality Improvement Program, 2010);
**Full operational definitions for MSQC data elements are in Appendix C;
***CPT code**= Current Procedural Terminology Modification code*

Exposure.

With the intent to protect the privacy of the participating hospitals, no variable was included in the data set that identified individual hospitals so the hospital-level variables of type, room assignment and *C. difficile* colonization pressure were not available to measure. Two important risk factors for CDI, prior operations and transfer from another facility could both be measured with data elements in the data set. Length of stay is an important risk factor for CDI postoperatively, however, only preoperative variables constructed the conceptual underpinnings of this study. Therefore, the variable of d*ays from hospital admission to operation* was used to measure a patients exposure to *C. difficile* while in the hospital prior to surgery. (See Table 3.4)

Table 3.4

Independent Variables for Exposure

Independent Variable	**In Data Set?**	**Type**	**Definition†**
1. Prior Operation (30 days)	YES	Dichotomous	Major surgical procedure performed within 30 days prior to the assessed operation.
2. Days from Hospital Admission to Operation (Preoperative length of stay).	YES	Continuous	Days from Hospital Admission to Operation**.**
3. Transfer from health care facility	YES	Categorical	Transfer status includes: - Admitted from home - Acute care hospital - Chronic care facility - Other

† Definitions are abbreviated from the ACS NSQIP variable data element descriptions (American College of Surgeons National Surgical Quality Improvement Program, 2010).

Figure 3.1 is a summary of all the independent variables within the conceptual

model components of *Host*, *Treatment-related* and *Exposure*.

Figure 3.1. Conceptual Model of *Clostridium difficile* Infection Risk with Independent Variables
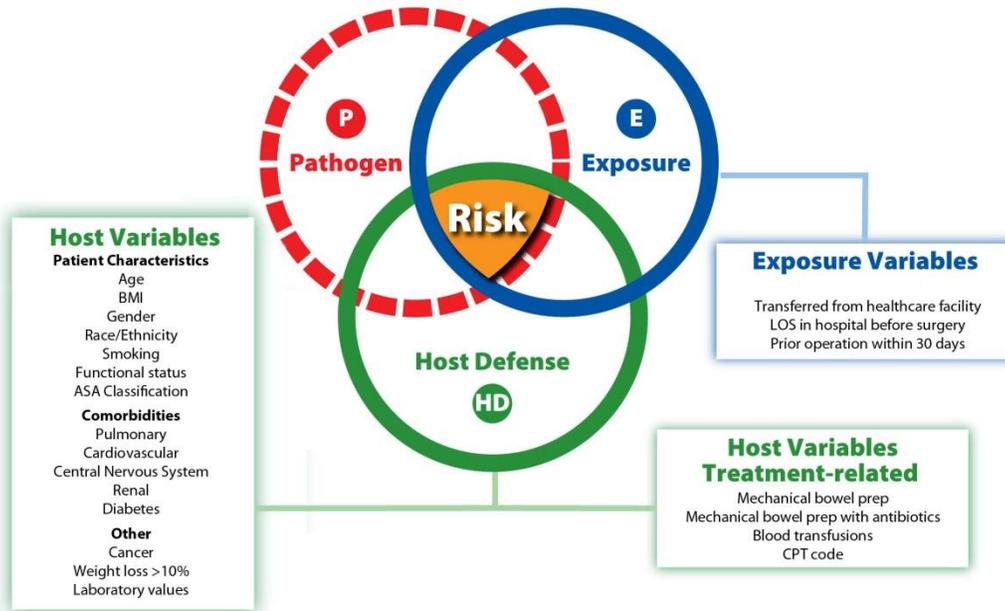
Analysis

Specific Aim 1: Determine the preoperative risk factors of colectomy patients diagnosed with CDI as compared with colectomy patients without CDI.

This aim serves as the foundation for prediction rule model development.

Univariate associations between independent variables and incidence of CDI were

estimated using χ^2 (chi-square test) and two-sample *t*-tests. The majority of preoperative

variables, therapeutic variables, and exposure variables were coded as dichotomous or

categorical variables, and χ^2 was used to estimate associations with the outcome, CDI.

The Fisher's exact test was done in those instances where the cell numbers were $\leq$ five

(IBM SPSS Statistics, 2011). A two-sample *t*-test was used to estimate association between *age*, *BMI*, *laboratory* values and preoperative *length of stay* as these variables are continuous measures.

Any variable with a *p*-value $\leq$ to 0.15 in the univariate analysis was considered as an independent variable for the prediction rule model. Allowing for a more lenient alpha level, rather than the traditional *p*-value of $\leq .05$, is recommended during univariate analysis to protect against the elimination of a variable that may have potential predictive value during the next step, logistic regression (Aim Two) (Bruce, 2010; Hosmer & Lemeshow, 2000).

Specific Aim 2: Integrate the most robust variables associated with CDI in the postoperative colectomy patient into a clinical prediction rule model.

This aim was accomplished in two steps. In the first step, binary logistic regression was used to determine the variables to include in the CPR. For the next step, the regression coefficients from the logistical regression were translated into a point-based scoring system.

Step 1.

Direct binary logistic regression was used to determine the variables to be included in a CDI prediction rule for postoperative colectomy patients. The direct method of logistic regression allows for evaluation of all the variables simultaneously, not in a specified order (sequential logistic regression) or in relation to the statistical criteria of the other variables (stepwise logistic regression) (Tabachnick & Fidel, 2007).

Since the evidence for risk factors of CDI is just beginning to reflect the new epidemiology of the emerging hypervirulent strain of infection, the relative importance of the predictor variables to the outcome is still being established. Therefore, no hypothesis about the order or importance of each variable was determined a priori and each predictor evaluated equally (Tabachnick & Fidel, 2007).

Independent variables found to be significantly associated with CDI at $p \leq .15$ in univariate analysis (Aim One), were entered into the logistic regression model. A significance level of $p \leq .05$ was the criterion established for the final model. Each of the variables were tested to see if they were excessively correlated (variance inflation factor > 10), with any of the other variables in the model. Variables that were significantly associated (*p*-value =.05) with the outcome, CDI, in the final model were included in creating the CDI prediction rule.

Although the variable of ASA classification was important to analyze in Aim One as a descriptive measure, it was removed from the primary regression analysis (Aim Two) because of its association with the other preoperative comorbidity variables measured for the model. Previous investigators have cited strong association between the ASA classification and the ACS NSQIP preoperative risk variables (Davenport, et al., 2006). In preparation for this analysis, the ASA variable was tested against the 20 variables of comorbidity. The ASA score had a statistically significant association with every other variable of comorbidity in the model (See Appendix D). The association between the ASA classification variable and the other variables entered into the regression model, would have the potential to undermine the effects of the variables on the outcome (Tabachnick & Fidel, 2007). And since the ACS NSQIP risk factors have

been found to be stronger predictors of mortality and morbidity than ASA classification (Davenport, et al., 2006), the opportunity to investigate the individual contribution of these factors in isolation from ASA was critical for building the internal validity of the CPR.

Step 2.

Using a previously established method (Kinlin, Kirchner, Zhang, Daley, & Fisman, 2010; Sullivan, Massaro, & D'Agostmo, 2004), the logistical regression model was translated into a clinical prediction rule with a point-based scoring system. The calculation of the point-based scoring system for the CPR was derived from each significant regression coefficient in the model divided by half of the lowest regression coefficient value. This method transforms the value of the regression coefficient into weighted integers whereby each variable was now assigned "points" reflective of the propensity of the risk for CDI in the model. A total risk score was then summed and quantified for the entire spectrum of individual point values (from highest to lowest). The predicted probability of each individual risk score was calculated using the equation in Figure 3.2.

Figure 3.2. Equation for the Calculation of Individual Risk Scores

$$p = \frac{1}{e^{-(-Bo + Bi \times S)} + 1}$$

p = predicted probability ; e^{-} = exponential function; S = score ; Bo = intercept; Bi = ½ of the smallest regression coefficient

While the odds ratios from a standard multivariable logistic regression models give an

estimate of the association between each individual risk factor, such odds ratios cannot provide a comprehensive assessment of risk for each individual. Such an overall assessment of risk for each individual patient is provided by clinical prediction rules derived from multivariable models, thus making the information from statistical models more useful for clinical practice (Sullivan, et al., 2004). Patients will be divided into high and low risk groups based on the distribution of the scores and the associated predicted probability. It is anticipated that the threshold for high risk may be approximately 20%. Risk scores for other conditions, most notably the Framingham cardiovascular score, which was one of the first scores developed to assess cardiovascular risk, use a threshold of 0.20 probability to define high risk (Beswick, Brindle, Fahey, & Ebrahim, 2008; Broedl, Geiss, & Parhofer, 2003). In the Framingham equations, individuals with low risk have 10% or less CHD event risk at 10 years, intermediate risk if their probability of CHD events is between 10% and 20%, and are defined as high-risk if their probability exceeds 20% (Beswick, et al., 2008; D'Agostino, Grundy, Sullivan, Wilson, & Group, 2001). Although other research has assigned a risk threshold for CDI as high as 40%, this was for the risk of recurrent disease, not primary disease, where the overall risk was expected to be much higher (Hu, et al., 2009).

Specific Aim 3: Evaluate the predictive accuracy of the CDI prediction rule.

A receiver operating characteristic (ROC) curve analysis was used to determine the accuracy of the prediction rule. As the area under the ROC curve approaches 1.0, the accuracy of the prediction rule increases. The area under the curve of .5 is considered a non-informative model and 1.0, a perfect model (Steyerberg, et al., 2008a). Reviewing

the set of statistics related to predictive accuracy, along with the ROC curves, will

provide information about the internal validation and accuracy of the prediction rule

.

Chapter IV
Results

The cohort included 2590 adult patients that were operated on for a colectomy

involving the removal of a portion of their colon with the CPT codes of open segmental

colectomy (44140), laparoscopic segmental colectomy (44204), ileocolic resection

(44160), and laparoscopic ileocolic resection (44205). Operations took place between 15

August 2007 and 30 June 2009 at an MSQC participating hospital. Of the 2590 patients,

293 (11.3%) were excluded because their surgery was classified as emergent (requiring

emergency surgical intervention). Another 17 patients (0.7%) were excluded because

they were they were outpatients and did not require an inpatient postoperative

hospitalization. An additional six patients were removed because the dependent variable

of CDI was missing. Finally, a total of 2274 inpatient colectomy patients were included

for analysis, 55 (2.4%) of which were positive for a postoperative C. difficile stool toxin

assay. (see Figure 4.1).

Figure 4.1. Flowchart of Colectomy Patient Cohort.
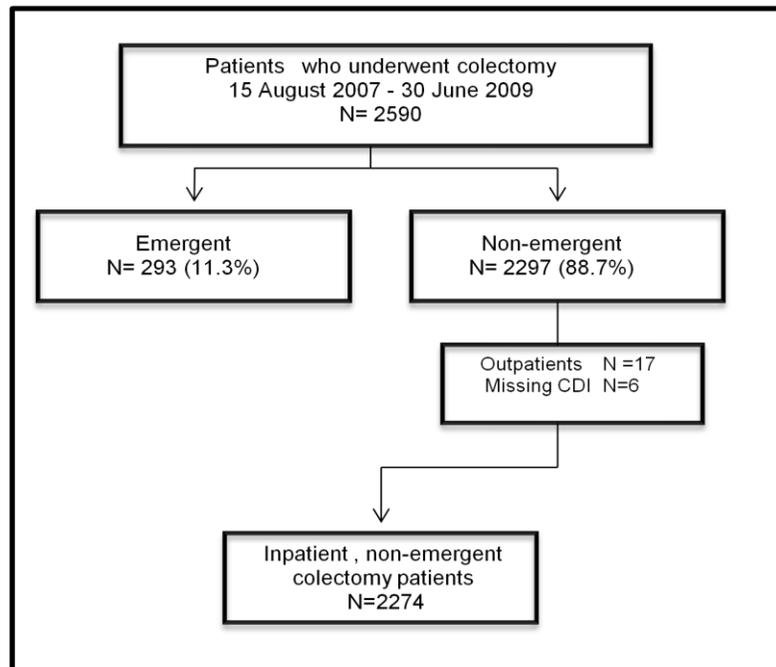
Because the ACS NSQIP has a reputation for high–quality clinical data

(Hamilton, Ko, Richards, & Hall, 2010), there was minimal incomplete data for any of

the independent variables (less than 1% total).   Since the number of incomplete data was

low, cases were assumed random and treated in the likewise deletion method during

analysis. Listwise deletion, or the exclusion of cases with missing data, gives valid

inferences in cases where missing data is minimal and assumed random (Allison, 2001).

Specific Aim 1: Determine the significant univariate associations between the preoperative risk factors of patients with CDI and without CDI.

Host Variables.

Patient characteristics. Significant univariate associations between the

preoperative risk factors of patients with CDI and without CDI are shown in Table 4.1.

Patients diagnosed with CDI were more likely to have a higher (i.e. less healthy)

American Society of Anesthesiologists (ASA) classification (p=.037) but there was no

association between Age and CDI.

Table 4.1

Univariate Analysis of Patient Characteristics and CDI

Patient Characteristics	Cohort N= 2274	No CDI N= 2219	CDI N= 55	p-value
Age	65.41 +/- 15.20	65.41 +/-15.18	65.56 +/- 16.141	.939[b]
BMI	28.11 +/- 6.20	28.10 +/- 6.19	28.68 +/- 7.062	.498[b]
Gender				.843
Male	1105 (48.6)	1079 (48.6)	26 (47.3)	
Female	1169 (51.4)	1140 (51.4)	29 (52.7)	
Race/ Ethnicity				.769
White	1715 (75.4)	1677 (75.6)	38 (69.1)	
Black or African American	259 (11.4)	249 (11.2)	10 (18.2)	
American Indian or Alaska	3 (.1)	3 (.1)	0	
Native Hawaiian or Pacific Islander	15 (.7)	14 (.6)	1 (1.8)	
Asian	281 (12.4)	275 (12.4)	6 (10.9)	
Hispanic				
Yes	20 (.9)	20 (.9)	0	.999[a]
No	2254	2254	55	
Smoking (current)				.909
Yes	427 (18.8)	417 (18.8)	10 (18.2)	
No	1847 (81.2)	1802 (81.2)	45 (81.8)	
Functional Status				
Prior to surgery				.399[a]
Independent	2127 (93.5)	2077 (93.6)	50 (90.9)	
Non-independent	147 (6.5)	142 (6.4)	5 (9.1)	
Prior to current illness				.487[a]
Independent	2184 (96.0)	2132 (96.1)	52 (94.5)	
Non-independent	90 (4.0)	87 (3.9)	3 (5.5)	
ASA				.0369[a]
1= No Disturbance	38 (1.7)	37 (1.7)	1 (1.8)	
2= Mild Disturbance	1120 (49.3)	1097 (49.4)	23 (41.8)	
3= Severe Disturbance	991(43.6)	968 (43.6)	23 (41.8)	
4= Life Threatening	120 (5.3)	113 (5.1)	7 (12.7)	
5= Moribund	5 (.2)	4 (.2)	1 (1.8)	

χ^2 *(Chi Square) Test unless otherwise indicated;* [a] *Fisher Exact Test;* [b] *t- Test. Abbreviations:* **BMI**= *body mass index;* **ASA**= *The American Society of Anesthesiology.*

Patient Comorbidities. As seen in Table 4.2, pulmonary and neurological morbidities were significantly associated with CDI in this cohort. Patients with CDI demonstrated greater ventilator dependence within 48 hours post surgery ($p = .015$) and a higher association of dyspnea ($p=.038$) with moderate exercise and at rest. Neurologically, CDI was strongly associated in patients with a history of TIA ($p=.029$), but no other neurological variables achieved statistical significance. Lastly, the number of patients with acute renal failure was approaching significance ($p=.158$) and those on dialysis, closer to achieving it ($p=.076$).

