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Management of metallo-β-lactamase-producing Enterobacterales infections: a modified Delphi study

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Background and objectives: Metallo-β-lactamase (MBL)-producing Enterobacterales infections are an urgent global healthcare problem with limited treatment options. To obtain greater understanding of international perspectives on optimal management of serious infections due to MBL-producing Enterobacterales, we used a modified Delphi process to elicit experts' opinion and establish consensus.

Methods: A Delphi panel comprising 10 expert physicians experienced in antimicrobial-resistant bacterial infection management were surveyed on epidemiology, disease, testing and management of MBL-producing Enterobacterales infections. Consensus statements were based on survey responses and reviewed by the panel for endorsement or revisions to achieve consensus during a virtual meeting.

Results: All panellists acknowledged MBL-producing Enterobacterales as a key source of antimicrobial resistance and infection in most countries. All agreed these infections have high morbidity and mortality, leading to the need for critical-level care, longer hospital stays and significant healthcare costs. The negative clinical and economic consequences of MBL-producing Enterobacterales are compounded by inappropriate use of multidrug antimicrobial regimens. Therefore, a specific MBL-targeting agent is considered desirable. When aztreonam-avibactam and cefiderocol are available, the preferred first-line treatment is aztreonam-avibactam, per *in vitro* data showing aztreonam-avibactam activity against >90% of New Delhi MBL-producing Enterobacterales. If aztreonam-avibactam or cefiderocol are unavailable, treatment options are limited to co-administration of antimicrobials. Regional differences made it difficult to achieve unanimous consensus across all survey questions due to differences in patient factors, local epidemiology and testing availability.

Conclusions: The Delphi panel reached consensus on optimal management of MBL-producing Enterobacterales, confirming need for targeted MBL treatment, with monotherapy preferred where available.

Introduction

Infections caused by multidrug-resistant Enterobacterales are increasing, and carbapenem-resistant Enterobacterales (including those producing metallo-β-lactamases [MBLs]) are of particular concern and considered an urgent global health threat for which treatment options are severely limited.[1–3]

Real-world evidence confirms that a delay in prescribing appropriate antibiotics is associated with an increased risk of morbidity and mortality in patients with severe Gram-negative infections, particularly in those with multidrug-resistant pathogens.[4–9] Specifically for infections associated with MBL-producing Enterobacterales, a recent systematic literature review highlighted reduced susceptibility to most standard-of-care antimicrobials, longer hospital stays compared with other infection groups and overall mortality between 18.8% and 57%.[10] This underscores the need for new and effective therapies, as well as specialized laboratory testing to avoid delays in diagnosis and treatment initiation.[10] Notably, none of the studies identified in the systematic literature review[10] assessed the efficacy of newer treatment options, such as cefiderocol or aztreonam-avibactam, and most of the research synthesized was from small, single-centre studies; data from large, multinational, prospective studies are lacking.

The multinational, prospective ASSEMBLE, REVISIT, CREDIBLE-CR and APEKS-NP studies highlighted that aztreonam-avibactam and cefiderocol, respectively, could be potential options for MBL-producing pathogens, with favourable outcomes when compared with the best available therapy.[11–13]

The objective of this Delphi study was to understand experts' perspectives on the optimal treatment of serious infections caused by MBL-producing Enterobacterales, and to facilitate consensus regarding the epidemiology, disease, testing and optimal management of these infections.

Materials and methods

Ethics

The study was conducted in accordance with generally accepted research practices, including recommendations for Conducting and Reporting of Delphi Studies for the methodology and reporting of results.[14–16] Further, this study received a 'not human subjects research' determination (RTI Office of Research Protection, STUDY00023007, 12 September 2024).

Study design and panellists

Panellists were internationally recognized experts as clinical practitioners, microbiologists or infectious disease specialists with experience in the treatment of antibiotic-resistant bacterial infections, and reflected diverse geographical regions. Pfizer Inc. sponsored this work. Each panellist provided written consent to participate and was contracted individually. Pfizer Inc. provided remuneration at fair market value to each panellist for their participation in the Delphi panel. The decision to publish was made by the author group and no remuneration was provided for authoring the manuscript.

