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Comparison of Risk Factors for Clostridium Difficile Infection Among Community Associated Cases and Healthcare Facility Associated Cases, September 2009- April 2011

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Abstract

Background

The incidence of *Clostridium difficile* infection (CDI) has been increasing in communities and healthcare associated settings in the last 25-50 years. *Clostridium difficile* is a Gram-positive bacteria found in the large bowel or colon that causes mild to severe intestinal conditions and sometimes death. The primary risk factors for development of CDI include healthcare exposure and recent antimicrobial use. The purpose of this study is to compare risk factors associated with CDI occurring in the Community to those associated with Healthcare Facility Associated CDI in the metro Atlanta population from September 1, 2009 – April 30, 2011.

Methods

Patients were identified through C. difficile surveillance program of the Georgia Emerging Infections Program (EIP). Prospective, population based, laboratory based surveillance for all positive C. difficile cases in the Georgia Health District 3 (HD3). Due to high volume of positive CDI, a stratified random 1:3 sampling scheme is used and cases are stratified by age and gender. Identified sampled cases undergo a retrospective Case Report Form completion and are classified in to three classifications: Community Associated (CA), Community Onset-Healthcare Facility Associated (CO-HCFA), and Healthcare Facility Onset (HCFO). An additional 1:10 sampling occurs for HCFO cases. Due to the sampling scheme, for this analysis CO-HCFA and HCFO cases were combined to make a Healthcare Facility Associated (HCFA) classification. Using SAS, a logistic regression analysis was performed to compare the associated risks between CA and HCFA classifications.

Results

The rate of CDI in the HD3 counties in Georgia is 84 per 100,000. The median age of infection is 63 and the age range in this study is 1 to 102 years old. CA cases represented 38% of the sampled population. CDI cases 65 and older were more likely to have a Healthcare association compared to CA-CDI cases ($p < 0.01$). HFCA-CDI cases were more likely to be exposed to the following antibiotics Cephalosporins, Metronidazole, and Vancomycin (all p values <0.01). In addition, HCFA-CDI cases were more likely to have the following underlying conditions Cardiovascular, Neurological, Tumors, Other Chronic Conditions, and Diabetes (all p values <0.0001) compared to CA-CDI Cases. HCFA-CDI cases had individuals that had two or more underlying conditions and had more individuals that were taking two or more antibiotics 14 days prior to a positive stool culture compared to CA-CDI cases (both chi square <0.0001).

Conclusion

CDI is prevalent in the metro Atlanta population and this study identifies the risk factors that are associated with Community Associated Cases and Healthcare Facility Associated Cases. Based on this population sample, antibiotics use and underlying conditions appear to be significant factors in HCFA-CDI cases compared to CA-CDI cases. This study supports literature about CDI and antimicrobial use and looks further in to the role underlying conditions play as a risk factor for HCFA-CDI cases.

KEY WORDS

Public Health, Clostridium difficile, healthcare associated infections, community associated infections, antibiotics, underlying conditions, age, Atlanta

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by

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CHAPTER I

Introduction

The incidence of *Clostridium difficile* infection (CDI) has been increasing in communities and healthcare associated settings in the last 25-50 years. *Clostridium difficile* is a Gram-positive bacteria found in the large bowel or colon that causes mild to severe intestinal conditions and sometimes death. Exposures to healthcare settings and antibiotic use have most often been cited as risk factors for CDI. In recent years, CDI has become more frequent, more severe, and more difficult to treat. Each year tens of thousands of people in the United States get sick from *C. difficile*, including some otherwise healthy people who are not hospitalized or taking antibiotics (Kyne, Hamel, Polavaram, & Kelly, 2002). Mild illness caused by CDI may resolve by discontinuing antibiotics. Severe symptoms require treatment with an antibiotic targeting *C. difficile* (Owens, Donskey, Gaynes, Loo, & Muto, 2008). The most common symptoms of mild to moderate *C. difficile* infection are watery diarrhea occurring three or more times a day for two or more days and mild abdominal cramping and tenderness (McDonald et al., 2005). More severe CDI can lead to colitis, pseudomembranous colitis, and death (Kyne et al., 2002).

Pathogenic strains of *C. difficile* produce two distinct toxins. Toxin A is an enterotoxin, and toxin B is a cytotoxin. Both are high-molecular weight proteins capable of binding to specific receptors on the intestinal mucosal cells. (Nusrat et al., 2001). CDI occurs from a disturbance of the normal bacterial flora of the colon, acquisition of *C. difficile*, and the release of toxins that cause mucosal inflammation and damage (Gronczewski et al., 2012). Antibiotic therapy is the key factor that alters the colonic flora (Owens et al., 2008). Acquisition occurs via the fecal – oral route (Jarvis, 1996) leading to either asymptomatic colonization or clinical disease. *C. difficile* forms heat-resistant spores that can persist in the environment for several

months to years. The hand picks up the bacteria from a surface that has minute amounts of fecal contamination and the bacterium finds its way to the mouth via touch, food, etc. However, unlike many other bacteria, *C. difficile* spores can survive in both hot and cold temperatures and is resistant to the action of many chemicals, including the alcohol-based hand sanitizers which makes killing this bacteria difficult (McDonald, 2005). Normal gut flora resists colonization and overgrowth with *C. difficile*. Transmission of *C. difficile* occurs primarily in healthcare facilities, where the environmental contaminations by *C. difficile* spores and exposure to antimicrobial drugs are common. Antibiotic use suppresses the normal flora allowing proliferation of *C. difficile* (Gronczewski et al., 2012; McDonald, 2005). However, *C. difficile* is no longer limited to healthcare environments and is increasing in the community in both healthcare and non-healthcare exposed populations (Henrich, Krakower, Bitton, & Yokoe, 2009).

The primary risk factors for development of *C. difficile* include healthcare exposure and recent antimicrobial use. Additional risk factors for acquisition include age greater than 65 and severe underlying illness. Healthcare exposure can occur from cross contamination situations. As *C. difficile* spores are dispersed by fecal matter, patient, staff, and environmental hygiene is vital (Jarvis, 1996). Staff cannot always avoid coming in contact with *C. difficile* spores and the main agent of transmission is often hands. In addition, another vehicle for transmission is hospital, long term care facility, or nursing home toilets. Environmental cleaning is important in healthcare facilities and the use of special disinfectants are needed because *C. difficile* spores are hardy and can survive for several months and are not killed by many cleaning agents alone (McDonald, 2005).

For most healthy people, *C. difficile* does not pose a health risk. The elderly, those with other illness, or taking antibiotics are at greater risk of infection. Using antibiotics increases the

chance of developing *C. difficile* infection. Antibiotics alter the normal levels of protective bacteria found in the intestines and colon. When the balance of the normal flora in our intestines and colon has been disrupted, *C. difficile* bacteria have the chance to thrive and produce toxins (Warny et al., 2005). These toxins cause inflammation of the bowel and cause mild to severe diarrhea. Age is also a risk factor for the development of disease. People ages 65 years and older are 10 times more likely to become infected with *C. difficile* compared to those less than 65 (Lambert, Dyck, Thompson, & Hammond, 2009).

C. difficile is very common in the Atlanta, Georgia metropolitan population based upon a population-based surveillance system established by the Georgia Emerging Infections Program in 2009. *C. difficile* cases are identified through toxin positive stool cultures, identified in hospital or reference laboratories. Eligibility requirements include being a resident of Health District 3 and being over 1 year of age on collection date. Population-based surveillance allows a comparison of Community Associated and Healthcare Facility Associated cases of CDI. Although risk factors for healthcare associated infection have been established, risk factors for community onset disease are less well understood. Active, population-based surveillance for CDI provides longitudinal study of the incidence rates of CDI Unlike many other studies of CDI, prospective, population-based surveillance is not restricted to outbreak investigation but rather, all reported cases between September 2009 and April 2011 occurring in Atlanta Health District 3 can be analyzed.

CDI surveillance data collected from September 1, 2009 to April 30, 2011 from 8 counties in metropolitan Atlanta, Georgia (Clayton, Cobb, Dekalb, Douglas, Gwinnett, Fulton, Newton, and Rockdale) were utilized for this project known as Health District 3 (HD3). An analysis was conducted to compare risk factors associated with *C. difficile* infections occurring in

the Community to those associated with Healthcare Facility Associated CDI Cases. The objectives of this investigation were to examine the antibiotic use and underlying conditions associated with CDI. In addition, age over 65 is a risk factor, so age will be considered in the analysis while comparing the two groups. This analysis will assist in better understanding CDI in a described population and determine whether there are differences between Community Associated infections and Healthcare Facility Associated infections.

CHAPTER II

Literature Review

Clostridium difficile Background

Clostridium difficile was first described in 1935 as part of the intestinal microflora in neonates. Although the severe form of *C. difficile* disease was first discovered in 1893, the pathogen was not actually identified as the causative agent of human disease until 1978 (McDonald *et al*). *C. difficile* is an anaerobic, spore-forming, toxigenic bacteria that is the most commonly recognized cause of infectious nosocomial diarrhea and one of the most common healthcare-associated pathogens (Campbell et al., 2009). *C. difficile* infection (CDI) is a toxin-mediated intestinal disease, and extra-intestinal manifestations are rare. *C. difficile* is recognized as the main cause of infectious diarrhea that develops in patients after hospitalization and antimicrobial treatment (Thomas *et al*). The association between antimicrobial therapy and CDI is very strong, as *C. difficile* can only colonize the gut if the normal intestine microbiota is disturbed or absent (Gronczewski *et al*). A case of *C. difficile* incidence (CDI) is defined as a positive toxin or nucleic acid *C. difficile* assay (Cohen et al., 2010). *C. difficile* can be detected in stool specimens.