Table 4.2

Univariate Analysis of Patient Comorbidities and CDI

Comorbidity	Cohort N= 2274	No CDI N= 2219	CDI N= 55	p-value
Pulmonary				
Dyspnea				.038
Yes	363 (16)	348 (15.7)	15 (27.3)	
No	1911 (84.0)	1871 (84.3)	40 (72.7)	
Ventilator Dependent (within 48				.015[a]
Yes	2266 (99.6)	6 (.3)	2 (3.6)	
No	8 (.4)	2213 (99.7)	53 (96.4)	
COPD				.774[a]
Yes	142 (6.2)	138 (6.2)	4 (7.3)	
No	2132 (93.8)	2081 (93.8)	51 (92.7)	
Cardiovascular				
History of CHF (within 30 days)				.999[a]
Yes	36 (1.6)	36.1 (1.6)	0	
No	2183 (98.4)	2183 (98.4)	55	
MI (within 6 months)				.486[a]
Yes	27 (1.2)	26 (1.2)	1 (1.8)	
No	2247 (98.8)	2193 (98.8)	54 (98.2)	
Cardiac Surgery (previous)				.999[a]
Yes	168 (7.4)	164 (74)	4 (7.3)	
No	2106 (92.6)	2055 (92.6)	51 (92.7)	
Angina (within 30 days)				.999[a]
Yes	26 (1.1)	26 (1.2)	0	
No	2248 (98.9)	2193 (98.8)	55 (100.0)	
Hypertension				.157
Yes	1318 (58.0)	1281 (57.7)	37 (67.3)	
No	956 (42.0)	938 (42.3)	18 (32.7)	
Central Nervous System				
Impaired Sensorium				.999[a]
Yes	8 (.4)	8 (.4)	0	
No	2266 (99.6)	2211 (99.6)	55	
CVA (with neurological deficit)				.999[a]
Yes	63 (2.8)	61 (2.7)	2 (3.6)	
No	2211 (97.2)	2158 (97.3)	53 (96.4)	

Review of Systems	Entire Cohort (N= 2274)	No CDI N= 2219	CDI N= 55	p-value
CVA (without neurological deficit)				.999[a]
Yes	65 (2.8)	64 (2.9)	1 (1.8)	
No	2209 (97.1)	2255 (97.1)	54 (98.2)	
Hemiplegia				.999[a]
Yes	19 (.8)	19 (.9)	0	
No	2255 (99.2)	2200 (99.1)	55	
TIA				.029[a]
Yes	98 (4.3)	92 (4.1)	6 (10.9)	
No	2176 (95.7)	2127 (95.9)	49 (89.1)	
Renal				
Acute Renal Failure				
Yes	7 (.3)	6 (.3)	1 (1.8)	.158[a]
No	2267 (99.7)	2213 (99.7)	54 (98.2)	
On Dialysis				
Yes	19 (.8)	17 (.8)	2 (3.6)	.076[a]
No	2255 (99.2)	2202 (99.2)	53 (96.4)	
Nutrition/Immune/Other				
Diabetes				.404
Yes	400 (17.6)	388 (17.5)	12 (21.8)	
No	1874 (82.4)	1831 (82.5)	43 (78.2)	
Disseminated Cancer				.713[a]
Yes	78 (3.4)	7 (3.4)	2 (3.6)	
No	2196 (96.6)	2143 (96.6)	53 (96.4)	
Weight loss >10%				.276[a]
Yes	90 (4.0)	86 (3.9)	4 (7.3)	
No	2184 (96.0)	2133 (96.1)	51 (92.7)	
Chemotherapy				.999[a]
Yes	15 (.7)	15 (.7)	0	
No	2259 (99.3)	2204 (99.3)	55 (100.0)	
Radiotherapy				.255[a]
Yes	12 (.5)	11 (.5)	1 (1.8)	
No	2262 (99.5)	2208 (99.5)	54 (98.2)	
Laboratory				
Hematocrit	37.760 +/-	37.779 +/-5.6815	37.011 +/-5.5034	.360
WBC	7.74 +/- 3.366	7.74 +/- 3.377	7.66 +/- 2.923	.872

χ^2 *(Chi Square) Test unless otherwise indicated;* [a] *Fisher Exact Test;* [b] *t- Test.   COPD= Chronic Obstructive Pulmonary Disease CHF= Congestive Heart Failure; MI =Myocardial infarction; CVA =cerebrovascular accident; TIA =transient ischemic attack; WBC =White blood cells.*

Treatment-related Variables.

As indicated in Table 4.3, use of a mechanical bowel preparation was not associated with a higher risk of CDI (p=0.785). Among patients who underwent a mechanic bowel preparation, use of preoperative oral antibiotics showed a lower trend with CDI than did the omission of oral antibiotics, although this was not statistically significant (p=.095). Unfortunately, there were no patients that had CDI who had received greater than four transfusions or packed red blood cells (PRBCs) so there was no detectable association. Additionally, this analysis did not support surgical procedure or approach (as designated by CPT codes) as a variable that was associated with CDI (p=.632 and p=.506).

Table 4.3

Univariate Analysis of Treatment-related Variables and CDI

Variable	Cohort N=2274(%)	No CDI N= 2219(%)	CDI N=55(%)	*p*
Bowel Preparation				.785
Yes	1712 (75.3)	1672(75.3)	40 (72.7)	
With oral antibiotics	690 (30.3)	679 (30.6)	11 (20)	.095
Without oral antibiotics	1022 (44.9)	993 (44.7)	29 (52.7)	
No	207 (9.1)	201(9.1)	6 (10.9)	
Exception	344 (15.1)	336 (15.1)	8 (14.5)	
Transfusion >4 U PRBCs				.999[a]
Yes	13 (.6)	13 (.6)	0	
No	2261 (99.4)	2206 (99.4)	55 (100.0)	
CPT Code				.632
44140 open segmental colectomy	850 (37.4)	831 (37.4)	19 (34.5)	
44160 open ileocolic resection	498 (21.9)	482 (21.7)	16 (29.1)	
44204 Laproscopic segmental colectomy	640 (28.1)	626 (28.2)	14 (25.5)	
44205 Laproscopic ileocolic resection	286 (12.6)	280 12.6)	6 (10.9)	
CPT Code				.506
Open	1348 (59.3)	1313 (59.2)	35 (63.6)	
Laproscopic	926 (40.7)	906 (40.8)	20 (36.4)	

[a] *Fisher Exact Test*
[b] *t- Test*
Chi Square Test unless otherwise indicated.

Exposure Variables.

No preoperative exposure variables identified in the conceptual model demonstrated any statistical significance (See Table 4.4). A *prior operation*, *length of stay before surgery* or *transfer from another facility* failed to confer statistical significance greater than ($p \leq 0.15$).

Table 4.4.

Univariate Analysis of Exposure Variables and CDI

Variable	Entire Cohort N=2274	No CDI N= 2219	CDI N=55	p Value
Prior Operation				
Yes	31 (1.4)	30 (1.4)	1 (1.8)	.534[a]
No	2243 (98.6)	2189 (98.6)	54 (98.2)	
Length of stay before surgery	1.36 +/- 8.412	1.36 +/- 8.51	1.36 +/- 2.61	.996[b]
Transfer from Healthcare facility				.534[a]
Admitted from home	2232 (98.2)	2178 (98.2)	54 (98.2)	
Acute Care Hospital	18 (.8)	18 (.8)	0	
Chronic Care Facility	20 (.9)	19 (.9)	1 (1.8)	
Other	4 (.2)	4 (.2)	0	

. χ^2 *(Chi Square) Test unless otherwise indicated;* [a] *Fisher Exact Test;*[b] *t- Test.*

In summary, eight variables were found to be statistically significant ($p \leq 0.15$) in the univariate analysis (See Figure 4.2). All the significant variables, with one exception, were related to patient comorbidities; Mechanical bowel preparation with oral antibiotics was significant from the treatment-related category. As mentioned in Chapter III, the *ASA* category was removed from Aim Two. Therefore, seven out of the eight significant variables were retained to integrate into the binary logistic regression model.

Figure 4.2. Summary of Significant Variables
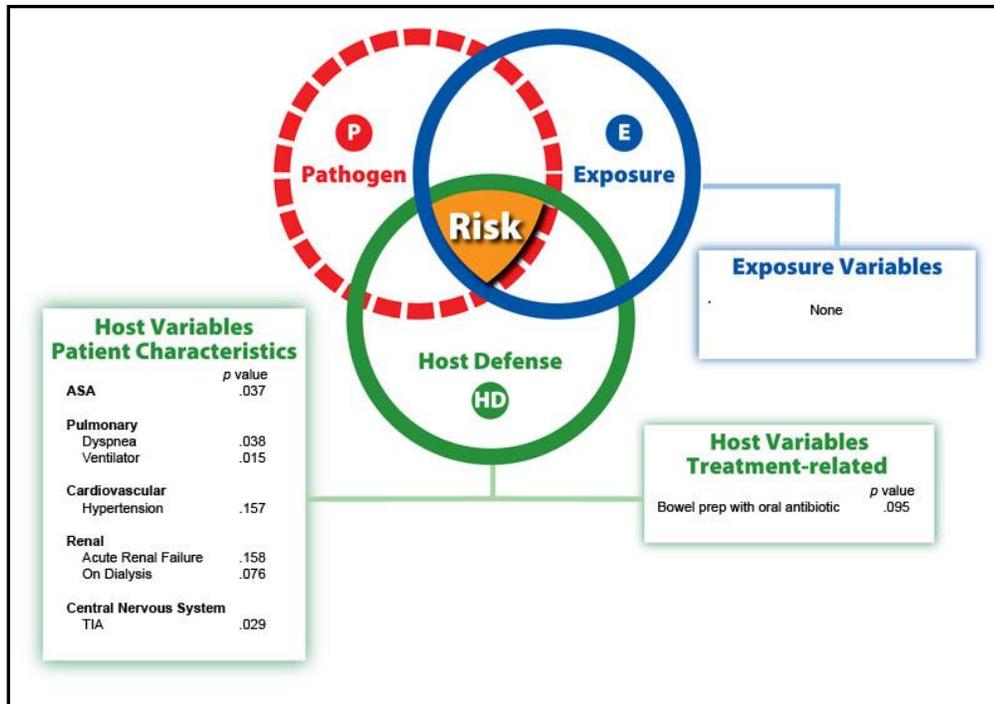
Specific Aim 2: Integrate the most robust variables associated with CDI in the postoperative colectomy patients into a binary logistic regression model.

The binary logistic regression was performed to test the association of CDI with the variables found to be statistically significant (p ≤ 0.15) in the univariate analysis (*dyspnea*, *ventilator* dependent, *hypertension*, *TIA*, *acute renal failure*, *dialysis* and *mechanical bowel preparation with oral antibiotics*).

As demonstrated in Table 4.5, *ventilator* use within 48 hours prior to surgery was the strongest predictor of CDI (OR [10.62]; CI, 1.60-67.325). Another pulmonary variable, shortness of breath (*dyspnea*) with moderate activity or rest, did not achieve

statistical significance but demonstrated a strong positive trend. Although the covariates

of *acute renal failure*, *dialysis* and *hypertension* were found to be associated on

univariate analysis, none retained significance as an independent predictor. A history of

transient ischemic attack (TIA) continued to be a strong independent predictor of CDI

(OR [2.527]; CI 1.035-6.170). In summary, only *ventilator* support and *TIA* were

independently associated with CDI as determined by binary logistic regression. As part

of the model checking, we examined interactions between the variables and none were

statistically significant (variance inflation factor <10).

Table 4.5

Binary Logistic Regression Model to Assess the Effect of Host Variables on CDI (Model I)

Variable	Regression coefficient	p	OR	95% CI	
				Lower	Upper
Acute Renal Failure	.178	.895	1.195	.083	17.094
Dialysis	1.116	.171	3.052	.618	15.077
Transient ischemic attack	.927	.042	2.527	1.035	6.170
Hypertension	.227	.450	1.255	.696	2.265
Ventilator	2.363	.012	10.620	1.675	67.325
Dyspnea	.580	.067	1.786	.960	3.321
Intercept	-4.079				

OR= Odds ratio; CI=confidence interval.
CDI=55; Total =2274

When the singular treatment variable (bowel preparation with oral antibiotic) was

added to the model, only *TIA* retained its statistical significance. Bowel preparation with

antibiotics was an insignificant predictor of CDI. In this logistic regression estimation, no patients with CDI had *acute renal failure* or *ventilator* use which prevented further analysis of these associations. (See Table 4.6).

Table 4.6

Model II: Binary Logistic Regression Model to Assess the Effect of Host Variables and Treatment Variable (Oral Antibiotics with Bowel Preparation)

				95% CI	
Variable		p	OR	Lower	Upper
Acute Renal Failure†	-	-	-	-	-
Dialysis	1.162	.289	3.196	.374	27.313
Transient ischemic attack	1.032	.042	2.806	1.040	7.575
Hypertension	.391	.272	1.479	.736	2.974
Ventilator††	-	-	-	-	-
Dyspnea	.572	.128	1.771	.848	3.699
Bowel Prep with oral antibiotics	-.591	.101	.544	.273	1.121
Intercept	-3.99				

OR= Odds ratio; CI=confidence interval.
† Acute Renal Failure variable demonstrated insufficient variability
†† Ventilator variable was a constant; all 1712 patients had a value of zero.

