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Consensus statement

Executive summary of the diagnosis and antimicrobial treatment of invasive infections due to multidrug-resistant *Enterobacteriaceae*. Guidelines of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC)



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ABSTRACT

The spread of multidrug-resistant *Enterobacteriaceae* related to the production of extended-spectrum β -lactamases (ESBL) and carbapenemases is a serious public health problem worldwide. Microbiological diagnosis and therapy of these infections are challenging and controversial. After the selection of clinically relevant questions, this document provides evidence-based recommendations for the use of microbiological techniques for the detection of ESBL- and carbapenemase-producing *Enterobacteriaceae*, and for antibiotic therapy for invasive infections caused by these organisms. The absence of randomized-controlled trials is noteworthy, thus recommendations are mainly based on observational studies, that have important methodological limitations, pharmacokinetic and pharmacodynamics models, and data from animal studies. Additionally, areas for future research were identified.

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Resumen ejecutivo del diagnóstico y tratamiento de infecciones invasivas causadas por *Enterobacteriaceae* multirresistentes. Guía de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC)

RESUMEN

La diseminación de *Enterobacteriaceae* multirresistentes en relación con la producción de beta-lactamasas de espectro extendido (BLEE) y carbapenemasas es un importante problema de salud pública en todo el mundo. Tanto el diagnóstico microbiológico como el tratamiento de estas infecciones son complicados

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Carbapenemasas
Betalactamasas de espectro extendido
Tratamiento

y controvertidos. Tras una selección de preguntas clínicamente relevantes, este documento proporciona recomendaciones basadas en la evidencia para el uso de técnicas microbiológicas para la detección de *Enterobacteriaceae* productoras de BLEE y carbapenemasas, y para el tratamiento antibiótico de las infecciones invasivas causadas por estos microorganismos. Es llamativa la ausencia de ensayos aleatorizados controlados, por lo que las recomendaciones se basan principalmente en estudios observacionales con importantes limitaciones metodológicas, modelos farmacocinéticos y farmacodinámicos y estudios en animales. Además, se han identificado áreas prioritarias de investigación futura.

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The dramatic worldwide increase in the rate of infections due to *Enterobacteriaceae* showing resistance to several first-line antimicrobial families in most countries over the last decade is recognized as a public health crisis. The very limited therapeutic options available for these organisms are a real challenge. To our knowledge, evidence-based guidelines with evidence-based recommendations on the microbiological diagnosis and treatment for infections caused by multidrug-resistant (MDR) and extensively drug-resistant (XDR) *Enterobacteriaceae* have not been published.

The main objective of this guideline is to provide evidence-based recommendations for the microbiological diagnosis and treatment of invasive infections caused by MDR and XDR *Enterobacteriaceae*, and specifically those producing extended-spectrum β -lactamases (ESBL) and carbapenemases. Additionally, areas for future research are identified. The guideline is focused on invasive infections.

This document is intended to be useful for all clinical microbiologists, for clinicians in direct charge of patients with the infections covered, and for consultants such as infectious diseases specialists, clinical microbiologists, hospital epidemiologists, and pharmacists, as well as policy makers in the field of antibiotic stewardship and quality-of-care professionals. It is the intention of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) to review these guidelines in 2016 or before in case of substantial changes in evidence.

This guideline was committed by SEIMC to a multidisciplinary group of Spanish clinicians and clinical microbiologists who are expert in the field. The authors selected a number of clinical questions by consensus based on their perceived clinical importance. Then a systematic review of the literature was performed in PubMed for each of them. The quality of evidence and the strength of recommendations were evaluated and decided by the authors according to the methodology previously used by the Infectious Diseases Society of America.

