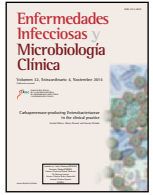Enfermedades Infecciosas
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Treatment of infections caused by carbapenemase-producing Enterobacteriaceae

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ABSTRACT

Keywords:
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Treatment of infections caused by carbapenemase-producing Enterobacteriaceae (CPE) is currently one of the most important challenges of infectious diseases. The available information is based on *in vitro* studies, some animal model data and a few case studies and retrospective cohorts; appropriate data are lacking or are very scarce for some old antibiotics that are still occasionally used. Because of the heterogeneity in clinical situations, in specific carbapenemases and in the susceptibility of isolates, individualized treatment decisions must usually be made. Here we review the different antibiotics that might be useful for treating infections caused by CPE.

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Tratamiento de infecciones causadas por enterobacterias productoras de carbapenemasas

RESUMEN

Palabras clave:
Resistencia a antimicrobianos
Multirresistencia
Tratamiento antimicrobiano
Carbapenemasas
Enterobacterias
Bacteriemias

El tratamiento de las infecciones causadas por las enterobacterias productoras de carbapenemasas (EPC) es uno de los retos más difíciles de las enfermedades infecciosas en la actualidad. La información disponible se basa en estudios *in vitro*, modelos animales y un escaso número de series de casos y estudios de cohortes retrospectivos; no existen datos, o son escasos, para algunos de los antibióticos "viejos" que a veces deben usarse. Es habitual que deban tomase decisiones individualizadas debido a la heterogeneidad de situaciones clínicas, carbapenemasas específicas y sensibilidad de los aislados. En este artículo se revisan los diferentes antibióticos que pueden ser útiles para el tratamiento de las infecciones por ECP.

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Introduction

Invasive infections caused by carbapenemase-producing Enterobacteriaceae (CPE) are associated with high rates of morbidity and mortality and are currently one of the most important challenges in antimicrobial therapy.[1] As we will review, high quality data to support clinical decisions for the treatment of CPE infections are scarce. The general principles of management of infections should always be applied, including early support therapy in the presence of severe sepsis or septic shock and timely and adequate source control (e.g., abscess drainage, catheter removal). Regarding antibiotic therapy, the prompt administration of active antibiotics is important in patients with severe infections; therefore, empirical therapy including antibiotics active against locally circulating strains should be considered in areas with high rates of CPE (e.g., outbreaks). Finally, therapy should be optimized based on the microbiological information. In this review we will summarize the available data concerning antibiotic therapy for infections due to CPE. Recommended doses are summarized in Table 1.

Carbapenems for the treatment of infections caused by CPE

A significant proportion of CPE are susceptible to imipenem, meropenem or doripenem (and only rarely to ertapenem). Therefore, it is worth investigating the potential usefulness of carbapenens in these infections.[2] In animal models with VIM- and NDM-producing

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Table 1
Recommended doses of antimicrobials potentially useful for invasive infections caused by carbapenemase-producing Enterobacteriaceae (CPE)

Drug	Recommended intravenous dose (normal renal function)	Comments
Carbapenems	Meropenem: 2 g every 8 h in extended infusion (3 h) for isolates with MIC ≤8 mg/L	More clinical experience with meropenem. To be considered as part of a combination regimen in all severe infections caused by CPE with MIC ≤8 mg/L
Aztreonam	1-2 g every 8 h (probably better in extended infusion)	No clinical experience for susceptible MBL-producing CPE
Ceftazidime	1-2 g every 8 h (probably better in extended infusion)	No clinical experience for susceptible OXA-48-producing CPE
Temocillin	2 g every 12 h (some authors recommend 2 g every 8 h or 6 g/day in continuous infusion)	No clinical experience for CPE. Not available in Spain
Colistin	Severe infections: loading dose 6-9 MU, followed by 4.5 g every 12 h or 3 MU every 8 h	To be considered as part of a combination regimen in all severe infections caused by CPE
Aminoglycosides	Gentamicin, tobramycin: 5-7 mg/kg/day. Amikacin: 15-20 mg/kg/day (higher dose may be needed in critically ill patients; monitoring blood levels is recommended)	Probably useful in monotherapy for urinary tract and catheter-related infections with catheter removal
		To be considered for combination therapy in severe infections
Tigecycline	Loading dose, 100 mg, followed by 50 mg/12 h. For isolates with borderline MIC (1-2 mg/L), consider doubling the dose (200 mg loading dose followed by 100 mg/12 h)	To be considered for combination therapy in severe infections. Low urinary concentrations
Fosfomycin (disodium)	4-6 g every 6-8 h	Scarce clinical experience. To be used in combination

