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Evaluation of three community-based hospitals for control and prevalence of *Clostridium difficile* infection

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Abstract. *Clostridium difficile* is a gram positive spore forming bacteria that is the primary cause of antibiotic associated diarrheas in the United States and Europe. The prevalence of *C. difficile* infections (CDI) in hospitals and long term care facilities has increased over the past decade and now represents a serious threat to patient health. Because *C. difficile* infections are caused by antibiotic therapy, alternative means of treatment are of interest. This study investigates the prevalence of *C. difficile* infection in three community hospitals and one research hospital and compares hospital prevalence data to state averages for Alabama and Mississippi and the national average. It was found that one community hospital exceeded the national average while two community hospitals and the research hospital were less than the national average of CDI. Both the standard infection ratio for *C. difficile* for Alabama and Mississippi were less than the national average. Data for January 1, 2013 – June 3, 2013 are included. To better control CDI, the Centers for Disease Control and Prevention (CDC) recommends better antibiotic stewardship, training for clinical pharmacists, and limited prescription of antibiotics for hospital and long term care facility patients. Alternative treatments for recurrent or non-responsive *C. difficile* infections include transplantation of fecal microbiota and probiotics. Several vaccines for *C. difficile* are currently under development or in clinical trials.

Introduction

*Clostridium difficile* is a gram positive, anaerobic, spore-former (CDC, 2012). The bacterium was first identified in the 1930s as part of the normal intestinal flora of human newborns and persists as part of the normal intestinal flora in children until about one year of age (Planche, 2013). One to five percent of healthy adults serve as asymptomatic carriers for *C. difficile* (Foglia et al., 2012; Planche, 2013).

Virulent strains of this organism produce three exotoxins: Toxin A (Tox A, TcdA), Toxin B (Tox B, TcdB), and *C. difficile* binary toxin (CDT, binary toxin). Tox A is an enterotoxin that specifically targets intestinal cells, while Tox B is a cytotoxin that causes fluid loss from intestinal cells (Foglia et al., 2012). CDT has been associated with more severe cases of *C. difficile* infection (CDI), particularly with recurrent infection and pseudomembrane formation though the exact function of CDT is still being determined (Stiles et al., 2014; Eckert et al., 2015).
Toxin production is linked to pathogenicity with most serological tests for CDI determining the presence or absence of Tox A and/or Tox B. Traditional serologic testing shows that *C. difficile* strains express different toxins based on region or country in which the sample is isolated. According to a study by Samra et al. (2002), a 1999 outbreak of *C. difficile* in a Canadian hospital found that 20.4% of *C. difficile* that resulted in CDI expressed both Tox A and Tox B while 8.9% expressed only Tox A and 11.5% expressed only Tox B. Huang et al. (2009) compared CDI incidence between two hospitals in Shanghai and Stockholm. Their study noted that all *C. difficile* strains isolated in the Stockholm samples expressed both Tox A and Tox B though CDT was expressed by only 8.7% of CDI strains. Shanghai data showed that 66% of CDI strains expressed both Tox A and Tox B, 33% expressed Tox B only, and 1.3% expressed Tox A, Tox B, and CDT. That study also noted that an increase in prevalence for Tox B expression without Tox A co-expression had been observed in Europe and Asia (Huang et al., 2009).

Only recent studies (Eckert et al., 2015; Ji et al., 2015) have begun to determine the prevalence of CDT expression. Ji et al. (2015) monitored toxin expression in Taipei from 2006-2008 by multiplex PCR and found that 1.7% of samples expressed only Tox B, 0.4% expressed both Tox A and Tox B, and 0.2% expressed Tox B and CDT. Data from Taipei showed that Tox B expression was increasing in CDI while Tox A expression seemed to be decreasing as *C. difficile* strain type changed over time (Ji et al., 2015). A molecular study looked at gene location of the three toxin genes and determined that Tox A and Tox B genes were within the same locus (pathogenicity locus or PaLoc) while the CDT genes were in the CDT locus (CdtLoc; Eckert et al., 2015).