A modified Delphi method was used to collect the panellists' expert opinions and judgements on treatment of serious infection caused by MBL-producing Enterobacterales and to develop a consensus on optimal management. The Delphi technique is a widely employed process utilized to achieve expert consensus.[17]

The study employed a mixed-methods approach, gathering expert opinions in two phases. Panellists completed an online survey before participating in a virtual consensus meeting (Figure 1).

Panellists reviewed pre-read materials before attending the virtual meeting. These materials comprised published or publicly available material related to key international guidelines for the treatment of MBL-producing Enterobacterales infections, clinical trial data of

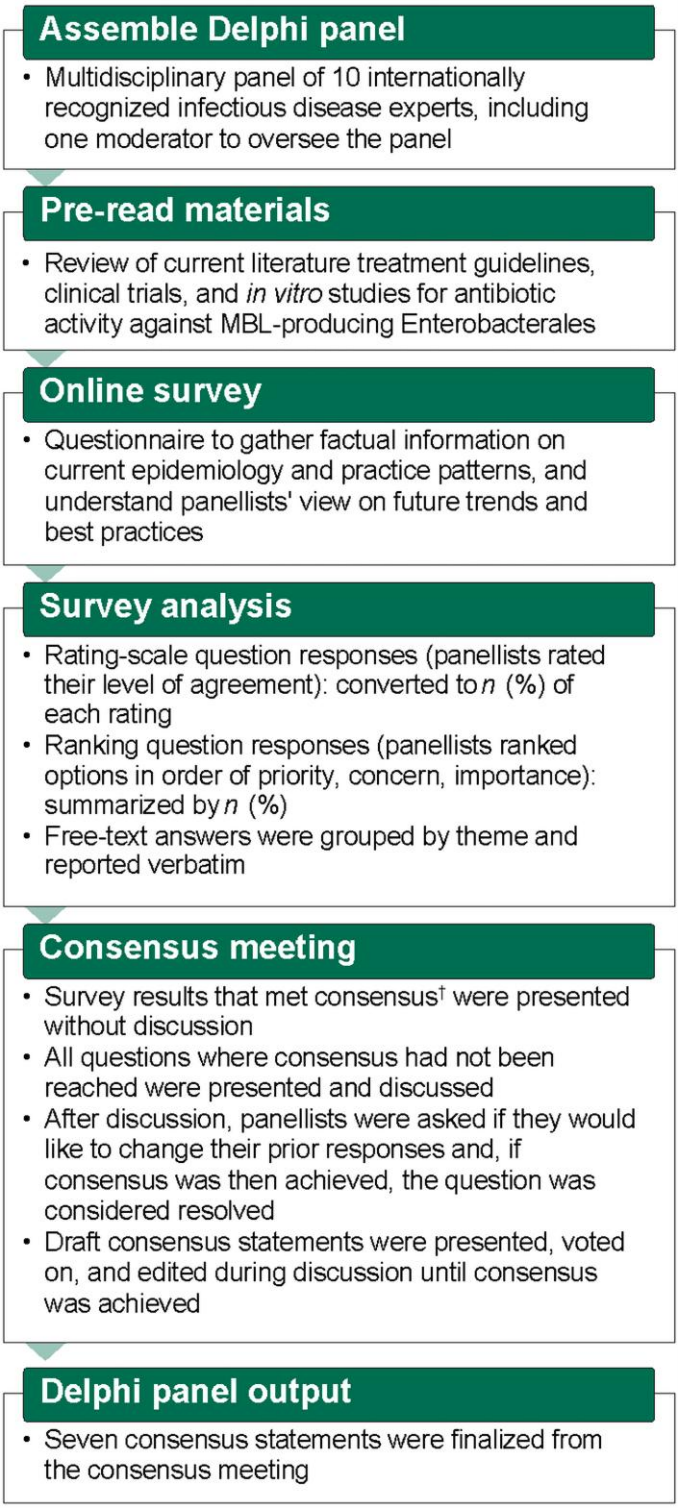

Figure 1. Modified Delphi process chart. †Consensus was defined as the achievement of all responses indicating agreement or disagreement with the statement, regardless of the agreement level. For rating-scale questions, consensus was defined as all responses indicating agreement or all responses indicating disagreement. For ranking questions, consensus was achieved when only two items in a list were ranked as first or second. Not all panellists voted for all questions due to audio issues.

cefiderocol, eravacycline, colistin and aztreonam-avibactam, *in vitro* studies of antibiotic activity against MBL-producing Enterobacterales, and include reviews of treatments for infections caused by MBL-producing Enterobacterales (Supplementary appendix).

