Infective endocarditis by carbapenem-resistant Gram-negative bacteria – a systematic review

Konstantinos Pitsikakis[1,#], *Michail Skandalakis*[2,#], *Konstantinos Fragkiadakis*[3], *Stella Baliou*[4], *Petros Ioannou*[5,*]

Abstract

Introduction **Infective endocarditis (IE) is a disease that may frequently lead to significant morbidity and is associated with high mortality rates. Even though IE is classically caused by Gram-positive bacteria, Gram-negative bacteria may seldom cause IE. Antimicrobial resistance (AMR) may pose significant problems in treating IE, especially for carbapenem-resistant pathogens. This study aimed to review all cases of IE by carbapenem-resistant Gram-negative bacteria in a systematic way and present information on epidemiology, clinical findings, treatment, and outcomes.**

Methods **A systematic review of PubMed, Cochrane Library, and Scopus (all published studies up to 6 August 2023) for published studies providing information on epidemiology, clinical findings, treatment, and outcomes of IE by carbapenem-resistant Gram-negative bacteria was performed.**

Results **A total of 24 studies containing data from 26 patients were included. Among all patients, 53.9% were male, and the median age was 66 years. Among all patients, 38.5% had a history of a prosthetic valve. The most commonly affected valve was the aortic, followed by the mitral valve. Fever, sepsis, emboli, and shock were the most frequent clinical findings. The most commonly isolated pathogens were *Pseudomonas aeruginosa, Klebsiella pneumoniae,* and *Acinetobacter baumannii*. Aminoglycosides, colistin, cephalosporins, and carbapenems were the most commonly used antimicrobials. Surgery was performed in 53.8% of patients. Mortality was 38.5%.**

Conclusions **The development of infection control measures and antimicrobial stewardship interventions is needed to reduce the spread of AMR and the likelihood of this fatal infection.**

Keywords **Infective endocarditis, carbapenem-resistant, multidrug resistant, extensively-drug resistant, *Pseudomonas, Klebsiella*.**

Introduction

Infective endocarditis (IE) is an infection of the endocardium, most commonly on the cardiac valves or a cardiovascular implantable electronic device (CIED) such as a pacemaker or an implantable cardiac defibrillator, and is associated with high mortality and morbidity rates.[1,2] In a relatively recent study, the hospital mortality for patients hospitalized with IE was 17%.[3] In another study, the 30-day and the one-year mortality in patients with IE were 14% and 30% respectively.[4] Even though Gram-positive bacteria, such as staphylococci, streptococci, and enterococci, are the most commonly isolated microorganisms in IE, adding up to 75% of isolated microorganisms, cases of Gram-negative microorganisms are occasionally reported.[5,6]

Antimicrobial resistance (AMR) is an emerging global threat, causing millions of deaths each year.[7] For example, about five million deaths were associated with AMR in 2019. Most of these deaths are associated with Gram-negative bacteria, such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae*.[7] Carbapenems had been traditionally considered important antimicrobials in the fight

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[1]School of Medicine, University of Crete, 71003 Heraklion, Greece; [2]School of Medicine, University of Crete, 71003 Heraklion, Greece; [3]MD, MSc, School of Medicine, University of Crete, 71003 Heraklion, Greece; [4]BSc, MSc, PhD, School of Medicine, University of Crete, 71003 Heraklion, Greece; [5]MD, MSc, PhD, School of Medicine, University of Crete, 71003 Heraklion, Greece.

*Corresponding author: Petros Ioannou, p.ioannou@uoc.gr
[#]These authors had equal contributions

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against bacteria with AMR. However, the development of carbapenem resistance is an emerging problem that significantly limits the therapeutic options in these patients. Carbapenem resistance can be associated with increased mortality rates.[8,9] More specifically, some pathogens, such as *A. baumannii*, can have multiple mechanisms of AMR that may make the pathogen resistant to most or even all antimicrobials.[10]

This study aimed to review all cases of IE by carbapenem-resistant Gram-negative bacteria in a systematic way and describe the epidemiology, clinical findings, treatment, and outcomes.

Methods

Data search

For the conduction of the present systematic review, we followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines, as they are more appropriate for systematic reviews assessing epidemiological studies.[11] PubMed, Cochrane Library and Scopus, were searched to identify eligible studies by using the text words: '(carbapenem OR meropenem OR imipenem OR ertapenem OR doripenem OR biapenem OR tebipenem OR panipenem) AND resist* AND endocarditis'. All studies published until 6 August 2023 were included in further analysis if eligible.

