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Primary Diagnoses Associated with Increased Risk of Hospital Onset *Clostridium difficile* Infection

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Primary Diagnoses Associated with Increased Risk of Hospital Onset *Clostridium difficile* Infection

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An abstract of
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Abstract

Primary Diagnoses Associated with Increased Risk of Hospital Onset *Clostridium difficile* Infection

By Laura Edison

Background: *Clostridium difficile* has emerged as a significant cause of healthcare-associated infections and the most common cause of healthcare associated diarrhea; increasing in incidence and severity over the last decade. The changing epidemiology and high cost of the disease has led to efforts to better understand the organism and how to stratify patients according to their risk of developing *Clostridium difficile* infection (CDI) in order to effectively direct infection control efforts and fairly report hospital infection rates. Little is known about risk stratification using administrative data sources, and primary diagnosis as a risk factor for infection has rarely been examined. This thesis examines hospital inpatient primary diagnoses as risk factors for Hospital Onset CDI (HO-CDI) using administrative data.

Methods: We conducted a retrospective cohort study using hospital discharge data from the 2009 Nationwide Inpatient Sample, Healthcare Cost and Utilization Project. HO-CDI was the dependent variable and defined as a non-primary diagnosis of CDI with a length of stay (LOS) greater than two days. The primary independent variable was the clinical category (CCS) of the primary diagnosis. LOS, number of chronic conditions, age category and transfer in from a healthcare facility were examined as possible confounders or effect modifiers.

Results: Of the 285 CCS examined using multivariate analysis, 23 yielded a significant risk difference greater than 10/1,000 discharges. All independent variables had a significant effect on the relationship of CCS to HO-CDI. The CCS that had the strongest association with HO-CDI are septicemia, HIV, cystic fibrosis and mycoses.

Conclusions: All of the CCS signifcantly associated with HO-CDI are surrogates for known risk factors, antimicrobial use and healthcare exposure. Administrative data can be used to determine which CCS are significantly associated with HO-CDI and can be used to assess a patient's risk for HO-CDI. This risk stratification will improve the ability of hospital and public health decison makers to allocate resources in preventing HO-CDI, and can help refine a national CDI reporting system to achieve risk-adjusted benchmarking of facility infection rates.

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Acronyms

C. difficile	*Clostridium difficile*
CCS	Clinical Classification Software, Clinical Category
CDI	*Clostridium difficile* Infection
CI	Confidence Interval
ELISA	Enzyme-Linked Immunosorbent Assay
HAI	Healthcare Associated Infection
HCUP	Healthcare Utilization Project
HHS	Health & Human Services Administration
HIV	Human Immunodeficiency Virus
HO-CDI	Hospital-Onset *Clostridium difficile* Infection
IBD	Inflammatory Bowel Disease
ICD9	International Classification of Disease, 9th Edition
LOS	Length of Stay
NIS	National Inpatient Survey
OR	Odds Ratio
PPIs	Proton Pump Inhibitors
RD	Risk Difference
RR	Risk Ratio
RT-PCR	Real-Time Polymerase Chain Reaction

Introduction

Clostridium difficile (*C. difficile*) was first identified in 1935 but it was not considered a pathogen until 1978, when it was identified as the source of cytotoxin in the stool of patients with pseudomembraneous colitis.(1) *C. difficile* has since emerged as a significant cause of healthcare-associated infections and the most common cause of healthcare associated diarrhea. *C. difficile* can cause a broad range of symptoms in patients, from mild diarrhea to sepsis and death. Over the last decade, *C. difficile* infections (CDI) have increased in frequency and severity. The changing epidemiology and high cost of the disease has led to efforts to better understand the organism and how to stratify patients according to their risk of developing CDI in order to effectively direct infection control efforts. This thesis examines hospital inpatient primary diagnoses as risk factors for Hospital Onset CDI (HO-CDI). Although clinical risk factors for CDI have been studied extensively, little is known about risk stratification using administrative data sources and yet such data are widely available and their utilization to supplement other surveillance data would appear feasible. The purpose of this thesis is to use administrative data to determine primary diagnoses that are independently associated with a secondary diagnosis of CDI in a national administrative healthcare database. This information can be used to better risk stratify patients, stratify patients based on their risk of infection, by healthcare facility using administrative data. This risk stratification will improve the ability of hospital and public health decison makers to

allocate resources in preventing HO-CDI, and can assist in the critical decisions that need to be made to refine a national CDI reporting system.

C. difficile Overview

Virulence and Pathogenesis

C. difficile is a spore-forming, gram-positive rod-shaped anaerobic bacillus. It can exist in two forms; the vegetative form which is oxygen sensitive, and the spore form which can survive easily in the environment. *C. difficile* is shed in feces and spread by the fecal-oral route. Infected or asymptomatically-colonized patients are the source of infection for other patients. The bacterial spores can easily spread from patient to patient on the hands and clothing of healthcare workers, and via surface contamination and other fomites. Exposure to *C. difficile* primarily occurs in healthcare facilities; although community associated *C. difficile* is increasingly recognized.(2-4)

Ingested spores are able to resist stomach acid and germinate into the vegetative form once they reach the small intestine. Clinical disease depends not only on spore ingestion, but disruption of normal colonic flora. Antimicrobial therapy can disrupt the normal flora which acts as a barrier against *C. difficile* colonization in the colon. Broad spectrum antibiotics that kill the colonic flora, such as cephalosporins, clindamycin and fluoroquinolones in particular, predispose a patient to CDI.(2) *C. difficile* is often resistant to these antimicrobials and thus can prosper as the other bacteria are being wiped out.(3)

Following acquisition and colonization in the large intestine, the bacteria produce virulence factors, or toxins, which cause disease in non-immune persons. Not all strains are toxigenic; toxin production is necessary to cause disease but does not guarantee disease. Pre-existing *C. difficile* colonization and humoral immunity can prevent or decrease the severity of disease.(4) The two main virulence factors are toxins A and B. A third toxin, known as binary toxin, appears to potentiate the virulence of toxins A and B. The amount of toxins A and B produced and the presence of binary toxin affect the virulence of the strain. These toxins bind to epithelial cells and cause inflammation, damage to the intestinal mucosa and fluid and mucus secretion. This leads to diarrhea and colitis including pseudomembranous colitis, a condition pathognomonic for CDI.(5)

Clinical Disease

C. difficile causes a wide spectrum of clinical conditions ranging from asymptomatic colonization, to mild non-bloody diarrhea and abdominal cramping, to cases with more severe diarrhea often accompanied by fever, nausea and dehydration. Severe cases can involve varying degrees of colitis, toxic megacolon, intestinal perforation, sepsis and even death.(4) Once infection is treated, there is a high rate of recurrence; between 15% and 35% of patients relapse within two months of the initial infection(6). It can be very difficult to distinguish between a recurring infection and a reinfection due to a new exposure.(2)

Diagnosis

Diagnosis is initiated when there is a clinical suspicion of CDI, particularly in patients who develop diarrhea after taking antibiotics for another condition and who have had exposure to a healthcare facility. While cases can develop to exposure to *C. difficile* in the community, most cases involve some degree of exposure to a healthcare setting. Cases are diagnosed based on a combination of clinical symptoms, and gross or histopathological evidence of pseudomembranous colitis or a laboratory positive assay. There are many laboratory assays in use, each with advantages and disadvantages. Cytotoxin assay has been considered the gold standard, with a sensitivity of 67-100% and a specificity of 85-100%, but it is expensive and has a slow turnaround time of at least 48 hours. Enzyme-linked immunosorbent assay (ELISA) is inexpensive and can generate results in a few hours. It has very good specificity but the sensitivity of 60% to 80% can produce false negative results. Newer molecular methods of diagnosis, such as real-time polymerase chain reaction (RT-PCR), have a high sensitivity of 84% to 94%, specificity up to 97% and a rapid turnaround time of roughly 24 hours. Their use is becoming more widespread and may increase diagnoses of CDI due to the high sensitivity. Stool culture is a very sensitive assay but is time consuming and is not very specific because non-toxigenic strains can be cultured and mistakenly labeled as the cause of disease. A stool culture is important for genetic fingerprinting which can be crucial for epidemiological investigations and better understanding of the organism.(3) Early diagnosis is critical for infection control and improving the prognosis through early

treatment, therefore RT-PCR or the rapid ELISA are often used initially but in conjunction with other methods for more accurate diagnosis.(2)

Treatment

The mainstay of treatment of CDI includes discontinuing the implicated antimicrobial therapy, initiating appropriate antimicrobial therapy, and administering supportive care. Metronidazole is the drug most commonly used to treat CDI, while vancomycin is used for more severe disease. Vancomycin has slightly better results when treating severe disease but concern about vancomycin-resistant E*nterococcu*s spp. encourages the use of metronidazole as the first line of defense. For complicated cases of disease, the two antimicrobials may be used together. Fidaxomicin has recently been approved for treatment of CDI and appears to be as effective as vancomycin. Fluid replacement to correct electrolyte imbalances is also a critical component of care when needed. There are many new therapies being tested for efficacy against CDI with varying degrees of success and concerns of drug resistance. These include nitazoxanide, rifamixin, ramoplanin, tigecycline and rifalazil. Probiotic therapy has been used with limited success and there is concern about possible complications in immunosuppressed patients. Passive immunotherapy with human antibodies for toxins A and B has had success but is quite expensive and needs further research. Anti-peristaltic agents, which slow fecal transit time through the gut and allow more time for toxin contact, should be avoided.(2, 3)

Prevention and Control

Prevention involves preventing contact with the bacteria and avoiding colonic conditions that favor CDI. Better antimicrobial prescribing practices, particularly limiting the use of high-risk antibiotics, are critical for preventing the disease. Proper hand hygiene and room and equipment disinfection are necessary at all times to prevent transmission from patients with inapparent CDI. Prevention will ultimately rely on a shift in the safety culture in healthcare settings through education of medical doctors, nurses and other staff.

Once CDI has been diagnosed, stringent contact precautions must be implemented. These include:

- Isolating the patient in a room with a private bathroom, or cohorting infected patients together in a room.
- All visitors and healthcare workers should wear gloves and gowns when entering the room and remove and discard them upon leaving the room.
- Proper hand washing with soap and water after removing gloves. Alcohol based hand sanitizers are not effective at killing spores.
- Dedicating equipment only to the infected patient when possible, otherwise disinfecting all equipment after each use.
- Using a hypochlorite based disinfectant to clean all environment surfaces and equipment frequently.

