The Rise of \textit{Clostridium difficile} in Florida

By

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ABSTRACT

*Clostridium difficile*, a bacterium that causes diarrhea in hospitalized patients, is on the rise in the United States as well as in other countries. This study was done to determine the extent of the problem in Florida’s acute care hospitals. The Agency for Healthcare Administration (AHCA) provided data for patients discharged from Florida’s acute care hospitals for the years 1998 through 2004.

This study will focus on changes in the prevalence of *Clostridium difficile* associated disease (CDAD) over time. The mortality and morbidity of patients that have CDAD will also be examined to show if the disease is increasing over time. Factors investigated in this study that may influence the prevalence of CDAD include gender, race, length of hospital stay, age, and the cost per patient discharged.

In Florida the prevalence of CDAD has risen from 3.41 per 1,000 discharged patients in 1998 to 8.11 per 1,000 discharged patients in 2004. The mortality increased from 9.48% for CDAD positive patients in 1998 to 10.11% for CDAD positive patients in 2004. Age plays a role in both the prevalence and mortality of this disease. In 2004 the mortality of patients who were positive for
Clostridium difficile was 4.1% for those individuals that were 30-40 years old compared to 0.54% mortality for those patients in the same age group that did not have CDAD. The corresponding mortality for the patients aged 70-80 for the year 2004 was 11.1% for persons who had CDAD and 3.58% mortality for patients discharged with no CDAD.

The analysis showed that CDAD prevalence is increasing in Florida acute care hospitals. During 1998-2004 mortality rates for patients diagnosed with CDAD is also increasing. This analysis also indicates that age is a factor that increases the death rates for patients that are CDAD positive. A more concerted effort to implement hospital techniques that prevent the increasing prevalence of Clostridium difficile in Florida hospitals is recommended.
Chapter One: Introduction

*Clostridium difficile* associated disease (CDAD) is the most common cause of nosocomial associated diarrhea (Mylonakis, Ryan, & Calderwood, 2001). In recent years, a noted increase in prevalence of CDAD has been documented in developed countries (Valiquette, Low, Pepin, & McGeer, 2004). This disease increase generates a concern for the well being of persons that are admitted to hospitals.

The two most notable increases of prevalence for this disease have been documented in Canada and the United States (US) (Valiquette et al, 2004). Encompassing the years 2002 to 2004 a region of Quebec, Canada experienced an increase from 2.1 discharges per 1000 admissions to a projected 18 discharges per 1000 by the end of 2004 (Valiquette et al, 2004). The increasing number of patient discharges positive for CDAD is not the only concern. Another concern is that the reports also show increasing death rates from this disease. In a region of Quebec, Canada the death rate from CDAD within 30 days after diagnosis increased from 4.7% in 1991/1992 to 13.8% in 2003 (Pepin, Valiquette, & Cossette, 2005c).

Recognizing that *Clostridium difficile* infections are increasing has prompted researchers from the US to evaluate the extent of increasing CDAD in this country. McDonald and his colleagues noticed that since 1996 the prevalence of CDAD has risen from 31 per 100,000 persons in 1996 to 61 per 100,000 in 2003 (McDonald, Owings, & Jernigan, 2006). McDonald et al also noted that age as a factor that increases the
prevalence of CDAD. For persons > 64 the prevalence of CDAD increased from 150 per 100,000 population in 1996 to over 325 discharges per 100,000 in 2003 (McDonald et al, 2006).

The CDAD increasing prevalence in the US has caused some researchers to investigate the extent of this problem at the state level. Florida is projected by 2010 to have over 3.5 million people that are 65 years and older (McCharen, 2000). Increasing CDAD prevalence in hospitals makes this disease a concern for doctors that are treating geriatric patients. McDonald et al noted that the region of the US that includes Florida has shown an increase in prevalence of CDAD from 20 per 100,000 persons in 1996 to over 40 per 100,000 persons in 2003 (McDonald et al, 2006).

This study will use a cross sectional study type format to determine the prevalence of *Clostridium difficile* for patients discharged from acute care hospitals in Florida. The cross sectional study format is the best format for providing this information on the prevalence of CDAD in Florida and will provide ideas for further research that is needed to reduce this disease in Florida. The AHCA data contains primary and secondary diagnose codes. These codes are presented in the data using the International Classification of Disease, 9th revision (ICD-9) format. The ICD-9 code for CDAD is ‘00845’ and a discharged patient is considered positive for this disease if the code is present in either the primary or secondary diagnosis code (Hart & Hopkins, 2004).

The questions that this research will answer include:

Question 1. Is the CDAD prevalence increasing in Florida?

Question 2. Are the mortality rates among CDAD patients increasing in Florida?
Question 3. Is patient age a contributing factor for increasing CDAD prevalence in Florida?

Question 4. Are patients with CDAD showing an increase in morbidity from the disease through the years of this study?

Question 5. Can an assumption be made as to when the ‘more virulent’ strain of Clostridium difficile entered Florida?

Other factors discussed are the change in length of hospital stay for patients that are infected with CDAD, and if gender and racial ethnicity play a role in being more susceptible to Clostridium difficile. These factors will be addressed in an effort to explain the prevalence of CDAD in Florida.

Although both antibiotics and infection control practices are pertinent topics for CDAD, unfortunately the AHCA data does not allow for a way to measure how these two factors are affecting hospitals in Florida. Information on these two subjects will be provided to give a more complete background of the disease and the direction some of the research is headed.

Information for this study was extracted from AHCA data. This study uses the hospital discharge data portion of the AHCA data. The data set includes all of the patients discharged from Florida’s acute care hospitals, not including federal hospitals. This study has been designed to research the effect of CDAD prevalence on patients discharged from Florida’s acute care hospitals.
Chapter Two: Background on *Clostridium difficile*.

**HISTORY**

*Clostridium difficile* is an anaerobic spore forming gram-positive rod that is the most common cause of nosocomial associated diarrhea. Originally named *Bacillus difficile*, *Clostridium difficile* was first described in the mid-1930s (Voth & Ballard, 2005). This bacterium typically has been considered a nuisance causing minor amounts of disease and delaying patients discharge from the hospital by a few days. In 1978, *Clostridium difficile* was identified as the primary cause of psuedomembranous colitis and was proven to be a primary isolate from the feces of humans undergoing clindamycin therapy (Voth & Ballard, 2005). Typically, *Clostridium difficile* has been difficult to remove from a hospital setting because of its spore production that allows the bacterium to survive longer in this environment. Testing for the bacteria has been difficult and labor intensive in the past. Many new tests have been invented to make recognition of the disease quicker and easier.

A report by the Canadian Medical Association discusses that the old style hospitals in Canada were not equipped to care for *Clostridium difficile* patients (Eggertson, 2005). Eggertson’s paper contains quotes from other articles that hospitals built 100 years ago were not capable of curtailing a hospital induced problem like *Clostridium difficile* (Eggertson, 2005). Eggertson’s article also discusses that some Canadian medical professionals are downplaying the increased prevalence of *Clostridium*
difficile (Eggertson, 2005). At the beginning of the 21st century the prevalence of CDAD in hospitals seemed to change and the first inklings of these changes started to appear in peer reviewed journals. Eggertson reports that at this time, especially in Montreal, a significant amount of increased patient discharges with CDAD started to occur together with an increase in deaths due to *Clostridium difficile* (Eggertson, 2005). Some authors have even labeled the problem as an epidemic (Eggertson, 2005). This bacterium is now starting to garner more press worldwide and has started to raise concerns because of increased prevalence of CDAD in more and more countries. These facts are one of the major reasons this research project is being done.

CLINICAL FEATURES

*Clostridium difficile* associated disease

*Clostridium difficile* manifests itself most readily as *Clostridium difficile* associated disease. Onset of symptoms usually occurs in 5-10 days after antibiotic use, but ranges from 1 day to up to 10 weeks after antibiotics are stopped (Oldfield, 2004). The extremes of the ranges (1 day and 10 weeks) for onset of symptoms are rare. Clinical symptoms include watery diarrhea, fever, loss of appetite, nausea, and abdominal pain/tenderness (CDC *Clostridium difficile*: Information for healthcare providers, 2005). This disease is the only nosocomial diarrhea from the *Clostridium* family that should readily be screened for in hospital settings (Heimesaat, Gransow, Leidinger, & Liesenfeld 2005).

Once the bacterium is in the intestinal tract it causes disease by secreting toxins. These toxins cause the problems associated with infections from *Clostridium difficile*, and also provide the means to more readily detect the disease (Voth & Ballard, 2005).
These toxins lead to more problems and contribute to a higher virulence of the bacterium. The other complications of the disease are asymptomatic colonization, diarrhea, pseudomembranous colitis, sepsis, toxic megacolon, colonic perforation, and death (CDC Clostridium difficile: Information for healthcare providers, 2005). Other conditions associated with the bacteria that cause more severe problems are white blood cell count of >20,000 or less than 1500 cells/mm cubed, abdominal pain associated with a pre-existing condition or post-operatively, or the presence of bowel wall thickening and ascites (determined by CT or abdominal radiography) (McEllistrem, Carman, Gerding, & Zheng, 2005).

Asymptomatic colonization is believed to be as high as 5% in normal adults. Some reports from long term care facilities set the disease carrier rate higher, but the numbers vary depending on the facilities pooled (Simor et al, 2002). Other reports show that this rate in adults may be as high as 20% of the people cultured (Oldfeild, 2004). This rate seems high compared to other published reports, but it is mentioned here to show the diversity of CDAD carrier rates. A person may carry the bacteria in their colon and not exhibit any symptoms and then in 2 months spontaneously defecate the remaining bacteria and not be a carrier.

Pseudo-membranous colitis

One of the symptomatic signs of CDAD is the presence of pseudomembranous colitis. The detection of psuedo-membranes is a highly specific indicator of CDAD and almost pathognomonic of the disease (Bouza, Munoz, & Alonso, 2005). Pseudomembranous colitis appears in less than 25% of the discharges of CDAD, and is characterized by white-yellowish plaques present anywhere in the colon (Bouza et al,
Pseudomembranous colitis is a good sign that the disease is present, but as stated does not always occur and would require a very invasive test to prove that it is present.

Perforated Colon and Toxic Megacolon

Some manifestations of *Clostridium difficile* in advanced stages are toxic megacolon and perforated colon. Toxic megacolon is a dilated colon with abdominal distention that is usually manifested in Crohn’s disease and ulcerative colitis patients (Nayer, Vetrivel, McElroy, Pai, & Koerner, 2005). The usual symptoms consistent with toxic megacolon are hemorrhagic and necrotic colitis from caecum to lower sigmoid colon sparing of the rectum. Toxic megacolon can become very dangerous and can lead to bowel surgery to repair the damage. In CDAD patients toxic megacolon is rare, but is a recognized complication (Nayar, Vetrivel, McElroy, Pai & Koerner, 2005). Perforated colon is another advanced stage of CDAD causing perforations in the wall of the colon.

Septicemia

Septicemia occurs when bacteria enters the bloodstream and causes an infection. This condition is very serious and if not treated can cause death. The treatment for septicemia is antibiotics. This condition, when discussing CDAD, can be caused by the disease or the treatment for septicemia can lead to an infection with *Clostridium difficile*. Septicemia is a problem inherent when using hospital discharge data, because the time for onset of septicemia is not recorded in the records.