Enterobacteriaceae, carbapenems were shown to significantly reduce bacterial counts, particularly when an adequate time above the minimum inhibitory concentration (MIC) ratio (T>MIC) was reached.[3-6] However, the results were poorer when carbapenems were used for KPC-producing *Klebsiella pneumoniae* isolates.[7,8] Results from some other models suggest the activity of carbapenems might vary depending on the carbapenemase type, and would be higher for metallo-beta-lactamases (MBLs) or carbapenem-resistant isolates not producing carbapenemases than for KPC or OXA-48.[5,9,10]

In stochastic pharmacokinetic/pharmacodynamic (PK/PD) models, a high probability of attaining >40% or 100% T>MIC by using optimized dosing of meropenem (2 g every 8 h in an extended infusion[7,11] or 6 g/day in a continuous infusion,[12,13] respectively) was predicted for strains with MICs up to 16 mg/L. Imipenem is usually less active and the total dose is limited by safety issues; doripenem could be substituted for meropenem, but there is almost no clinical experience with doses higher than 3 g/day.

Data on the clinical efficacy of monotherapy with carbapenems in patients with infections due to CPE are limited and restricted almost exclusively to KPC and VIM producers. A failure rate of approximately 30% was found in a recent review of previous papers;[1] the rate was 28% for the 42 cases of isolates with a carbapenem MIC ≤8 mg/L and 75% for the 8 cases with higher MICs. A systematic review identified 29 patients with bacteremia treated with carbapenems in monotherapy; mortality ranged in various series between 9% and 50%.[14] Another review including 421 episodes of bacteremia found 34 patients treated with an active carbapenem in monotherapy, of whom 11 (32%) died,[15] and in the most recent and larger compilation of 889 patients with infection due to CP-*K. pneumoniae*, 40% of those receiving monotherapy with an active carbapenem had a fatal outcome.[16] However, in a recent observational study of patients with bacteremia due to KPC or VIM-producing *K. pneumoniae*, mortality was 58% among 12 patients infected with strains showing imipenem or meropenem MIC ≤8 mg/L and treated with a carbapenem in monotherapy.[17] Conversely, this and other observational studies, as well as the above-mentioned reviews including patients with bacteremia due to KPC or VIM-producing *K. pneumoniae*, found that carbapenem-containing combinations used as empirical or definitive therapy were associated with the lowest mortality rates (8%-25% vs. an average death rate of 24%-44% with other regimens).[1,15-20] In two of these studies, the apparent effectiveness of carbapenem-based combinations was restricted to strains with MICs to imipenem or meropenem ≤8 mg/L.[17,18] Overall, it appears that monotherapy with carbapenems cannot be recommended in severe, invasive infections, but whether specific low risk patients can be treated with appropriate dosing of carbapenems alone should be studied.

Other beta-lactams

Aztreonam is not efficiently hydrolyzed by MBLs;[1] slow bactericidal activity against VIM-1-producing *K. pneumoniae* was shown in an *in vitro* model.[21] In addition, aztreonam was more effective than carbapenems against an aztreonam-susceptible, VIM-1-producing *Escherichia coli* in an *in vivo* rabbit intra-abdominal abscess model.[4] However, we could not find any published clinical studies providing data on the efficacy of aztreonam for the treatment of infections caused by MBL-producing Enterobacteriaceae. Furthermore, many clinical MBL-producing Enterobacteriaceae additionally carry extended-spectrum beta-lactamases (ESBLs) or other resistant determinants that confer resistance to aztreonam, which would limit the use of this antibiotic.

