Carbapenem-Resistant *Enterobacteriaceae*

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KEYWORDS

• Carbapenemase • KPC • Rapid diagnosis

KEY POINTS

- Carbapenem-resistant *Enterobacteriaceae* (CRE) have spread in health care settings worldwide in the last decade.
- Timely and accurate detection of CRE, in particular those producing carbapenemase is of paramount importance to guide clinicians and inform infection preventionists.
- Several phenotypic and genotypic methods are available for rapid detection of carbapenemase production that can be implemented and performed in clinical microbiology laboratories.
- Treatment usually consists of combination of active antimicrobial agents, but newer agents with improved activity and safety profiles are in late-stage clinical development.

INTRODUCTION

Carbapenem antibiotics are generally considered to be the most potent group of antimicrobial agents with proven efficacy in the treatment of patients with severe bacterial infections, including those caused by otherwise antimicrobial-resistant strains. The recent increase in the rates of carbapenem-resistant *Enterobacteriaceae* (CRE) among health care-associated *Enterobacteriaceae* species, in particular *Klebsiella pneumoniae*, is therefore a major cause for concern. This surge in CRE is mostly driven by the emergence and spread of carbapenemases, a specific group of β-lactamases that are capable of hydrolyzing carbapenems. Most strains that produce carbapenemases are resistant to carbapenems, and those that are not demonstrate reduced susceptibility to these agents.

Funding: The effort of Y. Doi was supported by research grants from the National Institutes of Health (R01AI104895, R21AI123747).
Transparency Declarations: Y. Doi has served on advisory boards for Meiji, Achaogen, Allergan, Curetis, and has received research funding from The Medicines Company for a study unrelated to this work. A. Iovleva declares no conflicts of interest.
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Clin Lab Med ■ (2017) ■–■
http://dx.doi.org/10.1016/j.cll.2017.01.005 **labmed.theclinics.com**

Three groups of carbapenemases—KPC, NDM, and OXA-48—are currently considered to be the 3 major β-lactamases of epidemiologic and clinical significance. In the United States, KPC is by far the most common carbapenemase produced by CRE,[1] but outbreaks of NDM-producing *Enterobacteriaceae* have been reported from US hospitals[2,3]; OXA-48–producing *Enterobacteriaceae* strains have also been reported sporadically.[4] It is essential that clinical microbiology laboratories be capable of recognizing CRE strains that produce these key groups of carbapenemases and refer them for further testing when appropriate to inform clinicians and infection preventionists. This review is intended to provide clinical microbiologists with an overview of the epidemiology, diagnosis, and clinical implications of CRE.

HISTORY OF CARBAPENEM-RESISTANT *ENTEROBACTERIACEAE*

The discovery and clinical application of antimicrobial agents constitutes one of the greatest public health achievements of the 20th century, drastically reducing mortality from common infectious diseases like pneumonia and diarrheal illnesses.[5] However, the introduction of every new class of antimicrobial agents has been eclipsed by the emergence of bacteria that are resistant to them. β-Lactams, arguably the most successful antimicrobial class used in clinical practice, have not been an exception in this regard. The introduction of ampicillin as an anti–Gram-negative aminopenicillin in the 1960s was quickly followed by the spread of *Escherichia coli* that produce TEM-1 β-lactamase, which is capable of hydrolyzing ampicillin.[6] To counter this, various oxyimino-cephalosporins (eg, cefotaxime, ceftazidime) were introduced in the 1980s, which were by design stable against hydrolysis by TEM-1 or SHV-1 (β-lactamase naturally produced by *K pneumoniae* and conferring ampicillin resistance). However, *Enterobacteriaceae* countered them several years later by generating variants of TEM-1 and SHV-1, which have extended the spectrum of hydrolysis to include not only aminopenicillins but also oxyimino-cephalosporins (thus the name extended-spectrum β-lactamases [ESBLs]).[6] ESBL producers were resistant to oxyimino-cephalosporins. Carbapenems were then introduced to clinics in the late 1980s and proved highly efficacious in the treatment of ESBL-producing *K pneumoniae* infections.[7]

Unfortunately, even carbapenems were not immune to the remarkable ability of *Enterobacteriaceae* to adapt to selective pressure. In the early 1990s, CRE emerged in Japan, followed by neighboring countries.[8] These strains produced metallo-β-lactamase (MBL) IMP-1, which was capable of hydrolyzing carbapenems and was encoded on plasmids that could transfer from one species to another. This was followed by discovery of VIM-1, another acquired MBL, which was initially identified from *Pseudomonas aeruginosa* in Italy and subsequently found in *Enterobacteriaceae*.[9] In the United States, a *K pneumoniae* strain with resistance to carbapenems was identified in 1996. This strain produced a novel carbapenemase that was later coined KPC for *K pneumoniae c*arbapenemase.[10] This KPC gene is encoded on a transferable plasmid and the enzyme is capable of hydrolyzing both oxyimino-cephalosporins and carbapenems efficiently. It became apparent by the early 2000s that KPC-producing *K pneumoniae* was rapidly becoming endemic at hospitals in parts of New York City.[11,12] Since then, KPC-producing *K pneumoniae* has spread across the continental United States and many other countries worldwide causing both outbreaks and endemicity in certain regions.[1]

In parallel to the expansion of KPC in the United States and elsewhere, another group of carbapenemases, OXA-48, emerged and spread mostly in *K pneumoniae* in the Mediterranean countries in the 2000s.[13,14] More recently, a novel group of MBL, NDM (*N*ew *D*elhi *m*etallo-β-lactamase), was identified and reported in