Death

The increase in deaths of patients that have been diagnosed with CDAD is a growing concern in Canada, United States, United Kingdom and other countries. McDonald and his colleagues reviewed the mortality from this disease for the year 2000
and 2003. They found that although the number of deaths had risen from 8000 in the year 2000 to 15000 in the year 2003, the percent mortality did not rise significantly in the years 2000 to 2003 (McDonald et al, 2006). Researchers have begun to notice that death is becoming a more common occurrence among patients that have *Clostridium difficile*. Death occurs in CDAD patients when the bacteria become too much for the body to recover from the disease or the treatment is ineffective. It is feasible that patients with *Clostridium difficile* could have other illnesses that predispose them for death.

**Epidemiology**

**Age**

A majority of the literature examined suggests that age is an important factor causing CDAD. An older patient is more likely to contract the disease (McDonald et al, 2006). The age factor is compounded by the fact that older people are more likely to be hospitalized. Increasing a person’s stay-time in a hospital increases the likelihood that the person will be introduced to the bacteria.

The other extreme, neonate and pediatric patients, have a low prevalence for CDAD (Tang, Roscoe, & Richardson, 2005). The interesting fact about neonates is that they tend to have higher colonization of the bacteria, as high as 64%, in their bowels, but the prevalence of CDAD in neonates is low (Tang et al, 2005). Tang and his colleagues recommended that routine testing of infants for *Clostridium difficile* is not necessary because of the low occurrence of disease among this age group (Tang et al, 2005).

**Gender and Racial Distributions**

Gender and racial distributions do not appear to predispose anyone for CDAD. No literature was found that suggested a factor associated with *Clostridium difficile* for
any gender or racial group to have a higher frequency of this disease than any other group. This makes sense because Clostridium difficile is caused by a bacterium that affects hospitalized patients, independent of gender or race.

Geographical distribution

An article by the Canadian medical association journal reported that too many hospitals in Montreal are battling outbreaks of Clostridium difficile (Eggertson & Sibbald, 2004). This report has been followed by other reports from Canada attempting to define the CDAD problem and why it is occurring. Another researcher from the Netherlands discusses outbreaks occurring in his country and refers to similar problems that the United Kingdom (UK), Canada, and the United States (US) are experiencing (Brierley, 2005). The CDAD problem is also reported by a researcher in Sweden indicating that this country is also experiencing an increasing prevalence of CDAD (Noren, 2005). These reports suggest that the prevalence of this disease is increasing and according to published reports occurs more frequently in developed countries. Therefore, the findings of this research paper that focuses on data generated in Florida may provide important information about CDAD prevalence.

Pre-existing medical conditions

Another factor considered for the epidemiology of CDAD is pre-existing medical conditions. Similar to the age factor, pre-existing complications from other diseases appear to create conditions for contracting CDAD. Any medical condition that requires a person to be placed on antibiotics and to have a prolonged stay in the hospital will increase a persons risk for an infection with Clostridium difficile. The risk of developing CDAD as a hospital outpatient is about 7.7 discharges per 100,000 patients, while the
inpatient risk rate can be as high as 25 to 60 discharges per 100,000, depending on the antibiotics used (Mylonakis et al, 2001).

One pre-existing condition that is believed to cause CDAD is the use of proton pump inhibitors (PPI). PPI are drugs that attempt to reduce the amount of acidity in the stomach. One such drug is Nexium®. Some authors believe that this class of drugs has contributed to the increasing prevalence of CDAD (Dial, Alrasadi, Manoukian, Huang, & Menzies, 2004; Kazakova, et al, 2006). Other researchers have noted PPI use, as a cause of increase in CDAD discharges, is heavily confounded by length of hospital stay and age of the patient (Pepin et al, 2005b). Other researchers found that PPI use did not significantly cause increases in CDAD (Loo et al, 2005). In an effort to look into community acquired CDAD, researchers are continuing to look at gastric acid and suppressive agents (such as PPI) as reasons why more persons that have no history of being in a hospital might be contracting CDAD (Dial, Delaney, Barkun, & Suissa, 2005). More research into this topic needs to be performed to make an accurate assessment of the affect of PPI on CDAD prevalence.

MICROBIOLOGY

The primary effect of *Clostridium difficile* on the human body are the production of two toxins produced during bacterial secretion. These toxins secreted by *Clostridium difficile* are labeled toxin A and toxin B. Toxin A is considered an enterotoxin and cytotoxin and toxin B is a cytotoxin (McDonald et al, 2006; Gerding, 2005). These toxins are considered the main virulence factors for the disease. The enterotoxin (toxin A) causes disease by increasing the release of water, which will lead to an increase in the release of electrolytes. This increase in the release of both electrolytes and water leads to
the diarrhea portion of the disease. The cytotoxin (both A and B) acts by killing neighboring cells that will in turn cause the inflammation associated with the disease. Some evidence is provided, however, that patients having no toxin A and having toxin B still have the disease (Voth & Ballard, 2005).

The toxins of *Clostridium difficile* are increasingly becoming important in identifying the extent of the disease. Voth and Ballard quoted that a relationship has been proven to exist between toxin levels and development of psuedomembranous colitis (Voth & Ballard, 2005). These toxins have also been important in the genetic mapping of the organism. Mapping of the organism, in the future, may lead to new mechanisms to limit the growth of the organism.

*Clostridium difficile* will grow in an anaerobic environment on normal blood agar, but this process is time consuming and other tests have been developed that shorten the time required for detecting CDAD toxin production (Voth & Ballard, 2005). Spore production readily occurs in a hospital environment. These spores carry the bacteria in a capsule that can withstand environmental pressures for many weeks and even months in some charges (Gerding, Johnson, Peterson, Mulligan & Silva, 1995). These spores are highly resistant to disinfectants and cleaning procedures.

**TRANSMISSION**

The most likely transmission of *Clostridium difficile* occurs from the hands of hospital personnel, fomites, or the environment surrounding hospital or nursing home buildings (Simor et al, 2002). Therefore, locating the sources of this bacterium in hospitals is very important. A patient who has *Clostridium difficile* and shares a room with a patient who uses antibiotics increases the CDAD prevalence for the antibiotic user.
(McConnell, 2002). Also, a person that shares bathroom facilities with an infected CDAD patient has an increased prevalence for CDAD. If the hospital facilities are not properly cleaned or the infected patients are not detected and isolated appropriately, then patients who share rooms with CDAD patients will have a significantly higher chance of contracting CDAD.

In Canada, Pepin and his colleagues have observed that the infrastructure of some of the Canadian hospitals contributed to the problem they are having with *Clostridium difficile* (Pepin et al, 2005b). Pepin and his colleagues refer to conditions such as old plumbing, walls that are decaying, and 4 to 6 patients per room as some of the infrastructure problems that persist in the hospitals of Quebec, Canada (Pepin et al, 2005b). Pepin also notes that the population of Quebec is aging, and along with an increased use of alcohol hand rubs, may have led to the increase in discharges noted in that country (Pepin et al, 2005b). Hospital objects that tend to carry the disease are commodes, bathing tubs, and electronic thermometers. These objects need to be monitored closely because of their propensity to carry spores of the bacteria (Gerding et al, 1995). Besides antibiotics, chemotherapeutic agents also seem to place patients at risk for the disease (Gerding, 2005).

**DIAGNOSIS**

In the past, diagnosis of *Clostridium difficile* relied solely on culture for detection. Patients with leukocytosis and hypoalbuminemia associated with their diarrhea should be considered candidates to test for the presence of *Clostridium difficile* toxins in their stool (Oldfield, 2004). The current hospital laboratory detection method is direct testing by enzyme immunoassay for toxin A and/or B which has a sensitivity and specificity of 88-
93% and 99-100% respectively (Tang et al, 2005; Russmann, Panthel, Bader, Schmitt, & Schaumann, 2007). This test provides a much more rapid detection of the bacteria. Patients in a hospital that are on antimicrobial therapy and discharge 3 or more watery or unformed stools in a 24 hour period should be tested for *Clostridium difficile*. Cell cytotoxicity testing with a sensitivity of 80-90% and specificity of 99-100% is considered the gold standard for detection of CDAD toxins, but can take up to 24 hours for detection so is not routinely used for rapid detection in a hospital setting (Price et al, 2006).

**TREATMENT**

**Antibiotics**

The first step in treatment of *Clostridium difficile* is to stop using the offending antibiotics (Oldfield, 2004). Some studies have shown that in 15-23% of CDAD discharges discontinuing use of the offending antibiotic can relieve symptoms (Aslam et al, 2005). In some instances changing treatment to a more effective antibiotic is necessary to not only make the patient better but also to prevent the occurrence of CDAD.

Metronidazole is the drug of choice when treating an infection with *Clostridium difficile* (Aslam et al, 2005). Oral Vancomycin is used in place of Metronidazole when patients fail therapy with Metronidazole, a more severe disease is encountered, or a patient is pregnant or less than 10 years old (Modena, Gollamudi, & Friedenberg, 2006). Metronidazole is considered the first choice to prevent further colonization of Vancomycin resistant enterococci (VRE) (Oldfield, 2004). Bacitracin and Teicoplanin have been used to treat CDAD, but are not considered the first line of antibiotics to treat the disease (Oldfield, 2004; Aslam et al, 2005).
There are antibiotics that are being studied as to their effectiveness against *Clostridium difficile*. Researchers are trying to find antibiotics that are more effective at killing *Clostridium difficile* and preventing the bacterium to gain resistance. Some researchers have looked more into the effectiveness of Metronidazole (Musher et al, 2005). Other researchers have investigated giving oral antibiotics versus intravenous antibiotics preoperatively (Wren, Ahmed, Jamal, & Safadi, 2005). The research into new drugs has led investigators to look at two drugs called Nitazoxanide and fusidic acid (Wullt & Odenholt, 2004; Aslam et al, 2005). This information on antibiotic usage is presented because of the important role that antibiotics play in the prevalence of CDAD.

Alternative methods

Alternative methods have been shown to be somewhat effective in treatment of CDAD. The methods in use include, with limited effectiveness, probiotics (introducing helpful bacteria into the colon), immunoglobulins, and steroids (Aslam et al, 2005). Some of the probiotics in use are yeasts, Bifid bacterium, Lactobacillus GG, L. rhamnosus, L casei, L. plantarum, and Enterococcus faecium (SF68) (Dendukuri, Costa, McGregor, & Brophy, 2005). Other methods in use are the use of Cholestyramine, which binds the toxins of *Clostridium difficile* and inactivates those toxins (Oldfield, 2004). Unfortunately, Cholestyramine inactivates Vancomycin when the two drugs are used together.

PREVENTION

Cleaner hospitals

Ways to prevent the patient from contracting the disease rely on adequate cleaning of the hospital rooms, equipment, and environment. *Clostridium difficile* spore
production allows the bacteria to survive for up to 60 days in the hospital environment. This presents a problem for housekeeping in the hospital. Appropriate agents that are sporicidal are needed when cleaning rooms that contained previous patients with *Clostridium difficile* (Wilcox et al, 2002). These agents can be tertiary ammonium, oxygen-based, hypochlorite disinfectants, and detergent based (Wilcox et al, 2002).