Study selection

The following criteria were required for inclusion of a study in the analysis: 1) Article published in English language; 2) Reporting information on microbiology, clinical characteristics, treatment, and outcomes. Exclusion criteria were the following: 1) Secondary research papers (such as reviews), editorials and any article not providing original information on the subject; 2) Studies not referring to humans; 3) Studies not published in the English language, 4) Studies not referring to IE by carbapenem-resistant Gram-negative bacteria. Two investigators (KP, MS) used Rayyan[12] to independently review the titles and abstracts of the articles that resulted from the systematic literature search and then retrieved and rescreened the full-text publications of potentially relevant articles. Any conflicts were solved with consensus. The included studies were searched for relevant articles in their references. For articles where a full-text was not available, attempts were made to communicate with the study authors to provide the full text.

Outcomes of interest

The primary outcomes of the current study were to record data on: a) the gender and age of patients with IE by carbapenem-resistant Gram-negative bacteria and b) the patients' outcomes. Secondary outcomes were to record data on a) the infected valve, b) the clinical characteristics of the patients, c) antimicrobial resistance to other antimicrobials, and d) the treatment that was administered.

Data extraction and definitions

In general, the present study follows the standard methodology that has been used by our study group for the study of IE in different settings.[13] The data were extracted from each eligible study by two investigators (MS, KP). Extracted data included the type of the study, the year the study was published, and the country where research was conducted; information on patient's demographics (gender and age); the medical history of the patients (such as previous cardiac valve replacement or cardiac surgery, time after cardiac valve replacement); data on microbiology and the infection (such as the infected valve, information regarding pathogen identification, and presence of any complications); the definitive treatment that was administered for the infection; whether patients underwent surgery along with antimicrobials, and the outcomes (such as mortality). Data on the microbiology of infection and the association of infection with mortality was recorded according to the studies' authors. The diagnosis of IE was also confirmed by the current study's investigators based on the data given by each study's authors and the modified ISCVID-Dukes' criteria if the diagnosis of IE was at least possible (presence of at least one major and one minor criterion or presence of at least three minor criteria) or if pathology established a diagnosis of

IE.[14] The complications that were recorded included any clinical deterioration or organ dysfunction that was considered by each study's authors to be associated with the IE. The quality of evidence of included studies' outcomes was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE).[15]

Statistical analysis

Data are presented as number (%) for categorical variables and median (interquartile range, IQR) or mean (± standard deviation, SD) for continuous variables. Categorical data were analyzed using Fisher's exact test. Continuous variables were compared using the Mann-Whitney U-test for non-normally distributed variables or the t-test for normally distributed variables. The above statistics were calculated with GraphPad Prism 6.0 (GraphPad Software, Inc., San Diego, CA, USA).

Results

Literature search

A total of 1,096 articles from PubMed, Cochrane Library, and Scopus were evaluated through the initial screening process. After reviewing the titles and abstracts, 36 articles were selected for review of the full text. From these studies, 18 were excluded from the review: eight articles could not be found, six articles were duplicates, and four were not associated with carbapenem-resistant Gram-negative bacteria. Additionally, six were included after a search of the references of the previously mentioned studies. Finally, 24 met the inclusion criteria of the present study.[16-39] Figure 1 shows a graphical representation of the study inclusion procedure.

Included studies' characteristics

The 24 studies that were eventually included in this analysis involved 26 patients. Supplementary Table 1 summarizes the characteristics of the studies included. Among them, 12 were conducted in Asia, 7 in Europe, 4 in North and South America, and 1 in Oceania. There were 21 case reports; thus, the overall quality of the evidence that contributed to this systematic review was rated as very low.[15]

Characteristics of IE by carbapenem-resistant Gram-negative bacteria

The age of patients with IE by carbapenem-resistant Gram-negative bacteria ranged from 18 to 83 years, the median age was 66 years, and 53.8% (14 out of 26 patients) were male. A history of a prosthetic cardiac valve was present in 38.5% (10 patients). Table 1 shows the epidemiology of patients with IE by carbapenem-resistant Gram-negative bacteria in detail.