In summary, after adjusting for variables that were statistically significant in the univariate analysis, the binary logistic regression revealed *ventilator* and *TIA* as the strongest independent predictors of CDI in this cohort (See Figure 4.3). When the

treatment-related variable (bowel preparation with oral antibiotics) was added to the

model, only the variable of TIA remained statistically significant. There was no

statistically significant association between the use of prophylactic oral antibiotics and

CDI.

Figure 4.3. Summary of Significant Variables from Binary Logistic Regression (Model I)
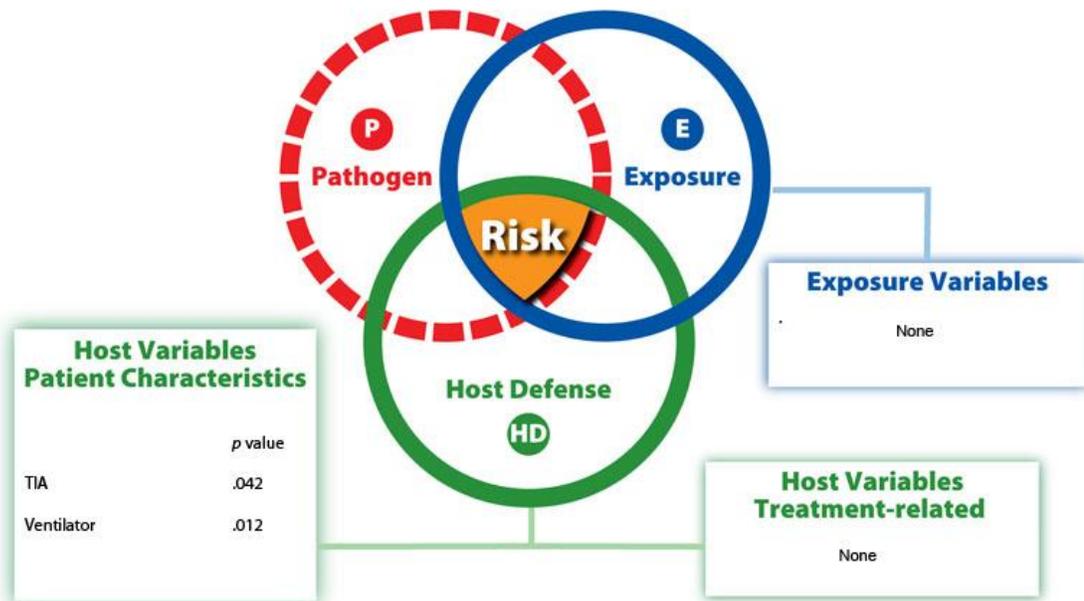
Specific Aim 3: Evaluation of the predictive ability of the CDI prediction rule.

A CPR point-scoring system was created from the regression coefficients from

Table 4.5 (Model I). Although both Model I (Table 4.5) and Model II (Table 4.6)

demonstrated equivalent measures of goodness of fit (Nagelkerke R Square= .03590 and

.03578, respectively), Model I was chosen because it included a more generalizable

patient population (562 additional patients that did not receive bowel preparation) and it

was the most parsimonious model for CPR development. The regression coefficients in

Model I were transformed into weighted point values and summed for estimates of risk

for CDI to develop the risk score (see Figure 4.4).

Figure 4.4. Six Step Process for Risk Score Development.

Step	Procedure
1	Estimate the parameters of the logistic regression model (regression coefficients and *p* value, OR and CI).

				95% CI	
Variable	Regression coefficient	p	OR	Lower	Upper
Acute Renal Failure	.178	.895	1.195	.083	17.094
Dialysis	1.116	.171	3.052	.618	15.077
Transient ischemic attack (TIA)	.927	.042	2.527	1.035	6.170
Hypertension (HTN)	.227	.45	1.255	.696	2.265
Ventilator	2.363	.012	10.620	1.675	67.325
Dyspnea	.058	.067	1.786	.960	3.321

Step	Procedure
2	Set the constant (the number of regression units that will correspond to one point or the intercept). (B_0) -4.079.
3	Determine the normalized value for each variable. The normalized value consists of dividing each variable by the lowest valued regression coefficient and rounding to the nearest integer. In this example, the smallest correlation coefficient is the variable of acute renal failure (.178). Half of the lowest value regression coefficient is called B_i in the model. Half of the smallest regression coefficient is .089 (.178/2).
4	Each variable is then divided by .089 and rounded to the nearest integer.

Variable	Regression coefficient	Divide by .089	Total	Integer
Dyspnea	.058	.058/.089	6.51	7
Ventilator	2.363	2.363/.089	26.55	27
HTN	.227	.227/.089	2.55	3
TIA	.927	.927/.089	10.4	10
Acute Renal Failure	.178	.178/.089	2	2
Dialysis	1.116	1.116/.089	12.53	13

Step	Procedure
5	Sum the individual point values. This score is the "*S*" in the equation.

6	Calculate the estimated predicted probability (p) for each score, S. This is the probability of CDI.

Estimate Predicted probability (p).

$$p = \frac{1}{e^{-(-Bo+Bi \times S)} + 1}$$

p = predicted probability ; e^- = exponential function; S = score;
Bo = the intercept; Bi = ½ of the smallest regression coefficient

Scor	Risk	Score	Risk
1	0.018164	32	0.226006
2	0.019821	33	0.241953
3	0.021626	34	0.258649
4	.023591	35	0.276078
5	0.025731	36	0.294215
6	0.028059	37	0.313028
7	0.0305	38	0.3324 8
8	0.033343	39	0.352516
9	0.036334	40	0.373086
10	0.039582	41	0.394126
11	0.043107	42	0.415567
12	0.046931	43	0.437331
13	0.051077	44	0.45934
14	0.055567	45	0.481508
15	0.060426	46	0.50375
16	0.065682	47	0.525977
17	0.071359	48	0.548101
18	0.077486	49	0.570036
19	0.084092	50	0.591701
20	0.091206	51	0.613014
21	0.098856	52	0.633904
22	0.107072	53	0.654301
23	0.115884	54	0.674147
24	0.125319	55	0.693387
25	0.135404	56	0.711976
26	0.146165	57	0.729877
27	0.157626	58	0.747061
28	0.169806	59	0.763506
29	0.182724	60	0.779198
30	0.196392	61	0.79413
31	0.210818	62	0.8083

Each patient (n=2274) in the cohort was then assigned a score based on the

presence of the weighted variable(s) (See Figure 4.5). The range of scores for the CPR

was from 1-62, however, within this cohort, the highest score attained was only 35. The

mean score was 6.47 for patients with CDI and 3.42 in patients without CDI; the median

scores were both three. As demonstrated in Figure 4.6, the patients that had CDI had a

greater percentage with higher scores. When subjected to the Mann-Whitney U test, the

results suggested that there was a statistically significant difference between the

underlying distributions of the scores of CDI patients and the scores of non-CDI patients

$(p \leq .001)$.

Figure 4.5 The probability of CDI by score.

Variable	Weighted Score
Dyspnea	7
Ventilator	27
HTN	3
TIA	10
Renal	2
Dialysis	13
Total	62
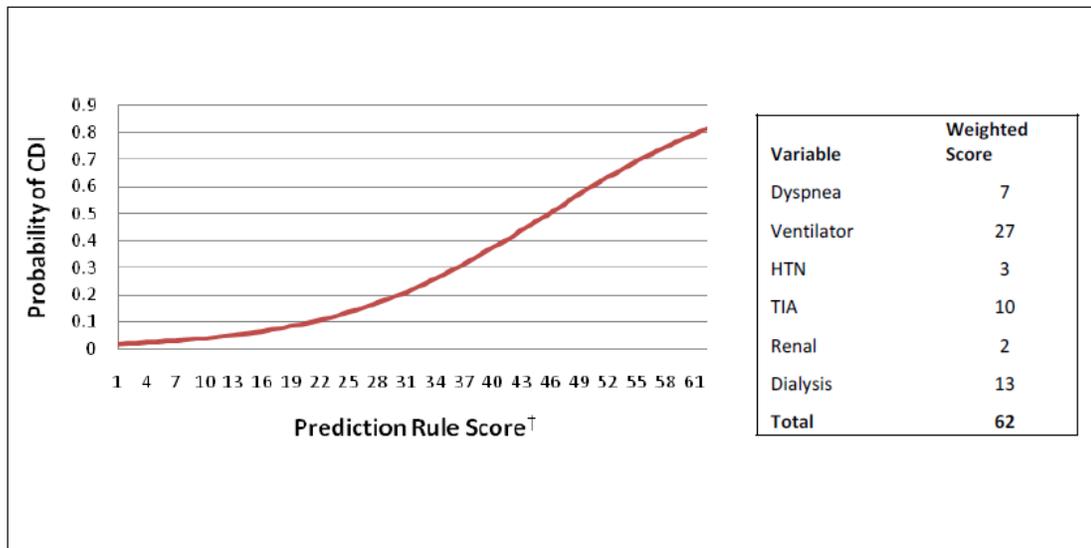
Figure 4.6 Distribution of CDI risk score in cohort (CDI vs. No CDI).
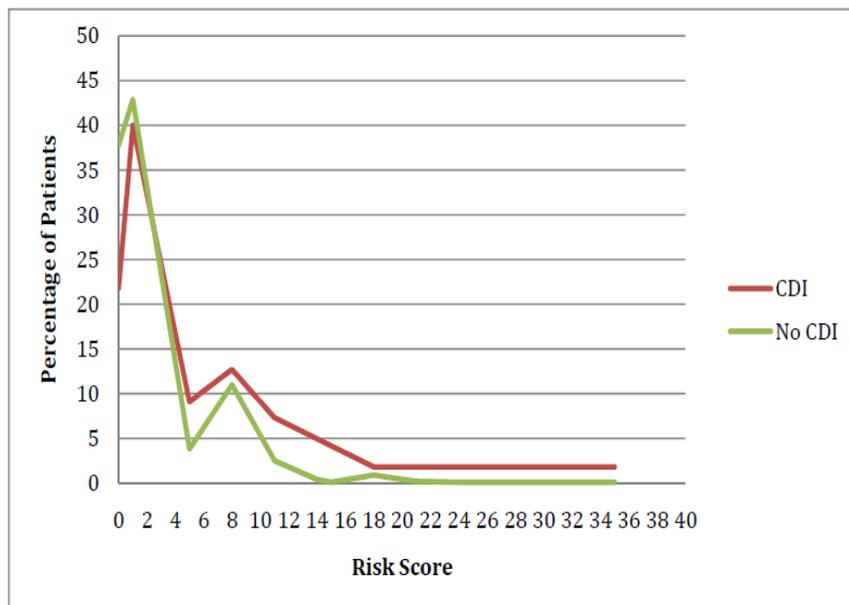
Using the predicted probabilities from Model I, the predictive ability was evaluated by the area under the ROC curve. The area under the ROC curve was 0.628 (95% CI 0.550-706) (see Figure 4.7).

Figure 4.7 ROC Curve for CDI.
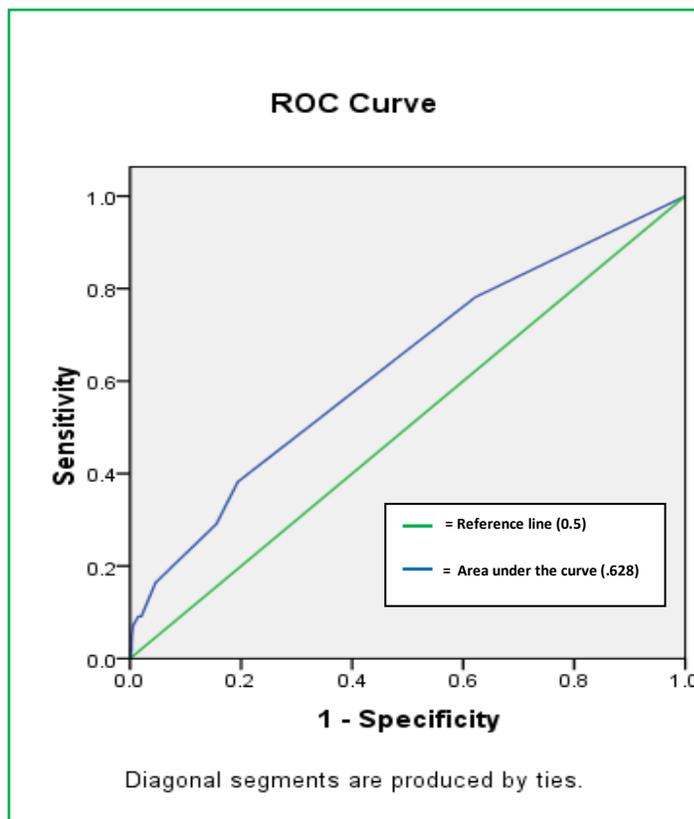
In this cohort, the probablity of CDI infection ranged from zero (score of one) to 0.27 (score of 35). A high risk patient was determined to be at a theoretical probability of risk of 0.18 (score of 29) which represented the top quartile of the distribution. A high risk threshold of approximately 20% has precedence in the literature for other risk score calculations, most notably the Framingham cardiovascular score which was one of the first scores developed to assess cardiovascular risk, use a threshold of 0.20 to define high

risk (Beswick, et al., 2008; Broedl, et al., 2003). In the Framingham equations,

individuals with low risk have 10% or less CHD event risk at 10 years, intermediate risk

if their probability of CHD events is between 10 and 20%, and are defined as high-risk if

their probability exceeds 20% (Beswick, et al., 2008; D'Agostino, et al., 2001)

The CPR was then analyzed for measures of sensitivity, specificity, positive

predictive value (PPV) and negative predictive value (NPV). The sensitivity and

specificity for the high risk patients with a score of 29 were 1.8% and 98.7%,

respectively. The PPV was 14.3% and NPV was 97.6%. See Table 4.8 for predictive

ability of sequential quartile scores of 8.5. 18.5, 29. The sensitivity and specificity for the

high risk patients with a score of 29 were 1.8% and 98.7%, respectively. The PPV was

14.3% and NPV was 97.6%. See Table 4.7 for the predictive ability for the sequential

cutoff scores of 5, 8.5. 18.5 and high risk score of 29.