Effective cleaning of hospital environments is also a topic that this study will be unable to access efficiently. The CDC recommendations in 2003 for appropriate cleaning agents to eradicate *Clostridium difficile* from the environment include meticulous cleaning of all surfaces followed by hypochlorite based germicides as appropriate (Schulster & Chinn, 2003). Two other groups of researchers also investigated which cleaning agents are the most effective at reducing the amount of *Clostridium difficile* in the environment and also decreasing the number of CDAD discharges. These researchers noted varying degrees of effectiveness (Fawley, Parnell, Verity, Freeman & Wilcox, 2005; Wilcox et al, 2003). Unfortunately, current data as to what cleaning agents are used routinely in Florida hospitals is not available. The CDC guidelines are the best recommendations to limit the amount of bacterium that persist in the environment.

**Isolation/Precautions for CDAD**

The CDC isolation precaution guidelines for *Clostridium difficile* are to place the patient in contact isolation for the duration of their illness (Garner, 2005). Contact precautions include placing the patient in a private room with their own bathroom or if a private room is not available placing them in a room with another CDAD patient. When both of these conditions can not be met patient placement needs to be carefully considered because of the infective nature of *Clostridium difficile*. Gloves should be
worn when entering the room and the gloves should be removed before leaving the room. Gowns should be worn if the caregiver is expected to have substantial contact with the patient, environmental surfaces or items in the patient’s room. Remove the gown before leaving the patient’s environment (Garner, 2005). Equipment to be used on the patient should be limited only to the patient whenever possible. Sharing of any patient care equipment should be done only after thorough cleaning and disinfecting of the equipment before using on another patient (Garner, 2005). Avoidance of rectal thermometers and cleaning the rooms of infected patients should be done with a 1:10 bleach solution (Bartlett, 2006). Diarrhea in an adult that has a history of recent antibiotic use is also to be considered for contact isolation so as to prevent a potential spread of *Clostridium difficile* even though CDAD status has not made (Gardner, 2005).

**Hand hygiene**

It is worthy of note here that the CDC recommendations for hand hygiene to prevent a patient from contracting any diseases, including CDAD. No specific recommendations have been given for *Clostridium difficile*, but in 2002 the appropriate recommendations for hand washing were given by the CDC. The first and most important recommendation that is given is if hands are visibly soiled with blood or body fluids (including feces) that they must be washed with soap (antibacterial or non-antibacterial) and water (Boyce and Pittet, 2002). This recommendation is a category IA meaning it is strongly recommended and strongly supported by studies on the topic. Other recommendations associated with CDAD are decontamination after contact with patient’s skin (category IB), decontamination of hands after contact with blood or body fluids when not visibly soiled (category IA), decontamination of hands after contact with
inanimate objects in the immediate vicinity of the patient (category II), and the
decontamination of hands after removing gloves (IB) (Boyce and Pittet, 2002).

Drug therapy

Monitoring of drug therapy is another effective means of preventing Clostridium
difficile. Over medication of patients is a way to increase the prevalence of CDAD in our
hospitals. Clindamycin and the Cephalosporin family of drugs are antibiotics that appear
to cause the most problems with infection rates of Clostridium difficile (Thomas,
Stevenson, Willliamson, & Riley, 2002). Other drugs that have attributed to cause the
disease are Fluoroquinolones, Macrolides, and intravenous beta-lactam/beta-lactam
inhibitors (Pepin et al, 2005). Research into which routinely used antibiotics are causing
discharges of CDAD is well documented and has value when considering the best drug to
give patients that require treatment with antibiotics (Starr, Martin, McCoubrey, Gibson,
& Poxton, 2003; Gopal, Mahankali, and Starke, 2003). Hospitals should responsibly
monitor drug use and especially the drugs that are known to cause discharges of CDAD.
Chapter Three: Literature Review: The rising trend of Clostridium difficile.

DISCHARGE DEFINITION AND CODING FOR CLOSTRIDIUM DIFFICILE

The coding used in this study is the International Classification of Diseases ninth revision (ICD-9), a coding method for hospital records. Clostridium difficile, toxic megacolon and perforated colon have their own specific ICD-9 code, and these codes are specific for determining exact diagnoses. A patient having Clostridium difficile is defined as any person that has tested positive for the bacteria or toxins and has documented more than three loose stools in any given day with any of these symptoms: fever, loss of appetite, nausea, and abdominal pain/tenderness (Oldfield, 2004; Dubberke, Reske, McDonald, and Fraser, 2006). Established verifiable psuedomembranous colitis is also a viable definition of the disease (CDC Clostridium difficile Information for Healthcare providers, 2005).

REPORTING OF SUSPECTED DISCHARGES IN HOSPITAL RECORDS

A person in a hospital has a medical chart filled out by a doctor. This chart upon discharge from the hospital is given to medical records coding personnel. These coders take the chart and use the ICD-9 code system to appropriately assign what the discharged patient was diagnosed with while in the hospital. Additionally, the coders are the persons who make it possible for the hospital to bill the patient for services rendered while in the hospital. Hospital billing relies on the coder assigning the correct ICD-9 code as an acknowledgement of the procedures that were relied upon to treat the patient while in the
hospital. If the coder does not do their job correctly then the patient is over or under charged. The hospital relies on good coders to make the right decisions for accounting and auditing purposes.

Researchers have used discharge information that rely on ICD-9 codes for correct recognition of CDAD. These researchers have tested the validity of using this coding system to correctly identify prevalence of CDAD. Scheurer and his colleagues attempted to show that CDAD prevalence can be appropriately determined by using discharged data. These researchers found that the ICD-9 codes closely approximate the true amount of Clostridium difficile infections that were in their hospital (Scheurer, Hicks, Cook, & Schnipper, 2006). They did note that including symptomatic patients whose test results are readily available at time of discharge is helpful to make a more accurate assessment of disease status (Scheurer et al, 2006). Dubberke and his colleagues also researched the of Clostridium difficile toxin assays with ICD-9 codes attributed to discharged patients (Dubberke et al, 2006). They found that good correlation existed between the two sources and that large scale use of discharge diagnosis codes can be effective in demonstrated prevalence of the disease (Dubberke et al, 2006).

CONDITIONS THAT ACCOMPANY CLOSTRIDIUM DIFFICILE

As discussed earlier there are conditions that Clostridium difficile can progress to. These conditions are perforated colon, toxic megacolon, sepsis, and death. Psuedomembranous colitis is not mentioned here because this condition cannot be differentiated from Clostridium difficile during coding and the disease can occur at the beginning of a Clostridium difficile infection. Sepsis is another condition that, using discharge data, is difficult to differentiate from whether or not a person had sepsis before
or after contracting *Clostridium difficile*. The above factors make it difficult to determine which disease caused which condition. In consideration of these factors this study will only list perforated colon, toxic megacolon and death as conditions that *Clostridium difficile* can progress to.

**GENETIC TYPES OF CLOSTRIDIUM DIFFICILE**

In the past few years a large amount of research has been completed to discover the gene structure of *Clostridium difficile*. In addition to the topic of toxins, the scientific community has been searching for strains of *Clostridium difficile* that have been prevalent more often than other strains. The scientific community believes that the presence of at least one of the toxins, either A or B, is necessary for disease, with enhanced virulence when both toxins are present (Martirosian, Szczesny, Cohen, & Silva, 2005). This is important when considering that the Center for Disease Control (CDC) and researchers from Canada have named the strain believed to be the cause of the majority of the new outbreaks as hyper virulent toxin type III ribotype 027 strain (Pepin et al, 2005c). This strain has also been referred to as North American pulso-type I (NAP1)/ribotype 027 (Louie, 2005). This strain has been implicated in a number of outbreak settings of CDAD (Cloud & Kelly, 2007). This strain has also been shown to produce about 15-20 times more toxin than a ‘normal strain’ of *Clostridium difficile* (Louie, 2005). This strain, or a close cousin to it, has also been identified in the UK (Pepin et al, 2005c). This strain is believed to be causing the new problems that are present now: increased prevalence of discharges, more co-morbidities, and higher mortality.
EPIDEMIOLOGY

Risk factors

*Clostridium difficile* associated diarrhea risk factors are important to understand and to be able to diagnose and treat hospitalized patients that may be susceptible to contracting the disease. Six conditions that can lead to CDAD are: history of antibiotic use, anti-neoplastic agents, age > 60 years, gastrointestinal surgery, enemas or stool softeners, and enteric feedings, especially post pyloric (Oldfield, 2004). All of these conditions in some way demonstrate the destruction of the normal commensal flora that exists in normal human large and small intestines. The two most prominent risk factors that have received the most attention are the use of antibiotics and age.

Antibiotics

Some antibiotics are more likely to cause *Clostridium difficile* than others, such as Clindamycin, but even Metronidazole and Vancomycin (both of which are considered for treatment of the disease) have been proven to be a cause of the disease (Oldfield, 2004). A study conducted in Paris, France by Blot and his colleagues determined that chemotherapeutic agents could cause CDAD (Blot, Escande, Besson, Barbut, Granpeix & Asselain, 2003).

Age

The age of a patient is consistently a concern for persons infected with *Clostridium difficile*. Patients >60 years old tend to have a higher prevalence rate, a worse prognosis, and have an increased chance for relapse. There are several reasons for these conclusions, most notably, older people are more susceptible to infections of all
kinds, have a higher chance of being in a hospital, and a higher chance of being on antibiotics. Pepin and his colleagues performed a study on what types of people are considered the highest risk for having CDAD (Pepin et al, 2005a). They researched several characteristics that could conceivably cause CDAD. They separated the years 1991-2004 in two year periods with age groups of ≤17, 18-64, and ≥65. In the early part of this study the 18-64 age groups always seemed to have more discharges of *Clostridium difficile*, but in 2003-2004 that changed drastically showing that the ≥65 age group has over twice as many discharges as the other 2 age groups combined (Pepin et al, 2005a). This is important because of the implications this disease has on geriatric patients. Pepin and his colleagues also noticed that those persons ≥65 also have a significant chance of relapse when compared to the relapse rate for the ≤17 year old age group (Pepin et al, 2005a). The published results of this study are important because drug regimens and testing may need to be adjusted to treat the increasing number of older patients that are contracting this infection.

The opposite end of the age spectrum is of concern as well. With a rising trend of CDAD it is only logical to be concerned with the effect on the very young. A group of researchers from Ontario, Canada undertook a project to determine the effectiveness of treating infants who contracted *Clostridium difficile* (Tang et al, 2005). Their research showed that the patients improved regardless of disease status or whether metronidazole was given or not. This research demonstrates, especially in the younger age groups, *Clostridium difficile* as a cause for diarrhea should not be routinely tested for, and that the diarrhea experienced by infants is routinely from a source other than *Clostridium difficile* (Tang et al, 2005).
Studies of prevalence

Canada

Studies of the rising trend of *Clostridium difficile* have been ongoing because hospitals are concerned about the nosocomial infection rates. Most reports on prevalence of *Clostridium difficile* prior to 2004 discuss a small prevalence for this disease with little threat for the disease becoming a problem. In 2004 the Canadian medical association, discussing infection rates after 2000 reported that a high rate of *Clostridium difficile* is occurring in hospitals in Montreal and 79 deaths had occurred so far (Eggertson and Sibbald, 2004). This preliminary report lacks baseline data or any data to show exactly how much the rates of infection have increased. The report does contain a number of quotes from people stating that the problem will probably become worse with the possibility that *Clostridium difficile* infections could become a serious problem. This report does not show the extent of the problem but mentions that a problem may exist. The Eggertson and Sibbald report is significant because after this report was issued, an influx of information on just how much the disease has increased has been reported and the seriousness of this problem persists in Canada based on the studies of other researchers.