Clinical Manifestation

The clinical manifestations of infection with toxin-producing strains of *C. difficile* range from asymptomatic carriage, mild or moderate diarrhea, to fulminant and sometimes fatal pseudomembranous colitis (Barbut et al., 1996; Cohen et al., 2010). Several studies have shown that 50% or more of hospital patients colonized by *C. difficile* are asymptomatic carriers, possibly reflecting natural immunity (Kyne et al., 2002). Symptoms of CDI usually begin soon

after acquisition, with a median time to onset of symptoms of 2-3 days(McFarland, Clarridge, Beneda, & Raugi, 2007).

C. difficile diarrhea may be associated with the passage of mucus or occult blood in the stool, but melena or hematochezia are rare. Fever, cramping, abdominal discomfort, and a peripheral leukocytosis are common but found in fewer than half of patients (Cohen et al., 2010). *C. difficile* ileitis or pouchitis has also been rarely recognized in patients who have previously undergone a total colectomy (McDonald et al., 2005). Patients with severe disease may develop a colonic ileus or toxic dilation and present with abdominal pain and distension but with minimal or no diarrhea. Complications of severe *C. difficile* colitis include dehydration, electrolyte disturbance, hypoalbuminemia, toxic megacolon, bowel perforation, hypotension, renal failure, systemic inflammatory response syndrome, sepsis, and death (Cohen et al., 2010).

Epidemiology

In 2002, the University of Pittsburgh Medical Center in the United States reported an increase of severe CDI, which focused attention on rising rates of CDI in Canada, the United States, and Europe (Henrich *et al*). According to McDonald *et al,* in 2006, the CDI discharge diagnosis rates in U.S hospitals exceeded 300,000 cases per year, which was an increase from less than 150,000 in 2000. It is currently estimated that there are approximately 500,000 cases of CDI per year in hospitals and long-term care facilities based on annual data from the State of Ohio in 2006 (Ohio Department of Health).

McDonald *et al* and others hypothesize that patients are exposed to *C. difficile* spores most often through contact with the hospital environment or health care workers And after taking an antibiotic, the person develops CDI if he/she acquires a toxigeneic *C. difficile* strain and lacks

an effective antibody response to the toxins. Lack of preexisting antibodies or timely antibody production may result in symptomatic CDI. Alternatively, if antitoxin antibodies are present or produced in a timely fashion, the patient may become asymptomatically colonized with *C. difficile*. Also, acquisition of a non-toxigenic *C. difficile* strain may lead to asymptomatic colonization. Colonized patients have been shown to be protected from CDI.

A veterinary model by Asha *et a*l helps to understand the pathogenesis of *C. difficile* in the intestine. *C. difficile* colonizes the intestine (colon) after disruption of the normal intestinal flora. However the roles of adhesion and biofilm production involved in the pathogenesis of *C. difficile* are unknown. The bacterial cells are free to begin with and then attach to host cells. Toxigenic strains produce toxin A and toxin B. Toxin B binds to the apical side of the cell and after internalization causes cytoskeletal changes that result in disruption of the tight junction, loosening the epithelial barrier. The disruption of the junction enables toxins A and B to cross the mucosal surface. Both toxins are cytotoxic and induce the release of various immunomodulatory mediators resulting in inflammation and the accumulation of neutrophils. The local inflammatory effects of CDI result in the formation of "volcano-like" lesions which can lead to pseudomembranes that form from the destruction of the intestinal cells and leukocytes.

C. difficile spores

C. difficile forms spores that are highly resistant to desiccation, chemical and extreme temperatures. Spores frequently contaminate the environment around patients with CDI, potentially persisting for months and even years (Ausiello C. M *et al*). More recently according to Fawley W.N *et al*, a study on cleaning products has shown spores can survive in the temperatures and disinfectant treatment of typical hospital laundering cycles and can cross-

contaminate bed linens during a wash cycles. *In vitro* exposure of *C. difficile* strain to sub-inhibitory concentrations of non-chlorine-based cleaning agents significantly increased sporulation capacity, an effect that is not generally seen with chlorine-based cleaning agents. Working-strength concentrations of five different cleaning agents inhibited the growth the *C. difficile in vitro* but only chlorine-based cleaning agents inactivated *C. difficile* spores.

Risk Factors

A number of factors that are known to increase risk for CDI are discussed below.

Antibiotics

Historically, the antimicrobials most commonly associated with CDI in well-conducted studies are clindamycin, penicillins, and cephalosporins. The increase use of fluoroquinolones among both inpatients and outpatients is now a common risk factor for CDI. The use of antibiotics are common and many studies have established the risk of antibiotics exposure associated with CDI (McDonald et al., 2005).

The negative effect of antibiotics on the gut flora is a risk factor for CDI. Patients are generally resistant to CDI if their normal gut flora is unaltered by antibiotics. Once antibiotic treatment begins, infection with a *C. difficile* strain that is resistant to the antibiotic is more likely while the antibiotic is being administered owing to the presence of the antibiotic on the gut. When the antibiotic treatment stops, the levels of the antibiotic in the gut diminish rapidly, but the microflora remains disrupted for a variable period of time, depending on the antibiotic. During this time period, patients can be infected with either resistant or susceptible *C. difficile*. After the microflora recovers from the antibiotic treatment, a process that may take months, colonization resistance to *C. difficile* is restores (Asha *et al*).

A number of recent studies have investigated the risks associated with various antibiotics in the development of CDI. Olsen et al reported that 96% of patients with symptomatic *C. difficile* infection had received antimicrobials within the 14 days before the onset of diarrhea and that all had received an antimicrobial within the previous 3 months.

Loo *et al* performed a case-control study of 237 patients with CDI in 12 Quebec hospitals. This study found an odds ratio of 3.9 for receipt of fluoroquinolones in the development of CDI and an odds ratio of 3.8 for cephalosporins. Antibiotic resistance testing demonstrated widespread fluoroquinolone resistance in the infecting CDI strain. It was proposed that frequent fluoroquinolone use contributed to the spread of the CDI NAP1/o27 strain within Quebec.

Other groups have similarly proposed that outbreaks in their institutions were facilitated by an increase in fluoroquinolones usage. Muto *et al*. describe an outbreak of CDI at a teaching hospital in Pittsburg following a change in the antibiotic formulary from ciprofloxacin to levofloxacin. Pepin *et al* analyzed the risk associated with different antibiotics for the development of CDI in Quebec and found fluoroquinolones to confer the highest risk and, due to their common usage, to also account for the highest population attributable fraction (36%).

Gaynes *et al*., in Atlanta, attributed an outbreak of CDI at a long term care facility to the switch in their formulary from levofloxacin to gatifloxacin which has an extended spectrum for anaerobic bacteria. This study was conducted to determine the cause of an increase rate of CDI in a long term care facility (LTCF). CDI cases were analyzed from October 2001 through June 2002. Cases were identified from positive enzyme immunoassay for *C. difficile* toxin A. The increase coincided with a formulary change from levofloxacin to gatifloxacin. A case-control study used randomly selected control subjects, a variety of risk factors, logistic regression

analysis demonstrated associations between CDI and use of clindamycin and gatifloxacin; gatifloxacin being associated with an increase of CDI during the outbreak period. In conclusion, this study was able to associate the outbreak with a formulary change from levofloxacin to gatifloxacin. The rates of CDI declined after a switch back to levofloxacin, concomitant with other control measures.

Underlying Condition

It was known previously that immunosuppression predisposes an individual to develop severe CDI. There have been, however, few controlled studies of CDI risk in HIV infection. Sanchez reviewed data from the Adult/ Adolescent Spectrum of HIV Disease (ASD) Project and found that *C. difficile* was the most commonly isolated bacterial cause of diarrhea in individuals with HIV during 1992-2002, accounting for 598 of 1115 (53.6%) bacterial agents identified. This high CDI risk is likely to be the result of frequent prophylactic and therapeutic antibiotic courses in HIV-infected individuals as well as their frequent visits to healthcare facilities.

A study by Nylund et al suggests an increase in CDI infection among hospitalized children, especially those hospitalized with medical conditions such as inflammatory bowel disease and immunosuppression. Also at risk are those hospitalized with conditions that require antibiotic administration.

Age

C. difficile is more common in elderly people, and old age may promote susceptibility to colonization and disease (Asha et al). While infants and young children frequently harbor *C. difficile* and its toxins, clinical infection is uncommon. More recently there have been reports of

populations affected by *C. difficile* that would normally be considered low risk. These populations include young healthy persons not exposed to a hospital environment or antimicrobial therapy and young pregnant women in the peripartum setting.

There is a high incidence and increased mortality among older patients that is attributed to the failure of these individuals to create an effective immune response when first exposed to the *C. difficile* toxins. This lack of immune response has also been associated with higher rates of recurrent disease (Kyne *et al*).

Residence

Community Associated

The *Morbidity and Mortality Weekly Report* of December 2005 highlighted concerning reports of severe CDI in individuals previously considered at low risk. The CDC investigated cases reported in peripartum women and cases of community acquired CDI. Voluntary participants were requested to report peripartum CDI cases nationally through epi-X, and locally in Pennsylvania and New Jersey for community acquired CDI during May and June of 2005. 10 peripartum CDI cases and 23 community acquired CDI cases were reviewed. Eight of the 33 patients had no documents exposure to antibiotics in the three months before onset of disease. Three of the eight had close contact with someone with a diarrheal illness and two isolates were available for strain typing, both stools detected excess toxins A and B.

