Investigation of Hand Hygiene and Antibiotic Stewardship Program Effects on Hospital Associated Clostridium Difficile Infections: A Retrospective Study

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INTRODUCTION

Clostridium difficile (C. difficile) is the leading cause of healthcare-associated infections in the United States. According to recent data from the Center of Disease Control (CDC's) National Healthcare Safety Network, 3644 U.S. hospitals reported 98,448 cases of hospital-onset clostridium difficile infections (CDI), with over 80% hospitals having one or more cases (Gould & McDonald, 2009). In 2014, a national prevalence survey found that Clostridium difficile was not only the most commonly reported pathogen, but caused 12% of health care-associated infections in the United States (Magill et al., 2014). Each year, an estimated 14,000 deaths are attributed to CDI, resulting in a mortality rate of 6.9% at 30 days after diagnosis and 16.7% at one year (E. Dubberke, 2012; Erik Dubberke et al., 2008). Consequently, it cost an estimated $5,000 - $7,000 in healthcare expenses per case, totaling at an estimated $1 billion to $1.6 billion dollars annually (Scott, 2009). Due to this epidemic, multiple hospitals across the United States have implemented prevention collaboratives in an effort to decrease the rate of CDI (Control & Prevention, 2015). As a result, the CDC indicated several of the participating hospitals observed an overall decrease in the incidence of CDI.

C. difficile is a gram positive anaerobic bacterium that causes potentially deadly diarrhea, which can be spread in healthcare settings (Kelly & LaMont, 2008; Paredes, Alsaker, & Papoutsakis, 2005). Most cases of CDI occur in patients previously exposed to prolonged cycles of antibiotics. As a patient takes antibiotics, their microflora, or "good bacteria", which protect against infections are decreased for several months. During this time, C. difficile in the

vegetative stage can invade the patient's intestines, colonize, and causes infection (Kuipers & Surawicz, 2008; Seekatz & Young, 2014). Most often C. difficile is contracted nosocomially, but can also be transferred from person to person through the fecal-oral route (Kyne, Farrell, & Kelly, 2001; Tabaqchali & Wilks, 1992). In most cases of antibiotic associated pseudomembranous colitis, C. difficile is the primary cause (Bartlett, 1994). CDIs are difficult to treat because of its ability to form endospores, which are resistant to extreme conditions including high temperatures, ultraviolet light, antiseptics, and antibiotics. They can survive in the environment for up to two years (Underwood et al., 2009). Due to this resistance, spores can remain in a patient's gastrointestinal tract for extended periods of time, causing recurrent CDIs following eradication of vegetative C. difficile.

Most vegetative bacterial cells are killed by the acidic environment in the stomach. However, C. difficile spores can survive this environment, allowing passage to the intestines. An increased incidence of CDI in some studies has been correlated with the use of proton pump inhibitors, particularly in combination with antibiotics (Dial, Delaney, Barkun, & Suissa, 2005; Dial, Delaney, Schneider, & Suissa, 2006). There is evidence that proton pump inhibitors can affect the microbiota of the gastrointestinal tract both by lowering the environmental pH and by a direct effect of the drug on bacteria (Altman et al., 2008) (Vesper et al., 2009).

In vitro studies suggest that the germination and outgrowth of the C. difficile endospore are dependent on the exposure of specific bile acids, primarily taurocholate in combination with glycine (Heeg, Burns, Cartman, & Minton, 2012; Sorg & Sonenshein, 2010). The dependency of C. difficile spore germination with bile acids is a direct result of their ability to

utilize sugars and undergo the metabolic process of amino acid fermentation to create ATP as a source of energy (Jackson, Calos, Myers, & Self, 2006). A polysaccharide capsule discourages phagocytosis of the C. difficile bacterium, while flagella facilitate its movement. As C. difficile colonize, the bacterium adheres to the colonic epithelium. By prioritizing growth over toxin production, C. difficile can exponentially grow and colonize dramatically before producing detectable toxins (Dupuy & Sonenshein, 1998). This can make identifying patients with a progressing CDI quite difficult when using toxin based screening.