Table 4.7

Stratified Risk Scores and Equivalent Measures of Predictive Ability

Cutoff Score	TN	FP	FN	TP	SENS	SPEC	PPV	NPV
5	1789	430	34	21	38.2%	80.6%	4.7%	98.1%
8.5	1874	345	39	16	29.1%	84.5%	4.4%	98.0%
18.5	2186	33	50	5	9.1%	98.5%	13.2%	97.8%
29	**2213**	**6**	**54**	**1**	**1.8%**	**99.7%**	**14.3%**	**97.6%**

TN=true negative; FP= false positive; FN= false negative; TP=true positive;SENS= sensitivity, SPEC= specificity; PPV=positive predictive value; NPV= negative predictive value

Chapter V
Discussion

Although many recent studies have led to tremendous success in reducing HAIs (Bode, et al., 2010; Pronovost, et al., 2006), no equivalent large-scale success has been reported to reduce CDI. The incidence of CDI continues to climb (Dubberke, et al., 2010; McDonald, et al., 2006), without evidence of a peak or plateau (Dubberke, et al., 2010), despite the national attention this epidemic has received (Parker-Pope, 2009; Sunenshine & McDonald, 2006). As the threat of CDI continues to escalate, and the traditional arsenal of antibiotic regimens are rendered ineffective, new strategies for prevention are needed on the front lines of defense. The purpose of this research was to begin the first phase in a series of studies to develop a clinical prediction rule (CPR) for the quantification of CDI risk in a population of colectomy surgical patients. A CPR to identify patients most vulnerable to CDI early in their hospitalization is a strategy to improve patient outcomes so that preventative interventions and treatments can be targeted to at-risk patients before, not in response to, infectious disease.

The construction of the CPR was achieved through three sequential aims. In Aim One and Aim Two, the risk factors for CDI were identified using univariate and binary logistic regression. The preoperative variables of mechanical *ventilation* and transient *ischemic attack* (TIA) were found to be the most robust significant predictors of CDI in this cohort. In Aim Three, the final multivariate model was transformed into a CPR weighted point-scoring system. The discriminative ability of area under the operator

receiver curve was modest at .628. Depending on the score cutoff the specificity and

sensitivity of the CPR ranged from 1.8%-38.2% and 80.6%-99.7%, respectively. This

study represents the first and largest regionally-based description of preoperative risk

factors for CDI in surgical patients using a clinical (not administrative) dataset.

Additionally, through the use of a CPR, the findings of this study have attempted to

quantify the risk of infection for translation into the clinical environment. Since surgical

patients now carry more than twice the burden of HAI than their medical counterparts

(Sax, et al., 2011), strategies to identify and protect vulnerable patients are becoming

increasingly more important.

In order to demonstrate the interrelated variables that contribute to the risk of

CDI, this chapter is organized around the components of the epidemiological triad of

infection (pathogen, host, exposure) that served as the underpinnings for the conceptual

model. Using the conceptual model as a blueprint for this discussion, the contribution of

each of the three components is addressed first separately, and then together, where the

theoretical components of the CPR intersect. In closing, the implications of this research

for health care professions, and specifically nurses, are delineated and recommendations

for a research agenda for CDI CPR are prescribed.

Incidence of *Clostridium difficile* Infection

In this cohort of 2274 surgical colectomy patients in Michigan, the incidence of

CDI was 2.4%. This incidence fits squarely within the range of one to six percent

reported in the literature for similar populations of postoperative colorectal patients

(Lesperance, et al., 2011; Southern, et al., 2010; Wren, et al., 2005; Zerey, et al., 2007).

However, comparisons across other surgical populations are difficult since the incidence

and consequence of CDI is not uniformly calculated and reported. Incidence reports of CDI are largely based on retrospective analyses (Lesperance, et al., 2011; Southern, et al., 2010; Wren, et al., 2005; Zerey, et al., 2007) or rely on large administrative databases (Lesperance, et al., 2011; Zerey, et al., 2007). Since the median length of stay for colectomy patients is six to seven days (Iyer, Saunders, & Stemkowski, 2009; Schmelzer, et al., 2008) and CDI incubation period can exceed this by several weeks (Palmore, Sohn, Malak, Eagan, & Sepkowitz, 2005; Sunenshine & McDonald, 2006), there is a greater possibility that the true rate of CDI is underestimated. Further confounding accurate data reporting is the fact that many patients with CDI received empiric treatment (when the physician may treat for CDI without ordering a definitive test) and are not reported. Thus, it is likely the true underlying incidence of CDI is probably higher than current estimates presume.

Regionally, across Michigan, the rate of CDI among hospital discharges doubled between 2002 and 2008 (Verlee, 2011) which is an alarming trend considering the propensity for underestimation of detection. This escalation parallels the national trend (Dubberke, et al., 2010) and is likely associated with the more virulent and severe type of CDI due to the NAP1/B1/027 strain. Although this study did not have access to typing of strains, unpublished preliminary reports have confirmed the emergence of the NAP1/B1/027 strain, and an associated ribotype 020 variant in Southeastern Michigan (S. Walk, personal communication, April 24, 2011). Both of these strains are superseding a less virulent strain that characterized CDI before 2003. Since this research examined a cohort of patients between the years 2007 and 2010, it likely captures the contemporary trends of the CDI epidemic in this high-risk subset of surgical patients.

Host Variables

Although, the variable *age* is a long-standing and repeatedly validated risk factor for CDI (Ang, et al., 2008; Crabtree, et al., 2007; Sunenshine & McDonald, 2006), this research did not find any appreciable difference between incidence of CDI and age in this cohort (p=0.939) on univariate analysis. Even when the variable *age* was divided in to dichotomous and categorical variables, no significant association between age and CDI could be detected (See Table 5.1). Being that the evidence for increasing age and CDI risk was an atypical finding, additional post hoc analyses were conducted. When the variable of *age* was added to the final model, there was still no significant association between CDI and age (*p*= 0.283, (95% CI, .989-.969)) and the variables of TIA and ventilator remained statistically significant. Furthermore, adjusting for age had a negligible effect on the predictive ability of the model (area under the curve .631, (95% CI, 0.554-0.709) versus .628, (95% CI, .550-.706) and model fit equivalent measures of goodness of fit (Nagelkerke R Square= .038 versus .036). However, an interesting finding was that the variable of dyspnea, close to achieving statistical significance previously (p=.067), decreased to less than .05 when age was added to the model (see Appendix E). This suggests that chronological age alone may not be a sufficient predictor of CDI risk but may in fact be a surrogate for other measures of frailty, such as pulmonary compromise. Including more defined measures of frailty, such as systemic inflammatory biomarkers and inflammatory related diseases (Chang, Weiss, Xue, & Fried, 2011), rather than chronological age, may be where more predictive and sensitive measures of CDI risk for CPR development will be best ascertained.

Table 5.1

Univariate Analysis of Age as a Continuous, Dichotomous and Categorical Variable

	Entire Cohort N=2274 (%)	No CDI N= 2219(%)	CDI N=55(%)	*p*
Continuous				
Age	65.41 +/- 15.20	65.41 +/-15.18	65.56 +/- 16.141	.934[b]
Dichotomous				.759
Less than age 65	1080 (47.5)	1055 (47.5)	25 (45.5)	
Greater than age 65	1194 (52.5)	1164 (52.2)	30 (54.5)	
Dichotomous				
Less than age 80	1837 (80.8)	1797(81)	40 (72.7)	.125
Greater than age 80	437 (19.2)	422 (19)	15 (27.3)	
Categorical				.349
18-39	115 (5.1)	112 (5)	3 (5.5)	
40-49	217 (9.5)	211 (9.5)	6 (10.9)	
50-59	442 (19.4)	432 (19.5)	10(18.2)	
60-69	509 (22.4)	499 (22.5)	10 (18.2)	
70-79	554(24.4)	543 (24.5)	11 (20)	
80-89	373 (16.4)	358 (16.1)	15 (27.3)	
90+	64 (2.8)	64 (2.9)	0	

χ^2 *(Chi Square) Test unless otherwise indicated;* [b] *t- Test*

Another potential explanation for the lack of association between age and CDI in this cohort, may be because surgical patient populations are generally younger and healthier than their medical counterparts (Southern, et al., 2010). The average age of a patient in this cohort was 65.41. The average age of patients with CDI in a similar cohort of only medical patients, was almost three years higher at 67.9 years-old (Southern, et al., 2010). For this reason, chronological age may not be as strong of an independent predictive variable for CDI in the elective surgical patient population as in their medical counterparts.

Similarly, although race and gender have both been reported as risk factors for CDI in other studies, neither variable demonstrated significance in this analysis. Lesperance et al. (2011) identified race as a statistically significant risk factor for CDI

when compared with their nondiseased controls but race was analyzed as a dichotomous variable (Caucasian vs. non-Caucasian) which may have decreased the variability in the sample population. Similarly, the risk of the female gender, identified as a risk factor in a study by Zerey et al (2007) and Crabtree et al (2007) lacked corroboration in other surgical cohorts (Crabtree, et al., 2007; Zerey, et al., 2007). In this study as well, there was no statistical difference between male and female genders and CDI risk. Therefore, uncertainty persists as to whether or not race or gender significantly contributes to a patient's risk of CDI.

In contrast, this study provides additional validation that patients with a higher severity of illness are at a higher risk for CDI. Patients with comorbidities reflecting a higher severity of illness (ventilator use and renal disease) were associated with a greater risk of disease. Although the ASA classification was not moved forward to the multiple variable regression models due to its association with other risk factors, an additional post-hoc analysis was conducted to determine the effect of the final model when adjusting for the effects of the ASA classification. Adjusting for ASA did not change the model results, as *ventilator* and *TIA* were still the only variables achieving a *p*- value of $\leq$ .05. In addition, there were no significant associations between CDI and ASA classification when analyzed as a categorical variable (with all five classifications) and as a dichotomous variable (classifications $\leq$ 3 vs. classifications of 4 & 5) nor was there any appreciable increase in the predictive accuracy of the model; the area under the ROC curve increased only marginally from .628 to .642 (see Appendix F).

Because the national rate of CDI continues to rapidly increase without a concomitant national increase in a population's severity of illness (Dubberke, et al.,

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2010), it suggests that a patient's severity of illness, while important, is not a singular 'stand-alone' variable that contributes to CDI risk. More likely, it is that the severity of illness in combination with other risk factors (such as antibiotic usage, proton pump inhibitor medication) may have an interactive effect on disease acquisition.

Since this dataset included a large number of comorbidities, it enabled the analysis of the umbrella term of "severity of illness" to be examined with greater detail. Respiratory covariates were of particular interest because they are often associated with CDI risk. Rodrigues et al. (2010) identified respiratory disease as an independent predictor of CDI and others have identified patients with mechanical ventilation as a risk factor of CDI either on univariate (Garey, et al., 2008; Lawrence, Dubberke, Johnson, & Gerding, 2007; Rodrigues, et al., 2010) or multivariate analysis (Dubberke, et al., 2007b). Although this study identified mechanical ventilation as a strong predictor of CDI, it is likely this association is mediated by the increased use of antibiotic therapy. Patients on mechanical ventilation generally have more antibiotic administration therefore, increase their risk of CDI. In other studies that have been able to control for antibiotic usage, the association of mechanical ventilation with CDI was either decreased (from an odds ratio of 9.7 to 1.9) (Dubberke, et al., 2007b) or removed (Garey, et al., 2008) when subjected to multivariate analysis. Since antibiotic use is likely in the causal pathway for CDI, the ability to control for the mediating effect of antibiotic use in this study may have produced a similar effect.

There is more accumulated evidence demonstrating an association between renal disease and CDI (Barany, Stenvinkel, Nord, & Bergstrom, 1992; Eddi, et al., 2010; Garey, et al., 2008; Kyne, et al., 2002; Pant, et al., 2011). The association is attributed to

a possible decrease or absence of gastric acid (achlorhydria or hypochlorhydria), the dose

or exposure to dialysis and/or a higher *C. difficile* pathogen load in the stool due to

deceased motility (Barany, et al., 1992; Eddi, et al., 2010). It is also reasonable to

assume that patients with renal disease or dialysis have had higher exposure to both

antibiotics and health care facilities, also significant risk factors for CDI. The fact that

both renal variables (acute renal failure or treatment with dialysis) were insignificant in

this population after the regression analysis is surprising given the clinical and empirical

evidence of renal disease's association with CDI. Eddi et al (2010), conducted an in-

depth analysis of patients with chronic kidney disease and found only those patients

suffering from end stage disease carried a risk for CDI (Eddi, et al., 2010). This may

help explain the insignificant finding; patients with end stage renal disease are not good

candidates for surgery and are likely not represented in this cohort. Renal disease, and

more specifically end stage renal disease, may be a stronger predictor of CDI in the

medical patient population.

Puzzling as it may be, a history of transient ischemic attacks and the subsequent

development of CDI had a significant and strong association in both univariate and

multiple variable analysis. The strong association between TIA and CDI does not appear

to have any precedence in the literature. Additionally, no other variables in the central

nervous system category (*cerebral vascular accident*, *hemiplegia/hemiparesis*, *impaired*

sensorium) were found to be statistically significant. If cerebral vascular accident (or

stroke) and TIA were both significant, the association with CDI could possibly be

attributed to alterations in intestinal immunity that are hypothesized to occur as part of

the post-stroke immunodepression sequela (Schulte-Herbruggen, Quarcoo, Meisel, &

Meisel, 2009). However, since only TIA, and not the more severe condition of stroke, was the only significant variable in this analysis, support for the immunomodulation effects of a cerebral vascular event cannot be fully supported as a possible mechanism for association between CDI and cerebrovascular events. As the stroke-induced changes within the intestinal microbiota become better understood, and future research reveals more evidence for a link between cerebrovascular events and CDI, the suppression of the intestinal population may emerge as a possible antecedent to infection.

Although the association of TIA with CDI may be a spurious finding, if it is in fact true, further independent study will be required to determine possible associated mechanisms. For example, this finding may be linked to a regional practice of prescribing drugs such as statins. Patients with a history of TIA's are often prescribed statin (HMG-CoA reductase) medication to reduce cholesterol plaques. The hypothesized connection between statins and CDI has been recently addressed in the medical literature (McGuire, Dobesh, Klepser, Rupp, & Olsen, 2009) as a possible drug-disease association.

