Systematic review of carbapenem resistant gram-negative infective endocarditis, treatment options and outcomes

ABSTRACT

Background: Gram negative infective endocarditis is rare and usually associated with intravenous drug use or significant healthcare exposure and prosthetic cardiac valves or devices. Carbapenem resistance is a growing concern worldwide with limited drug options for these infections especially serious high inoculum infections such as endocarditis.

Methods:A systematic review examining treatment options and outcomes was conducted with identification of 12 cases in the literature.

Results:*Pseudomonas aeruginosa* was the most common organism with left sided valvular involvement being most common. 18 different antibiotic regimens were used with surgery occurring in 5 cases (42%). In hospital mortality was 33% which increased at 6 months post episode. Increased age (p= 0.056) and CCI (p=0.006) appeared to be associated with death. Microbiological cure was more common in patients who received combination therapy with 2 active agents (75% successful) and combination therapy including an active beta-lactam agent (100% successful) but these did not meet statistical significance.

Conclusions: Recommendations for management of this rare condition based on this systematic review and other available evidence are summarised in this review. Management should generally involve multidisciplinary teams, combination therapy with at least 2 active agents including a beta-lactam agent where possible with consideration of surgery in all cases. Evidence is however limited with need for ongoing publication of cases and further research to guide therapy in the future.

Keywords: Carbapenem resistant gram negative, Infective Endocarditis, Treatment, Outcome

Word count: 4,311 words, excluding references.

1. INTRODUCTION

Infective endocarditis (IE) is an infection of intracardiac structures, most commonly the heart valves.(1) It is a universally fatal infection without treatment and is considered to be among the top four most life-threatening infections.(2) Diagnosis can be made using the modified Duke criteria, with a combination of clinical, microbiological, and imaging criteria.(3) A combination of positive blood cultures, clinical features, and changes on echocardiography can be used to make a diagnosis.(1) Recommended treatment regimens for native and prosthetic valve infections caused by specific organisms have been devised and recommended by European and American Societies.(2, 4) It is also now the best practice for patients to be managed by a multidisciplinary infective endocarditis team including infectious disease physicians, cardiologists, and cardiothoracic surgeons.(5)

Non – HACEK Gram negative infective endocarditis accounts for approximately 1.8% of all IE cases of infective endocarditis. The most common organisms involved were *Escherichia coli and Pseudomonas aeruginosa* followed by *Klebsiella* spp..(6) Originally thought to be a disease of intravenous drug users (IVDU), these infections are now more commonly seen in those with healthcare contact, cardiac devices, and immunosuppression. Patients have high rates of complications, with a mortality rate of approximately 24%, despite high rates of surgery (51%) in one series.(7)

For non-HACEK gram-negative infective, the American Heart Association recommends treatment with a beta-lactam combined with aminoglycoside or fluoroquinolone, in addition to surgery.(2) This is based on a limited number of cases, and no recommendations are given for treatment when carbapenem or multidrug resistance is present. Carbapenem resistance among gram-negative bacteria is increasing worldwide and is considered by the World Health Organization to be “one of the three greatest threats to human health.”(8) These organism are difficult to treat with limited antibiotic options and have a higher associated mortality.

Resistance most commonly occurs due to the production of a carbapenemase that can hydrolyze the antibiotic or impaired permeability due to porin mutations with or without additional resistance mechanisms.(9) There are different classes of carbapenemases, with the most important belonging to classes A, B, and D based on the Ambler molecular classification system. Examples include Klebsiella pneumoniae carbapenemase (KPC – class A), New Delhi metallo-beta-lactamase (NDM-1 class B), and OXA-type enzymes (class D). Combination therapies are often employed for carbapenem-resistant infections; however, there is still uncertainty regarding whether this is superior to monotherapy.(8) Even less is known about the ideal treatment for deep-seated high-inoculum infections, such as infective endocarditis.

A 5 patient case series of infective endocarditis due to multidrug-resistant gram-negative bacilli was reported by Durante-Mangoni et al. in 2014.(10) It suggested that multidrug-resistant (MDR) gram-negative bacteria are an emerging cause of IE in patients with prosthetic cardiac material and frequent healthcare contact. It reported a mortality rate of 80%, and failure to sterilize blood cultures was common despite the removal of infected cardiac material.

