Cochrane Library

Cochrane Database of Systematic Reviews

A comparison of different antibiotic regimens for the treatment of infective endocarditis (Review)

Martí-Carvajal AJ, Dayer M, Conterno LO, Gonzalez Garay AG, Martí-Amarista CE

Martí-Carvajal AJ, Dayer M, Conterno LO, Gonzalez Garay AG, Martí-Amarista CE.
A comparison of different antibiotic regimens for the treatment of infective endocarditis.
Cochrane Database of Systematic Reviews 2020, Issue 5. Art. No.: CD009880.
DOI: 10.1002/14651858.CD009880.pub3.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

A comparison of different antibiotic regimens for the treatment of infective endocarditis

Arturo J Martí-Carvajal[1,2], Mark Dayer[3], Lucieni O Conterno[4], Alejandro G Gonzalez Garay[5], Cristina Elena Martí-Amarista[6]

[1]Facultad de Ciencias de la Salud Eugenio Espejo, Universidad UTE (Cochrane Ecuador), Quito, Ecuador. [2]School of Medicine, Universidad Francisco de Vitoria (Cochrane Madrid), Madrid, Spain. [3]Department of Cardiology, Taunton and Somerset NHS Trust, Taunton, UK. [4]Medical School, Department of Internal Medicine, Infectious Diseases Division, State University of Campinas (UNICAMP), Campinas, Brazil. [5]Methodology Research Unit, Instituto Nacional de Pediatría, Mexico City, Mexico. [6]Department of Family Medicine, Northwell Health Southside Hospital, Bay Shore, New York, USA

Contact address: Arturo J Martí-Carvajal, arturo.marti.carvajal@gmail.com.

Editorial group: Cochrane Heart Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 5, 2020.

Citation: Martí-Carvajal AJ, Dayer M, Conterno LO, Gonzalez Garay AG, Martí-Amarista CE. A comparison of different antibiotic regimens for the treatment of infective endocarditis. *Cochrane Database of Systematic Reviews* 2020, Issue 5. Art. No.: CD009880. DOI: 10.1002/14651858.CD009880.pub3.

ABSTRACT

Background

Infective endocarditis is a microbial infection of the endocardial surface of the heart. Antibiotics are the cornerstone of treatment, but due to the differences in presentation, populations affected, and the wide variety of micro-organisms that can be responsible, their use is not standardised. This is an update of a review previously published in 2016.

Objectives

To assess the existing evidence about the clinical benefits and harms of different antibiotics regimens used to treat people with infective endocarditis.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase Classic and Embase, LILACS, CINAHL, and the Conference Proceedings Citation Index - Science on 6 January 2020. We also searched three trials registers and handsearched the reference lists of included papers. We applied no language restrictions.

Selection criteria

We included randomised controlled trials (RCTs) assessing the effects of antibiotic regimens for treating definitive infective endocarditis diagnosed according to modified Duke's criteria. We considered all-cause mortality, cure rates, and adverse events as the primary outcomes. We excluded people with possible infective endocarditis and pregnant women.

Data collection and analysis

Two review authors independently performed study selection, 'Risk of bias' assessment, and data extraction in duplicate. We constructed 'Summary of findings' tables and used GRADE methodology to assess the quality of the evidence. We described the included studies narratively.

Main results

Six small RCTs involving 1143 allocated/632 analysed participants met the inclusion criteria of this first update. The included trials had a high risk of bias. Three trials were sponsored by drug companies. Due to heterogeneity in outcome definitions and different antibiotics used data could not be pooled.

The included trials compared miscellaneous antibiotic schedules having uncertain effects for all of the prespecified outcomes in this review. Evidence was either low or very low quality due to high risk of bias and very low number of events and small sample size.

The results for all-cause mortality were as follows: one trial compared quinolone (levofloxacin) plus standard treatment (antistaphylococcal penicillin (cloxacillin or dicloxacillin), aminoglycoside (tobramycin or netilmicin), and rifampicin) versus standard treatment alone and reported 8/31 (26%) with levofloxacin plus standard treatment versus 9/39 (23%) with standard treatment alone; risk ratio (RR) 1.12, 95% confidence interval (CI) 0.49 to 2.56. One trial compared fosfomycin plus imipenem 3/4 (75%) versus vancomycin 0/4 (0%) (RR 7.00, 95% CI 0.47 to 103.27), and one trial compared partial oral treatment 7/201 (3.5%) versus conventional intravenous treatment 13/199 (6.53%) (RR 0.53, 95% CI 0.22 to 1.31).

The results for rates of cure with or without surgery were as follows: one trial compared daptomycin versus low-dose gentamicin plus an antistaphylococcal penicillin (nafcillin, oxacillin, or flucloxacillin) or vancomycin and reported 9/28 (32.1%) with daptomycin versus 9/25 (36%) with low-dose gentamicin plus antistaphylococcal penicillin or vancomycin; RR 0.89, 95% CI 0.42 to 1.89. One trial compared glycopeptide (vancomycin or teicoplanin) plus gentamicin with cloxacillin plus gentamicin (13/23 (56%) versus 11/11 (100%); RR 0.59, 95% CI 0.40 to 0.85). One trial compared ceftriaxone plus gentamicin versus ceftriaxone alone (15/34 (44%) versus 21/33 (64%); RR 0.69, 95% CI 0.44 to 1.10), and one trial compared fosfomycin plus imipenem versus vancomycin (1/4 (25%) versus 2/4 (50%); RR 0.50, 95% CI 0.07 to 3.55).

The included trials reported adverse events, the need for cardiac surgical interventions, and rates of uncontrolled infection, congestive heart failure, relapse of endocarditis, and septic emboli, and found no conclusive differences between groups (very low-quality evidence). No trials assessed quality of life.

Authors' conclusions

This first update confirms the findings of the original version of the review. Limited and low to very low-quality evidence suggests that the comparative effects of different antibiotic regimens in terms of cure rates or other relevant clinical outcomes are uncertain. The conclusions of this updated Cochrane Review were based on few RCTs with a high risk of bias. Accordingly, current evidence does not support or reject any regimen of antibiotic therapy for the treatment of infective endocarditis.

PLAIN LANGUAGE SUMMARY

Antibiotic therapy for the treatment of infective endocarditis

Review question

We aimed to assess the existing evidence about the clinical benefits and harms of different antibiotics regimens used to treat people with infective endocarditis.

Background

Infective endocarditis is an infection of the inner lining of the heart. It is a serious infection that is frequently fatal, and cardiac surgery is often required. Antibiotics are medicines that treat infections and are the cornerstone of treatment for infective endocarditis. Treatment of patients with infective endocarditis is nosocomial (in-hospital). Despite this, there are surprising differences between guidelines in their recommendations for antibiotic therapy. Furthermore, due to the dose and length of time that antibiotics must be given for, the antibiotics can have serious side effects, such as kidney and ear damage, and cause allergic reactions.

Study characteristics

We identified only six randomised controlled trials (studies in which participants are assigned to one of two or more treatment groups using a random method) that compared different antibiotic regimens, which included a limited number of participants. Each trial investigated different types and doses of antibiotics. The included studies were published between 1998 and 2019 and were conducted in the USA, Spain, Finland, and Denmark. The evidence is up-to-date as of 6 January 2020.

Key results

This first update confirms the findings of the original version of the review. Limited and low to very low-quality evidence suggests that the comparative effects of different antibiotic regimens in terms of cure rates or other relevant clinical outcomes are uncertain. The conclusions of this updated Cochrane Review were based on few randomised controlled trials with a high risk of bias. Accordingly, the current evidence does not support or reject any regimen of antibiotic therapy for the treatment of infective endocarditis.

Quality of evidence

The confidence in the results of this review is low to very low. The included studies had limitations in the way they were designed and performed, and three studies were sponsored by the manufacturer of the medicine that was assessed. Moreover, the limited number of people included in the studies led to uncertain results. Larger studies are required to provide more information about the best antibiotic regimens to treat people with infective endocarditis.

SUMMARY OF FINDINGS

Summary of findings 1. Levofloxacin compared with standard treatment for *Staphylococcus aureus* endocarditis

Levofloxacin compared with standard treatment for *Staphylococcus aureus* endocarditis

Patient or population: people with *Staphylococcus aureus* endocarditis
Settings: inpatients
Intervention: levofloxacin
Comparison: standard treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Standard treatment	Levofloxacin				
All-cause mortality during hospital stay and all-cause mortality at 1 year Follow-up: 28 days	**231 per 1000** [1]	**258 per 1000** (113 to 591)	**RR 1.12** (0.49 to 2.56)	70 (1 study)	⊕⊖⊖⊖ **very low** [2,3]	This information was from a trial conducted to assess bacteraemia by *Staphylococcus aureus* (FINLEVO Trial 2006).
Cure [4]	See comment	See comment	Not estimable[4]	-	See comment	The trial did not report information on cure.
Adverse events [4]	See comment	See comment	Not estimable[4]	-	See comment	The trial did not report information on adverse events for people with endocarditis.
Congestive heart failure [4]	See comment	See comment	Not estimable[4]	-	See comment	The trial did not report information on congestive heart failure.
Septic embolism [4]	See comment	See comment	Not estimable[4]	-	See comment	The trial did not report information on septic embolism.
Need for cardiac surgical interventions [4]	See comment	See comment	Not estimable[4]	-	See comment	The trial did not report information on need for cardiac surgical interventions.
Uncontrolled infection [4]	See comment	See comment	Not estimable[4]	-	See comment	The trial did not report information on uncontrolled infection.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Assumed risk was estimated using control risk group.
[2]Downgraded by one level for risk of bias. Limitations in the trial design and execution.
[3]Downgraded by two levels for imprecision due to small sample and very low number of events with an impact on the precision of effect estimates.
[4]Data on this outcome were not supplied for participants with endocarditis.

Summary of findings 2. Lipopeptide antibiotic (daptomycin) versus aminoglycoside (low-dose gentamicin) plus antistaphylococcal penicillin (nafcillin, oxacillin, or flucloxacillin) or glycopeptide antibiotic (vancomycin) for *Staphylococcus aureus* endocarditis

Lipopeptide antibiotic (daptomycin) versus aminoglycoside (low-dose gentamicin) plus antistaphylococcal penicillin (nafcillin, oxacillin, or flucloxacillin) or glycopeptide antibiotic (vancomycin) for *Staphylococcus aureus* endocarditis

Patient or population: people with endocarditis caused by *Staphylococcus aureus*
Settings: inpatients
Intervention: lipopeptide antibiotic (daptomycin)
Comparison: aminoglycoside (low-dose gentamicin) + antistaphylococcal penicillin (nafcillin, oxacillin, or flucloxacillin) or glycopeptide antibiotic (vancomycin)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Low-dose aminoglycoside + antistaphylococcal penicillin or vancomycin	Daptomycin				
All-cause mortality during hospital stay	See comment	See comment	Not estimable	-	See comment	The trial did not report information on all-cause mortality.

and all-cause mortality at 1 year [1]						
Cure Follow-up: 42 days	**360 per 1000**	**320 per 1000** (151 to 680)	**RR 0.89** (0.42 to 1.89)	53 (1 study)	⊕⊖⊖⊖ **very low** [2,3,4]	This information was from a trial conducted to assess either bacteraemia or endocarditis by *Staphylococcus aureus.*
Adverse events [1]	See comment	See comment	Not estimable	-	See comment	The trial did not report information on adverse events.
Congestive heart failure [1]	See comment	See comment	Not estimable	-	See comment	The trial did not report information on congestive heart failure.
Septic embolism [1]	See comment	See comment	Not estimable	-	See comment	The trial did not report information on septic embolism.
Need for cardiac surgical interventions [1]	See comment	See comment	Not estimable	-	See comment	The trial did not report information on the need for cardiac surgical interventions.
Uncontrolled infection [1]	See comment	See comment	Not estimable	-	See comment	The trial did not report information on uncontrolled infection.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Data on this outcome were not supplied for participants with endocarditis.
[2]Downgraded one level for risk of bias. Limitations in the trial design and execution.
[3]Downgraded two levels for imprecision due to small sample and very low number of events with an impact on the precision of effect estimates.
[4]Assumed risk was estimated using control risk group.

Summary of findings 3. Glycopeptide (vancomycin or teicoplanin) plus aminoglycoside (gentamicin) compared with beta-lactam (cloxacillin) plus aminoglycoside (gentamicin) for *Staphylococcus aureus* endocarditis in drug abusers

Glycopeptides (vancomycin or teicoplanin) plus aminoglycoside (gentamicin) compared with beta-lactam (cloxacillin) plus aminoglycoside (gentamicin) for *Staphylococcus aureus* endocarditis in drug abusers

Patient or population: people with endocarditis due to *Staphylococcus aureus* in drug abusers
Settings: inpatients
Intervention: glycopeptide (vancomycin or teicoplanin) + aminoglycoside (gentamicin)
Comparison: beta-lactam (cloxacillin) + aminoglycoside (gentamicin)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Beta-lactam + aminoglycoside	Glycopeptides + aminoglycoside				
All-cause mortality during hospital stay and all-cause mortality at 1 year	See comment	See comment	Not estimable	-	See comment	The trial did not report information on all-cause mortality.
Cure Follow-up: 12 weeks	**1000 per 1000**	**590 per 1000** (400 to 850)	**RR 0.59** (0.40 to 0.85)	34 (1 study)	⊕⊕⊖⊖ **low** [1,2,3]	This trial included 246 participants with either bacteraemia or infective endocarditis. Therefore, 34 participants means only 13.82% of the total sample size.
Adverse events Follow-up: 12 weeks	See comment	See comment	**RR 5.5** (0.33 to 91.44)	34 (1 study)	⊕⊖⊖⊖ **very low** [1,2]	There were no reported adverse events in the control group.
Congestive heart failure	See comment	See comment	Not estimable	-	See comment	The trial did not report information on congestive heart failure.
Septic embolism	See comment	See comment	Not estimable	-	See comment	The trial did not report information on septic embolism.
Need for cardiac surgical interventions	See comment	See comment	Not estimable	-	See comment	The trial did not report information on the need for cardiac surgical interventions.

Uncontrolled infection	See comment	See comment	Not estimable	-	See comment	The trial did not report information on uncontrolled infection.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level for risk of bias. Limitations in the trial design and execution of trial.
[2]Downgraded one level for imprecision due to small sample and very low number of events with an impact in the precision of the effect estimates.
[3]Assumed risk was estimated using control risk group.

Summary of findings 4. Beta-lactam (ceftriaxone) plus aminoglycoside (gentamicin) versus beta-lactam (ceftriaxone) for infective endocarditis due to penicillin-susceptible streptococci

Beta-lactam (ceftriaxone) plus aminoglycoside (gentamicin) versus beta-lactam (ceftriaxone) for infective endocarditis due to penicillin-susceptible streptococci

Patient or population: people with infective endocarditis due to penicillin-susceptible streptococci
Settings: inpatients
Intervention: beta-lactam (ceftriaxone) + aminoglycoside (gentamicin)
Comparison: beta-lactam (ceftriaxone)

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Ceftriaxone	**Ceftriaxone + gentamicin**				
All-cause mortality during hospital stay and all-cause mortality at 1 year	See comment	See comment	Not estimable	-	See comment	The trial did not report information on all-cause mortality.
Cure Follow-up: 3 months	**636 per 1000**	**439 per 1000** (280 to 700)	**RR 0.69** (0.44 to 1.10)	67 (1 study)	⊕⊕⊖⊖ **low** [1,2,3]	

Adverse events Follow-up: 3 months	**152 per 1000**	**88 per 1000** (23 to 339)	**RR 0.58** (0.15 to 2.24)	67 (1 study)	⊕⊖⊖⊖ **very low** [1,2,3]	The trial authors considered all adverse events to be related to the study drugs.
Congestive heart failure	See comment	See comment	Not estimable	-	See comment	The trial did not report information on congestive heart failure.
Septic embolism	See comment	See comment	Not estimable	-	See comment	The trial did not report information on septic embolism.
Need for cardiac surgical interventions Follow-up: 30 months	**152 per 1000**	**265 per 1000** (98 to 708)	**RR 1.75** (0.65 to 4.67)	67 (1 study)	⊕⊖⊖⊖ **very low** [1,2,3]	
Uncontrolled infection Follow-up: 30 months	**30 per 1000**	**29 per 1000** (2 to 451)	**RR 0.97** (0.06 to 14.88)	67 (1 study)	⊕⊖⊖⊖ **very low** [1,2,3]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level for risk of bias. Limitations in the trial design and execution.
[2]Downgraded one level for imprecision. Limitations due to small sample and very low number of events with an impact on the precision of effect estimates.
[3]Assumed risk was estimated using control risk group.