In the United Kingdom Dial *et al* examined the development of community acquired CDI. This large population case-control study examined gastric acid suppressive agents as a risk factor for the development of CDI. The authors identified 1233 patients with CDI who had not been hospitalized in the year prior to diagnosis and were therefore considered to have community

acquired CDI. Of the 833 patients who were diagnosed with the infection based on a positive toxin assay, only 284 (34%) had a documented history of antibiotic use within 90 days prior to diagnosis. These findings were in contrast with nosocomial CDI, for which the vast majority of patients have a history of recent antibiotic use.

Health Care Facility Associated

According to Miller *et al* hospitalization and exposure to a healthcare facility is a risk factor for the acquisition of CDI for many reasons. Healthcare exposure multiples the risk of CDI because it increases the likelihood of exposure to antibiotics, spore-contaminated environments, inadequate hand hygiene by health care workers and a highly susceptible elderly population of patients that may be hospitalized.

A study by Archibald et al addresses the rates of CDI in hospital settings. The authors reviewed *C. difficile* associated disease data from intensive care units (ICU) and hospital wide surveillance components of the National Nosocomial Infections Surveillance system hospitals during 1987- 2001. ICU CDI rates increased significantly in hospitals with more than 500 beds ($p<.01$) and correlated with the duration of ICU stay. CDI was highest in general hospitals versus other facility types, and the rates were significantly higher in winter months versus non-winter months ($p<0.1$).

Campbell et al described the disease burden and mortality rate of healthcare-onset CDI, suggesting that the incidence and severity of CDI is increasing in healthcare-related establishments. In 2006, active public reporting of healthcare-onset CDI was mandated for all Ohio hospitals and nursing homes. Incident rates were determined and stratified according to healthcare facility characteristics and death certificates that listed CDI were analyzed. There

were a total of 14,329 CDI cases reported, including 6,376 at 210 hospitals. The rate for initial cases was 6.4-7.9 cases/10,000 patient-days for hospitals and 1.7-2.9 cases/10,000 patient-days for nursing homes. Death certificates for 2006 listed CDI among the causes of death for 893 Ohio residents; between 2000-2006 this number increased more than 4-fold.

A case control study conducted in 1993 by Barbut et al looked at determining the prevalence of *C. difficile* in stool specimens of hospitalized patients sent to hospital microbiology laboratories, to assess the relationship between serotypes and toxigenicity of the strains isolated, and evaluate the clinical data. The presence of *C. difficile* was systematically investigated from January 1993- July 1993 by looking at 3921 stool samples sent for stool cultures to 11 French hospital microbiology laboratories. The prevalence in this population was compared with that of a group of 220 random hospital controls matched for age, department, and length of stay. Stool cultures from controls were collected by laboratory personnel for the purposes of the study; serotype and toxin production of the strains were determined and compared. Overall the prevalence of *C. difficile* in the cases were two times more than in the control group, and approximately 4 times as high in diarrheal stools compared to normally formed stools from controls. Strains were more frequently toxigenic in loose stools than those isolated from normally formed stools. Serotype C was more commonly found in patients, older than 65 years of age and those suffering from severe disabling disease, who had been treated with antibiotics and hospitalized for more than 1 week.

CHAPTER III

Methods

Patient Selection

Patients were identified through the *Clostridium difficile* Surveillance Program of the Georgia Emerging Infections Program (EIP). Since September of 2009 the GA EIP has performed prospective, population-based, laboratory-based surveillance for all the positive *C. difficile* cases in Georgia Health District 3 (HD3), the 8-county Atlanta metropolitan area. All residents aged one year and older in the surveillance areas from whom a positive C. difficile toxin enzyme immunoassay (EIA) or positive C. difficile nucleic acid assay (e.g PCR) from human stool or an ileostomy specimen was obtained were eligible for investigation. Clinical laboratories in the surveillance area, on a monthly basis, will provide a line list of positive *C. difficile* toxin assay test results and patient identifying information. Each positive assay result was cross-checked with a dataset containing previous line lists positive *C. difficile* toxin tests to determine if episodes were a duplicate, recurrent, or incident CDI case. A case of CDI was defined as a positive *C. difficile* test on an incident stool specimen. Cases with a positive stool specimen for *C. difficile* greater than 8 weeks after the last positive specimen were considered a new case (Baughman et al).

Study personnel retrospectively reviewed medical records using a standardized case report form (CRF) to abstract data on demographics, clinical characteristics, and outcomes. Cases were classified in to 3 categories: Healthcare Facility Onset (HCFO), Community Onset Healthcare Facility Associated (COHCFA), or Community Associated (CA). HCFO is defined as a case with the initial *C. difficile* positive specimen collected greater than four calendar days after

admission to a healthcare facility (i.e. acute care hospital, long-term care acute hospital, long term care facility). Community onset cases with an overnight stay at a healthcare facility in the twelve weeks prior to initial positive *C. difficile* result were classified as CO-HCFA. Cases with community onset without a documented overnight stay in a healthcare facility in the twelve weeks prior to initial positive specimen collection were classified as CA (Baughman et al).

Due to the high volume of positive *C. difficile* assays present in this population, a stratified random sampling scheme was used and cases were stratified by age and gender except for the youngest age group of males and females 1-17. All cases occurring in those 1-17 years of age were included in the analysis. For the remaining groups, male and females 18-44, 45-64, >65, only 1:3 CDI cases were sampled and a CRF was completed on those sampled (except September 2009 and October 2009). In the classification of HCFO, 1:10 cases were randomly selected for CRF completion (Baughman et al). Figure 1 represents a breakdown of the case selection used for analysis.

Due to the sampling scheme, for this analysis the classifications COHCFA and HCFO were combined to make a Healthcare Facility Associated (HCFA) category. Therefore the outcomes being described are CA and HCFA. The underlying conditions and antibiotics were grouped to form classifications for analysis (see appendix 1 and 2 for table representing the combinations).

Statistical Analysis

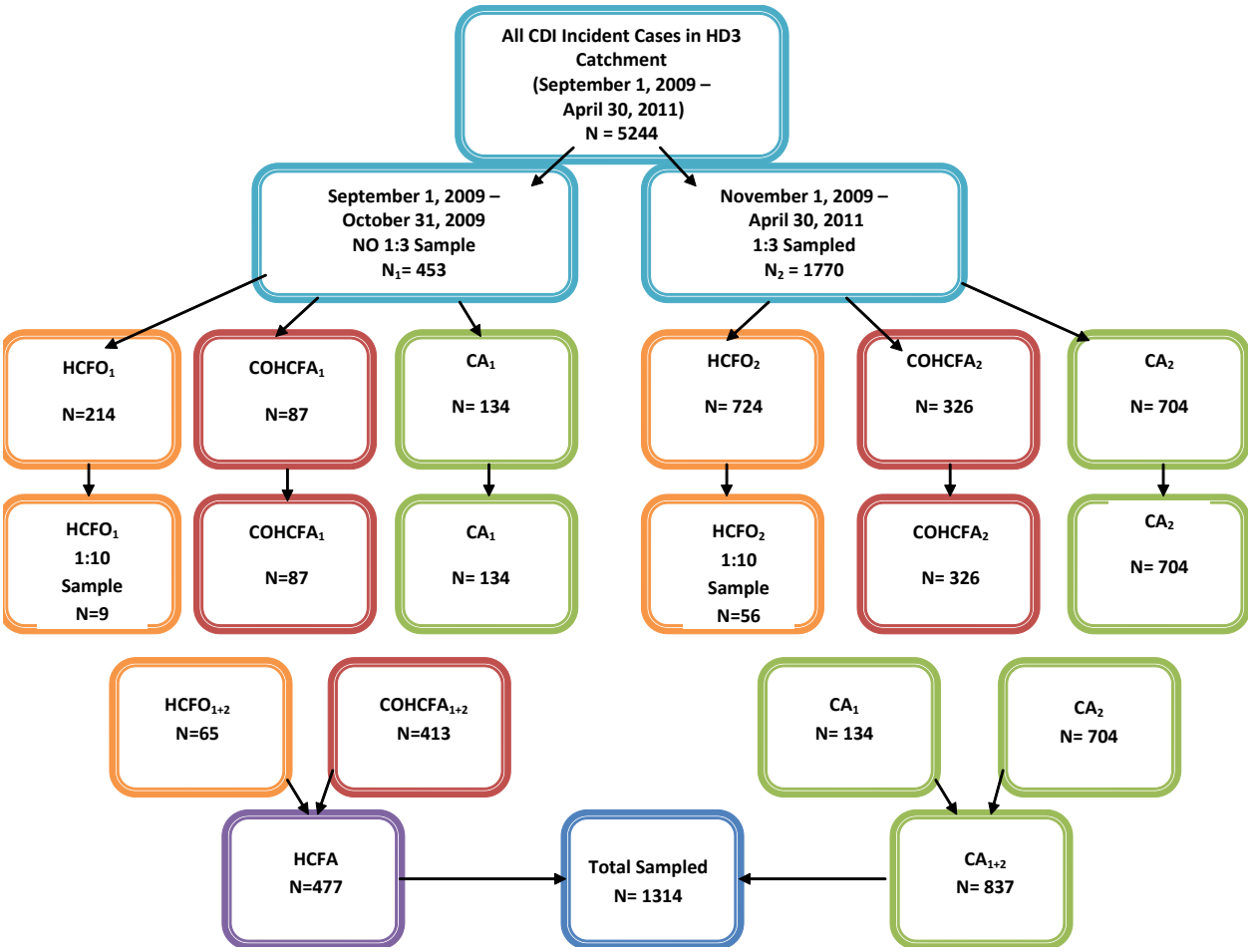
The study period for this analysis was from September 1, 2009 through April 30, 2011. Statistical analyses were performed using SAS, version 9.2 (SAS Institute, Cary, NC). A logistic regression was performed to identify risk factors significantly associated with the specified

outcomes. In addition, a chi squared analysis was then performed to evaluate the impact of being on no, one, or two or more antibiotics versus. The same analysis was performed for underlying conditions to see if a patient with CDI was more likely to have none, one, or two or more underlying conditions. Odds Ratios were also calculated to compare HCFA-CDI cases to CA-CDI cases when specifically looking at the relationships between either no antibiotics or no underlying condition compared to an individual antimicrobial classification or underlying condition group.