The theoretical hypothesis of a drug-disease association as a precursor to CDI has gained momentum as the rise in CDI has extended to patients without any previous antibiotic exposure. Without antibiotic exposure, the micro-environment of the gastrointestinal tract is left undisturbed. Thus, theories advocating other unknown mechanisms, besides antibiotic exposure, that allow the *Clostridium difficile* organism to take advantage of the microenvironment have gained strength. The associations between drugs that alter gastric acid suppression (proton pump inhibitors and histamine blockers) are one such example. While the statin drug class does not alter gastric acid suppression,

it does interfere with an important cellular mechanism on the Rho pathway (unrelated to their primary role of cholesterol reduction). The Rho pathway is described as a type of "molecular switch" that controls important regulatory cell functions such as cell proliferation, inflammation and apoptosis (McGuire, et al., 2009). When the Rho pathway is inhibited or "shut off" it leads to apoptosis of the colonic epithelium. Clostridium difficile toxins also inhibit the Rho pathway, although this inactivation occurs at a different site. While the beneficial effects of statins have been described (Roberts, Guallar, & Rodriguez, 2007; Zafrir, Laor, & Bitterman, 2010), the influence of two agents interrupting the Rho pathways at two different sites is unknown. Given that the number of patients on statins continues to increase (Ma, Sehgal, Ayanian, & Stafford, 2005), the synergic effects of *Clostridium difficile* toxins and statin drugs on the different sites of the Rho pathway is a hypothesis that deserves further inquiry (McGuire, et al., 2009). Only adequately powered prospective studies will be able to decisively identify the potential association between any drug-disease association between statins and CDI.

Treatment-related Variables

The most important finding in the treatment-related category was not what was found significant, but what was found insignificant. Mechanical bowel prep (with and without antibiotics) was found to have no association with an increased risk of CDI. These results contradict an earlier single-center study (Wren, et al., 2005) and add to the debate surrounding mechanical bowel preparation and CDI risk.

Mechanical bowel preparation (MBP), a long-standing preoperative standard of care for colorectal surgical patients, has been called into question as a possible precursor

to adverse outcomes, including CDI (Contant, et al., 2007; Guenaga, Matos, Castro, Atallah, & Wille-Jorgensen, 2005; Howard, White, Harden, & Ellis, 2009; Slim, et al., 2009; Wren, et al., 2005). The implication of MBP as a possible antecedent to CDI is because MBP disrupts the normal bowel flora and potentially sets the conditions for *C. difficile* to proliferate (Wren, et al., 2005). Determining an association between the rate of CDI and the practice of bowel preparation in this patient population is important because two risk factors for CDI, recent antibiotic therapy and disruption of the normal flora of the intestines, are direct consequences of bowel preparation.

In an effort to explore this association with more precision, an additional post hoc analysis was undertaken on this dataset (see Appendix G). Again, the incidence of CDI was the same in the patients that received MBP as in those that did not (p=0.95) and the same for those that received oral antibiotics with their bowel preparation versus those that did not (p=.088). Even after adjusting for characteristics that achieved $p \leq .05$ in preliminary analysis, there was no association of CDI with MBP or MBP with or without antibiotics (OR [0.96]; CI, 0.50-1.83) and OR [0.60]; CI 0.29-1.23). Therefore, the evidence in this study suggests that abandoning bowel preparation (both with and without oral antibiotics) to reduce the risk of CDI is premature and will require additional empiric evidence before clinical practice changes should be recommended (Krapohl, et al., 2011).

Exposure Variables

There is strong evidence to suggest environmental exposure to *C. difficile* has contributed to the increasing incidence of CDI (Cohen, S. H., et al., 2010). Although the three exposure variables analyzed in this study (prior operation, LOS before surgery and

transfer from another healthcare facility) were not associated with CDI in this research, it would be incorrect to dismiss them as unimportant. Patients who have had prior surgery, have been in the hospital for a longer period of time or have transferred from another facility will likely have a greater possibility of being exposed to *C.difficile*. The patients who become infected with CDI are generally treated and identified. However, if the patients are simply colonized, and not demonstrating signs of infection, they may still have the capacity to spread infections to other patients. Therefore, patients with these exposure variables who are colonized (not infected) may not demonstrate an increased risk of infection on an individual level, but may have a measurable effect on the incidence of CDI on the patients around them (i.e. expose others to infection). It may be possible that the exposure variables measured in this study contribute to CDI risk more from a collateral impact, at the hospital-level, than an individual impact. In order to better understand the effects at the hospital-level, a facility identifier as well as the ability to determine the type of hospital (medical center, academic or community) would help to better understand these influences. Additionally, the variables in this category should be expanded to include, *C. difficile* pressure, adherence to recommended environmental practices and recent emergency department visits (in addition to hospitalizations) all of which can help to further identify and understand the important trends between CDI and exposure variables.

Predicting the Risk of CDI with the CPR

The rule developed for this study, though only in the first phase of development, provides preliminary evidence for the variables necessary to quantify the risk of CDI.

The results from the CPR suggest host factors contribute, at least modestly, to the risk of CDI (area under the ROC curve .628). A 20% risk of CDI was translated into a score of greater than 29 on the CPR scoring system. Unfortunately, the sensitivity of the test was only 1.8% which translates into a 1.8% chance of patients with a score of 29 conferring a risk of CDI. A high specificity (99.7%) is important in detecting patients that are CDI negative, but the inability to effectively distinguish the high risk patients is a disappointing result of the CPR. Due to the poor sensitivity and positive predictive value of CPR, it is likely the low incidence of CDI in the sample (55 patients or 2.4%) and the absence of several variables in the dataset contributed to this finding. Important treatment related variables such as antibiotic use, proton pump inhibitors, tube feeding and exposure variables such as type of hospital, adherence to recommended environmental practices and staff/patient education may have contributed to the disappointing predictive ability in the final model. Since the causes of CDI are multifactorial, the inclusion of these additional variables in the future developmental phases of CPR development will help to achieve stronger predictive value and sensitivity.

The absence of the variable of antibiotic use may be considered by some to be particularly problematic considering that it is the most important and influential treatment-related variable missing from the model. However, since over 50% of hospitalized patients receive antibiotics (MacDougall & Polk, 2008), the addition of antibiotic use in the CPR may not have produced the desired discriminatory effect. This is especially true in this cohort of surgical patients that have probably received antibiotics in accordance with the Surgical Care Improvement Project (SCIP) guidelines (Bratzler & Houck, 2005). Other investigators have found including antibiotic use in a CPR to be

impractical and have focused instead on risk factors such as type of admission (surgical versus non-surgical) and ICU length of stay) both thought to have greater discrimination ability (Garey, et al., 2008). In the future, more specific definitions of antibiotic use including type, duration (Garey, et al., 2008) and use prior to hospitalization may prove to be more useful predictors of CDI risk.

Besides incomplete availability of variables, another reason for the modest results of the CPR may have been the methodology employed to construct the rule. There are two primary methods to develop point scoring systems for CPRs and the investigator determines whether the scoring requires a simple additive effect (points give for a risk factor that is present), or a weighted effect using an odds ratio or regression coefficient to calculate the score (Garey, et al., 2008). Since this study choose the latter method, the weights of the risk factors from the logistic regression model were quantified based on the regression coefficients. The parameters of the final model were then expanded so that the relative weights of the statistically insignificant variables were included in the final point system. Keeping the statistically insignificant variables in the final point system calculations, was an attempt to create a scoring system that reflected the strongest fit statistics (Nagelkerke R Square= .036) and retain variables believed to have clinical and theoretical significance to the final scoring point system. Otherwise, the score was reduced to a 2-predictor model (TIA and ventilator) with a lower fit statistic (Nagelkerke R Square= .021). Increasing the precision of the CPR will require additional prospective research to include the variables not included in this data set.

Because C. *difficile* does not appear to be responding to the standard infection control practices, enhanced measures to protect patients are necessary. The results of this

CPR suggest host variables, without the influence of other treatment-related and exposure variables, make a contribution to CDI risk. Unlike other HAIs that are predominately attributed to treatment-related variables such as urinary catheters, central lines, mechanical ventilation and surgical wounds, CDI may prove to be an HAI with a greater influence of intrinsic risk. Therefore, efforts to reduce CDI many benefit from an infection control strategy that augments standard infection control strategies such as hand washing and environmental decontamination, with those that take into consideration the comorbidities of the host. Future current infection control strategies may include choosing candidates for the testing of serologic markers and candidates for both passive and active immunization (Kelly & Kyne, 2011). As seen in Figure 5.1, most preventive strategies are targeted to reducing exposure rather than increasing patient (host) resistance (Cohen, S. H., et al., 2010; Vonberg, et al., 2008).
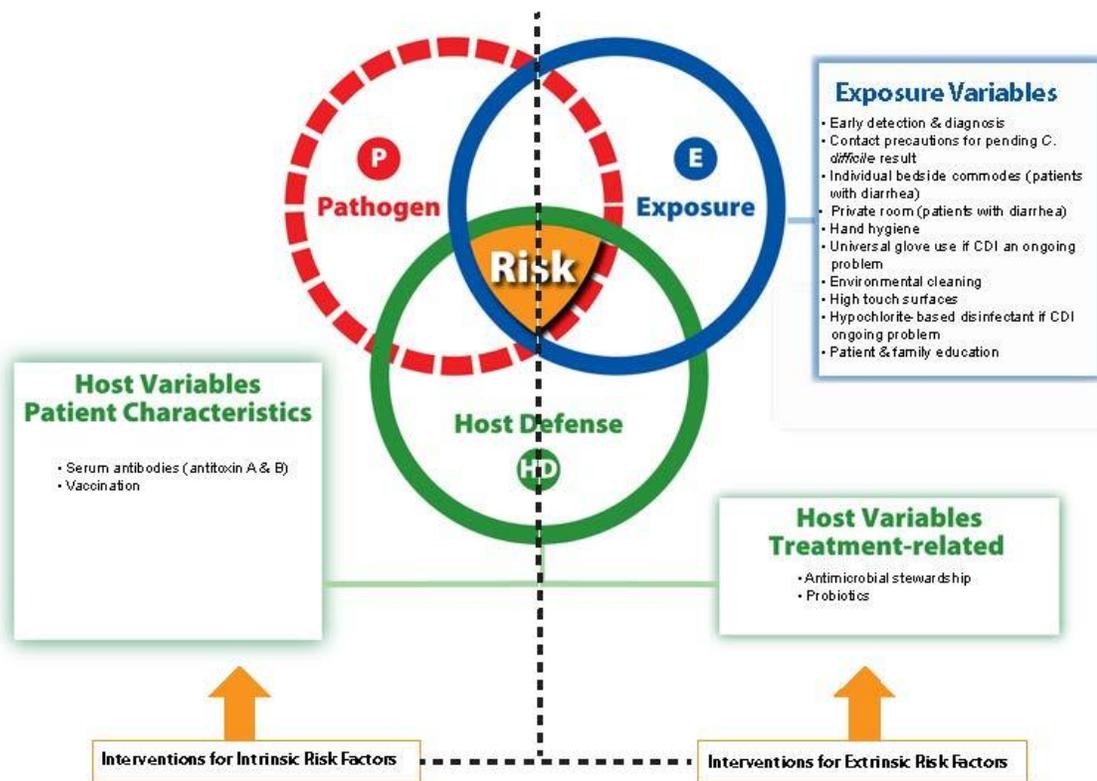
Figure 5.1. Clinical practice interventions to prevent CDI organized around conceptual model.

A CPR for CDI is an inexpensive, nonpharmaceutical and noninvasive method to incorporate the individual risk of patients into the broader infection control strategy. Instead of a horizontal (nonpathogen-directed) infection control strategy that relies on the "one-size-fits-all" approach, vertical (pathogen-directed) strategies, such as a CPR for CDI, are specifically directed to target the unique behavior of the *C. difficile* organism. For example, a preoperative surgical patient scoring at the threshold for high risk, may prompt a review of the antibiotic therapy by the antimicrobial stewardship committee, initiate standing orders for nurses to send down suspicious stool samples for prompt detection and diagnosis and, if not configured on the hospital ward or unit, placed in a private room. Considering the virulence of *C. difficile* and the consequences of CDI and

especially, recurrent CDI, interventions that are tailored to the offending *C. difficile* organism may prove to be worthwhile. If the goal is CDI elimination, not simply CDI reduction, implementation of more vertical (pathogen-directed) strategies, such as the CPR, are required to operationalize this goal.

Future Research

The next phase of CPR development for CDI requires a prospective study to include the variables missing from this analysis. Inclusion of additional variables in the next phase of research should be able to increase the predictive ability of the CPR and build on the preliminary evidence of this study. Host risk factors to strengthen the validity of the CPR include inflammatory bowel syndrome, fecal incontinence and/or systemic and serological markers for CDI and whether or not the patient had end stage renal disease.

Additionally, investigation of predictive risk factors that include frailty measures such as systemic inflammatory biomarkers and inflammatory-related diseases, rather than only chronological age, may prove to be worthwhile specially in this population where older patients are disproportionally affected by this disease (McDonald, et al., 2006). The specific contributors to frailty, or perhaps frailty itself, could yield important practice and research implications for CDI prevention.

The addition of treatment-related variables would also be expected to increase the ability to predict CDI. Important treatment- related variables such as antibiotic use, drug-disease associations (proton pump inhibitors and statins), tube feeding and exposure

variables such as type of hospital, adherence to recommended environmental practices, CDAD pressure, recent emergency department (ED) visits and prior hospitalizations require closer examination, especially in the surgical population (see Figure 5.2). In addition, it would be worthwhile to evaluate whether or not the Braden Scale for preventing pressure sores (Bergstrom, Braden, Kemp, Champagne, & Ruby, 1998; Bergstrom, et al., 1987; Braden & Bergstrom, 1988) has comparable predictive ability for other adverse outcomes such as HAI. Early, but unsubstantiated evidence, suggests that the predictive ability of a CPR for infection and a CPR for pressure sores may overlap (Tanner, et al., 2009).