The increased prevalence of CDAD not only persists in Canada, but it occurs in other parts of North America as reported by a number of researchers. Valiquette and his colleagues note that not very good records have been kept for this disease. They researched data accumulated during 1-½ years for discharges of *Clostridium difficile*
reported for a hospital in Montreal, Canada. They found that in January of 2002 the hospital had about 10 discharges of the disease, and in May of 2004 they had almost 40 discharges of the disease and with a high point for the disease in February of 2004 of almost 70 discharges (Valiquette et al, 2004). The prevalence rates for this data is 2.1 discharges per 1000 admissions in 2002, 10 discharges per 1000 in 2003, and a projected 18 discharges per 1000 admissions in 2004 (Valiquette et al, 2004). This report shows why Canada is concerned and has led Jacques Pepin and some of his colleagues to begin a formal research study of the complexity of the *Clostridium difficile* problem for Quebec, Canada.

Pepin and his colleagues researched the Canadian *Clostridium difficile* problem and issued four reports that attempt to define the various factors contributing to increased prevalence of *Clostridium difficile*. The first report reviewed the prevalence of CDAD from 1991 to 2003 at the Centre Hospitalier Universitaire de Sherbrooke (CHUS). This study is a retrospective chart review investigating details such as age, gender, CDAD acquired place, immunosuppression, and antibiotic treatments (Pepin et al, 2004). This hospital provided a well defined population making it possible for the researchers to estimate population based prevalence. The prevalence of CDAD in this Canadian region increased from 35.6 per 100,000 people in 1991 to 156.3 per 100,000 people in 2003 with the 65 years old or higher age group increasing from 102.0 to 866.5 per 100,000 people (Pepin et al, 2004). This study indicates that Canada has a legitimate problem with this disease that needs addressing. The factors contributing to higher prevalence of CDAD as indicated by the research report of Pepin et al include immunosuppression, tube feeding, and the place acquired (hospital versus community).
Pepin and his researchers next investigated if death rates and length of hospital stay were significant factors for the increased prevalence of this strain of bacteria. The following report confined the research to determine if co-morbidity contributed to the disease and also contributed to death in a patient that had CDAD (Pepin et al, 2005c). The database used for this study originated from records of the 687 bed tertiary hospital in Montreal, Canada. After 365 days the study showed that on average those patients that had been diagnosed with CDAD had a survival rate of about 65% as compared to the control subjects' survival rate for the same time period of about 80% (Pepin et al, 2005c). This indicates that a person who has CDAD has a higher probability of dying. Pepin and his colleagues also completed a 30 day co-morbidity survival rate study and compared the values to the survival rates of patients after 365 days. They reported for the 30 day study that CDAD merely precipitated an event that could have occurred in any discharge a few months later, but for the 365 day study, about one-sixth of the inpatients with CDAD died (Pepin et al, 2005c). This means that a person contracting CDAD has a higher chance of dying after one year than the group of people that are admitted to a hospital that have no record of CDAD. Pepin and his researchers attributed most of their infections to the NAP1/027 strain (Pepin et al, 2005c). Therefore, the survival probabilities for this strain may not necessarily compare to other strains of *Clostridium difficile*.

Some issues that have also been reported for Canada have been discussed earlier in this paper: a) the recurrence rate for metronidazole treatment is increasing and b) the propensity of fluoroquinolones to cause more discharges of CDAD (Pepin et al, 2005a; Pepin et al, 2005c). Both of these reports provide adequate evidence that the prevalence
of CDAD is increasing in Canadian hospitals. These reports provide significant factors contributing to the rising prevalence of CDAD and offer methods that the health community can use to reduce the rising prevalence of CDAD in our own communities. This report by Pepin and his colleagues show that the recurrence of CDAD after metronidazole therapy increased from 15.2% in 1991-1992 to 47.2% in 2003-2004 (Pepin et al, 2005a). This paper contains specific data for only one hospital and it could not be confirmed if the results of the survey apply to any other Montreal hospitals.

The November 2005 report by Pepin and his colleagues provides the most extensive research into antibiotics and their involvement with the disease. This report helps to visualize which drugs have the highest factors for contributing to the prevalence of CDAD in Montreal (Pepin et al, 2005b). The results reported may not apply to other hospitals reported by different researchers. The Pepin report also may not be useful because the patients’ antibiotics have been separated into many groups that decreases the population of discharges reported for each group.

One final study worthy of note that originated in Canada contains research data on the CDAD strain that emerged in Canada, discusses the toxin production for this new strain, and compares the prevalence of this strain compared to previous strains for this bacterium. This new strain is labeled NAP1/027 and is the strain that was discussed earlier in this paper. These researchers found that this strain produces 16 times more toxin A and 23 times more toxin B than control strains (Warny et al, 2005). This greater toxin production led these researchers to hypothesize that the new deadlier strain would increase the prevalence of CDAD. Intuitively this makes sense because an increase in toxin production would increase the prevalence of CDAD. A problem with this report is
that the report compares 15 NAP1/027 strains with 25 toxinotype 0 strains (Warny et al, 2005). The report did not appear to have a high number of discharges and this lowers the significance of the report. The culture and growth curve analysis results have been questioned by a group of researchers (Freeman, Fawley, Baines, & Wilcox, 2006). Freeman and her colleagues refute the methods to reproduce growth in vivo with in vitro analysis are not sound enough to give accurate results. The researchers did study the strains from the same geographical areas as the NAP1/027 strains so that geography could not be a factor that confounded the study (Freeman et al, 2006). The report by Warny and his colleagues does a good job of showing reasons why *Clostridium difficile* is starting to cause problems in other regions of the world, but the numbers for amount of toxin may be lower than reported by this research (Warny et al, 2005).

United States

Research results from Canada hospitals concerning *Clostridium difficile* prevalence may be important for US hospitals because Canada is a close neighbor. Valiquette et al researched the *Clostridium difficile* rates for Canada, and other areas of the world to demonstrate that the disease is also increasing in other parts of the world (Valiquette et al, 2004). These researchers used data from Oregon, Pittsburgh, and the US national nosocomial surveillance database. These three respective places all experienced some type of increase whether it was in CDAD prevalence or in mortality rates (Valiquette et al, 2004). More research into the disease in the United States needs to be done to determine the extent of the problem.

A study was completed by Clifford McDonald and his colleagues. These researchers used the National hospital discharge survey information records to conduct
their research. This study is one of the most comprehensive and thorough medical record studies performed on the topic of *Clostridium difficile* (McDonald et al, 2006). McDonald’s report is significant because it defines that the prevalence rates for *Clostridium difficile* are increasing in the US. McDonald et al shows that the prevalence of *Clostridium difficile* increased from 31/100,000 people in 1996 to 61/100,000 people in 2003 (McDonald et al, 2006). This report notes that the increased prevalence in the ≥65 year age group is disproportionately higher at 228/100,000 people as compared to the next younger age group, 45-64 year old, that had a prevalence of 40/100,000 people (McDonald et al, 2006). Another item of note is that this article also observed higher prevalence rates across the entire US with the northeast region of the US having the highest prevalence rates. It is interesting to note the South region, including Florida, has a prevalence rate of about 20 *Clostridium difficile* positive patient discharges per 100,000 people in 1996. This rate increased to just over 40 *Clostridium difficile* positive discharges per 100,000 people in 2003 (McDonald et al, 2006). This report demonstrates that the prevalence rates of CDAD are increasing in the US and also increasing in the south region of the US.

A previous study done at a statewide level was performed in Oregon (Chandler, Hedberg, & Cieslak, 2007). The prevalence of CDAD in Oregon increased from 1.4 to 3.3 discharges per 1,000 discharged patients from 1995 to 2002 (Chandler et al, 2007). These researchers were unable to find any notable changes in hospital practices that could have perpetuated the rise in prevalence. This reports use of a descriptive study is close in method type to the study that is being researched in this paper for the state of Florida.
United Kingdom

The United Kingdom, similar to U.S. and Canada, has also been experiencing a rise in prevalence rates of *Clostridium difficile* accompanied with a rise in death rates (Brierley, 2005). Rob Brierley discusses specifically the number of deaths was at 25 across 15 hospitals, but does not provide baseline information for CDAD prevalence in UK. Brierley does refer to some preliminary typing of some of the discharges that occurred at the Stoke Mandeville hospital, where the CDAD epidemic was believed to have begun. The preliminary typing indicates that the ribotype 027 strain has at least partial blame for the outbreak in the UK (Brierley, 2005). Valiquette and his colleagues report using information gleaned from the UK health protection agency communicable disease centre (Valiquette et al, 2004). This report shows that in 1986/87 the hospitals had <2000 discharges of *Clostridium difficile* as compared to >12,000 discharges in 2000/01 (Valiquette et al, 2004). This report demonstrates that the problem with this disease is not confined to Canada, but other parts of the world are experiencing the same *Clostridium difficile* problem.

Pepin and his colleagues also note that CDAD prevalence is increasing in the UK and that further research is needed to control these increases. They report that the prevalence of CDAD has doubled from 2001 to 2004 (Pepin et al, 2005a). The report contains preliminary information that ribotype 027 strain has spread to some areas of the U.K. and has contributed to the increased prevalence of CDAD for this country.

The previous articles discuss ribotype 027 strain typing to show that this strain in England is similar to the one observed in North America. Research by Warren Fawley and his colleagues included identifying the important subtypes of the disease in Leeds,
United Kingdom (Fawley et al, 2005). Fawley’s results showed on ward A that 95.2% of the *Clostridium difficile* infections were attributed to the PCR ribotype Ia, and in the other ward researched, ward B, the ribotype causing 97.5% of the discharges was type PCR ribotype Ia (Fawley et al, 2005). PCR ribotype Ia is similar to the NAP1/027 strain that has been identified in North America. Fawley also discusses that this strain seems to be thriving and growing and is becoming the more predominant strain in other parts of the U.K. as well.

Other countries

Warren Fawley’s typing of *Clostridium difficile* strains led him to report some instances of PCR type Ia, commonly referred to as ribotype 1, in Belgium and France (Fawley et al, 2005). An outbreak of CDAD was noted in Paris, France in 1996, but a specific strain of the bacteria was not identified as the culprit (Blot et al, 2003). This study attempted to define why *Clostridium difficile* is causing infections among chemotherapy patients. This report provides some evidence that outbreaks of this disease are occurring outside of the U.S., U.K., and Canada.

Norwegian researchers reported on *Clostridium difficile* infections observed in two university hospitals in Oslo, Norway. These researchers attempted to discover the extent of the infections caused by this bacterium by examining risk factors that may contribute to the increased prevalence of CDAD (Berild et al, 2003). The report focused on reasons for the disease outbreaks in their facilities. Berild and colleagues discuss prevalence of CDAD in two hospitals. In 1993 one hospital reported a prevalence of about 4 discharges of CDAD per 100,000 people as compared to that same hospital
having a prevalence of about 17 discharges of CDAD per 100,000 people in 2001 (Berild et al, 2003).

Sweden is another country reporting mortality rates caused by CDAD. Torbjorn Noren reports that the mortality rate for *Clostridium difficile* from a PCR ribotype 17 strain (serogroup C) was as high as 13% in the year 2000 (Noren, 2005). Noren’s report attempts to confirm that in Orebro county, Sweden the mortality rate is similar to rates reported by Canadian researchers. Noren’s report shows that high mortality rates are not confined to only North America but that other countries are experiencing strains of deadly *Clostridium difficile* infections.

