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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].

A case–control study in two Brazilian hospitals with 86 patients infected with MBL-producing *Pseudomonas aeruginosa* (MBL-PA) and 212 controls infected with non-MBL-PA found that exposure to quinolones or β-lactams, underlying neurological disease, presence of urinary tract infection and renal failure were independent risk factors for acquistion of MBL-PA infection [32].

Risk Factors for Outcome and Mortality

High mortality rates have been reported for infections caused by CPGNs. Rates for attributable mortality (i.e. where the presence of CPGN infection contributed significantly to the mortality) ranged between 51.2% and 95% for carbapenem-resistant *P. aeruginosa* infections [2,33] and between 18.9% and 48.0% for CRE infections [12,19,28].

Several independent risk factors for mortality have been identified (Table 2). Daikos *et al.* [19] reported that patients infected with VPKP exhibiting resistance to carbapenems (MIC >4 mg/L) had significantly higher mortality than those infected with carbapenem-susceptible VPKP (MIC ≤4 mg/L) or non-VPKP (all-cause 14-day mortality rates were 42.9% vs. 18.9% vs. 14.8, respectively). The effect of carbapenem resistance on mortality was probably mediated by the failure to provide effective antimicrobial therapy. VIM production had no effect on mortality.

Higher mortality rates were also detected for infections caused by MBL-PA than for those caused by non-MBL-PA (51.2% vs. 32.1%, respectively) by crude comparison. Mortality per 1000 patient-days also increased (17.3 days vs. 11.8 days, respectively) with MBL-PA. Multivariate analysis indicated that severe sepsis or septic shock and shorter usage of appropriate therapy for ≤72 h were significantly associated with increased mortality [33].

A literature review found that the crude mortality rate for CPE infections was 58.7% in patients with solid organ transplantation, and six of seven patients with liver transplantation succumbed to infection with these bacteria [34].

TABLE 2. Risk factors for mortality in patients infected with carbapenemase-producing Gram-negatives [7,8,12,19,28,29, 33,34]

Older age
Severity of underlying disease
Malignancy
Mechanical ventilation
Solid organ transplantation
Severe sepsis and/or septic shock
Carbapenem resistance
Inappropriate antibiotic therapy
Short duration (≤72 h) of appropriate antibiotic therapy
Lack of microbiological eradication at 7 days

In a retrospective cohort study in which 42% of patients had undergone solid organ transplantation and had bacteraemia with CRKP, 42% died at 30 days. Lack of microbiological eradication at 7 days was independently associated with 30-day mortality. A favourable clinical outcome was associated with adjunctive procedures performed for removal of the source of infection and microbiological clinical response at 7 days. Survival was not improved with early therapy and use of antibiotics that are active *in vitro* [29].

Patel *et al.* [28] reported that CRKP-infected patients died more frequently during hospitalization than those infected with carbapenem-sensitive *K. pneumoniae* (48% vs. 20%, respectively, p <0.001). Infection-related mortality was also significantly higher (38% vs. 12%, p <0.001) in patients with CRKP infections. Source control favoured better outcome, whereas timely administration of antibiotics that er active *in vitro* did not alter the mortality rate.

Schwaber *et al.* [8] found that CRKP isolation predicted death significantly after adjustment for severity of illness in a group of patients with *K. pneumoniae* clinical isolates (48 patients with CRKP vs. 56 with carbapenem-sensitive *K. pneumoniae*) and 59 control patients without *K. pneumoniae* isolation.

Treatment Options

Most of the data published in the literature on therapy have been related to CPKP; systematic data on the treatment of infections caused by other CPGNs are still scarcely available.

In vitro data

The most active antibacterial agents against CPE with either KPCs or MBLs are colistin, tigecycline, and fosfomycin, the former two being widely used for treatment of the respective infections. However, as shown in recent studies, selection of colistin-resistant and tigecycline-resistant mutants is increasing [35–38]. Clinical experience with the use of fosfomycin against CPE is limited [39], but the drug is known for its ability to readily select for resistance [40]. Among aminoglycosides, gentamicin has partly retained its *in vitro* efficacy against KPC and VIM producers (most NDM producers are resistant to all aminoglycosides, owing to production of 16S rRNA methylases). For carbapenems, these organisms generally have elevated MICs, but some isolates exhibit low MIC values despite the production of a carbapenemase. However, classification of a given CPE as carbapenem-susceptible may differ, depending on the use of either the CLSI recommendations [41] or the EUCAST recommendations (2012; http://www.eucast.org]. The issue is of clinical importance, as a

