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Combating the spread of carbapenemases in *Enterobacteriaceae*: a battle that infection prevention should not lose

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Abstract

The emergence of carbapenemases in *Enterobacteriaceae* has raised global concern among the scientific, medical and public health communities. Both the CDC and the WHO consider carbapenem-resistant *Enterobacteriaceae* (CRE) to constitute a significant threat that necessitates immediate action. In this article, we review the challenges faced by laboratory workers, infection prevention specialists and clinicians who are confronted with this emerging infection control issue.

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Introduction

When Kumarasamy *et al.* [1] published the first epidemiological report on the emergence of *Enterobacteriaceae* producing a new carbapenemase (New Delhi metallo-β-lactamase-1 (NDM-1)) in India, Pakistan and the UK in 2010, the impact on the medical and public health authorities was probably underestimated. Previously, other carbapenemases had been described in *Enterobacteriaceae*, the most clinically important being KPC, VIM, and IMP. However, since 2010 and the description of NDM-1, >975 articles related to carbapenemases, their mechanisms of action, epidemiology and treatment have been indexed in PubMed. The emergence of carbapenemases in *Enterobacteriaceae* has caused global concern among the scientific, medical and public health communities [2–11]. Both the CDC and the WHO consider carbapenem-resistant *Enterobacteriaceae* (CRE) to constitute a significant threat that necessitates immediate action [12,13]. In this article, we review the challenges faced by laboratory workers, infection prevention specialists and clinicians who are confronted with this emerging infection control issue.

CRE constitute a significant emerging threat to the public health and medical communities. Between 2001 and 2011, the National Nosocomial Infection Surveillance System/National Healthcare Safety Network data revealed that carbapenem resistance had increased ten-fold, from 1.6% to 10.4% in *Klebsiella* isolates, and four-fold, from 1.2% to 4.2%, in *Enterobacter* isolates. Even more concerning in the USA is that approximately 4% of acute-care hospitals but 18% of long-term acute-care hospitals (LTACHs) reported at least one CRE infection in the first half of 2012 (CDC website: http://www.cdc.gov/vitalsigns/hai/cre/). Of particular note is that production of carbapenemases is one of the mechanisms conferring resistance to carbapenems among *Enterobacteriaceae*. Once the CLSI lowered the interpretive breakpoints for carbapenems in 2010, a concomitant and anticipated increase in the proportion of reported CRE (including expanded-spectrum β-lactamase or AmpC hyperproducers combined with porin loss) that were not carbapenemase producers was seen. Furthermore, although antimicrobial testing is widely available in the usual clinical laboratory setting, phenotypic and genotypic testing to detect the presence of carbapenemases in

CRE is often lacking. For infection prevention specialists, these organisms are associated with high rates of morbidity and mortality [5], and, because of carbapenem resistance, therapeutic choices are extremely limited. For this reason, stopping their transmission should be a common goal.

Carbapenemases are most often located on genetic elements such as plasmids, which are mobile and can be easily shared among *Enterobacteriaceae*. *Klebsiella pneumoniae* carbapenemase (KPC) emerged in the USA in 2001, and is still the most common carbapenemase reported. Among the carbapenem-resistant *K. pneumoniae* strains recently reported from 14 hospitals in New York City, 29% were KPC producers [14]. Carbapenem resistance among invasive *K. pneumoniae* strains increased in many countries between 2005 and 2011, according to the European CDC report: five countries (Greece, Cyprus, Italy, Hungary, and Portugal) reported rates of CRE of >1%, as opposed to only two (Greece and Germany) in 2005 [15]. This interactive database provides up-to-date information on antimicrobial resistance in different European countries (www.ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/database/Pages/database.aspx.) KPCs have also been described in Asia, initially in China in 2004 and then in South Korea, Taiwan, and Singapore, and community acquisition is suspected [16].

However, beginning in 2009, several isolates carrying metallo-β-lactamases such as NDM, VIM and IMP have been documented in the USA, and are often imported from other countries. Although KPCs are endemic in some hospitals in the Mid-Atlantic USA, many of the metallo-β-lactamases have been isolated from patients who have received healthcare in other countries. Endemicity of NDM-1 in India was supported by data demonstrating that bacteria harbouring this enzyme were present in seepage and drinking water in New Delhi [17]. Few data are available from clinical settings in many parts of the world, because there is no well-defined national surveillance programme. NDM-1 distribution in the community in Singapore was also recently suggested, as it was found in 23% of all CRE isolates that revealed wide genetic diversity and no epidemiological link to other known endemic areas [16]. Finally, the worldwide spread of NDM-1 was recently reviewed and effectively presented by the use of interactive mapping [18].

Why Infection Prevention Matters

The plasmid carrying the gene encoding the carbapenemase enzyme also harbours other resistance genes, making *Enterobacteriaceae* potentially resistant to almost all of the antimicrobials included in our armamentarium [19]. Without existing appropriate treatment for patients, high rates of morbidity and mortality have been documented in different studies, reaching 70% in some of them, with an attributable mortality for bacteraemia of 50% [20]. Additionally, prolonged hospital stays and increased healthcare costs have been reported for CRE infections [19]. Moreover, *Enterobacteriaceae* (*Escherichia coli* in particular) cause most human infections, and the mortality rate is higher when resistance to multiple drugs is present [5]. Given the fact that limited therapeutic agents are available, good infection prevention practices (beginning with standard precautions that should always be emphasized as the cornerstone to prevent transmission) are the primary methods for stemming the spread of CRE in the healthcare setting (Table 1). Outbreaks involving these highly resistant microrganisms can result in several deaths and extensive disruption at a given institution until they can be contained.

Risk factors for colonization and/or infection with CRE mirror those previously associated with other multidrug-resistant organisms (Fig. 1). The risks of colonization and infection have been associated with critical illness and surgery, comorbid conditions, including organ or stem cell transplantation, the presence of a wound, the use of invasive devices or mechanical ventilation, and previous use of antimicrobials (including cephalosporins, carbapenems, and fluoroquinolones). Additionally, the risk of CRE colonization increases with: (i) an intensive-care unit stay; (ii) sharing a room with a known carrier of a CRE strain; (iii) being transferred between facilities or units; or (iv) prolonged hospitalization [21–28]. Of those colonized with a CRE strain, almost one in ten will subsequently show growth of the organism in a clinical sample [24]. Some of the risks can be minimized by the use of appropriate infection prevention practices.

TABLE 1. Infection prevention and antimicrobial stewardship recommendations published to prevent the spread of carbapenem-resistant *Enterobacteriaceae*

Required infection prevention measures
Implement a surveillance programme to identify potential carriers (screening)
Use contact isolation precautions for colonized and infected patients
Cohort colonized and infected patients
Enhance hand hygiene and support with audits
Increase the frequency of environmental cleaning
Limit the use of devices and remove unnecessary devices
Implement antimicrobial stewardship, including a programme
Educate healthcare workers about critical prevention measures
Suggested enhanced infection prevention measures
Limit patient transfers
One-to-one nursing
Decolonize patients with chlorhexidine gluconate baths