A one-minute hydrogen peroxide vapor treatment of heavily contaminated environments has recently been shown to be effective at reducing the spore burden and

preventing transmission. *C. difficile toxoid A and B v*accines are being tested to determine their role in preventing infection in high risk patients and preventing recurring infections, preliminary results indicate that they may play a role in prevention.(2, 3)

C. difficile Epidemiology and Attributable Cost

Over the last decade there has been a dramatic increase in the incidence and severity of CDI. From 2000 to 2008 there was a steady rise in incidence among hospitalized patients with a leveling off in 2009. In 2000 there were 33.2/100,000 hospital stays with a diagnosis of CDI, in 2009 there were 109.6/100,000. This represents a three-fold increase over the ten year period.(7) CDI recently replaced Methicillin-resistant *Staphylococcus Aureus* (MRSA) as the most common hospital-onset healthcare-associated infection (HAI).(8) In a review of all death certificates in the US from January 1st 2008 to December 31st 2008, CDI was the 18th leading cause of death in people 65 years and older. The age-adjusted death rate from CDI in all populations increased 15% from 2007 to 2008.(9) CDI has recently been recognized in populations previously thought to be at low risk of infection; these include peripartum women, healthy outpatients and people without antibiotic use.(10)

The change in incidence and severity of disease is largely associated with a hyper virulent strain of *C. difficile* that has caused outbreaks in the United States, Canada and Europe.(11) This strain is characterized variously, according to the typing system used, as BI/NAP1/027 and appears to produce 16 times higher concentrations of toxin A and 23 times higher concentration of toxin B in vitro than previously identified strains. It

also produces binary toxin.(12) This strain produces more severe disease which is often refractory to treatment leading to more complications, colectomies and death. It also has high levels of fluoroquinolone and cephalosporin resistance; the common use of these antibiotics may contribute to the successful spread of this strain.(11)

CDI poses a huge financial burden for the medical system. Multiple studies have linked increased costs with infection. A retrospective analysis of clinical data from six US hospitals between 2007 and 2008 estimated an attributable additional length of stay (LOS) for CDI of 2.2 days (95% CI: 0.7, 4.0) and attributable cost of $5,823 (95% CI: $1,477, $10,916).(13) A retrospective analysis of all hospital discharge data from 1999 to 2003 in Massachusetts estimates the US costs for CDI management at $3.2 billion dollars.(14) The authors recognize that this is likely an underestimation of the true cost.

Risk Factors

There are many known risk factors for CDI, the most important being antibiotic exposure which causes disruption of colonic microflora allowing *C. difficile* to flourish. Flouroquinolones are the most implicated class of antibiotics, but cephalosporins, penicillins and clindamycin also predispose a patient to CDI. While these four classes of antibiotics are the most commonly associated with CDI, most antibiotics have been linked to infection. Duration of therapy and the use of multiple antibiotics have also been associated with increased risk of developing CDI.(15-19) Another class of drugs associated with an increased risk of CDI is proton pump inhibitors (PPIs).(20) While these drugs decrease levels of stomach acid, the infective spores of *C. difficile* are relatively stomach acid-resistant suggesting this action is unlikely to explain the

increased risk. Instead PPIs and related drugs may alter the lower intestinal microbiota, albeit less dramatically than antibiotics. Meanwhile antineoplastic and immunosuppressive drugs inhibit an appropriate immune response to the bacteria leading to symptomatic CDI.(21-23)

Still other important risk factors include advanced age (7, 17, 19, 23-26), increased length of hospital stay (7, 20, 25), and admission from a healthcare facility (19, 23, 27). These factors are consistently and significantly associated with CDI in many studies.

Disease severity and underlying chronic conditions have also been associated with CDI. A prospective cohort study of 252 patients admitted to the hospital and receiving antibiotics found extremely severe underlying disease, as defined by clinicians, to be significantly associated with CDI, odds ratio (OR) 17.6 (95% CI: 5.28, 53.5).(28) A retrospective cohort study of hospitalized children with CDI at 22 freestanding US children's hospitals revealed that 67% had underlying chronic conditions.(29) All of the risk factors mentioned above tend to increase the risk of exposure to *C. difficile* and are often associated with increased antibiotic use leading to higher rates of CDI.

Comorbidities have been examined as risk factors for CDI with varying results. A retrospective review of discharges from the Healthcare and Utilization Project (HCUP) National Inpatient Survey (NIS) database between the years of 1993 and 2005 showed that patients with a CDI diagnosis had on average 10.2 diagnoses compared to 6.0 for patients without CDI.(25) A retrospective cohort study of 36,086 patients admitted to Barnes-Jewish Hospital in 2003 found the following comorbidities significantly

associated with CDI in this population on univariate analysis: myocardial infarction risk ratio (RR) 1.5 (95% CI: 1.1, 2.1), congestive heart failure RR 2.2 (95% CI: 1.8, 2.8), cerebral vascular disease RR 1.8 (95% CI: 1.2, 2.7), chronic obstructive pulmonary disease RR 1.5 (95% CI: 1.2, 2.0), peptic ulcer disease RR 1.9 (95% CI: 1.0, 3.5), mild liver disease RR 1.8 (95% CI: 1.1, 3.2), renal failure RR 2.5 (95% CI: 1.6, 4.2), and leukemia/lymphoma RR 5.1 (95% CI: 3.9, 6.8). On multivariate analysis, controlling for variables significant in the univariate model, only leukemia/lymphoma remained significant OR 2.3 (95% CI: 1.6, 3.2).(20)

A retrospective cohort study using the HCUP National Kids' Inpatient Database from the years 1997, 2000, 2003 and 2006 examined comorbidities as risk factors for CDI. The frequency of diagnoses was examined, with no distinction made between primary and other diagnosis code positions. This study found the following comorbidity categories significantly associated with CDI on multivariate analysis: Inflammatory bowel disease (IBD) OR 11.42 (95% CI: 10.16, 12.83), solid organ transplant OR 4.53 (95% CI: 3.92, 5.24), human immunodeficiency virus infection (HIV) OR 4.09 (95% CI: 3.16, 5.30), hematopoietic stem cell transplantation OR 3.31 (95% CI: 2.87, 3.82) and neoplastic disease OR 3.10 (95% CI: 2.89, 3.31). The following comorbidities were also found to be significant with ORs below 3.0: Fungal infection, cystic fibrosis, pancreatitis, hematologic disorders, gastrostomy, liver disease, malnutrition, renal disease, systemic lupus erythematosus, gastroesophageal reflux, bacterial infection, cardiac disease and appendicitis.(30)

The risk of developing CDI has been examined within the context of certain diseases. A multicenter study of over 44,000 HIV seropositive patients between 1992 and 2002 described an overall CDI incidence of 4.12/1,000 person years (95% CI: 3.75, 4.49) and an incidence of 9.59/1,000 person years (95% CI: 7.16, 13.65) in patients with an AIDS diagnosis.(31) These rates are significantly higher than the incidence of CDI in the general population. This study also found CDI to be the most common cause of bacterial diarrhea in HIV patients, accounting for 53.6% of confirmed bacterial diarrhea.

Cancer in children has been significantly associated with CDI. A review of discharges from the HCUP Kids' Inpatient Database from 2006 demonstrated that children with cancer accounted for 1% of all hospitalizations but accounted for 21% of all hospitalizations with a diagnosis of CDI. The rate of CDI was 15 times higher in children with cancer compared to those without cancer, 17.7 vs. 1.1 cases per 1000 discharges.(32)

A retrospective cohort study of admissions to the Barnes-Jewish Hospital between 1998 and 2004 showed inflammatory bowel disease (IBD), ulcerative colitis and Crohn's disease all to be significantly associated with CDI. Multivariate analysis of each disease category yielded the following odds of developing CDI, all results are significant at 0.01%: IBD OR 2.8 (95% CI: 2.0, 4.0), Crohn's disease OR 2.1 (95% CI: 1.3, 3.4) and ulcerative colitis OR 4.0 (95% CI: 2.4, 6.6).(33)

No studies have specifically examined primary diagnoses as risk factors for CDI; however two reviews of HCUP NIS data examine the most common primary diagnoses among patients with a secondary diagnosis of CDI. In 2005 the ten most common

primary diagnoses associated with CDI were: Sepsis (12.5%), pneumonia (6.7%), rehabilitation care (5.1%), fluid and electrolyte disorders (4.8%), acute and unspecified renal failure (3.9%), congestive heart failure (3.6%), urinary tract infections (3.6%), respiratory failure or arrest (3.3%), complication of device, implant or graft (2.9%), and aspiration pneumonia (2.7%).(25) The data from 2009 changes slightly with the following most common primary diagnoses: Sepsis (27.9%), pneumonia (7.5%), respiratory failure (6.5%), rehabilitation care (6.5%), complication of device, implant or graft (5.4%), congestive heart failure (4.9%), acute and unspecified renal failure (4.9%), complication of surgical procedure or medical care (4.2%), aspiration pneumonitis (3.7%), and urinary tract infections (3.5%).(7)

While many factors have been examined as risk factors for CDI, primary diagnosis has previously been under-examined, in part due to the small sample size of many of the studies, particularly during outbreak investigations, but it may be an important addition to the understanding of which patients are at increased risk of developing CDI.

C. difficile Surveillance and Mandatory Reporting

Hospitals and other inpatient facilities are increasingly being held accountable for healthcare acquired infections through state-mandated public reporting legislation and federal Medicare pay-for-reporting rule making. Several states have already mandated CDI reporting using CDC's National Healthcare Safety Network (NHSN) or similar systems. The Affordable Care Act of 2010 requires that a national reporting system for HAIs, including CDI, be functional in 2013. Hospital-onset CDI rates will be

made public on the Health and Human Services (HHS) Hospital Compare website in 2014. CDI reporting will be mandated under the "pay-for-reporting" system; acute care hospitals that are reimbursed under the Inpatient Prospective Payment System (IPPS) will be required to report CDI in order to get part of their reimbursement. Pay for performance, based on reported hospital rates of infection, will most likely follow at some point in the future. Public reporting of CDI rates and reimbursement based on infection rates mean that it is critical to identify more equitable methods to evaluate healthcare facility performance through risk adjusted bench-marking. In addition, it is critical for facilities to understand which patients are at the greatest risk to improve infection control among this population. Both of these challenges require an understanding of which variables affect a patient's risk of CDI.

To date there have been many challenges surrounding CDI surveillance. An informal CDI surveillance working group published case definitions in 2007, but until recently there was no standardized case definition for CDI. Cases are now categorized based on the location of onset of disease and exposure history into the following categories: Recurrent CDI; healthcare facility associated, healthcare facility onset CDI; healthcare facility associated, community-onset CDI; and community associated CDI. Case definitions have been established for each of these categories to improve and standardize surveillance and allow comparisons to be made across facilities and between studies.(34)

The analysis required to risk stratify patients so healthcare facilities can better understand how they can improve care and target high risk patient populations to

prevent infection includes not only factors the patient arrives at the hospital with, such as transfer in from another facility, conditions present on admission, age, current medications (eg: antibiotics and PPIs), but also facility controlled factors such as medications prescribed, interventions performed at the facility and LOS. Understanding how these factors interplay to increase risk can help a hospital improve care practices to avoid high risk interventions when possible and target high risk populations to decrease infection rates.

In order to compare infection control performance across facilities to determine how well a facility does at preventing infection it is necessary to consider the inherent risk a patient walks in with when a patient is admitted to a healthcare facility. This analysis includes the factors a healthcare facility cannot control which put patients at higher risk, such as transfer in, age, and conditions and medications present on admission.

While there are many limits to the use of administrative data to answer these questions, the data are easily accessible and can be used to make national, facility and discharge level estimates and may be useful for comparing facilities through the analysis of factors which increase a patient's risk on admission. One of these factors is the primary diagnosis, or reason for hospitalization. The purpose of this thesis is to understand which primary diagnoses are associated with increased risk of CDI when controlling for other factors that may be present on admission and are captured in the database. A better understanding of how to risk-stratify patients based on primary diagnosis can help facilities determine where to direct infection control efforts, and can

assist in the critical decisions that need to be made to refine a national CDI reporting system.

