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Clinical approach

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Treatment guidelines for multidrug-resistant Gram-negative microorganisms

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ABSTRACT

In recent years, new antimicrobials have been introduced in therapeutics, including new beta-lactam-beta-lactamase inhibitor combinations and cefiderocol in response to therapeutic needs in the face of increasing resistance. There are also different treatment guidelines for infections caused by these microorganisms that have been approved by different professional societies, including those of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the Infectious Disease Society of America (IDSA) and the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC). All of them are based on scientific evidence, but with differences in the weight of expert opinion in their recommendations. Both ESCMID and IDSA include recommendations for the treatment of extended-spectrum beta-lactamase-producing microorganisms. The IDSA is the only one including AmpC producers, all address the treatment of infections caused by carbapenem-resistant Enterobacterales and *Acinetobacter baumannii* and multidrug-resistant or difficult-to-treat *Pseudomonas aeruginosa*, and the IDSA and SEIMC include recommendations on the treatment of *Stenotrophomonas maltophilia*. Future guidelines should integrate new antimicrobials and new innovative management options not covered by current guidelines.

Keywords: multidrug resistant Gram-negatives, guidelines, beta-lactam-beta-lactamase inhibitor combinations, cefiderocol.

INTRODUCTION

The emergence of different resistance mechanisms affecting antimicrobials in recent years has significantly complicated the treatment of infectious diseases [1]. This fact has been reflected in the latest guidelines published on the treatment of infections caused by multidrug-resistant (MDR) gram-negative microorganisms. These guidelines include those agreed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the Infectious Disease Society of America (IDSA) and the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) [2-5]. One of the resistance mechanisms on which these guidelines have focused their attention is that due to the production of carbapenemases associated with mobile genetic elements. They have been described mainly in Enterobacterales, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* [6]. In this paper we briefly analyse their description, the initial approaches for the treatment of infection due to microorganisms expressing the acquired carbapenemases prior to the introduction of beta-lactam/beta-lactamase inhibitor combinations and cefiderocol, and the similarities and differences between current treatment guidelines.

TEMPORAL DESCRIPTION OF EXTENDED SPECTRUM BETA-LACTAMASES, PLASMID AMPC BETA-LACTAMASES AND CARBAPENEMASES

The successive emergence and spread of beta-lactamases, the main resistance mechanism affecting beta-lactam antibiotics in Gram-negative bacteria, has complicated the treatment of infections caused by these microorganisms, only partly mitigated by the succeeding introduction of new antimicrobials [7].

Extended spectrum beta-lactamases (ESBLs) were first described in 1983 as mutant derivatives from TEM-1 (Temoneira class A extended-spectrum β-lactamase), TEM-2 and SHV-1 (sulfhydryl variant of the TEM enzyme). They are character-

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ized for their hydrolytic activity of extended spectrum cephalosporins and aztreonam but not to methoxy-beta-lactams (temocillin and cefoxitin) and carbapenems. They are inhibited by clavulanic acid, sulbactam and tazobactam and also by the new beta-lactamase inhibitors (avibactam, varbobactam and relebactam). Later in 1991, CTX-M-1 (cefotaxime-hydrolyzing β-lactamase-Munich) ESBL were described. This enzyme inaugurates the family currently dominating the landscape of ESBLs all over the world, being plasmid derivatives of chromosomally encoded enzymes in *Kluyvera* spp. and mainly found in Enterobacterales [8].

The first report demonstrating that a chromosomal AmpC beta-lactamase (ampicillin chromosomal cephalosporinase) gene can be capture by a plasmid was performed in 1990. The report described transmissible resistance to methoxy- and oxyimino-beta-lactams mediated by the MIR-1 (Miriam Hospital) enzyme with the biochemical properties of a chromosomal AmpC beta-lactamase, showing that the bla_{MIR-1} gene was 90% identical to the bla_{AmpC} gene of *Enterobacter cloacae* [9]. This report inaugurates the description of several plasmid AmpC enzymes, also mainly described in Enterobacterales.