OXA-48-producers that do not coproduce any ESBL could be susceptible *in vitro* to broad-spectrum cephalosporins. Ceftazidime showed significant antibacterial activity in animal models against these types of isolates[10,22] and was even more effective than imipenem, ertapenem and piperacillin/tazobactam.[22] To our knowledge, however, clinical data are lacking. Unfortunately, most of these isolates also produce ESBL or AmpC enzymes, and therefore show high MIC to cephalosporins.

Temocillin is stable against ESBLs and AmpC enzymes. It has also been shown to retain some *in vitro* activity against KPC-producing Enterobacteriaceae , but not against OXA-48 or MBLs.[23-25] Again, clinical experience in the treatment of infections caused by these isolates is lacking.

Polymyxins

Although resistance is being increasingly reported, polymyxins are usually effective antimicrobial agents against CPE.[1,14] Two polymyxins are available for parenteral use, polymyxin E (or colistin) and polymyxin B. Although polymyxin B appears to have better clinical pharmacological features,[26] there is more clinical experience with colistin, which is the formulation available in Europe. Importantly, colistin has been used inadequately for years, particularly in critically ill patients, because the product information sheets contain inaccurate information.[27] The PK/PD parameter that best predicts colistin activity is the unbound area under the concentration time curve over the MIC ratio (AUC/MIC); an AUC/MIC ranging from 22.5 to 52.8 has been identified as an appropriate PK/PD target.[28-30] The traditional dosing schedule of colistin (2 MU/8 h)

Table 2
Review of published data on polymyxin therapy in severe infections caused by carbapenem-resistant *Klebsiella pneumoniae*

Author, year and reference	Types of infection	No. of patients	Loading dose	Daily dose	Outcome	Nephrotoxicity
Daikos, 2014[15]	Bacteremia	78	No	9 MU[a]	36% mortality (29% monotherapy, 54% combined)	NS
Qureshi, 2012[17]	Bacteremia	19	NS	NS	26% mortality (36% monotherapy, 12.5% combined)	NS
Tumbarello, 2012[18]	Bacteremia	61	Yes	6-9 MU/day[a]	33% mortality (50% monotherapy, 23% combined)	NS
Falagas, 2010[31]	Severe infections	18	No	3 to 9 MU[a]	28% clinical failure	NS
Paul, 2010[32]	Severe infections	104	No	6 MU[a]	52% mortality	6% needed hemodialysis
Satlin, 2010[33]	UTI	25	No	2.25 g/kg/day (1.1 to 3.3)[b]	64% microbiological clearance	37%
Dalphino, 2012[34]	Severe infections	13	9 MU[a]	9 MU/day[a]	23% clinical failure	17.8%
Capone, 2013[35]	Severe infections	36	NS	NS	28% mortality (40% monotherapy, 23% combined)	NS
Dubrovskaya, 2013[36]	Severe infections	40	25,000 U/kg[b]	25,000 U/kg/day[b]	28% mortality (57% monotherapy, 20% combined)	10%
Petrosillo, 2014[37]	Severe infections	24	In 7% of patients	6 MU/day[a]	31% mortality	12.7%
Kontopidou, 2014[38]	Severe infections	47	No	9 MU[a]	28% mortality (23% monotherapy, 33% combined)	NS

NS: not specified.
[a]Colistin.
[b]Polymixin.

is inappropriate, and plasma concentrations of colistin can remain under the MIC breakpoint (2 mg/L) for 48 h; the use of a loading dose (6 to 12 MU has been suggested) and administration of 9 MU in 2 or 3 doses would likely overcome these problems.[31,32] However, the available clinical information is scarce and based on case series or small subsets of patients from cohort studies. We found several case series and cohort studies reporting data on severe infections caused by carbapenem-resistant *K. pneumoniae* treated with polymyxins[17,19,20,33-40] (Table 2). Of note, the dose of colistin was suboptimal in the majority of these studies. Overall, mortality with colistin therapy was high (range 21%-50%), although lower than with other antimicrobials used in some studies, and usually higher when colistin was used in monotherapy (range, 23%-57%) than when used in combination (range, 12%-29%). Results might be improved when combined with a carbapenem, confirming *in vitro* data.[41] Importantly, resistance to polymyxins can develop if used in monotherapy for CPE.[39] However, a recent meta-analysis including diverse Gram negative organisms found no superiority of combination regimens with colistin.[42]