meaningful proportion of CPEs characterized as resistant according to CLSI interpretive criteria appear susceptible by the criteria of EUCAST, which has adopted higher carbapenem breakpoints. Of the remaining β-lactams, aztreonam, although not hydrolysable by MBLs, is of limited usefulness, as MBL-positive isolates frequently coexpress extended-spectrum β-lactamases.

Attempts have also been made to reveal potential synergism with several combinations of antimicrobial agents, commonly including colistin, by the use of time-kill experiments. Despite some conflicting results and the inherent limitations of this methodology, time-kill studies have indicated synergistic effects of colistin with various antibiotics, including tigecycline, carbapenems, rifampin, and doxycycline, against CPKP [42–44]. Also, combinations of colistin, meropenem or gentamicin with fosfomycin appear to be synergistic and partly prevent the selection of CPKP variants that are resistant to the latter agent [45]. It is of note that *in vitro* models simulating human pharmacokinetics suggest that carbapenems in optimized dosing regimens, either alone or in combination with tigecycline, may cause, within 24–48 h, a significant, although transient, reduction in the viable counts of KPC-producing *K. pneumoniae*, including isolates resistant to carbapenems [46].

Animal models

Experimental infections in several animal models have also been used to evaluate the efficacy of carbapenems. Given the magnitude of the problem caused by CPKPs, the number of these studies is remarkably small. Moreover, the therapeutic potential of colistin and tigecycline, which have become first-line antibiotics against CPKP infections, has not been assessed adequately in animal models. Nevertheless, the relevant studies have produced some interesting results indicating that carbapenems have their place in the treatment of CPKP infections. In the neutropenic murine thigh infection model, imipenem (60 mg/kg every 2 h) exhibited a significant bactericidal effect against VIM producers, with MICs of 2 and 4 mg/L (estimated T>MIC of 40%) [47]. With the same model and dosing scheme, meropenem has been found to be more effective (L. Tzouvelekis, unpublished data). Imipenem, meropenem, ertapenem and aztreonam have also been found to be efficacious against a carbapenem-susceptible, VIM-positive *E. coli* isolate in a rabbit peritoneal abscess model [48]. Similarly, doripenem has shown significant therapeutic potential in experimental infections caused by KPC-producing *K. pneumoniae* isolates, with MICs of up to 8 mg/L in both immunocompetent and neutropenic mice [49]. An ertapenem–doripenem combination has also been tested against KPC-producing *K. pneumoniae* in an immunocompetent murine thigh infection model, based on the notion that the high affinity of KPC for ertapenem would 'trap' the enzyme, thus facilitating the activity of doripenem. The relevant experimental data seem to support this interesting concept [50].

Clinical experience from a high-prevalence area

It is arguable whether reviewing the studies reporting on the efficacy of various antibiotic regimens for CPKP infections could lead to solid conclusions for optimal therapeutic approaches, as it is not possible to measure and adjust for various confounding factors that may affect patient outcome. On the other hand, it is unlikely that residual confounding could have significant impact on the results, given that CPKP usually affects patients who have common characteristics. Data from nine relevant studies conducted during 2004–2011 in Greek hospitals included 234 patients for whom adequate clinical information, the efficacy of the antimicrobial treatment and the susceptibility status of the infecting CPKP isolate to the antibiotic(s) used, were available [11,12,19,20,24,31,51–53]. Of the isolates, 132 produced a VIM-type MBL and 102 were KPC-positive. Two hundred and fifteen patients had BSIs (primary, secondary, or intravenous catheter-related), 14 had pneumonia, and the remaining five had other infections. Among the 234 patients included in the analysis, 111 (47.5%) received monotherapy (one drug was active *in vitro* against the infecting organism), 82 (35%) received combination therapy (at least two drugs were active *in vitro*), and the remaining 41 (17.5%) received 'inappropriate' therapy (no drug was active *in vitro*). It should be noted that the susceptibility to carbapenems was taken as reported in the relevant studies, in which the previous CLSI interpretive criteria were applied.

