Etiology of Community Acquired Clostridium Difficile-Associated Disease

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ABSTRACT: A review of literature related to community acquired *Clostridium difficile*-associated disease (CA-CDAD) was conducted. Nine relevant studies were identified using the Cumulative Index to Nursing and Allied Health (CINAHL) and MEDLINE-EBSCOhost databases. Clinical practice recommendations were obtained from the Centers for Disease Control and Prevention. The studies provided information about epidemiology of infection due to *C. difficile* in the community and interventions to reduce transmission. Multiple studies found underlying gastrointestinal disorders and use of cephalosporin antibiotics to be a risk factor. Another risk factor was administration of gastric acid suppressive drugs. No particular *C. difficile* strain was more likely to cause recurrence. Many positive cases for CA-CDAD lacked traditional risk factors such as recent antibiotic exposure. To reduce transmission of CA-CDAD, it should be considered in the differential diagnosis of diarrhea. Clinicians should collect specimens for culture based on patient history and current clinical presentation for patients with diarrhea. It is important that patients be taught the proper hygiene and cleaning protocols to reduce transmission.

INTRODUCTION

Clostridium difficile (*C. difficile*) is a gram positive, spore-forming toxin producing anaerobic rod bacteria that results in millions of deaths per year (McFee & Abdelsayed, 2009). *Clostridium difficile*-associated disease (CDAD) is caused by the toxins released from the bacteria *C. difficile*. The two toxins the bacteria produce are toxin A and toxin B, which cause colonic dysfunction and death (CDC, 2008). Symptoms of CDAD include watery diarrhea, fever, loss of appetite, nausea and abdominal pain (CDC, 2007). The clinical outcomes of CDAD range from asymptomatic colonization to mild diarrhea and more serious diseases such as pseudomembranous colitis, toxic megacolon, bowel perforation, sepsis, shock and death (Rupnik, Wilcox & Gerding, 2009).

Risk factors associated with CDAD are increased age, recent hospital admission, and previous use of antibiotics and conditions that may affect colonic flora (Kuijper & Van Dissel, 2008). Antibiotics are the primary risk factor for CDAD because the antibiotics disrupt the normal bowel flora and allow for *C. difficile* overgrowth. Antibiotics associated with higher risk for CDAD are clindamycin, cephalosporins, and floroquinolones (McFee & Abdelsayed, 2009). Although most cases of CDAD are associated with risk factors, many cases of community acquired CDAD (CA-CDAD) are not. (Kuijper & Van Dissel, 2008).

The Centers for Disease Control and Prevention (CDC) differentiate CA-CDAD from hospital acquired-CDAD; CA-CDAD is diagnosed when the onset of symptoms occurred while the patient was outside a healthcare facility and the patient had not been discharged from a healthcare facility within twelve weeks prior to symptom onset; or the onset of symptoms occurred within 48 hours after admission to a healthcare facility and the patient had no prior stay in a healthcare facility within twelve weeks before symptoms onset (CDC, 2007).

In 2000, a new strain of *C. difficile* was identified as North American pulsed-field 1 (NAP1). This new strain produces an extra toxin and increased amounts of toxin A and B. In addition, NAP1 causes increased morbidity and mortality. Studies suggest that NAP1 may be the most common strain in the community cases (CDC, 2008).

PROBLEM

CDAD is no longer viewed simply as a complication of hospital antibiotic treatment. What was once known only as a hospital-acquired nosocomial infection is now emerging in the community in large numbers. The community CDAD infection rate in the United States has been reported as 7.7 cases per 100,000 persons each year (Rupnik, Wilcox & Gerding, 2009). The CDC published similar findings in December 2005 of 7.6 cases per 100,000 persons each year (CDC 2005).

CDAD has also been reported in healthy children, pregnant women, and adults with no known risk factors. In 2005, CDC researchers showed that 8 (24%) of the 22 low risk patients infected with CDAD had no direct exposure to antibiotics, the leading risk factor (Kuijper & Van Dissel, 2008). In addition, CDC researchers expressed concerns in 2008 when a surveillance report in Connecticut found a quarter of CDAD cases could not be explained by traditional risk factors.

The CDC suggested that risk factors for acquiring CDAD in the community include contact with a contaminated healthcare environment and/or transmission from an infected person. *C. difficile* can be transferred from a contaminated environment because the spore form of *C. difficile* is heat stable and able to survive harsh environments, such as the acidic human stomach and surfaces ostensibly disinfected. Since most disinfectants do not kill the spore, it is likely that *C. difficile* is spread between healthcare providers and patients indirectly and directly (McFee & Abdelsayed, 2009).