Treatment options are limited and rely on in vitro susceptibility testing and the mechanisms of resistance. The use of polymyxin antibiotics, such as colistin, is often necessary despite this class falling out of favor in the past owing to toxicity and poor efficacy.(11) Newer antimicrobial agents that are active against carbapenemase-producing bacteria have now been developed, including new beta-lactams and beta-lactam–beta-lactamase inhibitor combinations such cefiderocol, ceftazidime-avibactam, and ceftolozane-tazobactam.(12, 13) There is limited experience of the use of these agents in the treatment of endocarditis.

Rationale

There is little literature on this rare and highly fatal disease, and given the growing rates of antimicrobial resistance and patient comorbidities, it is likely to be seen with an increasing frequency in the future. This review aims to synthesize and analyze treatment options and outcomes to guide the clinical management of this disease.

Objectives

1. Comparison of antibiotic, surgical, and experimental treatments with regard to patient outcomes in carbapenem-resistant gram-negative infective endocarditis
2. Summarise the current literature pertaining to carbapenem resistant gram-negative infective endocarditis
3. Provide recommendations for the treatment of carbapenem-resistant gram-negative infective endocarditis based on current evidence

2. METHODS

Protocol and registration

A systematic review of all cases of carbapenem-resistant gram-negative infective endocarditis caused by *Escherichia coli, Klebsiella pneumoniae or Pseudomonas aeruginosa* was performed. The study

was conducted and reported in accordance with the PRISMA statement(14) for transparent reporting of systematic reviews and meta-analyses, and registered with PROSPERO prior to commencement (CRD42019134153).

Eligibility criteria

All study types included humans with infective endocarditis caused by *E.coli, K.pneumoniae or P.aeruginosa*. Patients had to meet the Modified Dukes Criteria for Infective Endocarditis with organisms isolated in blood culture or valve tissue by culture or molecular-based methods. Studies must report on treatment, including antibiotics, surgery or experimental treatments, and patient outcomes. Only studies published in English were included in this meta-analysis. Studies must have been published within the last 15 years, given the improvements in supportive care that are likely to influence patient outcomes and low rates of carbapenem resistance among these organisms prior to this period.

Information sources

Studies were identified via online databases EMBASE and Medline with searches performed using the Ovid search engine and Scopus and Cochrane databases. References of the selected studies were also reviewed for relevant studies not found in the primary database search. Studies were retrieved electronically through the London School of Hygiene and Tropical Medicine (LSHTM) library. Articles that were not available online were obtained via the LSHTM library or local university/hospital library services.

Search

The following search strategy was used to identify studies:

"endocarditis AND (enterobacteriaceae OR gram negative OR escherichia coli OR klebsiella pneumoniae OR pseudomonas aeruginosa) AND (multidrug-resistant OR drug-resistant OR carbapenemase OR carbapenem)"

Limit of 15 years (2004-2019) and English were applied.

Study Selection

Two independent reviewers reviewed the results obtained from the search strategy were reviewed by 2 independent reviewers. Articles were first screened by title and then by abstract. The full versions were then retrieved and reviewed by each reviewer for the appropriateness of the final inclusion.

Data collection process

Following the selection of studies, data were extracted into a pre-specified form by two reviewers and compared to ensure agreement of results.

Data items

Study details, such as study design, number of cases, interventions, and outcome measures, were collected.

Patient details collected included demographics (age and sex), comorbidities, Charlson Comorbidity Index (CCI), risk factors for endocarditis, organism and resistance profile, valve involvement, and

interventions including antibiotics, surgery, and experimental treatments. Case outcomes, including outcome definitions by study and unit of measurement, were collected.

