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# How to use novel antimicrobials beyond official indications: an expert consensus

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**Objectives:** To establish a regional expert consensus on off-label indications for recently approved antimicrobials, based on a structured Delphi methodology, to support antimicrobial stewardship programs (ASPs) in Andalusia, Spain.

**Methods:** As part of the NEW_SAFE project, a modified Delphi process was employed involving 32 experts in Infectious Diseases and Intensive Care from 14 Andalusian hospitals. The process comprised three survey rounds evaluating off-label uses of eight drugs: ceftazidime-avibactam, ceftolozane-tazobactam, cefiderocol, ceftaroline, ceftobiprole, dalbavancin, tedizolid, and isavuconazole. Clinical scenarios were assessed under predefined conditions (efficacy/safety, ecological impact, and cost) and circumstances (empirical versus targeted use, resistance prevalence, PK/PD advantage).

**Results:** The expert panel reached positive consensus (≥80% agreement) on specific off-label targeted uses for all drugs except ceftobiprole. Empirical use was generally discouraged except under clear PK/PD advantages or resistance profiles without alternatives. Notably, dalbavancin, ceftaroline, and ceftazidime-avibactam received multiple targeted-use endorsements, particularly for endocarditis, osteoarticular infections, and bacteraemia. Isavuconazole was recommended for rare fungal infections and in cases where it offers pharmacological advantages.

**Conclusions:** This consensus supports the judicious off-label use of new antimicrobials in specific clinical scenarios where therapeutic gaps exist. The guidance prioritizes targeted treatment over empirical use, aligning with international ASP principles and WHO recommendations. These results provide a regional reference to optimize ASP initiatives focus on new antibiotic use while minimizing ecological impact and resistance development.

## Introduction

The worrisome increase in invasive infections caused by multidrug-resistant microorganisms has driven the development of several new drugs over the last decade. Most of these drugs have been approved by the FDA, the EMA, and the Spanish Agency for Medicines and Medical Products (Agencia Española del Medicamento y Productos Sanitarios, AEMPS) for specific syndromes, as defined in the pivotal trials (Table 1). However, these antibiotics are frequently used for indications other than those for which they were originally approved. Examples include the use of ceftaroline for bacteraemia and endocarditis[1] or the widespread use of dalbavancin for endovascular and osteoarticular infections, facilitating outpatient management of these conditions.[2,3]

For anti-Gram-negative agents such as ceftazidime-avibactam, ceftolozane-tazobactam, and cefiderocol, similar off-label uses have been reported. These include treatments for endovascular infections, osteomyelitis, and infections in specific populations not originally studied, such as patients with cystic fibrosis.[4–8] Regarding the new antifungal agent isavuconazole, it was initially approved for the primary treatment of invasive aspergillosis and mucormycosis in patients for whom amphotericin B is unsuitable.[9,10] Nevertheless, its use in other fungal infections has also been reported.[11]

Local antimicrobial guidelines, as part of Antibiotic Stewardship Programs (ASPs),[12,13] aim to modulate the indications for these drugs at each institution, typically following a literature review and subsequent expert consensus. Where local

**Table 1.** Approved indications of new drugs included in the NEW_SAFE project

| Drug | Indication (agency) | Reference: 1st author, year (PMID) |
|---|---|---|
| Ceftazidime-avibactam | IIAc (FDA, EMA, AEMPS) | *Mazuski 2016 (26962078)* |
| | ITUc, including pielonephritis (FDA, EMA, AEMPS) | *Wagenlehner 2016 (27313268)* |
| | HAP and VAP (FDA, EMA, AEMPS) | *Carmeli 2016 (27107460)* |
| | Infections caused by Gram-negatives bacilli without therapeutic alternatives options[a] (EMA, AEMPS) | |
| Ceftolozane-tazobactam | IIAc (FDA, EMA, AEMPS) | *Solomkin 2015 (25670823)* |
| | ITUc, including also pielonephritis (FDA, EMA, AEMPS) | *Wagenlehner 2015 (25931244)* |
| | HAP and VAP (FDA, EMA, AEMPS) | *Koleff 2019 (31563344)* |
| Cefiderocol | IIAc (FDA, EMA, AEMPS) | *Basetti 2021 (33058795)* |
| | ITUc, including also pielonephritis (FDA) | *Wunderick 2021 (33058798)* |
| | HAP and VAP (FDA) | |
| | Infections caused by Gram-negatives bacilli without therapeutic alternatives options[a] (EMA, AEMPS) | |
| Ceftaroline | SSTI (EMA, AEMPS) | *Corey 2010 (21115454)* |
| | CAP (EMA, AEMPS) | *File 2010 (21482566)* |
| | | *Zhong 2015 (25539586)* |
| Ceftobiprole | CAP (AEMPS) | *Awad 2014 (24723282)* |
| | HAP excluding VAP (AEMPS) | *Nicholson 2012 (22230331)* |
| | CAP, HAP, SSTI, SAB (FDA) | *Holland 2023 (37754204)* |
| | | *Overcash 2021 (32897367)* |
| Dalbavancin | SSTI (FDA, EMA, AEMPS) | *Boucher 2014 (24897082)* |
| | | *Jauregui 2005 (16231250)* |
| | | *Raad CID 2005 (15668859)* |
| Tedizolid | SSTI (FDA, EMA, AEMPS) | *Prokocimer 2013 (23403680)* |
| | | *Moran 2013 (24909499)* |
| Isavuconazol | Invasive aspergillosis and mucormycoses non-responding against amphotericin B | *Maertens 2016 (26684607)* |
| | | *Kullberg 2018 (30289478)* |

[a]According to phenotypic susceptibility profile.
CAP, community acquired pneumonia; HAP, hospital acquired pneumonia; IIAc, complicated intrabdominal infections; ITUc, complicated urinary infections; SAB, *Staphylococccus aureus* bacteraemia; SSTI, soft tissue infections; VAP, ventilator associated pneumonia.

regulation is absent, inappropriate use of these new drugs may occur, leading to an increase in adverse reactions and costs for the public healthcare system. Moreover, in Spain, off-label use must follow strict medical supervision to ensure patient safety, as failure to comply with these regulations may result in legal liability for healthcare professionals. In that scenario, a consensus document can provide guidance for evidence-based prescriptions, ensuring that clinical decisions are supported at by the best available data while mitigating risk. Although resistance to these antibiotics is not yet widespread, cases of treatment failure have already been documented.[14–16] Therefore, prioritizing the monitoring of their use and implementing specific ASP interventions are essential.