**STUDIES TO PREVENT THE INCREASING PREVALENCE OF CDAD**

The rising trend of CDAD is apparent and methods are needed to prevent the increased prevalence of this disease. Thomas J. Louie makes some suggestions based on various articles he has researched (Louie, 2005). His suggestions are reduction in patients in crowded wards, lower toilet to bed ratios, and increased infection control methods in hospitals to treat CDAD infections (Louie, 2005). These suggestions are given repeatedly by other researchers and are not new. One problem with these suggestions is that they require hospital funds to make the necessary changes. Therefore, research that identifies less expensive methods for preventing the prevalence of CDAD and growth of the bacteria are important.

One of the factors noted by researchers that can reduce *Clostridium difficile* infection rates is modifying the antibiotics given in hospital wards. In Western Australia Thomas and her colleagues accumulated data as they made efforts to curtail the prevalence of *Clostridium difficile* in their hospital (Thomas et al, 2002). These
researchers noted that the prevalence of *Clostridium difficile* has been increasing gradually at their hospital and methods were used to modify antibiotic usage in an attempt to curtail the increasing infection rates (Thomas et al, 2002). This hospital almost completely abolished the use of third-generation cephalosporins by the year 2000 in an effort to prevent further growth of the bacteria. This method decreased the prevalence from almost 3 discharges of CDAD per 1000 patients in 1993 to below 1 discharge of CDAD per 1000 patients in 2000. The other statistic of note is that by 2000, the amount of CDAD per occupied bed days (20 patients per 100,000 bed days) was at the lowest rate in this hospital since 1983 (Thomas et al, 2002). This is convincing research that using antibiotics appropriately can aid in lowering infection rates for CDAD. This report fails to record the alternative drugs used to treat patients. If the alternative drugs used in this hospital were Metronidazole and Vancomycin, then the data seems reasonable because Metronidazole and Vancomycin are drugs that have been used successfully to treat CDAD. The report contains a note that they used Clindamycin on a very limited level, which means that Clindamycin was not the drug of choice to replace the use of third-generation Cephalosporins. The amount of people in the study was high providing confidence that the values given are statistically significant.

A report by Vesta and colleagues attempted to show that no specific drug is responsible for discharges of CDAD (Vesta, Wells, Gentry, & Stipek, 2005). This research, although it had good intentions, did not have enough data points to be statistically significant. The report contained data for only 144 patients and separating the data into 9 drug categories reduced the statistical significance of the report too low to be comfortable with the conclusions. As discussed earlier, Pepin and his colleagues did
show that Floroquinolones, all Cephalosporins, Macrolides, and Clindamycin were factors affecting higher prevalence of *Clostridium difficile* in Quebec hospitals (Pepin et al, 2005b). This report used a database containing 7421 discharges of CDAD. The Pepin et al report concludes that the drugs studied do increase prevalence of CDAD in hospitals (Pepin et al, 2005b).

A previous paragraph noted that research studies reported on the efficacy of Metronidazole and Vancomycin in treating the newly emerging strains of *Clostridium difficile* (Freeman, Stott, Baines, Fawley, & Wilcox, 2005b). At Leeds, U.K. the resistance of *Clostridium difficile* bacteria to Vancomycin and Metronidazole remains small according to their research. Another effort to find new and more efficient drugs was undertaken by Jane Freeman and her colleagues. This report discusses the effectiveness of Ramoplanin compared to vancomycin in treating CDAD (Freeman, Baines, Jabes, & Wilcox, 2005a). This report uses hamsters and models treatment by randomizing injections into hamsters for CDAD treatment with either Ramoplanin or Vancomycin. This report showed that, while Vancomycin reduced the amount of bacteria in the intestines during treatment, Ramoplanin reduced both the amount of bacteria and the amount of spores, which Vancomycin failed to do (Freeman et al, 2005a). This suggests that ramoplanin could be a good alternative to Vancomycin. No reports on the effectiveness in humans were found. The research on hamsters is convincing, but further studies into the effectiveness for humans needs to be shown.
Chapter Four: Methods

STUDY DESIGN

This thesis is a descriptive cross-sectional study for the years 1998 thru 2004 to determine the prevalence of *Clostridium difficile* in Florida’s acute care hospitals. Hospital discharge data was analyzed to compare the prevalence, length of hospital stay, age, race, gender, and mortality over time for CDAD positive patients to determine if the values are changes from year to year. The data analysis also compared the mortality rates for CDAD positive patients to those patients that have no record of the disease.

STUDY POPULATION

The study population is persons discharged from Florida’s hospitals not including persons admitted to military hospitals. This data set contains all hospital discharges from Florida’s non-federal hospitals regardless of where the patients’ primary residence is.

INCLUSION CRITERIA

A discharged patient is considered to have CDAD when the primary or secondary diagnosis ICD-9 code is 00845. The discharge information from 1998 through 2004 is included in this study. The year that a person is discharged from the hospital is the year that that person is included in the data base.

EXCLUSION CRITERIA

This data set only contains information from Florida’s non federal hospitals. Data from other states or countries, nursing homes in Florida, and federal hospitals (military
and Veteran’s Association) in Florida are excluded. Patients with CDAD and are not
admitted to a hospital are also not included in this data set. Hospital discharge data
before 1998 and after 2004 are not included in this study.

DATA SOURCES

This study analyses data from the Agency for Healthcare Administration
(AHCA). The AHCA discharge data used in this study contains hospital discharges for
all non-federal hospitals in the state of Florida. This data, with permission of the Florida
Department of Health, is being used in this study to examine the effects of Clostridium
difficile on people being admitted to Florida’s acute care hospitals.

DATA MANAGEMENT

The large amount of information provided by this data required some preparation
to make it usable for the purposes of this study. The biostatistical software in use for this
study is Statistical Analysis Software (SAS) version 8.1 or higher. The data was
provided by year in separate SAS files. There are at least 31 different categories of
information. This information has been provided with no personal identifiers so no
confidentiality has been breached. The discharge information was provided in one-year
increments. There are some minor differences in the names for categories during some
years, and these differences have been changed so that the information could be
combined into one main dataset that contains all information from 1998-2004. Important
categories used in this study are year of discharge, discharge status, length of hospital
stay, gross charges, gender, principal diagnoses code, secondary diagnoses code, patient
age at admission, and patient race.
The information has been compiled on a yearly basis to determine the change over time for CDAD. The prevalence of CDAD has been determined by examining both the principal diagnosis codes and secondary diagnosis codes to establish if the patient was given the ICD-9 code of ‘00845’. The discharges of CDAD have been extracted from the ACHA data so that details of patients who have been diagnosed with the disease can be analyzed. After the group of \textit{Clostridium difficile} patients was extracted from the main data, the group was then compared to the remaining non-CDAD patients group to determine prevalence of CDAD. The comparison of \textit{Clostridium difficile} positive patient population to the non-diseased hospital patient population was done for each year (1998 through 2004) to determine if there are any differences.

Along with determining CDAD prevalence, the next major variable of interest is discharge status. Discharge status is important because this is the primary method for determining if a patient expired while in the hospital. The information provided in the data that explains discharge status was changed from the 10-11 discharge categories to two discharge categories, whether or not the discharged patient was alive or dead when they left the hospital. These changes allowed this study to determine the death prevalence rates for \textit{Clostridium difficile} positive patients. Changes to the discharge status were performed for both the \textit{Clostridium difficile} positive population and for the non-\textit{Clostridium difficile} positive population. Death as an outcome is not only important to establish for all patients, but also for all patients that are positive for \textit{Clostridium difficile}. 

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DEFINITION OF VARIABLES

Variables are explained in these paragraphs providing an understanding for interpreting the results of the data analysis. The length of hospital stay is determined by subtracting the date a person was discharged from the hospital from the time at which they entered the hospital. If a person is discharged from the hospital and then readmitted to the hospital at some later time after they have been discharged this event would be considered a new admission and the length of hospital stay would start over with the new admission regardless of what reason the new admission is for. Cost per patient is provided in the data and represents the total dollars charged to the patient.

A patient’s gender is given as male, female or other in the ACHA data. The race group is divided into 3 categories: white, black and other. The other category includes persons from races that include American Indian/Eskimo/Aleut, Asian or Pacific Islander, White Hispanic, Black Hispanic, and other.

As discussed previously, *Clostridium difficile* is given an ICD-9 code of 00845. Other conditions of note for this study are toxic megacolon and perforated colon. These conditions are coded as 556.9 and 569.83 respectively (Hart and Hopkins, 2004). These two conditions are discussed as they pertain to persons who have *Clostridium difficile*.

DATA ANALYSIS

This data has been analyzed on a year-by-year basis to more fully understand the effect that *Clostridium difficile* has had on the Florida hospital population. Starting with the year 1998, the data has been manipulated to estimate means and sequencing operations was performed to define if the variables important to this study are present. Values computed for this study include percent female, percent non-white, mortality,
total patients per year that were diagnosed with *Clostridium difficile*, mean age of population per year, average length of hospital stay per year, and total gross charges per patient per year. These values were then compared to the same values estimated for the *Clostridium difficile* positive group. The values were used to compare the *Clostridium difficile* positive population with the full discharged patient population for each year. The values for mortality among the CDAD patients were compared to the mortality for patients that did not have CDAD.

To expand the discussion about ages the data was divided into 11 age groups. The data was divided into 11 age groups to provide a better understanding concerning the role age plays in the disease process. The 11 age groups are ≤ 1, > 1-10, >10-20, >20-30, >30-40, >40-50, >50-60, >60-70, >70-80, >80-90, and >90. These age groups were then compared on a year by year basis to consider if changes in average length of hospital stay, prevalence, mortality rates, race distribution and gender percentages occurred over the years of the study.
Chapter Five: Results

STUDY POPULATION CHARACTERISTICS

Age

An analysis of the AHCA data yielded the following results: The median age for the non-CDAD patients discharged from Florida hospitals decreased from 56 in 1998 to 55 in 2004. The *Clostridium difficile* positive patients increased slightly from a median age of 74 in 1998 to a median age of 75 in 2004 (See appendix A). The percentage of persons with CDAD that are >60 years old is 74.7% in 1998 and 76.8% in 2004 (see appendix B). These numbers are much higher than the percentage of persons without CDAD that are > 60 years old [45.8% in 1998 and 43.6% in 2004] (see appendix B).

Table 1: Population of Florida, total number of acute care hospital discharges and the median ages of both the CDAD and non-CDAD groups of discharged patients for the years 1998-2004

<table>
<thead>
<tr>
<th>Variables</th>
<th>Year</th>
<th>1998</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total discharges</td>
<td></td>
<td>2.098</td>
<td>2.155</td>
<td>2.242</td>
<td>2.341</td>
<td>2.382</td>
<td>2.444</td>
<td>2.491</td>
</tr>
<tr>
<td>Ages (in years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median for non-CDAD</td>
<td></td>
<td>56</td>
<td>56</td>
<td>56</td>
<td>56</td>
<td>55</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>Median CDAD</td>
<td></td>
<td>74</td>
<td>74</td>
<td>74</td>
<td>75</td>
<td>75</td>
<td>75</td>
<td>75</td>
</tr>
</tbody>
</table>

Gender

The percentage of females in 1998 for the non-CDAD patient discharge population is 56.97% compared to 56.74% in 2004 (see table 2). The percentage of
females for the CDAD population group differs slightly from the non-CDAD group with 1998 having 57.98% female as compared to 2004 CDAD patients having 58.67% female. The gender distribution will be discussed, in reference to age group stratification, later in this chapter.