Methods

We conducted a retrospective cohort study to assess primary diagnoses as risk factors for HO-CDI in adults. This analysis was performed using hospital discharge data from the 2009 Nationwide Inpatient Sample (NIS), which is part of the Healthcare Cost and Utilization Project (HCUP) created by the Agency for Healthcare Research and Quality under The United States Department of Health and Human Services (HHS). HCUP is the result of a federal-state-industry partnership and contains multi-state healthcare data to be used for research and policymaking. HCUP contains a variety of software tools and databases, including the NIS database. NIS is an all-payer inpatient care database representing a 20% stratified, randomly selected sample of U.S. community hospitals including patients covered by Medicare, Medicaid, private insurance, and the uninsured. Community hospitals are defined as "all non-Federal, short-term, general, and other specialty hospitals, excluding hospital units of institutions" and include non-federal public and private hospitals, and university affiliated medical centers. It contains discharge level data for all patients from the hospitals sampled. The data are not patient level data and there are no identifiers to link multiple admissions; therefore individuals who are readmitted to the hospital will be present multiple times, there is no way to distinguish these as the same patient with the variables collected in NIS. Each record has a discharge weight variable designed to

help provide more accurate standard errors and confidence intervals when calculating national estimates. Healthcare facilities are stratified by zip code and region, a random sample of 20% of healthcare facilities in the US is taken and then weights are assigned to each facility to reflect the true number of hospitals in that stratum. Discharge level weights are derived from these facility rates and are all close to five (median discharge weight = 5.06), since the NIS is a 20% sample. Multiplying each discharge by the weight will give an estimate of the national number of similar discharges. The 2009 NIS database contains data for 7.8 million hospital stays from 1050 hospitals in 44 states.(35)

HO-CDI was defined as a non-primary diagnosis of CDI with a LOS ≥ three days. A non-primary diagnosis of CDI was defined as ICD-9 code 008.45 in diagnosis code position 2 through 25. We based this definition of HO-CDI on a standardized definition created by the CDI surveillance working group. The CDI working group defined HO-CDI as a patient with confirmed CDI and onset of symptoms more than 48 hours after admission to a healthcare facility.(34) A confirmed case of CDI is defined by symptoms including diarrhea or toxic megacolon coupled with a positive laboratory assay or histopathological evidence of pseudomembranous colitis. Pseudomembranous colitis is an infection of the large intestine with an overgrowth of *C. difficile*. We do not know when in the course of the hospital stay the symptoms began or when and how CDI was diagnosed because there is no diagnosis date associated with the ICD-9 codes or present on admission indicator in the NIS database. Therefore, we will use a LOS ≥ three days

and CDI in a non-primary diagnosis code position as a surrogate for a confirmed HO-CDI case.

We excluded discharges with the following characteristics from our analysis:

1. All patients under 18 years of age.
2. Patients with a primary diagnosis of CDI. Note: The primary diagnosis code should reflect the primary reason for the hospital admission. Therefore patients with CDI in the primary position would not qualify as acquiring HO-CDI during this hospital stay.
3. All patients with a LOS < three days.

In order to analyze primary diagnoses that could be risk factors for HO-CDI, we use the Clinical Classification Software (CCS) grouping system to manage the thousands of possible ICD-9 codes. CCS is a downloadable software tool developed by HCUP to combine diagnosis codes into 285 mutually exclusive and clinically meaningful categories (http://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp).(36) Each diagnosis code in a patient record has a corresponding CCS code. We further combined some categories: We grouped all solid tumor cancers into one category; all hematopoietic cancers into one category; all nutritional disorders into one category; all central nervous system infections into one category and all types of anemia into one category. In addition we removed diagnosis codes indicative of leukocytosis from the CCS category "Diseases of White Blood Cells" since leukocytosis can be caused by CDI.

A multivariate model was created to assess primary CCS category as a risk factor for HO-CDI. HO-CDI, as defined previously, was the dependent variable. Primary CCS

category was the primary independent variable. Age, LOS, number of chronic conditions and if the patient transferred in from another healthcare facility were the secondary independent variables considered as possible effect modifiers or confounders for the relationship. We divided age into three categories: 18 to 40 years, 41 to 64 years and greater than 64 years. LOS was divided on the median into two categories, 3-4 days and greater than 4 days. Transfer in was coded as "yes" if the patient transferred from any other healthcare facility and "no" if not. Number of chronic conditions was also divided on the median into two categories, 0-4 conditions and greater than 4 conditions. The chronic conditions variable is created by HCUP; the program to create this variable is available from HCUP (http://www.hcup-us.ahrq.gov/toolssoftware/chronic/chronic.jsp). It categorizes ICD-9 codes as chronic or not-chronic; the number of chronic ICD-9 codes is then summed in the new variable. A chronic condition is defined as a condition that lasts 12 months or longer and meets one or both of the following tests: (a) it places limitations on self-care, independent living, and social interactions; (b) it results in the need for ongoing intervention with medical products, services, and special equipment.(37)

We examined the following model:

$$\begin{aligned} HO - CDI \; = {} & Primary\ CCS + Age\ Category + LOS\ Category \\ & + Chronic\ Condtions\ Category + Transfer\ In \\ & + (Primary\ CCS \times Age\ Category) \\ & + (Primary\ CCS \times LOS\ Category) \\ & + (Primary\ CCS \times Chronic\ Conditions\ Category) \\ & + (Primary\ CCS \times Transfer\ In) \end{aligned}$$

SAS® version 9.2 (SAS Institute Inc., Cary, North Carolina) was used for all statistical analyses. A poisson regression was performed using the PROC GENMOD procedure to fit a generalized linear model to the data. The maximum likelihood method was used to obtain estimates for risk difference (RD). This procedure was performed on all primary CCS categories individually. The full model was then run and backwards selection was used to eliminate interaction terms when not statistically significant based on a type III analysis which computes likelihood ratio statistics for each term in the model. The interaction term with the highest p-value was eliminated and the model was then re-run without it until only significant interaction terms remained. Statistical significance was defined as a p-value < 0.05. When the model failed to converge, due to sparse data, the chronic conditions category was eliminated as an interaction term and the model was rerun. If it still failed to converge, the LOS category was eliminated as an interaction term, and then the age category variable if necessary. Each patient record was weighted to obtain national estimates as dictated by the NIS

database. The stratum-specific risk difference, 95% confidence limits and Wald chi-square p-value was reported when the interaction term was significant, or an adjusted risk difference when there was confounding. All statistics with a RD > 1% and p-values < 0.05 were reported. The large sample size resulted in even very small differences being statistically significant; we arbitrarily determined 1% to be clinically significant. Risk difference was reported as the excess number of discharges per 1,000 discharges, for example a 1% risk difference would be reported as 10/1,000 discharges.

Two by two tables were constructed using the SAS PROC SURVEYFREQ procedure to obtain general descriptive statistics from the database and the crude RD for each CCS. All statistics are weighted to reflect a national estimate, hence are greater than the true number of discharges reported in the database.

Results

Descriptive statistics for all discharges and cases (HO-CDI patients) from the 2009 database were obtained using univariate analysis and are reported in Table 1. The frequency does not represent the actual number of discharges in the database, but a national estimate calculated using the discharge weight assigned by HCUP that accounts for the stratified sample in the NIS database. Discharges with CDI as a primary diagnosis and discharges with a LOS < three days were excluded from all analyses. There are 206,035 discharges with HO-CDI, 1.02% of the total sample population of 20,208,319 discharges.

Age, LOS, number of chronic conditions and transfer from a healthcare facility are all independent risk factors for CDI in this population. Transfer status appears to have the strongest association with a risk of 2.59% for discharges that transfer in versus 0.88% for those that do not. Risk of HO-CDI increases with age: 0.32% of discharges of 18-40 year old patients, 0.87% of discharges of 41-64 year old patients and 1.43% of those of patients greater than 64 years old have HO-CDI. Risk of HO-CDI is higher with a longer LOS: 0.26% of discharges with a LOS between three and four days and 1.75% with a LOS greater than four days have HO-CDI. Risk of HO-CDI is higher in patients with more chronic conditions: 0.61% of discharges with four or fewer chronic conditions and 1.39% with more than four chronic conditions have HO-CDI.

Table 1: Characteristics of Discharges from the 2009 HCUP NIS Database*

	Total in Database	National Estimate (%)	HO-CDI in Database	HO-CDI National Estimate (%)	Risk (%)
All discharges	3,993,201	20,208,319 (100.0)	40,845	206,035 (100.0)	1.02
Age category					
18-40 Years	810,317	4,081,702 (20.20)	2,618	13,057 (6.34)	0.32
41-64 Years	1,313,959	6,640,775 (32.86)	11,462	57,589 (27.95)	0.87
>64 Years	1,868,925	9,485,841 (46.94)	26,765	135,389 (65.71)	1.43
LOS category					
3-4 Days	1,944,452	9,832,161 (48.65)	4,989	25,182 (12.22)	0.26
>4 Days	2,048,749	103,761,589 (51.35)	35,856	180,852 (87.78)	1.75
Number of Chronic Conditions					
0-4	1,887,852	9,557,777 (47.30)	11,574	58,851 (28.56)	0.61
>4	2,105,340	10,650,542 (52.70)	29,271	147,183 (71.44)	1.39
Transfer In					
No	3,664,805	18,558,767 (91.84)	32,212	163,281 (79.25)	0.88
Yes	328,396	1,649,552 (8.16)	8,633	42,754 (20.75)	2.59

*Excluding all discharges with LOS<3 days, and all discharges with a primary diagnosis of CDI.

Of the 285 CCS examined using multivariate analysis, 23 yielded a RD greater than 10/1,000 discharges, or 1.0%, in at least one stratum (see Table 2). All variables remained in the model in each analysis as either an interaction term or confounder and each analysis had at least one significant interaction term. Risk difference implies the number of excess discharges per 1,000 discharges in the strata that have HO-CDI. For example, there are 86.5 excess discharges per 1,000 discharges among patients that are greater than 64 years old, have a LOS greater than 4 days, more than 4 chronic conditions and transferred in from a healthcare facility, and that have a primary CCS of septicemia compared to the same group of patients without septicemia.

The CCS that have the strongest association with HO-CDI are septicemia (RD 11.6 – 86.5/1,000), HIV (11.1 – 78.6/1,000), cystic fibrosis (67.0/1,000) and mycoses (RD 12.4 – 65.4/1,000). Other significant CSS include: Respiratory failure, insufficiency or arrest; chronic ulcer of the skin; other inflammatory condition of skin; hematopoietic neoplasm; bacterial infection, unspecified site; peritonitis and intestinal abscess; infective arthritis and osteomyelitis; regional enteritis and ulcerative colitis; diseases of white blood cells (excluding leukocytosis); aspiration pneumonitis, food/vomitus; complications of surgical procedures or medical care; gangrene; other aftercare; acute and unspecified renal failure; viral infection; complication of device, implant or graft; diabetes mellitus with complications; urinary tract infections; and pneumonia. In all cases the crude RD is significantly lower than in the stratum with the highest RD. Tables 3 through 25 (see appendix B) report the stratum specific RDs, confidence intervals and p-values for each of the 23 significant CSS.