As C. difficile growth slows, production of its two virulence factors, enterotoxin (toxin A) and cytotoxin (toxin B), as well hydrolytic enzymes begins. If untreated, the production of toxins A and B result in increased vascular permeability, neutrophil and monocyte recruitment, production of tumor necrosis factor-alpha and pro-inflammatory interleukins, opening of epithelial cell junctions, and eventually epithelial cell apoptosis. The production of hydrolytic enzymes leads to connective tissue degradation, pseudomembrane formation, watery diarrhea, and eventually colitis (Weston, 2008).

The most common treatments for CDI are vancomycin and metronidazole, which eradicate C. difficile's cell wall inducing cell death (Kuipers & Surawicz, 2008; Zheng et al., 2007). However, these treatments are only viable for vegetative C. difficile, having little to no effect on C. Difficile spores. When standard treatment has failed, one strategy that has been shown to be effective in eradicating C. difficile in patients with recurrent CDIs is intestinal microbiota transplantation (IMT), also known as the fecal transplant. IMT is an alternative therapy for CDI patients that involve infusing intestinal microorganisms (in a suspension of a

healthy donor stool) into the intestine of an infected patient (Gough, Shaikh, & Manges, 2011). This allows for the restoration of a healthy microbiota, which theoretically will overpower the colonizing C. difficile. In a systematic literature review study of IMT treatment for recurrent CDI, IMT was shown to be highly effective in eradicating C. difficile, with resolution in 92% of patients (Gough et al., 2011).

One hospital method that has been shown to be highly effective in reducing the deterioration of patient's microflora, and in turn C. difficile infections, is the implementation of an antibiotic stewardship program (D. N. Gerding, Muto, & Owens, 2008). For example, the use of high-risk antibiotics (second-generation cephalosporins, third-generation cephalosporins, fluoroquinolones and clindamycin) has been positively correlated with a significant decrease in the CDI incident rate by 0.0047/100 bed-days per month (Mamoon A. Aldeyab et al., 2012). Further decreases were observed with implementing stewardship with medium-risk antibiotics (amoxicillin/clavulanic acid and macrolides).

Our goal in this study is to determine if there was a causal relationship between the use of hospital hand hygiene, the implementation of more sensitive PCR-based testing and the promotion of an antibiotic stewardship program on the rate of hospital-associated C. difficile infection (CDI).

METHODS

Study Design

A four-year retrospective study that compared the relationship between hospital hand hygiene, CDI test sensitivity and an antibiotic stewardship program to hospital-associated CDI rates was conducted from July, 2011 through September, 2015 at Southern Ohio Medical Center (SOMC). CDI rates were gathered at monthly intervals.

Hospital

SOMC is a 222-bed not-for-profit hospital providing emergency and surgical care to the residents of Ohio, with an average annual census of 13,000 patients admitted during the data acquisition period.

C. Difficile Prevention Strategy

Three primary prevention strategies were implemented in this study:

The *first* is the hand hygiene policy implemented in 2011 to prevent hospital-associated infections. In compliance with CDC, all employees were required to apply either soap and water or alcohol-based hand gel immediately before entering and immediately upon exiting a patient's room using readily accessible hand hygiene stations. Hand hygiene compliance was monitored and timely feedback was given to healthcare personnel if lapses in protocol were observed. Although alcohol-based hand gels are efficient in the prevention of MRSA, they are not efficient in eradicating C. difficile spores (Oughton, Loo, Dendukuri, Fenn, & Libman, 2009). Therefore, mechanical removal with soap and water was used when treating patients with CDI. To monitor hand hygiene compliance, random hospital-wide audits were conducted monthly on all employees. Each time a healthcare employee (of any type) entered or exited a patient's

room, the auditor recorded whether or not they applied soap and water and/or alcohol-based hand gel.

The *second* strategy is antibiotic stewardship. In July of 2014, an antibiotic stewardship team, which primarily focused to minimize the inappropriate use of broad spectrum antibiotics, was implemented. Physician compliance to the program was of utmost importance.

The *third* is preventing the transmission of C. difficile spores. Three methods have been implemented to curtail endospore transmission including: hand washing, isolation of positively screen C. difficile patients, and the use of disinfectants on the environmental surfaces. Asymptomatic patients with a history of C. Difficile are not put into isolation, but are screened for C. difficile. For an asymptomatic patient to be put into isolation, they must have tested positive for C. Difficile. Currently, this is an area of controversy, since some hospitals isolate patients based on history alone. In addition, an EPA-registered, quaternary ammonium-based, one step disinfectant with bactericidal properties, formulated to kill C. difficile spores, is used by environmental services at the hospital.