Table 2: The gender distribution of the CDAD and non-CDAD Florida acute care hospital patient groups for the years 1998-2004.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Year</th>
<th>1998</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-CDAD male, (millions)</td>
<td></td>
<td>.900</td>
<td>.926</td>
<td>.957</td>
<td>1.001</td>
<td>1.017</td>
<td>1.044</td>
<td>1.069</td>
</tr>
<tr>
<td>Non-CDAD female, (millions)</td>
<td></td>
<td>1.191</td>
<td>1.221</td>
<td>1.276</td>
<td>1.331</td>
<td>1.354</td>
<td>1.383</td>
<td>1.402</td>
</tr>
<tr>
<td>Non-CDAD percent Female</td>
<td></td>
<td>56.96</td>
<td>56.86</td>
<td>57.13</td>
<td>57.08</td>
<td>57.11</td>
<td>57.00</td>
<td>56.75</td>
</tr>
<tr>
<td>CDAD male</td>
<td></td>
<td>3,004</td>
<td>3,152</td>
<td>3,330</td>
<td>4,561</td>
<td>6,184</td>
<td>7,250</td>
<td>8,349</td>
</tr>
<tr>
<td>CDAD female</td>
<td></td>
<td>4,145</td>
<td>4,424</td>
<td>4,521</td>
<td>6,419</td>
<td>8,436</td>
<td>9,903</td>
<td>11,852</td>
</tr>
<tr>
<td>CDAD percent female</td>
<td></td>
<td>57.98</td>
<td>58.39</td>
<td>57.58</td>
<td>58.46</td>
<td>57.70</td>
<td>57.73</td>
<td>58.67</td>
</tr>
</tbody>
</table>

Racial distribution

Race distribution was analyzed using the factor percent non-white. The data was separated into 8 racial classes including no response to the question and a category named other. The percent non-white grouping was used to analyze the data for patients who enter Florida hospitals. The non-CDAD patient population of Florida has a racial distribution of 29.33 percent non-white in 1998 and 33.79 percent non-white in 2004 (see Table 3). For the *Clostridium difficile* positive patients the percent non-white is 18.17 in 1998 and 21.03 in 2004 (see Table 3).
Table 3: The racial distribution of the CDAD and non-CDAD Florida acute care hospital patient groups for the years 1998-2004.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Year</th>
<th>1998</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-CDAD white, (millions)</td>
<td></td>
<td>1.477</td>
<td>1.495</td>
<td>1.552</td>
<td>1.602</td>
<td>1.608</td>
<td>1.627</td>
<td>1.636</td>
</tr>
<tr>
<td>Non-CDAD black, (millions)</td>
<td></td>
<td>0.300</td>
<td>0.304</td>
<td>0.326</td>
<td>0.342</td>
<td>0.350</td>
<td>0.366</td>
<td>0.386</td>
</tr>
<tr>
<td>Non-CDAD other, (millions)</td>
<td></td>
<td>0.313</td>
<td>0.348</td>
<td>0.356</td>
<td>0.387</td>
<td>0.409</td>
<td>0.433</td>
<td>0.448</td>
</tr>
<tr>
<td>Percent non-white</td>
<td></td>
<td>29.33</td>
<td>30.27</td>
<td>30.52</td>
<td>31.23</td>
<td>31.92</td>
<td>32.94</td>
<td>33.79</td>
</tr>
<tr>
<td>CDAD white</td>
<td></td>
<td>5,850</td>
<td>5,976</td>
<td>6,189</td>
<td>8,795</td>
<td>11,770</td>
<td>13,870</td>
<td>15,953</td>
</tr>
<tr>
<td>CDAD black</td>
<td></td>
<td>617</td>
<td>643</td>
<td>774</td>
<td>995</td>
<td>1,388</td>
<td>1,635</td>
<td>2,154</td>
</tr>
<tr>
<td>CDAD other</td>
<td></td>
<td>682</td>
<td>957</td>
<td>888</td>
<td>1,190</td>
<td>1,462</td>
<td>1,648</td>
<td>2,094</td>
</tr>
</tbody>
</table>

Length of hospital stay

Length of hospital stay for *Clostridium difficile* positive patients is one of the largest differences between CDAD and non-CDAD patient populations. In 1998 the non-CDAD patient population average length of hospital stay was 4.94 days compared to 13.47 days for CDAD patients. In 2004 the average hospital stay for non-CDAD patients was 4.88 days and the average hospital stay for CDAD patients was 13.07 days (see table 4).

Table 4: The average length of stay in the hospital for CDAD and non-CDAD Florida acute care hospital patients for the years 1998-2004.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Year</th>
<th>1998</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of hospital stay (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean non-CDAD</td>
<td></td>
<td>4.94</td>
<td>4.93</td>
<td>4.85</td>
<td>4.82</td>
<td>4.85</td>
<td>4.86</td>
<td>4.88</td>
</tr>
</tbody>
</table>

In addition to average hospital stay for the total CDAD and non-CDAD patient populations, this study determined the average length of hospital stay for 11 age groups. The age groups showing the greatest difference between the non-CDAD group and those patients with CDAD are the age groups ≤ 1, >10-20, and >50-60 (see Appendix E).
Cost per patient

The non-CDAD average patient cost increased from $14,401 total charges per patient in 1998 to $25,561 per patient in 2004. These values are much smaller than the patients who contracted CDAD in Florida’s hospitals [$40,773 in 1998 and $63,003 in 2004, respectively] (see table 6 and appendix F). If you multiply the number of persons that had CDAD in 2004 times the additional days in the hospital, the total charge is over 750 million dollars greater than for the non-CDAD patients.

Table 6: The total cost per discharge for CDAD and non-CDAD Florida acute care hospital patients for the years 1998-2004.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Year</th>
<th>1998</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean non-CDAD</td>
<td>Total charges per discharge</td>
<td>14,401</td>
<td>15,459</td>
<td>16,756</td>
<td>18,472</td>
<td>21,204</td>
<td>23,549</td>
<td>25,561</td>
</tr>
<tr>
<td>Mean CDAD positive</td>
<td>40,773</td>
<td>42,983</td>
<td>48,179</td>
<td>51,287</td>
<td>57,603</td>
<td>61,047</td>
<td>63,003</td>
<td></td>
</tr>
</tbody>
</table>

Co-morbidities

Perforated colon affected 27 *Clostridium difficile* positive patients in 1998 and 56 in 2004 (see appendix G). The rate of perforated colon per 1,000 CDAD positive discharged patients is 3.78 in 1998 and 2.77 in 2004 (see appendix H). Toxic megacolon occurred in a higher number of CDAD patients, 44 in 1998 and 92 in 2004 (see appendix G). The rate of toxic megacolon per 1,000 CDAD positive patients is 6.15 in 1998 and 4.55 in 2004 (see appendix H).
CHANGES OF INTEREST IN POPULATION OVER TIME

Discharges

The total number of \textit{Clostridium difficile} positive patients from 1998 to 2004 was 7,149 to 20,201 (see Appendix I). The number of discharges of CDAD per 1,000 discharged patients is 3.40 in 1998 and 8.11 in 2004. Figure 10 shows that the prevalence of CDAD per 1,000 hospital patients continues to increase during the seven years of this study (see Appendix J). The total number of discharges in 2001 rose sharply to 10,980 as compared to 7,851 discharges in 2000. This rise in CDAD is also reflected by the rate per 1,000 patients which rose from 3.50 in 2000 to 4.69 in 2001. This number is important because CDAD prevalence was relatively constant before 2001. The research presented in this study also shows that in 2003 Florida had a rate of 99.9 discharges per 100,000 population of Florida (see appendix K).

Table 7: The number of CDAD positive discharges and CDAD discharges per 1,000 Florida hospital acute care discharged patients for the years 1998-2004.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Year</th>
<th>1998</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total discharges, millions</td>
<td>2.098</td>
<td>2.154</td>
<td>2.242</td>
<td>2.341</td>
<td>2.382</td>
<td>2.444</td>
<td>2.491</td>
<td></td>
</tr>
<tr>
<td>CDAD positive discharges</td>
<td>7,149</td>
<td>7,576</td>
<td>7,851</td>
<td>10,980</td>
<td>14,620</td>
<td>17,153</td>
<td>20,201</td>
<td></td>
</tr>
<tr>
<td>Total CDAD discharges per 1000 patients</td>
<td>3.40</td>
<td>3.51</td>
<td>3.50</td>
<td>4.69</td>
<td>6.13</td>
<td>7.02</td>
<td>8.11</td>
<td></td>
</tr>
</tbody>
</table>

This study also divides the patients in 11 age groups to determine the effect of CDAD on the groups. Figures 11 and 12 demonstrate that not only is the amount of CDAD discharges increasing in Florida, but the prevalence is also increasing (see appendices L and M). One example is the >80-90 age group. In 1998 the number of
CDAD discharges was 1735 and in 2004 the number of CDAD discharges increased to 5483 (see Appendix L). The CDAD prevalence per 1,000 discharged patients in the >80-90 age group is 6.95 in 1998 and 18.40 in 2004 (see Appendix M).

Gender for discharges in the individual age groups

The prevalence of CDAD discharges for gender and racial groups for 1998 through 2004 is shown in Appendices N thru S. Florida’s discharge data was separated into male and female groups with three racial groups, white, black and other races. Generally the female gender in the three racial groups demonstrates a greater prevalence difference when comparing the >1-10 age group to the >10-20 age group than the male gender of the same race. White females have the highest prevalence of all the gender groups (see appendix O). The ‘other’ male gender has the lowest prevalence in the older age groups (see appendix R).

Racial distribution for the age groups

Race was also investigated in this study to determine if race is an important factor. Prevalence in the white race group had the highest numbers for both male and female genders at 18.1 discharges per 1,000 white male >80-90 year old patients for 2004 and 21.2 discharges per 1,000 white female >80-90 year old patients in 2004 (see appendix N and O). The lowest prevalence for the >80-90 year old group was in the ‘other’ racial groups with 12.1 discharges per 1,000 other male patients in 2004 and 12.6 discharges per 1,000 other female patients in 2004 for that age group, gender, and race.

Length of hospital stay

The biggest change in length of hospital stay occurred in the ≤ 1 age group with a 1998 average length of stay of 12.31 days for a patient with CDAD and in 2004 that
value increased to 17.85 days (see table 2). Also note in table 2 that the largest difference in length of days stayed in the hospital for non-CDAD patients compared to CDAD patients is for the ≤ 1 age group. Note in the >90 age group that the CDAD patients in 1998 had an average length of hospital stay of 11.60 days and in 2004 the value is 9.67 days.

Deaths

The number of deaths for persons with CDAD was 678 in 1998, 735 in 1999, 761 in 2000, 1,144 in 2001, 1,575 in 2002, 1,831 in 2003 and 2,043 in 2004. The percent mortality for the CDAD positive and CDAD negative patients is shown in figure 17 (see appendix R). The percent mortality for the CDAD positive patients versus CDAD negative patients increases by over a point when comparing 2004 to 1998 (4.64 and 3.57 respectively).