IRB

This study was approved by the Georgia State University (Protocol #H12310) and Emory University's (Protocol #5558.0) IRBs, and the VA Research and Development Committee (Protocol #16622).

Figure 1: Flow Chart demonstrating the sample method used for this study.



CHAPTER IV

Results

Between September 1, 2009 and April 30, 2011, 5244 incident cases were identified by the GA EIP surveillance project. The incident rate of CDI in the Metro Atlanta population was 84 cases per 100,000 calculated using all incident cases in 2010 compared to 2010 census data. The median age was 63, with ages ranging from 1 to 102, and 61% of the cases studies were female.

Demographics of cases included in the study are shown in Table 1. In addition, 38% of the cases had no healthcare facility association and a majority of this sample was White/ Non-Hispanic (48%). Looking at the CA cases, the column percents show a similar distribution among age groups where in the CO-HCFA and HCFO the distribution of cases increase with age.

TABLE1 Description of Cases, September 2009 – April 2011

		CA n=837 (38%) (col %)	CO-HCFA n=413 (19%) (col %)	HCFO n=938 (43%) (col %)	Total (%)
Age					
	1-17	208 (25)	30 (7)	15 (1.6)	253 (12)
	18-44	179 (21)	65 (16)	81 (8.6)	325 (15)
	45-64	237 (28)	103 (25)	231 (25)	568 (26)
	65+	214 (26)	215 (52)	611 (65)	1039 (47)
Sex					
	Male	315 (38)	172 (42)	371 (40)	855 (39)
	Female	523 (62)	241 (58)	567 (60)	1330 (61)
Race/ Ethnicity					
	White/NH	308 (64)	228 (63)	516 (59)	1050 (48)
	Black/NH	151 (32)	114 (32)	344 (39)	607 (28)
	Hispanic	19 (4)	18 (5)	15 (2)	52 (2)
	Other	9	6	12	27 (1)
	Unknown	351	47	51	449 (21)

After the additional 1:10 HCFO sample, the case study population size reduced to 1314. Of the 938 HCFO cases, only 65 CRFs were completed due to the sampling method. Completed HCFO cases were combined with the CO-HCFA cases to make a HCFA-CDI group. Table 2 represents a description of the 1314 cases considered for analysis. The age group 65 years and older are significantly more likely to have a HCFA-CDI compared to CA-CDI group ($p<0.01$).

TABLE 2 Univariate Descriptions of Demographics

		CA (reference) n=837	HCFA n=477	p-value
Age				
	1-17 (reference)	208	30	
	18-44	179	72	
	45-64	237	120	
	65+	213	255	0.0013
Sex				
	Male (reference)	314	198	
	Female	523	280	0.5095
Race/ Ethnicity				
	White/NH (reference)	307	266	
	Black/NH	151	136	0.1979
	Hispanic	19	18	0.0448

Of the antibiotics that were examined, a univariate chi square analysis was performed to determine which antibiotic classifications were more of a risk factor for the HCFA-CDI group compared to the CA-CDI group (Table 3). Using no antibiotic exposure 14 days prior to stool collection as a reference group, fluoroquinolones, cephalosporins, and Vancomycin were significantly associated with the HCFA-CDI group compared to the CA-CDI group (p values <0.01). Among the underlying condition groups reviewed, a univariate chi square analysis determined that HIV/AIDS, cardiovascular disorders, neurological disorders, other chronic

conditions, and diabetes were significantly more associated with HCFA-CDI cases compared to CA – CDI cases.

TABLE 3 Univariate Analysis of Antibiotics

Antibiotics	CA (%)	HCFA (%)	p-value (chi sq)
None	395 (47)	185 (39)	0.0032
Fluoroquinolones	50 (7)	100 (21)	<0.0001
Cephalosporins	58 (7)	60 (13)	0.0006
Metronidazole	64 (8)	55 (12)	
Vancomycin	18 (2)	52 (11)	<0.0001
Penicillins & Carbopenems	76 (9)	48 (10)	
Clindamycin	26 (3)	6 (1)	
Macroloids	23 (3)	20 (4)	

TABLE 4 Univariate Analysis of Underlying Conditions

Underlying Conditions	CA (%)	HCFA (%)	p-value (chi sq)
None	434 (52)	73 (15)	<0.0001
HIV/AIDS	21 (3)	25 (5)	0.0096
Gastrointestinal	112 (13)	57 (12)	
Cardiovascular	38 (5)	106 (22)	<0.0001
Neurological	37 (4)	84 (18)	<0.0001
Tumors	54 (6)	47 (10)	
Other Chronic	118 (14)	211 (44)	<0.0001
Diabetes	81 (10)	129 (27)	<0.0001

An array function in SAS was used to determine the number of cases that were taking antibiotics 14 days prior to a positive stool or the number of underlying conditions an individual had. More HCFA-CDI cases (8%) were taking two or more antibiotics compares to CA-CDI cases (6%). In addition, there were more HCFA-CDI cases (16%) that had two or more underlying conditions compared to the CA-CDI group (9%).

TABLE 5 Logistic Regression of Antibiotics

Risk Factors	CA (reference)	HCFA	p-value
Antibiotics			
None (reference)	395	185	
Fluoroquinolones	27	44	0.0392
Cephalosporins	23	28	0.0041
Metronidazole	41	41	0.0026
Vancomycin	13	32	0.0008
Penicillins & Carbopenems	60	35	0.0959
Clindamycin	25	5	0.5603
Macroloids	17	15	0.1585
Other	118	55	0.4135
Unknown	116	36	0.6549

TABLE 6 Logistic Regression of Underlying Conditions

Risk Factors	CA (reference)	HCFA	p-value
Underlying Conditions			
None (reference)	434	73	
HIV/AIDS	14	9	0.0448
Gastrointestinal	79	29	0.0219
Cardiovascular	8	24	<0.0001
Neurological	22	32	<0.0001
Tumor	35	30	<0.0001
Other Chronic	83	126	<0.0001
Diabetes	81	129	<0.0001
Unknown	62	8	0.9035

A multivariate logistic regression was then used to determine the difference between the HCFA-CDI group compared to the CA-CDI group among the different risk factors (reference tables 5 and 6). The HCFA-CDI group was significantly more likely to be taking the following antibiotics 14 days prior to a positive stool collection: Cephalosporins, Metronidazole, and Vancomycin ($p < 0.01$) compared to no antibiotic use the CA-CDI group. The HCFA-CDI group

was also significantly more likely to have the following underlying conditions, Cardiovascular, Neurological diseases, Tumor, Other Chronic diseases, and Diabetes compared to no underlying condition in the CA-CDI group.

TABLE 7 Odds Ratio of Demographic

Risk Factor		**Odds Ratio (95% Wald CI)**
Age		
	1-17 (reference)	1
	18-44	1.7 (0.959, 2.896)
	45-64	1.5 (0.877, 2.587)
	65+	2.4 (1.414, 4.193)
Sex		
	Male (reference)	1
	Female	0.9 (0.682, 1.209)
Race Ethnicity		
	White N/H (reference)	1
	Black N/H	1.2 (0.889, 1.763)
	Hispanic	2.2 (1.006, 4.996)

TABLE 8 Odds Ratio of Antibiotics

Risk Factor		Odds Ratio (95% Wald CI)
Antibiotics		
	None (reference)	1
	Vancomycin	3.7 (1.716, 7.838)
	Cephalosporin	2.8 (1.382, 5.576)
	Metronidazole	2.3 (1.347, 4.089)
	Fluoroquinolones	1.9 (1.032, 3.497)
	Macroloids	1.9 (0.785, 4.410)
	Penicillins & Carbopenems	1.6 (0.922, 2.704)
	Clindamycin	0.7 (0.246, 2.136)

TABLE 9 Odds Ratio of Underlying Conditions

Risk Factor		Odds Ratio (95% Wald CI)
Underlying Conditions		
	None (reference)	1
	Cardiovascular	10.9 (4.498, 26.805)
	Other Chronic	6.2 (4.068, 9.367)
	Diabetes	5.4 (3.484, 8.251)
	Neurological	3.9 (2.006, 7.556)
	Tumors	3.6 (1.978, 6.469)
	HIV/AIDS	2.6 (1.022, 6.678)
	Gastrointestinal	1.9 (1.095, 3.200)

