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Infection Control Procedures to Prevent Transmission of Clostridium Difficile

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Abstract

Introduction: Nosocomial infections, also known as healthcare-associated infections, are a significant public health concern. According to recent data, C. diff infections are one of the most common healthcare-associated infections, with an estimated 500,000 cases occurring in the United States each year. The purposes of this review are to highlight the recent epidemiological data and to provide an overview of infection control procedures to prevent transmission of clostridium difficile in hospitals and tertiary care settings.

Methods: We systematically searched for controlled trials of interventions to reduce the rate of clostridium difficile in acute-care hospitals, using the biomedical electronic databases Ovid MEDLINE, EMBASE, The Cochrane Library, CINAHL, and the ISI Web of Knowledge. We included studies that assessed the effect of interventions on the rate of clostridium difficile in acute-care hospitals. Secondary studies, such as meta-analyses, were excluded. All titles and abstracts were independently screened by 2 reviewers to identify studies potentially eligible for inclusion and a full text review was performed to identify studies eligible for data extraction.

Results: Epidemiological studies show that MRSA, vancomycin-resistant enterococci and C. difficile are on the rise worldwide and that they have the potential to become important pathogens and endemic in North America. The emergence of community-acquired MRSA and the increasing number of hospital-acquired MRSA infections. Outbreak Reports and Intervention Studies of Nosocomial Infection (ORION) guidelines were published to raise the standards of research and publication of hospital epidemiology in order to facilitate the synthesis of evidence and to promote reporting transparency.

Conclusions: With regard to these issues, the clinicians should be guided by their local infection prevention and control policies and procedures. The use of a bundled approach to prevent infections based on local surveillance data for clostridium difficile of a given institution has been shown to work. The implications of the increases infection severity of disease and the successful management mandate the combined expertise of intensivists, surgeons, infectious disease physicians, pharmacists, infection prevention and control personnel, and the laboratorian.

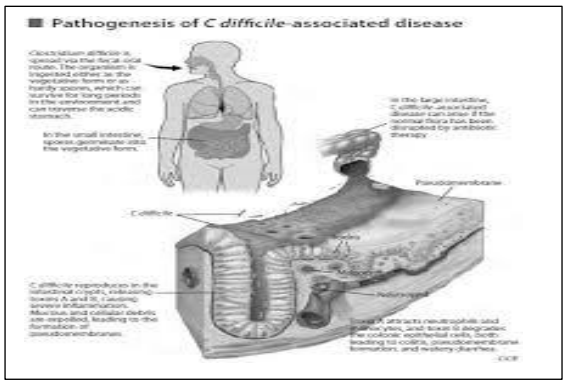
Keywords: Clostridium difficile, infections, Practices, Intensive-care, Surveillance.

Introduction

Clostridium difficile, also known as C. difficile or C. diff, is a type of bacteria that can cause infections in the intestines. These infections are known as C. diff infections. Recently reclassified as Chloridoids difficile, is a Gram-positive spore-forming ubiquitous bacterium. Toxigenic strains can cause C. difficile infection (CDI) with diverse clinical manifestations ranging from mild diarrhoea to life-threatening conditions. The most important modifiable risk factor for CDI is previous antibiotic treatment [1]. The infections can cause symptoms such as diarrhoea, abdominal pain, and fever [1]. In some cases, the infection can lead to more serious complications, such as inflammation of the colon (colitis) and sepsis (a life-threatening infection of the bloodstream). Clostridium difficile infections are most common in people who have recently taken antibiotics, as these medications can disrupt the balance of bacteria in the gut and allow C. diff to grow [2].

C. diff infections are also more common in older adults, especially those who are hospitalized or living in long-term care facilities. According to recent data, C. diff infections are one of the most common healthcare-associated infections, with an estimated 500,000 cases occurring in the United States each year. C. diff infections are more common in older adults and in people who have recently taken antibiotics, as these medications can disrupt the balance of bacteria in the gut and allow C. diff to grow [3]. Nosocomial infections, also known as healthcare-associated infections, are a significant public health big concern. These infections are caused by pathogens that are acquired during the course of receiving healthcare in a hospital or other healthcare setting. Nosocomial infections can have serious consequences, such as increased morbidity and mortality, prolonged hospital stays, and increased healthcare costs. To prevent the spread of nosocomial infections, it's important for healthcare workers to follow proper infection control procedures. These procedures may include using personal protective equipment (PPE), such as gloves and masks, practicing good hand hygiene, and cleaning and disinfecting surfaces and equipment [4].