This study investigated not only the mortality rate for each individual year, but also mortality rates for each age group per year. Figure 19, appendix T, shows the percent mortality for the 11 age groups. The mortality percent and the mortality per 10,000 discharged hospitalized patients is shown in Tables 8 and 9 (appendices W and X), respectively. The mortality of CDAD patients per 10,000 discharged patients for the >80-90 age group increased from 8.41 CDAD deaths in 1998 to 23.9 CDAD deaths in 2004. The >90 age group also had an increased death rate per 10,000 discharged patients of 10.4 CDAD deaths in 1998 to 32.6 CDAD deaths in 2004 (see Table 9, appendix X). Total numbers of discharges and deaths for the individual age groups and years is listed in tables 10, 11, and 12 (see appendices Y, Z, and AA respectively).
Chapter Six: Discussion

LIMITATIONS OF THE STUDY

The following are limitations when using large amounts of patient discharged data. The AHCA data does not identify someone that has multiple admissions to a hospital in the same year. This is a concern because a patient may have multiple admissions with *Clostridium difficile* infections in the same year. The recurrence rate of CDAD can be as low as 5% or as high as 20-25% (Pepin et al, 2005a; Schroeder, 2005). Authors’ opinions vary on this topic and recurrence rates for Florida are unknown. Other limitations include non-specific use of diagnose codes, transcription errors of those persons entering the data, and inaccurate diagnoses of patient’s disease.

The discharge data does not indicate the time at which a person contracted CDAD. Therefore, the length of hospital stay includes both the time a person was in the hospital before they contracted CDAD and the time they were in the hospital during recovery from CDAD. In summary, although the above five limitations do exist, these limitations are minor when compared to the information gleaned from the data and do not detract from the conclusions of this study.

STRENGTHS OF THE STUDY

Other than the pharmacy data, cleaning solvent, and background knowledge of certain patients, the AHCA data is complete and is the best available information for this large population. This data, although there could be missing information, is capable of
providing adequate information to perform the analysis and determine prevalence rates of *Clostridium difficile* in Florida hospitals.

A report by Peter Layde and his colleagues (Layde, et al, 2004) discusses the use of data sets similar to the AHCA data with the intent of showing the usefulness of these data sets. Layde et al, 2004 performed an analysis studying medical injury using hospital discharge data. Their results using validation studies shows relatively high specificity and sensitivity when comparing hospital discharge datasets to medical record reviews. No mention was made of the sensitivity and specificity actual values, but ICD-9 codes were used to determine medical injury. This method of verifying medical injury is similar to the method that is used to determine *Clostridium difficile* infection rates in this study. The Layde report (Layde et al, 2004) supports the conclusion that using AHCA data is an effective tool for obtaining prevalence for *Clostridium difficile*.

A pilot study using hospital discharge data to access the morbidity of Rotavirus was completed and this report also demonstrates the usefulness of statewide discharge data (Parashar, Chung, Holman, Ryder, Hadler, and Glass, 1999). The Parashar et al report, using the Connecticut statewide discharge hospital database, shows that 10.4% of all diarrhea associated hospitalizations were attributed to Rotavirus. This value nearly matches the nationally reported values for the Northeast region of the U.S. (Parashar et al, 1999200). Parashar and his colleague’s show that using statewide discharge data provides a useful tool for a research project and can be effective in measuring trends for disease in some states. The above two studies demonstrate that using information from hospital discharge data, although there may be a few limitations, provides a useful tool for tracking and monitoring of diseases at a statewide level.
A study that discusses *Clostridium difficile* more specifically discusses the effectiveness of using ICD-9 codes to correctly determine the amount of CDAD that is present in hospitals. Dubberke and his colleagues show that good correlation existed between *Clostridium difficile* toxin assay and ICD-9 code determination of the disease (Dubberke et al, 2006). This is important when considering the information provided in the AHCA hospital discharge data. The information provided in this study relies solely on the correct assignment of the ICD-9 code to CDAD to make an assessment of the persons that have the disease. The report by Dubberke (Dubberke et al, 2006) provides good evidence that using ICD-9 codes to determine disease status, especially in the discharge of *Clostridium difficile*, can be accurate and helpful to determine disease prevalence.

**INTERPRETATIONS OF RESULTS**

**Characteristics of the study population**

This study shows patients discharged from Florida hospitals have an increasing trend for contracting *Clostridium difficile*. The results of this study show that the number of discharged patients contracting *Clostridium difficile* has increased by more than 10,000 discharges when comparing 2004 to 1998. The disease rate per 1,000 patients showed almost a 2.5 times higher rate in 2004 than in 1998. The prevalence of CDAD change from 2000 to 2001 supports the theory that a new more highly virulent strain of the bacteria began to infect Florida patients in that year (see Appendix J). C. McDonald and his colleagues established a rate of 45 discharges per 100,000 U.S. population in the southern region of the United States for the year 2003 and the national average was established by McDonald as 61 per 100,000 U.S. population (McDonald et al, 2006).
These numbers are in contrast to the rate presented here which is 99.9 discharges per 100,000 population in Florida for the year 2003. These numbers show that CDAD is a significant patient problem in Florida’s acute care hospitals.

Age

Age is one of the most important factors with influence on the percentage of patients that become infected with \textit{Clostridium difficile}. Figure 2 demonstrates the importance of this factor by showing that over 70\% of the CDAD positive patients are over 60 years old compared to the non-CDAD population that is under 50\% (Appendix B). Our analysis demonstrates that older people have a higher prevalence of CDAD. Dividing the population into 11 age groups shows the effects of CDAD among different age groups in the population.

Age stratification

McDonald and his colleagues used 4 different age group categories to show how CDAD affects different aged individuals (McDonald et al, 2006). This study demonstrates, for CDAD infection rates, that as a person becomes older their chances increase dramatically for contracting CDAD. The other conclusion from this study is that during the years of the study CDAD prevalence has increased in all age groups (see Appendix M). This is especially evident among the older age groups. Another significant finding in this study occurs in the >1-10 age group. The CDAD prevalence per 1,000 patients shows a fairly constant increase among the age groups as they become older, but the >1-10 age group is almost twice as high as the next age group, >10-20. The >1-10 age group partially follows the pattern of the >30-40 age group which is 2 more
age groups ahead of it. In attempt to explain this we did gender and racial distributions to
discuss this interesting phenomenon.

Length of hospital stay and cost per patient

This study shows that a new more virulent *Clostridium difficile* bacteria strain
may be a good explanation for increasing prevalence of this disease. Length of hospital
stay and total charges at patient discharge are also factors that may support the conclusion
of this study. The increasing patient total costs may be enough incentive to motivate
researchers to provide more time and resources to patients that have been diagnosed with
CDAD in Florida hospitals. This study demonstrates that discharged patients who have
contracted *Clostridium difficile* are in hospitals an average of 9 days longer than patients
with no evidence of CDAD at a total increased cost of over $35,000 per patient. The
additional dollars equates to over 750 million spent to treat this disease in 2004 as
compared to what would have been spent if no patients contracted *Clostridium difficile*.

The ≤ 1 age group is puzzling especially when you view the change in average
length of hospital stay for the CDAD patients for 1998 and 2004. The over 5 more days
that 2004 patients spend in the hospital for this age group is not easy to explain. The
non-CDAD group does not seem to exhibit much of any change for the age groups from
the year 1998-2004. The other major difference seen in Table 5 is the >90 year old age
group CDAD population average length of hospital stay change from the year 1998 to
2004. This number decreased by almost 2 days. It is not known if hospitals are able to
diagnose these problems quicker, antibiotics are given in a better dosage so as to work
faster, or these patients are being discharged to a geriatric facility were they can be
treated and monitored more closely.
Gender

Although no previous published reports on *Clostridium difficile* have mentioned gender or race as a cause for this disease this study shows the distribution of gender and race for each age group as shown in Appendices N through S. Notice in almost all of these appendices a higher prevalence for CDAD females in all three of the racial groups. In 2003 the prevalence of CDAD female discharges for the >1-10 age group is over four times higher than the >10-20 age group for 2003 (see Appendix S). Two reasons for the higher female prevalence may be the lower prevalence for the >10-20 age group and the other may be the higher prevalence for the female gender when compared to the male gender of the same race (see appendices N thru S). This higher prevalence is difficult to explain using the discharge data and more research into these differences is needed. The older age groups show a consistent pattern for both gender and race groups with a higher prevalence for CDAD in the age groups over 50 years old.

Racial distribution

The race with the highest prevalence is white (see appendix N and O). Generally, the races tend to have a prevalence that is higher as a person is older. The prevalence is relatively constant when comparing the different races to each other. Except for the spike in the >80-90 age group prevalence for the black female group (Appendix O), black male, other male, and other female have nearly the same prevalence with the other racial group having a slightly lower prevalence than the black CDAD group (see appendix P thru S). Another difference is the lower CDAD prevalence shown in the female black group and
other race group >10-20 age group. These groups tend to have one half to one third the prevalence when compared to the prevalence for the other gender racial groups (see Appendix Q and S). Race at least in Florida does not seem to be a contributor to the rise in discharges for the CDAD disease.

Death rate information

The mortality rate for *Clostridium difficile* positive patients when compared to the mortality rate for patients who did not have the disease shows some interesting figures. Generally speaking the majority of the age groups in this study showed decreasing mortality rates for the patients who did not contract CDAD. This is in contrast to the CDAD positive patients who generally had a relatively constant mortality with the age groups that are >70 having increasing mortality. This information is consistent with reported increasing death rates observed in Canada, the United States, and the United Kingdom.

This study also shows that older patients are more susceptible to contract the disease and die. The data analysis shows that death rates for age groups that >70 years old have mortality rates over 10%. This percentage is in contrast to the mortality rate of lower than 7% among patients in the same age groups who did not have *Clostridium difficile*. When considering the change in mortality rates, of CDAD positive patients, over the years of this study, the >90 age group does show an increasing trend. This is in contrast to the decreasing mortality rate for patients in the same age group that do not contract CDAD.

A theory advocated at the beginning of this study was that a more virulent strain of *Clostridium difficile* would affect all age groups, not just the >60 age group. This is
the discharge for the >30-40 age group where the mortality rate increases from 2.89% in 1998 to 4.10% in 2004 (see appendix W). For the >50-60 age group this is not the case because the mortality rate decreases from 8.89% in 1998 to 6.41% in 2004 (see appendix W). The mortality rate is higher for Clostridium difficile positive individuals, but the rates don’t appear to be increasing for all age groups. Younger patients are dying with this disease, but do not appear, generally, to have a consistently increasing mortality rate over the years of this study. The increase in CDAD discharges leads to a higher number of deaths per 10,000 discharged patients by age group as shown in Table 9. The mortality percent in the >50-60 age group (Table 8) shows a slight decrease for the years of this study while the CDAD deaths per 10,000 discharged patients (Table 9) shows an increase indicating that the prevalence of CDAD discharges is increasing. The CDAD death rate per 10,000 discharged patients demonstrates that CDAD deaths are increasing in Florida’s acute care hospitals.

Co-morbidities and what they mean

The data in this study was analyzed to determine if toxic megacolon and perforated colon prevalence are also increasing. The analysis results demonstrate that prevalence for these two co-morbidity conditions are not increasing. It is not known if patients are dying faster and not having these conditions, if patients are becoming better before these conditions are diagnosed, or if doctors are just not reporting these conditions.