Blood cultures were positive in all cases of IE by carbapenem-resistant Gram-negative bacteria. Infection was polymicrobial in one case (3.8%), and the concomitantly isolated pathogen was *Staphylococcus epidermidis*. The most commonly isolated species were *Pseudomonas aeruginosa* in 38.5% (10 patients), *Klebsiella pneumoniae* in 23.1% (6 patients), and *Acinetobacter baumannii* in 15.4% (4 patients). Most strains were resistant to quinolones, aminoglycosides, and tetracyclines. Detailed information on microbiology and AMR can be seen in Table 1.

Fever was the most common clinical symptom and was present in 80.8% (21 patients), while 64.7% (11 patients) had sepsis, and 20% (five out of 25 patients) had shock. Embolic phenomena occurred in 28% (7 out of 25 patients), heart failure developed in 16% (4 out of 25 patients), a paravalvular abscess occurred in 16% (4 patients), while immunological phenomena were noted in 8% (2 patients). Detailed information on diagnosis and clinical presentation of IE by carbapenem-resistant Gram-negative bacteria can be seen in Table 2.

Treatment and outcomes of IE by carbapenem-resistant Gram-negative bacteria

The detailed treatment provided for the IE by carbapenem-resistant Gram-negative bacteria can be seen in Supplementary Table 1 and is also summarized in Table 2. Surgical management along with antimicrobial therapy was performed in 53.8% (14 out of 26 patients). Overall all-cause mortality was 38.5% (10 out of 26 patients) and was attributed directly to IE in 30.8% (8 patients).

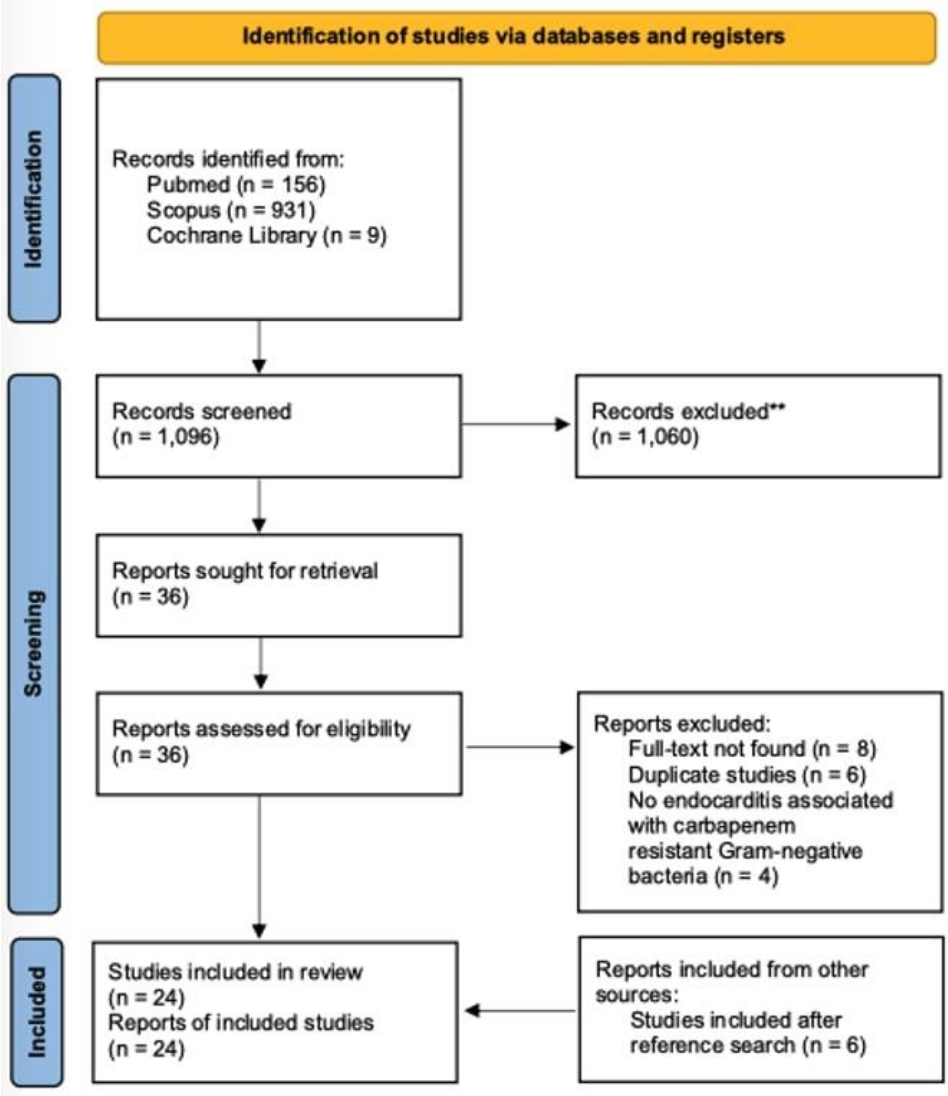

Figure 1. Flow diagram of study inclusion

Table 1. Epidemiology and microbiology of infective endocarditis by carbapenem-resistant Gram-negative bacteria in total and concerning mortality