Summary of findings 5. Fosfomycin plus imipenem compared with vancomycin for infective endocarditis due to methicillin-resistant *Staphylococcus aureus*

Fosfomycin plus imipenem compared with vancomycin for infective endocarditis due to methicillin-resistant *Staphylococcus aureus*

Patient or population: people with infective endocarditis due to methicillin-resistant *Staphylococcus aureus*
Settings: inpatients
Intervention: fosfomycin plus imipenem
Comparison: vancomycin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Vancomycin	Fosfomycin plus imipenem				
All-cause mortality during hospital stay and all-cause mortality at 1 year	1	–	**RR 7.00** (0.47 to 103.27)	8 (1 study[2])	⊕⊖⊖⊖ **very low** [3,4]	There were no events in the control group.
Cure Follow-up: not stated	**500 per 1000** [1]	**250 per 1000** (35 to 1000)	**RR 0.5** (0.07 to 3.55)	8 (1 study[2])	⊕⊖⊖⊖ **very low** [3,4]	
Adverse events Follow-up: not stated	**500 per 1000** [1]	**500 per 1000** (125 to 1000)	**RR 1.00** (0.25 to 4.00)	8 (1 study[2])	⊕⊖⊖⊖ **very low** [3,4]	
Congestive heart failure Follow-up: not stated	1	_	**RR 9** (0.64 to 126.85)	8 (1 study[2])	⊕⊖⊖⊖ **very low** [3,4]	There were no events in the control group.
Septic embolism Follow-up: not stated	See comment	See comment	Not estimable	-	See comment	The trial did not report information on septic embolism.
Need for cardiac surgical interventions Follow-up: not stated	**250 per 1000** [1]	**500 per 1000** (70 to 1000)	**RR 2.00** (0.28 to 14.20)	8 (1 study[2])	⊕⊖⊖⊖ **very low** [3,4]	
Uncontrolled infection Follow-up: not stated	See comment	See comment	Not estimable	-	See comment	The trial did not report information on uncontrolled infection.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1]Assumed risk was estimated using the control risk group.
[2]Spanish (10 sites).
[3]Downgraded two levels for risk of bias. Limitations in the trial design and execution.
[4]Downgraded two levels for imprecision. Limitations due to small sample and very low number of events with an impact on the precision of effect estimates.

Summary of findings 6. Partial oral treatment compared with conventional intravenous treatment of endocarditis on the left side of the heart (on native or prosthetic valves) and bacteraemia for *Streptococcus*, *Enterococcus faecalis*, *Staphylococcus aureus*, or coagulase-negative staphylococci

Partial oral treatment compared with conventional intravenous treatment of endocarditis on the left side of the heart (on native or prosthetic valves) and bacteraemia for *Streptococcus*, *Enterococcus faecalis*, *Staphylococcus aureus*, or coagulase-negative staphylococci

Patient or population: people with endocarditis on the left side of the heart (on native or prosthetic valves) with bacteraemia for *Streptococcus*, *Enterococcus faecalis*, *Staphylococcus aureus*, or coagulase-negative staphylococci
Settings: either inpatients or outpatients
Intervention: partial oral treatment
Comparison: conventional intravenous treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Conventional intravenous treatment	Partial oral treatment				
All-cause mortality during hospital stay and all-cause mortality at 1 year Follow-up: 6 months	**65 per 1000** [1]	**35 per 1000** (14 to 86)	**RR 0.53** (0.22 to 1.31)	400 (1 study[2])	⊕⊖⊖⊖ **very low** [3,4]	
Cure	See comment	See comment	Not estimable	-	See comment	The trial did not report information on cure.
Adverse events Follow-up: 6 months	**60 per 1000** [1]	**50 per 1000** (22 to 113)	**RR 0.83** (0.36 to 1.87)	400 (1 study[2])	⊕⊕⊖⊖ **low** [3,4]	
Congestive heart failure Follow-up: 6 months	**5 per 1000** [1]	**2 per 1000** (0 to 40)	**RR 0.33** (0.01 to 8.05)	400 (1 study[2])	⊕⊖⊖⊖ **very low** [3,4]	
Need for cardiac surgical interventions	**30 per 1000** [1]	**30 per 1000** (10 to 91)	**RR 0.99** (0.32 to 3.02)	400 (1 study[2])	⊕⊖⊖⊖ **very low** [3,4]	

Follow-up: 6 months						
Septic embolism Follow-up: 6 months	**15 per 1000**	**15 per 1000** (3 to 73)	**RR 0.99** (0.20 to 4.85)	400 (1 study[2])	⊕⊖⊖⊖ **very low** [3,4]	
Uncontrolled infection	See comment	See comment	Not estimable	-	See comment	The trial did not report information on uncontrolled infection.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Assumed risk was estimated using control risk group.
[2]Danish (15 sites).
[3]Downgraded one level for risk of bias. Limitations on the execution of trial. It was an open trial.
[4]Downgraded two levels for imprecision. Limitations due to small sample and very low number of events with an impact on the precision of effect estimates.

BACKGROUND

Description of the condition

Infective endocarditis is a microbial infection of a native or prosthetic heart valve, the endocardial surface, or an indwelling cardiac device (Cahill 2016). The diagnostic criteria include the combination of clinical, echocardiographic, and microbiological data, which are known as Duke's criteria (Baddour 2015). However, it is accepted that the sensitivity of the Duke classification is not optimal, particularly for prosthetic valve infective endocarditis. Recent guidelines have suggested the use of positron emission tomography or radiolabeled leukocyte scintigraphy in order to improve diagnostic accuracy (Habib 2015; Iung 2019a).

Extensive narrative reviews on infective endocarditis have been published that describe the pathophysiology, treatments, complications, and outcomes of this clinical entity (Avelana 2018; Baddour 2015; Burgos 2019; Hitzenbichler 2019; Khan 2017; Kobayashi 2019; Long 2018; Şimşek-Yavuz 2020). See Appendix 1 for types of infective endocarditis.

The incidence of infective endocarditis varies by country. Globally, the annual incidence of infective endocarditis has been estimated to be between 15 and 80 cases per million persons in population-based studies performed in Western countries (Iung 2019a; Iung 2019b). People with valve prostheses (> 4 per 1000) or with a history of infective endocarditis (> 10 per 1000) are at a higher risk (Iung 2019a). Right-sided infective endocarditis represents 5% to 10% of infective endocarditis cases (Delahaye 2019).

There are differences in the epidemiology of infective endocarditis between high- and low-income countries (Ambrosioni 2017). In high-income countries, the proportion of cases of endocarditis affecting prosthetic valves or cardiovascular implantable electronic devices has increased (Ambrosioni 2017; Cecchi 2015). Furthermore, there has been an increase in nosocomial cases and infective endocarditis caused by staphylococci and enterococci (Ambrosioni 2017; Cecchi 2015; Ursi 2019). On the other hand, in low-income countries, rheumatic heart disease remains the principal risk factor, and the most frequent causative agents are streptococci (Ambrosioni 2017).

According to the results of the European Infective Endocarditis registry, this complex clinical infectious entity remains a life-threatening disease with a high mortality despite improvements in diagnosis and therapy (Habib 2019). Infective endocarditis is a serious disease with an in-hospital mortality of 20%, a five-year mortality of 40%, and significant morbidity (Selton-Suty 2019). One potential reason for increasing mortality is the long latency from the onset of symptoms to reaching a definitive diagnosis of infective endocarditis, initiating appropriate treatment and an aging population (Cresti 2017; Iung 2019a; Mgbojikwe 2019). At-risk groups for developing infective endocarditis include people with valve replacements, congenital heart disease, chronic rheumatic heart disease, cardiac implantable electronic devices, nosocomial infection, HIV, diabetes mellitus, older age, cancer, poor oral hygiene, dialysis for renal impairment, and intravenous drug use (Amat-Santos 2015; Bai 2017; Beteille 2018; Burgos 2019; Egbe 2019; Elbatarny 2019; Krčméry 2019; Leahey 2019; Lin 2019; Lluri 2018; Meshaal 2018; Moriyama 2019; Muñoz-Moreno 2019; R 2018; Sadeghi 2019; Salvador 2017; Süzük 2016; Wei 2019; Yoshioka 2018). It has recently been demonstrated that the Sequential Organ Failure Assessment (SOFA) score could be useful for appraising the severity and outcome of individuals with endocarditis (Asai 2019).

Common causative organisms of infective endocarditis include Oral (or Viridans Group) streptococci (VGS) (Vinh 2016), *Staphylococcus aureus*, and enterococci (Beganovic 2018; Dhotre 2018; Erdem 2019; Krčméry 2019; Kumar 2019; Ogura 2019; Salvador 2017). In particular,VGS is found in the mouth, and it is thought that dental procedures can lead to bacterial endocarditis (Dhotre 2018). Current evidence shows that the most common causative agent of infective endocarditis is *S aureus* (Vogkou 2016). *S. aureus* is an organism associated with prosthetic valves and intravenous drug use (Elbatarny 2019). Slipczuk and colleagues conducted a comprehensive review of the changes in the microbiology of infective endocarditis over the past five decades (1960s to 2000s) (Slipczuk 2013). They noted that the proportion of cases caused by staphylococcal and enterococcal infections increased, whereas the numbers due to oral VGS decreased.

Overall, enterococci are the third most common causal microorganisms of infective endocarditis, causing 5–20% of cases (Skinner 2016).

The pathogenesis of infective endocarditis is very complex and starts with endocardial injury (Chopra 2007; Thiene 2006). The prototypical lesion of infective endocarditis, the vegetation, is a mass of platelets, fibrin, microcolonies of micro-organisms, and scant inflammatory cells (Karchmer 2009). In general, the endothelial lining of the heart and its valves is resistant to infection; however, very virulent micro-organisms, such as *S aureus*, are able to infect normal heart valves (Melehani 2016; Werdan 2014). Most often, the pathogenesis of infectious endocarditis begins with endothelial cell damage. Congenital or acquired cardiac lesions may induce continuous endocardial trauma via regurgitant flow or high-pressure jets of blood through stenotic lesions (Keynan 2013). Endothelial damage triggers thrombus formation caused by deposition of fibrin and platelets (Shannon 2010; Thurlow 2010). When transient bacteraemia occurs, bacteria can then reach these injury sites and colonise them (Keynan 2013; Widmer 2006). After colonisation, the surface is quickly covered by an additional layer of platelets and fibrin that is suitable for further colonisation, leading to progressive bacterial infection. Moreover, the injury site is further covered by a layer of exopolysaccharide that hinders the penetration of antibiotics (Daga 2011). There is proliferation of these micro-organisms and biofilm formation. Biofilm represents multilayered bacterial aggregate containing a polysaccharide and proteinaceous matrix that favours the bacteria to escape the immune system and hinders antimicrobial action (Colomer-Winter 2018; de Jong 2019; Flemming 2010; Flemming 2016; Guerra 2017; Nasser 2019; Tran 2019). After colonisation, an additional layer of platelets and fibrin cover the surface, leading to further colonisation and progressive bacterial infection and vegetation formation (Jung 2015). Vegetation is the prototypic lesion of infectious endocarditis, and is a mass of platelets, fibrin, micro-organisms, and inflammatory cells (Karchmer 2009).

The clinical features of infective endocarditis are highly variable and depend on the micro-organisms involved as well as the presence or absence of pre-existing heart disease (Song 2015; Sun 2015). The clinical presentation may be acute and rapidly progressive or subacute and chronic (Habib 2019). Fever is present in about 90% of those affected and is associated with various systemic symptoms such as loss of appetite and weight (Ba

2017; El Rafei 2016). A heart murmur is present in about 85% of people (Damasco 2019). The clinical features include neurological symptoms and signs (Champey 2016; Nascimento 2019; Sotero 2019). Infective endocarditis is a risk factor for stroke (Cantier 2019; Cao 2018; Shao 2019).

A recent meta-analysis found a better prognosis of infective endocarditis in people with mechanical valves compared with those with biological valves (Tao 2017); the clinical features of infective endocarditis are summarised in Appendix 2.

Infective endocarditis is generally thought to be lethal if left untreated, although evidence of infection may be found incidentally during valve surgery (Grisoli 2014). Successful treatment of infective endocarditis relies on microbial eradication by antimicrobial drugs; surgical intervention is sometimes needed to remove infected material and drain abscesses and reconstruct or replace damaged valves (Giacobbe 2019). However, the risk of mortality after surgical treatment of infective endocarditis is high due to several risk of factors, i.e., multivalvular affection, female sex, previous cardiac surgery, congestive heart failure, age, no blood cultures before referral, body mass index, renal failure, ischemic heart disease, inadequate response to medical treatment, prolonged aortic cross-clamp and cardiopulmonary bypass time, embolization, peri-annular extension of infection, *Staphylococcus aureus* infection, paravalvular abscess, vegetations > 2.2 cm, pericardial effusion, and septic or cardiogenic shock (Jakuska 2019; Nagy 2018; Singer 2017; Varela 2019).

Description of the intervention

Clinical pharmacology and microbiological spectrum

Many antimicrobial drugs have been used alone or in combination to treat infective endocarditis (Vinh 2016). These include beta-lactams, aminoglycosides, glycopeptides, oxazolidinones, complex macrocyclics, and quinolones (Cunha 2015; Drees 2006; Frank 2009; Pabilona 2015). See Appendix 3 for more details.

Antibiotic adverse reactions

The major antibiotic adverse reactions associated with the main antimicrobial drugs for treating infective endocarditis are well described (Granowitz 2008). See Appendix 3 for more details.

Guideline recommendations for the treatment of infective endocarditis

According to international guidelines, treatment of infective endocarditis should use bactericidal antibiotics, administered parenterally, at high dosages, typically for prolonged periods (four to six weeks) (Baddour 2015; Habib 2019). Where possible, the choice of antibiotic should be directed at the microbial agent isolated from blood cultures, according to the sensitivity pattern identified (Baddour 2015; Habib 2019). In general, the guidelines also recommend the combination of an aminoglycoside with a cell wall inhibitor (i.e. beta-lactams and glycopeptides) for synergistic bactericidal activity, to shorten the duration of therapy (e.g. oral streptococci) and to eradicate resistant organisms (e.g. *Enterococcus* spp.) (Baddour 2015; Habib 2019).

The recommended doses and schedules of the main antibiotics for treating infective endocarditis are shown in Appendix 3.

How the intervention might work

Appropriate antibiotic treatment is important to control local and systemic infection, eradicate the organisms from the vegetations, and reduce the risk of complications such as septic embolisation (Baddour 2015).

Why it is important to do this review

The recommended treatment of infective endocarditis still varies between guidelines (Murphy 2019; Saraste 2019). This first update of a review previously published in 2016, Marti-Carvajal 2016, has been performed to identify and review the latest evidence. This is of great importance, as is has been reported that around the world experts in infective endocarditis management do not follow international consensus guidelines on the particular point of the use of antibiotics (Tissot-Dupont 2017).

In summary, the principal research question of this updated Cochrane Review was: 'Which antibiotic regimens are superior in treating people with infective endocarditis?'. A secondary question was: 'What are the clinical benefits and harms of those regimens?'.

OBJECTIVES

To assess the existing evidence about the clinical benefits and harms of different antibiotics regimens used to treat people with infective endocarditis.

METHODS

Criteria for considering studies for this review

Types of studies

We included parallel randomised controlled trials (RCTs), randomised at the level of the participant. It is not possible to conduct a trial with another design for infective endocarditis. We included studies reported as full text, those published as abstract only, and unpublished data.

Types of participants

Adults (aged 18 years or older) with a definitive diagnosis of infective endocarditis, according to modified Duke's criteria (Durack 1994; Li 2000). This requires the presence of two major criteria, or one major and three minor criteria, or five minor criteria, or micro-organisms demonstrated by culture or histology of a vegetation, embolised vegetation, or in an intracardiac abscess, or histological evidence of active endocarditis (vegetation or intracardiac abscess) (Tam 2016).

Major criteria

- Positive blood cultures for infective endocarditis

In the absence of a primary focus, positive cultures from two separate blood cultures of one of the following typical organisms.

- Viridans group streptococci
- *Streptococcus bovis*
- HACEK group (*Haemophilus* species, *Actinobacillus actinomycetes comitants*, *Cardiobacterium hominis*, *Eikenella* species, *Kingella kingae*)
- Community-acquired *S. aureus* or enterococci

OR

- Persistently positive blood cultures of a micro-organism consistent with infective endocarditis

OR

- Single blood culture for *Coxiella burnetii* or antiphase I immunoglobulin (Ig)G antibody titre greater than 1:800

- Evidence of endocardial involvement
  - New valvular regurgitation

OR

- Positive echocardiogram (oscillating intracardiac mass in the absence of an alternative anatomic explanation OR abscess OR new partial dehiscence of prosthetic valve)

Minor criteria

- Predisposing heart condition OR intravenous drug use
- Fever (at least 38.0 °C)
- Vascular phenomena (arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhage, conjunctival haemorrhage, Janeway lesions)
- Immunological phenomena (glomerulonephritis, Osler's nodes, Roth spots, positive rheumatoid factor)
- Microbiological evidence of positive blood culture not meeting major criterion but excluding single positive culture for coagulase-negative staphylococci and organisms that do not cause endocarditis OR serological evidence of active infection with organism consistent with infective endocarditis.

We excluded people with possible infective endocarditis (e.g. with one major and one minor criteria, or three minor criteria).