During the virtual meeting, panellists were blinded to the identities of other panellists by assigning numbers to panellists and by prohibiting the use of cameras. All panellists consented to being unblinded to each other upon completion of the consensus-building exercise.

Web-based survey

The survey included questions designed to gather factual information (current epidemiology and practice patterns) and understand panellists' views on future trends, and best practices regarding the management of MBL-producing Enterobacterales infections (Figure 1). Survey questions aiming to evaluate panellists' views on treatment options for MBL-producing Enterobacterales were formulated based on expert guidelines and local epidemiology for the panellists' countries.[8,18]

Survey analysis

All responses were de-identified before sharing. Rating-scale responses were summarized by frequency of each rating, while ranking responses were summarized by presenting the frequency of each rank assigned to each item. In addition, associated free-text responses were reported verbatim. Standard methods were employed in analysing qualitative data.[19]

After the responses were reviewed and summarized, questions for which further discussion would be useful (as determined by the study team) were identified. In addition, the study team developed a set of preliminary consensus statements related to the optimal management of these infections based on the results of the survey.

Consensus meeting

The consensus meeting was led by the physician and Delphi expert moderators whose identities were disclosed to the panellists. The moderators used discretion to ensure that no panellist exerted undue influence on the discussion and used a discussion guide that included an overview of the meeting objectives, a review of the results of the online survey, a discussion of each survey question where consensus was not achieved and a discussion of each preliminary consensus statement regarding the optimal management of infections caused by MBL-producing Enterobacterales. Each preliminary consensus statement presented was voted on and discussed. The set of final consensus statements from this activity is the primary output of this study.

Consensus was defined according to criteria shown in Figure 1.

Presentation of survey results

Consensus discussion

Where consensus was not achieved in the survey, the discussion focused on understanding differences in perspectives among panellists. Each panellist had the opportunity to express their views and was subsequently asked if they wished to alter their initial assessment. If any panellist indicated that they would like to change their assessment, the moderators polled panellists to determine the new assessment. The question was resolved if the poll yielded responses that indicated consensus. Conversely, if the new assessment yielded responses indicating consensus had not been achieved, this was noted, and the moderator determined whether additional discussion was needed to understand the divergence in perceptions among panellists. The process was repeated until all questions for which consensus was not achieved in the initial survey was addressed.

Consensus statements

The moderator then presented each preliminary consensus statement and asked the panellists to indicate their level of agreement. Regardless of whether consensus was achieved at the first reading of each preliminary consensus statement, panellists were asked to provide the reason for their agreement or disagreement with the statement. If consensus was not achieved, the moderators had the ability to revise the statement at their discretion. On revision, panellists indicated their agreement or disagreement with the revised statement. If the statement was not revised after the discussion, the moderators then asked if any panellist would like to change their response to the consensus statement and, if so, the change was recorded. If consensus was not reached, the process was repeated at the discretion of the moderators. The results of the consensus discussion were noted, summarized and synthesized.

Results

The Delphi panel comprised 10 physician specialists in infectious diseases ($n=7$), intensive care ($n=2$), and clinical microbiology ($n=1$). All panellists had expertise and experience in the treatment of antibiotic-resistant bacterial infections and included geographic diversity including representation from Brazil, China, Germany, Greece, India, Israel, Italy, Qatar, Spain and the UK. The pre-meeting survey was fielded from 1 to 14 October 2024 and the consensus meeting occurred on 12 November 2024.