Outcomes that were originally considered by priority included:

1. Mortality
2. Clinical cure
3. Microbiological failure (MF)
4. Microbiological success (MS)
5. Adverse events
6. Recurrence

**As defined by the paper*

Risk of bias in individual studies

The risk of bias in each study was assessed by two reviewers using the ROBINS-I tool(15) for non-randomized studies of intervention or the CARE guidelines(16) for reporting of case reports depending on study type. Other specific considerations included information about susceptibility testing and identification of carbapenem resistance mechanisms, doses and durations of antibiotics used, and details of the surgical intervention performed.

Summary measures

Data were collected in a categorical format and continuous data as presented in the study and described in the data collection above.

Synthesis of results

Studies are summarized in table with the number of cases extracted, interventions assessed, and outcomes measured. Individual case data will be summarized in a table format, including demographics, valve involvement, interventions, and outcomes. Age, sex, CCI, risk factors for acquisition, organism, valve involvement, and acquisition were summarized with mean, median, and range calculated for continuous variables, with percentages calculated for categorical variables.

Risk of bias across studies

Publication bias was a significant limitation of this study. Cases with favorable outcomes are expected to be more likely to be reported in the literature. The overall mortality in this systematic review was expected to be over 24%, given that this was reported in the International Collaboration on Infective Endocarditis Prospective Cohort Study (ICE-PCS) for non-HACEK gram-negative infective endocarditis.(6)

Additional analyses

Additional analysis was performed to examine the associations between mortality and demographic or treatment factors. The comparison groups were death in hospital or alive to determine if there was a difference in age, CCI, surgical intervention, or antibiotic treatment regimen. The comparison groups of microbiological success and microbiological failure were also assessed for different antibiotic

treatment regimens. Microbiological success was defined as the study description of clearance of blood cultures and clinical cure following the cessation of antibiotics.

The R studio statistical package was used to compare the groups. Welch's 2 sample t-test of independent samples, unequal variance, and sample size were used as means for continuous variables. Fisher's exact test was used for categorical variables, using a 2 × 2 contingency table.

The quality of evidence and strength of the recommendations of this review will be determined using the GRADE format.(17)

3. RESULTS

Study selection

A total of 306 results were obtained during the initial search. 38 were selected based on title, study type, human research, and after removing duplicates. Following a review of the abstracts, 29 were left. Following a review of the full papers, 11 studies were selected for final inclusion based on the pre-specified criteria as above. Figure 1 shows a PRISMA flow diagram.