The whole document is available in the online version.¹

Recommendations

Microbiological diagnosis

- For detection of ESBL or carbapenemase-producing *Enterobacteriaceae* in surveillance samples, specific chromogenic media are recommended (BII); alternatively, molecular-based methods toward a specific target may be used (CIII).
- Confirmation of ESBL producers should be performed in isolates showing after screening increased MIC or reduced inhibition zone to third generation cephalosporins according to either EUCAST or CLSI criteria by microdilution (Etest is to be also considered) or disk diffusion (BII).
- The recommended phenotypic confirmation tests for ESBL production are those methods which use clavulanic acid as ESBL inhibitor. Either double-disk synergy test (DDST), combined-DDST (CDDST) or microdilution can be used; the best option is probably the use of CDDST with cefotaxime, ceftazidime, and ceftipime (BII).

- Confirmation of carbapenemase producers should be performed in isolates showing after screening increased carbapenem MIC ($>0.12 \mu\text{g/ml}$ or $<25 \text{ mm}$ for ertapenem and/or meropenem and/or $>1 \mu\text{g/ml}$ or $<23 \text{ mm}$ for imipenem) (BII). Meropenem is preferred for this purpose; imipenem is not recommended as a stand-alone screening test compound (CIII). In areas with high prevalence of class D enzymes (OXA-48-like), with isolates showing reduced susceptibility to carbapenems, screening with temocillin (either $30 \mu\text{g}$ disk diffusion or MIC, $\leq 10 \text{ mm}$ and $>64 \text{ mg/L}$, respectively) in the absence of synergy of other inhibitors may be used as a first-step method to identify an OXA-48 producer (BII).
- For phenotypic confirmation for carbapenemase production, the best option is the use of DDST or CDDST (which is commercially available and has been validated) using a carbapenem (usually meropenem) combined with specific class A, B, and C enzyme inhibitor (BII). However, since currently there are no available inhibitors for class D carbapenemases and temocillin as a marker is not specific for OXA-48-type carbapenemase, these enzymes must be confirmed by using a genotypic method (CIII).
- In the case rapid tests are needed to confirm the presence of ESBL or carbapenemase producers, molecular methods are recommended, according to local resources (BIII).

Therapy

Empirical therapy

- In case of sepsis potentially caused by *Enterobacteriaceae*, clinicians should evaluate the risk of ESBL producers considering both the epidemiological setting (e.g. rate of ESBL-producing microorganisms in a given institution) and individual risk factors (BII).
- The following individual risk factors should be assessed in all community-onset sepsis potentially caused by *Enterobacteriaceae* in order to evaluate the risk for ESBL producers: recent use of fluoroquinolones or cephalosporins; recent hospitalization; transfer from another healthcare facility, including long-term care facilities; Charlson index >3 ; and age >70 years (BII). Recent travel to high endemic areas must also be considered (BIII). The same risk factors should be considered for community-onset AmpC producers (BIII).
- ESBL producers should be considered for empirical therapy in patients with community-onset severe sepsis or septic shock potentially caused by *Enterobacteriaceae* if presenting at least one of the previous risk factors, and in patients with non-severe sepsis if more than 2 risk factors are present (CIII).
- If ESBL-coverage is decided for a community-onset infection, a carbapenem is of choice (BII); however, in case of complicated urinary tract infection (cUTI) a β -lactam/ β -lactamase inhibitor (BLBLI) plus an aminoglycoside (BII) or a third-generation cephalosporin (probably ceftazidime) plus an aminoglycoside (CIII) are alternatives, according to local prevalence of susceptibility to these drugs among ESBL producers.

- In nosocomial sepsis potentially caused by *Enterobacteriaceae*, individual risk factors (longer hospital stay, exposure to mechanical ventilation, and previous receipt of cephalosporins, fluoroquinolones or carbapenems) should be considered according to local epidemiology (e.g., local prevalence, outbreak) for decision about empirical therapy in order to cover for ESBL, AmpC and/or carbapenemase-producers (BIII). Because of the current rates of ESBL producers in Spanish centers, empirical therapy against ESBL producers is recommended in all patients with nosocomial infections potentially caused by *Enterobacteriaceae* and presenting with severe sepsis or septic shock (CIII).