Monotherapy vs. combined therapy

The efficacies of antimicrobial treatment regimens, as recorded in the aforementioned studies conducted in Greece,

TABLE 3. Efficacy of antimicrobial regimens used to treat infections caused by carbapenemase-producing *Klebsiella pneumoniae*

Antibiotic regimen	No. of patients (%)	Outcome success (%)	Failure (%)
Monotherapy			
Colistin	64 (24.2)	35 (54.7)	29 (45.3)
Tigecycline	8 (4.7)	5 (62.5)	3 (37.5)
Aminoglycoside	16 (6.8)	12 (75.0)	4 (25.0)
Carbapenem	23 (9.8)	18 (78.3)	5 (21.7)
Total	111 (47.5)	70 (63.1)	41 (36.9)
Combination therapy			
Two or more active drugs (carbapenem not included)	52 (22.2)	38 (73.1)	14 (26.9)
Two or more active drugs (carbapenem included)	30 (12.8)	28 (93.3)	2 (6,7)
Total	82 (35.0)	66 (80.5)	16 (19.5)
'Inappropriate' therapy	41 (17.5)	23 (56.1)	18 (43.9)
Total	234 (100)	159 (67.9)	75 (32.1)

are presented in Table 3. Monotherapy with either a carbapenem or an aminoglycoside (mostly gentamicin) resulted in moderate success rates that were higher than that observed with tigecycline, but the number of patients treated with the latter drug was too small to allow comparisons. Colistin was the least effective agent in the monotherapy group, as 29 of 64 colistin-treated patients were reported as having treatment failure rates similar to that observed for the patients receiving 'inappropriate' therapy. Thus, the efficacy of monotherapy was not satisfactory, mainly because of the inferior activity of colistin, which was used in 57.7% of the patients treated with a single drug. The overall success rate of combination therapy was significantly higher than that of monotherapy (p 0.01; OR 2.41; 95% CI 1.2–4.7). The antibiotics most frequently used in combination therapy, in descending order, were colistin (n = 63), aminoglycosides (n = 46), carbapenems (n = 30), tigecycline (n = 26), aztreonam (n = 2), and tetracyclines (n = 2). It is of note that, on division of the patients who received combination therapy into two groups on the basis of the inclusion of a carbapenem in the regimen, it was shown that the carbapenem-containing regimens were significantly more efficacious than the non-carbapenem-containing regimens (p 0.04; OR 5.15; 95% CI 1.1–24.5). We should nevertheless emphasize once more that the above estimations were based on crude data derived from various types of study without control groups for comparison.

Is there room for improvement?

The relatively high number of CPKP-infected patients treated with a single antimicrobial agent may, in part, reflect a recent trend towards monotherapy in hospital-acquired infections, as supported by the findings of recent meta-analyses of relevant studies [54,55]. However, our observations, despite their limitations, suggest that combination schemes, especially those including an active carbapenem, are superior to monotherapy in controlling serious infections caused by CPKP.

The poor performance of colistin monotherapy, as assessed here, is a matter of concern, as the drug is among the few drugs that are active against CPKP. Recent clinical observations support the view that the inferior efficacy of colistin monotherapy may be associated, among other factors, with suboptimal dosing regimens of the drug [56]. The currently administered dosing regimens of colistin result in relatively low plasma concentrations that are unable to have substantial bactericidal activity against the infecting organism [57]. An additional drawback of the standard regimens may be the delayed attainment of adequate drug concentrations. We therefore think that it is important to administer an initial loading dose of the drug and continue treatment with an adequate total daily dosage of colistin, in order to achieve efficacious levels according to current recommendations [58,59]. To better exploit the therapeutic potential of colistin against CPE, further studies, including pharmacokinetic/pharmacodynamic studies and clinical trials, are needed. Notwithstanding these issues, the findings presented herein do not necessarily mean that the drug should be regarded as unsuitable for the treatment of CPE infections. Indeed, the increased numbers of successful outcomes when it was combined with other active antibiotics, especially carbapenems, may indicate *in vivo* synergism. These observations are in line with the results of a previous review supporting the combination of colistin with other drugs in the treatment of KPC-producing *K. pneumoniae* infections [60].