However, with current antimicrobial armamentarium, acquired carbapenemases are the resistance mechanisms that most complicate prescribing old and new antimicrobials. They confer resistance to nearly all beta-lactams and isolates expressing carbapenemases also harbour resistance determinants to other antimicrobials such as aminoglycosides and/or fluoroquinolones [1]. Plasmid mediated carbapenemases were first described in *P. aeruginosa* in Japan in 1991, with IMP-1 (Imipenemase), a metallo-beta-lactamase or class B carbapenemase that was later found in different species of Enterobacterales. In 1996, class A carbapenemase, KPC-1 (*Klebsiella* producing carbapenemase) was recognized for the first time in the United States in an isolate of *Klebsiella pneumoniae*. In 1988 GES-1 (Guyana extended spectrum) enzyme, initially described as an ESBL, inaugurates this family with latter variants acquiring hydrolytic capacity against carbapenems. They are currently more relevant in *P. aeruginosa* but also in Enterobacterales [10]. In 2001, VIM-type metallo-beta-lactamases (Verone integron-encoded metallo-β-lactamase) were described in *P. aeruginosa* in Italy, in 2003 the class D carbapenemases derived from OXA-48 (oxacillin carbapenemase/oxacillinase) in Turkey in *K. pneumoniae*, and in 2008 NDM-1 (New Deli metallo-beta-lactamase) in Sweden in an infection due to a *K. pneumoniae* in a patient transferred from India [6].

In *A. baumannii*, acquired carbapenemases are dominated by OXA-23 and their derivatives and by the acquisition of NDM-1 metallo-beta-lactamase [11]. OXA-23 carbapenemase, widely distributed worldwide, was initially described as ARI-1. It was found in an *A. baumannii* isolate in 1985 in Scotland. Other relevant acquired carbapenemases are OXA-24, -51, -58, -134 and -143 demonstrating the facility of this microorganisms to capture resistance genes.

ANTIMICROBIAL TREATMENT PRIOR TO THE INTRODUCTION OF BETA-LACTAM/BETA-LACTAMASE INHIBITOR COMBINATIONS AND CEFIDEROCOL

The dispersion of the aforementioned enzymes and the absence of specific inhibitors of carbapenemases before their introduction in therapeutics made the treatment of infections in which carbapenemase-producing microorganisms were present extremely complicated. This situation was aggravated by the presence of other resistance mechanisms involving aminoglycosides or fluoroquinolones in these microorganisms. As treatment strategies, including in countries with limited access to new antimicrobials, the use of broad-spectrum beta-lactams was recommended despite the production of carbapenemase. The carbapenems with optimized treatment regimens were mostly used [12]. This recommendation was based on the use of high doses of meropenem (2 g every 8 hours) with extended perfusion time (3-4 hours) to improve the PK/PD parameter of time above the minimum inhibitory concentration (MIC). Both *in vitro* studies with killing curves and animal studies supported this recommendation. It was also sustained by the results observed in patients, with greater benefit being achieved by associating carbapenems (essentially meropenem) with antibiotics for which susceptibility had previously been demonstrated [12]. These antibiotics were colistin, aminoglycosides, fluoroquinolones, fosfomycin or tigecycline. Optimization of the use of carbapenems and improvement of the PK/PD parameter is briefly described in the rational documents on the EUCAST website (https://www.eucast.org/publications-and-documents/rd). Moreover, for metallo-beta-lactamase producing microorganisms the use of aztreonam were also recommended as this compound is not hydrolyzed by some of these enzymes [13]. Nevertheless, in many cases it uses was limited by the simultaneous production of an ESBL that affect aztreonam.