clostridium difficile infection (CDI) emerged in the beginning of the 21st century. It was reported in many areas (eg Canada United States Europe) and coincided with the outbreak of a new type of C difficile: polymerase chain reaction ribotype which was postulated to produce more toxins A and B and the major virulence factors of C difficile in vitro. It was also frequently associated with severe disease in patients. In hospitals, patients with CDI were associated with greater lengths of stay, rehospitalization, and additional healthcare expenditures [5]. More recently, numerous studies focused on outbreak situations or specific populations, such as patients treated in intensive care units (ICUs) or surgical wards. In the Hensgen et al study, the results showed that patients in ICUs or surgical wards have no relation to CDI 8; however Goorhuis et al showed that patients in ICUs or surgical wards usually have higher CDI rates than other patients. Whether



situations have a correlation to CDI still remains a controversy. Similar to all-cause hospital mortality CDI-related death increased at least 4-fold between 1999 and 2006. CDI-related death is difficult to identify because the existence of comorbidities is a risk factor for acquisition of the disease. Multiple outbreak investigations have concluded that CDI-related mortality frequently (14%-19%) occurs within 30 days. Surprisingly, an endemic study that matched cases and controls on the propensity to develop CDI concluded that CDI had no direct effect on mortality in the first 60 days. After 3 months, the attributable mortality was also only 6%. Dissemination of C difficile throughout the hospital may lead to serious outcomes in clinical therapy. There is a need for ongoing clinical and molecular surveillance of CDI. Therefore, given the limited data for risk factors associated with CDI, a systematic review was performed of the literature with meta-analysis to obtain a more accurate evaluation of the role of CDI in hospital mortality and the situations in hospital CDI [6].

The clinical presentations of CDI range from mild self-limited diarrhea to severe pseudomembranous colitis or toxic megacolon and perforation in a few cases . This bacterium is recognized as the leading cause of healthcare-associated diarrhea among adults from industrialized countries. Only toxigenic C. difficile strains are pathogenic. The main virulence factors are the two high molecular weight toxins, namely toxin A (or TcdA) and toxin B (or TcdB). They are both implicated in mucosal damage and inflammation. Recent studies using mutants for toxin A and/or B in hamster models of infection gave conflicting results. Authors suggested that toxin B was essential for virulence, whereas Kuehne et al. showed the importance of both toxins A and B in the virulence of strains. A third toxin, the C. difficile binary toxin (CDT), has been identified in up to 17% of the strains. This toxin could induce microtubule protrusion at the cell surface, thereby increasing the adherence to the epithelial cells . In the early 2000s, outbreaks of severe CDI with increased morbidity and mortality were described in North America [7]. The prevalence of C. difficile ribotype 078 has increased from 3 to 13% in Europe . In the Netherlands, this strain was found to affect younger people and was more frequently responsible for community CDI than PCR ribotype 027. Ribotype 078 has also been isolated in pigs and the strains have been shown to be genetically very similar to human isolates [40 ,41]. In Asia, large outbreaks and severe pseudomembranous colitis due to PCR ribotype 017 strains, which produces toxin B but not toxin A, have been described [8]. The main risk factors for CDI usually include age more than 65 years, duration of hospitalization, exposure to other patients with CDI, and antimicrobial use . All antibiotics may predispose a patient to CDI, but antibiotics with a high risk of infection include cephalosporins and clindamycin. The newer fluoroquinolones (moxifloxacin, gatifloxacin, and levofloxacin) have been increasingly reported as a significant risk factor of CDI due to the hypervirulent 027/BI/NAP1 strain . It is likely that the in-vitro resistance of the 027/BI/NAP1 strains to fluoroquinolones may have conferred an adaptative advantage for gut colonization.