Although the small number of patients treated with tigecycline monotherapy precludes definite conclusion as its *in vivo* activity against CPKP infections, combination regimens containing tigecycline along with one or two active drugs resulted in satisfactory success rates. Clinicians, however, must be aware that treatment of serious hospital infections such as ventilator-associated pneumonias and bacteraemia with tigecycline has been associated with an increased risk of death [61] (http://www.fda.gov/Drugs/DrugSafety/ucm224370.htm). The probable reasons are: (i) the fact that tigecycline is primarily bacteriostatic against Gram-negatives; and (ii) its low concentrations in various anatomical sites, including serum, urine, and epithelial lining fluid, which are commonly below the MICs for CPEs [62–64]. It is therefore necessary to determine, in clinical trials, those CPE infections that could be efficiently treated with tigecycline. At present, it seems reasonable to suggest the use of this drug as part of a combination therapy, considering the site of the CPE infection and the MIC of the microorganism. Unpublished data from Greece indicate that there is a clear trend towards tigecycline resistance among multidrug-resistant Gram-negatives, with *c.* 15% of CPKPs exhibiting MICs of >2 mg/L.

The issue of whether carbapenems should be used in the treatment of CPE infections is still unsettled [65]. The data presented here, however, indicate that carbapenems provide therapeutic benefit against CPKPs exhibiting MICs up to 4 mg/L, which is closer to the EUCAST breakpoints (2012; http://www.eucast.org). The fact that the carbapenem-containing regimens were the most efficacious among the combination schemes further underlines the therapeutic potential of these antibiotics. Also, the data from animal experimental infections summarized above, as well as from human studies [47–49,66,67], suggest that the pharmacokinetic/pharmacodynamic characteristics of carbapenems may allow adaptations that could be valuable in controlling CPE infections. For instance, the probabilities of attaining a 50% T>MIC target

for isolates with meropenem MICs of 4 and 8 mg/L are 100% and 85%, respectively, when the drug is given in a high-dose/prolonged-infusion scheme (3-h infusion of 2 g every 8 h) [68].

The success rate of 'inappropriate' treatment schemes was unexpectedly high. It was not feasible to reliably define factors associated with this observation. It is possible that catheter-related infections and non-immunocompromised patients were over-represented in the subgroup of successfully treated patients.

Fosfomycin was not included in any of the studies reviewed here. The therapeutic potential of this agent as part of combination regimens in CPE infections, including bacteraemia, has been discussed, but the published relevant data are quite limited. On the basis of unpublished experience with fosfomycin, given as an adjunct in combination schemes in a small number of patients with bacteraemia caused by CPKP, it appears that the usefulness of the drug is doubtful.

Measures Required for Controlling the Spread of Carbapenemase Producers

Some CPGNs cause local outbreaks, and the detection of a CPGN therefore often signifies an imminent outbreak. Because of the risk associated with these infections, closure or reduced activity of high-risk units is required. Therefore, the spread of CPGNs may incapacitate the healthcare system and limit the ability to provide invasive procedures and immunosuppressive therapy in a safe medical environment.

To design an effective control strategy to limit the spread of carbapenemases, the natural history, reservoirs and transmission of CPGNs have to be defined in a specific setting. The genes encoding carbapenemases are acquired in human pathogens. Thus, they are not generated *de novo* in a specific patient, but are rather acquired by the patient. For *Enterobacteriaceae*, the natural history of acquisition is the ingestion of a CPGN and colonization of the patient's GIT, where amplification may occur. The proportion of persons who become colonized after ingestion of CPGNs is unknown, but this is probably determined by multiple factors, such as the inocula ingested, the characteristics of the bacteria ingested, the patient's resistance to colonization through gastric acidity, and the normal gut microflora. After colonization with CPGNs has occurred, it may persist from days to months, and even years. Schechner *et al.* [9] identified fluoroquinolone use, transfer from another healthcare facility and admission ≤3 months after the first CRE isolation as predictors of persistent CRE rectal carriage. Saidel-Odes *et al.* [69], who studied CRKP carriers, found 16.1% rectal screen negativity at 2 weeks and 33% after 6 weeks. Thus, it appears that the median carriage time is 3 months; however, in a significant proportion of carriers, it may be longer. During this period of GIT carriage of CPGNs, shedding and transmission to other patients may take place. Moreover, transmission of mobile genetic elements containing the carbapenamase gene to other strains colonizing the GIT may occur, resulting in new CPGN clones and species, which, in turn, may be the source of new outbreaks [70–73]. In a subset of patients, CPGNs will migrate to a clinical site, such as the urinary tract, wounds, and medical devices, and infection will occur. The size of the subset that develops infection probably varies with patient and pathogen factors, as well as the characteristics of the competing gut flora and exposure to antibiotics. Borer *et al.* [74] described a southern Israeli hospital where a KPC outbreak was ongoing: of 464 patients identified by surveillance cultures as being GIT carriers of CRKP, 42 subsequently developed infection with a similar strain. The investigators identified invasive procedure, diabetes mellitus, solid tumour, tracheostomy, urinary catheter insertion and antipseudomonal penicillin as independent risk factors for infection among GIT carriers [74].

