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National Institute of Infectious Diseases and
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Control Division,
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<THE TOPIC OF THIS MONTH>
Carbapenem-resistant *Enterobacteriaceae* Infection, Japan

Carbapenem-resistant *Enterobacteriaceae* (CRE) is a group of *Enterobacteriaceae*, such as *Escherichia coli* and *Klebsiella pneumoniae* that are resistant to both carbapenems and broad-spectrum ß-lactams. CREs cause respiratory tract infections such as pneumonia, urinary tract infections, surgical site infections, catheter-related bacteremia, sepsis and meningitis. While more common among immune compromised patients, postoperative patients or patients treated with antimicrobials for an extended period of time, CREs may also cause infection in otherwise healthy patients. CREs are often the cause of nosocomial infections.

So far in Japan, the prevalence of CRE has been relatively low. For example, in 2013, meropenem-resistant isolates occupied less than 1% of the various representative *Enterobacteriaceae* bacteria isolates (Table 1). Meanwhile, in many other countries, the proportion of carbapenem resistance is increasing, and in the United States, 10.4% of the isolates belonging to the genus *Klebsiella* were carbapenem-resistant [MMWR, 62(9): 165-170, 2013]. The World Health Organization (WHO) considers strengthening the surveillance of antimicrobial resistance as a critical priority for member states (WHO, Antimicrobial resistance: global report on surveillance 2014, http://www.who.int/drugresistance/documents/surveillancereport/en/).

Carbapenem resistance mechanisms

Mechanism of carbapenem resistance includes production of various carbapenemases, production of AmpC type or extended-spectrum ß-lactamases combined with mutation(s) resulting in the decreased permeability of the cellular membrane (see p. 283 of this issue). Carbapenemase-producing bacteria are clinically important as they are often resistant not only to broad-spectrum ß-lactams but also to other classes of antimicrobials (see p. 284 of this issue).

Carbapenemase producers isolated in Japan are mostly of IMP genotype (see p. 285 of this issue), which can be easily detected by the sodium mercaptoacetic acid (SMA) disk method widely used in medical facilities in Japan. Isolates abroad, however, carry carbapenemases of NDM, KPC, or OXA-48 genotypes, whose detection requires use of methods other than SMA disk method (see p. 285 of this issue). As nosocomial infections due to CRE are more frequent abroad, patients who were treated in foreign medical facilities should be investigated for possible carriage of CREs so as to prevent the spread from such imported cases in Japan (see p.

Table 1. Proportion of *Enterobacteriaceae* resistant to meropenem, 2013, Japan

Enterobacteriaceae species	Meropenem resistant (%)
Escherichia coli	0.1
Klebsiella pneumoniae	0.2
Enterobacter cloacae	0.6
Enterobacter aerogenes	0.2
Citrobacter freundii	0.2
Citrobacter koseri	0.1
Proteus mirabilis	0.1

2013 Annual Report of Clinical Laboratory Division, Japan Nosocomial Infections Surveillance (JANIS: http://www.nih-janis.jp/), Ministry of Health, Labour and Welfare

Table 2. Laboratory criteria required for fulfilling definition of carbapenem resistance

a. MIC for meropenem ≥2µg/ml, or zone diameter of meropenem disk (KB) ≤22mm
b. Fulfillment of both i) and ii):
  i) MIC for imipenem ≥2µg/ml, or zone diameter of imipenem disk (KB) ≤22mm
  ii) MIC for cefmetazole ≥64µg/ml, or zone diameter of cefmetazole disk (KB) ≤12mm

MIC: minimum inhibitory concentration
See notification criteria (http://www.nih.go.jp/niid/images/iasr/35/418/de4181.pdf)

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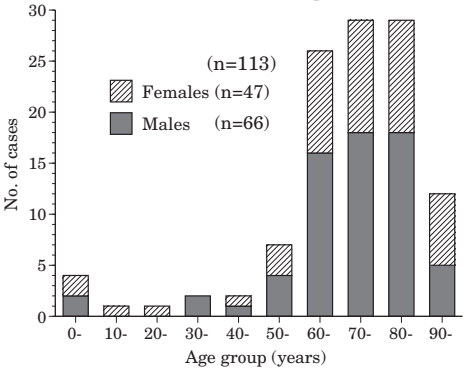
Figure. Age distribution of carbapenem-resistant *Enterobacteriaceae* infection cases, by gender, week 38 to 44 of 2014, Japan