Conflicting results have been published on the role of proton pump inhibitors (PPIs) and H 2 blockers in the development of CDI [9]. Theoretically PPIs could decrease gastric acidity, therefore promoting the survival and passage of vegetative cells in the gut. However, spores, which represent the most likely mode of contamination, are highly resistant to gastric acid. The emergence of CDI in populations previously at low risk (e.g. patients without previous exposure to antibiotics, young individuals, and pregnant women) has been increasingly reported . Patients in the community are also at risk for CDI, albeit at a considerably lower rate than hospitalized patients. Definitions of community-associated CDI (CA-CDI) have been recently standardized in order to simplify

comparison across facilities [10]. The incidence of community-associated CDI ranges from 6.9 to 46 cases per 100 000 person-years in the United States [11] and is estimated at 20-30 per 100 000 population in the United Kingdom . The origin of infection in patients with CA-CDI is still unknown. However, isolation of C. difficile in livestock, meat from different animals, vegetables, and even water in the United States and Europe has raised concerns about a possible route of contamination from food [11,12]. Similarities have been reported between strains isolated in animals or food and those isolated in humans, suggesting a possible link. Nevertheless, no documented outbreak to date has been related to food consumption, and evidence of C. difficile as a food-borne disease is still lacking. It is fairly difficult to predict how the epidemiology of CDI is going to evolve during the next decade. On one hand, it is likely that the incidence of C. difficile will increase in the short term, as a result of both mandatory notification of CDI in many countries and the use of more sensitive and rapid molecular-based methods for the diagnosis.

On the other hand, an early identification of CDI will improve implementation of infection control measures while new prevention strategies (such as vaccine or immunotherapy) or new treatments that reduce CDI recurrence rates will likely result in a gradual decrease of CDI incidence. The recent changes in CDI epidemiology highlight the need for more effective methods to prevent CDI. To date, most data have been acquired during outbreak periods, from a single institution where multiple interventions were implemented at the same time or sequentially making it difficult to determine which intervention is truly effective [13]. During the last decade, the epidemiology of clostridium difficile infections (CDIs) has changed dramatically worldwide. The purpose of this review are to highlight the recent epidemiological data and to provide an overview of infection control procedures to prevent transmission of clostridium difficile in hospitals and tertiary care settings.

Methods

We systematically searched for controlled trials of interventions to reduce the rate of CDI in acute-care hospitals, using the biomedical electronic databases Ovid MEDLINE, EMBASE, The Cochrane Library, CINAHL, and the ISI Web of Knowledge. We searched for articles published in 2022. Sets of relevant terms representing "Clostridium difficile" and "prevention" were obtained from subject headings and free-text database fields and combined with the "AND" operator for database searches. The search was limited to controlled clinical trials, pre-and post-test studies, controlled before-and-after studies, and interrupted time-series studies. Additional studies were identified by scanning the references of relevant publications, using the "Related Articles" feature in PubMed, and using the "Cited Reference Search" in the ISI Web of Science. We included studies that assessed the effect of interventions on the rate of CDI in acute-care hospitals. Secondary studies, such as meta-analyses, were excluded. All titles and abstracts were independently screened by 2 reviewers to identify studies potentially eligible for inclusion and a full text review was performed to identify studies eligible for data extraction. Disagreements were resolved by consensus. A single reviewer performed the data extraction. A random 50% of the studies were checked by a second reviewer for accuracy. Studies were coded by type and category of intervention. Categories were approved by consensus. Most studies were nonrandomized trials and quality-improvement-focused studies; 2 reviewers independently used the QI-Minimum Quality Criteria Set (QI-MQCS) tool 7 to evaluate the quality of studies. We reviewed the titles and abstracts of 65 articles for relevance and selected 26 for full-text review. About 23 studies encompass hospitals, mostly from the United States and European countries.

Results and discussion

Epidemiological studies show that MRSA, vancomycin-resistant enterococci and C. difficile are on the rise worldwide and that they have the potential to become important pathogens and endemic in North America. The emergence of community-acquired MRSA and the increasing number of hospital-acquired MRSA infections. In a study conducted in 11 emergency departments in the United States in August 2004, 78% of S. aureus skin and soft-tissue infections were due to community-acquired MRSA [14]. The

public has become increasingly aware of the threat posed by "superbugs" and, understandably, expects that hospitals do better to prevent transmission to patients. Data from the Canadian Nosocomial Infection surveillance Program show that, for every 1000 hospital admissions in 2007, there were 8.62 new patients with MRSA infection, 14 and that, in 2005, there were 1.32 new patients with vancomycin-resistant enterococci per 1000 admissions. A 6-month survey from November 2004 to May 2005 identified 4.5 patients with C. difficile-associated disease for every 1000 admissions [15]. This strain possesses several characteristics that may enhance its virulence. One of its toxin regulatory genes (tcdC) contains an 18-base pair deletion associated with hyperproduction of C. difficile toxins. The strain also produces a binary toxin uncommonly found in other strains of C. difficile.