Despite these major limitations, we believe colistin should be considered as an important option for targeted therapy for serious infections caused by CPE, for which the use of appropriate dosing is important. For patients with renal dysfunction and without renal replacement therapies, dosing recommendations according to nomograms is recommended.[32]

Aminoglycosides

A substantial proportion of CPE remain susceptible to some representatives of this family.[1] Although monotherapy with aminoglycosides has been considered as effective as other options in the treatment of patients with urinary tract infection (UTI), this is not the case for other types of infections for which these drugs are considered as inferior to beta-lactams or fluoroquinolones.[43] Thus, the potential synergistic effect of aminoglycosides in combination with other drugs has been studied *in vitro* against CPE with occasional contradictory results.[44-47]

The available clinical data are limited. Five patients with pneumonia due to KPC-2-producing *K. pneumoniae* received an aminoglycoside in combination with colistin (3) or tigecycline (2), all

of whom had a favorable outcome; an additional patient with bacteremia achieved clinical cure with gentamicin alone.[48] Another retrospective study on bacteremia due to KPC-producing *K. pneumoniae* reported good responses in 3 patients who received aminoglycosides in monotherapy (1 patient) or combined with tigecycline (2 patients).[19] A case report described a patient with endocarditis due to KPC-3-producing *K. pneumoniae* who fully recovered after antibiotic treatment with gentamicin plus colistin, without needing surgery.[49] In a cohort of 40 episodes of bacteremia due to OXA-48-producers, 8 of 12 patients who received aminoglycosides in combination with other antibiotics died, but 2 patients with catheter-related bacteremia treated with an aminoglycoside in monotherapy survived.[50] Furthermore, 2 pediatric patients admitted to the Intensive Care Unit (ICU) with bacteremia due to VIM-1-producing *Enterobacter cloacae* recovered with aminoglycoside therapy (one in monotherapy and the other in combination with cotrimoxazole).[51] In another series, clinical and microbiological responses were reported in 7 patients with UTIs due to KPC-producing Enterobacteriaceae who were treated with gentamicin monotherapy.[52] Finally, aminoglycosides were associated with higher rates of microbiological success in UTIs than colistin or tigecycline.[35]

In summary, and according to data from other populations, monotherapy with aminoglycosides could be considered for the treatment of less complicated infections due to CPE, such as catheter-related bloodstream infections (if the catheter is removed) or urinary tract infections. Otherwise, aminoglycosides should be used in combination.

Fosfomycin

Fosfomycin is active against many Gram-negative and Gram-positive organisms. Fosfomycin tromethamine, an oral formulation, is approved in some countries (including Spain) for the treatment of uncomplicated UTI; fosfomycin disodium is also available in some countries for parenteral use. The drug shows little toxicity, achieves high peak levels in serum and urine, and rapidly penetrates tissues. Unfortunately, resistance can develop when fosfomycin is used as monotherapy.[53] Fosfomycin retains activity against some CPE

isolates.[25,54-56] *In vitro* studies on combinations with other drugs have shown heterogeneous results.[45,57] However, combination therapy might prevent the development of resistance to this drug.[47]

Published data on the clinical use of fosfomycin are reduced to case series, and detailed information for all cases is not always specified. Many of the patients receiving fosfomycin in combination were seriously ill or had failed another regimen. In one series, fosfomycin was used in 8 ICU patients with invasive infections due to KPC-producing *K. pneumoniae* in combination with colistin, gentamicin and piperacillin-tazobactam; all achieved clinical and microbiological cure.[57] In another series, 2 of 5 patients with bacteremia due to OXA-48-producing *K. pneumoniae* who received fosfomycin plus colistin or tigecycline died.[50] Of note, in another article involving 3 severely ill immunocompromised patients with bacteremia due to KPC-producing *K. pneumoniae*, fosfomycin was added after failure of an initial combination regimen; the bacteremia relapsed and resistance to fosfomycin occurred.[58]