Figure 5.2. Conceptual Model of Clostridium difficile Infection Risk with Independent Variables
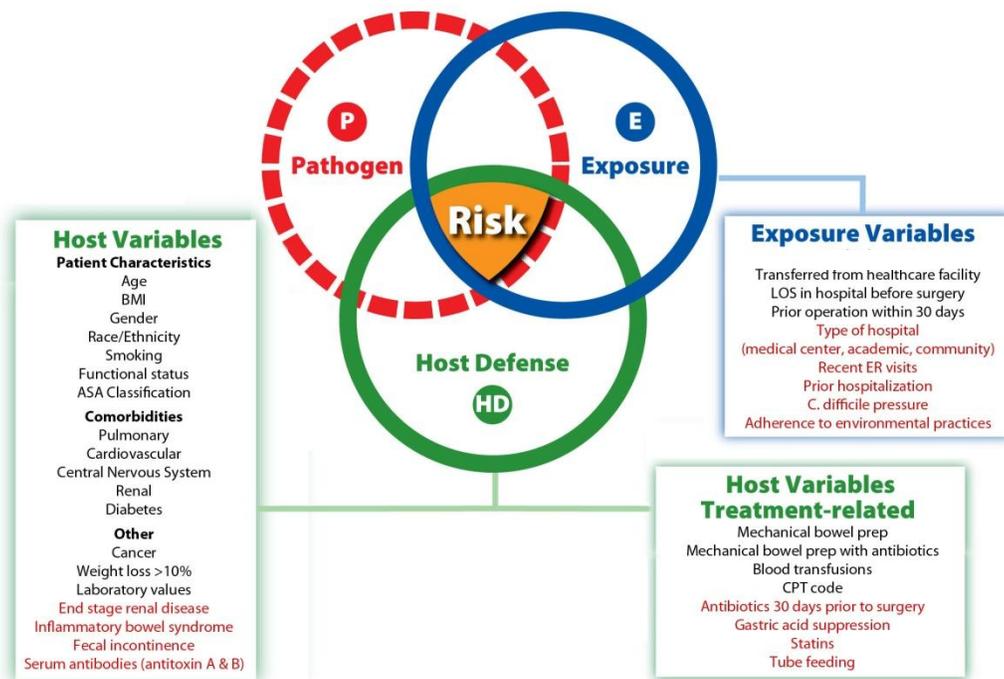
* *Analyzed (black) and missing (red).* **Abbreviations: BMI** *= body mass index;* **ASA** *= The American Society of Anesthesiology ;* **LOS** *=length of stay;* **ER** *= emergency room;* **CPT code** *= Current Procedural Terminology Modification code*

Although this study focused only on the preoperative risk factors of CDI *Host*, *Treatment-related* and *Exposure*, investigation of the intraoperative and postoperative

processes of care are also critical factors for understanding the precise contributions of CDI risk. The ability to isolate the day of CDI diagnosis in relation to the surgery could yield important clues as to the where the burden of infection is greatest. For example, if the majority of the patients in this study had contracted their infection during the later portion of their 30- day data collection window, precursors to infection may be attributed to use of post operative antibiotic dispensing for SSI's or other additional postoperative treatments after the postoperative period. In contrast, a determination of CDI infection during the hospital stay, or shortly thereafter, would imply that the risk factors for infection are closer to the surgical procedure itself. The ability to determine the precise window of CDI diagnosis is an important consideration for isolating the unique processes of care that contribute to the overall risk and has significant potential to inform future research.

For additional research conducted as part of the regional collaborative, data elements that are de-identified but include hospital-level information will make it possible to assess and adjust for any effects of clustering within hospitals. Efforts to correct for the clustering of effects within hospitals may be able to provide more definitive information for predictive risk factors and increase the confidence in the statistical findings. Future analysis using ACS NSQIP data may consider constructing variables from the preoperative patient comorbidity data elements in order to increase ability to determine additional potential associations.

At a national level, dedicated funding of the incidence and deadliness of HAI (to include CDI) should be better aligned with the resources available. For example, despite the large morbidity and mortality of HAI, there is substantially less funding for CDI than for other diseases such as HIV/AIDS (Donskey, 2011). Also at the national level is the impact of new CMS regulations that restrict reimbursement to hospitals for the cost of preventable patient injury and infection (Centers for Medicare and Medicaid Services, 2009). Although the policy does not currently include CDI, continuous assessment of the consequences of the new regulations at the local level will be necessary. Will it bring about a lasting change in the hospital culture? Increase preventive antibiotic treatment and inadvertently cause antibiotic resistance? Or, even worse, drive the reporting of the incidence of HAI underground? These are all emerging research questions that will require thoughtful analysis if the CMS regulations are expanded to include CDI.

Clinical Implications

Since HAI is the most common, problematic and avoidable adverse outcome a patient will have during their hospitalization, a more thorough assessment of HAI risk is overdue. HAI can no longer be attributed to simply "the cost of doing business," and nurses, at the bedside 24/7, are well positioned to influence change in this practice. CPR's are a potential strategy nurses could easily implement into practice in order to strengthen assessments, identify high-risk patients and guide preventative nursing interventions. And since CPR's build on a core of nursing practice, strong assessment skills, they have the potential to provide broader, deeper and sustained improvement in reducing HAI. Translating the risk of HAI into a simple, quantifiable, standardized

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score, via a CPR, would provide a nurse-driven strategy to tailor the environment for a patient's individual risk.

As suggested from the findings of this study, a CPR may be particularly useful in reducing the risk of CDI in colectomy surgical patients since the burden of risk may be influenced more by individual patient comorbidities than other device-related HAI such as urinary tract and central line-associated infections. For postoperative high-risk surgical colectomy patients, pro-active nursing interventions could include: (1) allocation of private bed space (if not routinely available) (2) standing nursing orders for initiating stool specimen collection and processing, (3) preemptive isolation (4) cohorting nursing of staff and/or patients (5) reinforced education to patients and visitors. These interventions, introduced prior to infection, not in response to it, represent an opportunity for nurses to influence the elimination of CDI by bolstering the traditional boundaries of defense. Unlike the medical profession that is focused on aggressive treatments, nurses are uniquely positioned to focus on the foremost weapon against CDI - primary prevention.

Finally and perhaps most important, is the understanding nurses have about the human consequences of CDI. While there is a plethora of literature that focuses on the economic costs of CDI such as length of stay and reimbursement shortfalls, rarely, if ever is there mention of the human cost of infection. Nurses are firsthand witnesses to the pain and suffering of the infection and the disruption to the normal rhythm of daily personal and professional life. The incontinence and urgency of bowel function is not only inconvenient, but exposes the patient to feelings of embarrassment and shame (Madeo & Boyack, 2010). Placing a patient in isolation, as the term describes, puts the

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patient at risk for loneliness and perhaps even a potential for increased adverse events

(Abad, Fearday, & Safdar, 2010; Morgan, Diekema, Sepkowitz, & Perencevich, 2009;

Stelfox, Bates, & Redelmeier, 2003). And the debilitation and fatigue that often

accompanies severe CDI compounds the seriousness of a patient's condition already

weakened by underlying illnesses or recent surgery. A patient with recurrent CDI

describes his experience in this excerpt:

> This illness has been very distressing. Sometimes I would be on the
> toilet and think I am done. I get about halfway back to the bedroom,
> then I have to go back again. Sometimes this would happen 3 times
> in a 15 minute period….I wouldn't wish this illness on anybody. C.
> difficile is one of the most terrible things that I have been dealing
> with my whole life and I have dealt with a lot of things since my
> kidney transplant . I hope this latest regimen of pills will cure me
> because I am going out of my mind. (Kelly, 2009, p. 955)

Ensuring patient comfort, dignity, and quality of life is the foundation

of nursing practice. Dedication of greater resources and attention to prevent

infection, rather than treating infection, is where nurses can keep this

foundation strong and eliminate the avoidable pain and suffering of CDI. By

leveraging existing data that is already available and collected, CPR's offer

an opportunity to better inform bedside clinicians and target preventative

interventions to the patients that will receive the greatest benefit.

Limitations

The limitations of this study are consistent with those inherent in conducting a

retrospective analysis and in those operating within the constraints of the MSQC, ACS

NSQIP dataset. Since the dataset was restricted to only those variables that were

collected as part of the ACS NSQIP and the MSQC Special Colectomy project, this study was unable to account for several important variables that would have likely made the model and CPR more robust (see Figure 5.2). This is an important and significant limitation that may have confounded the results.

Although the ACS NSQIP data set contains a rich pool of preoperative morbidities, consolidating some of the less frequent comorbidities (with occurrences less than five percent) may have been able to reveal stronger associations. Generally, the power of the analysis is reduced when the expected frequencies are less than one or when more than 20% of the variables have five or less cases (Tabachnick & Fidel, 2007). Therefore, important potential associations may have been missed. Consolidation of subsets of patient comorbidities into constructed variables such as 'cerebrovascular events' or 'cardiac conditions,' may have been able to determine a stronger association with the outcome.

Additionally, with the intent to protect the privacy of the participating hospitals, no variable was included in the data set that identified individual hospitals. This made it impossible to assess or adjust for any effects of clustering of hospitals or of patients within hospitals. Lack of a hospital identification variable prevented the validation of one of the critical assumptions of logistical regression, independence of observations (Tabachnick & Fidel, 2007). It is important to note that the opportunity to correct for the clustering effects in this investigation would have likely increased the error terms (standard error) and attenuated the statistical conclusions (Panageas, Schrag, Riedel, Bach, & Begg, 2003). Efforts to correct for the cluster-effects in future research will provide more definitive insights for the association of CDI and patient risk.

Although the methodology of ACS-NSQIP sampling protocol is carefully designed, sampling only the first seven surgeries from each month could invite selection bias. While it is still possible that some selection bias may have been introduced by not including every case from every hospital, narrowing the study to only elective cases makes it more likely that the similarities of any missed cases differed little from the recorded cases.

An important limitation in the design of the investigation is the possibility that some patients may have been lost to follow-up or seen subsequently outside of the collaborative hospitals. This would inadvertently diminish the incidence of CDI postoperative cases detected in this dataset. To reduce the possibility that postoperative CDI cases were missed, a 30-day follow-up by trained and dedicated surgical clinical reviewer's (SCR) (rather than reliance on discharge diagnoses from administrative databases) reduces the risk of missed post-operative CDIs.

There are three important shortfalls surrounding the definition and interpretation of CDI that deserve mention: (1) the reliance on only confirmed results of lab values (no empiric treatment or confirmation with diarrheal symptoms), (2) the necessity to distinguish the timeframes for diagnosis and (3) a more specific case definition for interfacility comparison of CDI. By limiting the definition of CDI as only those confirmed lab results of *C. difficile* toxin assay or culture, it is likely that some patients were treated empirically without evidence of infection. However, this situation represents what occurs in normal practice, during which a certain proportion of CDI will be empirically treated and a certain proportion will be under-diagnosed. Along the same lines, this study could not account for those patients that were only colonized with *C.*

difficile (tested positive) but did not exhibit diarrheal symptoms (not infected). The overall influence of patients that were only colonized, not infected, with *C. difficile* is believed to be minimal, if any at all, since these patients do not qualify for testing without the requisite diarrhea episodes.

Similarly, the definition of CDI in this study did not include any time frame for diagnosis. This is important to distinguish since patients with less than a 48 hour window of CDI diagnosis may be patients with a community-associated CDI rather than a true health care associated infection. Establishing a time frame for diagnosis would also be helpful to determine the processes of care that may have had a moderating influence on the outcomes (such as increased antibiotic use for patients on ventilators). Additionally, but probably highly unlikely, are patients that may have had an admission diagnosis of CDI misrepresented as a postoperative outcome. Finally, interfacility comparisons of CDI should include a case definition that includes the number of patient days as a denominator since the risk of CDI increases as the length of stay increases (Cohen, S. H., et al., 2010).

A widespread limitation of studying CDI in multiple inpatient locations is the failure to account for the different diagnostic testing techniques used within each hospital or contracted testing laboratory. Because diagnostic detection techniques were not standardized at the 24 hospitals in the MSQC, underestimation or overestimation of CDI could be a confounding variable for this study. A survey of the hospital sites at the initiation of the study in 2009, revealed that only one hospital site had switched to the more specific and sensitive PCR methodology. The majority of the sites reported using the enzyme immunoassay (EIA) toxin A and B diagnostic technique with a reported

sensitivity of about 80% (Gerding, 2010). As the demand for the more sensitive testing of *C. difficile* grows and the adoption of standardized testing techniques increases, this limitation will diminish in importance in future research.

Finally, the derivation and validation of the CPR was performed on the same cohort, however, the derivation of the CPR would best be validated on a different patient population. In this study, we derived the CPR and validated the rule on the same patient cohort. In order to generalize the results of the CPR to a wider patient population, the development and validation of the CPR on other patient populations is necessary to strengthen and refine predictive accuracy.

Conclusions

At the turn of the century, the most common cause of illness and death were from infectious diseases such as polio, small pox and influenza. With the onset of effective antibiotic therapy, morbidity due to infectious disease has been replaced with chronic disease conditions such as cancer, heart disease and diabetes. But the escalation in the number of pathogens resistant to traditional antibiotic treatments is a reminder of the persistent and challenging threat of infectious diseases, like CDI, that are reemerging with increasing virulence. This point is underscored by Richard Krause, MD, in his book titled "The Restless Tide: The Persistent Challenge of the Microbial World," where he describes a future of a constant and unrelenting struggle to contain infectious disease (Krause, 1981). When AIDS emerged one year after the book's completion, his foresight proved disturbingly accurate. Being that the microbial world holds the evolutionary advantage in its ability to mutate and multiply at a rapid rate, and with the pipeline of new antibiotic development is stalled (Gardam, Lemieux, Reason, van Dijk, & Goel,

2009), the traditional focus on curative treatment must be matched with an equally aggressive approach to prevention. In the battle of the infectious diseases that are healthcare acquired, only with a shift to a more comprehensive and proactive focus on primary prevention, will the catchy slogan of "chasing zero," become a reality.

Although not currently available, a clinical prediction rule to identify those at the greatest risk for HAI, may be a cost-effective, nontechnological, and nonpharmaceutical approach to translate evidence-based research into clinical bedside practice. This approach moves the nursing process "upstream," so that environmental challenges can be modified and /or individual defenses strengthened. As the results of this study suggest, the intrinsic factors of the host are significant predictors of infection risk and the ability to identify, recognize and quantify this risk provide an opportunity to prevent infection, not respond to it. An infection is sometimes likened to a war where a patient is relinquished to "fight" or "battle" an infection. But, one could argue that true victory is achieved only when an infection is averted. In the words of Sun Tzu, an ancient Chinese military general and philosopher from over 3000 years ago,

> *"For to win one hundred victories in one hundred*
> *battles is not the acme of skill. To subdue the enemy*
> *without fighting is the acme of skill." (Griffith, 1963,*
> *p. 94)*

Because nurses are uniquely positioned at the bedside 24/7, they are a powerful arbiter to prevent infection and will be a powerful force to stem the unrelenting, persistent and unforeseen tides of the future.