C. difficile can spread directly when a person touches a surface contaminated with feces and then touches a mucus membrane (Oriola, 2006). Equipment such as commodes and thermometers may be reservoirs for the bacteria. Indirect contact occurs when a health care provider spreads the bacteria through hand contact from one patient to another or contaminates a surface that is then touched by someone else (Oriola, 2006). Transmission can occur from an infected individual when a person carrying *C. difficile* sheds the bacteria in feces. In addition, alcohol based hand sanitizers do not kill *C. difficile* (McFee & Abdelsayed, 2009).

Jhung and his research team identified several human cases of CDAD caused by toxinotype V strains of *C. difficile*, which has been reported as a cause of epidemic disease in neonatal pigs and calves (Jhung et al., 2008). Although no study has been conducted on interspecies transmission of *C. difficile*, identification of the same strain of *C. difficile* in both humans and animals suggests a link (Jhung et al., 2008).

Transmission of *C. difficile* may occur in three ways. The first is exposure of humans and animals to the same environment. The second is indirect contact through contaminated produce, water or environment. Lastly, transmission can occur through consumption of products from food-producing animals (Jhung et al., 2008). Results from the study suggest toxinotype V *C. difficile* may cause CA-CDAD (Jhung et al., 2008)

PURPOSE

The purpose of this research project is to provide a comprehensive review of research findings about community-acquired CDAD. Findings from this study may show how *clostridium difficile* is spread from healthcare workers to the community, and suggest nursing interventions to reduce or prevent this transmission. Therefore, the results of this study can be applied to everyday practice to enhance patient outcomes.

METHOD

A review of the research literature related to CA-CDAD was conducted. Information was collected from the Cumulative Index to Nursing and Allied Health (CINAHL) and MEDLINE-EBSCOhost databases. Clinical practice recommendations from the CDC website were also used. Inclusion criteria for results included peer-reviewed articles written in the English language and both national and international studies. Key terms are *clostridium difficile, C. difficile* and *c-diff*.

BACKGROUND

Disease transmission can be explained by the chain of transmission. Disease occurs when an outside agent capable of causing disease meets a host that is vulnerable to the agent in an environment that allows the agent and the host to interact (CDC, 2004). The agent is the entity necessary to cause disease, typically a bacterium. The host is the person who is susceptible to the effect of the

agent. The environment is the conditions that influence the interaction of the agent and the host, which includes climatologic, biologic, social, and economic conditions. Agent, host, and environment come together to form the epidemiologic triangle of disease transmission (CDC, 2004).

FINDINGS

Nine studies provided information about epidemiology of infection due to *C. difficile* in the community and interventions to reduce transmission. The studies were conducted in a variety of settings including Sweden, the United Kingdom, Australia, Toronto, and the United States. Each study design was quantitative. Most studies were retrospective case-control studies. Of the nine studies, categories of the three different types of epidemiologic factors emerged. These factors form the epidemiologic triangle: host, agent, and environment.

HOST

In a study conducted in 1993 by Simor, Yake, and Tsimidis, three host variables were identified and associated with CDAD in a long term care facility. These variables were the presence of a nasogastric or gastrostomy tube (OR 6.5), urinary and fecal incontinence (OR 2.5), and the presence of more than three underlying diseases (OR 2.0).

Hirschhorn, Trnka, Onderdonk, Lee, and Platt (1994), identified 51 subjects in a retrospective study of CA-CDAD. The overall incidence rate was 7.7 cases per 1,000 persons per years. Twenty-two (43%) had a concurrent illness. A total of 16% had inflammatory bowel disease, and 8% had human immunodeficiency virus (HIV) infection. Lastly, 4% had a malignancy.

McFarland, Clarridge, Beneda, and Raugi (2007), used a conditional logistic model for all causes of CDAD, including CA-CDAD. The model found two statistically significant host risk factors: lower intestinal conditions (OR 2.8) and number of comorbidities (OR 1.3).

AGENT

Noren et al. (2004) used PCR ribotyping to type the different stool specimens obtained. There were 241 isolates of *C. difficile* from 241 patients and 89 isolates from 54 patients with recurrences, totaling 330 isolates

that underwent PCR ribotyping. Results found 53 distinct PCR ribotypes. The patterns of PCR ribotypes of *C. difficile* were similar in the hospital and in the community with the exception of type SE17. Of the 53 distinct PCR ribotypes, nine compromised 67% of isolates from the hospital and 59% from the community. SE17 was the most common ribotype and accounted for 22% of hospital acquired CDAD. Of the SE17 isolates studied, 93% were identified as hospital acquired. Therefore, SE17 is predominately a nosocomial infection. A total of 208 of the 330 specimens tested were classified as hospital acquired. The remaining 122 were community acquired. Of the patients with CDAD, 68 experienced recurrences. PCR ribotyping showed that in 90% of the recurrent episodes, the isolate was the same ribotypes as the initial ribotypes. The same nine major ribotypes that caused the initial infection were associated with recurrence. Therefore, no particular *C. difficile* strain was more likely to cause recurrence (Noren et al., 2004).