It is evident that, in certain regions, the spread of carbapenemases (NDM-1 and OXA-48) occurs primarily in the community via the faecal–oral route, either by foodborne or waterborne transmission. As with other enteric bacteria, waterborne outbreaks are often on a much larger scale than foodborne epidemics. Walsh *et al.* [75] detected bacteria with NDM-1 in 12 of 171 seepage samples and in two of 50 water samples in New Delhi. Indeed, NDM-1 was described in various community-acquired infections in India [73]. OXA-48 has been detected in patients with community-acquired infections and among those with no contact with the healthcare setting, suggesting community acquisition via food or water [76]. Control of the spread of carbapenemases via the water supply has not been investigated. However, it is very likely that improved sewage systems and their separation from potable water, and adequate chlorination, are the main measures required. Similarly, improved sanitation is required where the foodborne route is suspected. It is beyond the scope of this article to discuss control measures in areas where spread occurs via foodborne or waterborne outbreaks. However, in a globalized world, where travel, migration, medical tourism and trade between countries with different levels of sanitary conditions is common, repeated importation of CPGNs is to be expected from countries where these bacteria spread in the community.

In contrast, in western countries with safe water systems and better sanitation, carbapenemases are acquired almost

exclusively in the healthcare setting. The NDM-1 and OXA-48 enzymes, which are primarily imported from overseas, where they are acquired either in healthcare settings or in the community, may then result in nosocomial outbreaks in western countries [77–80]. The KPC and VIM enzymes, which were recognized initially in western countries, spread primarily in healthcare settings; even after 15 years of ongoing nosocomial outbreaks, community spread in western countries is still a rare event. However, even in developed countries, large reservoirs of carriers have accumulated, both in acute-care and long-term-care facilities in affected countries [13,25,81,82].

Thus, because of the large reservoirs both in healthcare settings and in the community in certain countries, and the lack of real-time information on the status of outbreaks, all healthcare facilities should be ready for the importation of CPGNs and their imminent in-hospital spread. Indeed, recently, the European Centre for Disease Prevention and Control (ECDC) has performed a risk assessment based on systematic reviews on the spread of CPE through patient transfer between healthcare facilities, with special emphasis on cross-border transfer [83]. The conclusions from the systematic reviews in the ECDC risk assessment were that cross-border transfer of patients from one healthcare facility to another is a risk factor for the transmission and spread of CPGNs into healthcare settings.

Several guidance documents on the control of CPGNs have been published over the last 3 years. Of special note are the documents by the US CDC [84], the ESCMID Expert Group [1], and European national experts [85]. Although there are some differences between these guidance documents, many similarities and common themes are the rule. Thus, these three documents should be read as complementing each other. The ECDC technical report [83] provides an exhaustive systematic review of the literature; eight intervention studies were identified. Interventions were based on a combination of two to seven infection control measures, which were implemented. Most interventions (n = 6) combined at least active surveillance cultures and control measures targeted at CPGN-colonized patients, such as contact precautions and/or cohort nursing. The results provided suggestive and consistent evidence for the effectiveness of combined interventions, including active surveillance culture for early detection of CPGN-colonized patients, contact precautions, and cohort nursing care for CPGN-colonized patients. Other measures have been employed, such as antibiotic restriction, promotion of hand hygiene and environmental surface decontamination, patient decolonization with antiseptic bathing, and healthcare staff education; however, their effectiveness is unclear. Environmental decontamination may play a more important role in eradicating non-fermentatives such as *Acinetobacter baumannii* and *P. aeruginosa*, which have the ability to survive on dry surfaces [86,87]. The Expert Group recommended active screening of all high-risk patients, the use of additional contact precautions, and dedicated staff/cohort nursing for all isolated patients who are confirmed carriers of CPGNs. Identifying high-risk patients and performing active surveillance by rectal screening of any patient transferred from a healthcare facility in another country is essential for preventing the introduction and transmission of CPGNs. In Israel, surveillance cultures were implemented as an integral part of a national plan to control CPGNs. Studies from several hospitals have documented the importance of this measure [88,89] (Table 4).

