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REVIEW ARTICLE

Clinical impact of *Clostridium difficile* colonization

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Clostridium difficile can cause antibiotic-associated diarrhea in hospitalized patients. Asymptomatic colonization by *C. difficile* is common during the neonatal period and early infancy, ranging from 21% to 48%, and in childhood. The colonization rate of *C. difficile* in adult hospitalized patients shows geographic variation, ranging from 4.4% to 23.2%. Asymptomatic carriage in neonates caused no further disease in many studies, whereas adult patients colonized with toxigenic *C. difficile* were prone to the subsequent development of *C. difficile*-associated diarrhea (CDAD). However, the carriage of nontoxigenic *C. difficile* strains appears to prevent CDAD in hamsters and humans. Risk factors for *C. difficile* colonization include recent hospitalization, exposure to antimicrobial agents or gastric acid-suppressing drugs (such as proton-pump inhibitors and H2 blockers), a history of CDAD or cytomegalovirus infection, the presence of an underlying illness, receipt of immunosuppressants, the presence of antibodies against toxin B, and Toll-like receptor 4 polymorphisms. Asymptomatic *C. difficile* carriers are associated with significant skin and environmental contamination, similar to those with CDAD, and contact isolation and hand-washing practices should therefore be employed as infection control policies for the prevention of *C. difficile* spread. Treating patients

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with asymptomatic *C. difficile* colonization with metronidazole or vancomycin is not suggested by the currently available evidence. In conclusion, asymptomatic *C. difficile* colonization may lead to skin and environmental contamination by *C. difficile*, but more attention should be paid to the clinical impact of those with *C. difficile* colonization.

Introduction

Clostridium difficile is the leading cause of antibiotic-associated diarrhea in hospitalized patients through the production of toxins A and B and, most likely, a binary toxin. The clinical manifestations range from mild diarrhea to pseudomembranous colitis, toxic megacolon, and even death. The incidence of *C. difficile*-associated diarrhea (CDAD) is increasing worldwide and in Taiwan.[1] In the USA, the reported case number of CDAD in 2005 (84/100,000) was nearly three times that in 1996 (31/100,000). The identified risk factors for CDAD include advanced age,[2,3] previous hospitalization,[2,4] the use of feeding tubes,[5] antimicrobial exposure,[2,4,6] and the use of proton pump inhibitors (PPIs).[4] Avoidance of unnecessary antimicrobial agents or gastric acid-suppressing agents, such as PPIs, in addition to contact isolation and hand washing, have been regarded as important infection control policies to prevent the spread of *C. difficile* in hospitals.[7] In addition to patients with CDAD, those with *C. difficile* colonization (CdC) have been regarded as potential reservoirs of *C. difficile* and it is a general belief that the number of patients colonized with *C. difficile* outnumbers that of patients with CDAD.[8] The incidence of CdC could be as high as 23.2% among hospitalized patients,[9] particularly among vulnerable populations, such as patients with cystic fibrosis (32.4%)[10] (Table 1).[8–10,16,18–22,25,26,30,35,37,40–42,45–48]

C. difficile isolates that are capable of producing toxins A and B are regarded as toxigenic; otherwise, they are considered nontoxigenic. Toxigenic *C. difficile* colonization (tCdC) has been described as an independent risk factor for the subsequent development of CDAD,[8,9] and nontoxigenic *C. difficile* has been used to treat relapsing CDAD.[11] However, the clinical significance of tCdC or nontoxigenic CdC (ntCdC) remains controversial, warranting more attention from clinicians, infection control staff, epidemiologists, and microbiologists. In this review, we aim to elucidate the epidemiology, clinical impact, risk factors, and infection control concerns of individuals with tCdC or ntCdC.

Epidemiology of *C. difficile* colonization

During the neonatal period and early infancy, asymptomatic colonization by *C. difficile* is common, ranging from 21% to 48% in some reports, particularly among those with prolonged hospitalization, low birth weight (<2500 g), or younger gestational age (<37 weeks) as well as those nursing in an incubator or delivered by cesarean birth (Table 2).[12,14,15,49,50] There was geographic variation in *C. difficile* colonization rates among infants, with 35% observed among Swedish infants compared to 4% in Estonian infants.[12] Infant susceptibility to *C. difficile* colonization may be due to the inability of their intestinal microbiota to resist CdC. Rousseau et al[13] have demonstrated that the presence of *C. difficile* in the gut of infants is associated with changes in the microbiota composition. CdC has also been noted during childhood, particularly among those with malignancy (19%) or inflammatory bowel disease (17%).[14,15]

Likewise, the colonization rates of *C. difficile* in adult hospitalized patients vary geographically. In Canada, as few as 4.4% of hospitalized patients had CdC at admission.[16] The prevalence rate of CdC has been reported as 4.4–3.3% in France, 7.9% in the UK, 2.1–18.4% in the USA, 14% in Israel, and 20–23.2% in Taiwan (Table 1). However, the rates cannot be compared between these studies, as their study designs (prospective or retrospective), detection methods (culture, cytotoxin assay, or polymerase chain reaction), target populations, and/or the inclusion of ntCdC varied. In the study by Lee et al,[17] changing incidence and clinical manifestations of CDAD were noted when introduction of the combination of glutamate dehydrogenase and toxin assay in Northern Taiwan.

Because *C. difficile* is often acquired from a nosocomial environment, additional cases of CdC have been discovered during hospitalization, with the figures of CdC higher than those at admission or at initial screening. For example, the prevalence rate of CdC was 2.1% (11/517) at initial screening and 50% (64/128) during follow-up for more than 1 month in a study conducted by Clabots et al.[18] In our prospective study, we found a CdC prevalence rate of 20.0% among hospitalized patients at an initial screening, with an additional 25.4% of the patients developing CdC during follow-up.[8]

Many reports have explored the prevalence rates of CdC among the elderly. In general, the elderly in nursing care units or long-term care facilities (LTCFs) had higher prevalence rates of CdC. Fecal CdC was detected in 4% of the elderly outside LTCFs in the UK[19] and in 0.6% of elderly individuals in Belgium.[20] Arvand et al[21] reported a typical finding that the prevalence of CdC was 4.6% (11/240) in nursing home residents versus 0.8% (2/249) in the elderly living outside LTCFs. However, such a figure may range from 10% in continuing care institutions[22] to 51% among LTCF residents.[23] With the increase in the elderly population worldwide, the potential clinical sources of *C. difficile* among the elderly, particularly those in LTCFs, require more clinical attention.

Other susceptible populations have been investigated in addition to the elderly, including individuals with cystic fibrosis, inflammatory bowel disease, or human immunodeficiency virus (HIV) infection. CdC has been noted in