Systematic Review

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

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 considered to be amongst the top 4 most life-threatening infections.(2)Diagnosis can be made using the modified Duke criteriawith a combination of clinical, microbiological and imaging criteria.(3) Most commonly a combination of positive blood cultures, clinical features and changes on echocardiogram can be used to make the diagnosis.(1) Recommended treatment regimens for native and prosthetic valve infections caused by specific organisms have been devised and recommended by the European and American Societies.(2, 4)It is also now best practice for patients to be managed by a multidisciplinary infective endocarditis team including infectious diseases physicians, cardiologists and cardiothoracic surgeons.(5)

Non – HACEK Gram negative infective endocarditis accounts for approximately 1.8% of all cases of infective endocarditis. The most common organisms involved are *Escherichia coli and Pseudomonas aeruginosa*followed by *Klebsiella* species.(6)Originally thought 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 and mortalityis around 24% despite high rates of surgery (51%) in one series.(7)

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

Resistance most commonly occurs due to production of a carbapenemase that is able to hydrolyse 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 class A, B and D based on 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 about whether this is superior to monotherapy.(8) Even less is known about the ideal treatment of 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 negatives are an emerging cause of IE in patients with prosthetic cardiac material and frequent healthcare contact. It reported a mortality of 80% and that failure to sterilize blood cultures was common despite removal of infected cardiac material.

Treatment options are limited and rely on in-vitro susceptibility testing and the mechanism of resistance present. Use of polymyxin antibiotics such as colistin is often necessary despite this class falling out of favour in the past due 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 growing rates of antimicrobial resistance and patient comorbidities it is likely to be seen with increasing frequency in the future. This review aims to synthesize and analyse treatment options and outcomes to guide clinical management of this disease.

Objectives

1. Compare antibiotic, surgical and experimentaltreatments with regards to patient outcomes for carbapenem resistant gram-negative infective endocarditis
2. Summarise the current literature pertaining to carbapenem resistant gram-negative infective endocarditis
3. Provide recommendations on 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 gramnegative 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).

Need for ethics approval was waved by the London School of Hygiene Ethics committee given the nature of the study.

Eligibility criteria

All study types were included involving humans with infective endocarditis caused by *E.coli, K.pneumoniae or P.aeruginosa*. Cases had to meet Modified Dukes Criteria for Infective Endocarditis with organism 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 outcome. Only studies available in English and published were included. Studies must have been published within the last 15 years given improvements in supportive care that are likely to influence patient outcomes and low rates of carbapenem resistance amongst these organisms prior to this period.

Information sources

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

Results obtained from search strategy were reviewed by 2 independent reviewers. Articles were first screened by title and then abstract. Full versions were then retrieved and reviewed by each reviewer for appropriateness for final inclusion.

Data collection process

Following selection of studies data was extracted into a pre-specified form by 2 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.

Case details collected including demographics (age, sex), comorbidities, Charlson Comorbidity Index (CCI), risk factors for endocarditis, organism and resistance profile, valve involvement and intervention including antibiotics, surgery and experimental treatments. Case outcomes were collected including outcome definitions by the study and unit of measurement.

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

Risk of bias in each study was assessed by 2 reviewers using the ROBINS-I tool(15) for non-randomised studies of intervention or the CARE guidelines(16) for reporting of Case reports depending on study type.Other specific considerations considered included information about susceptibility testing and identification of carbapenem resistance mechanisms, doses and durations of antibiotics used and details of surgical intervention performed.

Summary measures

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

Synthesis of results

Studies were to be summarised in table with number of cases extracted, interventions assessed, and outcomes measured. Individual case data will be summarised in table format including demographics, valve involvement, interventions and outcome. Age, gender, CCI, risk factors for acquisition, organism, valve involvement and acquisition were summarised with mean, median and range calculated for continuous variables with percentage calculated for categorical variables.