The largest series to date included 48 patients with serious infections caused by multidrug-resistant Gram-negative pathogens (41 had a KPC-producing *K. pneumoniae*) from Greece who received fosfomycin in combination with other antimicrobials (primarily colistin, tigecycline, gentamicin and meropenem); the median fosfomycin dose was 24 g per day. The most frequent infections were bloodstream infections (37%) and ventilator-associated pneumonia (29%). Overall, the success rate was 54%.[59] Concerning UTIs due to CPE, a retrospective study described 13 patients with carbapenem-resistant-*K. pneumoniae* treated with fosfomycin tromethamine; only 36% achieved microbiological cure despite good *in vitro* activity;[60] however, multiple confounding factors could have contributed to microbiological failures.

Tigecycline

Tigecycline is not affected by carbapenemases and thus remains active against a substantial proportion of CPE;[25,61] isolates with MIC ≤1 mg/L are considered susceptible according to EUCAST. As with other drugs, *in vitro* studies of combinations with other antibiotics provided diverse results.[25,44,62,63] Unfortunately, resistance is increasing in some areas, and development of resistance has been reported when used in monotherapy.[64,65]

Administration of tigecycline results in low concentrations in the blood, in the epithelial lining fluid of the lung and in urine, which has been suggested to be the reason for lower cure and higher mortality rates than comparators in meta-analyses.[66-68] However, tigecycline could be one of the last resorts for patients with multidrug-resistant and extensively drug-resistant isolates; thus, reviewing the published experience with this drug for CPE is of interest. Available reports are primarily based on retrospective data and include small numbers of cases in which tigecycline was usually used in combination. During an outbreak of KPC-2-producing *K. pneumoniae* in Greece, 6 patients with bacteremia and 2 patients with surgical site infections received tigecycline in combination with 2 or 3 other drugs, with favorable outcomes.[69] Kelesidis et al reviewed 12 patients with invasive CPE infections who received tigecycline in monotherapy (5 patients) or in combination (7 patients), and 91% achieved clinical cure.[66] In a review by Hirsch et al, 7 patients with invasive KPC-producing *K. pneumoniae* infections were successfully treated with tigecycline in monotherapy.[70] Additionally, 15 patients with bacteremia due to OXA-48-producing Enterobacteriaceae received tigecycline either in monotherapy (2 patients) or in combination (13 patients); the overall cure rate was 60%.[50]

Because of the concern regarding the low concentrations reached with conventional doses (100 mg loading dose followed by 50 mg every 12 hours), higher doses of tigecycline (up to 200 mg loading dose and 100 mg every 12 hours) are being investigated.[71] A retrospective cohort study was recently published including 100 ICU patients with infections (63% had ventilator-associated pneumonia) caused by multidrug-resistant Gram-negatives; 50 were KPC-producing *K. pneumoniae*. Forty-six patients receiving high tigecycline dosing (200 mg loading dose followed by 100 mg every 12 hours) were compared with 54 patients receiving standard dosing. Most patients received other concomitant antibiotics. The patients receiving the high dose had more frequent infections caused by isolates showing higher MICs (1-2 mg/L). Although there was no difference in mortality, high dosing was independently associated with an increased cure rate.[72]

Combination therapy

The primary reason for considering combination therapy in infections due to CPE is the experimental and clinical evidence that individual available drugs, even when correctly dosed, might not display optimal antimicrobial activity or are associated with poor outcomes. The potential impact of combination therapy on prevention of resistance development is also to be considered.[73-79]

As reviewed for individual antibiotics above, the synergistic potential of combinations against specific strains producing different types of carbapenemases has been evaluated, primarily using *in vitro* models. The effects might depend on the strains studied and on the methodology used, which probably explains the frequent inconsistency of results; no clear conclusion or recommendation can be obtained by analyzing these studies.[25,44-47,56,57,61-63,80-89] An interesting observation is the increase in the bactericidal effect of doripenem by concomitant ertapenem exposure against a KPC-3-producing *K. pneumoniae* (with doripenem MIC=4 mg/dL) in an *in vitro* and murine thigh model, although in the latter a bactericidal effect was not reached.[90] Of note, increasing the dose of ertapenem to 2 g/day abolished the additive effect.