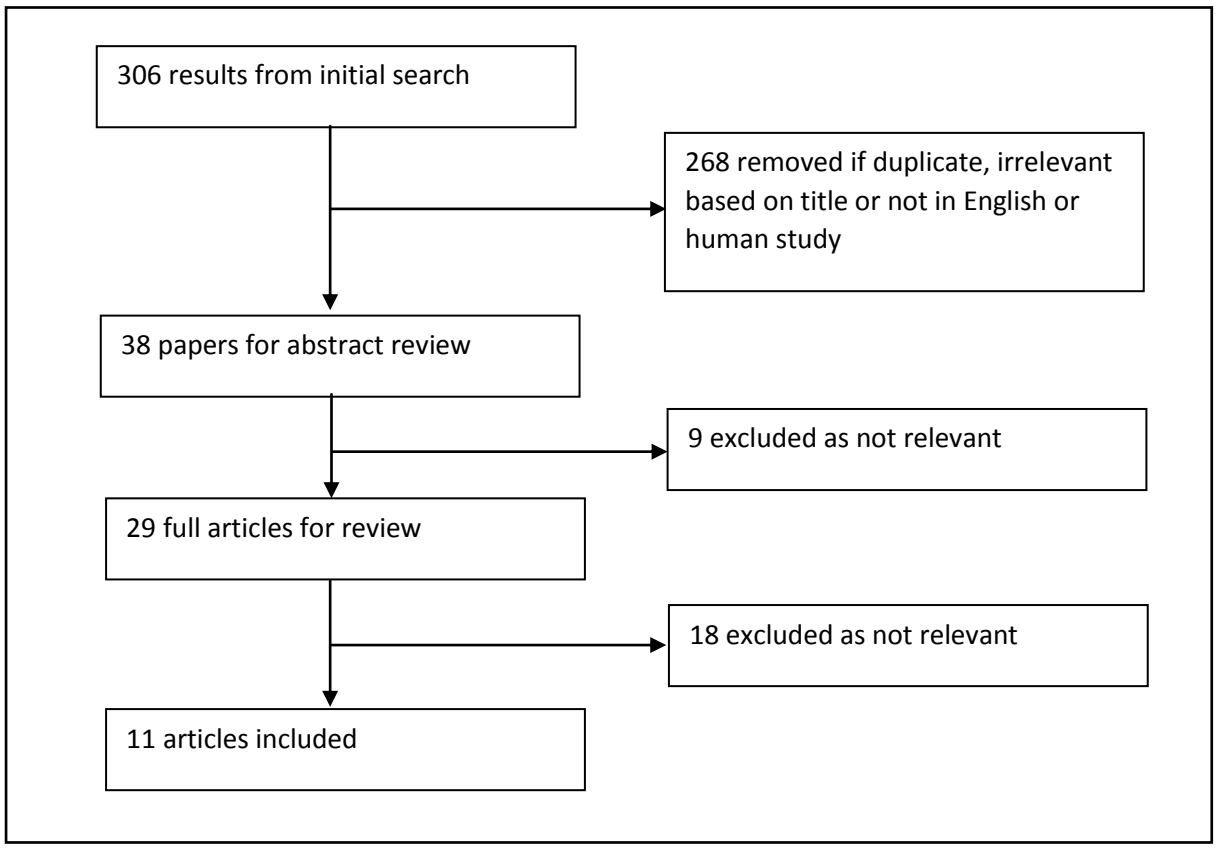

Figure 1: PRISMA flow diagram

Study characteristics

Study characteristics are summarized in Table 1, with notes on the year of publication, number of cases reported, and interventions addressed. All studies were case reports or case series, with the publication years ranging from 2009 to 2019. All the studies discussed antibiotic treatment. No previous studies have discussed experimental treatments other than antibiotics.

Table 1: study characteristics and risk of bias

Reference	Year	Study type	No of cases	Intervention	Risk of bias
Benenson et al.(18)	2009	Case report	1	AB	Low
Durante-Mangoni et al.(10)	2014	Case series	2	AB Surgery	Low
Naha et al.(19)	2014	Case series	1	AB Surgery	Low
Raymond et al.(20)	2014	Case report	1	AB	Low
Chaari et al.(21)	2015	Case report	1	AB	Low
Kim et al.(22)	2015	Case report	1	AB Surgery	Medium
Domitrovic et al.(23)	2016	Case report	1	AB Surgery	Low
Iacovelli et al.(24)	2018	Case report	1	AB	Low
Edgewroth et al.(25)	2019	Case report	1	AB Surgery	Low
Martin-Cazana et al.(26)	2019	Case report	1	AB Surgery	Low
Alegro et al.(27)	2019	Case report	1	AB	Low

AB - antibiotics

Risk of bias in individual studies

The risk of bias for each study is summarized in Table 1. The overall reporting of cases was good, with sufficient data necessary for review using adequate methodology as per the CARE guidelines for reporting case reports. Reporting of susceptibility and minimum inhibitory concentration (MIC) testing was good overall; however, different methods have been used in different studies. Most studies have identified the mechanisms underlying resistance. Kim et al.(29) were considered to have a higher risk of bias compared to the other studies, primarily because they did not include susceptibility profiles of the organism and only the antibiotics used without doses. Thus, it was inferred that the antibiotics used were susceptible.

Results of individual studies

The results and summary of cases and interventions are shown in Table 2. Twelve patients were identified with more than one episode of infective endocarditis. Age ranged from 5 to 83 years, with *P.aeruginosa* and *K.pneumoniae* cases identified, and no cases of *E.coli* infective endocarditis were identified. The resistance mechanism was identified in eight cases, including six carbapenemase-producing organisms and two pseudomonal isolates with porin channel mutations. *K.pneumoniae* carbapenemases include the KPC and NDM-1 genes and enzymes. *P.aeruginosa* isolates possessed Verona integron metallo-beta-lactamase (VIM).