Table 2: Primary CCS with HO-CDI risk difference greater than 10/1,000 discharges (1.00%) in the 2009 HCUP NIS database*

CCS	RD Range**	Crude RD[#]	Total HO-CDI
Septicemia	11.6 – 86.5	52.3	42,098
HIV	11.1 – 78.6	22.0	1,451
Cystic Fibrosis	67.0	10.3	142
Mycoses	12.4 – 65.4	24.1	771
Respiratory Failure; Insufficiency; Arrest	41.6 – 49.9	19.3	8,982
Chronic Ulcer of the Skin	48.6	16.8	1,636
Other Inflammatory Condition of Skin	38.1	4.2	94
Hematopoietic Neoplasm	10.7 – 37.9	25.6	3,081
Bacterial Infection; Unspecified Site	37.0	4.4	80
Peritonitis and Intestinal Abscess	14.3 – 34.2	14.2	594
Infective Arthritis and Osteomyelitis	30.8	8.6	1,261
Regional Enteritis and Ulcerative Colitis	11.4 – 28.6	13.0	1,664
Diseases of White Blood Cells	13.7 – 25.9	18.6	1,153
Aspiration Pneumonitis; Food/Vomitus	10.0 – 25.9	20.0	4,796
Complications of Surgical Procedures/Medical Care	15.0 – 24.0	7.1	5,978
Gangrene	13.7 – 21.2	14.1	765
Other Aftercare	19.2	17.2	700
Acute and Unspecified Renal Failure	10.4 – 19.1	11.0	6,255
Viral Infection	10.1 – 15.8	2.6	219
Complication of Device; Implant or Graft	10.0 – 15.7	6.9	7,745
Diabetes Mellitus with Complications	11.1 – 12.4	-0.2	2,360
Urinary Tract Infections	10.6 – 11.5	3.1	5,002
Pneumonia	10.7	2.7	10,047

*Detailed statistics reported in Appendix A. RD reported as excess discharges/1,000 discharges.

**RD Range = Stratum-specific RD rage from multivariate analysis, only reporting RD greater than 1.0% and $p < 0.05$. In descending order from highest RD within a CCS. RD reflects the weighted national estimate.

[#]Crude RD = Univariate analysis.

All strata in the HIV category are significant and there are 1,451 discharges in the category with HO-CDI. RD ranges from 11.1/1,000 (95% CI: 8.5, 13.7), $p<0.0001$ in the lowest stratum to 78.6/1,000 (95% CI: 62.5, 94.8), $p<0.0001$ in the highest. RD increases in a stepwise manner as age category, LOS and number of chronic conditions increase and with transfer in from a healthcare facility status (see Table 3).

All strata in the septicemia category are significant with the exception of the strata containing 18-40 year old patients with 0-4 chronic conditions, a 3-4 day LOS and who did not transfer in; the lowest risk group. There are 42,098 discharges in the category with HO-CDI. RD ranges from 11.6/1,000 (95% CI: 10.7, 12.6), p<0.0001 in the lowest stratum to 86.5/1,000 (95% CI: 84.5, 88.5), p<0.0001 in the highest. RD increases in a stepwise manner as age category, LOS and number of chronic conditions increase and with transfer in from a healthcare facility status with a few exceptions (see Table 4).

Seventeen of 24 strata are significant in the hematopoietic neoplasms and aspiration pneumonitis categories. There are 3,081 discharges with HO-CDI and the RD for hematopoietic neoplasms ranges from 10.7/1,000 (95% CI: 8.3. 13.2), p<0.0001 in the lowest stratum to 37.9/1,000 (95% CI: 33.9, 41.9), p<0.0001 in the highest (see Table 5). There are 4,796 discharges with HO-CDI and the RD for aspiration pneumonitis ranges from 10.0/1,000 (95% CI: 6.8, 13.2), p<0.0001 in the lowest stratum to 28.4/1,000 (95% CI: 25.5, 31.3), p<0.0001 in the highest (see Table 6).

Twelve of 24 strata are significant in the complications of surgical procedures or medical care category, and there are 5,978 discharges with HO-CDI. The RD for ranges from 15.0/1,000 (95% CI: 12.8, 17.1), p<0.0001 in the lowest stratum to 22.3/1,000 (95% CI: 20.2, 24.5), p<0.0001 in the highest (see Table 7).

Eleven of 24 strata are significant in the acute and unspecified renal failure category, and there are 6,255 discharges with HO-CDI. The RD ranges from 10.4/1,000

(95% CI: 8.0, 12.7), p<0.0001 in the lowest stratum to 19.1/1,000 (95% CI: 16.7, 21.4), p<0.0001 in the highest (see Table 8).

Eight of 24 strata are significant in the complication of device, implant or graft category, and there are 7,745 discharges with HO-CDI. The RD ranges from 10.0/1,000 (95% CI: 9.0, 10.9), p<0.0001 in the lowest stratum to 16.0/1,000 (95% CI: 14.2, 17.8), p<0.0001 in the highest (see Table 9).

Three of 24 strata are significant in the urinary tract infections category, and there are 5,002 discharges with HO-CDI. The RD ranges from 10.6/1,000 (95% CI: 8.4, 12.8), p<0.0001 in the lowest stratum to 11.5/1,000 (95% CI: 9.4, 13.6), p<0.0001 in the highest (see Table 10).

Five of 12 strata are significant in the gangrene category, and there are 765 discharges with HO-CDI. The RD ranges from 13.7/1,000 (95% CI: 11.4, 15.9), p<0.0001 in the lowest stratum to 21.2/1,000 (95% CI: 14.3, 28.2), p<0.0001 in the highest (see Table 11).

Five of 12 strata are significant in the viral infection category, and there are 219 discharges with HO-CDI. The RD ranges from 10.1/1,000 (95% CI: 0.7, 19.4), p=0.0342 in the lowest stratum to 15.8/1,000 (95% CI: 6.2, 25.4), p=0.0013 in the highest (see Table 12).

Two of 12 strata are significant in the diabetes mellitus with complications category, and there are 2,360 discharges with HO-CDI. The RD is 11.1/1,000 (95% CI: 8.4, 13.9), p<0.0001 in the lowest stratum and 12.4/1,000 (95% CI: 9.6, 15.2), p<0.0001 in the highest (see Table 13).

Three of four strata are significant in the peritonitis and intestinal abscess category, and there are 594 discharges with HO-CDI. The RD ranges from 14.3/1,000 (95% CI: 11.2, 17.3), p<0.0001 in the lowest stratum to 44.9/1,000 (95% CI: 35, 54.8), p<0.0001 in the highest (see Table 15).

All four strata are significant in the regional enteritis and ulcerative colitis category, and there are 1,664 discharges with HO-CDI. The RD ranges from 11.4/1,000 (95% CI: 10.3, 12.6), p<0.0001 in the lowest stratum to 28.6/1,000 (95% CI: 21.2, 36.0), p<0.0001 in the highest (see Table 16).

Two of four strata are significant in the respiratory failure, insufficiency or arrest category, and there are 8,982 discharges with HO-CDI. The RD is 41.6/1,000 (95% CI: 39.3, 43.9), p<0.0001 in the lowest stratum and 49.9/1,000 (95% CI: 47.8, 52.1), p<0.0001 in the highest (see Table 17).

Three of four strata are significant in the diseases of white blood cells category, and there are 1,153 discharges with HO-CDI. The RD ranges from 13.7/1,000 (95% CI: 11.3, 16.2), p<0.0001 in the lowest stratum to 25.9 /1,000 (95% CI: 23.1, 28.7), p<0.0001 in the highest (see Table 18).

Both strata are significant in the mycoses category, and there are 771 discharges with HO-CDI. The RD is 12.4/1,000 (95% CI: 10.2, 14.6), p<0.0001 in the lowest stratum and 65.4/1,000 (95% CI: 54.3, 76.6), p<0.0001 in the highest (see Table 20).

One of two strata is significant in the following categories: Pneumonia, there are 10,047 discharges with HO-CDI. The RD is 10.7/1,000 (95% CI: 9.2, 12.2), p<0.0001 (see Table 14); cystic fibrosis, there are 142 discharges with HO-CDI. The RD is 67.0/1,000

(95% CI: 28.8, 105.2), p=0.06 (see Table 19); chronic ulcer of the skin, there are 1636 discharges with HO-CDI. The RD is 48.6/1,000 (95% CI: 43.6, 53.7), p<0.0001 (see Table 21); other inflammatory condition of skin, there are 94 discharges with HO-CDI. The RD is 38.1/1,000 (95% CI: 21.2, 55.0), p<0.0001 (see Table 22); bacterial infection, unspecified, there are 80 discharges with HO-CDI. The RD is 37.0/1,000 (95% CI: 16.0, 57.9), p<0.0001 (see Table 23); infective arthritis and osteomyelitis, there are 1261 discharges with HO-CDI. The RD is 30.8/1,000 (95% CI: 25.8, 35.7), p<0.0001 (see Table 24); and other aftercare, there are 700 discharges with HO-CDI. The RD is 19.2/1,000 (95% CI: 15.2, 23.1), p<0.0001 (see Table 25).

Discussion

Risk of CDI varied greatly between different CCS categories and between strata. All of the independent variables included in this model are important confounders or effect modifiers of the relationship of CCS to CDI. The crude RD is significantly different than many of the stratum specific results, and results vary significantly between strata; hence analysis without these variables in the model would lead to significant bias. While the trend is for RD to increase with greater age, LOS, chronic conditions, and with transfer in from a healthcare facility, this trend does not always hold. Stratifying the analysis on so many levels left some cells with small counts which may not yield a statistic truly representative of the entire population in those strata.