An odds ratio was also calculated through the logistic regression and the outputs are viewed in tables 7, 8, and 9. Table 7 shows that the HCFA-CDI group was 2.4 times more likely to be 65 or older than the CA-CDI group (C.I 1.414, 4.193). The HCFA-CDI group was also 3.7 times more likely to be taking Vancomycin (C.I 1.716, 7.838), 2.8 times more likely to be taking Cephalosporins (C.I 1.382, 5.576), 2.3 times more likely to be taking Metronidazole (C.I 1.347, 4.089), and 1.9 times more like to be taking Fluoroquinolones (C.I 1.032, 4.410) than the CA-CDI group (table 8). The HCFA-CDI group is significantly more likely to have an underlying condition compared to the CA-CDI group (table 9). The HCFA-CDI group is 10.9 times more likely to have a cardiovascular disorder (C.I 2.298, 26.805), 6.2 times more likely to have another Chronic disorder (C.I 4.068, 9.367), 5.4 times more likely to have Diabetes (C.I 3.484, 8.251), 3.9 times more likely to have a Neurological disease (C.I 2.006, 7.556), 3.6 times more likely to have a Tumor (1.978, 6.469), 2.6 times more likely to have HIV/AIDS (C.I 1.022, 6.678), and 1.9 times more likely to have a Gastrointestinal disorder (C.I 1.095, 3.200) compared to the CA-CDI group.

CHAPTER V

Discussion

This study shows a significant difference in HCFA-CDI cases compared CA-CDI cases where HCFA-CDI is more associated with antimicrobial exposure 14 days prior to a positive stool collection and is more likely to have an underlying condition compared to the CA-CDI group. Although there is little comparable data on trends of community-associated compared to healthcare facility associated CDI in an urban setting, literature supports the findings that antibiotics and underlying conditions are risk factors for CDI (Asha, et al; Henrich et al, 2009). In addition, literature supports that healthcare facility associated infections are more likely to have exposure to antibiotics than cases not exposed to a healthcare facility (Thomas, Stevenson, & Riley, 2003).

The objective of this study was to describe *C. difficile* infection in the Atlanta population. Based on literature review, it was predicted that healthcare facility associated CDI cases would have greater associations of being on antibiotics 14 days prior to stool collection and have at least one underlying condition. After conducting the analysis, this hypothesis was proven to be correct. In addition, the rate of CDI infection based on 2010 incident cases, using the 2010 census data as the denominator, was calculated and determined to be 84 cases per 100,000 people.

The significance of antimicrobial associations was lower in the HCFA-CDI group than the expected based on literature review regarding particular classes of antibiotics. Based on the literature clindamycin, penicillins, cephalosporins, and fluoroquinoles are the most common antibiotics associated with CDI (McDonald). Clindamycin has shown to be associated with CDI due to clindamycin- resistant, toxigenic strains of *C. difficile* (Owens et al., 2008). In this

analysis, clindamycin did not have a significant association to CDI. This also may be true since clindamycin has been on the decline after being associated with so many *C. difficile* outbreaks (Owens et al., 2008). This seems to be the case for cephalosporins, which were targeted as risk factors for CDI and also related to outbreaks. Second and third generation cephalosporins were identified as chief risk factors for a *C. difficile* outbreak in a Veterans Administration medical center in New York (Owens et al., 2008). The literature supports cephalosporins as being a risk factor for CDI, my results support the literature on cephalosporins have a significant association of CDI. The literature also suggests that fluoroquinolones are associated with CDI outbreaks. *C. difficile* is a hardy bacterium that has become resistant to these antimicrobial agents (Asha et al., 2006). My results, however, supported a significant association of fluoroquinolone use in a univariate analysis, but no significant association in a multivariate analysis. Metronidazole and Vancomycin are antibiotics suggested for the treatment of CDI (Cohen et al., 2010). My results indicate that Metronidazole and Vancomycin are significantly being used in cases that have CDI 14 days prior to stool collection. Moving forward it will be interesting to see how Metronidazole and Vancomycin play a role in risk factors for CDI. The rates of antimicrobial resistant infections are on the rise, since these two drugs are most commonly used as treatment for CDI, public health precautions need to be considered to reduce the Metronidazole and Vancomycin exposure to patients without *C. difficile*.

Of studies that have been conducted solely on healthcare facility onset CDI, the co-morbidity of patients reflects similar findings to what this study presents, where chronic conditions are associated with HCFA-CDI (Fawley, 2007). Underlying conditions found to be associated with CDI in this study that differ from the current literature include cardiovascular diseases, Neurological diseases, Tumors, Other Chronic diseases, and Diabetes. Underlying

conditions found not to have a significant association with CDI that the literature suggested would include Immunosuppressive disorders and gastrointestinal disorders. There are no current hypotheses for why these two are not significant in this analysis.

Studies suggest than an increase in age puts patients at a higher risk of CDI than those younger than 65 (Kutty et al., 2010). The results from this study support literature in that patients 65 and older were more likely to have CDI than the younger age groups. In addition, the analysis concluded that CDI cases older than 65 are significantly more likely to be HCFA compared to CA.

This study represents an initial analysis on a specific population based on a surveillance system put in place via the Centers for Disease Control and Prevention and the Emerging Infections Program. This analysis can be used as a base line moving forward with surveillance for the metropolitan Atlanta area regarding rates of *C. difficile* in a population and risk factors associated with the infection. As the surveillance continues additional analysis can be conducted to analyze severity of infection among case classifications. Furthermore, it would be interesting to continue analysis on the antimicrobial associations with CDI in the Atlanta area, by continuing surveillance and data collection for antibiotics taken 14 days prior to stool collection, trends can be monitored to see if new resistance is forming based on the behavior of the clinical groups and hospitals in Atlanta.

There were limitations to this study. To begin with, the sampling scheme made initial analysis difficult due to the 1:3 sampling of all incident cases, then the additional 1:10 sample of HCFO cases. Initially, comparing the three groups would have been interesting, but due to the 1:10 HCFO sample, that population was too small to conduct an accurate analysis. In addition, proper weighting has not been established to make up for the small sample numbers. This study

also does not adjust for the 1:3 sampling scheme, so this data is representative of a third of the CDI population. In addition, the population analysis only consisted of those who had CDI, therefore comparing CDI cases to CDI cases made analysis less straight forward for determining the outcome variable.

The rate of *C. difficile* in the population being observed is higher than the rate of *C. difficile* in the United States, 76 per 100,000 (Redelings et al., 2007). CDI seems to be increasing over time which is either due to better testing methods, better surveillance, or an increase of cases (Redelings et al., 2007). To prevent *C. difficile* in the population a number of actions can be taken to reduce the incidence of CDI. First of all, hand washing and hygiene is very important, especially in the healthcare facility environment or when exposed to someone who has severe diarrhea. Secondly, reduce the amount of antibiotics that are prescribed in both inpatient and outpatient settings. This can be done by assuring that antibiotics are given after results of a positive culture for the assumed infection or disease. This leads in to the practice of antimicrobial stewardship, which is the approach to preventing emergence of antimicrobial resistance. According to a study by Fishman et al, 50% of antibiotics are prescribed unnecessarily. This also includes better physician – patient interaction, where patients are educated about the medications they are taking for their underlying conditions or antibiotics they are on for specific infections. Combinations of these underlying conditions and antibiotics may pose a higher risk for CDI. A third suggestion would be to conduct as a case control study, both looking at CA-CDI cases matched to a community control, and HCFA-CDI cases matched to a healthcare facility control. By conducting a case control interview, additional risk factors among the groups will become clearer as to why some people are getting CDI and some are not.

Conclusion

This study represents an analysis of one third of the CDI cases in the metro-Atlanta population. Surveillance on *C.difficile* is important as the Antimicrobial Resistance Infections are becoming more common. From this study we know that age greater than 65, being on antibiotics, and having an underlying condition are risk factors for HCFA-CDI cases compared to CA-CDI cases. The risk increases as patients are taking more than one antibiotic and have more than one underlying condition ($p < 0.0001$). Therefore, it is important to reduce the risk of exposure of *C. difficile* by using prevention methods discussed.