We excluded pregnant women with endocarditis because drugs such as tetracyclines and chloramphenicol have well-described fetal or neonatal adverse effects and should be avoided. In general, however, human studies on the safety of many antimicrobial agents in pregnancy and lactation are limited, and antimicrobial agents should be prescribed with caution (Leekha 2011).

We included trials with mixed populations, that is trials where only a subset of participants met our eligibility criteria. We obtained outcome data for the subset of interest.

Types of interventions

Antibiotic therapy (monotherapy or combinations) compared with any other active antibiotic treatment at any dose, administration route, or duration. We excluded surgical interventions.

We compared different antibiotic classes, used as single agents or in combination, as well as different durations of treatment. We compared antibiotics when used empirically and also when used against sensitive bacteria. We made the following comparisons.

- The standard antibiotics suggested by guidelines according to the sensitivity of isolated bacteria (Habib 2019).
  - *Streptococcus*
    - Penicillin (amoxicillin or ampicillin or penicillin G) or ceftriaxone for four weeks versus penicillin (amoxicillin or ampicillin or penicillin G) or ceftriaxone with gentamicin or netilmicin for two weeks, or vancomycin for four weeks with gentamicin for two weeks.
  - *Enterococcus*
    - Ampicillin or amoxicillin with gentamicin for four or six weeks versus vancomycin with gentamicin for six weeks.
  - *S aureus*
    - Cloxacillin or oxacillin for four or six weeks with gentamicin for three to five days versus vancomycin for four to six weeks with gentamicin for three to five days, or cloxacillin or oxacillin for four or six weeks with gentamicin for three to five days and rifampicin for six weeks or vancomycin for four to six weeks with gentamicin three to five days and rifampicin for six weeks.
    - Levofloxacin plus cloxacillin or dicloxacillin versus cloxacillin or dicloxacillin for 14 days.
- Standard antibiotics suggested by guidelines versus no standard regimen or new drugs, according to sensitivities of isolated bacteria.
- Different empirical antibiotics for treating native or prosthetic valve infective endocarditis.

Types of outcome measures

Primary outcomes

- All-cause mortality (without the time points).
- Cure, defined as: disappearance of fever, sterilisation of blood cultures, and normalisation of inflammatory markers during treatment and in the subsequent four weeks (Baddour 2015; Hoen 2006).
- Adverse events including treatment-related adverse events (TRAE) (Ioannidis 2004), at any time of the treatment. We defined TRAE as: "a response to a drug which is noxious and uninitiated and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic functions" (Nebeker 2004). We extracted the number of participants with at least one TRAE out of the total randomised in each study arm.

Secondary outcomes

- Incidence of septic embolism (number of participants out of the total randomised), at longest available follow-up.
- Incidence of congestive heart failure (number of participants out of the total randomised) at the first 15 days of treatment (arbitrary election).
- Quality of life (as measured by a validated scale), at longest available follow-up.
- Need for cardiac surgical interventions (valve reconstruction or valve replacement) (number of participants who underwent surgery of the total randomised), at longest available follow-up (Elmistekawy 2016).
  - Indication for cardiac surgical intervention:
    - ☐ haemodynamic compromise;
    - ☐ persistent or uncontrolled infection (or both) despite aggressive medical therapy;
    - ☐ embolisation.

- Uncontrolled infection (persisting infection, perivalvular extension), at longest available follow-up.
- Relapse of endocarditis (new onset of fever, chills, or other evidence of systemic toxicity caused by the same species within six months of the initial episode), at longest available follow-up.

Reporting one or more of the outcomes listed here in the trial was not an inclusion criterion for this review. However, when a published report did not appear to report one of our outcomes, we neither accessed the trial protocol nor contacted the trial authors to ascertain whether the outcomes were measured but not reported.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases on 6 January 2020:

- the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 1 of 12, 2020) (the Cochrane Library);
- Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE (Ovid, 1946 to 3 January 2020);
- Embase Classic and Embase (Ovid, 1947 to 3 January 2020);
- LILACS via Virtual Health Library (Latin American and Caribbean Health Science Information database) (BIREME, 1982 to 6 January 2020);
- CINAHL Plus with Full Text (Cumulative Index to Nursing and Allied Health Literature) (EBSCO, 1937 to 6 January 2020);
- Conference Proceedings Citation Index – Science (CPCI-S) on the Web of Science (Clarivate Analytics, 1990 to 6 January 2020).

The search strategies are shown in Appendix 4. The Cochrane sensitivity-precision maximising RCT filter was applied to MEDLINE, and for Embase, terms as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* were applied (Lefebvre 2011). For the other databases, except CENTRAL, an adaptation of the Cochrane RCT filter was applied.

We imposed no date or language of publication restrictions.

Searching other resources

We searched the World Health Organization (WHO) International Clinical Trials Registry Platform (apps.who.int/trialsearch/), US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov), and the ISRCTN (www.isrctn.com/) for ongoing and unpublished trials on 17 March 2020.

We checked the reference lists of all included trials identified by the above methods.

Data collection and analysis

We summarised data using standard Cochrane methods (Higgins 2011). We constructed 'Summary of findings' tables and used the GRADE approach to assess the quality of included studies.

Selection of studies

Two review authors (AMC, CMA) independently screened the titles and abstracts of all studies identified as a result of the search for potential relevance, coding them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. In case of disagreement, two review authors (AGG, MD) were asked to arbitrate. We retrieved the full-text study reports/publications, and three review authors (AMC, LOC) independently screened the full texts and identified studies for inclusion, and identified and recorded reasons for exclusion of ineligible studies. Any disagreements were resolved through discussion or by consulting a third review author (MD) if necessary. We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Liberati 2009).

Data extraction and management

Two review authors (AMC, AGG) independently extracted data from the included trials. We extracted the following data overall.

- Participants: demographics (mean age, age range, gender, country, N randomised, N lost to follow-up, N analysed, severity of condition, diagnostic criteria, inclusion criteria, exclusion criteria).
- Methodological characteristics of the trial (allocation concealment, blinding, etc.). These data were extracted and included in the 'Risk of bias' assessment. We also extracted information on the design, total duration of the study, number of study centres and location, study setting, and study date for the Methods section of the Characteristics of included studies tables.
- Interventions: characteristics of infective endocarditis (anatomic site, type of affected valve), type of antibiotic and characteristics of its administration (names, alone or in combination). We also extracted data about concomitant medications and excluded medications, if this information was available.
- Outcomes: clinical outcomes, either primary or secondary, such as were reported into the included trial, including time points reported.
- Notes: funding for trial, and notable conflicts of interest of trial authors.

We discussed any discrepancies. One review author (AMC) transferred data into Review Manager 5 (Review Manager 2014). Two review authors (AMC, MD, CMA) double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. Three review authors (LOC, AGG, CMA) spot-checked the study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Three review authors (AMC, LOC, AGG) independently assessed the risk of bias in pairs of each trial using a simple form, following the domain-based evaluation as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreements were resolved by discussion.

We assessed the following domains as low, high, or unclear risk of bias:

- generation of allocation sequence;
- allocation concealment;
- blinding (of participants, personnel, and outcome assessors);
- incomplete outcome data;

- selective reporting;
- other sources of bias.

See Appendix 5 for criteria used for assessing risk of bias.

Measures of treatment effect

We did not conduct a meta-analysis as studies used different antibiotic regimens. We will apply the following procedures in the future if possible.

For dichotomous data (incidence of septic embolism and incidence of congestive heart failure), we will present results as summary risk ratios (RRs) with 95% confidence intervals (CIs). For continuous data (quality of life), we will present results as mean difference (MD) if the studies report continuous data on the same scale and standardised mean differences (SMDs) with 95% CIs if studies report different scales.

We presented results as RRs with 95% CIs for all-cause mortality during hospital stay and all-cause mortality at one year, cure, adverse events including TRAEs, need for cardiac surgical interventions, uncontrolled infection, and relapse of endocarditis.

Unit of analysis issues

The unit of analysis was the participants with infective endocarditis. In the case of trials with more than two arms, we compared families of antibiotics, that is glycopeptides plus aminoglycoside versus beta-lactam plus aminoglycoside.

Dealing with missing data

We did not perform sensitivity analysis for per-protocol, worse-case, and best-case scenarios as no meta-analysis was performed (Hollis 1999). In the case of missing data on participants or missing statistics (such as standard deviations) in future updates, we will contact the trial authors.

Assessment of heterogeneity

We were unable to pool findings to perform meta-analysis as the studies used different antibiotic regimens. For future updates, we will use the I^2 statistic to measure statistical heterogeneity between the trials in each analysis if possible. The I^2 statistic describes the percentage of total variation across trials that is due to heterogeneity rather than to sampling error (Higgins 2003). In future updates, we will visually inspect the forest plots. There is substantial uncertainty in the value of I^2 when there is only a small number of studies, in which case we will also consider the P value from the Chi^2 test.

Assessment of reporting biases

If in future updates we include 10 or more trials, we will attempt to assess whether the review is subject to publication bias by using a funnel plot. If we detect asymmetry, we will explore other causes (e.g. selective outcome reporting, poor methodological quality in smaller studies, true heterogeneity) (Sterne 2011).

Data synthesis

We did not conduct a meta-analysis. For future updates, if the eligible trials are sufficiently comparable in their clinical characteristics, we will summarise their findings using both fixed-effect and random-effects models. In the presence of statistical heterogeneity and the absence of small-study effects, we expect the 95% CI from the random-effects model to include the 95% CI from the fixed-effect model. In such a case, we will report only the data using the random-effects model as it appropriately conveys heterogeneity. If substantial differences are observed between both models, we will investigate this further.

Subgroup analysis and investigation of heterogeneity

We anticipate clinical heterogeneity for the following participants and intervention characteristics, therefore we will carry out the following subgroup analyses in future updates if possible.

- People at highest risk for a complicated or lethal course of infective endocarditis (people with valvular prosthesis (mechanical or biological), people who have previously had endocarditis, people with certain congenital heart defects, and heart-transplant recipients who have developed a cardiac valvulopathy).
- People aged over 60 years.
- People with culture-negative endocarditis versus people with infective endocarditis with positive blood cultures.
- Right-sided versus left-sided infective endocarditis.
- Type of infective organism.
- People with native-valve endocarditis versus people with prosthetic-valve endocarditis.
- People with community-acquired endocarditis versus healthcare-associated endocarditis or endocarditis that developed after a surgical procedure.
- Monotherapy versus combination therapy.

We plan to restrict subgroup analysis to primary outcomes only (Higgins 2011).

Sensitivity analysis

For future updates, if sufficient trials are identified and pooled, we will conduct a sensitivity analysis comparing the results using all the included trials.

- Including only RCTs with a low risk of bias (Higgins 2011). It is unlikely that we will find many trials at low risk of bias in all 'Risk of bias' domains, therefore we will choose three core domains only: generation of allocation sequence, incomplete outcome data, and selective reporting bias.
- Sensitivity analyses taking concealment of allocation and attrition into consideration.

'Summary of findings' tables

We used the principles of the GRADE system to assess the quality of the body of evidence associated with all main outcomes (all-cause mortality during hospital stay and all-cause mortality at one year, cure, adverse events, TRAE, incidence of congestive heart failure, incidence of septic embolism, need for cardiac surgical intervention) (Guyatt 2008), and constructed 'Summary of findings' tables using GRADEpro GDT software (GRADEpro 2008). The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. Evaluation of the quality of a body of evidence considers within-study risk of bias, directness of the evidence, heterogeneity in the data, precision of effect estimates, and risk of publication bias (Balshem 2011; Guyatt

2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2011h).

One review author (AMC) constructed 'Summary of findings' tables, and another review author (AGG) assessed the quality of evidence: Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6.

RESULTS

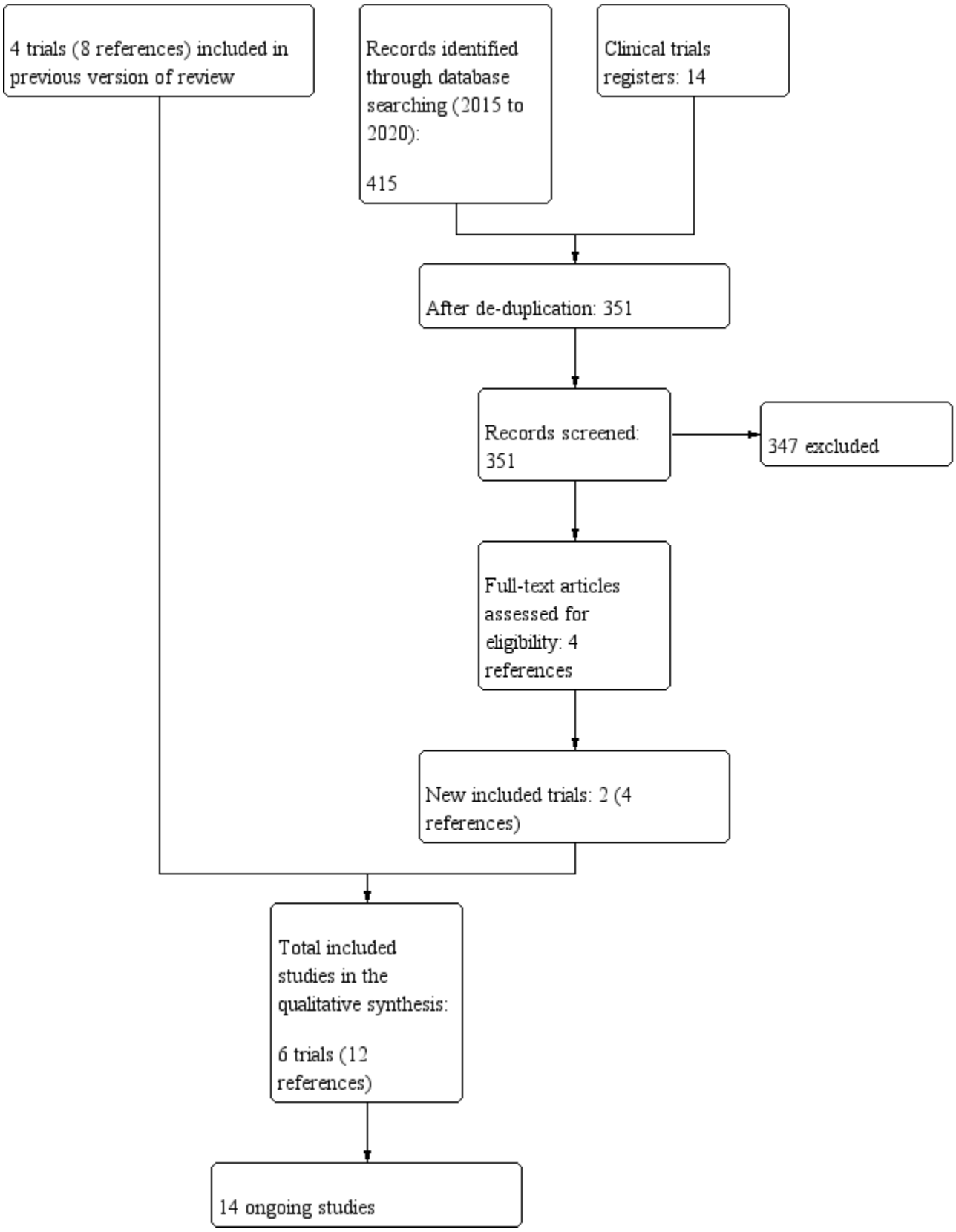
Description of studies

Results of the search

Searching from the previous review to January 2020 (latest search), we identified 415 records in the database searches and 14 records from clinical trials registers. There were 351 unique references after removal of duplicates. We excluded a further 347 references after title and abstract screening. We obtained the full texts of the remaining four references for more detailed examination. These four references were for two new RCTs (Pericas 2018; POET 2019).

This updated review includes a total of six RCTs, published between 1998 and 2019, involving 1143 participants (FINLEVO Trial 2006; Fortún 2001; Fowler 2006; Pericas 2018; POET 2019; Sexton 1998). See Figure 1 for details of study selection.

Figure 1. Study flow diagram.



The length of follow-up ranged from 28 days to six months. The trials varied in size, characteristics of participant populations, duration, drug dosage, and experimental design. For study details see Characteristics of included studies.

Included studies

For study details see Characteristics of included studies.

Interventions

The following comparisons were evaluated in the included trials.

A quinolone plus standard treatment versus standard treatment

A quinolone, levofloxacin, at a dose of 500 mg once daily for participants weighing less than 60 kg and 500 mg twice daily for participants weighing over 60 kg, administered both intravenously and orally, was compared with standard treatment. Standard treatment comprised cloxacillin or dicloxacillin 2 g every four hours, intravenously. Participants with contraindications to penicillin received cefuroxime (1.5 g every six hours, clindamycin 600 mg every six or eight hours, or vancomycin 1 g twice daily). When oral treatment was indicated, cloxacillin 500 mg every six hours, cephalexin or cefadroxil 500 mg every six hours, or clindamycin 300 mg every six hours was used. Doses were adjusted according renal function. Furthermore, an aminoglycoside, tobramycin or netilmicin at 1 mg/kg body weight every eight hours, and rifampicin 450 mg once daily for participants weighing under 50 kg and 600 mg once daily for participants weighing over 50 kg, oral or intravenously was used (FINLEVO Trial 2006).