Transfer in from a healthcare facility appears to have the biggest impact of the possible effect modifiers we examined. This is likely due to the increased exposure from

the original facility and increased antibiotic use. Antimicrobial therapy has been cited as the most commonly prescribed medication in long-term care facilities. Studies have found that 4% to 20% of patients in these facilities are asymptomatically colonized with *C. difficile*, creating a prime opportunity for exposure and infection in vulnerable patients.(38) Other studies have found a significant association between transfer in from a healthcare facility and risk of CDI.(19, 23, 27)

Advanced age, a high number of chronic conditions and increased LOS predispose a patient to CDI for similar reasons. They all tend to indicate patients with altered immunity, increased exposure to long-term or acute care facilities and increased antimicrobial therapy use. Our findings are consistent with many studies that have linked these factors with an increased risk of CDI.(7, 17, 19, 20, 23-26, 30)

Septicemia is the CCS with the strongest association with CDI, the highest RD is 86.5/1,000, and it has the most number of discharges with HO-CDI (72,098) by a substantial margin of 32,051 discharges. Septicemia is a common reason for hospitalization and septicemic patients receive intensive antimicrobial therapy and often have a long LOS due to the severity of illness. These factors explain why septicemia has the highest rate of HO-CDI. Septicemia has been shown to be a common diagnosis among patients with CDI.(7, 25)

HIV, diseases of white blood cells and hematopoietic neoplasms alter the immune response, particularly humoral immunity. This altered immunity increases the likelihood of symptomatic CDI.(39) Patients with these diagnoses are also frequently exposed to healthcare settings due to the chronic nature of the diseases and often take

antimicrobials to combat opportunistic infections, making them prime candidates for CDI. HIV is the only category where all of the strata are significant, and while only 1,045 discharges have HIV as a primary diagnosis, this population should be considered at high risk of HO-CDI. HIV has previously been associated with an increased risk of CDI.(30, 31) LOS appears to be the most important of the effect modifiers for predicting HO-CDI in discharges with hematopoietic neoplasms. This could be due to increased exposure time to the bacteria in the facility, increased likelihood that these patients would receive antineoplastic and antimicrobial therapy, or could involve some bias since patients with a longer LOS have a longer opportunity for the infection to be diagnosed and coded in the record. Leukemia and lymphoma have also been proven to have an increased association with CDI in earlier studies.(20)

While pneumonia has the lowest RD (10.7/1,000) of the 23 CSS and only one significant stratum, it has the second highest number of discharges with HO-CDI (10,047); pneumonia is a common diagnosis representing 3.88% of all discharges in this population. Conversely cystic fibrosis has a very high RD (67.0/1,000), yet it is a rare diagnosis particularly in patients over 18 years of age, therefore there are only 142 discharges with HO-CDI. These examples demonstrate that the extent of the problem cannot always be determined by the strength of the association. Both the excess risk and the number of discharges with disease are important to consider when utilizing this data to risk stratify patients and assess hospital infection rates. Patients with pneumonia and hospitalized patients with cystic fibrosis are usually on antimicrobial therapy which primes them for HO-CDI. Both of these diseases have been linked to an

increased risk of CDI or have been shown to be prevalent among patients with CDI.(7, 25, 30)

Other inflammatory conditions of the skin; bacterial infection; infective arthritis and osteomyelitis; gangrene; and urinary tract infection are all categories that tend to be treated with antibiotics. Other inflammatory conditions of the skin and bacterial infection have the highest RD of this group but less impact because both have fewer than 100 discharges with HO-CDI. These two CCS and infective arthritis and osteomyelitis have only one significant stratum, transfer in from a healthcare facility, which was the only significant effect modifier in these CCS and created significant interaction, indicating the large impact of transfer status. Of these CCS, only bacterial infection and urinary tract infection have been associated with increased risk of CDI or increased prevalence among patients with CDI in previous studies.(7, 30)

Viral infection and mycoses are not primarily treated with antibiotics, but antibiotics are often used to combat secondary infections. This coupled with the altered immune status of patients with active infections could account for the significance of these categories. Fungal infections have been shown to increase risk of HO-CDI in previous studies, but viral infections have not been implicated in the literature until now.(30)

Acute and unspecified renal failure; respiratory failure, insufficiency or arrest; and aspiration pneumonitis from food or vomitus are all associated with severe and often acute disease. Severe illness and consequent intensive medical care and antimicrobial use could account for the high RD in these categories. All three of these

categories have a large number of patients with HO-CDI (respiratory: 8,982, renal: 6,255 and aspiration 7,796) and have been associated with CDI in previous studies, hence should be considered important risk factors for HO-CDI.(7, 20, 25, 30)

Complications of surgical procedures or medical care; complication of device, implant or graft; other aftercare; chronic ulcer of the skin; and diabetes mellitus with complications are all associated with chronic conditions, long term care and antimicrobial use. The significant strata in all of these CCS transferred in from a healthcare facility with the exception of two strata with borderline significance in the complication of device, implant or graft category. Antimicrobial priming of the colon, increased exposure to healthcare settings and possibly altered immunity due to chronic disease or advanced age could account for the increased risk in these categories. With the exception of other aftercare, all of these CCS have a large number of discharges with HO-CDI, ranging from 1,636 to 7,745. Repeat admissions in these chronic care patients could lead to inflated estimates if some patients were counted more than once. Of these five CCS, only complications of surgical procedures or medical care, and complication of device, implant or graft have been shown to have a high prevalence among patients with CDI in previous studies.(7, 25)

Peritonitis and intestinal abscess, and regional enteritis and ulcerative colitis are likely associated with increased risk of HO-CDI not only because of a high likelihood of antimicrobial use but also because patients with these gastrointestinal diseases may already have compromised normal colonic flora and hence be more susceptible to CDI. In addition, patients with regional enteritis and ulcerative colitis may be on

immunosuppressive medications to control the autoimmune aspects of the disease, a known risk factor for CDI.(23) Ulcerative colitis and regional enteritis have previously been associated with an increased risk of CDI.(33)

The excess risk associated with the 23 CCS categories that remained significant in multivariate analysis can be linked to the two most important factors that are known to predispose patients to CDI or to increase the risk of symptomatic infection. All of the 23 CCS have a high likelihood of antimicrobial therapy and most carry a high likelihood of exposure to healthcare settings, including long term care facilities, due to severe or chronic disease. Other studies have also found that the conditions associated with CDI usually require antimicrobial use.(30) The likelihood of antimicrobial use and exposure to healthcare settings can explain why there appears to be a strong association between these CCS and HO-CDI. While some of the categories of disease that we found to be significant have also been shown to have an increased association with CDI in other studies, many have not. Primary diagnosis as a risk factor for HO-CDI has been under examined; our study introduces some novel insights about which are associated with an increased risk of HO-CDI and the use of administrative data to make this determination.

Strengths & Limitations

There are many advantages and disadvantages to using administrative data. The data are readily available to all hospital facilities and can be used to derive estimates at individual discharge or patient level, facility wide estimates or national estimates. Therefore these data could be used to compare facility and national estimates to gauge a facility's infection control performance in reference to the rest of the nation, however

there are serious limitations as well. This sample only includes data from 44 states so there could be sampling bias when using it to derive national estimates.

Because there are no patient identifiers, there is no way to parse out patients that are readmitted to the hospital with an ongoing CDI infection that may have been acquired on a previous visit. Therefore these patients could be counted twice but are actually only one case of HO-CDI, leading to slightly inflated estimates. We are also unable to determine if the patient had been in a healthcare facility recently, unless they transferred in directly. Exposure to *C. difficile* may have occurred at a different facility and could be erroneously attributed to the current facility. Not knowing a patient's admissions history also makes it difficult to define cases because case definitions are based on if and when a patient had previous healthcare facility exposure.(34)

The lack of a temporal indicator which specifies when CDI is diagnosed during the course of the hospital stay, or if it is present on admission, is another limitation. Since ICD9 codes are assigned on discharge, we do not know if the patient entered the hospital with CDI or when in the course of their stay they developed it; hence we are unable to accurately define cases as HO-CDI. In addition, many cases of HO-CDI are diagnosed once the patient has been discharged either because symptoms have not developed yet or because the laboratory results were not available when the patent was discharged. Therefore some cases of HO-CDI would be missed if ICD9 coding was done before the laboratory results were available.

There have been studies analyzing how well a diagnosis of CDI and HO-CDI in administrative data hold up against more accurate hospital data with laboratory

confirmation and a known time of onset. A retrospective cohort study of patients admitted to Barnes Jewish Hospital in 2003 was performed to compare administrative data ICD9 coding to confirmatory toxin assays, this study looked at total CDI, not HO-CDI specifically. The correlation was good (k=0.72, p<0.01).(40) Another study compared data from cases of CDI at five US hospitals. Laboratory confirmed cases of HO-CDI were compared to patients with a secondary diagnosis code of CDI. This study found that administrative data performed poorly for the diagnosis of HO-CDI, nearly half (47%) of HO-CDI cases as defined by ICD9 coding were actually community-onset cases.(41) In order to address this problem we eliminated all patients with a LOS < three days, which would eliminate many CO-CDI cases allowing the ICD9 code to be a more accurate depiction of true HO-CDI cases.

The use of ICD9 codes has other problems. Since coding is done on discharge, it is possible that the primary code is not the actual reason for admission and could be a more significant problem that developed during the hospitalization. The primary diagnosis in some cases could have developed as a result of complications from CDI. Disease of white blood cells is one example; this category includes a range of diseases and symptoms from leukopenia to leukocytosis. We removed leukocytosis from the category because it is commonly a response to CDI. Reimbursement also drives some ICD9 codes; if HO-CDI is poorly reimbursed there may be incentive not to use the code. CDI is slated to be a Centers for Medicare and Medicaid Services non-reimbursable diagnosis, when this happens facilities have incentive not to code for CDI and accurate coding may decrease making ICD9 codes inadequate for CDI surveillance.(41)

This study attempts to control for factors present on admission that increase a patient's risk of HO-CDI, factors the hospital cannot control. Ideally the severity of illness, exposure to healthcare facilities and the type of medication the patient is admitted with would be known and adjusted for, but this information is not available in administrative data. Number of chronic conditions can give an indication of ongoing medical problems, transfer in can indicate if a patient has known healthcare facility exposure although it can't quantify or qualify it, and based on the results of this study primary diagnosis may be an acceptable surrogate for antibiotic use. LOS is not present on admission but was included in the model because LOS not only increases the chance of exposure but also allows more time for a diagnosis and the accompanying ICD9 code to be assigned. We therefore felt that leaving it out of the model would introduce bias.

Conclusions and Recommendations

This analysis confirms what is currently known about the risk factors for HO-CDI. The two critical ingredients for infection are exposure and antimicrobial use. It also demonstrates that stratifying patients based on primary diagnosis and the other variables used may serve as a surrogate for and allow us to adjust for the need for antibiotic use and possible past exposure. All of these diagnoses can be linked to these two factors. The utility of this analysis lies not so much in the specific risk stratified results, but in the fact that administrative data can be used to risk stratify patients using the primary diagnosis category, even without detailed information about antimicrobial therapies; and that patients carry dramatically different risk of disease based on the factors we examined. Considering risk without stratifying based on the variables we

examined, and possibly more, would lead to a biased estimate. In many of these CCS there is a dramatic difference between the crude RD and some of the stratum specific estimates, for example one stratum of HIV has a RD of 78.6 with a crude RD of 22.0, a difference of 56.6. Controlling for these variables without considering interaction leads to an adjusted RD that tends to be lower than the crude RD, increasing the bias in these high RD stratum.

With required reporting of HAIs in the near future, it is critical to find ways to fairly compare rates of infection across healthcare facilities. This analysis demonstrates that using a rate of infection without accounting for patient factors would yield a biased estimate. Facilities that see severely ill or older populations of patients would naturally have higher rates of infection, as would facilities that have patients who transfer in from other facilities or have had recent hospital visits,(27) but they may perform as well in terms of infection control as a hospital with a lower rate when these patient factors are taken into consideration.

In order to get hospitals to report these adjusted hospital rates, it is necessary to present them with a reasonable way to obtain them. The benefit of administrative data is that they are readily available for all healthcare facilities and could easily be used for statistical analysis. Additionally, the HCUP database is adding a “present on admission” indicator which will be used to determine if a condition is acquired while in the hospital. This will enhance the accuracy of using these data for CDI surveillance by improving the specificity of the HO-CDI case definition. Understanding the variables that are already present in these data and can be used to adjust a patient’s risk is an important first step

in developing an equation for this adjusted rate of infection for a facility, this study greatly advances that understanding. Ultimately it will be necessary to develop an equation that weights patients based on their risk by accounting for the factors a patient enters the hospital with that increase their risk of infection, and to examine how this affects hospital infection rates. These weights may be used to calculate a hospital infection rate that can be compared to other hospitals. It is also possible that controlling for the variables we examined without considering stratification would generate an adjusted risk measure that would account for these patient characteristics. There is still much research that needs to be done to determine the best way to derive this formula and allow it to be used consistently across facilities. We will attempt to use the significant CCS exposed in this study and the understanding we gained of how the independent variables we examined affect risk to develop risk adjusted bench-marking of hospital infection rates.