In this context, the NEW_SAFE Project, an ASP intervention study focused on new antimicrobials, was developed in Andalusia, Spain from 2029 to 2022.[17] This communication aims to present the development and outcomes of the Andalusian consensus document on off-label indications for new drugs, established through a Delphi consensus methodology.

## Methods

This consensus was developed as part of an ASP intervention aimed at improving the use of new antibiotics in Andalucía, Spain; the study protocol was previously published.[17] Briefly, the NEW_SAFE project, a quasi-experimental intervention study for optimizing new antimicrobial use, was launched in Andalusia, funded by the Ministry of Health in 2019 (FIS-TED-2019-01). The project focused on antimicrobials introduced in the previous 5 years (2013–2018): ceftazidime-avibactam, ceftobiprole, ceftolozane-tazobactam, ceftaroline, dalbavancin, tedizolid, and isavuconazole. The study was conducted in two phases: a pre-intervention cohort phase, retrospectively analyzing all patients treated with any of these antimicrobials between January 2016 and December 2019, and a quasi-experimental intervention phase, which included developing a consensus document using the Delphi methodology[18] to guide the indications for these new drugs. This document was disseminated to participating hospitals, and audits of prescriptions were performed based on the established guidance.

A modified Delphi process was conducted to reach consensus on the off-label adequate indications for these new antimicrobials[18] based on unmet clinical needs, to guide ASP activities. The modified Delphi methodology involved convening an expert panel, designing the survey structure (including clinical situations to be evaluated), and conducting three rounds of electronic surveys to rate and finalize the candidate indications for inclusion in the consensus document.

### *Constitution of the expert panel*

The experts participating in this consensus were selected from the principal investigators (PIs) of the 14 Andalusian hospitals involved in the NEW_SAFE project.[17] These experts were primarily members of the ASPs at their respective institutions, supplemented by a group of selected experts in the field. Key clinical specialties related to the prescription of new antibiotics were represented: Internal Medicine, Infectious Diseases and Intensive Care.

Prior to developing the survey, a systematic review of the literature was conducted to identify off-label indications for the study drugs. Subsequently, a series of proposals for off-label indications was prepared, taking into account various conditions and circumstances of use (Table 2).

The conditions referred to the main conceptual factors that should be considered when deciding whether to use a particular antibiotic. The circumstances aimed to contextualize epidemiological or clinically significant factors that might influence the choice of an antibiotic.

For specific clinical situations (e.g. acute otitis media), under a specific condition (e.g. clinical efficacy and safety) and in a particular circumstance (e.g. empirical treatment), experts were asked to rate their agreement with using the evaluated drug (e.g. cefiderocol) as a therapeutic option. The rating scale ranged from strongly disagree (0 points) to strongly agree (5 points).

The questions were formulated as follows: '*Would you agree to use cefiderocol as an empirical treatment for acute otitis media, considering its clinical efficacy and safety?*' These questions were organized into charts, categorized by drug and condition.

**Table 2.** Conditions and circumstances related to antibiotic use included in the consensus survey

| Condition | Definition |
|---|---|
| Clinical efficacy and safety | Clinical efficacy and safety of the evaluated drug according to the available evidence |
| Ecological impact | Expected ecological impact of the drug according to the selection and induction of resistance mechanism according to the available evidence |
| Cost | Cost of the therapy according to the published and official prize |
| **Circumstance of use** | **Definition** |
| Empiric/targeted | Empiric refers to selection of the drug according to the clinical and epidemiological information before microbiological information is available. Targeted refers to the selection of the drug when phenotypic susceptibility report of a causative microorganism is available |
| High prevalence of a specific MDR/XR microorganism | High prevalence was defined as an endemic situation or a prevalence >15% of MRSA, ESBL Enterobacterales, ECP, MDR o XR *Pseudomonas aeruginosa* or *Acinetobacter baumannii* |
| Pk/PD advantage | The evaluated drug presents a pk/pd advantage such as less renal/hepatic toxicity, less drug-drug interaction, better distribution according to the treated focus or not expected adverse reaction/ intolerance in an specific patient compare with the possible alternative drugs (see Table S1 for specific PK/PD advantages for each drug). |

CRE, carbapenem resistant Enterobacterales; ESBL, extended spectrum betalactamase; MDR, multidrug resistant; MRSA, methicillin resistant *S. aureus*; PK/PD, pharmacokinetics/pharmacodynamic; XR, extreme resistant.

### *Rounds development, evaluation, and final consensus*

The Delphi survey was conducted in three rounds during the calendar year 2021 (February-March, May-June, October-November). In each round, participants completed an electronic survey and had the opportunity to include free-text comments. There were no contact among the participants. The experts were always contacted individually to maintain the confidentiality of their responses. A literature review was made available in an online repository for participants throughout the rounds.

The modified RAND/UCLA method was employed as the consensus methodology, omitting face-to-face meetings between consultation rounds.[19] Instead, an analysis was performed that integrated quantitative information and participant comments across the three rounds.

The consensus panel recommends the use of the evaluated drug when 80% or more of the responses align with scores of 4 or 5 (agree/strongly agree). Conversely, it does not recommend the use of the drug when 80% or more of the responses align with scores of 0 or 1 (disagree/strongly disagree).

### *Ethical considerations*

This consensus was approved as part of the NEW_SAFE project by the ethical committees of the participating centres.[17] All responses were anonymized and analyzed by independent investigators.

## Results

A total of 32 experts participated in the Delphi consensus, including 24 Infectious Diseases specialists and 8 Intensive Care physicians. The process was completed in three rounds.

The survey was structured into seven sections, each corresponding to one of the drugs evaluated (Supplementary material, Tables S2.1–S2.8, available as Supplementary data at *JAC-AMR* Online). Each section included a table where the rows listed the off-label indications identified in the prior literature review. The primary columns represented the circumstances of use, and nested within them were secondary columns representing the three conditions being evaluated (Supplementary material, Tables S2.1–S2.8).

The consensus results are visualized using coloured dots: green indicates a positive recommendation for use (≥80% agreement), yellow signifies a lack of consensus, and red denotes a negative recommendation for use (≥80% agreement against use). These dots correspond to each specific statement assessed in the survey (see Figures 1a–c, 2a–d and 3).