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COMPARISON OF RISK FACTORS FOR *CLOSTRIDIUM DIFFICILE* INFECTION AMONG COMMUNITY ASSOCIATED CASES AND HEALTHCARE FACILITY ASSOCIATED CASES, SEPTEMBER 1, 2009 – APRIL 30, 2011

Zirka Thompson
April 4, 2012
Georgia State Thesis Committee Members:
Dr. Lisa Casanova & Dr. Frances McCarty
EIP Principle Investigator: Dr. Monica Farley

1

BACKGROUND/ LITERATURE REVIEW

2

Background

- *Clostridium Difficile* (*C. Diff*) is an anaerobic, spore-forming, toxigenic bacteria that is the most commonly recognized cause of infectious nosocomial diarrhea and one of the most common healthcare-associated pathogens
- CDI = *C. diff* Infection

www.bioquellus.com

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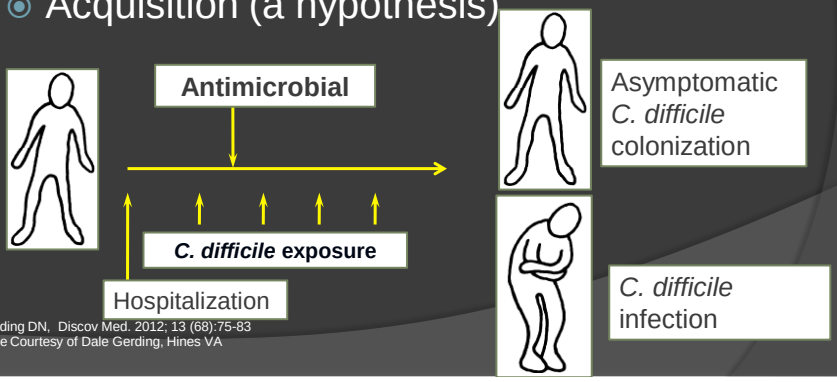
Clinical Manifestation

- Symptoms
  - Asymptomatic to mild or moderate diarrhea to fulminate or fatal colitis
- Acquisition (a hypothesis)



Gerding DN, Discov Med. 2012; 13 (68):75-83
Slide Courtesy of Dale Gerding, Hines VA

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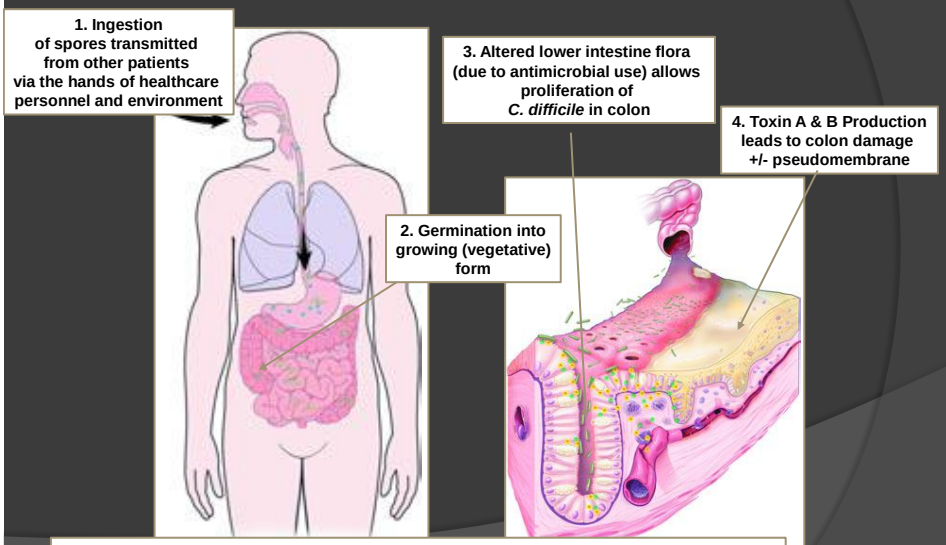
Pathogenesis



Sunenshine et al. Cleve Clin J Med. 2006;73:187-97.

Risk Factors: Antibiotics

- The negative effect of antibiotics on the gut flora is a risk for CDI
- 96% of patients with CDI received antimicrobials within the 14 days before the onset of diarrhea and all had received antimicrobial therapy within the previous 3 months (Olsen et al)
- Most common antimicrobial exposures: Clindamycin, penicillins, cephalosporins, & fluoroquinolones (McDonald)

6

Risk Factors: Underlying Conditions

- CDI was the most commonly isolated bacterial cause of diarrhea in individuals with HIV (Sanchez1992-2002).
- An increase in CDI was associated with hospitalized children with severe medical conditions such as IBD and Immunosuppressive diseases (Nyland).

7

Risk Factor: Age

- Several studies suggest CDI is more common in elderly people and old age may promote susceptibility
- High incidence and increased mortality among older patients attributed is to the failure of these individuals to create an effective immune response when first exposed to *C. difficile* toxins.

8

Healthcare Facility Associated (HCFA) CDI

- Hospitalization and exposure to healthcare facilities is a risk factor for acquisition for CDI (Miller et al).
- In 2006, in Ohio, 14,329 healthcare Onset CDI cases were reported in 210 hospitals (Ohio Dept of Public Health).

9

Community Associated (CA) CDI

- Populations now affected by CDI that would normally be at low risk
- In a large UK study, 34% of the non-hospitalized CDI diagnosis in the community had documented prior antibiotic use in previous 90 days (Dial et al)

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Objectives & Hypothesis

- Objective
  - Examine the differences in antimicrobial use and underlying conditions in CA vs HCFA CDI.
- H_0
  - There will be no difference in antimicrobial use and underlying condition between the CA and HCFA groups.

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METHODS

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Case Identification

- Identified through *Clostridium difficile* Surveillance Program at the Georgia Emerging Infections Program.
- Case Definition
  - Positive Toxin Assay
  - Age
  - HD3

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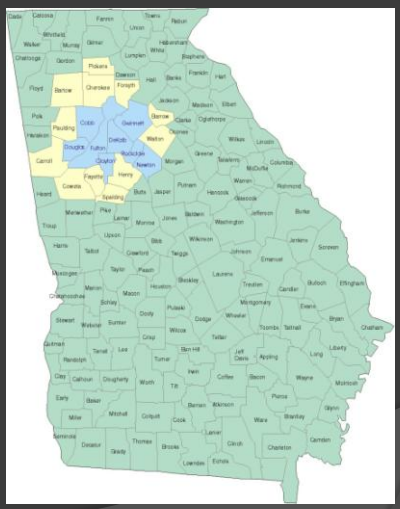
Case Identification

- HD3
  - Pop ~ 3.7 million
    - Clayton
    - Cobb
    - Dekalb
    - Douglas
    - Fulton
    - Gwinnett
    - Newton
    - Rockdale



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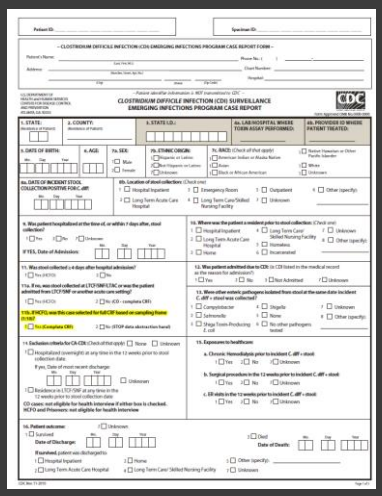
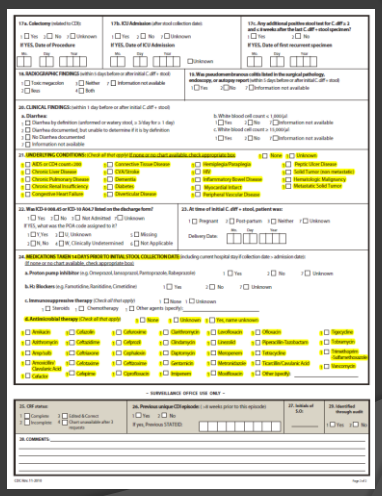
Case Report Forms (CRFs)



CLOSTRIDIUM DIFFICILE INFECTION (CDI) SURVEILLANCE
EMERGING INFECTIONS PROGRAM CASE REPORT



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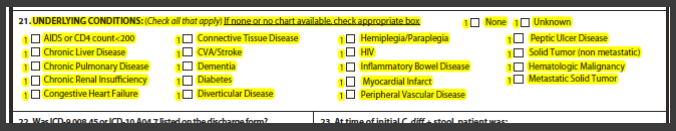
Data Collected from CRFs
Variables of Interest



21. **UNDERLYING CONDITIONS:** (*Check all that apply*) If none or no chart available, check appropriate box ☐ None ☐ Unknown

- ☐ AIDS or CD4 count <200
- ☐ Chronic Liver Disease
- ☐ Chronic Pulmonary Disease
- ☐ Chronic Renal Insufficiency
- ☐ Congestive Heart Failure
- ☐ Connective Tissue Disease
- ☐ CVA/Stroke
- ☐ Dementia
- ☐ Diabetes
- ☐ Diverticular Disease
- ☐ Hemiplegia/Paraplegia
- ☐ HIV
- ☐ Inflammatory Bowel Disease
- ☐ Myocardial Infarct
- ☐ Peripheral Vascular Disease
- ☐ Peptic Ulcer Disease
- ☐ Solid Tumor (non metastatic)
- ☐ Hematologic Malignancy
- ☐ Metastatic Solid Tumor

d. Antimicrobial therapy (*Check all that apply*) ☐ None ☐ Unknown ☐ Yes, name unknown

- ☐ Amikacin
- ☐ Azithromycin
- ☐ Amp/sulb
- ☐ Amoxicillin/ Clavulanic Acid
- ☐ Cefaclor
- ☐ Cefazolin
- ☐ Ceftazidime
- ☐ Ceftriaxone
- ☐ Cefotaxime
- ☐ Cefepime
- ☐ Cefuroxime
- ☐ Cefprozil
- ☐ Cephalexin
- ☐ Ceftizoxime
- ☐ Ciprofloxacin
- ☐ Clarithromycin
- ☐ Clindamycin
- ☐ Daptomycin
- ☐ Gentamicin
- ☐ Imipenem
- ☐ Levofloxacin
- ☐ Linezolid
- ☐ Meropenem
- ☐ Metronidazole
- ☐ Moxifloxacin
- ☐ Ofloxacin
- ☐ Piperacillin-Tazobactam
- ☐ Tetracycline
- ☐ Ticarcillin/Cavulanic Acid
- ☐ Other (specify): _____
- ☐ Tigecycline
- ☐ Tobramycin
- ☐ Trimethoprim -Sulfamethoxazole
- ☐ Vancomycin