CDI is the most common antibiotic associated diarrheal illness accounting for 10-20% of diarrheal illnesses in the US and UK (Planche, 2013). CDI can be either community acquired or nosocomial though more infections occur in hospitals and long term care facilities (Foglia et al., 2012). Twenty-five percent of nosocomial CDI occur in hospitals while 75% of cases occur in long term care facilities making this one of the major causes of morbidity and mortality in North America and Europe (Planche, 2013). A study by Bengualid et al. (2011) investigated CDI occurrence at St. Barnabas Hospital in the Bronx, New York from 2006-2008 and found that 57% of CDI cases were hospital acquired, 36% were acquired by contact with a healthcare provider, and 7% were community acquired. For patients who receive at least one antibiotic while in hospitals or long term care facilities, 7% will die from a *C. difficile* infection (Doernberg et al., 2012). CDI also increases health costs by 54% which translates into an additional $5,042 to $7,179 per case for a total of $897 million to $3.2 billion annually according to 2012 statistics (Doernberg et al., 2012; Foglia et al., 2012; Gebhart, 2012).

Sixty-three percent of all patients who enter a hospital or long term care facility are given at least one antibiotic (Doernberg et al., 2012). As with most diseases, the likelihood of mortality is increased with age and suppressed immunity. Patients over the age of 65 years are 90% more likely to die from CDI than younger patients (Gebhart, 2012). This, in part, is due to a decreased IgG response to Tox A and Tox B and has prompted the development of a bivalent vaccine by Sanofi Pasteur (Foglia et al., 2012; Planche, 2013).

For *C. difficile* to infect a patient, the patient must first have received an antibiotic which will decrease or eliminate normal intestinal flora. Patients must then come in contact with *C. difficile* bacteria or spores that then colonize the intestines. An active bacterial infection would produce toxins to induce the disease state (Planche, 2013).

Depending on which antibiotic a patient is given, the likelihood of a CDI may be increased. While all antibiotics may results in decreased intestinal flora, higher incidence of CDI has been shown with the use of clindamycin, cephalosporins, and fluoroquinolones (Planche, 2013). A study by Doernberg et al.
(2012) showed that doxycycline, when administered with ceftriaxone, a third generation cephalosporin that has been associated with a high rate of CDI, reduced the incidence of CDI by 79% compared to patients that did not receive doxycycline. Due to the different location of antibiotic absorption within the gastrointestinal tract, the Doernberg et al. (2012) study suggests that site specific disruption of normal flora influences the likelihood of developing CDI.

Infections with *C. difficile* present with mild colitis to severe pseudomembrane colitis. Colitis is an infection of the membrane of the colon and may result in diarrhea, dehydration, shock, colon enlargement or even rupture (CDC, 2012; Planche, 2013). Some infections are self-limiting, requiring no additional treatment other than time and hydration therapy, while other infections require treatment with metronidazole or vancomycin and longer hospital stays of up to three weeks (Foglia et al., 2012). Vancomycin is one of the “last ditch” antibiotics, so excessive use of this drug increases antibiotic resistance among surviving bacteria. Fidaxomicin (difficid) was approved for CDI treatment in 2011 and offers a more regional and specific approach to treating CDI as this antibiotic does not escape the gastrointestinal tract and targets only gram positive bacteria (Fox, 2011). Relapse of CDI is common, occurring in 20% of all CDI patients. Sixty-five percent of relapse patients will have chronic infection from *C. difficile* (Foglia et al., 2012).

The purpose of this study was to compare local hospital policies on *C. difficile* prevention and to determine *C. difficile* prevalence for each of the study hospitals. This study was conducted to compare hospital control policy for CDI and determine if differences between control policies influenced CDI prevalence. CDI control policy and hospital size were also considered. Three community based hospitals and one research hospital were included in the study. Both hospital policy and the prevalence of CDI were compared between the four study facilities.