A glycopeptide plus an aminoglycoside versus a beta-lactam plus an aminoglycoside

Vancomycin 500 mg intravenous every six hours with gentamicin 1.5 mg/kg every eight hours for two weeks, or teicoplanin 12 mg/kg every 24 hours, with a loading dose of 24 mg/kg given on the first day with gentamicin 1.5 mg/kg every eight hours for two weeks was compared with cloxacillin 2 g intravenously every four hours with gentamicin 1.5 mg/kg every eight hours for two weeks (Fortún 2001).

A lipopeptide antibiotic (daptomycin) versus either antistaphylococcal penicillins or a glycopeptide antibiotic plus an aminoglycoside

Daptomycin 6 mg/kg intravenously once daily was compared with standard therapy with either vancomycin 1 g every 12 hours or nafcillin, oxacillin, or flucloxacillin 2 g every four hours (depending on the susceptibility of the causative strain to methicillin) plus gentamicin 1 mg/kg intravenously every eight hours for the first four days. The duration of therapy was determined by the investigators, but the median duration of therapy was 14 days for daptomycin and 15 days for standard therapy (Fowler 2006).

A beta-lactam plus an aminoglycoside versus a beta-lactam alone

Ceftriaxone 2 g intravenously once daily for two weeks was compared with ceftriaxone 2 g intravenously once daily with gentamicin 3 mg/kg (of ideal body weight) once daily for two weeks (Sexton 1998).

Two studies determined gentamicin levels (Fortún 2001; Sexton 1998), and one study determined vancomycin and teicoplanin levels (Fortún 2001). One study did not report if the antibiotic levels were determined (Fowler 2006).

Fosfomycin plus imipenem versus vancomycin

Fosfomycin 2 g intravenously six hourly plus imipenem 1 g intravenously six hourly, adjusted for renal function, was compared with vancomycin 30 to 45 mg/kg daily intravenously divided into two to three doses, ensuring trough levels ≥ 15 mg/L (Pericas 2018). If the participant developed either treatment failure or renal failure with vancomycin, he/she was switched to the fosfomycin/imipenem group.

Partial oral treatment versus conventional intravenous treatment

After an initial period of conventional intravenous treatment, a switch to oral medication was compared to continuing with conventional intravenous treatment. This treatment strategy was based on the guidelines of the European Society of Cardiology (Habib 2015), with modifications endorsed by the Danish Society of Cardiology (Moser 2017). The composition, doses, and duration of different oral regimens are described in Appendix 6 and Appendix 7. No details were provided regarding the conventional intravenous therapy regimens (POET 2019).

Participants

The included trials involved a total of 1143 randomised participants (median 156.5; range 34 to 381).

Five trials reported the age of the participants, which ranged between 18 and 92 years (FINLEVO Trial 2006; Fortún 2001; Pericas 2018; POET 2019; Sexton 1998). Male participants were predominant in five trials: 60% in FINLEVO Trial 2006, 97.5% in Fortún 2001, 76% in POET 2019, and 80% in Sexton 1998. One trial did not report the gender of the participants (Fowler 2006). One trial showed inconsistency regarding the frequency of this variable between comparison groups (Pericas 2018).

Only two trials included people diagnosed as having definitive and probable endocarditis (FINLEVO Trial 2006; Fowler 2006). Four trials only included people with infective endocarditis (Fortún 2001; Pericas 2018; POET 2019; Sexton 1998). One trial only included right-sided endocarditis (Fortún 2001); two trials included left-sided endocarditis (POET 2019; Sexton 1998); and three trials reported data of participants irrespective of the side of the valve affected by endocarditis (FINLEVO Trial 2006; Fowler 2006; Pericas 2018).

The included trials were conducted to assess the effect of the intervention on different micro-organisms: methicillin-susceptible *S aureus* (Fortún 2001), *S aureus* (FINLEVO Trial 2006; Fowler 2006), and ceftriaxone-susceptible viridans group streptococci or *S bovis* endocarditis (Sexton 1998). Two trials only included endocarditis affecting native valves (Fortún 2001; Sexton 1998). Two trials involved participants with either native or prosthetic valves (Fowler 2006; POET 2019). Two trials reported data from participants with *S aureus* bacteraemia, a subset of whom had endocarditis: 70 participants in FINLEVO Trial 2006 and 52 participants in Fowler 2006.

Methods

The included trials were conducted between 1998 and 2019 and used a parallel design (FINLEVO Trial 2006; Fortún 2001; Fowler 2006; Pericas 2018; POET 2019; Sexton 1998). Five trials had two arms (FINLEVO Trial 2006; Fowler 2006; Pericas 2018; POET 2019; Sexton 1998), and one trial had three arms (Fortún 2001). There

were five multicentre trials (FINLEVO Trial 2006; Fowler 2006; Pericas 2018; POET 2019; Sexton 1998). One trial was conducted in Finland (FINLEVO Trial 2006), one trial in Denmark (POET 2019), two trials in Spain (Fortún 2001; Pericas 2018), and two trials in the USA (Fowler 2006; Sexton 1998). The follow-up of the trials ranged between 28 days, (FINLEVO Trial 2006) and six months (POET 2019). Four trials reported a priori sample size estimation (FINLEVO Trial 2006; Fowler 2006; Pericas 2018; POET 2019). The median number of outcomes reported by any trial was six (minimum four, maximum seven). One trial included a composite outcome involving four components (POET 2019). Two trials without a priori sample size estimation assessed six outcomes each (Fortún 2001; Sexton 1998).

Excluded studies

We excluded 10 RCTs that did not meet Duke's criteria for diagnosis of infective endocarditis (Abrams 1979; Fortún 1995; Gilbert 1991; Greenman 1984; Heldman 1996; Korzeniowski 1982; Levine 1991; Markowitz 1992; Ribera 1996; Stamboulian 1991). See Characteristics of excluded studies.

Ongoing trials

We identified 14 ongoing trials (CTRI/2008/091/000060; EUCTR 2016-003059-31; EUCTR 2017-001699-43; EudraCT 2008-008683-28; JPRN-UMIN 000032006; NCT00638157; NCT00695903; NCT02208063; NCT02701595; NCT02701608; NCT03138733; NCT03148756; NCT04222257; RBR-3p8g7n 2016). See Characteristics of ongoing studies.

Risk of bias in included studies

The risk of bias in the included trials is summarised in Figure 2 and Figure 3, and detailed in the Characteristics of included studies table.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

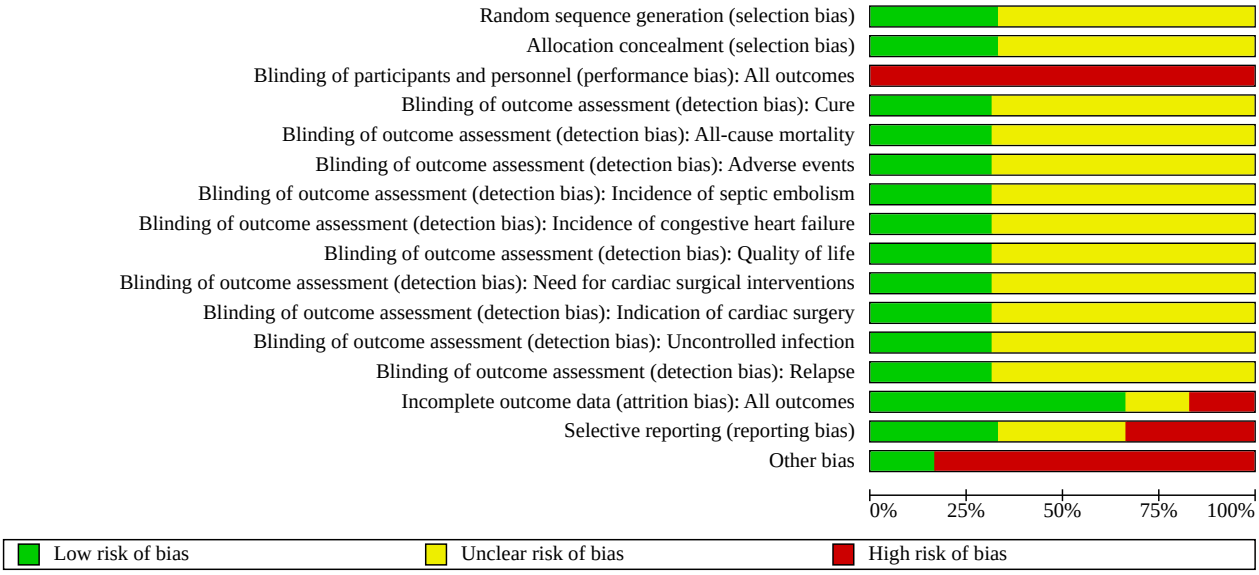
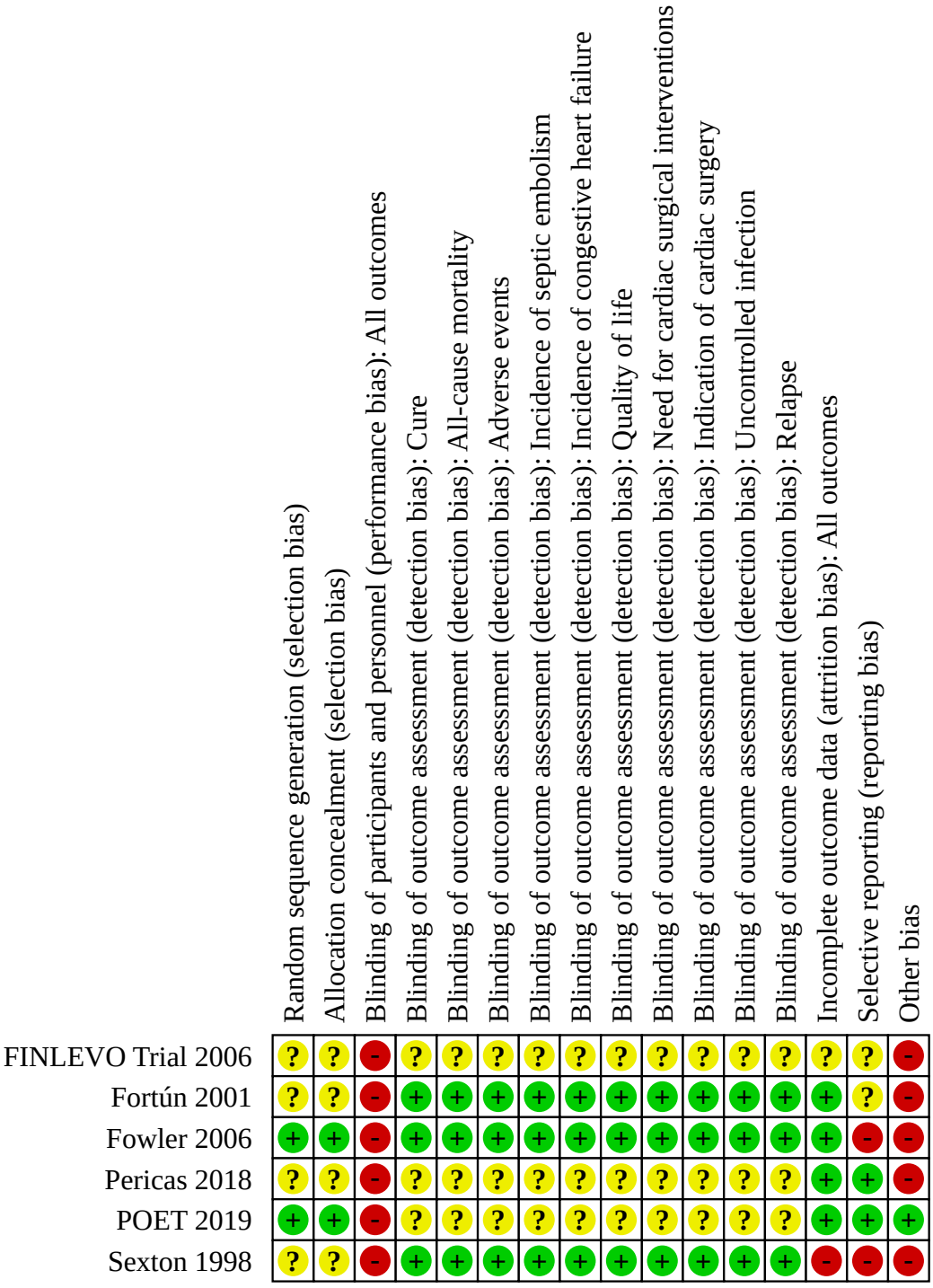


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



We considered all trials as at high risk of bias.

Allocation

Random sequence generation

The risk of bias arising from the method of generation of the allocation sequence was low in two trials (Fowler 2006; POET 2019). Four trials had an unclear risk of bias (FINLEVO Trial 2006; Fortún 2001; Pericas 2018; Sexton 1998).

Allocation concealment

The risk of bias arising from the method of generation of the allocation sequence was low in two trials (Fowler 2006; POET 2019). Four trials had an unclear risk of bias (FINLEVO Trial 2006; Fortún 2001; Pericas 2018; Sexton 1998).

Blinding

The risk of bias due to lack of blinding of participants and personnel was high in all trials (FINLEVO Trial 2006; Fortún 2001; Fowler 2006; Pericas 2018; POET 2019; Sexton 1998).

Blinding of outcome assessment (detection bias)

For all-cause mortality, the risk of bias was low risk in three trials, FINLEVO Trial 2006; Fortún 2001; POET 2019, and unclear in three trials (Fowler 2006; Pericas 2018; Sexton 1998).

For cure, we rated Fortún 2001, Fowler 2006, and Sexton 1998 as at low risk of bias for blinding of outcome assessment. We rated one trial as having an unclear risk of bias (Pericas 2018). POET 2019 did not assess this outcome.

For adverse events, three trials were at low risk of bias (Fortún 2001; POET 2019; Sexton 1998), and three trials were at unclear risk of bias for blinding of outcome assessment (FINLEVO Trial 2006; Fowler 2006; Pericas 2018).

For incidence of septic embolism, one trial was at low risk of bias (POET 2019), and five trials were at unclear risk of bias (FINLEVO Trial 2006; Fortún 2001; Fowler 2006; Pericas 2018; Sexton 1998).

For incidence of heart failure, one trial was at low risk of bias (POET 2019), and five trials were at unclear risk of bias (FINLEVO Trial 2006; Fortún 2001; Fowler 2006; Pericas 2018; Sexton 1998).

No trials assessed quality of life, thus we rated all trials as at unclear risk of bias for this domain (FINLEVO Trial 2006; Fortún 2001; Fowler 2006; Pericas 2018; POET 2019; Sexton 1998).

For the need for cardiac valve reconstruction or replacement, we assessed two trials as at low risk of bias (POET 2019; Sexton 1998), and four trials as at unclear risk of bias (FINLEVO Trial 2006; Fortún 2001; Fowler 2006; Pericas 2018).

For indication of cardiac surgery due to embolisation, haemodynamic compromise, or persistent infection, two trials were at low risk of bias (POET 2019; Sexton 1998), and four trials were at unclear risk of bias (FINLEVO Trial 2006; Fortún 2001; Fowler 2006; Pericas 2018).

For uncontrolled infection, two trials had a low risk of bias (Fowler 2006; Sexton 1998), and four trials had an unclear risk of bias (FINLEVO Trial 2006; Fortún 2001; Pericas 2018; POET 2019).

For relapse, two trials had a low risk of bias (Fortún 2001; POET 2019), and four trials had an unclear risk of bias (FINLEVO Trial 2006; Fortún 2001; Pericas 2018; Sexton 1998).

Incomplete outcome data

Risk of attrition bias was low in four trials (Fortún 2001; Fowler 2006; Pericas 2018; POET 2019), high in one trial (Sexton 1998), and unclear in one trial (FINLEVO Trial 2006).

Selective reporting

Risk of selective outcome reporting bias was low in two trials (Pericas 2018; POET 2019), high in two trials (Fowler 2006; Sexton 1998), and unclear in two trials (FINLEVO Trial 2006; Fortún 2001).

Other potential sources of bias

One trial had a low risk for other potential trial (POET 2019). Risk of other bias was high in five trials due to bias in the presentation of data, and design bias (FINLEVO Trial 2006; Fortún 2001; Fowler 2006; Pericas 2018; Sexton 1998).