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CDI Case Classifications

- Community Associated (CA)
  - Community onset without a documented overnight stay in a healthcare facility in the 12 weeks prior to initial positive *C. diff* stool
- Community Onset – Healthcare Facility Associated (COHCFA)
  - Community onset cases with an overnight stay at a healthcare facility in the 12 weeks prior to initial positive *C. diff* stool
- Healthcare Facility Onset (HCFO)
  - Case with initial *C. diff* positive specimen collected greater or equal to 4 calendar days after admission to a healthcare facility (acute care hospital, LTAC, LTCF, SNF)

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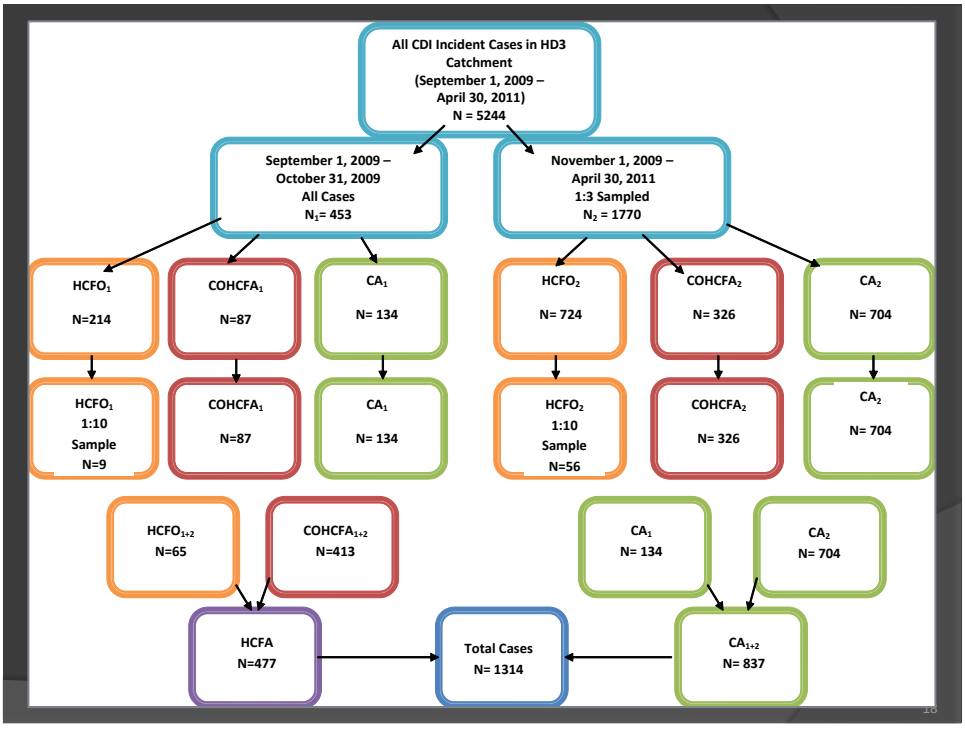

Statistical Analysis

- SAS Programming
  - Univariate
  - Logistic Regression

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RESULTS

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Rate of CDI in HD3, 2010

- 3067 Incident cases in 2010 in a population of 3,630,152 for an annual rate of 84 cases per 100,000.
- Cases ranged in age from 1-102 (mean 56, median 63)

21

Description of Cases, Sept 2009- April 2011

		CA n=837 (38%) (col %)	CO-HCFA n=413 (19%) (col %)	HCFO n=938 (43%) (col %)	Total (%)
Age					
	1-17	208 (25)	30 (7)	15 (1.6)	253 (12)
	18-44	179 (21)	65 (16)	81 (8.6)	325 (15)
	45-64	237 (28)	103 (25)	231 (25)	568 (26)
	65+	214 (26)	215 (52)	611 (65)	1039 (47)
Sex					
	Male	315 (38)	172 (42)	371 (40)	855 (39)
	Female	523 (62)	241 (58)	567 (60)	1330 (61)
Race/ Ethnicity					
	White/NH	308 (64)	228 (63)	516 (59)	1050 (48)
	Black/NH	151 (32)	114 (32)	344 (39)	607 (28)
	Hispanic	19 (4)	18 (5)	15 (2)	52 (2)
	Other	9	6	12	27 (1)
	Unknown	351	47	51	449 (21)

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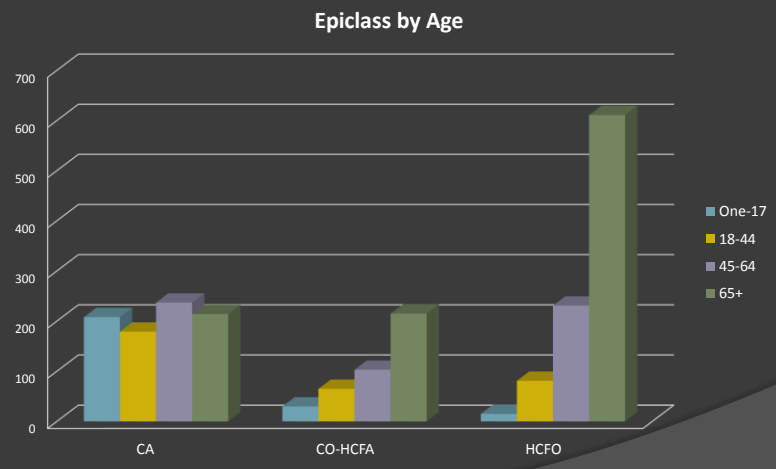
Description of Cases, Sept 2009- April 2011



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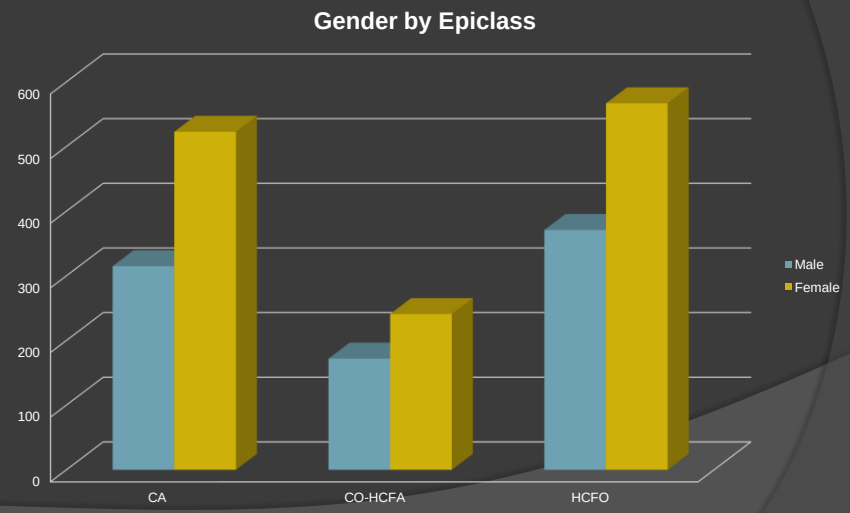
Description of Cases, Sept 2009- April 2011



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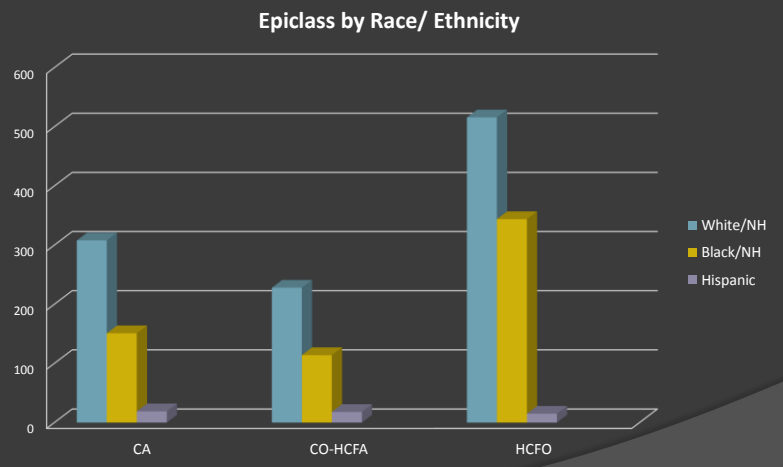
Description of Cases, Sept 2009- April 2011



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Univariate Descriptive Analysis

		CA (reference) n=837	HCFA n=477	p-value
Age				
	1-17 (reference)	208	30	
	18-44	179	72	
	45-64	237	120	
	65+	213	255	0.0013
Sex				
	Male (reference)	314	198	
	Female	523	280	0.5095
Race/ Ethnicity				
	White/NH (reference)	307	266	
	Black/NH	151	136	0.1979
	Hispanic	19	18	0.0448

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Univariate Analysis

Antibiotics	CA (%)	HCFA (%)	p-value (chi sq)
None	395 (47)	185 (39)	0.0032
Fluoroquinolones	50 (7)	100 (21)	<0.0001
Cephalosporins	58 (7)	60 (13)	0.0006
Metronidazole	64 (8)	55 (12)	
Vancomycin	18 (2)	52 (11)	<0.0001
Penicillins & Carbopenems	76 (9)	48 (10)	
Clindamycin	26 (3)	6 (1)	
Macroloids	23 (3)	20 (4)	

