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Interventional strategies and current clinical experience with carbapenemase-producing Gram-negative bacteria

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Abstract

The wide dissemination of carbapenemase-producing Gram-negatives (CPGNs), including enterobacterial species and non-fermenters, has caused a public health crisis of global dimensions. These organisms cause serious infections in hospitalized patients, and are associated with increased mortality. Cross-transmission is common, and outbreaks may occur in healthcare facilities where the infection control practices are inadequate. CPGNs exhibit extensive drug-resistant phenotypes, complicate therapy, and limit treatment options. Systematic data on therapy are limited. However, regimens combining two or more active agents seem to be more efficacious than monotherapy in carbapenemase-producing *Klebsiella pneumoniae* infections. Strict infection control measures, including active surveillance for timely detection of colonized patients, separation of carriers from non-carriers, and contact precautions, are of utmost importance, and may be the only effective way of preventing the introduction and transmission of these bacteria in healthcare settings.

Keywords: Carbapenemase, Gram-negatives, infection control, risk factors, treatment
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Introduction

Carbapenemase-producing Gram-negatives (CPGNs) have become a major concern worldwide [1,2]. Many factors, including the ease of international travel for medical tourism and migration, and the importation of food products, have been responsible for introducing these microorganisms to several countries far beyond their country of origin [3,4].

The extensive dissemination of carbapenemase-producing *Klebsiella pneumoniae* (CPKP) and, to a lesser extent, other clinically important carbapenemase-producing *Enterobacteriaceae* (CPE), such as *Escherichia coli*, has caused serious therapeutic problems that parallel the methicillin-resistant *Staphylococcus aureus* crisis two decades ago. In fact, a recent European trend analysis predicted that the number of bloodstream infections (BSIs) caused by third-generation cephalosporin-resistant *E. coli* are likely to surpass the number of methicillin-resistant *Staphylococcus aureus* BSIs in the near future [5]. *K. pneumoniae*, since its integration into the nosocomial flora in the early 1970s, consistently remains among the pathogens frequently involved in hospital-acquired infections. A characteristic trait of the species is its ability to acquire and maintain multidrug resistance plasmids, such as those encoding extended-spectrum β-lactamases, along with other resistance determinants. Today, *K. pneumoniae* has become the main reservoir of diverse plasmid-borne *bla* genes coding for the so-called carbapenemases, i.e. β-lactamases that hydrolyse almost all available β-lactams, including carbapenems, the most important being the KPCs and the metallo-β-lactamases (MBLs) VIM, IMP, and NDM [2,6,7]. It should be noted at this point that the term 'carbapenemase' reflects the clinical impact of carbapenem hydrolysis rather than a genuine preference of these enzymes for carbapenems

over other β-lactam substrates. The spread of CPKPs has reached epidemic proportions in various areas, such as some southern European countries, the north-eastern USA, the Indian subcontinent, and the Far East [2]. CPE isolates are invariably multidrug-resistant, carrying a wide variety of additional acquired determinants that mediate resistance to aminoglycosides as well as other clinically less important antimicrobials, such as co-trimoxazole, chlorampenicol, and nitrofurantoin [1]. Moreover, high-level resistance to fluorinated quinolones is commonly seen among these isolates, especially in CPKPs.

This article reviews the risk factors related to colonization, infection and mortality caused by CPGNs. Available *in vitro* and *in vivo* data are discussed in relation to the treatment of infections caused by these bacteria. Also, special emphasis is placed on reviewing infection control measures to prevent the spread of CPGNs.

Risk Factors for Colonization

Colonization prior to infection has usually been detected in the gastrointestinal tract (GIT) [8,9]; however, other sites, including the respiratory tree, surgical sites, and the urinary tract, are also commonly colonized [10–12].

Several risk factors have been identified for colonization with CPGNs (Table 1). The risk factors described in the literature may vary for different Gram-negative bacteria and also for the type of enzyme [9,12,13,15–18] (also see the section below, 'Measures required for controlling the spread of carbapenemase producers'). However, it should be noted that most of these studies on risk factors and outcome of infection were of the retrospective, case–control or cohort type, with small sample sizes. Study populations were usually mixed (intensive-care unit (ICU) and non-ICU settings) with varying lengths of follow-up.

In a recent cross-sectional survey [13], extended stay in hospital, staying with a colonized patient in the same room and a high number of known carriers in the ward were independent risk factors for carbapenem-resistant *K. pneumoniae* (CRKP) carriage. The results of a nested case–control study in the same paper showed that antibiotic exposure within the previous 3 months and colonization with other resistant pathogens were related to the carriage. Antibiotic exposure within the previous 3 months, receipt of co-amoxiclav and screening within 3 months of the first CRKP-positive culture were predictors of continued CRKP colonization.

In another study, persistent carriage was documented in patients who were transferred from another healthcare facility, had used fluoroquinolones previously, and were admitted within the last 3 months since the first carbapenem-resistant *Enterobacteriaceae* (CRE) isolation [9].

TABLE 1. Risk factors for colonization with carbapenemase-producing Gram-negatives [8,13,14]

Prior exposure to or current use of antibiotics
Use of a fluoroquinolone
Malignancy
Poor functional status
Non-surgical invasive procedure
Extended stay in hospital
Admission to intensive-care unit
Admission to post-acute-care units
Sharing a room with a known carrier
Diaper use

Types of Clinical Infection and Related Risk Factors

A wide spectrum of clinical infections are caused by CPGNs, and include primary or catheter-related bacteraemia [19–21], nosocomial pneumonia, including ventilator-associated cases [10,20,22], surgical site and wound infections [17,20], peritonitis [20], endocarditis [23], mediastinitis [24], and urinary tract infections [20]. Outbreaks have frequently been reported with CPKP [12,20,25–27], but also with other enterics and non-fermentatives [27].

Risk factors for infection include advanced age, severe underlying disease with high APACHE-II scores, mechanical ventilation [28], organ or stem cell transplantation [28,29], and extended stay in hospital [28]. Previous antibiotic use is almost always present as an independent risk factor for infection with these bacteria. Although prior use of carbapenems is a frequent culprit [21], use of any other antibiotics, including quinolones, β-lactamase inhibitor combinations, cephalosporins, and glycopeptides, have also been detected in the recent history of patients [24,28,30].

Analysis of 28 patients with VIM-1-producing *K. pneumoniae* (VPKP) bacteraemia in two Greek hospitals showed that younger age, multiple trauma, admission to an ICU, extended hospital stay and previous therapy with carbapenems, quinolones or cephalosporins were related risk factors. However, in multivariate analysis, none of these factors remained significant [31]. However, the same group later reported on a comparison of 67 patients with VPKP bacteraemia with 111 patients with non-VPKP infection, and found that prior exposure to more than three different classes of antibiotic, being in an ICU and prior use of carbapenems were significant independent predictors for infection [21]. During an outbreak with CRKP in a Puerto Rican Hospital, transfer between units, wounds and surgery were found to be independent risk factors for CRKP infection [17].