Farmacia Hospitalaria 49 (2025) T179–T183

Farmacia HOSPITALARIA
Órgano oficial de expresión científica de la Sociedad Española de Farmacia Hospitalaria
www.elsevier.es/farmaciahospitalaria

Protocol

[Translated article] National survey and consensus document on dosing strategies for beta-lactam antibiotics against multidrug-resistant gram-negative bacilli (MDR-GNB) in critically ill patients undergoing extracorporeal life-support techniques: The DOSEBL study protocol

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ARTICLE INFO

Article history:
Received 24 April 2024
Accepted 31 July 2024
Available online 15 December 2024

Keywords:
Pharmacokinetics
Beta lactam antibiotics
Gram-negative bacteria
Renal replacement therapy

ABSTRACT

Introduction: Infections caused by multidrug-resistant gram-negative bacilli (MDR-GNB) in critically ill patients present a challenge for timely and appropriate antibiotic treatment. This is particularly important in patients undergoing extracorporeal life-support techniques such as renal replacement therapy and extracorporeal membrane oxygenation. These techniques can introduce additional pharmacokinetic alterations, potentially leading to suboptimal exposure to antibiotics. This study aims to outline dosing strategies and therapeutic drug monitoring protocols for new β-lactam antibiotics effective against MDR-GNB in critically ill patients undergoing extracorporeal life-support techniques at a national level. Additionally, the study seeks to develop a consensus document, based on available evidence.

Methods: The project will comprise two main phases: I) a national survey and II) the development of a consensus document. This consensus document, undertaken according to ACCORD guidelines, will encompass: a) establishment of a multidisciplinary panel of experts, b) prospective registration of the consensus, c) evidence synthesis, d) modified Delphi rounds. The antimicrobials to be included will be: meropenem, ceftazidime/avibactam, ceftolozane/tazobactam, cefiderocol, meropenem/vaborbactam, imipenem/relebactam, and aztreonam. Extracorporeal life-support techniques will include continuous renal replacement therapy, conventional intermittent hemodialysis, and extracorporeal membrane oxygenation.

Discussion: The availability of extracorporeal life-support techniques has expanded significantly in recent years, alongside a rise in the prevalence of infections caused by MDR-GNB. There is a need to develop evidence-based tools of high quality to standardize dosing and monitoring strategies for new β-lactam antibiotics.

DOI of original article: https://doi.org/10.1016/j.farma.2024.07.010.
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https://doi.org/10.1016/j.farma.2024.11.005

Encuesta nacional y elaboración de un documento de consenso sobre estrategias de dosificación de antibióticos beta-lactámicos frente a bacterias gram-negativas multirresistentes (BGN-MDR) en pacientes críticos sometidos a técnicas de soporte vital extracorpóreas: Protocolo de estudio DOSEBL

Palabras clave:
Farmacocinética
Beta-lactámicos
Gram-negativos
Técnicas de reemplazo renal

R E S U M E N

Introducción: Las infecciones por bacterias gram-negativas multirresistentes (BGN-MDR) en pacientes críticos requieren un tratamiento antibiótico precoz y apropiado, lo que puede suponer un reto en pacientes sometidos a técnicas de soporte vital extracorpóreo, como las terapias de depuración renal y la circulación con membrana extracorpórea. El uso de estas técnicas puede comportar alteraciones farmacocinéticas adicionales, condicionando una exposición subóptima. El objetivo es describir las estrategias de dosificación y monitorización de los antibióticos b- lactámicos activos frente a BGN-MDR en pacientes críticos sometidos a técnicas de eliminación extracorpórea a nivel nacional y elaborar un documento consenso basado en la evidencia disponible.
Métodos: El proyecto consta de 2 fases: I) realización de una encuesta nacional y II) elaboración de un documento de consenso. El desarrollo de este documento conforme guía ACCORD comprenderá: a) constitución de un panel de expertos multidisciplinar y multicéntrico; b) registro prospectivo del proyecto de investigación; c) síntesis de evidencia (guía PRISMA) y d) rondas de consenso siguiendo metodología Delphi modificada. Los antimicrobianos a incluir serán: meropenem, ceftazidima/avibactam, ceftolozano/tazobactam, cefiderocol, meropenem/vaborbactam, imipenem/relebactam y aztreonam. Las técnicas de soporte vital extracorpóreo consideradas serán: terapia de reemplazo renal continua, hemodiálisis intermitente convencional y oxigenación con membrana extracorpórea.
Discusión: El número de indicaciones y centros que disponen de técnicas de soporte vital extracorpóreo ha aumentado considerablemente en los últimos años, así como los pacientes con infecciones por BGN-MDR, por lo que es crucial disponer de herramientas de calidad, basadas en la evidencia, que ayuden a armonizar las estrategias de dosificación y monitorización de los antibióticos b- lactámicos activos frente a BGN-MDR en estos escenarios.