### *Consensus for off-label indications of ceftazidime-avibactam*

Based on the efficacy and safety reported in the available scientific evidence, its current cost and expected ecological impact, the panel of expert RECOMMENDS the use of ceftazidime-avibactam as empirical treatment in infective endocarditis (native or prosthetic), primary bacteraemia (bacterial translocation), secondary bacteraemia associated with catheter or other devices, in osteomyelitis and septic arthritis, infections associated with joint prostheses or osteosynthesis material, skin and soft tissue infection, central nervous system (CNS) infections and in patients with cystic fibrosis or bronchiectasis syndrome when there is an PK/PD advantage of the evaluate antibiotic compared with other expected active alternatives. However, out of this circumstance, the expert RECOMMEND AGAINST the use of ceftazidime-avibactam as an empiric treatment regardless epidemiological circumstance (Figure 1a).

For the other scenarios explored the panel does not reach any consensus.

### *Consensus for off-label indications of ceftolozane-tazobactam*

Based on the efficacy and safety reported in the available scientific evidence, its current cost and expected ecological impact, this expert panel RECOMMENDS its use as targeted treatment without other available alternatives to treat infective endocarditis (native/prosthetic), primary bacteraemia, secondary bacteraemia associated with catheter or other devices, osteomyelitis and spondylodiscitis, skin and soft tissue infections including surgical wound infections, infections associated with surgical material osteosynthesis and prosthesis, complicated acute otitis media (abscesses and mastoiditis), pleural empyema and in respiratory superinfections in patients with cystic fibrosis. Apart from in endocarditis cases, its use is also recommended in empirical/targeted treatment when there is a PK/PD advantage compared with other active alternatives. The expert panel RECOMMEND AGAINST the general use of ceftolozane-tazobactam in empirical treatment regardless the prevalence of multidrug resistant/extreme resistant (MR/XR) microorganisms (Figure 1b).

For the other scenarios explored the panel does not reach any consensus.

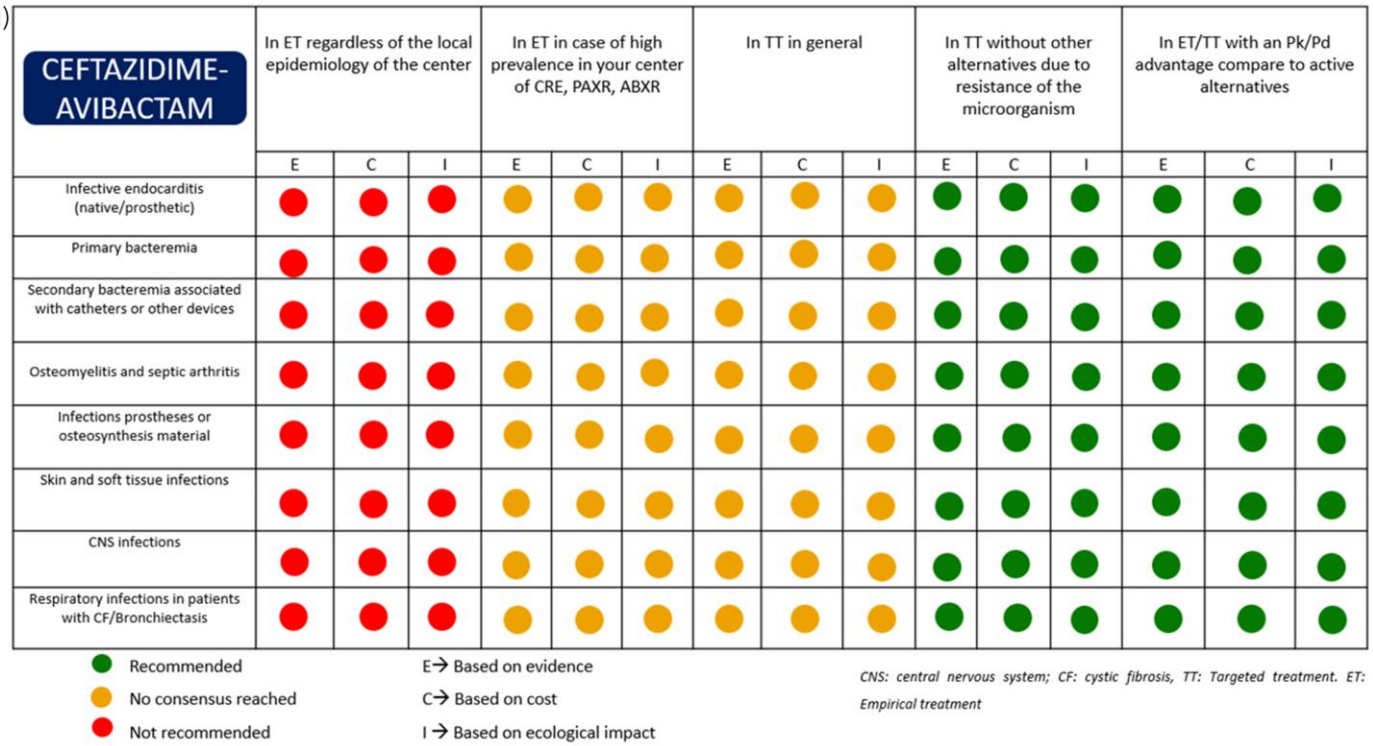
### *Consensus for off-label indications of cefiderocol*

Based on the efficacy and safety reported in the available scientific evidence, its current cost and expected ecological impact, the NEW_SAFE panel RECOMMENDS the use of cefiderocol in targeted treatment to treat infections caused by resistance microorganisms without alternative drugs available (according to the phenotypic profile described in the antibiogram) of the following syndromes: primary bacteraemia, secondary bacteraemia associated with catheters or other devices, osteomyelitis and septic arthritis, infections associated with joint prostheses or osteosynthesis material, intra-abdominal infections (including those with bloodstream infections), pleural empyema, respiratory infections in patients with cystic fibrosis or bronchiectasis syndrome. In all these cases, apart from endocarditis, osteomyelitis, infections associated with joint prostheses or osteosynthesis material or CNS infections, its use is also recommended in empirical/targeted treatment without other alternatives due to PK/PD problems (Figure 1c).

The expert panel RECOMMEND AGAINST its general use as empirical treatment regardless of the high prevalence of MR/XR. In addition, in targeted treatment it is NOT RECOMMENDED when there are alternative drugs available in the case of infective endocarditis (native/prosthetic), in primary bacteraemia, in osteomyelitis and septic arthritis, in infections associated with joint prostheses or osteosynthesis material, in case of pleural empyema and CNS infections.

