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Carbapenem-resistant Enterobacteriaceae

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ABSTRACT

Carbapenem-resistant Enterobacteriaceae (CRE) is a bacterial family difficult to treat with high resistance rates to broad-spectrum antibiotics. Patients following up in long-term-care facilities are the most affected by CRE infections and colonization. Carbapenem resistance rates are increasing despite all precautions, and the infections caused by CRE continues with high mortality. CRE surveillance is recommended by the Centers for Disease Control and Prevention (CDC) related to characteristics of health care facilities, point prevalence, or active surveillance. Mechanical ventilation, urinary or intravenous catheters, and long-term antibiotic use are the main risk factors for CRE infections. Treatment options are limited with older agents and mainly depend on aminoglycosides, polymyxins, and fosfomycin. Moreover, combination therapies and high-dose regimens are the other salvage strategies. This review study examined the epidemiology, precaution strategies, and treatment for CRE infections.

Key words: Carbapenem-resistant, Enterobacteriaceae, nosocomial infection

INTRODUCTION

Members of Enterobacteriaceae family; particularly *Klebsiella pneumoniae*, cause serious and life-threatening infections that have a significant mortality rate. Moreover, the treatment options are becoming limited with increasing resistance. The health care–-related infections due to carbapenem-resistant Enterobacteriaceae (CRE) have been reported increasingly from all over the world in recent years (1-3). The CRE infections were first reported in the 1990s, but have reached the levels that can cause problems in clinical practice (4). Recent studies showed that exposure to carbapenem-resistant (CR) *K. penumoniae* is independently related to in-hospital mortality, and mortality rates are significantly higher in patients who develop CRE infections (1,2,5,6).

Carbapenem-resistant Enterobacteriaceae

Previously resistance of members of Enterobacteriaceae family to carbapenem was defined as being insensitive to doripenem, meropenem, or imipenem, and also being resistant to all third-generation cephalosporins. However, in November 2015, ertapenem resistance was added to the list, and being resistant to all cephalosporins was removed from the definition (7). The CRE control guide of the Centers for Disease Control and Prevention (CDC) defined the CRE resistance as being resistant to any carbapenem antibiotic (i.e., minimum inhibitory concentrations of $\geq$4 μg/mL for doripenem, meropenem, or imipenem OR $\geq$2 μg/ml for ertapenem) or documentation of carbapenemase production. Further, the bacteria that are intrinsically resistant to imipenem (i.e., *Morganella morganii, Proteus spp., Providencia* spp.) should be resistant to non-imipenem carbapenems, and one of the polymerase chain reaction, modified Hodge test, Carba NP, or metallo-β-lactamase tests should be used to determine carbapenemase production (7). The breakpoints for carbapenem resistance according to the European Committee on Antimicrobial Susceptibility Testing and the Clinical & Laboratory Standards Institute (CLSI) are presented in Table 1 (8, 9).

Carbapenemases

Currently the most important mechanism for the development of carbapenem resistance is the production of the enzymes called "carbapenemases" by the microorganisms, which hydrolyze carbapenems. Carbapenemases hydrolyze not only carbapenems but also the broad-spectrum antibiotics oxyimino-cephalosporins and cephamycins, and they are

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Table 1: Breakpoints for carbapenem resistance.

Carbapenem	Disk diffusion breakpoints (mm)			MIC breakpoints (mg/L)		
			CLSI M100-S22 (9)			
	S	I	R	S	I	R
Imipenem	≥23	20-22	≤19	≤1	2	≥4
Meropenem	≥23	20-22	≤19	≤1	2	≥4
Ertapenem	≥22	19-21	≤18	≤0.5	1	≥2
Doripenem	≥23	20-22	≤19	≤1	2	≥
			EUCAST (8)			
	S		R	S		R
Imipenem	≥22		≤16	≥2		≤2
Meropenem	≥22		≤16	≥2		≤2
Ertapenem	≥25		≤22	≥0.5		≤0.5
Doripenem	≥24		≤21	≥1		≤1

CLSI M100-S22, Clinical & Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing.

responsible for the resistance to a broad group of antibiotics (10). Carbapenemases are categorized into molecular classes A, B, and D according to the classification of beta-lactamase family (11). The distribution of carbapenemases according to microorganisms in which they were identified is presented in Table 2 (11).

Class A Carbapenemases

They are the enzymes responsible for the carbapenem resistance in *Enterobacteriaceae* family, particularly *K. penumoniae*. KPC enzymes were first extracted from *K. pneumoniae* isolates in many epidemics in the USA, and then they were reported from other gram-negative microorganism all over the world (12, 13).

Class B Metallo-Beta-Lactamases

These enzymes use zinc cation to hydrolyze β-lactam ring, they are sensitive to chelators such as EDTA, and they are resistant to clavulanic acid, sulbactam, and tazobactam. They are responsible for the resistance to all beta-lactam antibiotics but not the monobactams (14). They belong to five clinically important families: IMP, VIM, SPM, GIM, and SIM. Typically, they can be transmitted by plasmids to *Acinetobacter*, primarily *Pseudomonas aeruginosa*, and other nonfermenting gram-negative and enteric bacteria (15).