Summary of bias, confounding, and chance

This study was limited to patients discharged from Florida’s acute care hospitals. This is important because information from nursing care facilities and federal hospitals is
missing from the information that was provided. The results of this study should not be
used as a predictor of CDAD prevalence for nursing care facilities or federal hospitals in
Florida. This study also lacks the ability to be used as a comparison to other states in the
U.S.

The major confounder that could occur is age. The study intentionally grouped
the data for each year to reduce the effects of age as a confounder on the analyzed results.
Age affects mortality, but because we are estimating rates per year and comparing these
rates on an annual basis, and the age of the patient population does not change very much
over the years of this study, it is concluded that age and its effects as a confounding factor
has been controlled for during the analysis. This study further limits the affects of age by
stratifying the population into 11 age groups and looking at discharge and death trends
among the age groups.

Chance is not a factor in this study. All of the known patient discharge data from
acute care hospitals in Florida is included in this study, therefore, p-values are not
calculated because this study uses population data.

CONCLUSIONS

Prevalence of *Clostridium difficile* in Florida’s acute care hospitals is increasing. The mortality of patients who have CDAD remains relatively constant except for patients
that are >70 that show an increasing mortality through the years of the study. This is in
contrast to a decreasing mortality for those patients that have no CDAD. These increases
make this a serious disease for persons hospitalized in Florida’s acute care facilities. This
study demonstrates that age is a factor for higher CDAD prevalence. The variables
length of hospital stay, race and gender show little affect on the increased prevalence
*Clostridium difficile* infections. The ‘more virulent’ strain of CDAD most likely entered Florida in the year 2001. The values and figures in this study provide the most current available information for affects of this disease on patients discharged from Florida’s acute care hospitals. The trends noted in this study show the disease prevalence to be increasing and the emphasis should be to develop and implement preventative methods that decrease the prevalence of CDAD.

**RECOMMENDATIONS**

Further explanation is needed to discuss the prevalence of CDAD. Adjusting this study to further explain the prevalence at a county level would help to explain exactly what areas of Florida are affected the most. Using the results of this statewide descriptive study for an in depth analysis is recommended for individual hospitals to find ways to reduce the prevalence of CDAD. This could be accomplished by creating a group of hospitals to act as satellites for a CDAD analysis, make changes in the group of hospitals that would decrease prevalence of CDAD, and compare the changed prevalence of CDAD with hospitals that are not part of the satellite group. This CDAD analysis would give opportunities for health care professionals to implement more effective methods of treating the disease and preventing the disease from spreading to other patients.
References


Chandler, R. E., Hedberg, & Cieslak, P. R., (2007), Clostridium difficile – Associated Disease in Oregon: Increasing Incidence and Hospital-Level Risk Factors, Infection Control and Hospital Epidemiology, Vol. 28, No. 2.


Appendices
Appendix A

Figure 1: Florida hospital patients, median age, discharged with and without CDAD, 1998-2004.
Figure 2: Florida hospital patients, percent >60 years old, discharged with and without CDAD, 1998-2004.
Figure 3: Florida hospital patients, percent non-white, discharged with and without CDAD, 1998-2004.
Figure 4: Average length of hospital stay for CDAD and non-CDAD discharged patients from Florida hospitals, 1998-2004.
Appendix E

Table 5: Florida non-CDAD and CDAD patient’s average length of hospital stay, days, 1998-2004.

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<td>11.33</td>
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Figure 5: Florida average patient hospital cost at discharge, $/patient, for CDAD and non-CDAD patients, 1998-2004.
Figure 6: Florida hospital discharges, toxic megacolon and perforated colon, for *Clostridium difficile* positive patients, 1998-2004.
Figure 7: Florida toxic megacolon and perforated colon discharges per 1,000 positive CDAD discharged patients, 1998-2004.
Appendix I

Figure 8: Florida *Clostridium difficile* positive patients discharged from hospitals, 1998-2004.
Figure 9: Florida patients contracting CDAD per 1,000 discharged patients, 1998-2004.
Figure 10: CDAD positive patients per 100,000 persons in Florida, 1998-2004.
Appendix L

Figure 11: Patients discharged from Florida hospitals, positive for *Clostridium difficile*, by age group, 1998-2004.
Figure 12: Florida CDAD positive patients per 1,000 patients discharged, by age group, 1998-2004.
Appendix N

Figure 13: CDAD prevalence per 1,000 Florida discharged white male patients 1998-2004.
Figure 14: CDAD prevalence per 1,000 Florida discharged white female patients, 1998-2004
Appendix P

Figure 15: CDAD prevalence per 1,000 Florida discharged black male patients, 1998-2004
Figure 16: CDAD prevalence per 1,000 Florida discharged black female patients, 1998-2004.
Appendix R

Figure 17: CDAD prevalence per 1,000 Florida discharged other race male patients, 1998-2004.
Figure 18: CDAD prevalence per 1,000 Florida discharged other race female patients, 1998-2004.
Figure 19: Florida hospital patients, percent mortality, CDAD and non-CDAD, 1998-2004
Appendix U

Figure 20: Florida hospital patients, percent mortality, non-CDAD by 11 age groups, 1998-2004.
Appendix V

Figure 21: Florida hospital patients, percent mortality, CDAD positive patients by 11 age groups, 1998-2004.
## Appendix W

Table 8: The mortality percent for CDAD discharges in Florida acute care hospitals, by age group, 1998-2004.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Year 1998</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
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<td>4.20</td>
<td>4.25</td>
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<td>7.44</td>
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<td>6.75</td>
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<td>8.76</td>
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## Table 9: Florida mortality of CDAD patients per 10,000 discharged patients, by age group, 1998-2004.

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<th>2003</th>
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Appendix Y

Table 10: Discharges of *Clostridium difficile* in Florida’s acute care hospital, percent of discharges for each year, 1998-2004.

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<tr>
<th>Age Group</th>
<th>Year</th>
<th>Total Number of Discharges</th>
<th>1998 Discharges (%)</th>
<th>1999 Discharges (%)</th>
<th>2000 Discharges (%)</th>
<th>2001 Discharges (%)</th>
<th>2002 Discharges (%)</th>
<th>2003 Discharges (%)</th>
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<td>108 (1.38)</td>
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<td>199 (1.81)</td>
<td>236 (1.61)</td>
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### Appendix Z

Table 11: Total deaths for Florida non-CDAD discharged patients and the percent of deaths per year, 1998-2004.

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<td>16484 (29.7)</td>
<td>16845 (29.5)</td>
<td>16273 (29.3)</td>
<td>16573 (29.1)</td>
<td>15939 (28.2)</td>
<td>15198 (27.5)</td>
<td>14481 (26.9)</td>
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</tr>
<tr>
<td>&gt;80 - 90</td>
<td>111357</td>
<td>15561 (28.1)</td>
<td>16323 (28.6)</td>
<td>15922 (28.6)</td>
<td>16209 (28.4)</td>
<td>16217 (28.7)</td>
<td>15795 (28.6)</td>
<td>15330 (28.4)</td>
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<tr>
<td>&gt;90</td>
<td>32576</td>
<td>4361 (7.87)</td>
<td>4792 (8.39)</td>
<td>4493 (8.08)</td>
<td>4780 (8.39)</td>
<td>4802 (8.51)</td>
<td>4796 (8.68)</td>
<td>4552 (8.44)</td>
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<tr>
<td>Totals</td>
<td>390689</td>
<td>55416</td>
<td>57089</td>
<td>55596</td>
<td>56976</td>
<td>56454</td>
<td>55272</td>
<td>53926</td>
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Table 12: Florida total death numbers for the CDAD patients and the percent of death for each year, 1998-2004.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Year</th>
<th>Total Number of Deaths 1998-2004</th>
<th>1998 deaths (%)</th>
<th>1999 deaths (%)</th>
<th>2000 deaths (%)</th>
<th>2001 deaths (%)</th>
<th>2002 deaths (%)</th>
<th>2003 deaths (%)</th>
<th>2004 deaths (%)</th>
</tr>
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<tr>
<td>≤ 1</td>
<td>12</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>4 (0.35)</td>
<td>4 (0.25)</td>
<td>1 (0.05)</td>
<td>3 (0.15)</td>
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<tr>
<td>&gt;1 - 10</td>
<td>9</td>
<td>3 (0.44)</td>
<td>1 (0.14)</td>
<td>2 (0.26)</td>
<td>1 (0.09)</td>
<td>1 (0.06)</td>
<td>1 (0.05)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>&gt;10 - 20</td>
<td>22</td>
<td>1 (0.15)</td>
<td>2 (0.27)</td>
<td>2 (0.26)</td>
<td>3 (0.26)</td>
<td>2 (0.13)</td>
<td>8 (0.44)</td>
<td>4 (0.20)</td>
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<tr>
<td>&gt;20 - 30</td>
<td>49</td>
<td>6 (0.88)</td>
<td>8 (1.09)</td>
<td>6 (0.79)</td>
<td>5 (0.44)</td>
<td>9 (0.57)</td>
<td>11 (0.60)</td>
<td>4 (0.20)</td>
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<tr>
<td>&gt;30 - 40</td>
<td>116</td>
<td>9 (1.33)</td>
<td>9 (1.22)</td>
<td>10 (1.31)</td>
<td>9 (0.79)</td>
<td>24 (1.52)</td>
<td>26 (1.42)</td>
<td>29 (1.42)</td>
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<td>&gt;40 - 50</td>
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<td>22 (3.24)</td>
<td>26 (3.54)</td>
<td>32 (4.20)</td>
<td>34 (2.97)</td>
<td>45 (2.86)</td>
<td>56 (3.06)</td>
<td>51 (2.50)</td>
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<tr>
<td>&gt;50 - 60</td>
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<td>52 (7.67)</td>
<td>43 (5.85)</td>
<td>54 (7.10)</td>
<td>68 (5.94)</td>
<td>92 (5.84)</td>
<td>115 (6.28)</td>
<td>121 (5.92)</td>
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<tr>
<td>&gt;60 - 70</td>
<td>1220</td>
<td>105 (15.5)</td>
<td>113 (15.4)</td>
<td>113 (14.8)</td>
<td>154 (13.5)</td>
<td>197 (12.5)</td>
<td>258 (14.1)</td>
<td>280 (13.7)</td>
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<tr>
<td>&gt;70 - 80</td>
<td>2750</td>
<td>220 (32.4)</td>
<td>231 (31.4)</td>
<td>237 (31.1)</td>
<td>331 (28.9)</td>
<td>536 (34.0)</td>
<td>548 (29.9)</td>
<td>647 (31.7)</td>
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<tr>
<td>&gt;80 - 90</td>
<td>3007</td>
<td>210 (31.0)</td>
<td>242 (32.9)</td>
<td>249 (32.7)</td>
<td>424 (37.1)</td>
<td>527 (33.5)</td>
<td>644 (35.2)</td>
<td>711 (34.8)</td>
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<tr>
<td>&gt;90</td>
<td>771</td>
<td>50 (7.37)</td>
<td>60 (8.16)</td>
<td>56 (7.36)</td>
<td>111 (9.70)</td>
<td>138 (8.76)</td>
<td>163 (8.90)</td>
<td>193 (9.45)</td>
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<tr>
<td>Totals</td>
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<td>678</td>
<td>735</td>
<td>761</td>
<td>1144</td>
<td>1575</td>
<td>1831</td>
<td>2043</td>
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