Risk of bias across studies

Publication bias will be a significant limitation of this review. It was expected that cases with favourable outcomes are more likely to be reported in the literature. Overall mortality in this systematic review was expected to be over 24% given 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 look for associations with mortality and demographic or treatment factors. Comparison groups chosen were death in hospital or alive to determine if there was a difference in age, CCI, surgical intervention or antibiotic treatment regimen. Comparison groups of microbiological success and microbiological failure were also assessed for different antibiotic treatment regimens. Microbiological success was defined as study description of clearance of blood cultures and clinical cure following cessation of antibiotics.

R studio statistical package was used for comparison of groups. Welch's 2 sample t-test of independent samples, unequal variance and sample size was used for means of continuous variables. Fishers exact test was used for categorical variables using 2x2 contingency table.

Quality of evidence and strength of recommendations of this review will be made using the GRADE format.(17)

3. RESULTS

Study selection

306 results were found on initial search. 38 were selected based on title, study type, research in humans and after removing duplicates. Following review of abstracts 29 were left. Following review of full papers 11 studies were selected for final inclusion based on pre-specified criteria as above.See figure 1 for PRISMA flow diagram.

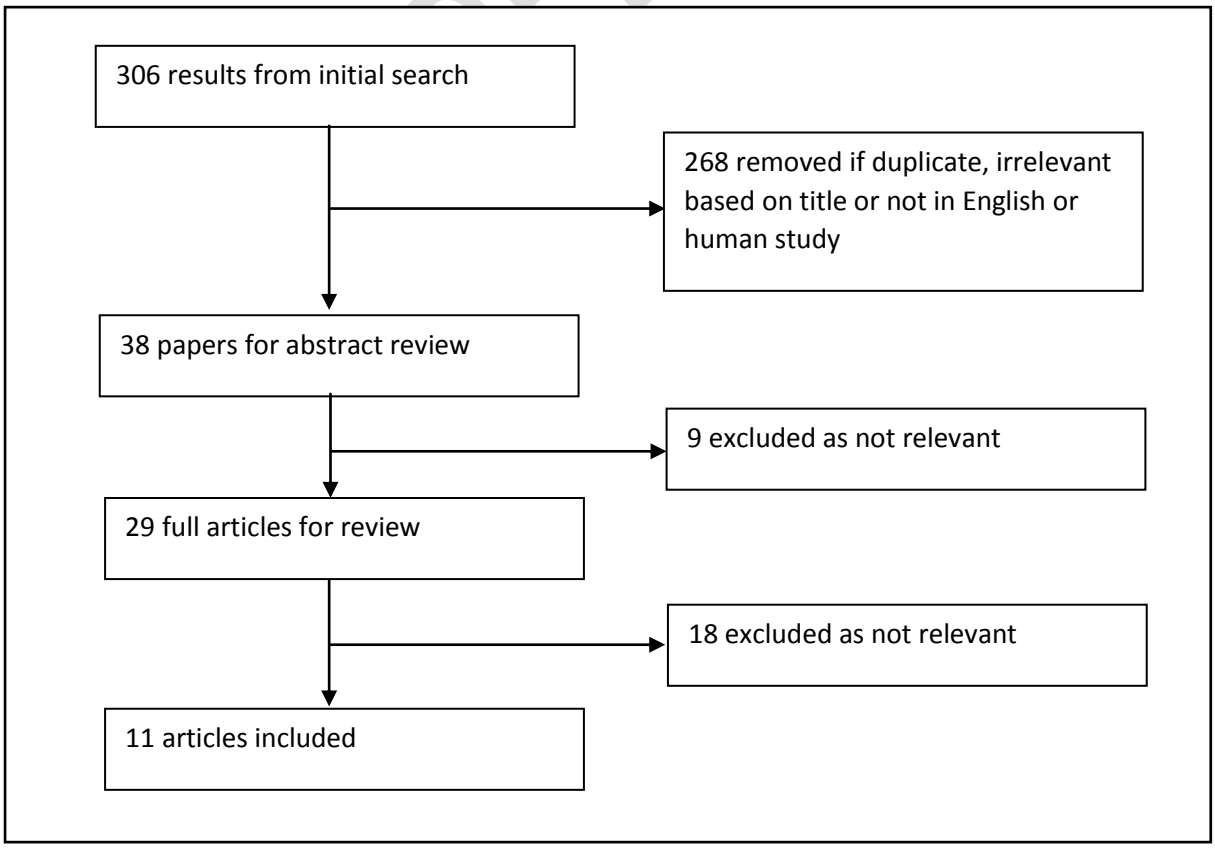

Figure 1: PRISMA flow diagram

Study characteristics

Study characteristics are summarised in table 1 with notes on year of publication, number of cases reported, and interventions addressed. All studies were case reports or case series with the years of publication ranging from 2009 to 2019. All studies discussed antibiotic treatment. No studies 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.(25)	2009	Case report	1	AB	Low
Durante-Mangoni et al.(10)	2014	Case series	2	AB Surgery	Low
Naha et al.(26)	2014	Case series	1	AB Surgery	Low
Raymond et al.(27)	2014	Case report	1	AB	Low
Chaari et al.(28)	2015	Case report	1	AB	Low
Kim et al.(29)	2015	Case report	1	AB Surgery	Medium
Domitrovic et al.(30)	2016	Case report	1	AB Surgery	Low
Iacovelli et al.(31)	2018	Case report	1	AB	Low
Edgewroth et al.(32)	2019	Case report	1	AB Surgery	Low
Martin-Cazana et al.(33)	2019	Case report	1	AB Surgery	Low
Alegro et al.(34)	2019	Case report	1	AB	Low

AB - antibiotics

Risk of bias in individual studies