Table 2: Summary of cases

Case	Demographics	Organism*	Valve	AB regimens	Surgery	Follow - up
1	18 M	*K.pneumoniae* KPC	MV	COL/GEN[a] – 6wk	No	12mo alive
2	83 M	*P.aeruginosa* VIM	AVR	COL/MER/CTX	No	MF Death in hospital
3	55 M	*P.aeruginosa* VIM	AV	COL/MER	AV replacement + splenectomy	MF Death in hospital
4	22 F	*P.aeruginosa*	AV	COL - 4 wk.	AV replacement + splenectomy	12 mo. alive
5	77 F	*K.pneumoniae* CPO	AVR	COL/TIG	No	MF Death in hospital
6	67 M	*K.pneumoniae* NDM-1	AV	COL/TIG – 7 wk.	No	Alive at 10 wk. Resolution on TOE
7	37 F	*P.aeruginosa*	TVR	1. COL/CIP – 6wk 2a COL – 6wk pre TVR (MF) 2b COL – 6wk post TVR (MF) 2c COL/CIP/RIF – 6wk post redo TVR	1. TVR mechanical 2. TVR with bioprosthetic then redo TVR with aortic homograft	10mo between episodes Alive 12mo after episode 2
8	58 F	*P.aeruginosa* OprD	AVR	1. COL/MER/OTHER[b] – 8wk	AVR with homograft	MS Survived hospital
9	49 M	*K.pneumoniae* KPC	RA	1a COL/MER/OTHER[c] (MF) 1b CAZ-AVI/ERT - >6wk	No	Died 6mo after dc - no signs of infection reported
10	78 F	*P.aeruginosa* OprD	AV	1a COL/GEN (MF) 1b COL/CFD – 3wk post AVR	AVR	Alive 9mo
11	5M	*P.aeruginosa*	TV	1a TOB/MER (MF) 1b TOL-TAZ/TOB – 6wk	No	Alive at 6mo
12	51M	*K.pneumoniae*	AV	1a CAZ-AVI/AMK – 2wk 1b CAZ-AVI/IMI – 4 wk.	No	MS Died in hospital

MV – mitral valve, AV – aortic valve, AVR – aortic valve replacement, TV – tricuspid valve, TVR – tricuspid valve replacement, RA – right atrium, COL – colistin, GEN – gentamicin, MER – meropenem, CTX – cotrimoxazole, TIG – tigecycline, CIP – ciprofloxacin, RIF – rifampicin, CAZ-AVI – ceftazidime-avibactam, ERT – ertapenem, CFD – cefiderocol, TOB – tobramycin, TOL-TAZ – ceftolozane-tazobactam, AMK – amikacin, IMI – imipenem, dc – discharge, TOE – transoesophageal echocardiogram

** resistance mechanism if known, a – GEN ceased after 3 weeks, b – 3rd drug used was amikacin then doxycycline, c – 3rd drug used was fosfomycin or tigecycline*

Valve involvement was variable, and included both native and prosthetic valves. Four cases involved the use of prosthetic valves. Eighteen different antibiotic regimens were identified in all the 12 cases. Earlier studies primarily used colistin-based regimens in combination with other agents including aminoglycosides, carbapenems, and tigecycline. Later studies often used novel beta-lactam agents in combination with other agents, usually aminoglycosides or high-dose carbapenems. Novel beta-lactam agents, including the beta-lactam beta-lactamase combination agents ceftazidime-avibactam and ceftolozane-tazobactam, as well as cefiderocol. Surgery occurred in 5 cases with variable details of the procedure performed. Outcome descriptions and follow-up details were limited; thus, we decided to focus on the outcomes of death in hospital and microbiological success/failure with regard to different antibiotic treatment regimens. Case 7 described recurrence after completion of therapy with 6 weeks of colistin and ciprofloxacin in addition to mechanical tricuspid valve replacement. Recurrence occurred 10months later with Pseudomonas aeruginosa infection and involvement of mechanical tricuspid valve replacement. Surgery was again required, with two repeat surgeries with tricuspid valve replacement with aortic homograft followed by 6 weeks of combination therapy with colistin, rifampicin, and ciprofloxacin.