ENVIRONMENT

In 1986, a study was undertaken by Riley, Wymer, Bamford and Bowman that demonstrated that several antibiotics were the central cause of CA-CDAD. The antibiotic most associated with the disease was clindamycin.

A prospective nationwide study of CDAD was carried out in Sweden during 1995. Karlström et al. found that 28% of all cases of CDAD involved no hospitalization within the preceding four weeks to diagnosis, defined as CA-CDAD (1998). Of the cases defined as community acquired, the majority were diagnosed in primary care. In addition, 88% had taken antibiotics in the previous six weeks (Karlström et al., 1998).

In 2000, Levy et al. identified two cephalosporins with increased risk for developing CDAD in the ambulatory care setting, cephalexin (OR 7.5, CI 1.8-34.7) and cefixime (OR 6.4, CI 1.2-39.0).

Dial, Delaney, Barkun, and Suissa (2005) conducted a study to determine if gastric acid suppressive drugs increased the risk for CA-CDAD. A total of 1672 patients were identified as having CDAD, and of those, 1233 (74%) infections were considered community acquired. There was a noteworthy increase in the rate of cases diagnosed as community acquired, from less than 1 per 100,000 persons in 1994, to 22 per 100,000 in 2004. Also, records showed from 1994 to 2004 a decrease in the number of antibiotic prescriptions and an increase in proton pump inhibitor prescriptions. The researchers found exposure to antibiotics as a risk factor for all cases of CDAD. In a second analysis examining only CA-CDAD, researchers found proton pump inhibitor exposure to have an adjusted rate ratio of 2.9 (CI 2.4-3.4) and H2-receptor antagonists to have a adjusted rate ratio of 2.0 (CI 1.6-2.7). Therefore, there is an increased risk for CA-CDAD with gastric acid suppressive drugs. Also, in the 90 days prior to diagnosis, only 37% of the cases had antibiotic exposure (Dial, Delaney, Barkin & Suissa, 2005).

In a study conducted by McFarland, Clarridge, Beneda, and Raugi (2007), 184 patients were diagnosed with CDAD. Twenty patients of the 184 patients (11%) had community acquired cases. More than half of the patients with CA-CDAD had no prior antibiotic exposure. Also, the patients with CA-CDAD experienced shorter duration of hospitalization and lower mortality. The majority of the patients with CDAD were treated with either metronidazole or vancomycin. Drugs considered to be high risk factors of developing CA-CDAD were clindamycin (OR 29.9) and penicillin (OR 4.1). Also, taking multiple antibiotics during the same time period increases risk for CA-CDAD (OR 1.4).

Wilcox, Mooney, Bendall, Settle, and Fawley (2008) found several risk factors for developing CA-CDAD. Exposure to antibiotics in the previous four weeks, particularly multiple agents (p < 0.001), aminopenicillins (p < 0.05), and oral cephalosporins (p < 0.05), were significantly more frequent among cases than controls. Hospitalization in the preceding six months was significantly associated with CA-CDAD (45% versus 23%; p = 0.022). Almost half the cases had not received antibiotic therapy in the month before *C. difficile* detection, and approximately one third experienced neither exposure to antibiotics nor recent hospitalization. Contact with infants younger than two years old was also considered a risk factor (14% versus 2%; p = 0.02).

DISCUSSION

Host

Simor, Yake, and Tsimidis (1993) found urinary and fecal incontinence to be a risk factor for CA-CDAD. The risk for infection may be due to an increase risk for fecal-oral transmission. Results from pulse-field gel electrophoresis

showed diversity among the strains carried by each resident, suggesting the origin of infection is endogenous rather than exogenous. Exogenous bacteria are introduced internally to the gastrointestinal tract from the external world. Endogenous bacteria are part of our body's normal flora.

In their study, which was similar in form to others, Hirschhorn, Trnka, Onderdonk, Lee and Platt (1994) found underlying disease and gastrointestinal conditions such as inflammatory bowel disease to be a risk factor.