**Materials and Methods**

**Facility description**

Four hospitals ranging from small regional facilities to larger area hospitals were included in the study. Eliza Coffee Memorial Hospital is a for profit facility (Reid, 2014). Huntsville Hospital, Magnolia Regional Health Care, and the University of Alabama at Birmingham Hospital are not-for-profit facilities (healthgrades.com, 2014). Eliza Coffee Memorial Hospital (ECM) is a 358-bed community hospital located in Florence, Alabama. ECM was established in 1919 and is a member of the RegionalCare Health Partners (ECM, 2014). Huntsville Hospital (Huntsville) is an 881-bed community hospital located in Huntsville, Alabama. Huntsville serves as a regional medical center for south-central Tennessee and north Alabama. The second largest hospital in Alabama and sixth largest publically owned hospital in the U.S., Huntsville was established in 1895 (Huntsville, 2014). Magnolia Regional Health Center (MRHC) is a 200-bed community hospital located in Corinth, Mississippi. MRHC was founded in 1965 (MRHC, 2014). The University of Alabama at Birmingham Hospital (UAB) is a 1046-bed clinical research facility. UAB hospital is part of the UAB Health Care System and serves patients all over the state of Alabama and worldwide (UAB, 2014a).

**Criteria for evaluation**

The *C. difficile* management (treatment) and control (prevention) policy for each hospital was reviewed and compared with the Centers for Disease Control and Prevention (CDC) recommendations for control of CDI. Hospital policies were obtained from hospital websites or personal interviews with hospital safety officers.

**Prevalence calculations**

Prevalence of CDI at each institution was determined using the website http://data.medicare.gov. Data.medicare.gov collects information on the occurrence of infectious disease, treatment complication, patient perception of
hospital staff, and timeliness and effectiveness of patient care among other measures. Data provided by the website are reported using a standardized infection ratio (SIR) to compare the number of infections occurring within a specific period of time at a specific hospital to a national value. Data for the national value is reported to and published by the National Healthcare Safety Network. In brief, an SIR of 0 indicates that no infections have occurred at that hospital while an SIR less than 1 indicates that the number of infections is below the national average. An SIR greater than 1 indicates that the number of infections is above the national average (Data.medicare.gov, 2014).

Data are reported for each of the four hospitals, the state of Alabama, the state of Mississippi, and the national average for the first and second quarter of 2013 (January 1, 2013 – June 3, 2013).

### Results

#### Facility policy evaluation

The CDC recommends that healthcare facilities take standard precautions in preventing cases of CDI and controlling the spread of *C. difficile*. Such precautions include regulation of antibiotics (antibiotic stewardship), isolation of patients demonstrating CDI symptoms, hand sanitation by washing with soap and water, limiting crossover of equipment used between patients, use of protective clothing when caring for *C. difficile* patients, and thorough cleaning of patient rooms with a regulated sporocide cleaner (CDC, 2012). As part of this study, policies at three area hospitals (MRHC, ECM, and Huntsville) and one research hospital (UAB) were compared to the CDC’s recommendations. Each of the four hospitals followed general CDC guidelines with respect to hand hygiene, use of personal protective equipment (protective clothing), equipment care, patient placement within the ward(s), and environmental cleaning and disinfection (Bullard, 2014; Neumann, 2014; Reid, 2014; Tipton, 2014; UAB, 2014b). MRHC, ECM, and Huntsville reported additional regulations on respiratory equipment use, safe work practices with respect to infectious disease patients, and handling of hospital linens (Bullard, 2014; Reid, 2014; Tipton, 2014). A comparison between CDC recommendation and individual study hospital control policy is presented in Table 1.

#### Facility CDI prevalence

Data.medicare.gov released data collected by the National Healthcare Safety Network, part of the CDC. Data for CDI were collected from January 1, 2013 thru June 3, 2013. The national SIR for CDI was 1.0 for the study period. For MRHC, the SIR was 1.301. For ECM, the SIR was 0.730. For Huntsville, the SIR was 0.642. For UAB, the SIR was 0.888. The SIR for the state of Alabama was 0.652 while for Mississippi the SIR was 0.562 (Data.medicare.gov, 2014). These data are summarized in Figure 1.