Appendices

Appendix A.   Summary of Research Studies

Title	Purpose	Design	Setting/Sample	Results	Comments
Clostridium difficile-associated disease in a setting of endemicity: Identification of novel risk factors (Dubberke, et al., 2007b)	Identify risk factors for CDAD	Retrospective Cohort	N=36,275 patients, 382 had CDAD. Barnes-Jewish Hospital; January 1, 2003, through December 31, 2003.	Independent risk factors: increasing age, admissions in the past 60 days, hypoalbuminemia, leukemia or lymphoma, mechanical ventilation, gastric acid suppression, IV vancomycin, 1st, third or 4th generation cephalosporins. Increasing CDAD pressure was a strong predictor.	Endemic setting- no associated outbreak
Evaluation of *Clostridium difficile*-associated disease pressure as a risk factor for C difficile-associated disease (Dubberke, et al., 2007a)	Evaluate CDAD pressure as a risk factor for CDAD	Retrospective cohort and nested case-control	N=36,275 patients, 382 had CDAD. Barnes-Jewish Hospital; January 1, 2003, through December 31, 2003.	CDAD pressure may be an independent risk factor for CDAD. Future studies that evaluate risk of CDAD should control for CDAD pressure. Adjusted for demographics, severity of illness, medications received (chemotherapy, gastric acid suppressors, antidiarrheals or narcotics, and antibiotics), and abdominal procedures or surgery performed.	
Underlying disease severity as a major risk factor for nosocomial *Clostridium difficile* diarrhea.(Kyne, et al., 2002)	Determine the diagnostic accuracy of an index of underlying disease severity for CDI.	Retrospective (primary cohort) and prospective (secondary cohort)	Primary cohort (n=300); secondary cohort (n=252). An urban teaching hospital affiliated with a medical school.	Primary cohort: The rate of C diff increased with increasing disease severity, age and renal disease. Secondary cohort: rate of C diff increased with transfer from another facility, increasing illness severity, recent hospitalization, tube feeding and aminoglycoside use.	Used Horn's Index to measure disease severity
The burden of *Clostridium difficile* in surgical patients in the U.S. (Zerey, et al., 2007)	Provide a national estimate of the burden of CDI in surgical	Retrospective analysis; Agency for Healthcare Research &	N=1,553,597 and 8113 with CDI; 997 hospitals in 37 states.	Highest incidence of CDI: Age >64, Medicare, Northeast hospital location, large, urban, teaching	CDI most prevalent after emergency operations and among

Title	Purpose	Design	Setting/Sample	Results	Comments
	patients	Quality National Inpatient Sample Database.		hospital, emergency operation, surgical procedures of colectomy, small bowel resection and gastric resection were associated with the highest risk of CDI. MULTIVARIATE ANALYSIS: independent predictor of LOS (16 days), 3.4 fold increase in the mortality rate. Also demonstrated cost of $77,000	patients having intestinal tract resections.
Acquisition of *Clostridium difficile* and *Clostridium difficile* – associated diarrhea in hospitalized patients receiving tube feeding. (Bliss, et al., 1998)	Incidence of CDI in tube-fed patients	Prospective cohort	76 tube-fed and 76 non-tube fed patients; University affiliated Veterans Affairs Medical Center	Hospitalized tube-fed patients had a greater risk of CDI. Postpyloric tube feeding had highest risk. Duration of surveillance (time in hospital) was identified as a predictive risk factor	
Lack of association between the increased incidence of *Clostridium difficile* associated disease and the increasing use of alcohol-based hand rubs. (Boyce, Ligi, Kohan, Dumigan, & Havill, 2006b)	Association between use of alcohol-based hand rubs and the increased incidence of CDI.	Observational	Measured the number of liters of ABHR used per 1000 patient days. Single –center, University affiliated community teaching hospital. Years 2000-2003.	No evidence that the incidence of CDAD increased with increase in alcohol-based hand rubs.	
Evaluation of hospital room assignment and acquisition of Clostridium difficile infection. (Shaughnessy, et al., 2011)	Evaluate the risk of acquiring CDI after the discharge of a patient with CDI that had previously occupied hospital room.	Retrospective cohort	N = 1844, 134 cases of CDI Medical intensive care unit (MICU), Tertiary care hospital	A prior room occupied with a patient with CDI is a significant risk factor for CDI acquisition.	
A clinical risk index for Clostridium difficile infection in hospitalized patients receiving broad-spectrum antibiotics (Garey, et al., 2008)	Create a clinical risk index that would predict those at high risk for CDI	Retrospective cohort	N= 54,226, and 392 positive for CDI; Single-center, medical center. March 2005-October 2007;	Independent predictors: Age, dialysis, nonsurgical admission, LOS in ICU.	
The effect of hospital-acquired Clostridium difficile Infection on Hospital mortality (Oake, et al., 2010)	CDI and inpatient mortality	Retrospective cohort	N=136.877 admissions; and 1393 CDI; 2002-2009. Ottawa Hospital	CDI was independently associated with an increased risk of death. Patients with CDI were older, had more comorbidities, inpatient admissions, ER visits and more likely to be admitted urgently.	
Use of Hypochlorite Solution to Decrease	Use of hypochlorite	Observational	Barnes- Jewish Hospital,	Effectiveness of environmental cleaning	

Title	Purpose	Design	Setting/Sample	Results	Comments
Rates of Clostridium difficile–Associated Diarrhea. (McMullen, et al., 2007)	solution to reduce rate of CDI		university- affiliated tertiary care facility	with a bleach solution in both a MICU and SICU reduced the rate of CDI.	
The acquision and outcome of ICU acquired C. diff in a single center in the UK (Ang, et al., 2008)	Explore CDI rates and mortality	Retrospective, cohort	N= 62 patients, Single center; April 2004-April 2007.	Increasing age, APACHE score and gender associated with mortality (univariate analysis). Age is an independent predictor of mortality.	Risk factors for mortality
Clostridium difficile in cardiac Surgery: Risk Factors and Impact on Postoperative Outcome (Crabtree, et al., 2007).	Identify preoperative risk factors in cardiac surgery	Retrospective, cohort	N= 8,405 , 66 patients with CDI; incidence of 0.79% (0.70% at institution A and 1.09% at institution B),	Independent prognostic factors for CDI by multivariate analysis included advancing age, female sex, blood product transfusion and increasing cumulative days of antibiotic administration.	Data goes back to 1997
Postoperative *Clostridium difficile*-associated diarrhea (Southern, et al., 2010)	Preoperative factors associated with postoperative CDI	Retrospective, cohort	N= 3904 patients with abdominal operations at Montefiore Medical Center	Significant findings: Exposure to preoperative antibiotics, PPI's, prior hospitalization and low albumin. Risk of CDAD particularly strong for high risk antibiotics- 3rd and 4th generation cephalosporins, flouroquinolones, clindamycin and imipenim/meropenim.	Postoperative CDI is a disease that is different from CDI on the medical service, with different exposure profiles and better outcomes
The morbidity of Clostridium difficile infection after elective colonic resection- results from a national population database. (Lesperance, et al., 2011)	Examine national trends in incidence and outcomes associated with CDI after colonic resection	Retrospective cohort 2004-2006 Nationwide Inpatient Sample (NIS) provided by the Department of Health and Human Services.	N= 695,010. CDI occurred in 1.4% of patients Single center b/w 2004 & 2006	Significant findings: CDI associated with higher pulmonary gastrointestinal complications as well as an increased length of stay and mortality. CD colitis patients more frequently held Medicare insurance. Pre-existing comorbid illnesses included congestive heart failure, chronic pulmonary disease, obesity, malnutrition, renal failure and peripheral vascular disease.	
Mortality and risk stratification in patients with Clostridium difficile -associated diarrhea(Bhangu, et al., 2010)	Identify prognostic risk factors	Retrospective Cohort	N= 158 CDI ; single-center, large teaching hospital	Increased risk of mortality with age over 80, ASA score 3-5, leukocytosis, low C reactive protein and hypoalbuminemia. General surgical patients were younger than medical patients or orthopedic patients. Variability exists between different specialties.	Mortality risk
Clostridium difficile-positive stool: A retrospective	Determine risk factors for CDI	Retrospective cohort	N=4992, 151 patients with CDI; Single institution.	Significant risk factors: history of CDI, bed adjacent to CDI patient	

Title	Purpose	Design	Setting/Sample	Results	Comments
examination of risk factors(Howitt, et al., 2008)			Tertiary teaching hospital	or same room, severity of illness (Horn's index), multiple antibiotics, patient age, gastrointestinal surgery; carbapenens and tetracyclines.	
Emergence of Fluoroquinolones as the Predominant Risk Factor for Clostridium difficile–Associated Diarrhea (Pepin, et al., 2005)	Risk of CDAD associated with specific classes of antibiotics	Retrospective cohort study	N=7421 episodes of care (5619 patients). CDI in 293 patients. Teaching hospital	Administration of fluoroquinolones emerged as the most important risk factor for CDAD,	During an epidemic
Clostridium difficile infection in general surgery patients: Identification of high-risk populations(Rodrigues, et al., 2010)	Characterize the incidence and associations of CDI in general surgical inpatients	Retrospective cohort	N= 21,371; 101 (0.47%) with CDI; Single center- large tertiary general surgical unit	Significant findings: Age, gastrointestinal disease, malignancy, respiratory disease, circulatory, diabetes, anemia, gastrointestinal surgery.	
Identification of risk factor for the development of *Clostridium difficile*-associated diarrhea following treatment of polymicrobial surgical infections(Metzger, et al., 2010)	Identify risk factors of CDI in surgical patients following treatment of polymicrobial infections	Retrospective cohort	N= 4178 surgical infections, 98 with CDI	Only age and APACHE II were independently associated with CDI	11 year dataset
Preoperative oral antibiotics in colorectal surgery increase the rate of *Clostridium difficile* colitis (Wren, et al., 2005)	Determine if the use of oral antibiotics in bowel preparation results in a higher rate of postoperative CDI	Retrospective, cohort	n=304 (13 women) ; Single institution	CDI higher in patients who received oral antibiotics (7.4%) when compared with patients that did not receive oral antibiotics (2.6). No differences for the variable of cathartic type	
Specific risk factors for Clostridium difficile-associated diarrhea: A prospective, multicenter, case control evaluation (Vesta, et al., 2005)	Risk factors of CDI with particular attention to antibiotic use	Retrospective, case-controlled, elective surgery patients		There were no significant differences in antibiotic use between cases and controls. Severity of illness (Horn's Index) was higher in CDI patients (p=.0022).	
Predicting Clostridium difficile toxin in hospitalized patients with antibiotic-associated diarrhea (Peled, et al., 2007)	Compare the clinical characteristics of patients who developed CDI associated diarrhea	Prospective; single center	N=217 patients who received antibiotics and developed diarrhea	Significant risk factors : Impaired functional capacity, watery diarrhea, use of a proton pump inhibitor, use of a histamine receptor blocker, leukocytosis, and hypoalbuminemia	
Chronic kidney disease as a risk factor for Clostridium difficile infection (Eddi, et al., 2010)	Determine association between chronic kidney disease and CDI	Case-control; single center, urban hospital	N=188, 2 year period	No significant difference in prevalence of chronic kidney disease and CDI. Patients with end-stage renal disease were significantly associated with CDI.	

Appendix B. Michigan Surgical Quality Collaborative (MSQC) Colectomy Project Data Collection Tool

Michigan Surgical Quality Collaborative
COLECTOMY PROJECT

IDN_____ Date of operation_____ CPT code_____

PAYMENT SOURCE	
Medicare	
Medicaid	
BCBSM/BCN	
Other	
None/UTD	

PRE-OPERATIVE			
Clear Liquids	Yes	No	
Bowel prep	Exception	Yes	No
	If no exception:	Mag Citrate	
		Fleet phosphosoda	
		Fleet enema	
		PEG	
		Other, specified prep	
		Other, unknown type	
		w/ antibiotics	
		None ordered	
Patient Compliance	Taken as ordered		
	Partially taken		
	Not taken		
	No documentation		
Presentation	Obstruction		
	Perforation		
	Neither		
	Both		

LABORATORY		
	value	date/time
Glucose		
HbA1c		

OPERATIVE			
Antibiotic(s)	Exception	Yes	No
	None ordered	Yes	No
	If no exception:	drug/dose	date/time

OPERATIVE (CONT'D)			
VTE Prophylaxis	Exception	Yes	No
	If no exception:	Heparin	
		LMWH	
		SCD's	
		None	
Hi glucose			
Fecal contamination		Yes	No
Unplanned splenectomy		Yes	No
Ureteral stents		Yes	No
Ureteral injury/repair		Yes	No
Wound left open		Yes	No
EBL			
Epidural placed		Yes	No

POST-OPERATIVE			
Temp		C or F	
VTE	Exception	Yes	No
	If no exception:		date/time
		Heparin bid	
		Heparin tid	
		LMWH	
		SCD's	
		None	
Anastomotic leak	None		
	Antibiotics only		
	Percutaneous drain		
	Reoperation	new anastomosis	
		proximal diversion	
		end stoma	
C diff		Yes	No
Ileus		Yes	No
Mechanical obstruction		Yes	No
Glucose	POD 1		
	POD 2		

	date	CPT	ICD9
Reoperation(s)			

	date	ICD9	
Readmission(s)			

COMMENTS:
_____
9/3/08

Appendix C. Operational Definitions of MSQC Variables

COLECTOMY PROJECT DEFINITIONS

Data Element	Definition	Variable	Response Options
Pre-operative			

Mechanical bowel prep	The intent of this prep question is to look at physician practice patterns in the patient undergoing a planned, elective colectomy.
	
	The purpose of a bowel prep is to cleanse the bowel of particulate material and decrease the number of bacteria in the colon, in an attempt to decrease the number of infectious complications of surgery. A variety of cathartics and/or enemas may be used for mechanical bowel cleansing.
	
	Some surgeons are proceeding with elective colectomies with no mechanical bowel prep. This is based on clinical trial results which show no benefit to mechanical bowel prep. However, the majority of US surgeons continue to use bowel prep.
	
	As part of a bowel prep, oral antimicrobials specific to intestinal surgery may be given, usually within 18 hours prior to surgery. As these antibiotics are less well absorbed,
		• Exception /Yes/No
		• Magnesium citrate
		• Fleet Phospho-soda
		• Fleet enema(s)
		• Polyethylene glycol (PEG) electrolyte solutions (GoLYTELY, Nu-Lytely, HalfLytely, MiraLAX, etc)
		• Other, specified prep
		• Other, unknown type
		• **With antibiotics**
		• None ordered
		• Information unavailable
			• Exception may be appropriate for a variety of reasons including:
			  o Emergency cases
			  o Patients admitted after testing reveals surgery is imminent (same admission)
			  o Patient presenting with abdominal pain, admitted, worked up, taken to OR
			• If no exception, enter all listed preps that apply.
			• The ordering of any of these preps alone or in combination would qualify as meeting this criterion.
			• Use Other, specified prep if there is documentation that a cathartic and/or enema not listed was ordered.
			• Use Other, unknown type if there is documentation that a prep was ordered, but the type is not specified.
			• None ordered indicates that no prep was recommended. This would be a deliberate act by the surgeon to NOT give enemas or cathartics prior to surgery, not an act of omission.
			• Enter Information unavailable only in those cases where attempts to determine whether or not the patient was prepped have failed. This is a documentation issue.
			
			Note: Antibiotics with bowel preparation are not the same as peri-operative prophylactic parenteral antibiotics.