The clinical significance of the binary toxin is uncertain, because strains that produce this toxin but are negative for toxins A and B appear to be non-pathogenic in traditional animal models of disease. The currently circulating NAP1/027 strains are resistant to fluoroquinolone antimicrobials such as moxifloxacin [16]. This may provide the organism with a competitive advantage, especially in healthcare facilities with considerable use of this class of drugs. The epidemic NAP1/027 strain of C. difficile also appears to be capable of hype sporulation, and this may be associated with prolonged survival in the inanimate environment, facilitating transmission of the organism. PATHOGENESIS C. difficile produces two toxins that are associated with disease: toxin A and toxin B. Strains of C. difficile that do not produce these toxins are non-pathogenic. The toxins bind to the colonic epithelial cell surface, are internalized, and catalyze the glucosylation of cytoplasmic proteins, leading to an acute inflammatory reaction and cell death. A local cytokine response contributes to the development of pseudo-membrane formation.

Inflamed mucosal surfaces studded with adherent raised yellow and white plaques characterize pseudomembranous colitis, the hallmark of severe C. difficile infection; histologically, these pseudo-membranes are composed of neutrophils, fibrin, mucin, and cellular debris. It was initially thought that toxin A played a more critical role in the pathogenesis of C. difficile-associated diarrhea, but recent studies have determined that it is toxin B that is essential for C. difficile virulence. Not everyone infected with the organism experiences diarrhea. In fact, colonization with C. difficile appears to be protective against the onset of symptomatic disease. In one study, diarrhea developed in only 1% of those colonized with C. difficile on admission to hospital, compared with 3.6% of those who were not colonized on admission but who subsequently acquired the organism [17]. The immune response to C. difficile toxins appears to be critical in determining whether symptoms will develop after exposure to the organism. After colonization, a high serum antibody response to toxin A is protective, whereas patients with a low antibody response are more likely to develop diarrhea. Approximately 2% to 5% of healthy adults, and as many as 20% to 40% of those who are hospitalized, are colonized with C. difficile. Nosocomial acquisition of the organism increases with duration of hospital stay. In one study, approximately 1% of patients who had been hospitalized for less than 1 week were colonized with C. difficile, whereas the rate was as high as 50% in those who had been admitted for more than 4 weeks [18]. Acquisition of C. difficile in the community without exposure to a healthcare environment occurs less often, although this may be increasing. The primary reservoirs of C. difficile in hospitals and LTCFs include colonized or infected patients and their contaminated environment. Environmental contamination with C. difficile occurs commonly, and spores can survive in the environment for months. The organism can be found around toilets and commodes and on floor surfaces, bedding, furniture, telephones, and medical equipment. One outbreak in a nursing home was associated with transmission of C. difficile by the re-use of contaminated electronic thermometers.

Additional evidence suggesting an important role for the inanimate environment may be found in the observation that there is greater risk of infection occurring in roommates or in those who are admitted to a room previously occupied by a patient with C. difficile. As levels of environmental contamination increase, so too does the prevalence of healthcare

worker hand carriage of the organism, and this has been associated with C. difficile transmission and outbreaks in hospital and nursing home settings. A study demonstrating that consistent glove use was associated with lower rates of C. difficile infection also supports the importance of hand carriage of the organism as a means of transmission [19]. The normal fecal bacterial flora appear to confer "colonization resistance" inhibiting C. difficile acquisition; factors associated with altered enteric flora increase the risk of C. difficile infection. The major factor contributing to acquisition of the organism is systemic antimicrobial use, especially exposure to clindamycin, extended-spectrum cephalosporins, or fluoroquinolones. C. difficile infection may follow even a single dose of antibiotics or surgical antimicrobial prophylaxis. In hospitalized patients who receive antibiotics, many variables have been associated with greater risk of developing C. difficile-associated diarrhea, including duration of hospitalization; presence of underlying comorbidities; gastrointestinal surgery; nonsurgical gastrointestinal procedures; tube feeding; and use of antiulcer medications, laxatives, or stool softeners [20].