Introduction

Intensive care units (ICUs) are facing the challenge of rising infection rates by multidrug-resistant Gram-negative bacteria (MDR-GNB), due to their significant impact on mortality. It is crucial to ensure timely and appropriate antibiotic therapy by optimizing administration and limiting the emergence of resistance.[1] Given their safety profile and broad spectrum, β-lactams are the most commonly prescribed antibiotics in ICUs. They are often administered as an empirical regimen in situations that require early appropriate antibiotic therapy, such as septic shock.[2] However, critical patients present pathophysiological challenges, including hypoalbuminemia or systemic inflammatory response syndrome, which can lead to alterations in the pharmacokinetic (PK) parameters of antimicrobials. These altered parameters, such as clearance and volume of distribution, can impact PK/PD targets, as well as antimicrobial efficacy and safety.[3] In addition, further alterations in antimicrobial exposure can be caused by extracorporeal life-support (ECLS) techniques, such as renal clearance therapies and/or extracorporeal membrane oxygenation (ECMO), which are commonly used.[4]

ECMO is a life-support technique indicated for respiratory and/or cardiac failure refractory to conventional therapies, and its use has increased significantly in recent years. Optimal use of antimicrobials is crucial for these patients, who are highly susceptible to nosocomial infections due to the use of invasive devices, prolonged hospitalization, and immunosuppression.[5] Drug adsorption to the ECMO circuit is one of the phenomena that can lead to PK changes by increasing the volume of distribution and decreasing plasma concentrations and clearance. Potential adsorption is influenced by circuit factors and the physicochemical properties of the drug, the most relevant of which are lipophilicity and binding to plasma proteins. Hemodilution is another phenomenon associated with ECMO, which mainly affects hydrophilic drugs with a low volume of distribution (less than 1 L/kg), such as β-lactams antibiotics.[4–6]

Renal clearance techniques are commonly used in ICUs, such as continuous renal replacement therapy (CRRT) or conventional intermittent hemodialysis (HD), which have different effects on clearance and antibiotic exposure.[7] In order to avoid therapeutic failure and the development of antimicrobial resistance, it is essential to adapt the dose to the technique used and to the properties of the drug, paying particular attention to those that are predominantly eliminated by the kidneys.[8] Previous studies have emphasized the importance of monitoring β-lactam plasma concentrations in patients undergoing CRRT and/or ECMO, due to the variability in drug exposure and its role in optimizing dosing.[9,10]

Moreover, antibiotic dosing guidelines are typically based on studies conducted with healthy volunteers and may not account for the unique needs of critically ill patients, particularly those requiring ECLS. In fact, there is limited evidence on the PK behavior and, consequently, the dosing regimens, of some antimicrobials indicated for MDR-GNB infections in ECLS patients, particularly for antimicrobials for which there is less experience of use.[8,11]

There are specific center guidelines and protocols that provide antimicrobial dosing recommendations for ECLS patients, although discrepancies are common. In addition, some hospitals use therapeutic drug monitoring (TDM) as a tool to guide antimicrobial dosing adjustments.[12,13] These aspects underscore the need to assess the variability in dosing strategies for β-lactams effective against MDR-GNB and the importance of developing a standardized guideline.

The first phase of the study will evaluate, at a national level, the methods used by healthcare staff to determine the dosing strategies for different β-lactam antibiotics effective against MDR-GNB in critically ill patients receiving ECLS, including techniques such as CRRT, HD, and ECMO. Secondary objectives of the first phase include the following:

- To evaluate the level of concordance in dosing regimens and the sources used for their selection across staff and hospitals.
- To describe to what extent TDM has been implemented, as well as the healthcare professional responsible for making dosage adjustment recommendations.
- To describe the use of loading doses, and extended or continuous perfusions in this population.

The second phase of the study will develop a consensus document on dosing recommendations for β-lactams active against MDR-GNB in patients with ECLS.

Methods

Phase 1: National survey

The first phase of the study will comprise a national survey of different healthcare staff involved in the use of antimicrobials in ECLS. The drugs under study will be meropenem, ceftazidime/avibactam, ceftolozane/tazobactam, cefiderocol, meropenem/vaborbactam, imipenem/relebactam, and aztreonam.

Survey data collection

In the first part, data will be collected on staff and participating hospitals, including specialty, age, and sex; hospital characteristics, such as total number of beds and ICU beds; implementation of antimicrobial stewardship programmes; and availability of various ECLS techniques.