Post-operative Outcome Variable			
Clostridium difficile colitis	Clostridium difficile colitis (C difficile or C diff) is an inflammation of the colon caused by the clostridium difficile bacterium, occurring primarily in individuals who have been using antibiotics. Manifestations are fever, diarrhea, cramps, and abdominal tenderness. is the most common infection acquired by patients when they are in the hospital. Common	Yes/No	• C diff must occur post-operatively, within 30 days of OR. • To answer Yes, C diff must be verified by laboratory detection of the toxin in the stool or by a positive stool culture • Empiric treatment alone would not qualify.

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Appendix D. Associations of ASA Classification and Comorbidity Variables

ASA and comorbidity	ASA(1-5)	ASA (≥ 3 vs. 4 &5)
	p	p
ASA * Dyspnea- Binary	0.000	0.000
ASA * Ventilator Dependent within 48 hours	0.000	0.000
ASA * Severe COPD history	0.000	0.000
ASA * CHF within 30 days	0.000	0.000
ASA * Myocardial infarction (within 6 months)	0.000	0.000
ASA * Previous cardiac surgery	0.000	0.000
ASA * Angina	0.000	0.000
ASA * Hypertension	0.000	0.000
ASA * Impaired sensorium (within 48 hours)	0.000	0.000
ASA * CVA/ residual neurologic deficit (history)	0.000	0.015
ASA * CVA/ no neurologic deficit (history)	0.000	0.000
ASA * Hemiplegia or Hemiparesis	0.000	0.000
ASA * TIA (history)	0.000	0.001
ASA * Acute Renal Failure	0.000	0.000
ASA * Currently requiring or on dialysis	0.000	0.000
ASA * Disseminated Cancer	0.000	0.515
ASA * >10% loss of body weight (last 6 months)	0.017	0.619
ASA * Chemotherapy (within 30 days)	0.726	0.842
ASA * Radiotherapy (within 90 days)	0.416	0.089
ASA * Diabetes	0.000	0.000

Appendix E. Post-Hoc Analysis of Clostridium difficile Infection Adjusted for Age

A. Binary Logistic Regression Model to Assess the Effect of Host Variables on CDI Adjusted for Variable of Age.

Variable	Regression coefficient	p	OR	95% CI Lower	95% CI Upper
Acute Renal Failure	.216	.871	1.241	.092	16.795
Dialysis	1.113	.166	3.045	.629	14.739
Transient Ischemic Attack	1.010	.029	2.745	1.108	6.803
Hypertension	.346	.284	1.413	.750	2.663
Ventilator	2.314	.014	10.115	1.607	63.676
Dyspnea	.644	.046	1.904	1.010	3.588
Age	-.011	.283	.989	.969	1.009
Constant	-3.453				

B.   ROC Curve for Model I Adjusted for Variable of Age

Diagonal segments are produced by ties.

Area Under the Curve

	95% CI Lower Bound	95% CI Upper Bound
.631	.554	.709

Appendix F. Post-Hoc Analysis of Clostridium difficile Infection Adjusted for ASA Classification

Binary Logistic Regression of Model I to Assess the Effect of Host Variables on CDI Adjusted for Variable of ASA (Score of ≤ 3 vs. Score 4,5).

Variable	Regression Coefficient	p	OR	95% CI Lower	95% CI Upper
Acute Renal Failure	.087	.948	1.091	.081	14.726
Dialysis	.974	.237	2.649	.527	13.302
Transient Ischemic Attack	.896	.050	2.450	.999	6.006
Hypertension	.205	.497	1.228	.679	2.221
Ventilator	2.013	.042	7.488	1.080	51.906
Dyspnea	.500	.127	1.649	.867	3.138
ASA (≤ 3 vs. 4,5)	.502	.286	1.652	.657	4.154
Constant	-4.585				

ROC Curve for Model I Adjusted for Variable of ASA (Score of ≤ 3 vs. Score 4,5).

Diagonal segments are produced by ties.
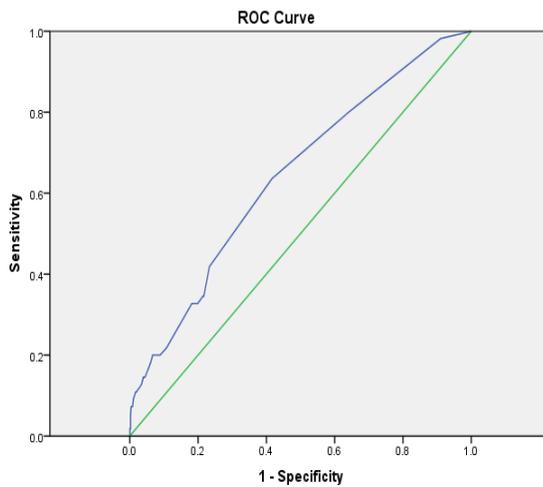
Area Under the Curve

Area	Asymptotic 95% Confidence Interval Lower Bound	Asymptotic 95% Confidence Interval Upper Bound
.642	.568	.715

Binary Logistic Regression of Model I to Assess the Effect of Host Variables on CDI Adjusted for Variable of ASA Score.

	Regression coefficient	p	OR	95% CI Lower	Upper
Variable	**Regression coefficient**	**p**	**OR**	**Lower**	**Upper**
Renal	-.014	.993	.986	.047	20.549
Dialysis	.999	.228	2.717	.535	13.794
Transient Ischemic Attack	.929	.044	2.533	1.024	6.266
Hypertension	.269	.399	1.309	.700	2.448
Ventilator	1.994	.077	7.342	.803	67.098
Dyspnea	.547	.107	1.728	.889	3.360
ASA Class 1 (Reference)		.812			
ASA Class 2	-.141	.947	.869	.014	55.314
ASA Class 3	-.567	.761	.567	.015	21.798
ASA Class 4	-.732	.694	.481	.013	18.444
ASA Class 5	-.182	.920	.834	.024	28.956
Constant	-3.494				

ROC Curve for Model I Adjusted for Variable of ASA (Score of ≤ 3 vs. Score 4,5).

Diagonal segments are produced by ties.

Area Under the Curve

	Asymptotic 95% Confidence Interval	
Area	Lower Bound	Upper Bound
.642	.568	.715

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Table 1. Patient characteristics and use of mechanical bowel preparation prior to colectomy*

Variable	Bowel Preparation N=1685 (74%)	No Bowel Preparation N=578 (25%)	p-value
Age	65.61 +/- 14.54	64.84 +/- 17.05	.331
Body mass index	28.36 +/- 6.31	27.35 +/- 5.83	.001
Sex			.113
Male	836 (49.6)	264 (45.7)	
Female	849 (50.4)	314 (54.3)	
Race/ Ethnicity			.135
White	1259 (74.7)	449 (77.8)	
Other	426 (25.3)	128 (22.2)	
Preoperative functional status			.000
Independent	1603 (95.1)	513 (88.8)	
Dependent	82 (4.9)	65 (11.2)	
Type of Resection			.000
segmental	1157 (68.7)	324 (56.1)	
ileocolic	528 (31.3)	254 (43.9)	
ASA			.000[a]
1= No Disturbance	27 (1.6)	11 (1.9)	
2= Mild Disturbance	860 (51.0)	256 (44.3)	
3= Severe Disturbance	723 (42.9)	262 (45.3)	
4= Life Threatening	74 (4.4)	45 (7.8)	
5= Moribund	1 (0.1)	4 (0.7)	
Dyspnea			.289
None	1425 (84.6)	478 (82.7)	
Moderate or at rest	260 (15.4)	100 (17.3)	
Chronic obstructive pulmonary disease			.427
Yes	101 (6.0)	40 (6.9)	
No	1584 (94.0)	538 (93.1)	
Pneumonia			.999[a]
Yes	6 (0.4)	2 (0.3)	
No	1679 (99.6)	576 (99.7)	
Congestive heart failure			.000
Yes	16 (0.9)	20 (3.5)	
No	1669 (99.1)	558 (96.5)	
History of myocardial infarction			.023
Yes	15 (0.9)	12 (2.1)	
No	1670 (99.1)	566 (97.9)	

Acute Renal Failure			.001[a]
Yes	1 (0.1)	6 (1.0)	
No	1684 (99.9)	572 (99.0)	
Dialysis			.186[a]
Yes	11 (0.7)	7 (1.2)	
No	1674 (99.3)	571 (98.8)	
Steroid Use			.003
Yes	57 (3.4)	36 (6.2)	
No	1628 (96.6)	542 (93.8)	
Malnourished (>10% Loss of body weight)			.191
Yes	61 (3.6)	28 (4.8)	
No	1624 (96.4)	550 (95.2)	
Disseminated CA			.108
Yes	52 (3.1)	26 (4.5)	
No	1633 (96.9)	552 (95.5)	
Bleeding Disorder			.000
Yes	72 (4.3)	47 (8.1)	
No	1613 (95.7)	531 (91.9)	
Transfusions			.001[a]
Yes	4 (0.2)	9 (1.6)	
No	1681 (91.8)	569 (98.4)	
Sepsis			.000
Yes	60 (3.6)	88 (15.2)	
No	1625 (96.4)	490 (84.8)	
Transfer from another healthcare facility			.011
Admitted from home	1661 (98.6)	560 (96.9)	
Transferred from an acute care hospital	9 (0.5)	9 (1.6)	
Transferred from a chronic care facility	14 (0.8)	6 (1.0)	
Other	1 (0.1)	3 (0.5)	

[a] *Fisher exact test; parentheses denote column percentages* Patients with only fleet enema were considered not to have bowel preparation*

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Table 1. Patient characteristics and comorbidities of use of oral antibiotics among patients who underwent mechanical bowel preparation prior to colectomy.*

Variable	Bowel preparation with oral antibiotics N = 684 (41%)	Bowel preparation without oral antibiotics N = 1001(59%)	p-value
Age	65.07 +/- 13.93	65.98 +/- 14.93	.203
Body mass index	28.72 +/- 6.411	28.11 +/-6.24	.052
Sex			.041
Male	360 (52.6)	476 (47.6)	
Female	324 (47.4)	525 (52.4)	
Race/ Ethnicity			.000
White	563 (82.3)	696 (69.5)	
Other	121 (17.7)	305 (30.5)	
Preoperative functional status			.093
Independent	600 (95.1)	945 (94.4)	
Dependent	84 (4.9)	56 (5.6)	
Type of Resection			.000
segmental	534 (78.1)	623 (62.2)	
ileocolic	150 (21.9)	378 (37.8)	
ASA			.656[a]
1= No Disturbance	8 (1.2)	19 (1.8)	
2= Mild Disturbance	349 (51.0)	511 (51.0)	
3= Severe Disturbance	299 (43.7)	434 (42.4)	
4= Life Threatening	28 (4.1)	46 (4.6)	
5= Moribund	0 (0.0)	1 (0.1)	
Dyspnea			.454
None	573 (83.8)	852 (85.1)	
Moderate or at rest	111 (16.2)	149 (14.9)	
Chronic obstructive pulmonary disease			.999
Yes	41 (6.0)	60 (6.9)	
No	643 (94.0)	941 (94.0)	
Pneumonia			.043[a]
Yes	5 (0.7)	1 (0.1)	
No	679 (99.3)	1000 (99.9)	
Congestive heart failure			.220
Yes	4 (0.6)	12 (1.2)	
No	680 (99.4)	989 (98.8)	
History of myocardial infarction			.313
Yes	8 (1.2)	7 (0.7)	
No	676 (98.8)	994 (99.3)	

Acute renal failure			.999[a]
Yes	0 (0.0)	1 (0.1)	
No	684 (100.0)	1000 (99.9)	
Dialysis			.133[a]
Yes	7 (1.0)	4 (0.4)	
No	677 (99.0)	997 (99.6)	
Steroid Use			.050
Yes	16 (2.3)	41 (4.1)	
No	668 (97.7)	960 (95.9)	
Malnutrition (>10% l oss of body weight)			.073
Yes	18 (2.6)	43 (4.3)	
No	666 (97.4)	958 (95.7)	
Disseminated CA			.239
Yes	17 (2.5)	35 (3.5)	
No	667 (97.5)	966 (96.5)	
Bleeding Disorder			.773
Yes	28 (4.1)	44 (4.4)	
No	656 (95.9)	957 (95.6)	
Transfusions			.651[a]
Yes	1 (1.1)	3 (0.3)	
No	683 (99.9)	998 (99.7)	
Sepsis			.012
Yes	15 (2.2)	45 (4.5)	
No	669 (97.8)	956 (95.5)	
Transfer from another healthcare facility			.357[a]
Admitted directly from home	674 (98.5)	987 (98.6)	
Transferred from an acute care hospital	2 (0.3)	7 (0.7)	
Transferred from a chronic care facility	7 (1.0)	7 (0.7)	
Other	1 (0.1)	0 (0.0)	

[a]*Fisher's exact test; parentheses denote column percentages*

Table 3. *Clostridium difficile* infection vs. mechanical bowel preparation.

	Cohort N= 2263	No CDI N= 2209	CDI N= 54	*p* value
Bowel Preparation				0.948
Yes	1685 (74.5%)	1645 (74.5%)	40 (74.1%)	
No	578 (25.5%)	564 (25.5%)	14 (25.9%)	

Table 4. *Clostridium difficile* infection vs. mechanical bowel preparation with and without antibiotics.

	Cohort N= 1685	No CDI N= 1645	CDI N= 40	*p* value
Bowel Preparation				.088
with oral antibiotic	684 (40.6%)	673 (40.9%)	11 (27.5%)	
without oral antibiotic	1001 (59.4%)	972 (59.1%)	29(72.5%)	

Table 5. Bivariate and multiple variable analyses of mechanical bowel preparation and oral antibiotics on *Clostridium difficile* infection.

Variable	Unadjusted Odds Ratio, (95% confidence interval [CI])	Adjusted*** Odds Ratio (95% CI)
Use of mechanical bowel preparation*	OR=.980 (0.53-1.81)	OR=.957 (.50- 1.83)
No mechanical bowel preparation	REFERENCE	
Use of oral antibiotics**	OR=.548 (0.27-1.10)	OR=.598 (0.29-1.23)
No oral antibiotics	REFERENCE	

*Full cohort
**Cohort that used mechanical bowel preparation
***adjusted for characteristics that achieved p<0.05 individual associations with CDI in preliminary analyses:

Bowel prep (in full cohort) - body mass index, preoperative functional status, type of resection, ASA status, congestive heart failure, history of myocardial infarction, acute renal failure, steroid use, bleeding disorder, transfusions, sepsis and transfer from healthcare facility.

Use of oral antibiotics (in full cohort) - body mass index, sex, race, type of resection, pneumonia, steroid use and sepsis.

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