Characteristic	All patients (n=26)*	Survived (n=16)	Died (n=10)	P value
Male, n (%)	14 (53.8)	9 (56.3)	5 (50)	1.000
Age, median (IQR) in years	66 (49.8-73.3)	62 (42.3-67.8)	67 (54-79)	0.177
Predisposing factors				
Prosthetic valve, n (%)	10 (38.5)	6 (37.5)	4 (40)	1.000
CVC, n (%)	6 (23.1)	2 (12.5)	4 (40)	0.163
Immunosuppression, n (%)	5 (19.2)	2 (12.5)	3 (30)	0.340
Previously on antimicrobials, n (%)	5/24 (20.8)	2/14 (14.3)	3 (30)	0.615
ESRD on dialysis, n (%)	4 (15.4)	0 (0)	4 (40)	0.014
CIED, n (%)	3 (11.5)	2 (12.5)	1 (10)	1.000
Previous IE, n (%)	2 (7.7)	2 (12.5)	0 (0)	0.508
Post-cardiac surgery, n (%)	2/24 (8.3)	0/15 (0)	2/9 (22.2)	0.130
Known colonization by carbapenem-resistant pathogen, n (%)	1 (3.8)	1 (6.3)	0 (0)	1.000
Rheumatic fever, n (%)	0 (0)	0 (0)	0 (0)	NA
Congenital heart disease, n (%)	0 (0)	0 (0)	0 (0)	NA
Bad teeth hygiene or recent dental work, n (%)	0 (0)	0 (0)	0 (0)	NA
Microbiology				
Polymicrobial, n (%)	1 (3.8)	1 (6.3)	0 (0)	1.000
Pseudomonas spp., n (%)	10 (38.5)	8 (50)	2 (20)	0.218
Klebsiella spp., n (%)	7 (26.9)	5 (31.5)	2 (20)	0.668
Acinetobacter spp., n (%)	5 (19.2)	2 (12.5)	3 (30)	0.340
Stenotrophomonas spp., n (%)	2 (7.7)	1 (6.3)	1 (10)	1.000
Achromobacter spp., n (%)	1 (3.8)	0 (0)	1 (10)	0.385
Chryseobacterium spp., n (%)	1 (3.8)	0 (0)	1 (10)	0.385
Antimicrobial resistance				
Quinolone, n (%)	15/24 (62.5)	9/14 (64.3)	6 (60)	1.000
Aminoglycoside, n (%)	13/24 (54.1)	6/15 (40)	7/9 (77.8)	0.105
Tetracyclines, n (%)	6/15 (40)	4/8 (50)	2/7 (28.6)	0.608
TMP-SMX, n (%)	4/12 (33.3)	2/7 (28.6)	2/5 (40)	1.000
Colistin, n (%)	4/20 (20)	3/13 (23.1)	1/7 (14.3)	1.000
Chloramphenicol, n (%)	0/9 (0)	0/5 (0)	0/4 (0)	1.000

CIED – cardiovascular implantable electronic device; **CVC** – central venous catheter; **ESRD** – end-stage renal disease; **IQR** – interquartile range; **NA** – not applicable; **TMP-SMX** – trimethoprim-sulfamethoxazole.
*Data are out of the number of patients stated on top unless otherwise stated.