For the other scenarios explored the panel does not reach any consensus.

(a)




(b)

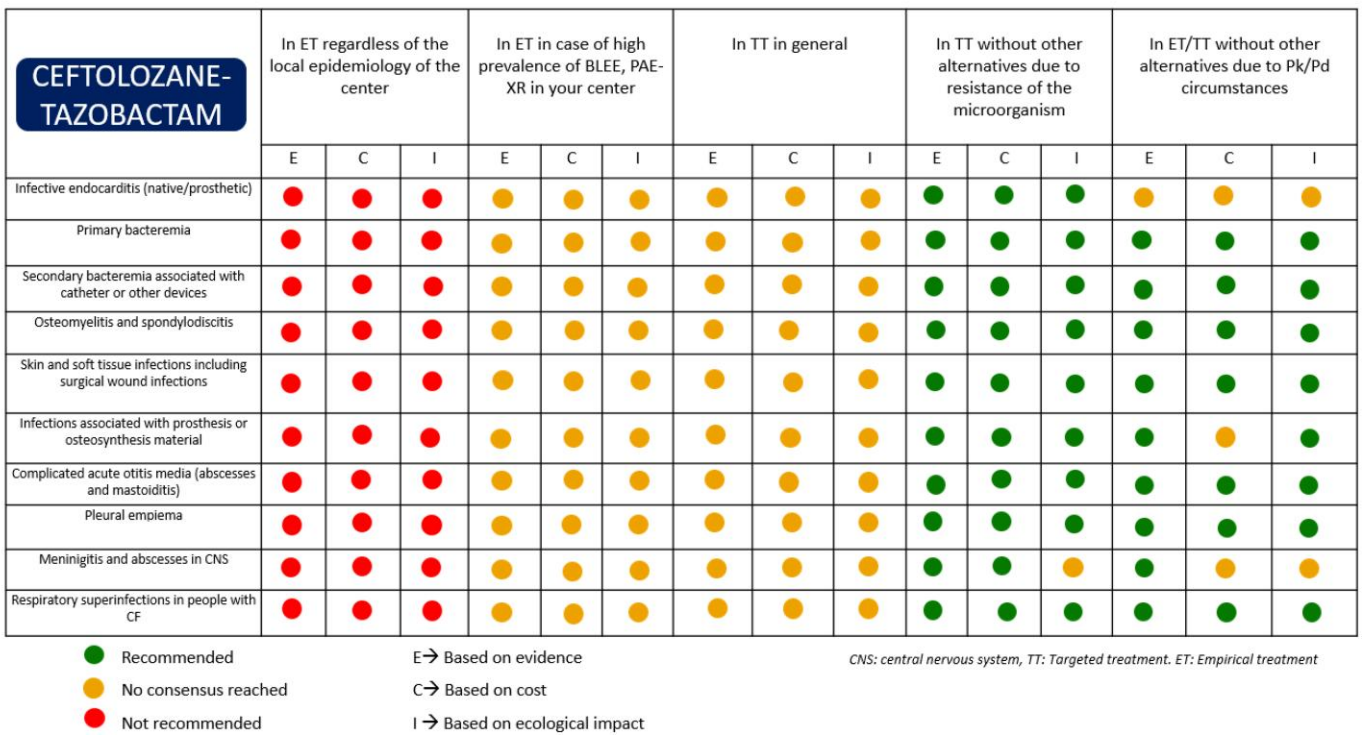



**Figure 1.** (a) Consensus for off-label indications of ceftazidime-avibactam. (b) Consensus for off-label indications of ceftolozano-tazobactam. (c) Consensus for off-label indications of cefiderocol.

(c)

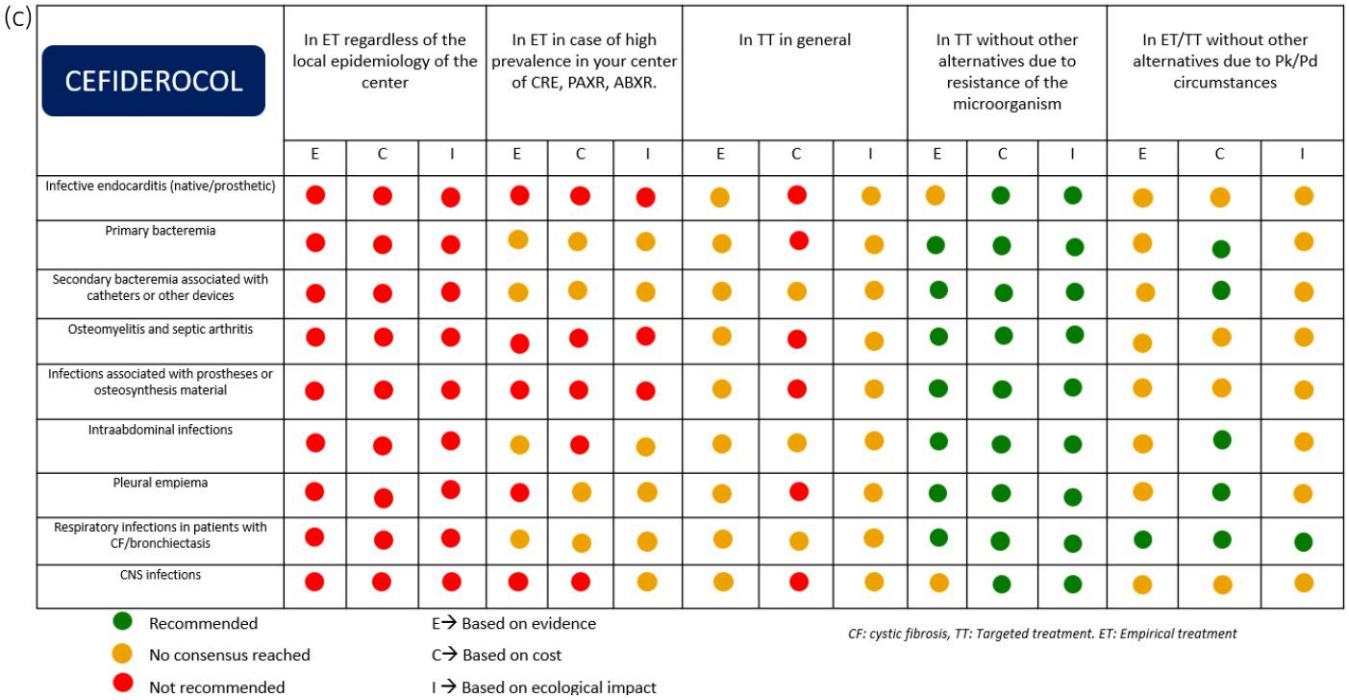



**Figure 1.** Continued

### *Consensus for off-label indications of ceftobiprole*

Based on the efficacy and safety reported in the available scientific evidence, its current cost and expected ecological impact, the NEW_SAFE panel of experts RECOMMEND AGAINST the use of ceftobiprole in any of the off-label indications (infective endocarditis, primary or secondary bacteraemia associated with catheter or other devices, pneumonia associated with mechanical ventilation, cystic fibrosis or bronchiectasis syndrome, common or complicated skin or soft tissue, osteomyelitis, septic arthritis or infection associated with prostheses or osteosynthesis material) according to the conditions and circumstances explored regardless of the prevalence of multi-drug resistant *Staphylococcus aureus* (MRSA) neither as targeted treatment.