Effects of interventions

See: **Summary of findings 1** Levofloxacin compared with standard treatment for *Staphylococcus aureus* endocarditis; **Summary of findings 2** Lipopeptide antibiotic (daptomycin) versus aminoglycoside (low-dose gentamicin) plus antistaphylococcal penicillin (nafcillin, oxacillin, or flucloxacillin) or glycopeptide antibiotic (vancomycin) for *Staphylococcus aureus* endocarditis; **Summary of findings 3** Glycopeptide (vancomycin or teicoplanin) plus aminoglycoside (gentamicin) compared with beta-lactam (cloxacillin) plus aminoglycoside (gentamicin) for *Staphylococcus aureus* endocarditis in drug abusers; **Summary of findings 4** Beta-lactam (ceftriaxone) plus aminoglycoside (gentamicin) versus beta-lactam (ceftriaxone) for infective endocarditis due to penicillin-susceptible streptococci; **Summary of findings 5** Fosfomycin plus imipenem compared with vancomycin for infective endocarditis due to methicillin-resistant *Staphylococcus aureus*; **Summary of findings 6** Partial oral treatment compared with conventional intravenous treatment of endocarditis on the left side of the heart (on native or prosthetic valves) and bacteraemia for *Streptococcus*, *Enterococcus faecalis*, *Staphylococcus aureus*, or coagulase-negative staphylococci

Results were based on 632 participants from 1143 randomised participants. This is due to the fact that three trials were conducted in participants with *S aureus* bacteraemia (FINLEVO Trial 2006; Fowler 2006; Pericas 2018), which included a subset of participants with infective endocarditis, but treated a broader range of participants; we have only included the data from the participants with endocarditis. See Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6.

Primary outcomes

All-cause mortality

Quinolones (levofloxacin) plus standard treatment (antistaphylococcal penicillin (cloxacillin or dicloxacillin), aminoglycoside (tobramycin or netilmicin), and rifampicin) versus standard treatment

One trial showed inconclusive evidence regarding all-cause mortality at 28 days and 3 months (8/31 (26%) with levofloxacin

plus standard treatment versus 9/39 (23%) with standard treatment alone; risk ratio (RR) 1.12, 95% confidence interval (CI) 0.49 to 2.56; very low-quality evidence) (FINLEVO Trial 2006).

Glycopeptides (vancomycin or teicoplanin) plus an aminoglycoside (gentamicin) versus a beta-lactam (cloxacillin) plus an aminoglycoside (gentamicin)

One trial described no deaths at least 12 weeks after completion of therapy (Fortún 2001).

Fosfomycin plus imipenem versus vancomycin

One trial showed inconclusive evidence in terms of all-cause mortality at six months (3/4 (75%) with fosfomycin plus imipenem versus 0/4 (0%) with vancomycin; RR 7.00, 95% CI 0.47 to 103.27; very low-quality evidence) (Pericas 2018).

Partial oral treatment versus conventional intravenous treatment

One trial showed inconclusive evidence regarding all-cause mortality at six months (7/201 (3.48%) with partial oral treatment versus 13/199 (6.53%) with conventional intravenous treatment; RR 0.53, 95% CI 0.22 to 1.31; very low-quality evidence) (POET 2019).

Cure

Lipopeptide antibiotics (daptomycin) versus aminoglycoside (low-dose gentamicin) plus antistaphylococcal penicillins (nafcillin, oxacillin, or flucloxacillin) or glycopeptide antibiotics (vancomycin)

One trial found no conclusive evidence between the two regimens for cure (9/28 (32%) with daptomycin versus 9/25 (36%) with low-dose gentamicin plus antistaphylococcal penicillin or vancomycin; RR 0.89, 95% CI 0.42 to 1.89; very low-quality evidence) (Fowler 2006).

Glycopeptides (vancomycin or teicoplanin) plus an aminoglycoside (gentamicin) versus a beta-lactam (cloxacillin) plus an aminoglycoside (gentamicin)

One trial showed conclusive evidence between the regimens for cure (13/23 (56%) with glycopeptides plus aminoglycoside versus 11/11 (100%) beta-lactam plus an aminoglycoside; RR 0.59, 95% CI 0.40 to 0.85; low-quality evidence) (Fortún 2001).

Beta-lactam (ceftriaxone) plus an aminoglycoside (gentamicin) versus a beta-lactam alone (ceftriaxone)

One trial found inconclusive evidence between the regimens for cure (15/34 (44%) with beta-lactam plus aminoglycoside versus 21/33 (64%) with beta-lactam alone; RR 0.69, 95% CI 0.44 to 1.10; low-quality evidence) (Sexton 1998).

Fosfomycin plus imipenem versus vancomycin

One trial showed inconclusive evidence between the regimens for cure (1/4 (25%) with fosfomycin plus imipenem versus 2/4 (50%) with vancomycin; RR 0.50, 95% CI 0.07 to 3.55; very low-quality evidence) (Pericas 2018).

Treatment-related adverse events

Glycopeptides (vancomycin or teicoplanin) plus an aminoglycoside (gentamicin) versus a beta-lactam plus an aminoglycoside (cloxacillin plus gentamicin)

One trial showed no conclusive evidence with regard to TRAEs (5/23 (22%) with glycopeptides plus aminoglycoside versus 0/11 (0%) with beta-lactam plus aminoglycoside; RR 5.50, 95% CI 0.33 to 91.44; very low-quality evidence) (Fortún 2001).

A beta-lactam (ceftriaxone) plus an aminoglycoside (gentamicin) versus a beta-lactam alone (ceftriaxone)

One trial found inconclusive results with regard to TRAEs (3/34 (8.8%) with beta-lactam plus aminoglycoside versus 5/33 (15%) with a beta-lactam alone; RR 0.58, 95% CI 0.15 to 2.24; very low-quality evidence) (Sexton 1998).

Fosfomycin plus imipenem versus vancomycin

One trial showed inconclusive evidence in terms of adverse events (2/4 (50%) with fosfomycin plus imipenem versus 2/4 (50%) with vancomycin; RR 1.00, 95% CI 0.25 to 4.00; very low-quality evidence) (Pericas 2018).

Partial oral treatment versus conventional intravenous treatment

One trial showed inconclusive evidence regarding adverse events (10/201 (4.97%) with fosfomycin plus imipenem versus 12/199 (6.03%) with vancomycin; RR 0.83, 95% CI 0.36 to 1.87; low-quality evidence) (POET 2019).

Secondary outcomes

Incidence of septic embolism

Partial oral treatment versus conventional intravenous treatment

One trial showed inconclusive evidence regarding septic embolism (3/201 (1.49%) with fosfomycin plus imipenem versus 3/199 (1.50%) with vancomycin; RR 0.99, 95% CI 0.20 to 4.85; very low-quality evidence) (POET 2019).

Incidence of congestive heart failure

Fosfomycin plus imipenem versus vancomycin

One trial showed inconclusive evidence in terms of congestive heart failure (4/4 (100%) with fosfomycin plus imipenem versus 0/4 (0%) with vancomycin; RR 9.00, 95% CI 0.64 to 126.85; very low-quality evidence) (Pericas 2018).

Partial oral treatment versus conventional intravenous treatment

One trial showed inconclusive evidence regarding congestive heart failure (0/201 (0%) with partial oral treatment versus 1/199 (0.5%) with conventional intravenous treatment; RR 0.33, 95% CI 0.01 to 8.05; very low-quality evidence) (POET 2019).

Quality of life

No trials assessed quality of life.

Need for cardiac surgical intervention (valve reconstruction or replacement) intervention

A beta-lactam (ceftriaxone) plus an aminoglycoside (gentamicin) versus a beta-lactam (ceftriaxone) alone

One trial found inconclusive results in terms of need for a cardiac surgical intervention (9/34 (26%) with beta-lactam plus aminoglycoside versus 5/33 (15%) with beta-lactam alone; RR 1.75, 95% CI 0.65 to 4.67) (Sexton 1998).

A beta-lactam (ceftriaxone) plus an aminoglycoside (gentamicin) versus a beta-lactam alone (ceftriaxone)

One trial reported that one participant in the control group had a pedunculated mobile vegetation at the time of surgery (Sexton 1998).

Fosfomycin plus imipenem versus vancomycin

One trial showed inconclusive evidence in terms of need for a cardiac surgical intervention (2/4 (50%) with fosfomycin plus imipenem versus 1/4 (25%) with vancomycin; RR 2.00, 95% CI 0.28 to 14.20; very low-quality evidence) (Pericas 2018).

Partial oral treatment versus conventional intravenous treatment

One trial showed inconclusive evidence regarding need for a cardiac surgical intervention (6/201 (2.98%) with partial oral treatment versus 6/199 (3.01%) with conventional intravenous treatment; RR 0.99, 95% CI 0.32 to 3.02; very low-quality evidence) (POET 2019).

Uncontrolled infection

A beta-lactam (ceftriaxone) plus an aminoglycoside (gentamicin) versus a beta-lactam (ceftriaxone) alone

One trial found no conclusive results in terms of uncontrolled infection (1/34 (2.9%) with a beta-lactam plus an aminoglycoside versus 1/33 (3.0%) with a beta-lactam alone; RR 0.97, 95% CI 0.06 to 14.88; very low-quality evidence) (Sexton 1998).

Relapse of endocarditis

A beta-lactam (ceftriaxone) plus an aminoglycoside (gentamicin) versus a beta-lactam alone (ceftriaxone)

One trial reported no relapses in either group (Sexton 1998).

Fosfomycin plus imipenem versus vancomycin

One trial showed inconclusive evidence in terms of relapse of endocarditis (0/4 (0%) with fosfomycin plus imipenem versus 1/4 (25%) with vancomycin; RR 0.33, 95% CI 0.02 to 6.37; very low-quality evidence) (Pericas 2018).

Partial oral treatment versus conventional intravenous treatment

One trial showed inconclusive evidence regarding relapse of endocarditis (5/201 (2.48%) with partial oral treatment versus 5/199 (2.51%) with conventional intravenous treatment; RR 0.99, 95% CI 0.29 to 3.37; very low-quality evidence) (POET 2019).

DISCUSSION

Summary of main results

This updated Cochrane Review aimed to assess the clinical benefits and harms of different antibiotic regimens to treat infective endocarditis. Six small RCTs, involving 1143 randomised participants, of which 632 were analysed, met our inclusion criteria. The trials were conducted using modified Duke's criteria to diagnose infective endocarditis. We concluded that our main finding suggesting that one antibiotic regimen is not superior to another is uncertain. The included trials had a high risk of bias and were underpowered, and three trials were sponsored by drug companies.

The six included trials used different treatment schedules in terms of antibiotics used, routes of administration, and duration of treatment:

- a fluoroquinolone (levofloxacin) versus standard treatment comprised of an antistaphylococcal penicillin (cloxacillin or dicloxacillin) plus an aminoglycoside (tobramycin or netilmicin) and rifampicin (FINLEVO Trial 2006);
- a glycopeptide (vancomycin or teicoplanin) plus an aminoglycoside (gentamicin) versus a beta-lactam (cloxacillin) plus an aminoglycoside (gentamicin) (Fortún 2001);
- a lipopeptide antibiotic (daptomycin) versus an aminoglycoside (low-dose gentamicin) plus antistaphylococcal penicillins (nafcillin, oxacillin, or flucloxacillin) or glycopeptide antibiotics (vancomycin) (Fowler 2006);
- fosfomycin plus imipenem versus vancomycin (Pericas 2018);
- partial oral treatment versus conventional intravenous treatment (POET 2019); and
- a beta-lactam (ceftriaxone) plus an aminoglycoside (gentamicin) versus a beta-lactam (ceftriaxone) alone (Sexton 1998).

Four trials reported the main outcome of this Cochrane Review, all-cause in-hospital mortality and all-cause mortality at one year. These trials found no conclusive differences between treatment regimens (FINLEVO Trial 2006; Fortún 2001; Pericas 2018; POET 2019).

The included trials showed inconclusive effects with regard to cure rates, TRAEs, the need for cardiac surgical intervention, uncontrolled infection, incidence of septic emboli, congestive heart failure, and relapse of endocarditis. No trials assessed quality of life.

Overall completeness and applicability of evidence

The data from this updated Cochrane Review suggest that there is insufficient evidence to conclude that there is no difference in either clinical benefits or in the frequency of treatment-related adverse events related to the antibiotics used to treat infective endocarditis. Antistaphylococcal penicillins may be more effective than glycopeptides.

The six small trials included participants with different comorbidities and micro-organisms who received different treatment schedules in terms of antibiotic used and duration of therapy, therefore we were unable to conduct a meta-analysis.

The conclusions of this review are based on RCTs with a high risk of bias. Due to insufficient data, we were unable to draw conclusions to guide practice. Recommendations for antibiotic treatment of endocarditis in current guidelines are based on expert consensus, due to a lack of evidence from RCTs to support them (Baddour 2015; Habib 2019). Data from this review were insufficient to refute or corroborate such recommendations. These findings support what was noted by Paterson 2013, that there is a need for RCTs to define optimal treatment regimens for this serious infection.

This updated review identified six trials assessing many outcomes with small sample sizes. Consequently, it is likely that at least one type I error was made (Delorme 2016; Senn 2007). Two trials without sample size estimation included many outcomes. These trials therefore have a high risk of uncertainty of clinical significance (Mascha 2018; Sormani 2017).

Quality of the evidence

We conducted GRADE assessments. The quality of evidence of the six included trials is shown in Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6. Overall, the included trials had a high risk of bias (Figure 2; Figure 3) due to poor trial design and reporting related to failure to conceal allocation, blinding, selective outcome reporting of the six trials for the main outcomes assessed (all-cause mortality during hospital stay and all-cause mortality at one year, cure, TRAEs, incidence of septic embolism, incidence of congestive heart failure, quality of life, and need for cardiac surgical intervention). Furthermore, we downgraded the quality of the evidence for serious imprecision due to small sample sizes and low number of events.

Potential biases in the review process

The main potential bias in this review was the exclusion of 10 RCTs of antibiotic therapy for the treatment of infective endocarditis because they did not apply modified Duke's criteria for diagnosis (Durack 1994). Von Reyn's old criteria were outperformed by Duke's (Bayer 1994; Von Reyn 1981). There is sufficient long-standing evidence to support the superiority of Ducke's criteria over Von Reyn's old criteria (Durack 1994; Holland 2016; Naber 2001), although Duke's criteria are not perfect (Iung 2019a; Olaison 1996). Today, Dr von Reyn's statement remains valid: "Infective endocarditis is a diagnosis that can only be confirmed unequivocally by examination of the endocardium at surgery or autopsy" (Von Reyn 1981).

In a systematic review process, there is a group of biases known as significance-chasing biases, such as publication bias and selective outcome reporting bias (Ioannidis 2010). Selective outcome reporting bias operates through suppression of information on specific outcomes and is similar to study publication bias in that 'negative' results remain unpublished (Ioannidis 2010). Regarding the risk of selective outcome reporting bias, this updated Cochrane Review found two trials with a low risk (Pericas 2018; POET 2019), two trials with a high risk (Fowler 2006; Sexton 1998), and two trials with an unclear risk (FINLEVO Trial 2006; Fortún 2001). See Figure 2; Figure 3.

Agreements and disagreements with other studies or reviews

This first update found no new systematic reviews to be discussed in this section. Consequently, our results are similar to two non-Cochrane Reviews (Falagas 2006; Yung 2007). These two reviews differed in their eligibility criteria. One review only looked at the management of right-side endocarditis in intravenous drug users (Yung 2007), whereas the other review limited itself to looking specifically at the role of aminoglycosides in combination with beta-lactams to treat endocarditis (Falagas 2006). Our Cochrane Review had no restrictions on micro-organism, clinical population, or antimicrobial agent. Falagas 2006 included a pooled analysis, an approach we decided to avoid due to the heterogeneity in outcome definitions and differences in the composition of the antibiotic regimens. This heterogeneity, along with a paucity of identified trials, prevented us from performing any meta-analysis. Yung 2007 did not pool results because of clinical heterogeneity. Despite these differences, the reviews reached similar results, that is that the evidence from the included trials was insufficient to support or reject one antimicrobial regimen over another.

AUTHORS' CONCLUSIONS

Implications for practice

This first update confirms the findings of the original version of the review. Limited and very low-quality evidence suggests that the comparative effects of different antibiotic regimens in terms of cure rates or other relevant clinical outcomes are uncertain. The conclusions of this updated Cochrane Review were based on few randomised controlled trials with a high risk of bias. Accordingly, the current evidence does not support or reject any regimen of antibiotic therapy for the treatment of infective endocarditis.

Implications for research

Infectious endocarditis is a rare disease caused by different micro-organisms, which vary according to the population at risk. This is an obstacle to the conduct of randomised controlled trials, and should therefore indicate a need for the co-operation of different clinical centres.

Randomised controlled trials are needed to assess the clinical benefits and harms of the use of antibiotic regimens for treating infective endocarditis. These trials should be high-quality randomised trials, with a priori calculation of sample sizes, to assess the clinical benefits and harms of antibiotics to treat infective endocarditis, as noted by Paterson 2013. The trials should be designed according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement (Chan 2013), and reported according to the CONSORT statement for improving the quality of reporting of efficacy and harms in clinical research (Ioannidis 2004; Moher 2010). Future trials should be planned following the Foundation of Patient-Centered Outcomes Research Institute recommendations (Basch 2012; Gabriel 2012; McKinney 2012).

ACKNOWLEDGEMENTS

We acknowledge Georgia Salanti, Petros Georgoulas, Joey SW Kwong, and Ricardo Hidalgo for participating in the protocol of this Cochrane Review.