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Appendix A: Additional Methods

This appendix documents some of the processes and decisions that were used to derive the final model.

- We initially considered comorbidities and primary diagnoses as risk factors, but determined that comorbidities are too driven by events that occur in the hospital to be used to evaluate a patients risk on admission. Comorbidities could also be a result of CDI. We therefore eliminated comorbidities from the study.
- We considered many measures of association and initially planned to use a ratio. We discovered that the ratio gave a misrepresentation of the problem in many strata where disease was rare and hence the denominator was very small. A small increase in cases resulted in a very high ratio, even though there were few cases. We found risk difference to be a more accurate reflection of the true burden of disease.
- We initially ruled out many of the CCS based on the cRD, but determined that the stratification was significant enough that a CCS with an insignificant cRD could still have significant stratum specific RDs. We therefore ran the full model on all CCS.
- We initially included discharges with a LOS<3 days that did not have HO-CDI in the dataset for analysis. We then determined that those patients could not be at risk of disease since HO-CDI can't be diagnosed within the first 48 hours of hospitalization so we excluded them from the dataset.

- LOS was initially broken down into three categories. Sensitivity analysis indicated that there was a very small difference when only two categories were used so we changed the categorization to simplify the model.
- Due to the large size of the database (almost 4,000,000 discharges) there were many stratum specific estimates that were significant at alpha=0.05 but were not clinically meaningful, this lead to the decision to use a RD of 1.0% and Wald p-value<0.05.

Appendix B: Tables

Table 3: HO-CDI risk difference in the HIV CCS category from the 2009 HCUP NIS database.

	Total (%)		
Discharges in Category	45099 (0.22*)		
In Category with HO-CDI	1451 (3.21**)		
Risk difference = excess discharges/1,000 within the stratum, weighted national estimate.			
	RD	**95% CI**	**p-value**
18-40 yrs, 0-4 Chronic Conditions, Transfer No, 3-4 Days LOS	11.1	(8.5, 13.7)	<0.0001
18-40 yrs, 0-4 Chronic Conditions, Transfer No, >4 Days LOS	15.1	(12.1, 18.0)	<0.0001
18-40 yrs, 0-4 Chronic Conditions, Transfer Yes, 3-4 Days LOS	45.9	(34.7, 57.1)	<0.0001
18-40 yrs, 0-4 Chronic Conditions, Transfer Yes, >4 Days LOS	49.9	(38.8, 61.0)	<0.0001
18-40 yrs, >4 Chronic Conditions, Transfer No, 3-4 Days LOS	16.3	(12.2, 20.4)	<0.0001
18-40 yrs, >4 Chronic Conditions, Transfer No, >4 Days LOS	20.3	(16.8, 23.7)	<0.0001
18-40 yrs, >4 Chronic Conditions, Transfer Yes, 3-4 Days LOS	51.1	(39.7, 62.5)	<0.0001
18-40 yrs, >4 Chronic Conditions, Transfer Yes, >4 Days LOS	55.1	(44.1, 66.1)	<0.0001
41-64 yrs, 0-4 Chronic Conditions, Transfer No, 3-4 Days LOS	15.2	(12.4, 18.0)	<0.0001
41-64 yrs, 0-4 Chronic Conditions, Transfer No, >4 Days LOS	19.2	(16.2, 22.2)	<0.0001
41-64 yrs, 0-4 Chronic Conditions, Transfer Yes, 3-4 Days LOS	50.0	(38.8, 61.3)	<0.0001
41-64 yrs, 0-4 Chronic Conditions, Transfer Yes, >4 Days LOS	54.0	(42.9, 65.1)	<0.0001
41-64 yrs, >4 Chronic Conditions, Transfer No, 3-4 Days LOS	20.4	(16.8, 24.1)	<0.0001
41-64 yrs, >4 Chronic Conditions, Transfer No, >4 Days LOS	24.4	(21.6, 27.2)	<0.0001
41-64 yrs, >4 Chronic Conditions, Transfer Yes, 3-4 Days LOS	55.2	(44.0, 66.5)	<0.0001
41-64 yrs, >4 Chronic Conditions, Transfer yes, >4 Days LOS	59.2	(48.4, 70.0)	<0.0001
>64 yrs, 0-4 Chronic Conditions, Transfer No, 3-4 Days LOS	34.6	(21.7, 47.6)	<0.0001
>64 yrs, 0-4 Chronic Conditions, Transfer No, >4 Days LOS	38.6	(25.9, 51.4)	<0.0001
>64 yrs, 0-4 Chronic Conditions, Transfer Yes, 3-4 Days LOS	69.5	(52.8, 86.1)	<0.0001
>64 yrs, 0-4 Chronic Conditions, Transfer Yes, >4 Days LOS	73.4	(57.0, 89.8)	<0.0001
>64 yrs, >4 Chronic Conditions, Transfer No, 3-4 Days LOS	39.8	(26.8, 52.9)	<0.0001
>64 yrs, >4 Chronic Conditions, Transfer No, >4 Days LOS	43.8	(31.2, 56.4)	<0.0001
>64 yrs, >4 Chronic Conditions, Transfer Yes, 3-4 Days LOS	74.6	(58.0, 91.3)	<0.0001
>64 yrs, >4 Chronic Conditions, Transfer Yes, >4 Days LOS	78.6	(62.5, 94.8)	<0.0001
Crude	22.0	(19.0, 18.4)	

* % of total discharges in sample with exclusions

**% of discharges in category with HO-CDI

Table 4: HO-CDI risk difference in the septicemia CCS category from the 2009 HCUP NIS database.

	Total (%)		
Discharges in Category	693867 (3.43*)		
In Category with HO-CDI	42098 (6.07**)		
Risk difference = excess discharges/1,000 within the stratum, weighted national estimate.			
	RD	**95% CI**	**p-value**
18-40 yrs, 0-4 Chronic Conditions, Transfer No, >4 Days LOS	34.2	(32.8, 35.6)	<0.0001
18-40 yrs, 0-4 Chronic Conditions, Transfer Yes, 3-4 Days LOS	28.4	(26.1, 30.8)	<0.0001
18-40 yrs, 0-4 Chronic Conditions, Transfer Yes, >4 Days LOS	56.3	(54.0, 58.7)	<0.0001
18-40 yrs, >4 Chronic Conditions, Transfer No, 3-4 Days LOS	15.7	(14.3, 17.1)	<0.0001
18-40 yrs, >4 Chronic Conditions, Transfer No, >4 Days LOS	43.6	(42.1, 45.1)	<0.0001
18-40 yrs, >4 Chronic Conditions, Transfer Yes, 3-4 Days LOS	37.9	(35.4, 40.3)	<0.0001
18-40 yrs, >4 Chronic Conditions, Transfer Yes, >4 Days LOS	65.8	(63.3, 68.2)	<0.0001
41-64 yrs, 0-4 Chronic Conditions, Transfer No, 3-4 Days LOS	11.6	(10.7, 12.6)	<0.0001
41-64 yrs, 0-4 Chronic Conditions, Transfer No, >4 Days LOS	39.5	(38.4, 40.7)	<0.0001
41-64 yrs, 0-4 Chronic Conditions, Transfer Yes, 3-4 Days LOS	33.8	(31.5, 36.0)	<0.0001
41-64 yrs, 0-4 Chronic Conditions, Transfer Yes, >4 Days LOS	61.7	(59.5, 63.9)	<0.0001
41-64 yrs, >4 Chronic Conditions, Transfer No, 3-4 Days LOS	21.1	(19.9, 22.2)	<0.0001
41-64 yrs, >4 Chronic Conditions, Transfer No, >4 Days LOS	49.0	(47.9, 50.0)	<0.0001
41-64 yrs, >4 Chronic Conditions, Transfer Yes, 3-4 Days LOS	43.2	(40.9, 45.5)	<0.0001
41-64 yrs, >4 Chronic Conditions, Transfer yes, >4 Days LOS	71.1	(69.0, 73.2)	<0.0001
>64 yrs, 0-4 Chronic Conditions, Transfer No, 3-4 Days LOS	27.0	(26.0, 28.1)	<0.0001
>64 yrs, 0-4 Chronic Conditions, Transfer No, >4 Days LOS	54.9	(53.8, 56.0)	<0.0001
>64 yrs, 0-4 Chronic Conditions, Transfer Yes, 3-4 Days LOS	49.2	(46.9, 51.4)	<0.0001
>64 yrs, 0-4 Chronic Conditions, Transfer Yes, >4 Days LOS	77.1	(74.9, 79.2)	<0.0001
>64 yrs, >4 Chronic Conditions, Transfer No, 3-4 Days LOS	36.4	(35.3, 37.5)	<0.0001
>64 yrs, >4 Chronic Conditions, Transfer No, >4 Days LOS	64.3	(63.4, 65.2)	<0.0001
>64 yrs, >4 Chronic Conditions, Transfer Yes, 3-4 Days LOS	58.6	(56.3, 60.8)	<0.0001
>64 yrs, >4 Chronic Conditions, Transfer Yes, >4 Days LOS	86.5	(84.5, 88.5)	<0.0001
Crude	52.3	(51.0, 53.5)	

* % of total discharges in sample with exclusions

**% of discharges in category with HO-CDI

Table 5: HO-CDI risk difference in the hematopoietic neoplasm CCS category from the 2009 HCUP NIS database.

	Total (%)		
Discharges in Category	86402 (0.43*)		
In Category with HO-CDI	3081 (3.57**)		
Risk difference = excess discharges/1,000 within the stratum, weighted national estimate.			
	RD	**95% CI**	**p-value**
18-40 yrs, 0-4 Chronic Conditions, Transfer No, 3-4 Days LOS	15.9	(11.9, 19.8)	<0.0001
18-40 yrs, 0-4 Chronic Conditions, Transfer No, >4 Days LOS	32.3	(28.4, 36.1)	<0.0001
18-40 yrs, 0-4 Chronic Conditions, Transfer Yes, >4 Days LOS	25.2	(19.6, 30.8)	<0.0001
18-40 yrs, >4 Chronic Conditions, Transfer No, 3-4 Days LOS	21.5	(16.9, 26.1)	<0.0001
18-40 yrs, >4 Chronic Conditions, Transfer No, >4 Days LOS	37.9	(33.9, 41.9)	<0.0001
18-40 yrs, >4 Chronic Conditions, Transfer Yes, 3-4 Days LOS	14.4	(8.2, 20.6)	<0.0001
18-40 yrs, >4 Chronic Conditions, Transfer Yes, >4 Days LOS	30.8	(25.3, 36.3)	<0.0001
41-64 yrs, 0-4 Chronic Conditions, Transfer No, 3-4 Days LOS	10.7	(8.3, 13.2)	<0.0001
41-64 yrs, 0-4 Chronic Conditions, Transfer No, >4 Days LOS	27.1	(24.6, 29.6)	<0.0001
41-64 yrs, 0-4 Chronic Conditions, Transfer Yes, >4 Days LOS	20.0	(15.1, 24.9)	<0.0001
41-64 yrs, >4 Chronic Conditions, Transfer No, 3-4 Days LOS	16.4	(13.3, 19.4)	<0.0001
41-64 yrs, >4 Chronic Conditions, Transfer No, >4 Days LOS	32.8	(30.5, 35.0)	<0.0001
41-64 yrs, >4 Chronic Conditions, Transfer yes, >4 Days LOS	25.6	(21.1, 30.2)	<0.0001
>64 yrs, 0-4 Chronic Conditions, Transfer No, >4 Days LOS	19.1	(16.8, 21.5)	<0.0001
>64 yrs, 0-4 Chronic Conditions, Transfer Yes, >4 Days LOS	12.0	(7.2, 16.9)	<0.0001
>64 yrs, >4 Chronic Conditions, Transfer No, >4 Days LOS	24.8	(22.7, 26.8)	<0.0001
>64 yrs, >4 Chronic Conditions, Transfer Yes, >4 Days LOS	17.7	(13.2, 22.2)	<0.0001
Crude	25.6	(22.8, 28.4)	

* % of total discharges in sample with exclusions

**% of discharges in category with HO-CDI

Table 6: HO-CDI risk difference in the aspiration pneumonitis; food/vomitus CCS category from the 2009 HCUP NIS database.