For the other scenarios explored the panel does not reach any consensus (Figure 2a).

### *Consensus for off-label indications of ceftaroline*

Based on the efficacy and safety reported in the available scientific evidence, its current cost and expected ecological impact, the NEW_SAFE panel RECOMMENDS the use of ceftaroline in targeted treatment when there is no other alternatives due to resistances of the microorganism causing the infection or in empirical and targeted treatment in which ceftaroline offers a PK/PD advantage in the following circumstances: infective endocarditis (native or prosthetic), in primary bacteraemia, in secondary bacteraemia associated with catheter or other devices, in infections of the CNS, in nosocomial pneumonia or pneumonia associated with mechanical ventilation, in skin and soft tissue infection not included in the approval infections (Fournier´s gangrene, diabetic foot, deep muscle abscesses or necrotizing fasciitis), osteomyelitis and septic arthritis, infection associated with joint prostheses or osteosynthesis material, complicated urinary tract infections, intra-abdominal infections and ENT infections (Figure 2b).

The expert panel RECOMMEND AGAINST the use of ceftaroline in empirical treatment regardless of the local epidemiology of the centre in the aforementioned circumstances.

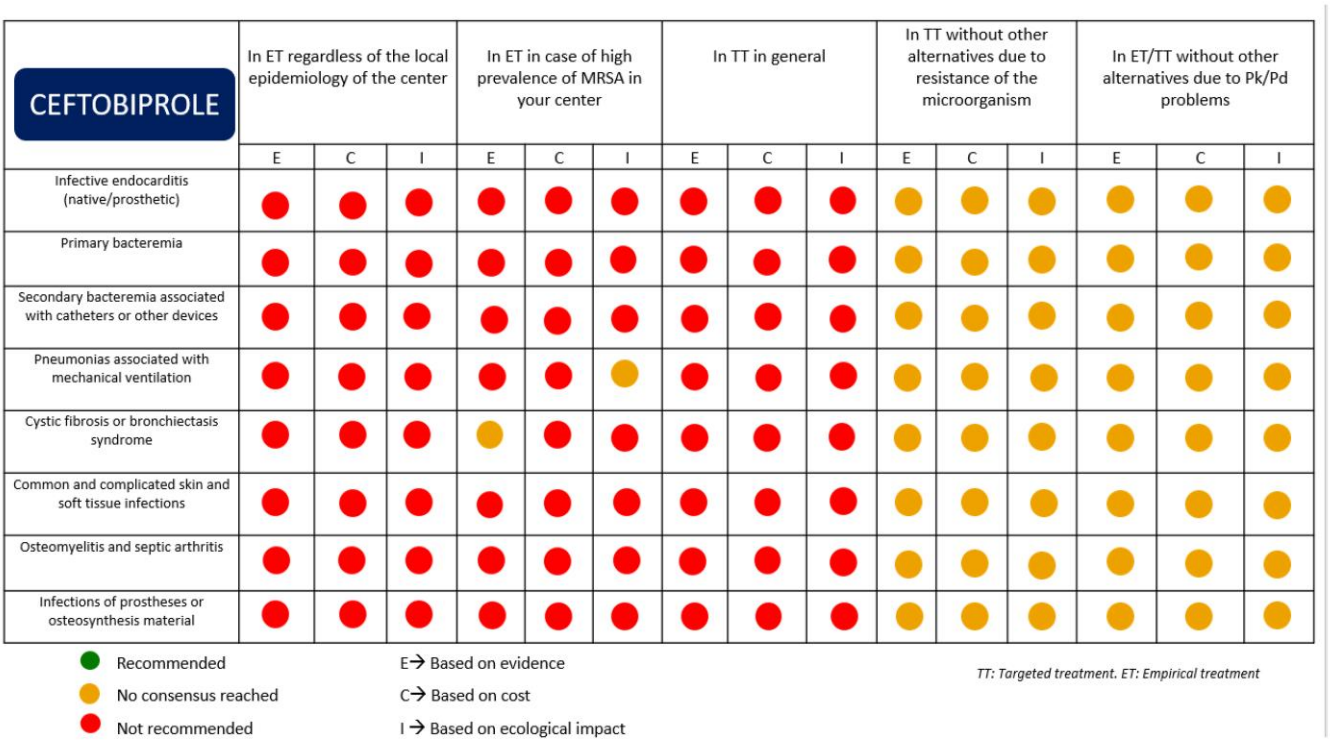
For the other scenarios explored the panel does not reach any consensus.

### *Consensus for off-label indications of tedizolid*

Based on the efficacy and safety reported in the available scientific evidence, its current cost and expected ecological impact, the NEW_SAFE panel of experts RECOMMENDS the use of tedizolid as a targeted treatment without other alternatives due to microorganism resistances in the following indications: septic osteomyelitis and arthritis, nosocomial and mechanical ventilation-associated pneumonia, infections associated with joint prostheses or osteosynthesis material (not meeting this recommendation based on cost) and in infections due to mycobacteria and other slow-growing gram-positive pathogens that require prolonged treatment (the latter recommendation only based on ecological impact) (Figure 2c).

