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National Institute of Infectious Diseases and Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labour and Welfare

<THE TOPIC OF THIS MONTH>
Clostridioides difficile infection in Japan

Clostridioides difficile infection (CDI)

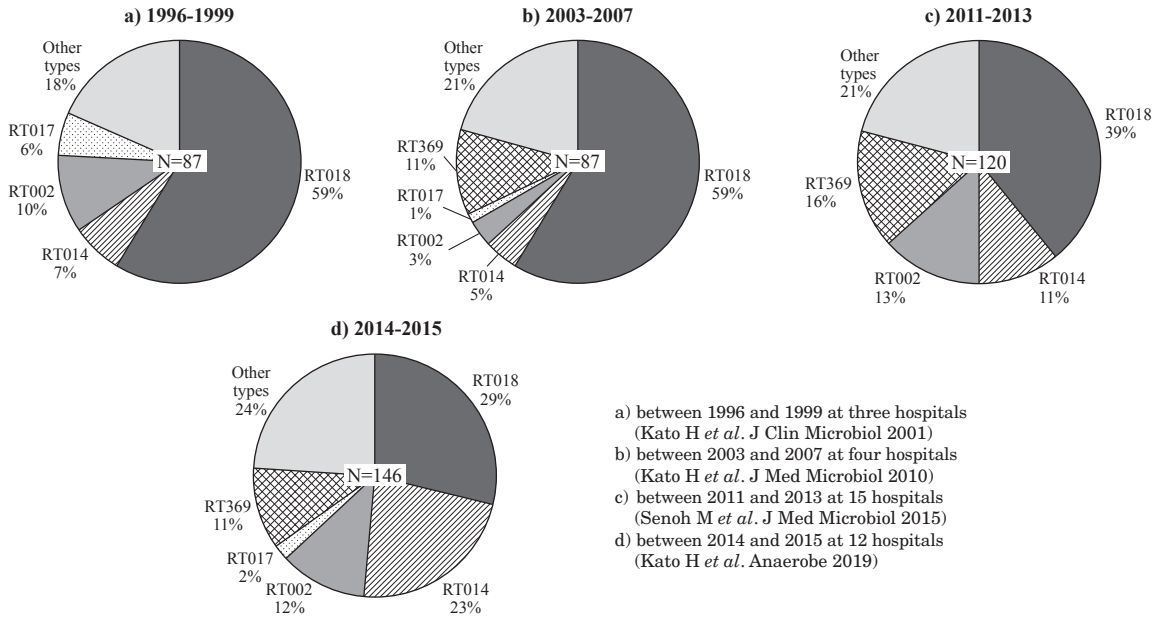
Clostridioides (Clostridium) difficile is an obligate anaerobic Gram-positive spore-forming bacillus. Toxins produced by the organism include toxin A, toxin B, and binary toxin.

C. difficile infection (CDI) is an intestinal infection that often develops when the disruption of the gut microbiota occurs (dysbiosis) by the use of antimicrobial agents. Host factors, such as advanced age and underlying disease, influence the onset of the disease, and CDI is more common in the elderly. The symptoms range from mild diarrhea to toxic megacolon and ileus, and it may be fatal in some cases (see pp. 37 and 38 of this issue). CDI is diagnosed when pseudomembranes are observed by colonic endoscopy, but there are many cases of CDI without pseudomembrane formation. CDI often recurs and patients with multiple recurrences present a difficult challenge for retreatment. On the other hand, inpatients, in particular, are often asymptomatically colonized by *C. difficile*. Patients without intestinal symptoms do not require testing or treatment.

Epidemiology of CDI

In North America and Europe, CDI is of great concern, and surveillance and infection control for CDI are being conducted nationally. In "Antibiotic resistance threats in the United States 2019", which was issued by the Centers for Disease Control and Prevention, *C. difficile* is listed as one of five pathogens that are an "urgent threat", and infection control for CDI is performed under political leadership in the US (https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf). In the UK, from 2007 every hospital was mandated to report all of the cases of CDI, and the increased awareness of CDI led to its decreased incidence (see p. 39 of this issue). In contrast, in Japan, the awareness of CDI is low, and infection control against CDI not only in healthcare settings, but also in administrative settings is significantly behind that in North America and Europe. Although the incidence of CDI has been reported to be low in Japan, a recent multicenter prospective study revealed that the overall CDI incidence in 12 hospitals was 7.4/10,000 patient-days, which is as high as those in North America and Europe. As CDI is rarely suspected in outpatients with diarrhea (see p. 37 of this issue), the actual status of community-acquired CDI in Japan is unknown.

From a molecular epidemiological point of view, CDI due to PCR-ribotype (RT) 027 (BI/NAP1/027) has been repeatedly reported



a) between 1996 and 1999 at three hospitals (Kato H *et al*. J Clin Microbiol 2001)
b) between 2003 and 2007 at four hospitals (Kato H *et al*. J Med Microbiol 2010)
c) between 2011 and 2013 at 15 hospitals (Senoh M *et al*. J Med Microbiol 2015)
d) between 2014 and 2015 at 12 hospitals (Kato H *et al*. Anaerobe 2019)

Figure. Distribution of PCR-ribotypes in clinical isolates of *Clostridioides difficile* in Japan

PCR-ribotype (RT) 018 and its subtypes, 014 and 002 were toxin A-positive, toxin B-positive, binary toxin-negative; RT017 and RT369 were toxin A-negative, toxin B-positive, binary toxin-negative. Binary toxin-positive isolates were included in other types (RT027 *C. difficile* was found in one patient in each of studies b) and c)).