Both the number of comorbidities and the presence of lower intestinal conditions were significant risk factors for CDAD in a study conducted by McFarland, Clarridge, Beneda, and Raugi (2007). These conditions affect normal intestinal microflora similarly to antibiotics, thereby increasing the risk for CDAD. People who have inflammatory bowel disease have a disrupted colonic flora. Lower intestinal conditions such as polyps may alter the body's normal ability to resist overgrowth (McFarland, Clarridge, Beneda & Raugi, 2007).

Agent

Noren et al. (2004) found that CDAD is usually due to endogenous infection. Apart from type SE17 strain being mostly nosocomial, no *C. difficile* strain had superior transmission ability or ability to cause recurrent infection.

Environment

Karlström et al. (1998) reported an increase in the number of CDAD. A total of 5, 133 CDAD cases were recorded in 1995, compared to 86 in 1978. A possible explanation for the increase is an increase in the number of broad-spectrum cephalosporins prescribed in Sweden during the study timeframe. Most of the patients with CA-CDAD had taken antibiotics prior to diagnosis.

Dial, Delaney, Barkun, and Suissa (2005) performed a large population study and found gastric acid suppressive drugs were associated with an increased risk of CA-CDAD. There was a greater association with proton pump inhibitors and CA-CDAD than H2-receptor antagonists. These results may rise because the degree of acid suppression is greater in proton pump inhibitors than H2-receptor antagonists. Furthermore, a decrease in gastric acid is known to be a risk factor for acquiring other causes of diarrhea, such as cholera. In addition,

when gastric acid is suppressed, there is an association of colonization of the upper gastrointestinal tract, which is normally sterile (Dial, Delaney, Barkin & Suissa, 2005). Although antibiotic exposure is a major risk factor for the disease, there is a significant number of CA-CDAD with no history of antibiotic use 90 days prior to diagnosis.

CA-CDAD with no history of antibiotics is a trend seen in most published studies. Therefore, reliance on antibiotic history could contribute to missed diagnoses. However, exposure to antibiotics, especially cephalosporins, are still a leading risk factor.

LIMITATIONS

In this integrated review of the research literature, there were a number of limitations. Most studies were retrospective studies that relied on medical records for data. Therefore, the studies were limited by the fact that primary care medical records were not available. Also, emergency department records did not always state previous antibiotic use. Another limitation was a lack of access to medical records from other care providers. Some patients may not have sought medical care in some instances, or physicians may not have considered or recorded the diagnosis of diarrhea in the medical record. In general practice, most laboratories only performed testing based on requests from the physicians for community acquired specimens; therefore, it is likely that only symptomatic patients were tested.

One study (Levy et al., 2000) looked at medical claims rather than medical records. This limits the amount of information received. For example, the medical claim dose not report the dose or duration of antibiotic prescribed.

The laboratory tests performed to detect *C. difficile* toxins could also be a limitation. Each study qualified community acquired disease versus hospital acquired disease differently. In addition, each test has the potential to give false results. Furthermore, *C. difficile* isolates that were not typed could not be studied for different *C. difficile* variants.

A majority of the nine studies examined had a large population pool. However, two did not (Simor, Yake & Tsimidis and McFarland, Clarridge, Beneda & Raugi). These two studies cannot be generalized because both

the long term care population and veterans population respectively consists of mostly older adults with a significant number of comorbidities.

RECOMMENDATIONS FOR NURSING

Education

Public health nurses draw from the core competencies for nursing in designing and implementing community-based interventions. The core competencies should be used to guide baccalaureate nursing curricula. To strengthen nursing curricula, one key core competency is awareness of the assessment: the skill needed to evaluate the integrity and comparability of data and identify gaps in data sources. Another core competency of importance is policy development awareness of the baccalaureate nurse to translate policy into organizational plans, structures, and programs. It is important to evaluate data from research studies to determine their integrity because not all studies should be used to change policy and procedures. Policy development is vital to improve patient outcomes and help eliminate communicable diseases (Association of Community Health Nursing Educators, 2003).

Pratice

The CDC recommends that clinicians teach their patients to limit transmission and inquire about similar cases in household members and close contacts. It is important that patients be taught proper hygiene and cleaning protocols to reduce transmission. To reduce transmission of CA-CDAD, CDAD should be considered in the differential diagnosis of diarrhea. Clinicians should collect specimens for culture based on patient history and current clinical presentation for patients with diarrhea. Lastly, clinicians should routinely ask about similar cases in household members and close contacts.

Research

Future research should include a standard definition of CA-CDAD. More research is needed to look at high risk populations, such as pregnant women, infants, and children. Further research should focus on different types of study.

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