C. Difficile Screening and Testing Methods

Our study used laboratory testing guidelines for C. difficile as outlined by The Society for Healthcare Epidemiology of America (SHEA) and The Infectious Disease Society of America (IDSA) (Cohen et al., 2010). Patients exhibiting three or more loose watery bowel movements (diarrhea) within a 24 hour period are tested for C. difficile. However, as part of a nursing protocol, asymptomatic patients with one loose bowel movement were often screened.

Two types of screening methods were used for identifying CDI; Toxin A and B Enzyme Immunoassay (toxin A/B EIA), and Polymerase Chain Reaction assays (PCR assays). Toxin A/B EIA test for the presence of C. difficile toxin A and toxin B in a patient's stool sample. The run time for a single toxin A/B EIA can take between thirty minutes to two hours and up to 24 hours for a STAT C. difficile result. We consider the toxin A/B EIA too insensitive to be used as the stand alone test to exclude CDIs. If a toxin A/B EIA yields a negative result, it is required to test the specimen two to three more times, which may increase the time to confirm a negative diagnosis to several days. For the average symptomatic patient, toxin A/B EIA screening is conducted three times to increase the test's sensitivity.

In January of 2013, SOMC adopted PCR-based testing as the main CDI diagnosing method. PCR assays yield the highest sensitivity for detecting the presence of CDI through amplified DNA testing of the C. difficile toxin genes. PCR assays are significantly more rapid, taking approximately an hour to obtain a result with a 30% increase in sensitivity.

There are multiple testing algorithms that different hospitals and labs use for determining the presence of C. difficile in a stool. However, these algorithms were not used. PCR testing is only permitted on liquid stools and only one test every seven days, because a single stool specimen can rule out the presence of C. difficile. It is possible to detect C. difficile spores in the stool of patients who are just carrying C. difficile, and do not have a C. difficile associated disease. Thus, only symptomatic patients were tested with this method. If a specimen is not liquid, it is not tested, and thereby minimizes the risk of false positives. The only exception to this is when ileus is suspected in an asymptomatic patient.

Specimens that test positive must also be interpreted in the context of the patient's history and presentation. Nearly everyone who has C. difficile associated disease has a history of antibiotic usage in the past 3 months. This is important when deciding whether the onset of diarrhea is caused by C. difficile. "Test of cure" C. difficile PCR was not conducted, because lingering spores that would test as positive are possible even though the patient's symptoms may have resolved. The only "test of cure" necessary for C. difficile is the resolution of symptoms.

RESULTS

Figure 1

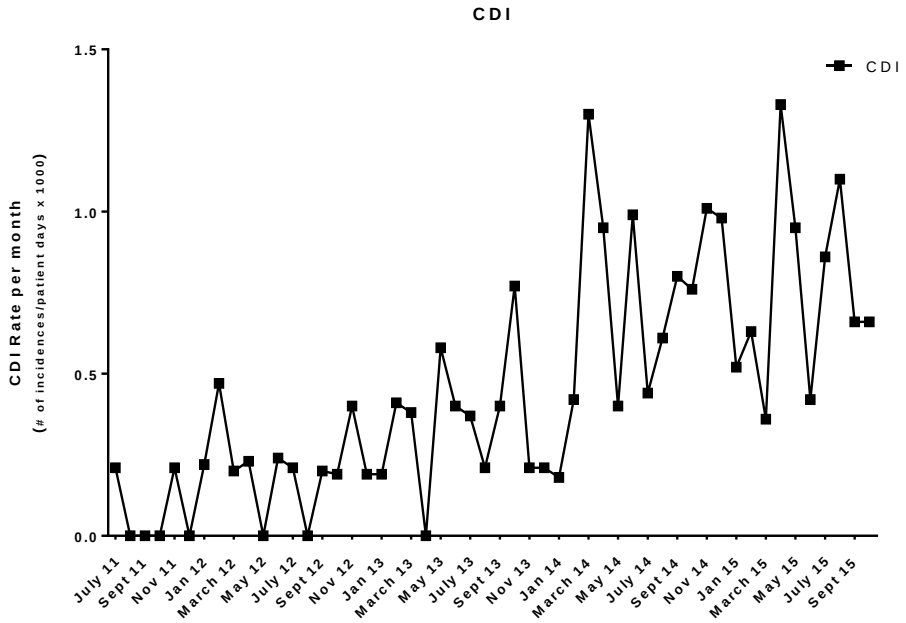

Figure 1: The rate of C. Difficile infections per month from July 2011 to September 2015 at SOMC. The number of C. Difficile infection with hygiene protocol implementation in 2011, antibiotic stewardship program

implementation in July 2014, and PCR screening method implementation in January 2013.