CURRENT TREATMENT GUIDELINES FOR MULTIDRUG-RESISTANT GRAM-NEGATIVE MICROORGANISMS

The similarities and differences in the methodology used in the different guidelines are shown in table 1, as well as their contents. Both the ESCMID and SEIMC guidelines were established performing a systematic review of the literature. In the first case, the recommendations were strictly classified using the GRADE methodology, while in the SEIMC guideline they were classified using the IDSA recommendations with the addition of expert opinions. In the case of the IDSA, the literature review was not strictly systematic and the recommendations were based on similar criteria to those of the SEIMC but with a greater weight on the expert opinion [2-5].

In terms of content, both ESCMID and IDSA include recommendations on the treatment of ESBL-producing microorganisms, while IDSA is the only one that includes AmpC producers. In contrast, they all address the treatment of car-

Table 1 **Current guidelines from different societies in the management of infections due to multidrug-resistant gram-negative microorganisms**

	ESCMID	IDSA	SEIMC
Date of publication	16 December 2021	31 March 2022 / 3 July 2022	28 July 2022
Methodology	Literature systematic review with evidence classified with GRADE	Literature nonsystematic review + panellist's clinical experience	Literature systematic critical review with evidence classified with IDSA quality standards + panelist's expert opinion
3rd gen. cephalosporin resistant (ESBL) Enterobacterales	√	√	-
Chromosomal inducible and plasmid AmpC Enterobacterales	-	√	-
Carbapenem-resistant Enterobacterales	√	√	√
Difficult to treat *Pseudomonas aeruginosa*	√	√	√
Carbapenem-resistant *Acinetobacter baumannii*	√	√	√
Stenotrophomonas maltophilia	-	√	√

ESBL: extended spectrum beta-lactamase

bapenem-resistant Enterobacterales and *A. baumannii* and MDR or difficult-to-treat (DTR) *P. aeruginosa* (2,3). Finally, the IDSA and the SEIMC guidelines include recommendations on the treatment of *Stenotrophomonas maltophilia* (2-4).

Treatment of extended-spectrum beta-lactam-producing Enterobacterales (ESCMID and IDSA guidelines). Empirical treatment of ESBL producing Enterobacterales is not addressed in any of the ESCMID and IDSA guidelines [2-4]. They only established targeted recommendations. In case of severe infections, the use of carbapenems (meropenem and imipenem, or ertapenem, the last one only in the absence of septic shock) is preferred over penicillin combinations with beta-lactamase inhibitors (piperacillin-tazobactam or amoxicillin-clavulanic acid). In both cases, these recommendations are supported by the results of the Merino trial and *in vitro* susceptibility data [14]. Both also contain recommendations to minimise the use of carbapenems to avoid selective pressure on carbapenemase-producing microorganisms. ESCMID recommend the use of piperacillin-tazobactam or amoxicillin-clavulanate in low-risk patients or in patients with non-severe infections or also together with quinolones and co-trimoxazole as step-down therapy once the susceptibility profile is known. For this situation, the IDSA only recommends quinolones and co-trimoxazole.

Both guidelines address urinary tract infections (UTI) due to ESBL producing Enterobacterales. In ESCMID guidelines, aminoglycosides or fosfomycin (i.v.) are recommended for complicated UTI (cUTI) without septic shock. The IDSA only specifically addresses uncomplicated UTI (uUTI), recommending the use of nitrofurantoin, co-trimoxazole, oral fosfomycin, aminoglycoside (single dose) or piperacillin-tazobactam. Both guidelines agree to avoid the use of new beta-lactam/beta-lactamase inhibitor combinations or cefepime, except in cystitis with clinical improvement. The use of tigecyline in not recommended due to poor urinary elimination.

Treatment of AmpC producing Enterobacterales (IDSA guidelines). IDSA guidelines are the only one that includes recommendations for the treatment of AmpC producing Enterobacterales [3]. They are stratified regarding the risk for clinically significant AmpC production and microorganism. *Serratia marcescens, Morganella morganii* and *Providencia* spp. are considered at low-risk and treatment should be selected according to the susceptibility testing results.