We express our gratitude to Alma Adler and Nicole Martin for supporting us during the development of the first version of this review.

We want to express our gratitude to Rosa María Finizola, Alma Arrioja, Raquel González, Karen Aguero, Alvis Castillo, and Elizabeth de Mora from Asociación Cardiovascular (ASCARDIO), Barquisimeto, Edo. Lara, Venezuela, for their valuable support during the development of the first version of this review.

We acknowledge Evangelo Boumis (peer reviewer) and Janet Yarrow (consumer reviewer) for improving the quality of the first update of this review. We are also grateful to Lisa Winer for valuable copy edits.

REFERENCES

References to studies included in this review

FINLEVO Trial 2006 *{published data only}*

Ruotsalainen E, Järvinen A, Koivula I, Kauma H, Rintala E, Lumio J, Finlevo Study Group. Levofloxacin does not decrease mortality in *Staphylococcus aureus* bacteraemia when added to the standard treatment: a prospective and randomized clinical trial of 381 patients. *Journal of Internal Medicine* 2006;**259**(2):179-90. [PMID: 16420547]

Fortún 2001 *{published data only}*

Fortún J, Navas E, Martínez-Beltrán J, Pérez-Molina J, Martín-Dávila P, Guerrero A, et al. Short-course therapy for right-side endocarditis due to *Staphylococcus aureus* in drug abusers: cloxacillin versus glycopeptides in combination with gentamicin. *Clinical Infectious Diseases* 2001;**33**(1):120-5. [PMID: 11389505]

Fowler 2006 *{published data only}*

Cosgrove SE, Vigliani GA, Fowler VG Jr, Abrutyn E, Corey GR, Levine DP, et al. Initial low-dose gentamicin for *Staphylococcus aureus* bacteremia and endocarditis is nephrotoxic. *Clinical Infectious Diseases* 2009;**48**(6):713-21. [PMID: 19207079]

* Fowler VG Jr, Boucher HW, Corey GR, Abrutyn E, Karchmer AW, Rupp ME, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. *New England Journal of Medicine* 2006;**355**(7):653-65. [PMID: 16914701]

Kanafani Z, Boucher H, Fowler V, Cabell C, Hoen B, Miro JM, et al. Daptomycin compared to standard therapy for the treatment of native valve endocarditis. *Enfermedades Infecciosas y Microbiología Clínica* 2010;**28**(8):498-503. [PMID: 20188444]

Rehm SJ, Boucher H, Levine D, Campion M, Eisenstein BI, Vigliani GA, et al. Daptomycin versus vancomycin plus gentamicin for treatment of bacteraemia and endocarditis due to *Staphylococcus aureus*: subset analysis of patients infected with methicillin-resistant isolates. *Journal of Antimicrobial Chemotherapy* 2008;**62**(6):1413-21. [PMID: 18782781]

Pericas 2018 *{published data only}*

* Pericàs JM, Moreno A, Almela M, García de la Mària C, Marco F, Muñoz P, FOSIMI Investigators. Efficacy and safety of fosfomycin plus imipenem versus vancomycin for complicated bacteraemia and endocarditis due to methicillin-resistant Staphylococcus aureus: a randomized clinical trial. Clinical Microbiology and Infections 2018;**24**(6):673-6. [PMID: 29408610]

del Rio A, Gasch O, Moreno A, Pena C, Cuquet J, Soy D, et al. Efficacy and safety of fosfomycin plus imipenem as rescue therapy for complicated bacteremia and endocarditis due to methicillin-resistant Staphylococcus aureus: a multicenter clinical trial. *Clinical Infectious Diseases* 2014;**59**(8):1105-12. [PMID: 25048851]

POET 2019 *{published data only}*

Iversen K, Host N, Bruun NE, Elming H, Pump B, Christensen JJ, et al. Partial oral treatment of endocarditis. *American Heart Journal* 2013;**165**(2):116-22. [PMID: 23351813]

* Iversen K, Ihlemann N, Gill SU, Madsen T, Elming H, Jensen KT, et al. Partial oral versus intravenous antibiotic treatment of endocarditis. *New England Journal of Medicine* 2019;**380**(5):415-24. [PMID: 30152252]

Sexton 1998 *{published data only}*

Sexton D, Tenenbaum M, Wilson W, Steckelberg J, Tice A, Gilbert D, et al. Ceftriaxone once daily for four weeks vs. ceftriaxone plus gentamicin for two weeks for the treatment of penicillin susceptible Streptococcal endocarditis. *Clinical Infectious Diseases* 1996;**4**:23889.

* Sexton DJ, Tenenbaum MJ, Wilson WR, Steckelberg JM, Tice AD, Gilbert D, et al. Ceftriaxone once daily for four weeks compared with ceftriaxone plus gentamicin once daily for two weeks for treatment of endocarditis due to penicillin-susceptible streptococci. Endocarditis Treatment Consortium Group. *Clinical Infectious Diseases* 1998;**27**(6):1470-4. [PMID: 9868662]

References to studies excluded from this review

Abrams 1979 *{published data only}*

Abrams B, Sklaver A, Hoffman T, Greenman R. Single or combination therapy of staphylococcal endocarditis in intravenous drug abusers. *Annals of Internal Medicine* 1979;**90**(5):789-91. [PMID: 434682]

Fortún 1995 *{published data only}*

Fortún J, Pérez-Molina JA, Añón MT, Martínez-Beltrán J, Loza E, Guerrero A. Right-sided endocarditis caused by *Staphylococcus aureus* in drug abusers. *Antimicrobial Agents and Chemotherapy* 1995;**39**(2):525-8. [PMID: 7726526]

Gilbert 1991 *{published data only}*

Gilbert DN, Wood CA, Kimbrough RC. Failure of treatment with teicoplanin at 6 milligrams/kilogram/day in patients with *Staphylococcus aureus* intravascular infection. The Infectious Diseases Consortium of Oregon. *Antimicrobial Agents and Chemotherapy* 1991;**35**(1):79-87. [PMID: 1826594]

Greenman 1984 *{published data only}*

Greenman RL, Arcey SM, Gutterman DA, Zweig RM. Twice-daily intramuscular ceforanide therapy of *Staphylococcus aureus* endocarditis in parenteral drug abusers. *Antimicrobial Agents and Chemotherapy* 1984;**25**(1):16-9. [PMID: 6703681]

Heldman 1996 *{published data only}*

Heldman AW, Hartert TV, Ray SC, Daoud EG, Kowalski TE, Pompili VJ, et al. Oral antibiotic treatment of right-sided staphylococcal endocarditis in injection drug users: prospective randomized comparison with parenteral therapy. *American Journal of Medicine* 1996;**101**(1):68-76. [PMID: 8686718]

Korzeniowski 1982 *{published data only}*

Korzeniowski O, Sande MA. Combination antimicrobial therapy for *Staphylococcus aureus* endocarditis in patients addicted to parenteral drugs and in nonaddicts: a prospective study. *Annals of Internal Medicine* 1982;**97**(4):496-503. [PMID: 6751182]

Levine 1991 *{published data only}*

Levine DP, Fromm BS, Reddy BR. Slow response to vancomycin or vancomycin plus rifampin in methicillin-resistant *Staphylococcus aureus* endocarditis. *Annals of Internal Medicine* 1991;**115**(9):674-80. [PMID: 1929035]

Markowitz 1992 *{published data only}*

Markowitz N, Quinn EL, Saravolatz LD. Trimethoprim-sulfamethoxazole compared with vancomycin for the treatment of *Staphylococcus aureus* infection. *Annals of Internal Medicine* 1992;**117**(5):390-8. [PMID: 1503330]

Ribera 1996 *{published data only}*

Ribera E, Gomez-Jimenez J, Cortes E, del Valle O, Planes A, Gonzalez-Alujas T, et al. Effectiveness of cloxacillin with and without gentamicin in short-term therapy for right-sided *Staphylococcus aureus* endocarditis. A randomized, controlled trial. *Annals of Internal Medicine* 1996;**125**(12):969-74. [PMID: 8967707]

Stamboulian 1991 *{published data only}*

Stamboulian D, Bonvehi P, Arevalo C, Bologna R, Cassetti I, Scilingo V, et al. Antibiotic management of outpatients with endocarditis due to penicillin-susceptible streptococci. *Reviews of Infectious Diseases* 1991;**13**(Suppl 2):160-3. [PMID: 2017645]

References to ongoing studies

CTRI/2008/091/000060 *{published data only}*

CTRI/CTRI/2008/091/000060. A clinical trial to study the safety and efficacy of combination drug, vancomycin and ceftriaxone compared to vancomycin in mild to severe bacterial infections. who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2008/091/000060 (date registered 7 May 2008).

EUCTR 2016-003059-31 *{published data only}*

EUCTR 2016-003059-31. Study to assess the efficacy, safety and pharmacokinetics of CF-301 compared with placebo in addition to standard-of-care antibiotic therapy in blood infections caused by S. aureus, including heart valve infections. who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2016-003059-31 (start date 2 November 2017).

EUCTR 2017-001699-43 *{published data only}*

EUCTR2017-001699-43. A study to assess the efficacy and safety of ceftobiprole medocaril compared to daptomycin in the treatment of Staphylococcus aureus bacteremia, including infective endocarditis. who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2017-001699-43 (start date 13 December 2018).

EudraCT 2008-008683-28 *{published data only}*

EUCTR 2008-008683-28. Evaluación de la eficacia y la seguridad de la combinación de fosfomicina (F) e imipenem (I) para el tratamiento de la endocarditis infecciosa (EI) sobre válvula nativa o protésica por S. Aureus resistente a meticilina (SARM). who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2008-008683-28 (start date 23 September 2009).

JPRN-UMIN 000032006 *{published data only}*

JPRN-UMIN 000032006. An open-label randomized controlled trial of ampicillin/cloxacillin and ceftriaxone for empirical treatment of infective endocarditis. who.int/trialsearch/Trial2.aspx?TrialID=JPRN-UMIN000032006 (first received 31 March 2018).

NCT00638157 *{published data only}*

NCT00638157. Phase 4 Efficacy and safety study of cubicin® with and without combination therapy in S. aureus infective endocarditis (SAIE). clinicaltrials.gov/ct2/show/NCT00638157 (first received 18 March 2008).

NCT00695903 *{published data only}*

NCT00695903. Phase 2 study of safety, efficacy, and pharmacokinetics of higher doses of daptomycin and vancomycin in MRSA bacteremia (HDSAB). clinicaltrials.gov/ct2/show/NCT00695903 (first received 12 June 2008).

NCT02208063 *{published data only}*

NCT02208063. A phase 3 telavancin Staphylococcus aureus (S. aureus) bacteremia trial. clinicaltrials.gov/ct2/show/NCT02208063 (first received 4 August 2014).

NCT02701595 *{published data only}*

NCT02701595. Oral switch during treatment of left-sided endocarditis due to multi-susceptible streptococcus. clinicaltrials.gov/ct2/show/NCT02701595 (first received 8 March 2016).

NCT02701608 *{published data only}*

NCT02701608. Oral switch during treatment of left-sided endocarditis due to multi-susceptible staphylococcus. clinicaltrials.gov/ct2/show/NCT02701608 (first received 8 March 2016).

NCT03138733 *{published data only}*

NCT03138733. Ceftobiprole in the treatment of patients with Staphylococcus aureus bacteremia. clinicaltrials.gov/show/nct03138733 (first received 3 May 2017).

NCT03148756 *{published data only}*

NCT03148756. Efficacy and safety of dalbavancin compared to standard of care antibiotic therapy for the completion of treatment of patients with complicated bacteremia or infective endocarditis. clinicaltrials.gov/show/nct03148756 (first received 11 May 2017).

NCT04222257 *{published data only}*

NCT04222257. Short-course antibiotic treatment in gram-positive cocci infective endocarditis (SATIE). clinicaltrials.gov/ct2/show/NCT04222257 (first received 9 January 2020).

RBR-3p8g7n 2016 *{published data only}*

RBR-3p8g7n. Clinical trial of telavancin versus standard intravenous therapy in the treatment of subjects with Staphylococcus aureus bacteremia including infective

endocarditis. apps.who.int/trialsearch/Trial2.aspx?TrialID=RBR-3p8g7n (first received 3 August 2016).

Additional references

Amat-Santos 2015

Amat-Santos IJ, Ribeiro HB, Urena M, Allende R, Houde C, Bedard E, et al. Prosthetic valve endocarditis after transcatheter valve replacement: a systematic review. *JACC. Cardiovascular Interventions* 2015;**8**(2):334-46. [PMID: 25700757]

Ambrosioni 2017

Ambrosioni J, Hernandez-Meneses M, Tellez A, Pericas J, Falces C, Tolosana JM, et al. The changing epidemiology of infective endocarditis in the Twenty-First Century. *Current Infectious Disease Reports* 2017;**19**(5):21. [PMID: 28401448]

Anderson 2008

Anderson VR, Perry CM. Levofloxacin: a review of its use as a high-dose, short-course treatment for bacterial infection. *Drugs* 2008;**68**(4):535-65. [PMID: 18318569]

Asai 2019

Asai N, Shiota A, Ohashi W, Watanabe H, Shibata Y, Kato H, et al. The SOFA score could predict the severity and prognosis of infective endocarditis. *Journal of Infection and Chemotherapy* 2019;**25**(12):965-71. [PMID: 31320197]

Avelana 2018

Avelana PM, Aurelio M, Swieszkowski S, Nacinovich F, Kazelian L, Spenato M, et al. Infective endocarditis in Argentina. Results of the EIRA 3 study [Endocarditis infecciosa en la República Argentina. Resultados del estudio EIRA 3]. *Revista Argentina de Cardiología* 2018;**86**(1):21-9. [biblio-990513]

Ba 2017

Ba DM, Mboup MC, Zeba N, Dia K, Fall AN, Fall F, et al. Infective endocarditis in Principal Hospital of Dakar: a retrospective study of 42 cases over 10 years. *Pan African Medical Journal* 2017;**26**:40. [PMID: 28451018]

Baddour 2015

Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Tleyjeh IM, Rybak MJ, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation* 2015;**132**(15):1435-86. [PMID: 26373316]

Bai 2017

Bai AD, Agarwal A, Steinberg M, Showler A, Burry L, Tomlinson GA, et al. Clinical predictors and clinical prediction rules to estimate initial patient risk for infective endocarditis in Staphylococcus aureus bacteraemia: a systematic review and meta-analysis. *Clinical Microbiology and Infection* 2017;**23**(12):900-6. [PMID: 28487168]

Balshem 2011

Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology* 2011;**64**(4):401-6. [PMID: 21208779]

Basch 2012

Basch E, Aronson N, Berg A, Flum D, Gabriel S, Goodman SN, et al. Methodological standards and patient-centeredness in comparative effectiveness research: the PCORI perspective. *JAMA* 2012;**307**(15):1636-40. [PMID: 22511692]

Bayer 1994

Bayer AS, Ward JI, Ginzton LE, Shapiro SM. Evaluation of new clinical criteria for the diagnosis of infective endocarditis. *American Journal of Medicine* 1994;**96**(3):211-9. [PMID: 8154508]

Beganovic 2018

Beganovic M, Luther MK, Rice LB, Arias CA, Rybak MJ, LaPlante KL. A review of combination antimicrobial therapy for Enterococcus faecalis bloodstream infections and infective endocarditis. *Clinical Infectious Diseases* 2018;**67**(2):303-9. [PMID: 29390132]

Beteille 2018

Beteille E, Guarana M, Nucci M. Infective endocarditis in neutropenic patients with viridans streptococci bacteraemia. Clinical Microbiology and Infection 2018;**24**(8):916-7. [PMID: 29559393]

Burgos 2019

Burgos LM, Cracco MA, Fernandez Oses P, Iribarren AC, Ronderos R, Nacinovich F. Infective endocarditis in Argentina: what have we learned in the last 25 years ? [Endocardtis infecciosa en ARGENTINA: ¿Qué aprendimos en los últimos 25 años?]. *Medicina* 2019;**79**(4):257-64. [PMID: 31487244]

Cahill 2016

Cahill TJ, Prendergast BD. Infective endocarditis. *Lancet* 2016;**387**(10021):882-93. [PMID: 26341945]

Cantier 2019

Cantier M, Sabben C, Adle-Biassette H, Louedec L, Delbosc S, Desilles JP, et al. Neurologic complications of infective endocarditis: a joint model for a septic thromboembolism and inflammatory small vessel disease. *Critical Care Medicine* 2019;**47**(8):e685-92. [PMID: 31149963]

Cao 2018

Cao GF, Liu W, Bi Q. Stroke in patients with infective endocarditis: a 15-year single-center cohort study. *European Neurology* 2018;**80**(3-4):171-8. [PMID: 30485851]

Cecchi 2015

Cecchi E, Chirillo F, Castiglione A, Faggiano P, Cecconi M, Moreo A, et al. Clinical epidemiology in Italian registry of infective endocarditis (RIEI): focus on age, intravascular devices and enterococci. *International Journal of Cardiology* 2015;**190**:151-6. [PMID: 25918069]