Findings from the survey

The following section outlines the points where there was general consensus prior to the Delphi panel meeting, and the questions marked for discussion at the meeting.

Epidemiology

There was consensus that MBL-carrying Gram-negative pathogens are increasingly spreading as a source of antimicrobial resistance in the panellists' countries and hospitals (Table S1, available as Supplementary data at *JAC-AMR* Online). Nine of the ten panellists reported that over the past 5 years, the incidence of carbapenemase-producing Enterobacterales (CPEs) had increased in their countries and hospitals, and one panellist reported no change (Tables S2 and S3). Notably, all agreed that incidence of New Delhi metallo-β-lactamase (NDM) had increased. On average, *Klebsiella pneumoniae* carbapenemase (KPC) and NDM, followed by oxacillinase-48 (OXA-48), comprised the largest proportion of CPEs observed in hospitals, while imipenemase (IMP) and Verona integron-encoded metallo-β-lactamase (VIM) accounted for smaller proportions (Table S4).

Nine panellists agreed/strongly agreed that MBLs are one of the most worrisome mechanisms of resistance to consider when dealing with a multidrug-resistant Gram-negative Enterobacterales infection, although one panellist strongly disagreed (Table S5). In terms of the panellists' respective countries, eight panellists agreed that NDM represented the majority of MBLs in Enterobacterales, with similar results for their hospitals (Table S6). IMP was the least common in seven of the panellists' countries, VIM was the least common for the other three (Table S7), with similar results for the panellists' hospitals (Table S8). There were mixed opinions on the implications of

co-existence of MBLs with other β-lactamases, and this was flagged for further discussion in the virtual meeting (Table S9).

Panellists stated that NDM was seen alone sometimes or most of the time but added that it may also be co-expressed with KPC, VIM, OXA-48-like or with other class A β-lactamases. Eight panellists never saw NDM with IMP (Table S10). In terms of colonization/carrier status, five panellists knew patient status sometimes, two had this information most of the time, and three always knew at the time of deciding on empiric treatment (Table S11).

Disease and treatment

Infections caused by MBL-producing Enterobacterales were recognized by many panellists as being associated with high morbidity, mortality, need for critical care and burden on healthcare systems (Table S12). All panellists agreed that greater knowledge of colonization and reliable testing could help guide earlier and tailored treatment of CPE and MBL-CPE (Table S13).

The panellists agreed that several patient and disease characteristics, including the source and severity of infection, allergies and known colonization with MBLs are at least moderately important when choosing therapy (Table S14). In terms of treatment selection for patients with serious MBL-CPE infections, *in vitro* AST results, reliability of available testing methods and clinical data on the pathogen and likely resistance mechanisms were considered very/extremely important by most panellists (Table S15).

The importance of following guidelines was flagged for further discussion (Table S16). There was general agreement, however, that symptoms of MBL infections overlap with those of other bacterial infections, complicating differentiation solely on clinical presentation (Table S17). Additionally, β-lactams were generally preferable to other antimicrobial classes for treatment of serious infections caused by MBL-CPE. Most experts preferred to prescribe licensed antimicrobials, when available, over a drug without an approved indication (Table S17).

Renal and liver toxicity, tissue penetration and safety were cited as the most important considerations when prescribing an antibiotic for resistant Gram-negative infections. Impact on the microbiome, use as monotherapy, less frequent dosing and inoculum effect generally appeared to be less important factors (Table S18). There was consensus that multidrug resistance due to production of an MBL increases the likelihood of inappropriate initial therapy and the risk of adverse outcomes (Table S19). Nine panellists said they would be extremely likely to choose an MBL-targeting agent for MBL-producing Enterobacterales (with one being somewhat likely; Table S20); this question was selected for discussion at the consensus meeting. Colistin, tigecycline and fosfomycin had the highest availability in the panellists' countries (Table S21). Notably, at the time of the Delphi survey (October 2024), aztreonam-avibactam was only available in one of the panellists' countries (Germany) and the standard of care for MBL- and NDM-producing Enterobacterales after introduction of this agent, as well as current practices, were selected for discussion at the consensus meeting (Tables S22–S28).