In addition, the panel of experts RECOMMENDS the use of tedizolid as an empirical or targeted treatment without other alternatives for PK/PD problems in osteomyelitis and septic arthritis, in prosthetic infections and infections associated with osteosynthesis material (not reaching a consensus on this indication based on the evidence), in hospital-acquired pneumonia and pneumonia associated with mechanical ventilation (recommending its use only based on evidence) and in infections caused by mycobacterial and other slow-growing gram-positive pathogens that

(a)

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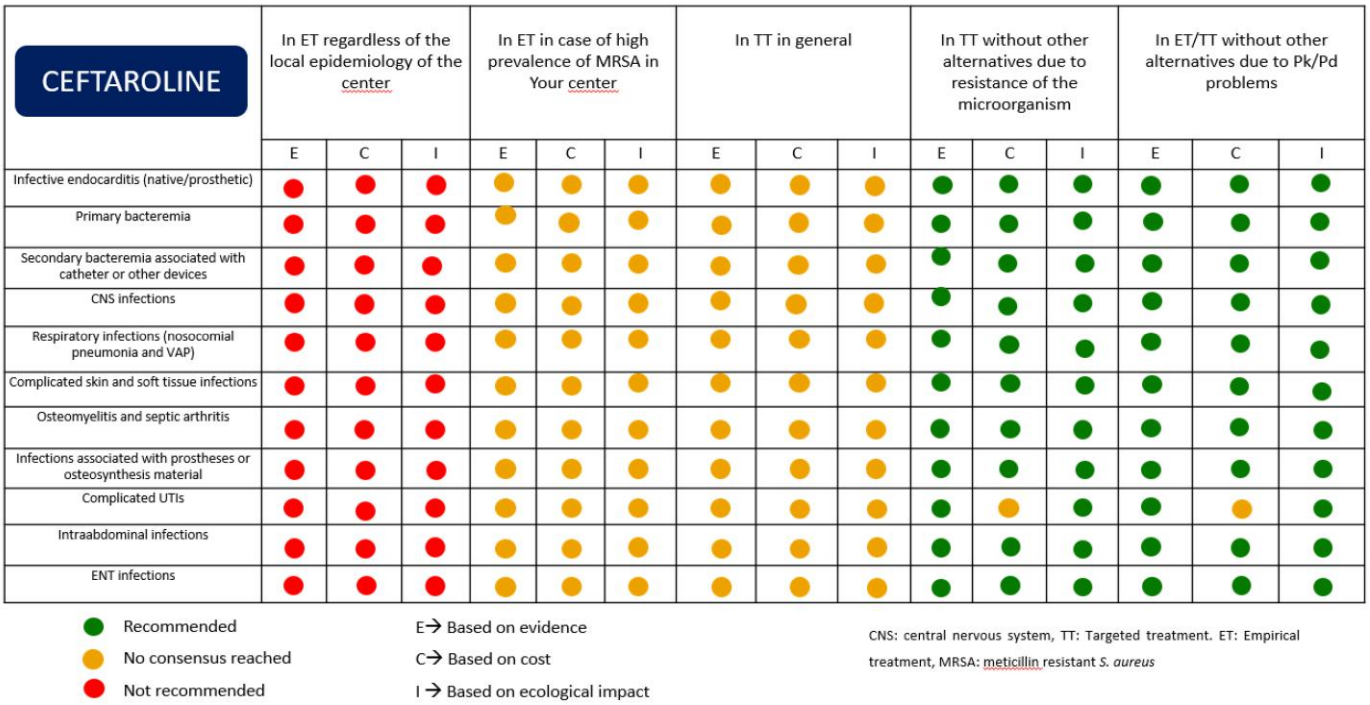


**Figure 2.** (a) Consensus for off-label indications of ceftobiprole. (b) Consensus for off-label indications of ceftaroline. (c) Consensus for off-label indications of tedizolid. (d) Consensus for off-label indications of dalbavancin.

require prolonged treatment (this last recommendation being only based on the ecological impact).

The panel of experts RECOMMEND AGAINST the use of tedizolid as empirical treatment regardless of the local epidemiology of the centre in the indications explored. In addition, the expert panel RECOMMEND AGAINST the use of tedizolid in targeted therapy on the basis of cost in the above circumstances except, in osteomyelitis and septic arthritis,

(c)

**TEDIZOLID**

| | In ET regardless of the local epidemiology of the center | | | In TT in general | | | In TT without other alternatives due to resistance of the microorganism | | | In ET/TT without other alternatives due to Pk/Pd problems | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | E | C | I | E | C | I | E | C | I | E | C | I |
| Infective endocarditis (native/prosthetic) | 🔴 | 🔴 | 🔴 | 🟡 | 🔴 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 |
| Primary bacteremia | 🔴 | 🔴 | 🔴 | 🟡 | 🔴 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 |
| Secondary bacteremia associated with catheters or other devices | 🔴 | 🔴 | 🔴 | 🟡 | 🔴 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 |
| Osteomyelitis and septic arthritis | 🔴 | 🔴 | 🔴 | 🟡 | 🟡 | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 |
| Infections associated with prosthesis or osteosynthesis material | 🔴 | 🔴 | 🔴 | 🟡 | 🟡 | 🟡 | 🟢 | 🟡 | 🟢 | 🟡 | 🟢 | 🟢 |
| Intraabdominal infections (including bacteraemia) | 🔴 | 🔴 | 🔴 | 🟡 | 🔴 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 |
| Nosocomial pneumonia and VAP | 🔴 | 🔴 | 🔴 | 🟡 | 🔴 | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟡 |
| UTIs and bladder catheter-associated infections | 🔴 | 🔴 | 🔴 | 🟡 | 🔴 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 |
| CNS infections | 🔴 | 🔴 | 🔴 | 🟡 | 🔴 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 |
| Infections by mycobacteria and other slow-growing pathogens G+ (prolonged treatment) | 🔴 | 🔴 | 🔴 | 🟡 | 🔴 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟢 |

🟢 Recommended
🟡 No consensus reached
🔴 Not recommended

E→ Based on evidence
C→ Based on cost
I → Based on ecological impact

UTI: urinary tract infection, CNS: central nervous system, TT: Targeted treatment. ET: Empirical treatment

(d)

**DALBAVANCIN**

| | In ET regardless of the local epidemiology of the centre | | | In ET in case of high prevalence of MRSA in your centre | | | In TT in general | | | In TT without other alternatives due to resistance of the microorganism | | | In ET/TT without other alternatives due to Pk/Pd problems | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | E | C | I | E | C | I | E | C | I | E | C | I | E | C | I |
| Infective endocarditis (native/prosthetic) | 🔴 | 🔴 | 🔴 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 |
| Primary bacteremia | 🔴 | 🔴 | 🔴 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 |
| Secondary bacteremia associated with catheters or other devices | 🔴 | 🔴 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 |
| CNS infections | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 |
| Community, nosocomial and ventilated-associated pneumonias | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 |
| Complicated skin and soft tissue infections (off-label) | 🔴 | 🔴 | 🔴 | 🟡 | 🔴 | 🟡 | 🟡 | 🟡 | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 |
| Osteomyelitis and septic arthritis | 🔴 | 🔴 | 🔴 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 |
| Infections associated with prostheses or osteosynthesis material | 🔴 | 🔴 | 🔴 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 |
| Complicated UTIs or acute pyelonephritis | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 | 🟡 |
| Intraabdominal infections | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🔴 | 🟡 | 🟡 | 🟡 | 🟢 | 🟡 | 🟡 |