Our results do not support improving C. difficile infection rates by hospital hand hygiene alone as the sole intervention. We found that since 2011, the overall CDI rate has increased tenfold (0.073% to 0.702%). During this time period, very few instances of a decreasing trend were observed. In addition, our data shows no reduction in C. difficile infection rates during implementation of antibiotic stewardship. However, the compliance of staff and physicians to both of the methods could be the cause for the lack of reduction in infection rates.

Our results do support a significant increase in sensitivity for C. difficile testing using PCR assays ($p < 0.05$). This observation suggests that PCR-based testing for CDI diagnosis has a higher sensitivity for detecting the presence of C. difficile toxins compared to other methods and will result in a more accurate diagnosis of CDI.

DISCUSSION

Placing alcohol-based hand antiseptics in easily-accessible areas of all units in the hospital is successful in improving hand hygiene compliance (John M. Boyce, 2000; Cookson et al., 2001). Alcohol-based hand antiseptics placed conveniently at the point of care allows healthcare employees to effectively reduce vegetative bacteria on their hands much faster. However, C. difficile spores negate these beneficial effects of alcohol-based hand antiseptics (Wullt, Odenholt, & Walder, 2003).

One could hypothesize that the absence of a relationship between CDI rates and hospital hand hygiene in our study is due to the mistaken use of alcohol-based antiseptics instead of mechanical hand washing. By eliminating competing bacteria in the facility's microbiome, it is theoretically possible that this even promoted CDI (J. M. Boyce, Ligi, Kohan, Dumigan, & Havill, 2006; Horner, Mawer, & Wilcox, 2012; Jabbar et al., 2010; McFarland, Mulligan, Kwok, & Stamm, 1989).

PCR assays vs. toxin A/B EIA. There has been much debate on whether PCR assays or toxin A/B EIA are most effective in testing for C. difficile toxins. According to a recent study, approximately 90% of laboratories in the United States prefer toxin A/B EIA opposed to PCR, because they are easy to use and cost efficient (Johnson et al., 2001). However, toxin A/B EIA has been shown to lead to low negative predictive values leading to false-positive results, due to their low sensitivity (Gould & McDonald, 2009). As a result multiple tests are needed for a positive confirmation, which lengthens the time frame for diagnosis.

Generally, the majority of C. difficile colonized in a person exists as spores (McFarland et al., 1989). Since only one PCR assay needs to be run, eliminating a CDI diagnosis is much faster. It is beneficial to diagnosis patients early with CDI, so that treatment can begin before the spores germinate. However, the downside to this is the possibility of colonization causing a false positive in an uninfected patient with loose bowel movements. This was prevented by only permitting PCR assays to symptomatic patients. If the stool specimen is not liquid, it was not tested.

The CDC has indicated that PCR is “too sensitive”, postulating that it detects colonization within the organism, instead of the disease itself. An accompanying commentary stated that up to 15% of hospitalized patients are colonized with C. difficile, but is the etiological agent of diarrhea in only 5-10% of them. This suggests that the low positive predictive value of PCR assays (44.7%) translates into false positives for infectious disease, and emphasizes the importance of analyzing patient history with the test results.

After the antibiotic stewardship team’s implementation, the first decreasing trend in CDI rates (-0.07% from January-June 2015) since PCR assays were in place was observed. Dancer, et al., have observed that an antibiotic stewardship program restricting the use of ciprofloxacin and ceftriaxone can reduce CDI by over 70% (Dancer et al., 2013). Our program restricted the use of several antimicrobials; however, we did not see an overall trend in reduction.

The antimicrobial stewardship team placed a strong focus on thoroughly educating the physicians and promoting their compliance. They provided a selection of lower risk antimicrobials (for other infections) when possible, and encouraged avoiding antibiotics unless an indicated condition was present. It was found that an effective antibiotic stewardship initiative is essential to slowing the incidence of CDI.