Chambers 2001a

Chambers HF. The aminoglycosides. In: Hardman JG, Limbird LE, editors(s). Goodman & Gilman's. The Pharmacological

Basis of Therapeutics. 10th edition. New York: McGraw Hill, 2001:1219-38. [ISBN: 0-07-135469-7]

Chambers 2001b

Chambers HF. Protein synthesis inhibitors and miscellaneous antibacterial agents. In: Hardman JG, Limbird LE, editors(s). Goodman & Gilman's. The Pharmacological Basis of Therapeutics. 10th edition. New York: McGraw Hill, 2001:1239-71. [ISBN: 0-07-135469-7]

Champey 2016

Champey J, Pavese P, Bouvaist H, Kastler A, Krainik A, Francois P. Value of brain MRI in infective endocarditis: a narrative literature review. *European Journal of Clinical Microbiology and Infectious Diseases* 2016;**35**(2):159-68. [PMID: 26585337]

Chan 2013

Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;**346**:e7586. [PMID: 23303884]

Chen 2009

Chen LF, Kaye D. Current use for old antibacterial agents: polymyxins, rifamycins, and aminoglycosides. *Infectious Disease Clinics of North America* 2009;**23**(4):1053-75. [PMID: 19909897]

Chopra 2007

Chopra P, Gulwani H. Pathology and pathogenesis of rheumatic heart disease. *Indian Journal of Pathology & Microbiology* 2007;**50**(4):685-97. [PMID: 18306530]

Colomer-Winter 2018

Colomer-Winter C, Gaca AO, Chuang-Smith ON, Lemos JA, Frank KL. Basal levels of (p)ppGpp differentially affect the pathogenesis of infective endocarditis in Enterococcus faecalis. *Microbiology* 2018;**164**(10):1254-65. [PMID: 30091695]

Cosgrove 2009

Cosgrove SE, Vigliani GA, Fowler VG Jr, Abrutyn E, Corey GR, Levine DP, et al. Initial low-dose gentamicin for *Staphylococcus aureus* bacteremia and endocarditis is nephrotoxic. *Clinical Infectious Diseases* 2009;**48**(6):713-21. [PMID: 19207079]

Cresti 2017

Cresti A, Chiavarelli M, Scalese M, Nencioni C, Valentini S, Guerrini F, et al. Epidemiological and mortality trends in infective endocarditis, a 17-year population-based prospective study. *Cardiovascular Diagnosis and Therapy* 2017;**7**(1):27-35. [PMID: 28164010]

Cunha 2015

Cunha BA, Brahmbhatt K, Raza M. Haemophilus parainfluenzae aortic prosthetic valve endocarditis (PVE) successfully treated with oral levofloxacin. *Heart and Lung* 2015;**44**(4):317-20. [PMID: 25998992]

Daga 2011

Daga S, Shepherd J, Callaghan G, Hung R, Dawson D, Padfield G, et al. Platelet receptor polymorphisms do not influence *Staphylococcus aureus*-platelet interactions or infective endocarditis. *Microbes and Infection* 2011;**13**(3):216-25. [PMID: 21044892]

Damasco 2019

Damasco PV, Correal JCD, Cruz-Campos ACD, Wajsbrot BR, Cunha RGD, Fonseca AGD, et al. Epidemiological and clinical profile of infective endocarditis at a Brazilian tertiary care center: an eight-year prospective study. *Revista da Sociedade Brasileira de Medicina Tropical* 2019;**52**:e2018375. [PMID: 31188916]

de Jong 2019

de Jong NWM, van Kessel KPM, van Strijp JAG. Immune evasion by Staphylococcus aureus. *Microbiology Spectrum* 2019;**7**(2):GPP3-0061-2019. [PMID: 30927347]

Delahaye 2019

Delahaye F, De Gevigney G. Infective endocarditis and specific situations: right heart, valve prosthesis, cardiac implantable electronic device [Endocardites infectieuses: formes particulieres (coeur droit, prothese valvulaire, dispositif electronique intracardiaque)]. *Presse Medicale* 2019;**48**(5):549-55. [PMID: 31109767]

Delorme 2016

Delorme P, de Micheaux PL, Liquet B, Riou J. Type-II generalized family-wise error rate formulas with application to sample size determination. *Statistics in Medicine* 2016;**35**(16):2687-714. [PMID: 26914402]

Dhotre 2018

Dhotre S, Jahagirdar V, Suryawanshi N, Davane M, Patil R, Nagoba B. Assessment of periodontitis and its role in viridans streptococcal bacteremia and infective endocarditis. *Indian Heart Journal* 2018;**70**(2):225-32. [PMID: 29716699]

Drees 2006

Drees M, Boucher H. New agents for *Staphylococcus aureus* endocarditis. *Current Opinion in Infectious Diseases* 2006;**19**(6):544-50. [PMID: 17075329]

Dryden 2011

Dryden MS. Linezolid pharmacokinetics and pharmacodynamics in clinical treatment. *Journal of Antimicrobial Chemotherapy* 2011;**66**(Suppl 4):iv7-15. [PMID: 21521707]

Durack 1994

Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. *American Journal of Medicine* 1994;**96**(3):200-9. [PMID: 8154507]

Egbe 2019

Egbe AC, Vallabhajosyula S, Akintoye E, Connolly HM. Trends and outcomes of infective endocarditis in adults with tetralogy of Fallot: a review of the national inpatient sample database. *Canadian Journal of Cardiology* 2019;**35**(6):721-6. [PMID: 31151707]

El Rafei 2016

El Rafei A, DeSimone DC, DeSimone CV, Lahr BD, Steckelberg JM, Sohail MR, et al. Beta-haemolytic streptococcal endocarditis: clinical presentation, management and outcomes. *Infectious Diseases (London, England)* 2016;**48**(5):373-8. [PMID: 26950685]

Elbatarny 2019

Elbatarny M, Bahji A, Bisleri G, Hamilton A. Management of endocarditis among persons who inject drugs: a narrative review of surgical and psychiatric approaches and controversies. *General Hospital Psychiatry* 2019;**57**:44-9. [PMID: 30908961]

Elmistekawy 2016

Elmistekawy E, Chan V, Mesana T. Surgical management: indications, timing and surgical techniques. In: Chan K-L, Embil JM, editors(s). Endocarditis: Diagnosis and Management. London: Springer-Verlag, 2016:153-79. [DOI: 10.1007/978-3-319-27784-4_8]

Erdem 2019

Erdem H, Puca E, Ruch Y, Santos L, Ghanem-Zoubi N, Argemi X, et al. Portraying infective endocarditis: results of multinational ID-IRI study. European Journal of Clinical Microbiology and Infectious Diseases 2019;**38**(9):1753-63. [PMID: 31187307]

Falagas 2006

Falagas ME, Matthaiou DK, Bliziotis IA. The role of aminoglycosides in combination with a beta-lactam for the treatment of bacterial endocarditis: a meta-analysis of comparative trials. *Journal of Antimicrobial Chemotherapy* 2006;**57**(4):639-47. [PMID: 16501057]

Falagas 2007

Falagas ME, Giannopoulou KP, Ntziora F, Vardakas KZ. Daptomycin for endocarditis and/or bacteraemia: a systematic review of the experimental and clinical evidence. *Journal of Antimicrobial Chemotherapy* 2007;**60**(1):7-19. [PMID: 17550889]

Flemming 2010

Flemming HC, Wingender J. The biofilm matrix. *Nature Reviews. Microbiology* 2010;**8**(9):623-33. [PMID: 20676145]

Flemming 2016

Flemming HC, Wingender J, Szewzyk U, Steinberg P, Rice SA, Kjelleberg S. Biofilms: an emergent form of bacterial life. *Nature Reviews. Microbiology* 2016;**14**(9):563-75. [PMID: 27510863]

Frank 2009

Frank U, Tacconelli E. Treatment of the most frequent types of bacterial endocarditis. In: Frank U, Tacconelli E, editors(s). The Daschner Guide to In-Hospital Antibiotic Therapy. Heidelberg: Springer Medizin Verlag, 2009:211-4. [ISBN: 978-3-540-48347-2]

Gabriel 2012

Gabriel SE, Normand SL. Getting the methods right - the Foundation of Patient-Centered Outcomes Research. *New England Journal of Medicine* 2012;**367**(9):787-90. [PMID: 22830434]

Giacobbe 2019

Giacobbe DR, Corcione S, Salsano A, Del Puente F, Mornese Pinna S, De Rosa FG, et al. Current and emerging pharmacotherapy for the treatment of infections following open-heart surgery. *Expert Opinion on Pharmacotherapy* 2019;**20**(6):751-72. [PMID: 30785333]

Gould 2011

Gould FK. Linezolid: safety and efficacy in special populations. *Journal of Antimicrobial Chemotherapy* 2011;**66**(Suppl 4):iv3-6. [PMID: 21521705]

GRADEpro 2008 [Computer program]

The GRADE Working Group GRADEpro. Brozek J, Oxman A, Schünemann H, Version 3.2 for Windows. The GRADE Working Group, 2008.

Granowitz 2008

Granowitz EV, Brown RB. Antibiotic adverse reactions and drug interactions. *Critical Care Clinics* 2008;**24**(2):421-42. [PMID: 18361954]

Grisoli 2014

Grisoli D, Million M, Edouard S, Thuny F, Lepidi H, Collart F, et al. Latent Q fever endocarditis in patients undergoing routine valve surgery. *Journal of Heart Valve Disease* 2014;**23**(6):735-43. [PMID: 25790621]

Guerra 2017

Guerra FE, Borgogna TR, Patel DM, Sward EW, Voyich JM. Epic immune battles of history: neutrophils vs. Staphylococcus aureus. *Frontiers in Cellular and Infection Microbiology* 2017;**7**:286. [PMID: 28713774]

Gupta 2011

Gupta A, Biyani M, Khaira A. Vancomycin nephrotoxicity: myths and facts. *Netherlands Journal of Medicine* 2011;**69**(9):379-83. [PMID: 21978980]

Guyatt 2008

Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ. What is "quality of evidence" and why is it important to clinicians? *BMJ* 2008;**336**(7651):995-8. [PMID: 18456631]

Guyatt 2011a

Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence - imprecision. *Journal of Clinical Epidemiology* 2011;**64**(12):1283-93. [PMID: 21839614]

Guyatt 2011b

Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence - inconsistency. *Journal of Clinical Epidemiology* 2011;**64**(12):1294-302. [PMID: 21803546]

Guyatt 2011c

Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, et al. GRADE guidelines: 5. Rating the quality of evidence

- publication bias. *Journal of Clinical Epidemiology* 2011;**64**(12):1277-82. [PMID: 21802904]

Guyatt 2011d

Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 8. Rating the quality of evidence - indirectness. *Journal of Clinical Epidemiology* 2011;**64**(12):1303-10. [PMID: 21802903]

Guyatt 2011e

Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. *Journal of Clinical Epidemiology* 2011;**64**(12):1311-6. [PMID: 21802902]

Guyatt 2011f

Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence - study limitations (risk of bias). *Journal of Clinical Epidemiology* 2011;**64**(4):407-15. [PMID: 21247734]

Guyatt 2011g

Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**(4):383-94. [PMID: 21195583]

Guyatt 2011h

Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *Journal of Clinical Epidemiology* 2011;**64**(4):395-400. [PMID: 21194891]

Habib 2015

Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, ESC Scientific Document Group. 2015 ESC guidelines for the management of infective endocarditis: the task force for the management of infective endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *European Heart Journal* 2015;**36**(44):3075-128. [PMID: 26320109]

Habib 2019

Habib G, Erba PA, Iung B, Donal E, Cosyns B, Laroche C, et al. Clinical presentation, aetiology and outcome of infective endocarditis. Results of the ESC-EORP EURO-ENDO (European infective endocarditis) registry: a prospective cohort study. *European Heart Journal* 2019;**40**(39):3222-32. [PMID: 31504413]

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60. [PMID: 12958120]

Higgins 2011

Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hitzenbichler 2019

Hitzenbichler F, Olic J, Hanses F, Salzberger B, Fischer M, Baessler A. Current treatment of endocarditis: innovations and controversies [Aktuelle therapie der endokarditis: neuerungen und kontroversen]. *Der Internist* 2019;**60**(10):1111-17. [PMID: 31444523]

Hoen 2006

Hoen B. Epidemiology and antibiotic treatment of infective endocarditis: an update. *Heart* 2006;**92**(11):1694-700. [PMID: 17041124]

Holland 2016

Holland TL, Baddour LM, Bayer AS, Hoen B, Miro JM, Fowler VG Jr. Infective endocarditis. *Nature Reviews. Disease Primers* 2016;**2**:16059. [PMID: 27582414]

Hollis 1999

Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *BMJ* 1999;**319**(7211):670-4. [PMID: 10480822]

Humphries 2013

Humphries RM, Pollett S, Sakoulas G. A current perspective on daptomycin for the clinical microbiologist. *Clinical Microbiology Reviews* 2013;**26**(4):759-80. [PMID: 24092854]

Ioannidis 2004

Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Annals of Internal Medicine* 2004;**141**(10):781-8. [PMID: 15545678]

Ioannidis 2010

Ioannidis JP. Meta-research: the art of getting it wrong. *Research Synthesis Methods* 2010;**10**(3-4):169-84.

Iung 2019a

Iung B, Duval X. Infective endocarditis: innovations in the management of an old disease. *Nature Reviews. Cardiology* 2019;**16**(10):623-35. [PMID: 31175343]

Iung 2019b

Iung B. Infective endocarditis. Epidemiology, pathophysiology and histopathology [Endocardite infectieuse. Epidemiologie, physiopathologie et anatomopathologie]. *Presse Medicale* 2019;**48**(5):513-21. [PMID: 31056234]

Jakuska 2019

Jakuska P, Ereminiene E, Muliuolyte E, Kosys V, Pavlavicius L, Zukovas G, et al. Predictors of early mortality after surgical treatment of infective endocarditis: a single-center experience. Perfusion 2019;**Sep 4**:Online ahead of print.. [DOI: 10.1177/0267659119872345] [PMID: 31480970]

Jung 2015

Jung CJ, Yeh CY, Hsu RB, Lee CM, Shun CT, Chia JS. Endocarditis pathogen promotes vegetation formation by inducing intravascular neutrophil extracellular traps through activated platelets. *Circulation* 2015;**131**(6):571-81. [PMID: 25527699]

Karchmer 2009

Karchmer AW. Infective endocarditis. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, et al, editors(s). Harrison's Principles of Internal Medicine. 17th edition. New York: McGraw-Hill, 2009:440-7. [ISBN: 978-0-07-147743-7]

Keynan 2013

Keynan Y, Rubinstein E. Pathophysiology of infective endocarditis. *Current Infectious Disease Reports* 2013;**15**(4):342-6. [PMID: 23737237]

Khan 2017

Khan ZA, Hollenberg SM. Valvular heart disease in adults: infective endocarditis. *FP Essentials* 2017;**457**:30-8. [PMID: 28671807]

Kobayashi 2019

Kobayashi T, Ando T, Streit J, Sekar P. Current evidence on oral antibiotics for infective endocarditis: a narrative review. *Cardiology and Therapy* 2019;**8**(2):167-77. [PMID: 31535282]

Krčméry 2019

Krčméry V, Hricak V, Fischer V, Mrazova M, Brnova J, Hulman M, et al. Etiology, risk factors and outcome of 1003 cases of infective endocarditis from a 33-year National Survey in the Slovak Republic: an increasing proportion of elderly patients. *Neuro Endocrinology Letters* 2019;**39**(8):544-9. [PMID: 30927759]

Kumar 2019

Kumar M, Anstadt EJ, Lopetegui Lia N, Siddiqi MH. Streptococcus viridans endocarditis affecting all four valves. Cureus 2019;**11**(5):e4635. [PMID: 31312561]

Lagace-Wiens 2012

Lagace-Wiens P, Rubinstein E. Adverse reactions to beta-lactam antimicrobials. *Expert Opinion on Drug Safety* 2012;**11**(3):381-99. [PMID: 22220627]

Leach 2011

Leach KL, Brickner SJ, Noe MC, Miller PF. Linezolid, the first oxazolidinone antibacterial agent. *Annals of the New York Academy of Sciences* 2011;**1222**:49-54. [PMID: 21434942]

Leahey 2019

Leahey PA, LaSalvia MT, Rosenthal ES, Karchmer AW, Rowley CF. High morbidity and mortality among patients with sentinel admission for injection drug use-related infective endocarditis. *Open Forum Infectious Diseases* 2019;**6**(4):ofz089. [PMID: 30949535]

Leekha 2011

Leekha S, Terrell CL, Edson RS. General principles of antimicrobial therapy. *Mayo Clinic Proceedings* 2011;**86**:156-67. [PMID: 21282489]

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Leyva 2008

Leyva S, Leyva E. Fluoroquinolonas. Mecanismos de acción y resistencia, estructura, síntesis y reacciones fisicoquímicas importantes para propiedades medicinales. Boletín de la Sociedad Química de México 2008;**2**(1):1-13.