Risk of bias for each study is summarised in table 1. Overall reporting of cases was good with sufficient data necessary for review with 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 were used by different studies. Most studies identified resistance mechanism. Kim et al.(29) was considered to have a higher risk of bias compared to the other studies primarily as it did not include susceptibility profiles of the organism and only the antibiotics used without doses. It has been inferred from this that the antibiotics used were susceptible.

Results of individual studies

Results and summary of cases and interventions are shown in table 2. 12 cases were identified some with more than one episode of infective endocarditis. Age ranged from 5 to 83 with *P.aeruginosa* and *K.pneumoniae* cases identified, no cases of *E.coli* infective endocarditis were identified. Resistance mechanism was identified in 8 cases which included 6 carbapenemase producing organisms and 2 pseudomonal isolates with porin channel mutations. *K.pneumoniae*carbapenemases included KPC and NDM-1 genes/enzymes. The *P.aeruginosa* isolates possessed Verona integronmetallo-betalactamase (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. 4 cases involved prosthetic valves. 18 different antibiotic regimens were identified across the 12 cases. Earlier studies used primarily Colistin based regimens often in combination with other agents including aminoglycosides, carbapenems and tigecycline. Later studies often used novel beta-lactam agents in combination therapy with other agents – usually aminoglycosides or high dose carbapenems. Novel beta-lactam agents used include the beta-lactam beta-lactamase combination agent ceftazidime-avibactam and ceftolozane-tazobactam as well as cefiderocol. Surgery occurred in 5 cases with variable detail of procedure performed. Outcome descriptions and follow up details were limited and thus it was decided to focus on outcomes of death in hospital and microbiological success/failure with regards to different antibiotic treatment regimens. Case 7 described a recurrence post completion of therapy with 6 weeks of colistin and ciprofloxacin in addition to mechanical tricuspid valve replacement. Recurrence occurred 10months later with pseudomonas aeruginosa and involvement of the mechanical tricuspid valve replacement. Surgery was again required with 2 re-do surgeries the final with a tricuspid valve replacement with aortic homograftfollowed by 6 weeks of combination therapy with colistin, rifampicin and ciprofloxacin.

Synthesis of results

Summary of demographics, infection type, interventions and outcomes are given in table 3.Median age was 50 years and male sex was more common than female. Previous cardiac surgery with prosthetic valve was a risk factor in the minority of cases at 33%. Left sided heart involvement was most common at 83% with healthcare associated and nosocomial associated infections being more common than community making up 25% and 67% respectively.