Data from several retrospective cohort studies on patients with bloodstream infections due to KPC or VIM-1-producing *K. pneumoniae*[17-20,91,92] and reviews of case series[1,15,16,57,70,93] suggest that definitive treatment with a combination of at least two active antibiotics is associated with a lower treatment failure and mortality, but the benefit was not evident in others.[50,91] In some of these studies, combination therapy was associated with lower mortality after controlling for confounders by multivariate analysis.[17,19,20] Analysis of subgroups appeared to show that the results of monotherapy were particularly worse than combination therapy in patients with more severe underlying diseases, higher severity of sepsis, pneumonia and bacteremic infections.[17,92] However, caution is needed because these studies share some important limitations, including their retrospective nature, the lack of strict criteria for assignment of the treatment arm, and potential survivor bias. In fact, a recent meta-analysis (including not only Enterobacteriaceae , but all carbapenem-resistant Gram-negatives) found no benefit of combination regimens including colistin.[42] Nevertheless, if combination therapy is to be used, available data are insufficient to provide recommendations for the best combinations. Clinical experience with dual carbapenem therapy (doripenem or meropenem plus ertapenem) is limited to anecdotal cases.[94,95]

With the available data, we believe using combination therapy is to be strongly considered in severe, difficult to treat infections due to CPE; monotherapy, preferably with an active aminoglycoside, should be considered an option for UTI. Inclusion of carbapenems (administered in optimized dosing, e.g., meropenem 2 g every 8 h in extended infusion) as part of these combinations is recommended for strains with a carbapenem MIC ≤8 mg/L; whether carbapenems are useful for isolates with higher MIC is unknown.

Conclusions

Despite the fact that carbapenemases are rapidly spreading worldwide, available data to support recommendations are scarce.

Although results from several retrospective cohorts suggest that combination therapy is more effective than monotherapy, particularly with severe infections caused by KPC- (and to a lesser extent, VIM-) producing *K. pneumoniae*, however some important limitations of these studies should be taken into account. Nevertheless, until more data are available, we recommend combination therapy for severe and complex infections caused by CPE, including a carbapenem (at least for isolates with MIC ≤8-16 mg/L, and used in optimized dosing) and another fully active drug (drugs to be considered include colistin, tigecycline, aminoglycosides and fosfomycin); a third active drug could be considered in selected cases. Clinical data are needed on aztreonam for susceptible isolates producing MBL and cephalosporins for susceptible OXA-48-producers. For less severe infections and UTIs, monotherapy with an active appropriate drug can also be considered. Nevertheless, individualized treatment decisions must be made considering the severity of the infection, the source, the susceptibility to the various agents, and possibly the specific carbapenemase involved.

Areas for future research

Beyond the need to develop new antimicrobial agents, some research needs are evident. First, the *in vitro* and animal models for investigating the potential benefits of combination regimens must be optimized so the results can be reproducible and can be of more use in guiding clinical studies. Second, better observational studies overcoming the limitations of the studies available are urgently needed. Finally, the design and development of randomized controlled trials comparing different options in varying clinical circumstances must be a priority for funding agencies.

Funding

Conflicts of interest

J.R.B. was speaker for MSD, AstraZeneca, Astellas, Novartis, Janssen and Pfizer, was consultant for MSD, AstraZeneca, Astellas, Roche and Anchaogen, and received funds for research from Gilead and Novartis. J.M.C. was speaker for MSD, Astellas, Novartis, and Pfizer, was consultant for AstraZeneca. C.G. was speaker for Novartis, Pfizer and Astellas, and received a research grant from Astellas. J.A.M. has no conflicts of interest.

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