Testing

The lack of available, reliable and practical phenotypic antibiotic susceptibility testing (AST) methods may negatively impact clinical decision-making (Table S29). Susceptibility tests for tigecycline were routine in all countries, whereas tests for fosfomycin or colistin/polymyxin B were only routine in six countries (with special request required in some other countries). Susceptibility tests for cefiderocol and ceftazidime-avibactam plus aztreonam almost always required special request or were not available (Table S30). The availability of reliable AST was reported to be the highest for tigecycline, followed by colistin and fosfomycin (Table S31). Reliable testing was less available for cefiderocol and ceftazidime-avibactam plus aztreonam and was generally not available for aztreonam-avibactam at the time of the survey (October 2024). A variety of AST methods were used, including broth microdilution, AST disks and AST gradient strips (Table S32). The time taken for detection of MBLs and culture and sensitivity results for relevant agents varied by panellist from 6 to 12 h to >2 days, and was flagged for discussion during the virtual meeting (Table S33).

Delphi panel: key discussion points of survey responses

The following section outlines those areas where a general consensus was not reached in the online survey and led to discussion in the virtual meeting.

Epidemiology

Expert opinion was mixed on whether co-existence of other β-lactamases (including carbapenemases) alongside MBLs may complicate treatment, with half of the panellists stating very much/extremely and the other half stating not at all/somewhat (Table S9).

Disease

Panellists had a low level of agreement on the importance of various guidelines and sources of evidence in treatment selection for MBL infections, and some panellists indicated that national or local hospital guidelines were not available in their region (Table S16).

Treatment

If an MBL-producing Enterobacterales pathogen was identified, most panellists agreed they would select an MBL-targeted agent, although there was no consensus on agents that target all CPEs or an agent that also covers non-fermenting Gram-negative pathogens (Table S20). Additional discussion around treatment selection is provided in the Supplementary appendix.

Testing

The time taken for MBL detection varied between panellists (Table S33), who highlighted that this is dependent on the sample type and the methods used. Additional discussion of testing techniques across different specimens and local epidemiology is provided in the supplementary appendix.

Delphi panel: key discussion of draft consensus statements

Based on responses to the online survey, seven draft consensus statements were developed by the study team for discussion amongst the panel during the virtual meeting (Table S34).

Table 1. Delphi panel: findings from the consensus meeting

Final consensus statement *Updates made during the meeting are bold and italicized*	Votes for agreement with draft statement			Rationale for updates to statements
	Neither agree nor disagree	Agree	Strongly agree	
Epidemiology				
MBL-producing Gram-negative pathogens are a major source of antimicrobial resistance and infections in most countries. The distribution of carbapenemases is changing, with an increase of NDM as the predominant MBL ***in many regions***. Co-expression of different β-lactamases in MBL-producing Enterobacterales can be observed and may complicate treatment strategy.	1	6	3	Update made based on a comment that NDM may not be the predominant MBL in all countries.
Disease				
Infections caused by MBL-producing Enterobacterales are associated with high morbidity, high mortality, ***potential*** need for critical-level care, significant cost to the healthcare system, and increased length of hospitalization. The symptoms of MBL-producing Enterobacterales infections often overlap with those of other bacterial infections, making it difficult to differentiate based on clinical presentation alone.	—	5[a]	4[a]	Update made based on a comment that not all patients with MBL-producing Enterobacterales infections will require critical-level care.
Treatment				
Important patient factors to consider when choosing a treatment for infections caused by MBL-producing Enterobacterales include the site (or type) of infection, severity of infection, renal function and immune status. Important drug factors to consider ***include drug effectiveness***, safety, toxicity issues (renal and hepatic), pharmacokinetics, tissue penetration, drug class and available clinical data.	—	6	4	Update made based on a comment that the mention of drug effectiveness is required and 'include' should be added to the statement as this is not a comprehensive list of factors.
When pathogens are sensitive, β-lactams are preferred to other antimicrobial classes for the treatment of serious infections caused by MBL-producing Enterobacterales. When MBL-producing Enterobacterales is identified, a targeted MBL treatment is preferable. When available, ***monotherapy*** is preferred to co-administration of multiple medicines, ***and a licensed drug is preferred over one without an approved indication.***	—	5	5	Update made based on a comment that 'licensed drug' should be replaced with 'monotherapy' and a separate sentence on the 'licensed drug' should be drafted.
At present, in hospitals where antibacterials such as aztreonam-avibactam and cefiderocol are not yet available ***in most countries***, the ***preferred treatment option*** for infections caused by MBL-producing Enterobacterales is the co-administration of ceftazidime-avibactam plus aztreonam.	1	8	1	Update made based on a comment that if ceftazidime-avibactam plus aztreonam is not available, then additional treatment options such as colistin and tigecycline should be added. 'Standard of care' should be replaced with 'preferred treatment option'.
When aztreonam-avibactam and cefiderocol are available, the ***preferred*** first-line treatment for infections caused by MBL-producing Enterobacterales will be aztreonam-avibactam.				Further update made based on a comment to highlight that more balance is required in the second statement as there is no 'standard of care' based on current evidence, which resulted in replacement of 'standard of care' with 'preferred'.
Testing				
Multidrug resistance due to the production of MBLs increases the likelihood of inappropriate initial antibiotic regimens, which increases the risk of morbidity and mortality. Knowledge of local epidemiology and patient MBL colonization status, ***alongside other risk factors***, may help guide earlier initiation of appropriate treatment.	1	3	6	Update made based on a comment to add 'alongside other risk factors' to the statement.