For *Enterobacter cloacae, Klebsiella aerogenes* and *Citrobacter freundii*, considered as moderate- to high-risk, recommendations include to avoid piperacillin/tazobactam, ceftriaxone (also cefotaxime) or ceftazidime, even if tested susceptible *in vitro* (except in uUTI). Cefepime is recommended if MIC values are lower than 2 mg/L (even if ceftriaxone is tested *in vitro* susceptible). In this guideline, the carbapenems are aloud when cefepime MICs are higher or equal of 4 mg/L. Moreover, they recommend not to use new beta-lactam/beta-lactamase inhibitors combinations (ceftazidime/avibactam or ceftolozane/tazobactam) or cefiderocol and to reserve them for carbapenemase producers. Also, co-trimoxazole or fluoroquinolones are recommended if tested *in vitro* susceptible and nitrofurantoin in uUTI if tested *in vitro* susceptible. Unfortunately, the IDSA guidelines do not include specific recommendations for infections due to microorganisms with plasmid AmpC enzymes. However, with current knowledge, recommendations can be similar of that performed for *E. cloacae, K. aerogenes* and *C. freundii* [15].

Treatment of carbapenemase producing Enterobacterales (ESCMID, IDSA and SEIMC guidelines). Current recommendations of all three guidelines for the treatment of car-

Table 2 **Summary of recommendations in the ESCMID, IDSA and SEIMC guidelines for the treatment of infections due to carbapenemase producing Enterobacterales. Dosages of the different antimicrobials are those included in the Summary of Product Characteristics (SmPC).**

Society Year of publication	Carbapenemase type KPC	 OXA-48	 MBL
ESCMID 2021	Ceftazidime-avibactam* Meropenem-vaborbactam	Ceftazidime-avibactam	Ceftazidime-avibactam + aztreonam Cefiderocol
	Non-severe infection: Aminoglycosides (UTI) or tigecycline (not in bacteraemia /pneumonia)		
IDSA 2022	Ceftazidime-avibactam Meropenem-vaborbactam Imipenem-relebactam	Ceftazidime-avibactam	Ceftazidime-avibactam + aztreonam Cefiderocol
	UTI → Aminoglycosides, cefiderocol, meropenem Abdominal → Tigecycline, eravacycline		
SEIMC 2022	Ceftazidime-avibactam Meropenem-vaborbactam	Ceftazidime-avibactam	Ceftazidime-avibactam + aztreonam Cefiderocol
	Alternative → Combined therapy (meropenem, colistin, tigecycline, aminoglycosides...)		

UTI: urinary tract infection.

bapenemase producing Enterobacterales pivot on the use of new beta-lactam/beta-lactamase inhibitor combinations and cefiderocol [2,4,5]. Table 2 summarized these recommendations according to different carbapenemases. For systemic infections, all of them agree on the use of cetazidime-avibactam or meropenem-vaborbactam just for KPC producers and IDSA also mention imipenem-relebactam. Moreover, all also agree on the use of ceftazidime/avibactam for OXA-48 producers and in combination with aztreonam for metallo-beta-lactamase producers. For the latest, cefiderocol is also mentioned.

Alternatively, for non-severe infections ESCMID guidelines recommend the use of aminoglycosides in UTI or tigecycline in infections other than bacteraemia and pneumonia due to low favourable PK/PD parameter in these infections. IDSA guidelines also recommend aminoglycosides in UTI as well as cefiderocol and meropenem and for intraabdominal infections, tigecycline and eravacycline. Lastly, SEIMC guidelines includes alternatively meropenem, colistin, tigecycline, or aminoglycosides guided by in vitro susceptibility and/or local epidemiology.