Definitive treatment of invasive infections caused by ESBL-producing *Enterobacteriaceae*

- Carbapenems are the drugs of choice for invasive infections caused by ESBL- and AmpC-producing *Enterobacteriaceae* (BII). Ertapenem is suggested for patients without septic shock and isolates with MIC ≤ 0.25 mg/L to avoid the selective pressure on *Pseudomonas aeruginosa* posed by group-2 carbapenems (CII). For other infections, imipenem or meropenem are recommended (BII); the experience with doripenem is scarce but it is probably as useful (CIII).
- In vitro active BLBLI (specifically, amoxicillin/clavulanic acid and piperacillin/tazobactam) are reasonable alternatives for bacteraemic UTI or biliary tract infections caused by ESBL-producing *Escherichia coli*, and may be used as carbapenem-sparing regimens; the recommended doses for patients with normal renal function are: 2/0.2 g/8 h in 30 min for amoxicillin/clavulanic acid and 4/0.5 g/6 h in 30 min or 4/0.5 g in extended infusion/8 h (or/6 h in critically ill patients) for piperacillin/tazobactam (CII). Data for other infection or *Enterobacteriaceae* are scarce.
- There is insufficient data to recommend the use of active cephalosporins for invasive infections caused by ESBL producers according to EUCAST or CLSI breakpoints; however, until more data are available, we recommend caution when considering the use of these drugs; their use is only recommended as an alternative option for the treatment of non-severe UTI sepsis in low-risk patients (CIII).
- There is insufficient data to recommend the use of cephamycins, fluoroquinolones, aminoglycosides, trimethoprim-sulfamethoxazole, colistin or fosfomicin. For fully susceptible isolates there is no reason to expect different efficacy than in non-ESBL producers (CIII).

Treatment of invasive infections caused by carbapenemase-producing *Enterobacteriaceae* (CPE)

- Therapy must be individualized according to susceptibility results, source of infection and severity of disease (CII). According to general knowledge in management of infections, source control and support therapy are key aspects in the management of these infections (BII).
- Combination therapy is recommended for severe infections caused by KPC-producing *Klebsiella pneumoniae* (CII), and possibly for other carbapenemase-producing *Enterobacteriaceae* until more data are available (CIII). There is no data to support combination therapy for patients with mild infections for which fully active drugs, useful for the specific type of infection, are available; therefore, we recommend monotherapy for such infections, and particularly for non-severe UTIs (CIII).
- Monotherapy with a carbapenem is not recommended for patients with invasive infections caused by CPE but may be considered in cases of mild invasive infections if adequate source control is readily achieved and the isolate is susceptible according to EUCAST or CLSI breakpoints; the typical example would be

sepsis from the urinary tract, without urinary tract obstruction or severe sepsis or septic shock (CIII).

- For patients in which combination therapy is indicated, a regimen with a carbapenem (see preferred drug and recommended dose below) plus one or two fully active drugs (including colistin, tigecycline, an aminoglycoside or fosfomicin, the latter preferably as a third drug) is recommended if the carbapenem MIC is ≤ 8 mg/L; this applies mainly to patients with severe infections caused by KPC-producing *K. pneumoniae* (BII). We suggest a similar approach for other carbapenemases until more data are available (CIII). No recommendation can be given for using the combination of ertapenem plus doripenem or meropenem for KPC producers (unresolved issue).
- There is not enough data to recommend including a carbapenem in combination regimens if minimal inhibitory concentration (MIC) is > 8 mg/L; if this is the case, carbapenems are probably useless, particularly if MIC is > 16 mg/L; we recommend including at least two fully active drugs in the combination regimen according to susceptibility testing and source of infection (drugs to be considered: colistin, aminoglycosides, fosfomicin and tigecycline) (CIII).
- Patients with less severe invasive infections and cUTIs might be treated with carbapenem-sparing combinations (drugs to be considered: colistin, aminoglycosides, fosfomicin, tigecycline – the latter not for UTI) or even monotherapy (see above) (CIII).
- Dosing of all administered drugs should be optimized to increase the probability of reaching the appropriate pharmacodynamics target (BII); in the case of carbapenems, we recommend using meropenem at 2 g every 8 h in extended infusion (BII).