Synthesis of results

A summary of demographics, infection type, interventions, and outcomes is presented in Table 3. The median age was 50 years, and males were more common than females. Previous cardiac surgery with a prosthetic valve was a risk factor in a minority of cases (33%). Left sided heart involvement was most common (83%), with healthcare-associated and nosocomial-associated infections being more common than community infections (25% and 67%, respectively).

Surgical intervention was performed in 5 cases. Eighteen different antibiotic regimens were used, including 3 monotherapy regimens. Eight combination therapies with one active drug, including one with an active beta-lactam, were used. Seven combination regimens were used with two active drugs, including three active beta-lactam agents. Microbiological success occurred in 10 of 18 regimens (56%), and death in the hospital occurred in 4 of 12 cases (33%).

Table 3: Demographics and clinical characteristics

Demographics	N or median (range)	% or mean
Age	53(5-83)	50
Female	5	42%
CCI	1.5 (0 – 7)	2.6
Previous cardiac surgery	4	33%
Organism		
P.aeruginosa	7	58%
K.pneumoniae	5	42%
Heart involvement		
Left	10	83%
Right	2	17%
Source		
Community	1	8%
HCA	3	25%
Nosocomial	8	67%

HCA – healthcare associated

Risk of bias across studies

Publication bias remains a significant risk factor influencing the results and any associations and observations. A mortality of over 24% was expected based on prior evidence, with a mortality rate of 33% in hospitals in this study.

Additional analysis

The association between death and the risk factors of age and CCI is shown in Table 4 and was calculated using an independent t-test with unequal variance. The association between death and treatment is also shown in Table 4, and was considered based on the final antibiotic regimen used using Fisher's exact test. Age and CCI were significantly higher in the hospital death group (p = 0.006), with an average CCI of 1.25 in those who survived and 5.5 in those who died. Given the small sample size, no significant association was found between interventions and death.

Table 4: Risk factors and treatment compared to mortality

	Death in hospital N (%) or mean	Alive N (%) or mean	P value
Age	66.5	41.75	0.056*
CCI	5.5	1.25	0.006*
Surgery N =5	1 (20)	4 (80)	0.576^
Monotherapy N= 1	0 (0)	1 (100)	1^
Any combination therapy N= 11	4 (36)	7 (64)	1^
Combination therapy with 2 active drugs N = 5	1 (20)	4 (80)	0.576^
Beta-lactam therapy with activity N = 4	1 (25)	3 (75)	1^

** Welch's 2 sample t-test, ^Fishers exact test*

The association between microbiological success and treatment is shown in Table 5, and was analyzed based on the 18 completed antibiotic regimens used for individual episodes of infective endocarditis using Fisher's exact test.Microbiological failure occurred in more than half of the patients who received monotherapy or combination therapy with only one active drug. Combination therapy with 2 active drugs or an active beta-lactam agent had higher rates of microbiological success, although the p-values did not reach statistical significance in this analysis.

Table 5: Antibiotic regimens and treatment failure

Treatment	MF N (%)	MS N (%)	P value[#]
Monotherapy N = 3	2 (67)	1 (33)	0.559
Combination therapy with 1 active drugs N = 8	5 (63)	3 (37)	1
Combination therapy with 2 active drugs N = 7	1 (14)	6 (86)	0.066
Beta-lactam therapy with activity N = 4	0 (0)	4 (100)	0.091

Fishers exact test

4. DISCUSSION

This study found that carbapenem-resistant gram-negative infective endocarditis is a rare disease, with only 12 cases reported in the literature. *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*are the most common causes of carbapenem resistance owing to carbapenemase or porin mutations. Prosthetic heart valves are a risk factor for the development of infection, but are not necessary for the development of infection based on the findings of this study, with most patients having native valves. Left-sided valve involvement was also more common, as was healthcare and nosocomial acquired infections. Increased age and Charlson comorbidity index appear to be associated with increased mortality.