Table 2. Clinical characteristics, diagnosis, treatment and outcomes of patients with infective endocarditis by carbapenem-resistant Gram-negative bacteria in total and concerning mortality

Characteristic	All patients (n=26)*	Survived (n=16)	Died (n=10)	P value
Method of diagnosis				
Transthoracic echocardiography, n (%)	11/25 (44)	8/15 (53.3)	3 (30)	0.414
Transesophageal echocardiography, n (%)	11/25 (44)	5/15 (33.3)	6 (60)	0.241
Autopsy, n (%)	3/25 (12)	NA	3 (30)	NA
Valve localization				
Aortic valve, n (%)	15 (57.7)	8 (50)	7 (70)	0.428
Mitral valve, n (%)	8 (30.8)	5 (31.3)	3 (30)	1.000
Tricuspid valve, n (%)	3 (11.5)	3 (18.8)	0 (0)	0.262
Pulmonary valve, n (%)	0 (0)	0 (0)	0 (0)	NA
Multiple valves, n (%)	2 (7.7)	1 (6.3)	1 (10)	1.000
Clinical characteristics				
Fever, n (%)	21 (80.8)	14 (87.5)	7 (70)	0.340
Sepsis, n (%)	11/17 (80.7)	6/11 (54.5)	5/6 (83.3)	0.333
Embolic phenomena, n (%)	7/25 (28)	2/15 (13.3)	5 (50)	0.075
Shock, n (%)	5/25 (20)	1/15 (6.7)	4 (40)	0.121
Paravalvular abscess, n (%)	4/25 (16)	1/15 (6.7)	3 (30)	0.267
Heart failure, n (%)	4/25 (16)	1/15 (6.7)	3 (30)	0.267
Immunologic phenomena, n (%)	2/25 (8)	1/15 (6.7)	1 (10)	1.000
Treatment				
Duration of treatment in weeks, median (IQR)	7.7 (6-10)	7.7 (6-10)	NA	
Aminoglycoside, n (%)	12/24 (50)	9/15 (60)	3/9 (33.3)	0.400
Colistin, n (%)	10/24 (41.7)	7/15 (46.7)	4/9 (44.4)	1.000
Cephalosporin, n (%)	7/24 (29.2)	7/15 (46.7)	0/9 (0)	0.022
Carbapenem, n (%)	6/24 (25)	2/15 (13.3)	4/9 (44.4)	0.150
Quinolone, n (%)	6/24 (25)	2/15 (13.3)	4/9 (44.4)	0.150
Tetracycline, n (%)	5/24 (20.8)	2/15 (13.3)	3/9 (33.3)	0.326
TMP-SMX, n (%)	4/24 (16.7)	1/15 (6.7)	3/9 (33.3)	0.130
Rifampicin, n (%)	4/24 (16.7)	2/15 (13.3)	2/9 (22.2)	0.615
Antipseudomonal penicillin, n (%)	3/24 (12.5)	1/15 (6.7)	2/9 (22.2)	0.533
Sulbactam, n (%)	2/24 (8.3)	1/15 (6.7)	1/9 (11.1)	1.000
Aztreonam, n (%)	1/24 (4.2)	1/15 (6.7)	0/9 (0)	1.000
Fosfomycin, n (%)	2/24 (8.3)	2/15 (13.3)	0/9 (0)	0.511
Surgical management, n (%)	14 (53.8)	11 (68.8)	3 (30)	0.105
Outcomes				
Deaths due to infection, n (%)	8 (30.8)	NA	NA	
Deaths overall, n (%)	10 (38.5)	NA	NA	

IQR – interquartile range; **NA** – not applicable; **PCR** – polymerase chain reaction; **TMP-SMX** – trimethoprim-sulfamethoxazole.

*Data are out of the number of patients stated on top unless otherwise stated.

Statistical analysis of IE by carbapenem-resistant Gram-negative bacteria

A statistical comparison of patients with IE by carbapenem-resistant Gram-negative who survived with those who died revealed that those who died were more likely to have a history of end-stage renal disease on dialysis and were less likely to have received treatment with cephalosporins for the episode of IE. The results of the statistical comparison can be seen in Table 1 and Table 2.

Discussion

This study described the characteristics of the patients who developed IE by carbapenem-resistant Gram-negative bacteria. The most commonly infected valve was the aortic one. The most frequent clinical findings included fever and sepsis. Aminoglycosides and colistin were the most commonly used antimicrobials, while 38.5% of patients died.

Antimicrobial resistance is emerging as a major public health issue, with significant effects on human health, due to considerable morbidity and mortality.[40] The most common and important pathogens associated with AMR are the ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species). More specifically, carbapenems had been previously considered potent antibiotics for treating infections by Gram-negative microorganisms with AMR. However, the emergence of carbapenem resistance has significantly reduced the available options for treating these highly resistant pathogens.[41-43]

IE by Gram-negative bacteria is a rare condition since, in most cases, IE is caused by Gram-positive bacteria; however, in the case of IE by bacteria that do not belong to the HACEK group (*Haemophilus species*, *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*), mortality can be high.[44-47] This is particularly important in the case of Gram-negative bacteria harboring important AMR mechanisms, as is the case of *A. baumannii* and *Klebsiella* spp.[48,49] The current study is the first that addresses the issue of IE by carbapenem-resistant pathogens.