Class D OXA Carbapenemases

OXA carbapenemase production leads to resistance to carbapenems and penicillins, but not to cephalosporins. Four families of OXA-type beta-lactamases (OXA-23, OXA-24, OXA-40, and OXA-58) have been described in *Acinetobacter baumannii* isolates (16).

CRE Epidemiology

The prevalence of CR members of Enterobacteriaceae family has increased in the last decade in many geographical regions of the world, including the USA and Europe. The resistance to one of the three carbapenems (imipenem, meropenem, and doripenem) in Enterobacteriaceae isolates, which was reported to the National Health Security Network (NHSN) in 2011, reached 4.2%. This increase in resistance was mostly reported for *K. pneumoniae* strains (1.6%–10.4%) (17). According to the NHSN, the prevalence of 2009–2010 CR *Klebsiella* strains has reached 12% in invasive device-related infections (18).

Table 2: Distribution of carbapenemases according to microorganisms (11) .

Microorganism	Class A (KPC, GES)	Class B (MBL)	Class D (OXA)
Pseudomonas aeroginosa	+	+	+
Acinetobacter baumannii		+	+
Klebsiella pneumoniae	+	+	+
Klebsiella oxytoca	+	+	
Esherichia coli	+	+	+
Proteus mirabilis	+	+	+
Serratia marscescens	+	+	
Entrobacter spp.	+	+	
Citrobacter freundii	+	+	
Morganella morganii		+	
Salmonella enterica	+		

Table 3: Carbapenem resistance rates in Turkey (34-37).

Çalışma	Microorganism	Year	Imipenem (%)	Meropenem (%)
MYSTIC	Gram negatives	2007	2.4	0.7
HITIT-2	K.pneumoniae	2009	3.2	
COMPACT	Enterobacteriaceae spp.	2012	2.1	1.7
Köseoğlu Eser	Enterobacteriaceae spp.	2014	5.7	1.9

In Europe, CRE isolates have been identified in France, Finland, Germany, Italy, Greece, Norway, Poland, and Sweden since 2005 (19-25). In Europe, CRE isolates have become important nosocomial pathogens in countries such as Greece, Italy, Israel, and Turkey. Epidemics, particularly related to CR *Klebsiella* spp., have been reported more frequently worldwide (3, 26-29). According to the 2011 data in Asia-Pacific countries, the mean resistance rate was 9% in CR *Klebsiella* spp. isolates and ranged between 0% and 25% (30). The prevalence rates of CR *Klebsiella* spp. rates in blood circulation were 68%, 27%, and 15% in European countries Greece, Italy, and Cyprus, respectively, and many epidemics throughout the countries were reported (31). According to the regional resistance surveillance program data, which evaluates the resistance of microorganisms in 12 Asia-Pacific countries, carbapenem resistance was 0%–25% (mean 9%) for K. pneumoniae isolates, and 0%–50% (mean 26%) for *P. aeuroginosa* isolates (30). CR *K. pneumoniae* was first reported in 2001 in Turkey with an isolated strain, and since then, hospital epidemics due to CR *K. pneumoniae* were reported (32, 33). Carbapenem resistance rates reported in different studies conducted in Turkey are presented in Table 3.

K. pneumoniae carbapenemase-type carbapenemase is endemic in countries close to Turkey, but the mechanism of primary carbapenem resistance in Turkey was found to be related to OXA-type enzymes (particularly OXA-48) (38). OXA-48-producing strains have been reported from the Middle East, India, and Europe (29, 39, 33). KPC-producing members of Enterobacteriaceae family is considered to be endemic in the USA, Israel, and Greece (12, 26, 40-42).

CRE Surveillance

Suggestions regarding CRE screening are categorized under two headings as point prevalence and screening of patients with high infection risk. If t no case has been identified in a unit previously, a point prevalence study can determine the CRE frequency in that unit rapidly. High-risk infections, all patients who stayed in the same room, or patients who took service and care from the same health care personnel should be screened. Specimens are generally taken from stool, rectum, perirectal area, and, in specific occasions, wound and urine. Active surveillance systems and chlorhexidine bath are recommended for preventing against CRE infections. Active surveillance defines screening of patients at admission and periodically after then (7).

If a new case is identified at a center where CRE is rarely or never isolated, precautions for contact isolation should be taken, units should be warned about hand hygiene and contact precautions, and educational support should be provided to the units. CDC recommends screening of patients who are epidemiologically relevant for CRE, performing a point prevalence study in the unit in case of identification of CRE, and establishing a cohort from the patients or health personnel. Basic precautions and supportive interventions should be implemented in all emergency and long-term treatments and nursing care applications in hospitals or units that have frequent CREs. CDC has developed a terminology to identify the CRE surveillance and also algorithms for surveillance and precautions. CRE identification is recommended primarily for *Klebsiella* species and *Escherichia coli*, and screening for other agents is recommended according to the local data (7).