Detection, diagnosis and confirmation of the presence of carbapenemases is important for surveillance, infection control and treatment purposes. Ideally, detection of carbapenemases for active screening purposes should have a short turn-around time and be available at the point of care, to ensure timely implementation of infection control measures, in order to effectively prevent spread. Identifying patients who are at high risk of colonization or infection with CPGNs and performing active screening by rectal swab on admission to healthcare facilities is strongly advocated, and this practice is now becoming more widespread in healthcare settings. The implementation of more extensive active surveillance during outbreaks is also recommended (e.g. follow-up surveillance at regular time intervals and/or for all contacts with confirmed cases). To confront the risk of CPGNs, successful infection control measures based on early detection and containment through isolation and cohorting are required.

A pro-active approach is strongly recommended [90]. This approach assumes that allocating resources up front will allow earlier detection and containment. Because of the logarithmic escalation of such an outbreak, it is more cost-effective to combat the problem before it has been established. The pro-active approach aims to achieve eradication even when this is difficult and resource-consuming, and, when this is not feasible, will aim

TABLE 4. Recommended control measures for spread of carbapenemase-producing Gram-negatives [1,84,85,88,89]

General recommendation
Improved sanitary measures in the outpatient setting
Strongly suggested
Limitation of patient transfer between healthcare facilities
Active screening of patients transferred from a high-risk institution/country
In-hospital contact precautions and cohorting for already colonized patients
Recommended, but effectiveness unclear
Application of an antibiotic stewardship programme
Restricted use of any antibiotics, particularly fluoroquinolones, broad-spectrum cephalosporins and penicillins, and carbapenems
Avoid unnecessarily long duration of antibiotic treatment
Promotion of hand hygiene
Environmental surface decontamination
Decolonization of patients with antiseptic bathing
Education of healthcare personnel
Closure or reduced activity of high-risk units

at containment at the lowest achievable levels of spread. When a CPGN is detected, the responsible infection control personnel should be immediately alerted, and a pre-prepared plan to contain and eradicate CRGN spread should be implemented. Only a fraction of the colonized population may be detected by the use of clinical specimens, and patients with unrecognized and asymptomatic colonization may serve as a reservoir for transmission of the pathogens [25,91]. Thus, the detection of these unrecognized carriers is essential for successful control.

The ESCMID Expert Group also recommended that all interventions should be coordinated on a regional, national or even international level and across the healthcare system [1]. This is supported by experience from Israel, the USA, and elsewhere [92,93]. Guidelines for effective intervention must be prepared before CPGNs have entered the region, and should be implemented immediately upon detection of CPGNs by clinical culture. Communication channels at the local, regional and national levels should be established in advance, in order to facilitate rapid notification and feedback. In settings in which the prevalence of CRE infections is low, the main goal should be complete eradication. Screening should be performed for all patients who have had epidemiologically significant contact with the index case (e.g. hospitalization on the same ward, and treatment by the same staff), and epidemiological investigation should be carried out in cases of nosocomial cross-transmission. Alerts of previously identified CPGN carriers should be provided for every re-admitted patient. Cohorting of patients with dedicated staff is warranted, and has been one of the main factors in the Israeli national intervention [92].

Although control measures are expensive and may be difficult to implement, if we consider the impact of associated infections, then intensive, rigorous control programmes seem to be justified, as early intervention has a much higher likelihood of aborting an epidemic, and, in the long term, is much less costly than confronting an epidemic. The success of the intervention should be monitored constantly, and, when failure is observed, root-cause analysis should be performed.

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