The median age of patients with IE by carbapenem-resistant Gram-negative bacteria herein was 66 years, which is relatively higher than the age at diagnosis of patients with IE by non-HACEK Gram-negative bacilli in the literature, which ranges from 40 to 63 years.[45,50,51] A male predominance was noted in the present review, as was the case in patients with IE by non-HACEK Gram-negative bacilli.[45,50,51] A history of a prosthetic valve was noted in 38.5% of patients with IE by carbapenem-resistant Gram-negative bacteria. That rate is close to the one reported in studies of IE by non-HACEK Gram-negative bacilli, which was within the range of 30% to 59%.[45,50,51] A CIED was present in 11.5% in the current review, while, in other studies with patients suffering from IE by non-HACEK Gram-negative bacilli, the rate was as high as 29%.[45,50,51] A CVC was present in 23.1% of patients with IE by carbapenem-resistant Gram-negative bacteria, a rate close to that noted in other reports with IE by non-HACEK Gram-negative bacilli, where it ranged from 17% to 20%.[45,50] Recent antimicrobial use was noted in the medical history of 20.8% of patients with IE by carbapenem-resistant Gram-negative bacteria, while, in another study with data on patients suffering from IE by non-HACEK Gram-negative bacilli, the rate was 40%.[51] A previous episode of IE was noted in the medical history of 7.7% in the present review. In other studies providing data on patients with IE by non-HACEK Gram-negative bacilli, that rate varied widely from 0 to 67%.[45,50,51]

The most commonly infected valve was the aortic one, at 57.7%, and the mitral valve, at 30.8%. These rates were different in two other reports of IE by non-HACEK Gram-negative bacilli, with the mitral valve being the most common valve infected in 31%, followed by the aortic one in 24% in the first study,[45] and the aortic valve being the most commonly infected in 42%, followed by the tricuspid valve in 33% in the second report.[50]

As for clinical presentation, fever was the most commonly encountered symptom noted in 80.8% of patients, while 64.7% were septic. In other studies with IE by non-HACEK Gram-negative bacilli, fever was reported in 92%.[45,50] Heart failure was reported in 16% of patients with IE by carbapenem-resistant Gram-negative bacteria, which is within the range of the rate seen in cases of non-HACEK Gram-negative IE which is from 8% to 37%.[45,50] Embolic phenomena in IE by carbapenem-resistant Gram-negative bacteria were noted in 28%, which is close to the rate in non-HACEK Gram-negative bacilli IE which is from 17% to 65%.[45,50,51] Immunological phenomena in the present review

were noted in 8%, a rate lower than the one noted in IE by non-HACEK Gram-negative bacilli, which is from 25% to 27%.[45,50,51] Diagnosis of a paravalvular abscess was performed in 16% of patients with IE by carbapenem-resistant Gram-negative bacteria. This was lower than the rate noted in patients suffering from IE by non-HACEK Gram-negative bacilli, which was within the range of 25% to 42%.[45,50]

The most frequently isolated species in the present study were *Pseudomonas*, *Acinetobacter*, and *Klebsiella*. This is no surprise since these three pathogens are well-known to harbor significant mechanisms of AMR, and, more specifically, many clinical isolates of all these three pathogens have been described to have carbapenem resistance.[52-55] Other species were identified herein, such as *Chryseobacterium* or *Achromobacter*. However, these pathogens may be overrepresented herein since cases of IE by *Pseudomonas*, *Acinetobacter*, and *Klebsiella* may have been underreported relative to the more rarely isolated isolates of *Chryseobacterium* and *Achromobacter* in patients with IE.