All three guidelines also specifically address UTIs. ESCMID guidelines mention cUTI and recommend aminoglycosides, particularly plazomycin despite this drug in not currently marketed, co-trimoxazole and intravenous fosfomycin. IDSA differentiates cystitis and cUTI and pyelonephritis. For cystitis several antimicrobials are recommended and include fluoroquinolones (ciprofloxacin or levofloxacin), co-trimoxazole, nitrofurantoin, single dose of an aminoglycoside and meropenem or colistin as an alternative. For cUTI and pyelonephritis, meropenem high dose as first choice or an aminoglycoside as an alternative. SEIMC differentiated low- and high-risk patients. For the former, first line recommendation is an aminoglycoside or co-trimoxazole and as an alternative similar recommendation than IDSA plus fosfomycin. In high-risk patients the antimicrobials are an aminoglycoside and fosfomycin.

Treatment of multi-drug resistant/difficult to treat *Pseudomonas aeruginosa* (ESCMID, IDSA and SEIMC guidelines). All guidelines stratified recommendations according to the patients (low-risk or non-severe and severe) or when combination therapy is needed [2-5] (Table 3). For low-risk or non-severe, ESCMID is the most conservative with old antibiotics if tested *in vitro* susceptible. IDSA includes new antimicrobials (ceftolozane-tazobactam, imipenem-relebactam, ceftazidime-avibactam) or a single dose of an aminoglycoside for uUTI. SEIMC preferred recommendation is ceftolozane-tazobactam and as an alternative ceftazidime-avibactam or cefiderocol. For severe cases, ESCMID only recommends ceftolozane-tazobactam and IDSA on top of this combination also imipenem-relebactam, ceftazidime-avibactam and cefiderocol in cUTI. SEIMC preferred recommendation is ceftolozane-tazobactam and as an alternative ceftazidime-avibactam, imipenem-relebactam, colistin or cefiderocol.

ESCMID and IDSA do not routinely recommended combination therapy but if used, it should be based in two *in vitro* active antibiotics. Nevertheless, if preferred regimen has no *in vitro* activity it should be combined with an aminoglycoside. SEIMC only recommends combination therapy in severe infections and those with high inoculum to avoid risk of developing resistance mechanism. Recommendations includes ceftolozane-tazobactam or ceftazidime-avibactam with an active aminoglycoside or colistin, fosfomycin if MIC values are lower than 128 mg/L with an active compound. Moreover, rifampicin should be avoided even in combination.

Carbapenem resistant *Acinetobacter baumannii* (ESCMID, IDSA and SEIMC guidelines)

Carbapenem resistance in *A. baumannii* is currently due to

Table 3 **Summary of recommendations in the ESCMID, IDSA and SEIMC guidelines for the treatment of infections due to multi-drug resistant/difficult to treat *Pseudomonas aeruginosa*. Dosages of the different antimicrobials are those included in the Summary of Product Characteristics (SmPC).**

Infection type /combination therapy	ESCMID	IDSA	SEIMC
Low-risk, non-severe	Old antibiotics with in vitro activity	Ceftolozane-tazobactam or imipenem-relebactam or ceftazidime-avibactam or single dose aminoglycoside (uUTI)	Preferred: Ceftolozane-tazobactam Alternative: Ceftazidime-avibactam, or cefiderocol (uUTI)
Severe	Ceftolozane-tazobactam cefiderocol (cUTI)	Ceftolozane-tazobactam or imipenem-relebactam or ceftazidime-avibactam or cefiderocol (cUTI)	Preferred: Ceftolozane-tazobactam Alternative: Ceftazidime avibactam, imipenem-relebactam or colistin
Combination therapy	Not routinely recommended but if used, select two active antibiotics	Not routinely recommended but if preferred regimen has no in vitro activity combine with an aminoglycoside	Only in severe infections and those with high inoculum: - Ceftolozane-tazobactam or ceftazidime-avibactam with an active aminoglycoside or colistin - Fosfomycin (<128 mg/L) with an active compound - Avoid rifampicin, even in combination

uUTI: uncomplicated urinary tract infection; CUTI: complicated urinary tract infection