Colistin

- Colistin should be preserved for treating infections produced by *Enterobacteriaceae* strains showing resistance to all β -lactam antibiotics (CIII).
- Colistin is suggested as part of the empirical treatment of patients with severe infections if participation of CPE is suspected, such as in outbreaks or colonized patients (CIII).
- When using colistin and until more data are available, we recommend the use of a loading dose of 9 MU and subsequent high, extended-interval maintenance doses (4.5 MU/12 h) in critically-ill patients and patients with severe sepsis or septic shock with creatinine clearance above 50 mL/min; maintenance dose should be individually adjusted according to creatinine clearance according to published nomograms (CIII).
- Data to recommend a loading dose in non-critically ill patients with non-severe infections are unavailable (unresolved issue); maintenance dosing with 4.5 MU/12 h (or alternatively 3 MU/8 h) is suggested, but renal function should be closely monitored (CIII).
- No recommendations can be given for patients with extreme weights (unresolved issue).
- We recommend 1–2 MU of colistin every 12 h for patients undergoing intermittent hemodialysis. Whenever possible, hemodialysis should be conducted at the end of the dosing interval to minimize the clearance of colistin. If this is not possible, a supplemental dose at the end of the dialysis should be considered (CIII). For patients undergoing continuous venovenous haemofiltration, even though the data are not consistent, a dose of 9 MU/day is suggested (CIII).

Fosfomicin

- Experience with fosfomicin for the treatment of invasive infections caused by MDR and XDR *Enterobacteriaceae* is limited; however, in patients with limited options, fosfomicin (4–6 g

every 6 h to 8 g every 8 h) may be considered as part of a combination regimen including at least one more active agent (CIII).

Aminoglycosides

- Based on the experience of non-MDR *Enterobacteriaceae* infections, monotherapy with an active aminoglycoside may be considered for the treatment of cUTI caused by MDR and XDR *Enterobacteriaceae*. Toxicity should be closely monitored (BII).
- Monotherapy with aminoglycosides for other invasive infections is not recommended. For such infections, combination therapy with other drugs is suggested (BII). However, aminoglycosides are to be considered as an accompanying agent in all combination regimens according to the susceptibility results with closely monitoring of toxicity (CIII).

Aztreonam and cephalosporins for susceptible CPE

There is no clinical experience with aztreonam or cephalosporins for the treatment of invasive infections due to susceptible MBL- or OXA-48-producing *Enterobacteriaceae*, respectively. Very scarce in vitro and animal model data suggest that they may be useful; if considered, we recommend using these drugs in combination except in cUTI (CIII).

Tigecycline

- Tigecycline monotherapy should be avoided whenever possible (AI); exceptions may be selected patients with mild cIAI and cSSSI infections caused by XDR *Enterobacteriaceae* with other few adequate alternative options (CIII).
- Tigecycline should be considered as part of a combination regimen in patients with infections other than UTI caused by *Enterobacteriaceae* producing either ESBLs (if a carbapenem-spare regimen is to be used) or carbapenemases when tigecycline MIC is ≤ 1 mg/L (CIII).

- Higher dose of tigecycline (150 mg loading dose followed by 75 mg/12 h, or 200 mg loading dose followed by 100 mg/12 h) should be considered for patients in septic shock, VAP or *Enterobacteriaceae* with MIC ≥ 1 mg/L, but adverse events should be carefully monitored (BIII).

Conflict of interest

JRB was consultant for MSD, AstraZeneca, Pfizer, Roche, Novartis, Astellas and Anchaogen; speaker for MSD, AstraZeneca, Pfizer, Novartis and Astellas; and received research grants from Novartis and Gilead. CG was speaker for Novartis, Pfizer and Astellas; and received a research grant from Astellas. JPH was speaker and consultant for MSD, Astellas, Astra-Zeneca, Novartis, Pfizer and Basilea. GB was speaker for Pfizer, Novartis, Astellas and Janssen; and received research grants from Pfizer. All other authors have no conflict of interest.

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