Precaution strategies

Precautions for all centers that deliver emergency and long-term health care can be collected under eight headings.

1. Hand hygiene: Hand hygiene should be promoted, adherence to hand hygiene and feedbacks should be monitored, and access points to hand hygiene should be provided and enhanced.
2. Contact precautions: Patients with CRE colonization or infection should be placed in accordance with contact precautions, and strict contact precautions should be implemented. Preventive measures should be taken during transfers to high-risk units; health care personnel should be

educated; adherence and feedback should be monitored, and follow-up should be continued; and clinicians and infection control committees should be informed.

3. Health care personnel should be educated.
4. The use of invasive equipment should be decreased.
5. Establishing patient and worker cohorts: Health care personnel should be separated even if the patients stay in the same room. If single-occupancy rooms are limited, these patients should be separated as the highest-infection-risk group (e.g., patients with incontinence).
6. The information should be given to or taken from the laboratory.
7. Antibiotic use should be appropriately managed.
8. CRE screening: It is performed for identifying colonized patients in contact with CRE-carrying patients; cultures can be taken from stool, rectum, and perirectal area.

Supportive interventions with basic precautions include active surveillance and chlorhexidine bath application (44).

Risk factors for CRE

Many studies that evaluated risk factors in patients with CRE colonization and infection revealed that health care and antibiotic use were the most important risk factors. Debilitated patients, hospitalization at an intensive care unit, and using carbapenem, cephalosporin, fluoroquinolone, and vancomycin are among the other risk factors related to CR *K. pneumoniae* colonization and infection (1, 5, 27, 44). A limited number of studies found that endoscopic procedures were also potential risk factors for CRE infections (45-47). The CRE isolation rate from clinical specimens in patients with CRE colonization ranged between 8.8% and 47% (48-52), and these positive cultures generally (86%) represent a real infection (49). The predictive factors for the development of infection in patients with CRE colonization were found as hospitalization at an intensive care unit, application of central venous catheter, exposure to antibiotics, previous invasive surgery, and presence of diabetes (48, 49). The mortality rates in invasive infections such as bloodstream infections due to CREs can reach up to 40%. When this was compared with the invasive infections due to carbapenem-sensitive members of Enterobacteriaceae family, the mortality rate was found to be significantly higher (1, 2, 51). Age, mechanical ventilation, malignity, heart disease, and staying at an intensive care unit were found to be associated with increased mortality in CR *K. pneumoniae* infections (1, 5, 6). Removal of catheter and elimination of infection foci by debridement or drainage were found to be independently associated with the survival (1). Correa et al. compared patients infected with CR and carbapenem-sensitive *K. pneumoniae*, and reported that the mortality rates were higher in patients with CR *K. pneumoniae* (50% vs 27.5%), but the difference was not statistically significant ($P = 0.085$) (52). Jiao et al. evaluated the risk factors and mortality indicators for CR *K. pneumoniae* infection/colonization in their retrospective study. They reported that glycopeptide use, cefoperazone–sulbactam use, and tracheostomy were the independent risk factors for CR K. pneumoniae infection/colonization compared with carbapenem-sensitive *K. pneumoniae* infection/colonization. Also, advanced age was reported as an independent risk factor for mortality in CR *K. pneumoniae* infection/colonization (53).

Treatment

Infections due to multiresistant gram-negative bacilli are difficult to treat, and progress with treatment failure and high mortality (54, 55). An exact treatment regimen could not be established to date due to the lack of randomized trials and differences in patient groups (56). Generally, combination therapies and antibiotics are recommended to be applied in highest available doses in serious infections. Treatment options include carbapenems, aztreonam, colistin, aminoglycosides, tigecycline, fosfomycin, and, if sensitive, then quinolones and trimethoprim sulfamethoxazole (54, 57).

According to the current knowledge about the first-line treatment regimens for infections due to CR *K. pneumoniae*, colistin and high-dose meropenem treatment is recommended for bloodstream and pulmonary infections; colistin, high-dose meropenem, and tigecycline are recommended for gastrointestinal system and gallbladder infections; and fosfomycin and high-dose meropenem are recommended for urinary system infections. Alternative treatment regimens include gentamycin, fosfomycin, rifampicin, and high-dose tigecycline as alternative options (57). A study evaluated the treatment success of carbapenem monotherapy in patients infected with carbapenemase-producing *Enterobacteriaceae*, and found that the success rates were associated with the minimum inhibitory concentration of carbapenem (54). An analysis by Lee and Burgess evaluated combination therapy and monotherapy, and revealed that 49 patients (47%) took monotherapy and 56 patients (53%) took combination therapy. Treatment failure was found to be significantly higher in patients that took monotherapy (49% vs 25%; $P = 0.01$), and no significant difference was found between combination therapies (55).

CONCLUSIONS

Infections caused by CRE are currently important health care problems that need strict control measures owing to their association with increased mortality and limited treatment alternatives. Health care facilities have been recommended to be aware of the status of surveillance strategies. Appropriate treatment options need to be developed with continuous research.

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