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Univariate Analysis

Underlying Conditions	CA (%)	HCFA (%)	p-value (chi sq)
None	434 (52)	73 (15)	<0.0001
HIV/AIDS	21 (3)	25 (5)	0.0096
Gastrointestinal	112 (13)	57 (12)	
Cardiovascular	38 (5)	106 (22)	<0.0001
Neurological	37 (4)	84 (18)	<0.0001
Tumors	54 (6)	47 (10)	
Other Chronic ☆	118 (14)	211 (44)	<0.0001
Diabetes	81 (10)	129 (27)	<0.0001

☆ Other Chronic includes: Chronic Pulmonary Disease, Chronic Liver Disease, & Chronic Renal Insufficiency

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Risk Factor Index

Co-Morbidity Index			
	CA	HCFA	Total
0	515	98	613
1	209	171	380
≥2	113	208	321

Antibiotic Use Index			
	CA	HCFA	Total
0	557	237	794
1	202	135	337
≥2	78	105	183

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Analysis: Logistic Regression

Risk Factors	CA (reference)	HCFA	p-value
Antibiotics			
None (reference)	395	185	
Fluoroquinolones	27	44	0.0392
Cephalosporins	23	28	0.0041
Metronidazole	41	41	0.0026
Vancomycin	13	32	0.0008
Penicillins & Carbopenems	60	35	0.0959
Clindamycin	25	5	0.5603
Macroloids	17	15	0.1585

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Analysis: Logistic Regression

Risk Factors	CA (reference)	HCFA	p-value
Underlying Conditions			
None (reference)	434	73	
HIV/AIDS	14	9	0.0448
Gastrointestinal	79	29	0.0219
Cardiovascular	8	24	<0.0001
Neurological	22	32	<0.0001
Tumor	35	30	<0.0001
Other Chronic	83	126	<0.0001
Diabetes	81	129	<0.0001

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Analysis: Odds Ratio

Risk Factor		Odds Ratio (95% Wald CI)
Age		
	1-17 (reference)	1
	18-44	1.7 (0.959, 2.896)
	45-64	1.5 (0.877, 2.587)
	65+	2.4 (1.414, 4.193)
Sex		
	Male (reference)	1
	Female	0.9 (0.682, 1.209)
Race Ethnicity		
	White N/H (reference)	1
	Black N/H	1.2 (0.889, 1.763)
	Hispanic	2.2 (1.006, 4.996)

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Analysis: Odds Ratio

Risk Factor		Odds Ratio (95% Wald CI)
Antibiotics		
	None (reference)	1
	Vancomycin	3.7 (1.716, 7.838)
	Cephalosporin	2.8 (1.382, 5.576)
	Metronidazole	2.3 (1.347, 4.089)
	Fluoroquinolones	1.9 (1.032, 3.497)
	Macroloids	1.9 (0.785, 4.410)
	Penicillins & Carbopenems	1.6 (0.922, 2.704)
	Clindamycin	0.7 (0.246, 2.136)

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Analysis: Odds Ratio

Risk Factor		Odds Ratio (95% Wald CI)
Underlying Conditions		
	None (reference)	1
	Cardiovascular	10.9 (4.498, 26.805)
	Other Chronic	6.2 (4.068, 9.367)
	Diabetes	5.4 (3.484, 8.251)
	Neurological	3.9 (2.006, 7.556)
	Tumors	3.6 (1.978, 6.469)
	HIV/AIDS	2.6 (1.022, 6.678)
	Gastrointestinal	1.9 (1.095, 3.200)

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DISCUSSION

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Discussion

- Significant findings
  - Age
    - Known= Age
  - Antibiotics
    - Known= Fluoroquinolones, Clindamycin*, Cephalosporins, Penicillins
    - Unknown= Metronidazole & Vancomycin
  - Underlying Conditions
    - Known = HIV / Gastrointestinal*
    - Unknown = everything else

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Discussion

- Clindamycin
  - Dr. Ray, Grady HAI Study
- Gastrointestinal Diseases
  - Reasons for being insignificant
    - HCFO, 1:10 Sample – causing under-representation.

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Strengths & Limitations

- Strengths
  - One of a few studies that analyzes a population based surveillance data focusing on community acquired infection.
- Limitations
  - The Sampling!
  - First person to analyze the GA CDI data
  - CA case data collection by Chart Reviews only.
  - Difficult to make findings generalizable.

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CDI Prevention

- Hand washing and hygiene
  - Especially in the healthcare facility environment or when exposed to someone with diarrhea
  - Specific hand washing technique
- Reduce Antibiotics that are prescribed in both inpatient and outpatient settings
  - According to Fishman 50% of antibiotics are prescribed unnecessarily.

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Suggestions for Future Studies

- Conduct a Case – Control study (CDC planning to start 2014)
- Collect additional information on CRF's including antibiotics taken 3 months prior vs. 14 days prior to positive stool collection (beginning with all 2012 cases- BAM!)

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Big Thanks to:

- Georgia State Thesis Committee
  - Dr. Casanova & Dr. McCarty for all your patience, assistance, and guidance.
- EIP
  - CDI Team: Dr. Farley, Wendy Baughman, Leigh Ann Clark, Andrew Revis (and Big Thanks to Amy Holst).
- CDC – for allowing me to analyze this GA data.
- Friends & Family for much needed support and encouragement.

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I'm ready for your…

QUESTIONS?

THANK YOU FOR YOUR TIME AND ATTENTION

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Institute of Public Health
College of Health & Human Sciences
Georgia State University
Master of Public Health

THESIS DEFENSE ANNOUNCEMENT

TITLE OF THESIS: Comparison of Risk Factors for Clostridium Difficile Infection among Community Associated Cases and Healthcare Facility Cases; September 2009 – April 2011

THESIS CHAIR: Dr. Lisa Casanova

STUDENT'S NAME	DATE	TIME	PLACE
Zirka Thompson	April 4, 2012	11:00am	Petite room 203

ABSTRACT

Background

The incidence of *Clostridium difficile* infection (CDI) has been increasing in communities and healthcare associated settings in the last 25-50 years. *Clostridium difficile* is a Gram-positive bacteria found in the large bowel or colon that causes mild to severe intestinal conditions and sometimes death. The primary risk factors for development of CDI include healthcare exposure and recent antimicrobial use. The purpose of this study is to compare risk factors associated with CDI occurring in the Community to those associated with Healthcare Facility Associated CDI in the metro Atlanta population from September 1, 2009 – April 30, 2011.

Methods

Patients were identified through C. difficile surveillance program of the Georgia Emerging Infections Program (EIP). Prospective, population based, laboratory based surveillance for all positive C. difficile cases in the Georgia Health District 3 (HD3). Due to high volume of positive CDI, a stratified random 1:3 sampling scheme is used and cases are stratified by age and gender. Identified sampled cases undergo a retrospective Case Report Form completion and are classified in to three classifications: Community Associated (CA), Community Onset-Healthcare Facility Associated (CO-HCFA), and Healthcare Facility Onset (HCFO). An additional 1:10 sampling occurs for HCFO cases. Due to the sampling scheme, for this analysis CO-HCFA and HCFO cases were combined to make a Healthcare Facility Associated (HCFA) classification. Using SAS, a logistic regression analysis was performed to compare the associated risks between CA and HCFA classifications.

Results

The rate of CDI in the HD3 counties in Georgia is 84 per 100,000. The median age of infection is 63 and the age range in this study is 1 to 102 years old. CA cases represented 38% of the sampled population. CDI cases 65 and older were more likely to have a Healthcare association compared to CA-CDI cases ($p < 0.01$). HFCA-CDI cases were more likely to be exposed to the following antibiotics Cephalosporins, Metronidazole, and Vancomycin (all p values <0.01). In addition, HCFA-CDI cases were more likely to have the following underlying conditions Cardiovascular, Neurological, Tumors, Other Chronic Conditions, and Diabetes (all p values <0.0001) compared to CA-CDI Cases. HCFA-CDI cases had individuals that had two or more underlying conditions and had more individuals that were taking two or more antibiotics 14 days prior to a positive stool culture compared to CA-CDI cases (both chi square <0.0001).

Conclusion

CDI is prevalent in the metro Atlanta population and this study identifies the risk factors that are associated with Community Associated Cases and Healthcare Facility Associated Cases. Based on this population sample, antibiotics use and underlying conditions appear to be significant factors in HCFA-CDI cases compared to CA-CDI cases. This study supports literature about CDI and antimicrobial use and looks further in to the role underlying conditions play as a risk factor for HCFA-CDI cases.

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Institute of Public Health
College of Health & Human Sciences
Georgia State University
Master of Public Health

RESULTS OF THESIS DEFENSE

TO:	Associate Dean for Academic Affairs, CHHS
FROM:	Thesis Committee Chairperson

RE: Results of Thesis Defense

STUDENT'S NAME Zirka Thompson	PANTHER ID NUMBER 001-17-9606
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The above named candidate defended a thesis entitled:

The following results are reported:
- ○ SUCCESSFULLY DEFENDED
- ⊗ SUCCESSFULLY DEFENDED PENDING REVISIONS
- ○ UNSUCCESSFUL

COMMENTS: Incorporate comments provided by committee

APPROVALS: Signatures below indicate acknowledgment of results reported above.

STUDENT'S SIGNATURE	DATE 4/4/12	COMMITTEE MEMBER	DATE
COMMITTEE CHAIRPERSON	DATE 4/4/12	COMMITTEE MEMBER	DATE
COMMITTEE MEMBER	DATE 4/4/12	COMMITTEE MEMBER	DATE

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