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from North America and some European countries since 2004, attracting worldwide attention. It is known that the RT027 strain emerged in North America and rapidly spread to Europe after acquiring resistance to fluoroquinolones. In Japan, in a 2007 administrative contact entitled "Thorough measures against nosocomial infections caused by *Clostridium difficile* or multidrug-resistant *Pseudomonas aeruginosa* (MDRP)", the Ministry of Health, Labour and Welfare notified thorough measures against nosocomial infection by *C. difficile*, including infection by the RT027 strain. However, isolation of RT027 is currently rare in Japan (Figure in p. 35).

Among the Japanese isolates, RT018, RT014, RT002, RT369, and RT017 account for more than 75%. The most dominant types are RT018 and its subtypes, and RT018 predominance has been recognized since the 1990s (Figure in p. 35). RT018 isolates are highly resistant to antimicrobials, such as fluoroquinolones and clindamycin, and the selective pressure of antimicrobials used conventionally, is presumed to be one of the factors for the predominance of this strain. The RT018 strain is also prevalent in Italy and Korea, and the association between RT018 infection and disease severity was reported. In Japanese hospitals, CDI cases due to RT018 often cluster and RT018 is an important epidemic strain causing nosocomial outbreaks (see p. 41 of this issue). The RT002 strain has been associated with severe disease in Hong Kong, and serious cases and outbreaks have also been observed in Japan (see pp. 37 and 38 of this issue); it is considered to be a strain that should be paid attention to.

CDI in the veterinary field and one-health

It is relatively recent that studies on CDI in the veterinary field have become full-scale from the perspective of one-health (see p. 42 of this issue), whereas CDI in industrial animals and pets has been examined previously. Although there have been no reports of food poisoning to date, attention has been paid for CDI and intestinal colonization by *C. difficile* in animals in relation to food contamination.

Diagnosis of CDI

A recent multicenter prospective study demonstrated the correlation between CDI test frequency and CDI incidence rate in patients with diarrhea/colitis, revealing the importance of laboratory testing in patients with diarrhea/colitis to diagnose CDI. Laboratory tests include enzyme immunoassay (EIA) detecting toxins (toxin A/toxin B) and glutamate-dehydrogenase (GDH) in stool specimens, *C. difficile* culture, nucleic acid amplification test (NAAT) detecting the toxin B gene (*tcdB*) in stool specimens, and NAAT, which detects the binary toxin gene and presumptive RT027 *C. difficile*, in addition to *tcdB*. However, there is no omnipotent test for diagnosing CDI. It is necessary to perform multiple tests under appropriate diagnostic stewardship and make a diagnosis in combination with clinical symptoms (see p. 44 of this issue).

Treatment of CDI

Antimicrobial agents, if inciting dysbiosis, should be discontinued or changed. Antimicrobials for CDI include metronidazole, vancomycin, and fidaxomicin. Use of human monoclonal antibody against *C. difficile* toxin B, and fecal microbiota transplantation (as a clinical study in Japan), have been introduced as new treatments for repeated recurrences (see p. 46 of this issue). For fulminant CDI cases that do not respond to medical treatment, emergency surgery is necessary. Total colectomy or subtotal colectomy is performed, but diverting loop ileostomy may also be used to preserve the colon. Probiotics do not have therapeutic efficacy against CDI.

Prevention of CDI

Implementation of antibiotic stewardship program and discontinuation of unneeded antacids are effective to reduce the risk of CDI.

For infection control of CDI, it should be noted that disinfectants commonly used for hand hygiene, such as alcohol, are ineffective against *C. difficile* spores, and that asymptomatic carriers exist among hospitalized patients. When the prevalence is high, hand hygiene with running water and soap is essential. CDI patients should be placed on contact precautions. As asymptomatic carriers can also be a source of infection, it is important to ensure that all inpatients are placed on thorough standard precautions, particularly in excretion assistance.

CDI is a disease that occurs, especially in healthcare facilities and wards where many elderly patients and patients requiring antibiotic treatment are hospitalized. When the number of new disease cases exceeds that of normal levels, the situation is described as an outbreak. Once a CDI outbreak occurs, it is markedly difficult to control (see pp. 38 and 41 of this issue). To detect signs of outbreaks and provide a guide for the appropriate use of antibiotics, it is important to keep track of the baseline of CDI incidence and frequency of laboratory testing at all times.

As elderly patients are often transferred between multiple hospitals and institutions, CDI is an infectious disease for which infection control in the community should be considered. In particular, at many small- and medium-sized hospitals that have not earned additional reimbursement for infection prevention, more attention should be paid to CDI because the elderly account for the majority of patients, and infection control measures, including laboratory testing systems, are insufficient. The role of local governments, including health centers, in the control of CDI infection will become even more important in the future (see pp. 41 and 47 of this issue).

Next agenda

In Japan, the biggest problem in CDI control and prevention is the low awareness and understanding of CDI. It is necessary to share correct information not only with medical institutions, but also with organizations related to health and hygiene such as facilities for the elderly and local governments.

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Environmental Health and Food Safety, the Ministry of Health, Labour and Welfare, and quarantine stations, have provided the above data.

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