Surgical intervention is common and may be required to assist in source control and microbiological cure. Various antibiotic regimens have been used, with combination therapies being the most common.The antibiotics used depend on in vitro susceptibility testing and the mechanisms of resistance. Microbiological failure occurred in most patients who received monotherapy or combination therapy with only one active drug. Combination therapy with two active drugs or a beta-lactam agent resulted in higher rates of microbiological success; however, this difference was not statistically significant. This is in line with the recommendations of the American Heart Association for the treatment of gram-negative endocarditis. Death occurred in 33% of the reported cases, and actual death rates are likely much higher given the publication bias, likely resulting in increased publishing of cases with better outcomes. This is above the expected level based on mortality from the Infected endocarditis prospective collaborative project.

Consideration of organism MIC to specific antibiotics and therapeutic drug monitoring and drug dosing should be considered given the high rates of mortality, relapse, and development of resistance. Monotherapy with continuous infusion has been demonstrated to be superior to intermittent dosing in animal models.(28) Target beta-lactam antibiotic levels should be individualized to patients aiming to achieve concentrations above the organism MIC for as much as the dosing interval as possible with targets of 100% of the dosing interval and 100% at four times the MIC suggested by some experts.(29)

New beta-lactam beta-lactamase inhibitor combinations ceftolozane-tazobactam and ceftazidime-avibactam, as well as the new siderophore cephalosporin cefiderocol, were successfully used in cases identified in this review. Ceftolozane-tazobactam is a fixed-dose combination of a cephalosporin and a beta-lactamase inhibitor.(30) It is stable against many beta-lactamase enzymes and overcomes carbapenem resistance in the setting of porin and efflux pump mutations, and is an option for carbapenem-resistant Pseudomonas infections such as case 11 in this series.(31) It is

hydrolyzed by carbapenemase enzymes and, thus, is not useful for the treatment of isolates possessing these enzymes. Ceftazidime-avibactam, another new fixed-dose combination, can inhibit most class A and D carbapenemase enzymes and was successfully used in two cases in this series, including K. pneumoniae possessing a KPC enzyme.(12) Ceftazidime-avibactam and other similar combinations were not active against class B metallo-β-lactamases. Cefiderocol was used in case 10 in this review because of its ability to enter bacterial cells via iron channels via its siderophore-like property with stability against most beta-lactamase enzymes, including metallo-beta-lactamases.(13, 32)

With increasing antibiotic resistance and the lack of new antibiotics, alternative treatments are being investigated. Bacteriophage and phage therapies involving bacterial viruses are of growing interest.(33)Its use in humans is primarily experimental and documented in rare case reports. In vitro and animal models have demonstrated their potential utility. An animal and in vitro model of *Pseudomonas aeruginosa* endocarditis by Oechslin et al.(34) demonstrated similar killing by a cocktail of Pseudomonas bacteriophages to ciprofloxacin monotherapy, with synergy seen when used in combination.

Limitations

As previously discussed, publication bias was the most significant limitation of this study. A total of 12 cases have been found in the literature, and given the small numbers and observational nature of the case reports, the quality of evidence behind recommendations is low according to the GRADE quality of evidence.

Conclusions

Carbapenem-resistant gram-negative infective endocarditis remains a rare disease with high mortality and is difficult to treat. It is most commonly caused by *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* with native left-sided heart valve involvement. It is frequently associated with healthcare exposure, and mortality is higher in patients with advanced age and increasing comorbidities. Antibiotic therapy must be guided by in vitro antibiotic susceptibility testing along with routine combination therapy. Novel beta-lactam agents are currently available and may improve the outcomes of this disease. The quality of evidence to guide treatment is low based on the GRADE quality of evidence. The recommendations for the treatment of carbapenem-resistant gram-negative infective endocarditis based on this review and the current literature are as follows:

1. All patients were managed by a multidisciplinary team involving infectious disease specialists, clinical microbiology, cardiology, and cardiothoracic surgery.
2. Combination therapy with at least two active agents should be administered for a minimum of 6 weeks, including a beta-lactam agent, if possible.
3. Surgical intervention for source control should be considered in patients expected to experience microbiological therapy failure.
4. Continuous or prolonged infusions and therapeutic drug monitoring should be considered if available

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AUTHORS CONTRIBUTIONS

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