	Total (%)		
Discharges in Category	159577 (0.49*)		
In Category with HO-CDI	4796 (3.01**)		
Risk difference = excess discharges/1,000 within the stratum, weighted national estimate.			
	RD	**95% CI**	**p-value**
18-40 yrs, 0-4 Chronic Conditions, Transfer No, >4 Days LOS	13.1	(11.0, 15.2)	<0.0001
18-40 yrs, 0-4 Chronic Conditions, Transfer Yes, >4 Days LOS	18.3	(15.1, 21.6)	<0.0001
18-40 yrs, >4 Chronic Conditions, Transfer No, >4 Days LOS	10.6	(8.1, 13.0)	<0.0001
18-40 yrs, >4 Chronic Conditions, Transfer Yes, >4 Days LOS	15.8	(12.4, 19.3)	<0.0001
41-64 yrs, 0-4 Chronic Conditions, Transfer No, >4 Days LOS	18.9	(16.7, 21.0)	<0.0001
41-64 yrs, 0-4 Chronic Conditions, Transfer Yes, 3-4 Days LOS	12.5	(9.1, 15.8)	<0.0001
41-64 yrs, 0-4 Chronic Conditions, Transfer Yes, >4 Days LOS	24.1	(20.8, 27.4)	<0.0001
41-64 yrs, >4 Chronic Conditions, Transfer No, >4 Days LOS	16.4	(14.5, 18.2)	<0.0001
41-64 yrs, >4 Chronic Conditions, Transfer Yes, 3-4 Days LOS	10.0	(6.8, 13.2)	<0.0001
41-64 yrs, >4 Chronic Conditions, Transfer yes, >4 Days LOS	21.6	(18.5, 24.7)	<0.0001
>64 yrs, 0-4 Chronic Conditions, Transfer No, 3-4 Days LOS	11.5	(10.0, 13.0)	<0.0001
>64 yrs, 0-4 Chronic Conditions, Transfer No, >4 Days LOS	23.1	(21.5, 24.8)	<0.0001
>64 yrs, 0-4 Chronic Conditions, Transfer Yes, 3-4 Days LOS	16.7	(13.7, 19.8)	<0.0001
>64 yrs, 0-4 Chronic Conditions, Transfer Yes, >4 Days LOS	28.4	(25.5, 31.3)	<0.0001
>64 yrs, >4 Chronic Conditions, Transfer No, >4 Days LOS	20.6	(19.4, 21.9)	<0.0001
>64 yrs, >4 Chronic Conditions, Transfer Yes, 3-4 Days LOS	14.2	(11.3, 17.1)	<0.0001
>64 yrs, >4 Chronic Conditions, Transfer Yes, >4 Days LOS	25.9	(23.2, 28.6)	<0.0001
Crude	20.0	(18.1, 20.9)	

* % of total discharges in sample with exclusions

**% of discharges in category with HO-CDI

Table 7: HO-CDI risk difference in the complications of surgical procedures or medical care CCS category from the 2009 HCUP NIS database.

	Total (%)		
Discharges in Category	347203 (1.72*)		
In Category with HO-CDI	5978 (1.72**)		
Risk difference = excess discharges/1,000 within the stratum, weighted national estimate.			
	RD	**95% CI**	**p-value**
18-40 yrs, 0-4 Chronic Conditions, Transfer Yes, 3-4 Days LOS	15.0	(12.8, 17.1)	<0.0001
18-40 yrs, 0-4 Chronic Conditions, Transfer Yes, >4 Days LOS	17.0	(14.8, 19.1)	<0.0001
18-40 yrs, >4 Chronic Conditions, Transfer Yes, 3-4 Days LOS	16.6	(14.3, 18.9)	<0.0001
18-40 yrs, >4 Chronic Conditions, Transfer Yes, >4 Days LOS	18.6	(16.5, 20.8)	<0.0001
41-64 yrs, 0-4 Chronic Conditions, Transfer Yes, 3-4 Days LOS	16.0	(13.9, 18.1)	<0.0001
41-64 yrs, 0-4 Chronic Conditions, Transfer Yes, >4 Days LOS	18.0	(15.9, 20.2)	<0.0001
41-64 yrs, >4 Chronic Conditions, Transfer Yes, 3-4 Days LOS	17.6	(15.4, 19.9)	<0.0001
41-64 yrs, >4 Chronic Conditions, Transfer yes, >4 Days LOS	19.7	(17.5, 21.8)	<0.0001
>64 yrs, 0-4 Chronic Conditions, Transfer Yes, 3-4 Days LOS	20.3	(18.1, 22.5)	<0.0001
>64 yrs, 0-4 Chronic Conditions, Transfer Yes, >4 Days LOS	22.3	(20.2, 24.5)	<0.0001
>64 yrs, >4 Chronic Conditions, Transfer Yes, 3-4 Days LOS	21.9	(19.7, 24.2)	<0.0001
>64 yrs, >4 Chronic Conditions, Transfer Yes, >4 Days LOS	24.0	(21.9, 26.0)	<0.0001
Crude	7.1	(6.2, 8.1)	

* % of total discharges in sample with exclusions

**% of discharges in category with HO-CDI

Table 8: HO-CDI risk difference in the acute and unspecified renal failure CCS category from the 2009 HCUP NIS database.

	Total (%)		
Discharges in Category	297102 (1.47*)		
In Category with HO-CDI	6255 (2.11**)		
Risk difference = excess discharges/1,000 within the stratum, weighted national estimate.			
	RD	**95% CI**	**p-value**
18-40 yrs, 0-4 Chronic Conditions, Transfer Yes, >4 Days LOS	12.7	(10.0, 15.4)	<0.0001
18-40 yrs, >4 Chronic Conditions, Transfer Yes, >4 Days LOS	10.8	(8.3, 13.4)	<0.0001
41-64 yrs, 0-4 Chronic Conditions, Transfer No, >4 Days LOS	11.6	(10.4, 12.8)	<0.0001
41-64 yrs, 0-4 Chronic Conditions, Transfer Yes, >4 Days LOS	14.6	(12.2, 17.0)	<0.0001
41-64 yrs, >4 Chronic Conditions, Transfer yes, >4 Days LOS	12.7	(10.4, 15.0)	<0.0001
>64 yrs, 0-4 Chronic Conditions, Transfer No, >4 Days LOS	16.2	(15.1, 17.3)	<0.0001
>64 yrs, 0-4 Chronic Conditions, Transfer Yes, 3-4 Days LOS	12.2	(9.8, 14.7)	<0.0001
>64 yrs, 0-4 Chronic Conditions, Transfer Yes, >4 Days LOS	19.1	(16.7, 21.4)	<0.0001
>64 yrs, >4 Chronic Conditions, Transfer No, >4 Days LOS	14.3	(13.4, 15.2)	<0.0001
>64 yrs, >4 Chronic Conditions, Transfer Yes, 3-4 Days LOS	10.4	(8.0, 12.7)	<0.0001
>64 yrs, >4 Chronic Conditions, Transfer Yes, >4 Days LOS	17.2	(15.0, 19.5)	<0.0001
Crude	11.0	(9.8, 12.2)	

* % of total discharges in sample with exclusions

**% of discharges in category with HO-CDI

Table 9: HO-CDI risk difference in the complication of device; implant or graft CCS category from the 2009 HCUP NIS database.

	Total (%)		
Discharges in Category	158353 (0.78*)		
In Category with HO-CDI	7745 (1.69**)		
Risk difference = excess discharges/1,000 within the stratum, weighted national estimate.			
	RD	**95% CI**	**p-value**
18-40 yrs, 0-4 Chronic Conditions, Transfer Yes, >4 Days LOS	14.6	(12.7, 16.5)	<0.0001
18-40 yrs, >4 Chronic Conditions, Transfer No, >4 Days LOS	10.0	(9.0, 10.9)	<0.0001
18-40 yrs, >4 Chronic Conditions, Transfer Yes, >4 Days LOS	15.7	(13.8, 17.6)	<0.0001
41-64 yrs, 0-4 Chronic Conditions, Transfer Yes, >4 Days LOS	13.7	(11.9, 15.6)	<0.0001
41-64 yrs, >4 Chronic Conditions, Transfer yes, >4 Days LOS	14.9	(13.1, 16.7)	<0.0001
>64 yrs, 0-4 Chronic Conditions, Transfer Yes, >4 Days LOS	14.8	(13.0, 16.7)	<0.0001
>64 yrs, >4 Chronic Conditions, Transfer No, >4 Days LOS	10.2	(9.6, 10.9)	<0.0001
>64 yrs, >4 Chronic Conditions, Transfer Yes, >4 Days LOS	16.0	(14.2, 17.8)	<0.0001
Crude	6.9	(6.0, 7.7)	

* % of total discharges in sample with exclusions

**% of discharges in category with HO-CDI

Table 10: HO-CDI risk difference in the urinary tract infections CCS category from the 2009 HCUP NIS database.

	Total (%)		
Discharges in Category	378017 (1.87)		
In Category with HO-CDI	5002 (1.32)		
Risk difference = excess discharges/1,000 within the stratum, weighted national estimate.			
	RD	**95% CI**	**p-value**
41-64 yrs, >4 Chronic Conditions, Transfer yes, >4 Days LOS	10.6	(8.4, 12.8)	<0.0001
>64 yrs, 0-4 Chronic Conditions, Transfer Yes, >4 Days LOS	10.7	(8.5, 12.8)	<0.0001
>64 yrs, >4 Chronic Conditions, Transfer Yes, >4 Days LOS	11.5	(9.4, 13.6)	<0.0001
Crude	3.1	(2.3, 0.039)	

* % of total discharges in sample with exclusions

**% of discharges in category with HO-CDI

Table 11: HO-CDI risk difference in the gangrene CCS category from the 2009 HCUP NIS database.