Surgical intervention occurred in 5 cases. 18 different antibiotic regimens were used including 3 monotherapy regimens. 8 combination therapies with 1 active drug were used including 1 with an active beta-lactam. 7 combination regimens were used with 2 active drugs including 3 with active beta-lactam agents. Microbiological success occurred in 10 out of 18 regimens (56%) and death in 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 for influencing the results and any associations and observations made. A mortality over 24% was expected based on prior evidence with a mortality of 33% in hospital occurring in this study.

Additional analysis

Association between death and risk factors of age and CCI are shown in table 4 and was calculated using independent t-test with unequal variance. Association between death and treatment is also shown in table 4 and was considered based upon final antibiotic regimen used using fisher's exact test.Age and CCI were higher in the death in hospital group with CCI meeting statistical significance with a p value of 0.006 with the average CCI being 1.25 in those that survived and 5.5 in those that died. Given small numbers 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*

Association between microbiological success and treatment is shown in table 5 and was analysed based upon 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 cases receiving monotherapy or combination therapy with only 1 active drug. Combination therapy with 2 active drugs or an active beta-lactam agent had higher rates of microbiological success although with p-values not reaching 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 has found that carbapenem resistant gram-negative infective endocarditis is a rare disease with only 12 cases published in the literature. *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*are the most common cause with carbapenem resistance due tocarbapenemase enzymes or porin mutations. Prosthetic heart valves are a risk factor for development of infection but are not necessary for infection to develop 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 infection. Increased age and Charlson comorbidity index appear to be associated with increased mortality.

Surgical intervention is common and may be required to assist with source control and microbiological cure. Various antibiotic regimens have been used in the past with combination therapies being most common. Antibiotics used depended on in-vitro susceptibility testing and mechanisms of resistance. Microbiological failure occurred in most patients receiving monotherapy or combination therapy with only 1 active drug. Combination therapy with 2 active drugs or with a beta-lactam agent resulted in higher rates of microbiological success however this was not statistically significant. This is in line with recommendations for treatment of gram negative endocarditis by the American Heart Association. Death occurred in 33% of the reported cases, actual death rates are likely much higher given a publication bias likely resulting in increased publishing of cases with better outcomes. This is above the expected level based on the mortality from the Infected endocarditis prospective collaborative project.

Consideration of organism MIC to specific antibiotics and the consideration of 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.(18) Target beta-lactam antibiotic levels should be individualised 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 4 times the MIC suggested by some experts.(19)

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 by this review. Ceftolozane-tazobactam is a fixed dose combination of a cephalosporin and beta-lactamase inhibitor.(20) 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.(21) It is however

hydrolysed by carbapenemase enzymes and thus not useful in the treatment of isolates possessing these enzymes.Ceftazidime-avibactam another new fixed dose combination is able to inhibit most class A and D carbapenemase enzymes and was successfully used in 2 cases in this series including for a K.pneumoniae possessing a KPC enzyme.(12) Ceftazidime-avibactam and other similar combinations are however not active against class B metallo-beta-lactamases.Cefiderocolwas used in case 10 from this review with utility due to its ability to enter bacterial cells via iron channels via its siderophore like property with stability against most beta-lactamase enzymes including metallo-beta-lactamase's.(13, 22)

With growing antibiotic resistance and lack of new antibiotics alternative treatments are being investigated. Bacteriophages or phage therapy involving bacterial viruses are of growing interest.(23)Use in humans is primarily experimental and documented in rare case reports. In-vitro and animal models have demonstrated potential utility. An animal and in-vitro model of *Pseudomonas aeruginosa* experimental endocarditis by Oechslin et al.(24)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 is the biggest limitation to this study.A total of 12 cases have been found in the literature and given these small numbers and the observational nature of the case reports the quality of evidence behind recommendations islow according to GRADE quality of evidence.

Conclusions

Carbapenem resistant gram-negative infective endocarditis remains a rare disease that has a 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 those of advanced age and increasing comorbidities. Antibiotic therapy must be guided by in-vitro susceptibility testing of antibiotics with combination therapy routinely used. Novel beta-lactam agents are now available and may improve outcomes in this disease. The quality of evidence to guide treatment islow based on GRADE quality of evidence. Recommendations for treatment of carbapenem resistant gram negative infective endocarditis based on this review and the current literature are as follows:

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

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