🟢 Recommended
🟡 No consensus reached
🔴 Not recommended

E→ Based on evidence
C→ Based on cost
I → Based on ecological impact

*CNS: central venous system, TD: Targeted treatment. ET: Empirical treatment*

**Gangrene, diabetic foot, psoas abscess, necrotizing fasciitis, mediastinitis).*

**Figure 2.** Continued

and in infections prosthetic or associated with osteosynthesis material.

For the other scenarios explored the panel does not reach any consensus.

### *Consensus for off-label indications of dalbavancin*

Based on the efficacy and safety reported in the available scientific evidence, its current cost and expected ecological impact,

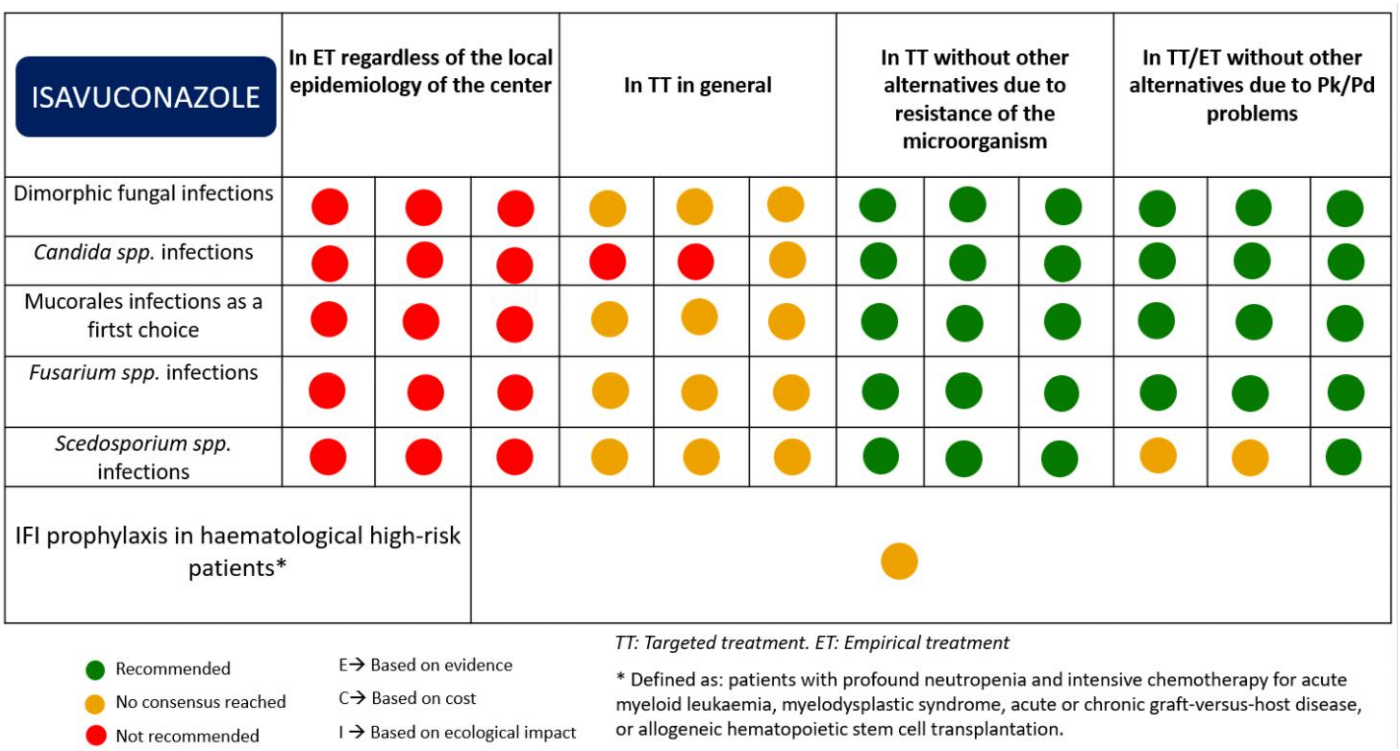


**Figure 3.** Consensus for off-label indications of isavuconazole.

the NEW_SAFE panel of experts RECOMMENDS the use of dalbavancin as targeted treatment without other alternatives due to resistance of the microorganism and as empirical or targeted treatment without other alternatives due to PK/PD problems in the following circumstances: infective endocarditis (native/prosthetic), primary bacteraemia, secondary bacteraemia and those associated with catheters or other devices, complicated skin and soft tissue infections others than the approved indications (Fournier's gangrene, diabetic foot, psoas abscess, necrotizing fasciitis, mediastinitis…), osteomyelitis and septic arthritis and in associated infections to prosthesis or osteosynthesis material (Figure 2d).

Furthermore, the expert panel RECOMMENDS AGAINST the use of dalbavancin as empirical treatment regardless the high prevalence of MRSA for treating CNS infections, community-acquired, nosocomial and ventilator-associated pneumonia, complicated urinary tract infections and acute pyelonephritis or in intra-abdominal infections. Neither in empirical treatment of complicated skin and soft tissue infections (out of the approved indications) based on cost.

For the other scenarios explored the panel does not reach any consensus.

### *Consensus for off-label indications of isavuconazole*

The panel of experts RECOMMENDS the use of isavuconazole in targeted treatment when there are no alternatives due to resistance of the microorganism in the following circumstances: fungal infections due to dimorphic fungi (*Histoplasma spp.*, *Blastomyces spp.*, *Sporothrix spp.*, *Paracoccidioides spp.*, *Coccidioides spp.*, *Lacazia spp.*, *Emmansia spp.*, *Talaromyces spp.*), infections caused by *Candida spp.* (either candidemia, disseminated or hepato-splenic candidiasis), infections caused by *Cryptococcus spp.* and other yeasts (*Trichosporon spp.*), *Fusarium spp.* or *Scedosporium spp* (Figure 3).