	Total (%)		
Discharges in Category	31469 (0.16*)		
In Category with HO-CDI	765 (2.43**)		
Risk difference = excess discharges/1,000 within the stratum, weighted national estimate.			
	RD	**95% CI**	**p-value**
18-40 yrs, Transfer Yes, >4 Days LOS	19.8	(2.2, 37.4)	0.0278
41-64 yrs, Transfer Yes, >4 Days LOS	14.7	(7.2, 22.1)	0.0001
>64 yrs, Transfer No, >4 Days LOS	13.7	(11.4, 15.9)	<0.0001
>64 yrs, Transfer Yes, 3-4 Days LOS	14.6	(7.3, 21.9)	<0.0001
>64 yrs, Transfer Yes, >4 Days LOS	21.2	(14.3, 28.2)	<0.0001
Crude	14.1	(10.3, 18.0)	

* % of total discharges in sample with exclusions

**% of discharges in category with HO-CDI

Table 12: HO-CDI risk difference in the viral infection CCS category from the 2009 HCUP NIS database.

	Total (%)		
Discharges in Category	28745 (0.14)		
In Category with HO-CDI	219 (0.76)		
Risk difference = excess discharges/1,000 within the stratum, weighted national estimate.			
	RD	**95% CI**	**p-value**
18-40 yrs, Transfer Yes, 3-4 Days LOS	14.4	(4.9, 24.0)	0.003
18-40 yrs, Transfer Yes, >4 Days LOS	10.1	(0.7, 19.4)	0.0342
41-64 yrs, Transfer Yes, 3-4 Days LOS	15.8	(6.2, 25.4)	0.0013
41-64 yrs, Transfer Yes, >4 Days LOS	11.4	(2.1, 20.7)	0.0168
>64 yrs, Transfer Yes, 3-4 Days LOS	12.5	(3.1, 22.0)	0.0093
Crude	2.6	(0.3, 4.8)	

* % of total discharges in sample with exclusions

**% of discharges in category with HO-CDI

Table 13: HO-CDI risk difference in the diabetes mellitus with complications CCS category from the 2009 HCUP NIS database.

	Total (%)		
Discharges in Category	326732 (1.62)		
In Category with HO-CDI	2360 (1.0)		
Risk difference = excess discharges/1,000 within the stratum, weighted national estimate.			
	RD	**95% CI**	**p-value**
>64 yrs, Transfer Yes, 3-4 Days LOS	12.4	(9.6, 15.2)	<0.0001
>64 yrs, Transfer Yes, >4 Days LOS	11.1	(8.4, 13.9)	<0.0001
Crude	-0.2	(-1.0, 0.6)	

* % of total discharges in sample with exclusions

**% of discharges in category with HO-CDI

Table 14: HO-CDI risk difference in the pneumonia CCS category from the 2009 HCUP NIS database.

	Total (%)		
Discharges in Category	784609 (3.88)		
In Category with HO-CDI	10047 (1.28)		
Risk difference = excess discharges/1,000 within the stratum, weighted national estimate.			
	RD	**95% CI**	**p-value**
>64 yrs, Transfer Yes, >4 Days LOS	10.7	(9.2, 12.2)	<0.0001
Crude	2.7	(2.1, 3.3)	

* % of total discharges in sample with exclusions

**% of discharges in category with HO-CDI

Table 15: HO-CDI risk difference in the peritonitis and intestinal abscess CCS category from the 2009 HCUP NIS database.

	Total (%)		
Discharges in Category	24372 (0.12)		
In Category with HO-CDI	594 (2.44)		
Risk difference = excess discharges/1,000 within the stratum, weighted national estimate.			
	RD	**95% CI**	**p-value**
0-4 Chronic Conditions, Transfer No	34.2	(24.3, 44.1)	<0.0001
>4 Chronic Conditions, Transfer No	14.3	(11.2, 17.3)	<0.0001
>4 Chronic Conditions, Transfer Yes	44.9	(35.0, 54.8)	<0.0001
Crude	14.2	(9.9, 18.5)	

* % of total discharges in sample with exclusions

**% of discharges in category with HO-CDI

Table 16: HO-CDI risk difference in the regional enteritis and ulcerative colitis CCS category from the 2009 HCUP NIS database.

	Total (%)		
Discharges in Category	71855 (0.36*)		
In Category with HO-CDI	1664 (2.32**)		
Risk difference = excess discharges/1,000 within the stratum, weighted national estimate.			
	RD	**95% CI**	**p-value**
0-4 Chronic Conditions, Transfer No	11.4	(10.3, 12.6)	<0.0001
0-4 Chronic Conditions, Transfer Yes	23.4	(16.1, 30.7)	<0.0001
>4 Chronic Conditions, Transfer No	16.6	(14.4, 18.8)	<0.0001
>4 Chronic Conditions, Transfer Yes	28.6	(21.2, 36.0)	<0.0001
Crude	13.0	(10.5, 15.5)	

* % of total discharges in sample with exclusions

**% of discharges in category with HO-CDI

Table 17: HO-CDI risk difference in the respiratory failure; insufficiency; arrest CCS category from the 2009 HCUP NIS database.

	Total (%)		
Discharges in Category	307244 (1.52*)		
In Category with HO-CDI	8982 (3.06**)		
Risk difference = excess discharges/1,000 within the stratum, weighted national estimate.			
	RD	**95% CI**	**p-value**
Transfer Yes, 3-4 Days LOS	41.6	(39.3, 43.9)	<0.0001
Transfer Yes, >4 Days LOS	49.9	(47.8, 52.1)	<0.0001
Crude	19.3	(18.0, 20.7)	

* % of total discharges in sample with exclusions

**% of discharges in category with HO-CDI

Table 18: HO-CDI risk difference in the diseases of white blood cells (excluding leukocytosis) CCS category from the 2009 HCUP NIS database.

	Total (%)		
Discharges in Category	40123 (1.01*)		
In Category with HO-CDI	1153(2.87**)		
Risk difference = excess discharges/1,000 within the stratum, weighted national estimate.			
	RD	**95% CI**	**p-value**
0-4 Chronic Conditions, >4 Days LOS	19.9	(16.9, 22.9)	<0.0001
>4 Chronic Conditions, 3-4 Days LOS	13.7	(11.3, 16.2)	<0.0001
>4 Chronic Conditions, >4 Days LOS	25.9	(23.1, 28.7)	<0.0001
Crude	18.6	(14.9, 22.3)	

* % of total discharges in sample with exclusions

**% of discharges in category with HO-CDI

Table 19: HO-CDI risk difference in the cystic fibrosis CCS category from the 2009 HCUP NIS database.

	Total (%)		
Discharges in Category	6968 (0.04)		
In Category with HO-CDI	142 (2.04)		
Risk difference = excess discharges/1,000 within the stratum, weighted national estimate.			
	RD	**95% CI**	**p-value**
Transfer Yes	67.0	(28.8, 105.2)	0.06
Crude	10.3	(2.7, 17.8)	

* % of total discharges in sample with exclusions

**% of discharges in category with HO-CDI

Table 20: HO-CDI risk difference in the mycoses CCS category from the 2009 HCUP NIS database.

	Total (%)		
Discharges in Category	22502 (0.11*)		
In Category with HO-CDI	771 (3.43**)		
Risk difference = excess discharges/1,000 within the stratum, weighted national estimate.			
	RD	**95% CI**	**p-value**
Transfer No	12.4	(10.2, 14.6)	<0.0001
Transfer Yes	65.4	(54.3, 76.6)	<0.0001
Crude	24.1	(18.8, 29.4)	

* % of total discharges in sample with exclusions

**% of discharges in category with HO-CDI

Table 21: HO-CDI risk difference in the chronic ulcer of the skin CCS category from the 2009 HCUP NIS database.

	Total (%)		
Discharges in Category	60663 (0.30*)		
In Category with HO-CDI	1636 (2.70**)		
Risk difference = excess discharges/1,000 within the stratum, weighted national estimate.			
	RD	**95% CI**	**p-value**
Transfer Yes	48.6	(43.6, 53.7)	<0.0001
Crude	16.8	(13.8, 19.8)	

* % of total discharges in sample with exclusions

**% of discharges in category with HO-CDI

Table 22: HO-CDI risk difference in the other inflammatory condition of skin CCS category from the 2009 HCUP NIS database.

	Total (%)		
Discharges in Category	6564 (0.03)		
In Category with HO-CDI	94 (1.44)%		
Risk difference = excess discharges/1,000 within the stratum, weighted national estimate.			
	RD	**95% CI**	**p-value**
Transfer Yes	38.1	(21.2, 55.0)	<0.0001
Crude	4.2	(-2.4, 10.8)	

* % of total discharges in sample with exclusions

**% of discharges in category with HO-CDI

Table 23: HO-CDI risk difference in the bacterial infection; unspecified site CCS category from the 2009 HCUP NIS database.

	Total (%)		
Discharges in Category	5434 (0.02*)		
In Category with HO-CDI	80 (1.46**)		
Risk difference = excess discharges/1,000 within the stratum, weighted national estimate.			
	RD	**95% CI**	**p-value**
Transfer Yes	37.0	(16.0, 57.9)	<0.0001
Crude	4.4	(-2.7, 11.6)	

* % of total discharges in sample with exclusions

**% of discharges in category with HO-CDI

Table 24: HO-CDI risk difference in the infective arthritis and osteomyelitis CCS category from the 2009 HCUP NIS database.

	Total (%)		
Discharges in Category	67271 (0.33*)		
In Category with HO-CDI	1261 (1.87**)		
Risk difference = excess discharges/1,000 within the stratum, weighted national estimate.			
	RD	**95% CI**	**p-value**
Transfer Yes	30.8	(25.8, 35.7)	<0.0001
Crude	8.6	(6.3, 10.9)	

* % of total discharges in sample with exclusions

**% of discharges in category with HO-CDI

Table 25: HO-CDI risk difference in the other aftercare CCS category from the 2009 HCUP NIS database.

	Total (%)		
Discharges in Category	25347 (0.13*)		
In Category with HO-CDI	700 (2.76**)		
Risk difference = excess discharges/1,000 within the stratum, weighted national estimate.			
	RD	**95% CI**	**p-value**
Transfer Yes	19.2	(15.2, 23.1)	<0.0001
Crude	17.4	(12.7, 22.2)	

* % of total discharges in sample with exclusions

**% of discharges in category with HO-CDI

Appendix C: Emory IRB Exemption Letter

EMORY UNIVERSITY | Institutional Review Board

August 19, 2011

RE: Determination: No IRB Review Required
Title: Comorbidities associated with increased risk of hospital acquired Clostridium Difficile infection (CDI).
PI: Laura Edison

Dear Ms. Edison:

Thank you for requesting a determination from our office about the above-referenced project. Based on our review of the materials you provided, we have determined that it does not require IRB review because it does not meet the definition(s) of "research" with "human subjects" or the definition of "clinical investigation" as set forth in Emory policies and procedures and federal rules, if applicable. Specifically, in this project, you will be conducting data analysis of publicly available and de identified data sets.

This determination could be affected by substantive changes in the study design, subject populations, or identifiability of data. If the project changes in any substantive way, please contact our office for clarification.

Thank you for consulting the IRB.

Sincerely,

Andrea Goosen, MPH
Research Protocol Analyst
This letter has been digitally signed

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