Importantly, most carbapenem-resistant pathogens in the current study were sensitive to antimicrobials such as trimethoprim-sulfamethoxazole, tetracyclines as well as colistin. Thus, even though carbapenem may not be a viable option in infections by these pathogens, there are still some other options that could be used for treating these infections. However, not all antimicrobials may be useful for every infection. For example, tigecycline may not be an adequate option for treating IE since it may not achieve adequate levels in the blood.[56] Another important consideration is that some of the included studies date back to 2000, thus, the AMR data presented in the present review may not represent the current situation. AMR rates for the abovementioned antibiotics may be even higher. For the same reason, many antimicrobials presented herein may discord with the currently published guidelines on the treatment of carbapenem-resistant pathogen infections.[43] For example, some antibiotics such as cefiderocol, imipenem/cilastatin/relebactam, or meropenem/vaborbactam have been accepted for human use recently, later than the time some of the studies presented herein had been published.[9,57]

Based on the previously mentioned data on AMR, it is no surprise that aminoglycosides, colistin, and some beta-lactams, such as cephalosporins or carbapenems, were used for treating IE by carbapenem-resistant bacteria. The use of beta-lactams may sound controversial, given that a carbapenem-resistant pathogen would be expected to be resistant to all these antibiotics. However, most of these antibiotics were given in combination. Antimicrobial combinations are well known to have synergy in many cases of co-administration. For example, tigecycline, colistin, and ampicillin/sulbactam (due to the lack of sulbactam as a single drug in the market), or tigecycline, colistin, and meropenem are well-known combinations used for the treatment of XDR *A. baumannii*.[10,58] On the other hand, antimicrobial combinations such as meropenem with colistin have also been extensively used in the era of carbapenem-resistant Gram-negative bacteria before the development of imipenem/cilastatin/relebactam, and meropenem/vaborbactam. However, the evidence regarding the efficacy and the safety of this antimicrobial combination is still controversial.[59,60]

Mortality was high, with two out of five patients dying, and most of them succumbing due to the IE by carbapenem-resistant Gram-negative bacteria. This mortality rate was higher than the one in studies including data on patients suffering from IE by non-HACEK Gram-negative bacilli, where the mortality rate was within the range of 0% to 24%.[45,50,51] However, the one-year mortality in these studies was up to 30%, implying that IE by non-HACEK Gram-negative bacilli is a lethal disease.[50,51] This further highlights the need to implement adequate infection control measures and antimicrobial stewardship interventions to reduce the spread of AMR and reduce the likelihood of lethal infections, including IE, by these highly resistant bacteria.[61]

This systematic review has some limitations that should be noted. First, it primarily includes information derived from case reports. Thus, the

results presented herein should be read cautiously since the quality of evidence overall was very low. Additionally, the number of included patients is very low to derive safe conclusions. This is associated with the specific and narrow aim of this systematic review that limits the pool of included cases. Consequently, the results could have been significantly affected by publication bias. Thus, further studies are warranted to allow safe results to be drawn.

Conclusions

To conclude, this study presents the epidemiological, clinical, and microbiological characteristics of patients with IE by carbapenem-resistant Gram-negative bacteria, as well as their treatment and outcomes. Most infections were caused by *Pseudomonas*, *Klebsiella*, and *Acinetobacter* species. Even though AMR was high to many antibiotics, there were still some available options for treatment; however, pharmacokinetic and pharmacodynamic issues may reduce the available options for treatment. Mortality was high; thus, the development of infection control measures and antimicrobial stewardship interventions is needed to reduce the spread of AMR and the likelihood of fatal infection.

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Supplementary Table 1. Characteristics of the included studies