(National Epidemiological Surveillance of Infectious Diseases: as of November 5, 2014)

Table 3. Notified cases of carbapenem-resistant *Enterobacteriaceae* infection, week 38 to 44 of 2014, Japan

Enterobacteriaceae species	Number of cases
Enterobacter cloacae	34
Enterobacter aerogenes	22
Escherichia coli	19
Klebsiella pneumoniae	15
Citrobacter spp.	5
Others & not described	18
Total	113

[National Epidemiological Surveillance of Infectious Diseases, as of November 5, 2014, since compulsory reporting of all cases started in week 38 (September 19, 2014)]

287 of this issue, IASR 35: 200-201, 2014, IASR 34: 237-238, 2013 and IASR 34: 238-239, 2013).

National Epidemiological Surveillance of Infectious Diseases–reporting criteria and current trends

CRE infection is a category V infectious disease under the Infectious Diseases Control Law. Physicians who make the diagnosis of CRE infection must notify all cases (see http://www.nih.go.jp/niid/images/iasr/35/418/de4181.pdf for reporting criteria). Only infections determined to be caused by CRE are notifiable; asymptomatic CRE carriers are not. For determining carbapenem resistance, resistance to meropenem or resistance to both imipenem and cefmetazole are methods currently used (Table 2). Among them, use of meropenem is most recommended on account of its sensitivity and specificity (IASR 35: 156-157, 2014). Imipenem resistance was included in the reporting criteria because imipenem has been widely used as an indicator in the clinical setting. However, in order to exclude those that are resistant to imipenem but susceptible to other cephem antimicrobials and do not produce carbapenemase (e.g. Genus *Proteus*), reporting is limited to those resistant to both imipenem and cefmetazole.

Since compulsory reporting of all cases started in week 38 (19 September 2014), 113 CRE infection cases were notified through week 44, among whom 66 were male and 47 female (see p. 288 of this issue). The age of the patients ranged from 0 year to 97 years; among them 88 (78% of all the cases) were aged 65 years or above (Figure). CRE was isolated from 47 (42%) aseptic specimens, such as blood, ascites, and cerebrospinal fluid; the isolation was most frequent from blood (n=27).

Among 113 cases, 109 cases were reported as domestically acquired and one case abroad. Twenty three cases were considered as healthcare-associated infections, such as infection due to medical devices or surgical site infections. Among 113 cases diagnosed as CRE infection, 31 cases were based on resistance to meropenem, 41 cases by resistance to both imipenem and cefmetazole and 39 cases based on both methods.

Half of the reported CRE cases were infections by *Enterobacter* spp. (Table 3). Most carbapenem resistance of *Enterobacter* spp. was not due to production of carbapenemases but rather due to production of class C ß-lactamase associated with reduced cellular membrane permeability. The current practice of notifying carbapenemase non-producing bacteria resistant to broad-spectrum ß-lactams is being reviewed with regards to implications for public health.

Horizontal gene transfer and nosocomial infection

In most cases, the carbapenemase gene is found on plasmids. It is transmitted to other bacteria belonging to *Enterobacteriaceae* by conjugation or other horizontal gene transfer mechanisms. Some *Enterobacteriaceae* bacteria possessing carbapenemase gene may be phenotypically susceptible to carbapenems. Such bacteria may become carbapenem-resistant through elevated expression of the drug resistance gene(s) or through cellular membrane change and capable of transmitting the resistance gene(s) to other bacteria of other species. As such events may go unnoticed, such possibilities should be kept in mind for surveillance. In fact, dissemination of the carbapenem resistance gene to multiple bacteria species in the clinical setting has already been reported (see pp. 289 & 290 of this issue).

Asymptomatic CRE carriers are not rare. Although they are not notifiable, if they are hospitalized and a nosocomial outbreak is suspected, such carriers should be reported to health centers according to the notice issued by the Director of Guidance of Medical Service Division, Health Policy Bureau, Ministry of Health, Labour and Welfare (17 June 2011: Isei-shi-hatsu 0617 No.1), and necessary measures taken promptly with assistance of an existing local network of medical institutions. Though this notice will be updated soon, the requirements for notification will remain unchanged. If genotyping or further analysis of resistance gene(s) is deemed necessary for infection control purposes, research institutes, including the National Institute of Infectious Diseases, should be consulted.

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 Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Food Safety, the Ministry of Health, Labour and Welfare, and quarantine stations, have provided the above data.

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