For antimicrobial monitoring, the following aspects will be reviewed: (a) availability of TDM at the hospital, specifying the drugs eligible for monitoring, including aminoglycosides, glycopeptides, oxazolidinones, quinolones, colistin, β-lactams, and β-lactamase inhibitors; and (b) the application of TDM in clinical practice (when available) for suspected toxicity, therapeutic failure, or investigational use, covering aspects of result interpretation such as clinical context, PK/PD targets, microbiological data, and the personnel responsible for interpretation.

Questions will be included on the literature source consulted for antibiotic dose adjustment in different ECLS techniques.

Given that antibiotic dosing may vary depending on the indication and patients' conditions, the clinical context of severe infections, such as septic shock, has been considered in relation to answering these questions.

Data will be collected on the loading dose, maintenance dose, and type of infusion used for each antibiotic and specific technique (HD, CRRT, or ECMO).

The survey will be conducted using the RedCap platform.

Distribution of the survey

The survey will be distributed through the mailing lists of various scientific societies to reach a range of healthcare professionals involved in the management of the antimicrobials described in patients receiving ECLS. The information obtained will be used exclusively for research purposes, and consent will be obtained for data management and interpretation. Participation will be anonymous and completely voluntary. Each professional participating in the study will complete a digital data collection notebook on the RedCap platform.

Analysis of results

The results of the survey will be analyzed and compared in order to identify differences between staff and hospitals, both in terms of dosage and sources consulted, as well as the level of concordance of the different dosages with the recommendations of other sources, such as the summary of product characteristics.

Statistical analysis will include descriptive statistics by subgroup based on each antibiotic and ECLS used. Qualitative variables will be expressed as absolute and relative frequencies, and continuous variables will be expressed as mean and standard deviation, or median and interquartile range (IQR), depending on the normality of the data. Data analysis will be performed using SPSS 20.0 v2.1 (IBM, Chicago, IL).

Phase 2. Review of the evidence and preparation of the consensus document

In the second phase, the available evidence will be reviewed in order to develop a consensus document on the dosing strategies for β-lactams active against MDR-GNB in critically ill patients receiving ECLS. The development stages will be as follows.

a) Creation of a multihospital multidisciplinary group

A multi-centre, multidisciplinary expert group of around 21 members will be established. Selection will be based on their expertise and experience in order to cover all key aspects of correct antimicrobial dosing in the study population. The group will include experts with wide-ranging experience in the clinical management of critically ill patients, the use of extracorporeal techniques (HD, CRRT, and ECMO), the selection and administration of appropriate anti-infective agents, and their pharmacokinetics and PDs.

The study will include experts in infectious diseases, such as internists, intensivists, anesthesiologists, nephrologists, hospital pharmacists, microbiologists, and other staff involved in the prescription and selection of doses for the preselected antimicrobials. The snowball technique will be employed to recruit experts, stopping when all relevant areas of expertise are saturated.[14] The number of experts will be odd rather than even to prevent tied scores. Experts will be contacted by email or telephone, and will receive online training on the project objectives once they have accepted the invitation to participate in the project. All participants, including invited experts, must explicitly declare the absence of conflicts of interest by completing the International Committee of Medical Journal Editors disclosure form (https://www.icmje.org/disclosure-of-interest/).

b) Prospective registration of the study protocol

To facilitate consultation and ensure project transparency of results, the prospective registration of the study protocol and data availability will be managed on open access platforms such as the Open Science Framework (https://osf.io/).

c) Evidence summary

The objective of this stage is to collect all available evidence on the posology of the selected antibiotics in ECLS patients, for evaluation by the Delphi panel (stage d).[15] A systematic literature review will be conducted following the PRISMA methodology,[16] covering at least 2 databases and the gray literature (PubMed, Scopus, Cochrane Library, Google Scholar) for all articles published in English or Spanish on adult populations (over 18 years), with no exclusions based on time, study design, or sample size. Studies that evaluate dosing and/or administration patterns of the selected antibiotics in ECLS patients will be included. The preselected antimicrobials will be meropenem, ceftazidime/avibactam, ceftolozane/tazobactam, cefiderocol, meropenem/vaborbactam, imipenem/relebactam, and aztreonam. Exclusion criteria will be as follows: studies not conducted in humans, studies in pediatric populations (less than 18 years of age), articles in languages other than English or Spanish, clinical cases or case series with fewer than 5 patients, letters to the editor, and abstracts or conference communications.

The following information will be collected on each included article: year of publication, author, inclusion criteria, number of patients, study population, exposure measurement, outcome variables, and risk estimation, among others.

Methodological quality will be assessed using validated assessment tools such as AGREE II[17] or other tools specific to the design of the source document.