Study	Number of patients	Age (years)	Gender	Site of infection n (%)	Microbiology of infection, n (%)	Treatment administered, n (%)	Infection outcomes, n (%)
Aydin et al.,[16] 2000	1	40	Male	AoV	*Stenotrophomonas maltophilia*	Antipseudomonal penicillin TMP-SMX	Clinical cure[a] Deaths overall
Olut et al.,[17] 2005	1	45	Female	AoV	*Acinetobacter baumannii*	Quinolone Aminoglycoside	Clinical cure Deaths overall Deaths due to IE
Bomb et al.,[18] 2007	1	58	Male	AoV	*Chryseobacterium meningosepticum*	Antipseudomonal penicillin Quinolone Rifampicin	Clinical cure Deaths overall Deaths due to IE
Benenson et al.,[19] 2009	1	18	Male	MV	*Klebsiella pneumoniae*	Colistin Aminoglycoside	Clinical cure Deaths overall
Ahmadi et al.,[20] 2009	1	66	Male	AoV MV	*Acinetobacter lwoffii*	NR Surgical management	Clinical cure Deaths overall
Katayama et al.,[21] 2010	1	78	Female	MV	*Stenotrophomonas maltophilia*	Antipseudomonal penicillin Quinolone Tetracycline TMP-SMX Surgical management	Clinical cure Deaths overall Deaths due to IE
Raymond et al.,[22] 2014	1	77	Female	AoV	*Klebsiella pneumoniae*	Aminoglycoside Tetracycline	Clinical cure Deaths overall Deaths due to IE
Naha et al.,[23] 2014	1	22	Female	MV	*Pseudomonas aeruginosa*	Colistin Surgical management	Clinical cure Deaths overall
Vergara-Lopez et al.,[24] 2014	1	68	Male	AoV	*Klebsiella oxytoca*	Fosfomycin Aminoglycoside	Clinical cure Deaths overall
Durante-Mangoni et al.,[25] 2014	3	55, 82, 83	2 male, 1 female	IED 1 (33.3) AoV 2 (66.7)	*Acinetobacter baumannii* 1 (33.3) *Pseudomonas aeruginosa* 2 (66.7)	Carbapenem 3 (100) Colistin 3 (100) Aminoglycoside 1 (33.3) Rifampicin 1 (33.3) TMP-SMX 1 (33.3) Surgical management 2 (66.7)	Clinical cure 1 (33.3) Deaths overall 3 (100) Deaths due to IE 2 (66.7)
Chaari et al.,[26] 2015	1	67	Male	AoV	*Klebsiella pneumoniae*	Colistin	Clinical cure Deaths overall
Patel et al.,[27] 2015	1	51	Male	MV	*Acinetobacter baumannii*	NA	Clinical cure Deaths overall Deaths due to IE

Study	Number of patients	Age (years)	Gender	Site of infection n (%)	Microbiology of infection, n (%)	Treatment administered, n (%)	Infection outcomes, n (%)
Chen et al.,[28] 2015	1	56	Female	TrV	*Acinetobacter baumannii*	Sulbactam Cephalosporin Surgical management	Clinical cure Deaths overall
Domitrovic et al.,[29] 2016	1	58	Female	AoV	*Pseudomonas aeruginosa*	Carbapenem Colistin Aminoglycoside Rifampicin Tetracycline Surgical management	Clinical cure Deaths overall
Kantarcioglu et al.,[30] 2016	1	50	Female	TrV	*Klebsiella pneumoniae*	Tetracycline Surgical management	Clinical cure Deaths overall
Xia et al.,[31] 2018	1	66	Female	AoV MV	*Achromobacter xylosoxidans*	Quinolone TMP-SMX	Clinical cure Deaths overall Deaths due to IE
Gürtler et al.,[32] 2019	1	66	Male	AoV	*Pseudomonas aeruginosa*	Cephalosporin Quinolone Aminoglycoside Surgical management	Clinical cure Deaths overall
Prescott et al.,[33] 2019	1	66	Male	MV	*Pseudomonas aeruginosa*	Cephalosporin Colistin Fosfomycin Surgical management	Clinical cure Deaths overall
Peghin et al.,[34] 2019	1	49	Male	IED	*Pseudomonas aeruginosa*	Cephalosporin Aminoglycoside Surgical management	Clinical cure Deaths overall
Edgeworth et al.,[35] 2019	1	78	Female	AoV	*Pseudomonas aeruginosa*	Cephalosporin Aminoglycoside Carbapenem Colistin Surgical management	Clinical cure Deaths overall
Dvoretsky et al.,[36] 2021	1	68	Male	AoV	*Klebsiella pneumoniae*	Sulbactam Carbapenem Aminoglycoside Tetracycline	Clinical cure Deaths overall Deaths due to IE
Alghoribi et al.,[37] 2021	1	40	Female	TrV	*Klebsiella pneumoniae*	Cephalosporin Aztreonam	Clinical cure Deaths overall
Lima et al.,[38] 2022	1	72	Male	AoV	*Pseudomonas aeruginosa*	Cephalosporin Aminoglycoside Surgical management	Clinical cure Deaths overall
Walczak et al.,[39] 2023	1	80	Female	MV	*Pseudomonas aeruginosa*	Colistin Quinolone Aminoglycoside Rifampicin Surgical management	Clinical cure Deaths overall

[a]Defined as clinical resolution of the infection as a result of treatment.

AoV – aortic valve; **IE** – infective endocarditis; **IED** – implantable electronic device; **MV** – mitral valve; **NA** – not applicable; **TMP-SMX** – trimethoprim-sulfamethoxazole; **TrV** – tricuspid valve.