Continued

Table 1. *Continued*

Final consensus statement *Updates made during the meeting are bold and italicized*	Votes for agreement with draft statement			Rationale for updates to statements
	Neither agree nor disagree	Agree	Strongly agree	
Rapid tests for resistance mechanisms in conjunction with phenotypic tests are ***important*** in the management of suspected infections caused by MBL-producing Enterobacterales.	—	3[a]	6[a]	Update made based on a comment that 'are needed' may be an issue for countries that lack availability of molecular tests; 'molecular tests' should be replaced with 'rapid tests'.

Updates to achieve consensus at the meeting are in bold and italics.
MBL, metallo-β-lactamase; NDM, New Delphi metallo-β-lactamase.
[a]Audio issues prevented one panellist from voting on two statements.

These included one statement on epidemiology, one on disease, three on treatment/optimal management of infections caused by MBL-producing Enterobacterales, and two on testing. The distribution of votes on each of the draft consensus statements and how they developed during the discussion to the final consensus statements are presented in Table 1.

Discussion

Using the modified Delphi method, this study aimed to gain consensus from a global group of infectious disease specialists on the epidemiology, treatment, testing and optimal management of MBL-producing infections. The study was structured as a preliminary survey (with pre-reading materials provided beforehand to ensure an equal baseline of knowledge) followed by a virtual meeting to discuss the main findings of the survey. Consensus was observed in the survey within key areas questioned, and seven consensus statements were agreed upon during the virtual meeting.

As is to be expected with a study of this type, there was some variation in the level of agreement between panellists from diverse geographic areas on questions surrounding standard of care and testing times, and the study was designed to allow opportunity for discussion and potential alignment in the virtual meeting.

Consistent with recent literature,[4–8] there was strong consensus amongst the panellists on the increasing spread of MBL-carrying Gram-negative pathogens as well as the mechanism of resistance, with all panellists noting increased incidence of NDM. Moreover, there was high agreement on the associations between MBL-producing Enterobacterales infections with high mortality and morbidity, increased length of hospitalization and increased healthcare costs. However, there was less agreement on the association between MBL-producing Enterobacterales and the need for critical-level care; thus, the consensus statement on disease was revised to accommodate this opinion and reach consensus (Table 1). Other updates to the draft consensus statements reflected variability in resources or discrepancy of their use between different countries (Table 1). Notably, the consensus statements on treatment were updated to factor in the importance of expert knowledge of drug effectiveness in treatment decision-making (Table 1). A consensus was reached on the preference for a monotherapy approach over the co-administration of multiple medicines. In addition, the same statement was updated during the discussion to include that the use of a licensed drug is preferable to selection of a drug without an approved indication (Table 1).