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**Table 1.** A comparison of safety policies used by Eliza Coffee Memorial Hospital (ECM), Huntsville Hospital (Huntsville), Magnolia Regional Health Center (MRHC), the University of Alabama at Birmingham Hospital (UAB), and the Centers for Disease Control and Prevention’s (CDC) recommendations.

<table>
<thead>
<tr>
<th>Metric</th>
<th>CDC</th>
<th>ECM</th>
<th>Huntsville</th>
<th>MRHC</th>
<th>UAB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic stewardship</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Patient isolation</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hand hygiene</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Limit crossover of equipment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Use of PPE&lt;sup&gt;1&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Patient room cleaned with sporocide</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Respiratory protection for staff</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Special handling of linens</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup>Personal protective equipment
The purpose of this study was twofold: 1) to compare control policy for *C. difficile* at four hospitals and 2) to compare incidence of CDI at each healthcare facility. Hospital control policy was compared between the four facilities within the study (Table 1). SIR data for the incidence of CDI was compared between each facility and with national and state averages (Fig. 1).

The incidence and control policy for *C. difficile* infection was compared at three regions hospitals and one research hospital. It was assumed that the regional hospitals would have the same basic protocols for preventing CDI while the research hospital would have stricter regulations or possibly employ basic CDC guidelines and experimental control schemes. Examination of ECM, MRHC and Huntsville *C. difficile* policy showed that these hospitals exceed CDC regulations for CDI control by requiring respiration protection for hospital staff and stricter environmental decontamination (Bullard, 2014; Reid, 2014; Tipton, 2014). UAB did not require additional environmental decontamination procedures or the use of respiration equipment (UAB, 2014b). *C. difficile* is typically spread through ingestion of live bacterial cells or spores so the use of gloves and protective clothing should be sufficient to prevent *C. difficile* cell or spore transmission. It is also possible that UAB uses a stronger sporocide cleaner than the regional hospitals.

The incidence of CDI for each of the four hospitals was compared to state and national incidence of CDI using data from the National Healthcare Safety Network. The national incidence of CDI for the first two quarters (January 1- June 3) of 2013 was 1.0. It is the goal of all healthcare facilities to be below this benchmark. MRHC was the only hospital evaluated that exceeded the national incidence. MRHC had an SIR of 1.301, a value that was also higher than the Mississippi state value (SIR = 0.562). Alabama hospitals, both community-based facilities and the research hospital, were below the national average. UAB had the highest SIR value (SIR = 0.888) while Huntsville had the lowest SIR value (SIR = 0.642). ECM had a SIR = 0.730. The Alabama state average for CDI was SIR = 0.652 (Data.medicare.gov, 2014). While UAB did have the highest SIR of the three Alabama hospitals, it is still below the national SIR of 1.0. The higher SIR may be due to the type of patients that UAB receives. UAB hospital accepts a wide range of patients and serves as the state hospital for serious illness and injury or highly immunocompro-

![Figure 1. Standard Infection Ratio (SIR) for the national average, the state of Alabama, the state of Mississippi, Magnolia Regional Health Center (MRHC), Eliza Coffee Memorial Hospital (ECM), Huntsville Hospital (Huntsville), and the University of Alabama at Birmingham Hospital (UAB). Data are reported from 1 January 2013 to 3 June 2013.](image-url)
mised patients. It would be expected that patients at such a critical care facility would be on potent antibiotic therapy for either treatment or prevention of nosocomial infections which would increase the likelihood of CDI.

CDI incidence could not be linked to hospital control policy. MRHC had the highest SIR (SIR = 1.301) yet reported the same control procedures as ECM (SIR = 0.730) and Huntsville (SIR = 0.642). The National Healthcare Safety Network does not report incidence data based on age or health condition which would influence patient susceptibility to CDI.