Prior data suggests that 30-50% of all hospitalized patients receive some kind of antimicrobial/antibiotic treatment (Metjian, Prasad, Kogon, Coffin, & Zaoutis, 2008). The use of antibiotics in over 50% of cases in the United States was deemed unnecessary and/or inappropriate (Fishman, 2006). Since most cases of CDI occur in patients previously exposed to prolonged cycles of antibiotics, this poses a serious threat for CDI.

As part of the antibiotic stewardship program, a semi-annual antibiogram was put in place to monitor the use of antibiotics. This provides statistics of what antibiotics are effective against different organisms, and provides information on narrow spectrum drugs for those organisms. It has been shown that increasing the duration of patient exposure to antimicrobials increases the risk of resistant organisms colonizing (McGowan, 1983). The antibiogram assists in preventing the overuse of broad-spectrum drugs, while preserving the effectiveness of the antibiotics available. Over usage of antibiotics puts a selective pressure on microorganisms to develop resistance, so by using the antibiogram a physician can select the appropriate antibiotic to alleviate an infection.

The goal of an antibiotic/antimicrobial stewardship program is to treat all patients with the appropriate antibiotic that is both cost effective and of least toxicity, while optimizing its dosage, duration of treatment, and de-escalation in order to help prevent the spread of infection (Fishman, 2006; Piacenti & Leuthner, 2013; Shlaes et al., 1997). It is crucial that we control and monitor specific antibiotic usage throughout the hospital by integrating hospital guidelines, staff education, and enforcement of infection control policies (Piacenti & Leuthner, 2013). In several hospitals that placed restrictions on antimicrobials, similar to our study, a reduction in both the incidence and prevalence of resistant organisms was observed (Bamberger & Dahl, 1992; Berk, Alvarez, Ortega, Verghese, & Holtsclaw-Berk, 1986; BETTS et al., 1984; D. Gerding et al., 1991; King, White, Todd, & Conrad, 1992; McGowan, 1994; Pear, Williamson, Bettin, Gerding, & Galgiani, 1994; Van Landuyt, Boelaert, Glibert, Gordts, & Verbruggen, 1986; YOUNG, SEWELL, KOZA, & CLARRIDGE, 1985). In another study, the

incorporation of an antibiotic stewardship program was shown to significantly decrease the rates of selected nosocomial infections (Frank et al., 1996).

Recently, C. difficile-associated diarrhea has posed major threat to patients prescribed antibiotics, deeming it more a public health concern than antimicrobial resistance (Piacenti & Leuthner, 2013). In a secondary/tertiary-care hospital in Quebec, an interrupted time-series analysis studied the influence a nonrestrictive antibiotic stewardship program had on the incidence of nosocomial C. difficile-associated disease during an epidemic. They found from 2003-2004 to 2005-2006, total and targeted antibiotic usage decreased by 23% and 54%, respectively, and a 60% decrease in the incidence of nosocomial C. difficile associated disease was observed (Valiquette, Cossette, Garant, Diab, & Pépin, 2007). In a similar study that evaluated the impact of antibiotic stewardship focused on high-risk antibiotics, they found a borderline significant reduction in high-risk antibiotic usage associated with a significant reduction in the CDI rate by 0.0047/100 bed days per month (M. A. Aldeyab et al., 2012). In several other published studies, antibiotic stewardship programs have demonstrated to be highly successful in the improvement of patient outcomes, reducing CDIs in hospital settings, and reducing readmission rates (Bishop, Parry, & Hall, 2013; Dortch et al., 2011; Fridkin & Srinivasan, 2013; Goff et al., 2012; Malani et al., 2013; Pasquale et al., 2014; Yong, Buising, Cheng, & Thursky, 2010).

All things considered, when faced with the current crisis of the emerging incidences of CDIs and C. difficile associated diseases amongst hospitals, our data shows no improvement in infection rates with hand hygiene and antibiotic stewardship programs. Despite these odds,

infectious disease specialists still highly recommended that hospitals incorporate similar prevention strategies based off of the results of other studies (Goldstein et al., 2015). However, our results do suggest PCR assays should be used to screen and diagnose C. difficile infections in patients. Utilizing PCR screening methods which provide quick and accurate results may help prevent the spread of C. difficile between patients.

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