OXA carbapenemases, mainly OXA-23 and its derivatives, and to a lesser extent metallo-beta-lactamases, mainly NDM and VIM derivatives [11]. Recommendations are classified regarding infection type and *in vitro* susceptibility of ampicillin-sulbactam. This recommendation is base in the intrinsic activity of sulbactam alone but tested in combination with ampicillin. In mild to moderate infections, if *A. baumannii* tested ampicillin-sulbactam susceptible, this is the first option in all guidelines with colistin as an alternative [3-5]. Nevertheless, all of them include other alternatives such as tigecycline high dose in ESCMID guidelines, minocycline and cefiderocol (refractory to other antibiotics) in IDSA guidelines and ampicillin-sulbactam high dose in combination with colistin or aminoglycosides or minocycline or tygecycline high dose in SEIMC guidelines.

In mild to moderate infections due to ampicillin-resistant *A. baumannii* there are relevant differences between different guidelines. ESCMID recommend polymyxins or tigecycline with high dose, IDSA recommend ampicillin-sulbactam high dose in combination with a second active agent and SEIMC recommend cefiderocol in combination with colistin or a triple therapy in pan-drug resistant isolates.

In severe infections, all guidelines recommend combination therapy with two active agents but with specific remarks. ESCMID recommend to avoid polymyxin-meropenem or polymyxin-rifampicin combinations, IDSA recommend to avoid rifampicin, fosfomycin in any combination and polymyxin-meropenem without a third (active) agent and SEIMC recommend cefiderocol (as part of combination) but avoiding rifampicin.

It is of note that none of the guidelines include new beta-lactam beta-lactamase inhibitor combinations in their recommendations due to the absence of inhibitory activity of the current inhibitors to carbapenemases that are actually present in *A. baumannii* [11]. One exception could be when KPC carbapenemases are present, in which meropenem-varbobactam or imipenem-relebactam might be useful. Nevertheless, this situation is currently rare from an epidemiological point of view.

Stenotrophomonas maltophilia (IDSA and SEIMC guidelines)

S. maltophilia is intrinsically resistant to several antimicrobials, including beta-lactams and aminoglycosides. IDSA and SEIMC guidelines include recommendations for infections due to this pathogen [3]. For mild infection, preferred treatment is co-trimoxazole and minocycline in monotherapy and as an alternative tigecycline, levofloxacin or cefiderocol in monotherapy. Expressly advises to avoid the use of ceftazidime.

For moderate to severe infection at least three different approaches are recommended: i) combination of co-trimoxazole plus minocycline, ii) initiation of co-trimoxazole in monotherapy with latter addition of minocycline (preferred), tigecycline, levofloxacin or cefiderocol if there is a delay in clinical improvement with co-trimoxazole alone and iii) ceftazidime-avibactam plus aztreonam, when intolerance or inactivity of other agents are anticipated.

FUTURE CHALLENGES

There are several challenges that should be addressed in the near future as epidemiology of different resistant mechanisms that impact in the selection of antimicrobial agents is rapidly changing and new antimicrobial do no cover all the expectation [7]. Among these challenges we can enumerate the

presence of MDR pathogens in extrahospitalary patients, in nursing homes and in long-term care facilities, the increased description of isolates with more than one carbapenemase, the implementation of new strategies for the reimbursement of new antimicrobials and future new antimicrobials such as gepotidacin and new combinations such as cefepime-taniborbactam, cefepime-zidebactam, cefepime-enmetazobactam, ceftaroline-avibactam, aztreonam-avibactam, ceftibuten-avibactam, sulbactam-durlobactam that should integrate in the guidelines. Moreover, the introduction of new diagnostic techniques or potentially new (therapeutic) strategies such as fecal microbiota transference, the use of phages and endolysins or gene editing (CRISPR.Cas) should be also positioning in the management of infections due to MDR pathogens.

CONFLICT OF INTEREST

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