The importance of following published guidance and sources of evidence varied between panellists, with several panellists advising that national or local hospital guidelines are unavailable. Of note, consensus was not reached on the importance of following European Society of Clinical Microbiology and Infectious Diseases and Infectious Diseases Society of America guidelines, possibly reflecting regional differences of the panellists, the importance of clinician judgement based on experience, and potentially outdated evidence by the time of their publication. Only three panellists were aware of the MBL colonization status for every patient before they selected empiric treatment, suggesting that for most patients, screening is situation dependent. Panellists also differed on the availability, reliability and ease of performing AST for eravacycline, cefiderocol and ceftazidime-avibactam plus aztreonam. Importantly, however, strong consensus was reached on the likelihood of choosing an agent that targets MBLs in the treatment of MBL-producing Enterobacterales.

Given current guidelines for the treatment of MBL-producing Enterobacterales, and the likelihood of co-expression with additional resistance mechanisms, fluoroquinolones and aztreonam alone were not considered as viable treatment options in the pre-meeting survey and the subsequent panel discussion. As already mentioned, there was strong agreement by the panellists that when pathogens are sensitive, β-lactams are preferable to other classes of antimicrobials for the treatment of serious infections caused by MBL-producing Enterobacterales, and this recommendation was included in the consensus statements on treatment and endorsed by all panellists.

For the current study, the panellists considered literature available up to the time of the online meeting (November 2024) when making their recommendations. Of note, the GAME CHANGER study of cefiderocol versus standard of care for hospital-acquired

and healthcare-associated bacterial blood infection was published more recently.[20] Overall, this study showed that cefiderocol was non-inferior to standard of care for the primary endpoint of all-cause mortality 14 days after randomization. Results were similar for cefiderocol to standard of care in patients with isolates shown to be carbapenem resistant, although patients receiving cefiderocol fared less well when they had confirmed MBL-producing Enterobacterales isolates (5 of 16 patients [31%] receiving cefiderocol and 0 of 11 patients [0%] receiving standard of care had died at 14 days). These findings are consistent with the panellists' experience (see Supplementary Appendix) and do not change the conclusions made.

The findings of this study are supported by the strengths of the Delphi methodology. Firstly, the international panel of experts, as well as the level of clinical experience of the panel, suggests that the findings are of global significance, especially where availability of resources differs by country. The modified Delphi process used in this study is widely accepted, and using this approach minimizes bias in gathering insights from experts. This was achieved principally through anonymization of panel participants, which was upheld throughout the study. Moreover, where qualitative data were reported, data analysis followed standard analytical methods guided by principles of researcher neutrality and systematic processes.[19,21]

Limitations

Although there was broad geographic representation, the study involved a small sample of 10 panellists, which may limit the generalizability of the findings. Furthermore, not all panellists ultimately voted in the polling for each of the seven consensus statements due to audio issues. Despite this, consensus could still be achieved from those who did vote, according to the definition of consensus applied throughout the study, and the final statements were endorsed by all panellists. In addition, this Delphi study was based on information available up to the end of 2024. Nevertheless, all authors continue to endorse its findings.

Conclusion

The Delphi panel attained consensus across seven statements encompassing epidemiology, disease, testing and treatment of MBL-producing Enterobacterales. The panellists confirmed that when MBL-producing Enterobacterales is identified, a targeted MBL treatment is preferred and, when available, a monotherapy is preferable to co-administration of multiple medicines.

An experienced international panel of experts supports the use of targeted MBL monotherapy as a means of addressing the urgent global health challenge of managing patients with infections caused by multidrug-resistant bacteria.

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Declaration of generative AI in scientific writing

Pfizer's generative artificial intelligence-assisted technology, MAIA (Medical Artificial Intelligence Assistant, was used in the production of this manuscript to write the initial draft. After using this tool, the authors reviewed and edited the content as needed, and take full responsibility for the content of the publication.

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Supplementary data

Tables S1 to S34 are available as Supplementary data at *JAC-AMR* Online.

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