Because antibiotics are the single common denominator in all CDIs, better stewardship of antibiotics is required to reduce the incidence of C. difficile infections. A two-year study conducted at Hairmyres Hospital in Glasgow, Scotland, found that it was possible to decrease hospital-wide incidence of CDI by using alternative antibiotic therapy. From January 2008 until December 2009, physicians were not allowed to prescribe third generation cephalosporins or quinolones. Ceftriaxone, a third generation cephalosporin, and ciprofloxacin, a second generation fluoroquinolone, were banned from routine use with the exception of the intensive care unit. For either ceftriaxone or ciprofloxacin to be used in patient care, the prescribing physician had to receive permission from a hospital regulation committee that consisted of senior physicians, hospital pharmacists, and the hospital microbiologist. If permission was granted and no alternative antibiotics could be used, the hospital microbiologist supervised administration of the antibiotic directly to the patient at the time of dosage. By removing third generation cephalosporins and quinolones from the hospital pharmacy and prescribing alternative antibiotics, the incidence of CDI was decreased by 77% (Dancer et al., 2013). This suggested that better antibiotic stewardship with respect to antibiotic selection and stricter regulation of problematic antibiotics would reduce nosocomial-related CDI.

The CDC also advocates stricter antibiotic regulation. Antibiotics should be used only when necessary and not as a means of prophylaxis. Due to the high rate of overprescribing antibiotics, the CDC recommends that the task of antibiotic stewardship should be given to trained clinical pharmacists (Gebhart, 2012).

Infectious diseases should be controlled through better handwashing practices and disinfection of hard surfaces with bleach solution (Gebhart, 2012). Bleach has been shown to decrease CDI incidence because sodium hypochlorite kills C. difficile spores. However, sporocide wipes have not been shown to be an effective means of eliminating C. difficile spores from surfaces due to the limited contact time of the sporocide compound with the surface. Contact times of 5 minutes or greater were effective in reducing spore load of two C. difficile strains on solid surfaces (Siani et al., 2011).

When cases of CDI do occur, prompt treatment is required. When CDI is suspected, a change in antibiotic therapy is recommended. Oral metronidazole is the antibiotic of choice for mild cases of CDI while oral vancomycin is used for severe cases. Recurrence may occur with both metronidazole and vancomycin though fidaxomicin may yield fewer cases of recurrent CDI (Planche, 2013). Tigecycline also shows promise in the treatment of CDI (Doernberg et al., 2012).

Because antibiotic treatments are the cause of CDI and show mixed results, two alternatives have been recommended: probiotics and fecal transplant. Probiotics may provide more benefit as a preventative measure rather than as CDI therapy, because probiotics have not been shown to produce long-term changes in intestinal flora. A study in mice showed that Clostridium scindens, a normal flora species, offered protection against C. difficile by converting liver compounds to anti-C. difficile compounds which prevent C. difficile colonization (Baggaley, 2014). Baggaley (2014) also reported that a pilot study including 24 bone marrow transplant patients receiving radiation and antibiotic therapy did not develop CDI when C. scindens was found as part of their normal intestinal flora.
Fecal transplant, or fecal microbiota therapy, shows more promise than probiotics in treating CDI but is expensive (Planche, 2013). UAB uses fecal transplants for confirmed CDI patients who have had multiple recurrence of CDI despite changes in antibiotic therapy or infections that do not respond to aggressive antibiotic therapy (Rodriguez, 2012).

Several vaccines are currently under development or are being tested in clinical trials. The vaccine by Sanofi Pasteur, targeting both Tox A and Tox B, was granted fast track status by the United States Food and Drug Administration in early 2011 (Kaye, 2011). To date, this is the most promising option for a vaccine as Sanofi’s vaccine targets both toxins and is already in the second phase of clinical trials (Foglia et al., 2012). Other vaccines currently under development target lipoteichoic acid residues (Cox et al., 2013), surface polysaccharides (Martin et al., 2013), or chemically inactivated toxins (Karczewski et al., 2014) in C. difficile. No vaccine for the CDT toxin has been developed for C. difficile.

C. difficile infections represent a significant nosocomial threat in modern healthcare. As with other bacterial infections, better antibiotic stewardship and personal and environmental sanitation standards are required to prevent CDI transmission. Careful selection of the appropriate antibiotic to treat illness is essential for limiting CDI. Once CDI has occurred, prompt treatment with changes in antibiotic therapy and possible fecal transplant provide better survival rates for affected patients.

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References


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