Screening, data extraction, and quality analysis will be conducted by independent peer review with concordance analysis.

d) Consensus rounds following a modified Delphi methodology

The study investigators will independently draft an initial list of clear, precise, and feasible recommendations based on the findings of the systematic review and the phase 1 survey. The drafting of potential recommendations will initially be piloted on a sample of 2–3 drugs across different techniques, followed by a group discussion to clarify

the distinction between review findings and the resulting recommendations. Finally, this process will be extended to all the drugs. The preliminary list of recommendations, including references and the quality of evidence, will undergo multiple voting rounds with participation from the entire multidisciplinary panel of invited experts, following the modified Delphi method.[18] The RedCap platform will be used for these rounds of questionnaires. A 7-point scale will be used for voting to assess the level of agreement with the content of each recommendation. The scale will range from "strongly agree" to "strongly disagree", with "agree", "somewhat agree", "neither agree nor disagree", "somewhat disagree", and "disagree" as intermediate response options. The agreement rate for approving each statement will be calculated by summing the "strongly agree" and "agree" responses. The number of survey rounds will depend on the level of agreement between the participants; the same scale will be used for all rounds. The responses of the expert group will be pseudo-anonymized throughout the process.

An objective method, based on the Average Percentage of Majority Opinions (APMO), will be used to establish the threshold or cutoff point for recommendation approval. A recommendation will be considered as agreed if more than 50% of the experts respond with "strongly agree" or "agree" on a 7-point scale. Conversely, if more than 50% of participants respond with "disagree" or "strongly disagree," the recommendation will be considered as not agreed. The APMO consensus threshold will be calculated by summing the total number of majority agreed and not-agreed recommendations, dividing by the total number of responses received and multiplying by 100%. Recommendations exceeding the APMO threshold will be considered to have achieved consensus. For individual recommendations that reach consensus in each round, the IQR will be used to assess the level of agreement among the experts. The IQR will be obtained as the difference between the first and third quartiles of the experts' responses on the 7-point scale. An IQR of 0 will indicate a very high level of agreement (where more than 50% of stakeholders give identical responses); an IQR of 1 will indicate a good level of agreement (where more than 50% of responses fall within less than 2 scale points); and an IQR of 2 or more will indicate a low level of agreement (where more than 50% of responses span more than 2 scale points). Additionally, a sensitivity analysis will be conducted using an arbitrary approval threshold of 70%.[19] Data will be analyzed using Stata v16 software (StataCorp, College Station, TX).

Recommendations classified as non-consensus in previous Delphi survey rounds will be discussed individually in a final online meeting. The experts will determine the level of agreement that will serve as the exclusion threshold, and will vote anonymously using an electronic meeting platform, such as Zoom or Teams, to select the recommendations from the final set.

Discussion

In recent years, there has been a significant increase in the number of indications requiring ECLS, the number of hospitals offering this technique, and the prevalence of patients with MDR-GNB infections. Ensuring optimal antimicrobial therapy in critically ill patients undergoing ECLS is challenging due to technique-specific pharmacokinetic complexities combined with the pathophysiological changes inherent in these patients. Conventional dosing regimens do not take into account such changes, so it is crucial to select those that are appropriate for these clinical situations, with the aim of maximizing efficacy and limiting toxicity, given the impact of inappropriate antibiotic therapy on clinical outcomes in critically ill patients with severe infections.[18]

While some studies provide recommendations on antimicrobial dosing strategies for patients on ECLS, specific evidence on β-lactams effective against MDR-GNB remains limited.[8,18] We suspect that clinical practice varies across hospitals, both in terms of decision-making processes and in the final dosing regimen administered.

This situation highlights the need to understand the current use of these drugs and to develop high-quality, evidence-based tools—analyzed and agreed by a multidisciplinary panel of experts—to harmonize and optimize dosing and monitoring strategies for β-lactam antibiotics.

Funding

The project received a SEFH Working Group Grant in the 2023–2024 call.

Data exchange

The results of the surveys will be published anonymously on Open Science Forum.

CRediT authorship contribution statement

Alba Pau-Parra: Writing – original draft, Project administration, Investigation, Funding acquisition, Conceptualization. **María Núñez-Núñez:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Svetlana Sadyrbaeva Dolgova:** Writing – review & editing, Funding acquisition, Conceptualization. **Laura Doménech Moral:** Writing – review & editing, Writing – original draft, Funding acquisition. **Eva Campelo Sánchez:** Writing – review & editing, Writing – original draft, Funding acquisition. **Leonor del Mar Periañez Parraga:** Writing – review & editing, Writing – original draft, Investigation, Funding acquisition. **Khalid Saeed Khan:** Writing – review & editing, Writing – original draft, Methodology. **Sònia Luque Pardos:** Writing – original draft, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

Khalid Saeed Khan is a researcher at the University of Granada under the Beatriz Galindo program (senior modality) of the Spanish Ministry of Education; María Núñez-Núñez has a research contract from the Carlos III Research Institute (Juan Rodés JR23/00025).

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