Colonization pressure, defined as the total daily exposure to patients with C. difficile infection divided by length of stay at risk, has been found to be a significant risk factor for development of C. difficile-associated disease in hospitals; although colonization pressure has not been studied in LTCFs, it would seem to make sense that this would also be relevant in those settings [21]. Two recent studies determined variables associated with severe or complicated C. difficile infection, defined as infection associated with death, admission to an intensive care unit, or the need for a colectomy. In prospective surveillance for C. difficile infection conducted in Canadian hospitals, the attributable mortality was 3.5 times as high in patients aged 65 and older as in younger adults (7.3% vs 2.2%; Po.001), and in a multivariate analysis, older age was independently associated with greater risk of severe disease and an adverse outcomes [22]. Admission from another hospital or from a nursing home was also associated with an adverse outcome. Outbreak Reports and Intervention Studies of Nosocomial Infection (ORION) guidelines were published to raise the standards of research and publication of hospital epidemiology in order to facilitate the synthesis of evidence and to promote reporting transparency; the aim of this initiative was to enable readers to relate studies to their own experience, and assess the degree to which the results can be generalized to other settings [23]. This study used the ORION statement to synthesize knowledge of interventions aimed at preventing and controlling CDI in hospitals. A literature search of intervention studies was conducted in PubMed with the following combination of Medical Subject Heading terms: 'clostridium difficile infection'; 'intervention study'; 'interrupted time series'; 'prevention'; 'control measures'; 'intervention'; and 'cohorting'. All English-and French-language articles published between January 1982 and December 2013 (last update March 2014) were included. The search yielded 109 potentially relevant articles. Among the 31 studies selected initially, 21 were included in the final review [24].

The strategy was to select studies that had been designed, as claimed by their authors, as intervention studies. CDI rate were also excluded. In one article describing a two-phase intervention in a CDI cluster, only the second phase was reported because the first phase was an outbreak control. A modified root cause analysis tool was evaluated in one study to minimize risk factors associated with CDI and manage cases when they occurred. Although it was not overtly an intervention study, as there were doubts about the study design, the decision was made to include it in this review [25]. Two reviewers (NK and NV) screened article titles and abstracts in the initial search to identify those appropriate for inclusion. Subsequently, the full text of articles was read by each reviewer. The results of both reviewers were compared and, in the case of disagreement, were resolved through discussion. The ORION checklist for intervention studies was used to obtain information related to preventing and controlling CDI in hospitals. Other ORION items not directly related to infection control are treated, when necessary, in the Discussion. Setting (country and hospital data), baseline CDI policies, definitions of CDI and healthcare-associated CDI (HCA-CDI), study design, intervention(s), observed results and effect on CDI rate are reported below. Twenty-one observational studies with planned interventions, published between 1990 and 2013, were

reviewed. Setting The reviewed studies were conducted in the USA (52.4%) UK (28.6%) Canada (9.5%), results on C. difficile. Most studies were performed in university hospitals, and some studies were limited to particular wards or rooms. In two studies, the interventions were undertaken in more than one hospital [26].

Conclusions

The infection prevention and control department and the hospital epidemiologist should determine whether an outbreak or increased CDI rate is occurring. Despite the fact that alcohol does not kill C difficile spores and that alcohol-based hand hygiene products are less effective than handwashing with soap and water at removing spores from the hands of volunteers, it is still not recommended to preferentially wash hands with soap and water after caring for a patient with CDI in non-outbreak settings. Potential explanations for these findings are that gloves are effective at preventing health-care worker hand contamination, poor adherence to hand hygiene when soap and water is the preferred method, and contamination of hands after gloves are removed by the health-care worker using the same sink as the patient. Although there are no studies that demonstrate the effectiveness of soap and water at preventing CDI, it is recommended to preferentially use soap and water for hand hygiene in outbreak settings because of the concern that alcohol-based hand hygiene products do not remove C. difficile spores. With regard to these issues, the clinicians should be guided by their local infection prevention and control policies and procedures. The use of a bundled approach to prevent CDI based on local surveillance data for CDI of a given institution has been shown to work. The implications of the increases in CDI and severity of disease and the successful management of CDI mandate the combined expertise of intensivists, surgeons, infectious disease physicians, pharmacists, infection prevention and control personnel, and the laboratorian.

Conflict of interests

The authors declared no conflict of interests.

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