Furthermore, the expert panel RECOMMENDS the use of isavuconazole in empirical/targeted treatment of infections caused by the above-mentioned microorganisms when isavuconazole presents some PK/PD advantage over the usual alternatives.

Additionally, out of the previous circumstances, the panel RECOMMENDS AGAINST the use of isavuconazole as targeted therapy in the treatment of *Candida spp.* infections (either candidemia or disseminated or hepato-splenic candidiasis) based on scientific evidence and individual cost of the drug.

The expert panel RECOMMENDS AGAINST the use of isavuconazole as empirical treatment regardless of the local epidemiology of the centre.

For the other scenarios explored the panel does not reach any consensus.

## Discussion

In this work, we present a consensus in which a group of expert clinicians addresses the need for guidance in using new antibiotics in specific circumstances beyond their official indications.

As a summary, most recommendations focus on targeted treatments and clinical situations where new drugs offer superior PK/PD profiles compared with alternatives. In general, the panellists agreed against the empirical use of these new antibiotics, regardless of local hospital epidemiology.

Several key aspects merit discussion regarding this work. First, was this consensus necessary considering existing guidelines? Second, is the Delphi method an appropriate tool to address this need? And, was the methodology appropriately executed, and did it encompass the most relevant clinical questions?

### *The need for a consensus*

Antibiotic prescription requires significant expertise to select the most clinically effective option with the least ecological impact. This involves understanding infectious diseases therapeutics, PK/PD features, and up-to-date knowledge of the epidemiology and dynamics of multidrug-resistant pathogens. Evidence-based guidelines are proven to be one of the most consistent and effective interventions within ASPs.[13]

In recent years, various guidelines have been published to assist in the use of new antibiotic drugs, primarily focusing on treating multidrug-resistant microorganisms. Examples include the ESCMID guidelines for Gram-negative pathogens,[20] the IDSA guidance,[21] and the British Infection Association guidance for MRSA.[22] While these documents provide recommendations for targeted treatments, which represented 18% of prescriptions in our hospitals during the last decade,[23] they often lack guidance for specific populations, such as transplant recipients or immunocompromised patients.

In the absence of guidance, misuse of these drugs may lead to the rapid emergence of resistance. Moreover, without established standards, evaluating prescription quality and conducting audits—the cornerstone of ASPs—becomes challenging. This consensus serves as the first comprehensive approach, alongside recent guidelines focused on targeted treatments of MRSA[22] and multidrug-resistant gram-negative pathogens,[20,21] that integrates the use of new drugs across a broader range of clinical indications.

### *Suitability and implementation of the Delphi method*

The Delphi method is widely used for expert consensus, particularly in situations with limited or conflicting evidence. Although expert opinion ranks lowest in the hierarchy of evidence,[24] this method allows experts to reach collective agreement by anonymously reviewing summarized literature, small cohorts, and case series when clinical trials are unavailable.

The Delphi approach offers several advantages: anonymity, iteration, controlled feedback, and statistical consensus. In this study, anonymity was ensured throughout the process, feedback was provided after each round through detailed reports, and consensus rules were explicitly defined and visually represented for transparency and clarity. These steps align with best practices for Delphi-based consensus development.[25]

However, certain limitations arose during the development of the survey. Notably, clinical severity was not explicitly considered in questions about empirical treatment in high-prevalence settings of multidrug-resistant organisms. This omission may have biased responses, reflecting the local epidemiology of the experts' regions. In Andalusia, the prevalence of carbapenem-resistant Enterobacterales remains low (1 −< 5%, according to ECDC 2023 reports).[26] Resistance rates are slightly higher for meropenem-resistant *Pseudomonas aeruginosa* (5%–10%), while other pathogens, such as MRSA and carbapenem-resistant *Acinetobacter* spp., exhibit resistance rates between 25% and 50%, though these are limited to specific populations. A pertinent question arises: At what resistance threshold should these new drugs be included in empirical therapy? Literature suggests that a prevalence exceeding 10% might justify broad-spectrum or combination therapy for severe or complicated infections.[27]

### *Limitations of this work*

Several limitations should be noted. First, recently commercialized antibiotics such as meropenem-vaborbactam, imipenem-relebactam, delafloxacin, and oritavancin were not included. Second, indications for evaluated drugs such as ceftazidime-avibactam, ceftolozane-tazobactam, and cefiderocol have evolved including broader indications in case of multidrug resistant microorganisms with non-alternative options, and current consensus may not reflect these updates. And finally, important clinical variables, such as infection severity and specific populations (e.g. pregnant women or certain immunocompromised patients), were not considered, limiting the applicability of recommendations.

### *Conclusion*

The key message is clear: experts participating in this panel, working in low-resistance prevalence settings, concluded that new antibiotics should be reserved for targeted situations where no valid alternatives are available. This aligns with the core principles of ASPs and international recommendations, such as those from WHO, which classify these drugs in the 'RESERVE' group.

This consensus should be interpreted cautiously, considering the specific epidemiological context. However, it serves as an essential first step in developing ASP-focused programs for the judicious use of these critical drugs.

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## Transparency declarations

P. R. -G. has participated as an advisor for Shionogi and Advanz, and has served as a speaker for Menarini. J. R. B., L. V. D. S., J. J. C. -O., C. H. -R., I. M. -G., J. P. -S., J. E. C. -D., F. J. M. -M., M. A. -A., G. O. -B., S. L. -C., M. Á.

E. -M., A. M. -A., S. S. -D., F. A. -S., P. J. -A., and Z. R. P. -B. declare no conflicts of interest.

### *Author contributions*

J. R. -B., P. R. -G., L. V. D. S., J. J. C. -O., C. H. -R., I. M. -G., J. P. -S., J. E. C. -D., F. J. M. -M., A. M. -A., G. O. -B., S. L. -C., M. A. E. -M., S. S. -D., F. A. -S., and P. J. -A. conceived the study. Z. R. P. -B., L. V. D. S., M. A. -A., J. R. B. and P. R. -G. designed the study. Z. R. P. -B. obtained funding for the research. P. R. -G. wrote the first draft of the manuscript. P. R. -G., L. V. D. S. and Z. R. P. -B. are the study coordinators and Z. R. P. -B. is the leader of the coordinating team. All authors reviewed, edited and approved the final version of the paper.

## Supplementary data

Supplementary S2.1 to S2.8 is available as Supplementary data at *JAC-AMR* Online.

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