Li 2000

Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clinical Infectious Diseases* 2000;**30**(4):633-8. [PMID: 10770721]

Liberati 2009

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of Clinical Epidemiology* 2009;**62**(10):e1-34. [PMID: 19631507]

Lin 2019

Lin CJ, Chua S, Chung SY, Hang CL, Tsai TH. Diabetes mellitus: an independent risk factor of in-hospital mortality in patients with infective endocarditis in a new era of clinical practice. *International Journal of Environmental Research and Public Health* 2019;**16**(12):2248. [PMID: 31242695]

Liu 2010

Liu HH. Safety profile of the fluoroquinolones: focus on levofloxacin. *Drug Safety* 2010;**33**(5):353-69. [PMID: 20397737]

Lluri 2018

Lluri G, Levi DS, Miller E, Hageman A, Sinha S, Sadeghi S, et al. Incidence and outcome of infective endocarditis following percutaneous versus surgical pulmonary valve replacement. *Catheterization and Cardiovascular Interventions* 2018;**91**(2):277-84. [PMID: 28895275]

Long 2018

Long B, Koyfman A. Infectious endocarditis: an update for emergency clinicians. *American Journal of Emergency Medicine* 2018;**36**(9):1686-92. [PMID: 30001813]

Mascha 2018

Mascha EJ, Vetter TR. Significance, errors, power, and sample size: the blocking and tackling of statistics. *Anesthesia and Analgesia* 2018;**126**(2):691-8. [PMID: 29346210]

McKinney 2012

McKinney M. 'Time is of the essence'. PCORI moves to implement comparative effectiveness research, funding. Modern Healthcare 2012;**42**(5):12-3. [PMID: 22356074]

Melehani 2016

Melehani JH, Duncan JA. Inflammasome activation can mediate tissue-specific pathogenesis or protection in Staphylococcus aureus infection. *Current Topics in Microbiology and Immunology* 2016;**397**:257-82. [PMID: 27460814]

Meshaal 2018

Meshaal MS, Labib D, Said K, Hosny M, Hassan M, Abd Al Aziz S, et al. Aspergillus endocarditis: diagnostic criteria and

predictors of outcome, a retrospective cohort study. *PLOS ONE* 2018;**13**(8):e0201459. [PMID: 30092074]

Mgbojikwe 2019

Mgbojikwe N, Jones SR, Leucker TM, Brotman DJ. Infective endocarditis: beyond the usual tests. *Cleveland Clinic Journal of Medicine* 2019;**86**(8):559-67. [PMID: 31385793]

Moher 2010

Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;**340**:c869. [PMID: 20332511]

Moriyama 2019

Moriyama N, Laakso T, Biancari F, Raivio P, Jalava MP, Jaakkola J, et al. Prosthetic valve endocarditis after transcatheter or surgical aortic valve replacement with a bioprosthesis: results from the FinnValve Registry. *EuroIntervention* 2019;**15**(6):e500-7. [PMID: 31113766]

Moser 2017

Moser C, Elming H, Helweg-Larsen J, Christensen JJ, Jensen KT, Smerup MH, et al. Infectious endocarditis. Danish guidelines [Infektiøs endocarditis]. www.nbv.cardio.dk/endocarditis (accessed 28 February 2019).

Murphy 2019

Murphy DJ, Din M, Hage FG, Reyes E. Guidelines in review: Comparison of ESC and AHA guidance for the diagnosis and management of infective endocarditis in adults. *Journal of Nuclear Cardiology* 2019;**26**(1):303-8. [PMID: 29923105]

Muñoz 2007

Muñoz P, Rodriguez-Creixems M, Moreno M, Marin M, Ramallo V, Bouza E. Linezolid therapy for infective endocarditis. *Clinical Microbiology and Infection* 2007;**13**(2):211-5. [PMID: 17328738]

Muñoz-Moreno 2019

Muñoz-Moreno MF, Ryan P, Alvaro-Meca A, Valencia J, Tamayo E, Resino S. National temporal trend analysis of infective endocarditis among patients infected with HIV in Spain (1997-2014): a retrospective study. *Journal of Clinical Medicine* 2019;**8**(8):E1167. [PMID: 31382658]

Naber 2001

Naber CK, Bartel T, Eggebrecht H, Erbel R. Diagnosis of endocarditis today: Duke criteria or clinical judgment? [Endokarditisdiagnostik Heute: Duke-Kriterien oder klinische Einschatzung?]. *Herz* 2001;**26**(6):379-90. [PMID: 11683068]

Nagy 2018

Nagy M, Alkady H, Abo Senna W, Abdelhay S. Predictors of surgical outcome in isolated prosthetic mitral valve endocarditis. *Asian Cardiovascular and Thoracic Annals* 2018;**26**(7):517-23. [PMID: 30185074]

Nailor 2009

Nailor MD, Sobel JD. Antibiotics for Gram-positive bacterial infections: vancomycin, teicoplanin, quinupristin/dalfopristin, oxazolidinones, daptomycin, dalbavancin, and telavancin. *Infectious Diseases Clinics of North America* 2009;**23**(4):965-82. [PMID: 19909893]

Nascimento 2019

Nascimento CA. Embolic complications in infective endocarditis: how can we predict using a Risk Evaluator Score (SORTIE or ABCDE) [Complicações embólicas na endocardite infecciosa: como poderemos prever usando Escore Avaliador do Risco (ABCDE ou SORTIE)]. *ABC Imagem Cardiovascular* 2019;**32**(4):251-3. [PMID: biblio-1023850]

Nasser 2019

Nasser A, Moradi M, Jazireian P, Safari H, Alizadeh-Sani M, Pourmand MR, et al. Staphylococcus aureus versus neutrophil: scrutiny of ancient combat. *Microbial Pathogenesis* 2019;**131**:259-69. [PMID: 31002964]

Nebeker 2004

Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. *Annals of Internal Medicine* 2004;**140**(10):795-801. [PMID: 15148066]

Ogura 2019

Ogura N, Tomari K, Takayama T, Tonegawa N, Okawa T, Matsuoka T, et al. Group A streptococcus endocarditis in children: 2 cases and a review of the literature. *BMC Infectious Diseases* 2019;**19**(1):102. [PMID: 30704409]

Olaison 1996

Olaison L, Hogevik H. Comparison of the von Reyn and Duke criteria for the diagnosis of infective endocarditis: a critical analysis of 161 episodes. *Scandinavian Journal of Infectious Diseases* 1996;**28**(4):399-406. [PMID: 8893406]

Pabilona 2015

Pabilona C, Gitler B, Lederman JA, Miller D, Keltz TN. Prosthetic valve endocarditis with valvular obstruction after transcatheter aortic valve replacement. *Texas Heart Institute Journal* 2015;**42**(2):172-4. [PMID: 25873834]

Paterson 2013

Paterson DL. Determining research priorities for clinician-initiated trials in infectious diseases. *Medical Journal of Australia* 2013;**198**(5):270-2. [PMID: 23496404]

Petri 2001a

Petri WA Jr. Penicillins, cephalosporins, and other β-lactam antibiotics. In: Hardman JG, Limbird LE, editors(s). Goodman & Gilman's. The Pharmacological Basis of Therapeutics. 10th edition. New York: McGraw Hill, 2001:1189-218. [ISBN: 0-07-135469-7]

Petri 2001b

Petri WA Jr. Drug used in the chemotherapy of tuberculosis, *Mycobacterium avium* complex disease, and leprosy. In: Hardman JG, Limbird LE, editors(s). Goodman & Gilman's. The Pharmacological Basis of Therapeutics. 10th edition. New York: McGraw Hill, 2001:1273-94. [ISBN: 0-07-135469-7]

R 2018

R M, V R, Nambi PS, Ramakrishnan B, Gopalakrishnan R, Sathyamurthy. Profile of infective endocarditis: at a tertiary care referral centre. *Journal of the Association of Physicians of India* 2018;**66**(6):60-5. [PMID: 31331138]

Review Manager 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Sadeghi 2019

Sadeghi S, Wadia S, Lluri G, Tarabay J, Fernando A, Salem M, et al. Risk factors for infective endocarditis following transcatheter pulmonary valve replacement in patients with congenital heart disease. *Catheterization and Cardiovascular Interventions* 2019;**94**(4):625-35. [PMID: 31471941]

Salvador 2017

Salvador VB, Chapagain B, Joshi A, Brennessel DJ. Clinical risk factors for infective endocarditis in Staphylococcus aureus bacteremia. *Texas Heart Institute Journal* 2017;**44**(1):10-5. [PMID: 28265207]

Saraste 2019

Saraste A, Knuuti J. Guidelines in review: Comparison of ESC and AHA guidance for the diagnosis and management of infective endocarditis in adults. Are the differences clinically relevant? The European perspective. Journal of Nuclear Cardiology 2019;**26**(1):309-12. [PMID: 30132186]

Selton-Suty 2019

Selton-Suty C, Goehringer F, Venner C, Thivilier C, Huttin O, Hoen B. Complications and prognosis of infective endocarditis [Complications et pronostic de l'endocardite infectieuse]. *Presse Medicale* 2019;**48**(5):532-8. [PMID: 31056233]

Senn 2007

Senn S, Bretz F. Power and sample size when multiple endpoints are considered. *Pharmaceutical Statistics* 2007;**6**(3):161-70. [PMID: 17674404]

Shannon 2010

Shannon O, Morgelin M, Rasmussen M. Platelet activation and biofilm formation by *Aerococcus urinae*, an endocarditis-causing pathogen. *Infection and Immunity* 2010;**78**(10):4268-75. [PMID: 20696834]

Shao 2019

Shao IY, Elkind MSV, Boehme AK. Risk factors for stroke in patients with sepsis and bloodstream infections. *Stroke* 2019;**50**(5):1046-51. [PMID: 30896327]

Shrestha 2014

Shrestha NK, Mason P, Gordon SM, Neuner E, Nutter B, O'Rourke C, et al. Adverse events, healthcare interventions and healthcare utilization during home infusion therapy with daptomycin and vancomycin: a propensity score-matched cohort study. *Journal of Antimicrobial Chemotherapy* 2014;**69**(5):1407-15. [PMID: 24398341]

Singer 2017

Singer M, Alkady H, Mohsen T, Roushdy A, Akl AK, Mashaal M. Predictors of surgical outcome in isolated tricuspid valve endocarditis: single center experience of 60 patients. *Thoracic and Cardiovascular Surgeon* 2017;**65**(8):634-8. [PMID: 28922673]

Skinner 2016

Skinner S, Wudel B, Sanche SE. Microbiology of infective endocarditis and microbiologic diagnosis. In: Chan K-L, Embil JM, editors(s). Endocarditis: Diagnosis and Management. London: Springer-Verlag, 2016:49-66. [DOI: 10.1007/978-3-319-27784-4_9]

Slipczuk 2013

Slipczuk L, Codolosa JN, Davila CD, Romero-Corral A, Yun J, Pressman GS, et al. Infective endocarditis epidemiology over five decades: a systematic review. *PLOS ONE* 2013;**8**(12):e82665. [PMID: 24349331]

Song 2015

Song JK. Infective endocarditis involving an apparently structurally normal valve: new epidemiological trend? *Korean Journal of Internal Medicine* 2015;**30**(4):434-42. [PMID: 26175567]

Sormani 2017

Sormani MP. The most frequently asked question to a statistician: the sample size. *Multiple Sclerosis* 2017;**23**(5):644-6. [PMID: 28273773]

Sotero 2019

Sotero FD, Rosario M, Fonseca AC, Ferro JM. Neurological complications of infective endocarditis. *Current Neurology and Neuroscience Reports* 2019;**19**(5):23. [PMID: 30927133]

Sterne 2011

Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;**343**:d4002. [PMID: 21784880]

Sun 2015

Sun BJ, Choi SW, Park KH, Jang JY, Kim DH, Song JM, et al. Infective endocarditis involving apparently structurally normal valves in patients without previously recognized predisposing heart disease. Journal of the American College of Cardiology 2015;**65**(3):307-9. [PMID: 25614430]

Süzük 2016

Süzük S, Kaskatepe B, Cetin M. Antimicrobial susceptibility against penicillin, ampicillin and vancomycin of viridans group Streptococcus in oral microbiota of patients at risk of infective endocarditis. *Le Infezioni in Medicina* 2016;**24**(3):190-3. [PMID: 27668898]

Tam 2016

Tam JW, Shaikh N, Bybel B, Jassal DS. Diagnostic approach to endocarditis. In: Chan K-L, Embil JM, editors(s). Endocarditis: Diagnosis and Management. London: Springer-Verlag, 2016:91-116. [DOI: 10.1007/978-3-319-27784-4]

Tao 2017

Tao E, Wan L, Wang W, Luo Y, Zeng J, Wu X. The prognosis of infective endocarditis treated with biological valves versus mechanical valves: a meta-analysis. *PLOS ONE* 2017;**12**(4):e0174519. [PMID: 28407024]

Thiene 2006

Thiene G, Basso C. Pathology and pathogenesis of infective endocarditis in native heart valves. *Cardiovascular Pathology* 2006;**15**(5):256-63. [PMID: 16979032]

Thornhill 2015

Thornhill MH, Dayer MJ, Prendergast B, Baddour LM, Jones S, Lockhart PB. Incidence and nature of adverse reactions to antibiotics used as endocarditis prophylaxis. *Journal of Antimicrobial Chemotherapy* 2015;**70**(8):2382-8. [PMID: 25925595]

Thurlow 2010

Thurlow LR, Thomas VC, Narayanan S, Olson S, Fleming SD, Hancock LE. Gelatinase contributes to the pathogenesis of endocarditis caused by *Enterococcus faecalis*. *Infection and Immunity* 2010;**78**(11):4936-43. [PMID: 20713628]

Tissot-Dupont 2017

Tissot-Dupont H, Casalta JP, Gouriet F, Hubert S, Salaun E, Habib G, et al. International experts' practice in the antibiotic therapy of infective endocarditis is not following the guidelines. *Clinical Microbiology and Infection* 2017;**23**(10):736-9. [PMID: 28323194]

Torres 2010

Torres MJ, Blanca M. The complex clinical picture of beta-lactam hypersensitivity: penicillins, cephalosporins, monobactams, carbapenems, and clavams. *Medical Clinics of North America* 2010;**94**(4):805-20. [PMID: 20609864]

Tran 2019

Tran PM, Feiss M, Kinney KJ, Salgado-Pabon W. ϕSa3mw prophage as a molecular regulatory switch of Staphylococcus aureus beta-toxin production. *Journal of Bacteriology* 2019;**201**(14):e00766-18. [PMID: 30962356]

Ursi 2019

Ursi MP, Durante Mangoni E, Rajani R, Hancock J, Chambers JB, Prendergast B. Infective endocarditis in the elderly: diagnostic and treatment options. *Drugs and Aging* 2019;**36**(2):115-24. [PMID: 30488173]

Varela 2019

Varela Barca L, Navas Elorza E, Fernendez-Hidalgo N, Moya Mur JL, Muriel Garcia A, Fernandez-Felix BM, et al. Prognostic factors of mortality after surgery in infective endocarditis: systematic review and meta-analysis. *Infection* 2019;**47**(6):879-95. [PMID: 31254171]

Vilhena 2012

Vilhena C, Bettencourt A. Daptomycin: a review of properties, clinical use, drug delivery and resistance. *Mini Reviews in Medicinal Chemistry* 2012;**12**(3):202-9. [PMID: 22356191]

Vinh 2016

Vinh DC, Embil JM. Treatment of endocarditis. In: Chan K-L, Embil JM, editors(s). Endocarditis: Diagnosis and Management. London: Springer-Verlag, 2016:181-280. [DOI: 10.1007/978-3-319-27784-4_9]

Vogkou 2016

Vogkou CT, Vlachogiannis NI, Palaiodimos L, Kousoulis AA. The causative agents in infective endocarditis: a systematic review comprising 33,214 cases. *European Journal of Clinical Microbiology and Infectious Diseases* 2016;**35**(8):1227-45. [PMID: 27170145]

Von Reyn 1981

Von Reyn CF, Levy BS, Arbeit RD, Friedland G, Crumpacker CS. Infective endocarditis: an analysis based on strict case definitions. *Annals of Internal Medicine* 1981;**94**(4 Part 1):505-18. [PMID: 7011141]

Wang 2014

Wang SZ, Hu JT, Zhang C, Zhou W, Chen XF, Jiang LY, et al. The safety and efficacy of daptomycin versus other antibiotics for skin and soft-tissue infections: a meta-analysis of randomised controlled trials. *BMJ Open* 2014;**4**(6):e004744. [PMID: 24961714]

Warren 2008

Warren RE. Daptomycin in endocarditis and bacteraemia: a British perspective. *Journal of Antimicrobial Chemotherapy* 2008;**62 Suppl 3**:iii25-33. [PMID: 18829722]

Wei 2019

Wei XB, Su Z, Liu YH, Wang Y, Huang JL, Yu DQ, et al. Age, creatinine, and ejection fraction (ACEF) score: a simple risk-stratified method for infective endocarditis. *QJM: Monthly Journal of the Association of Physicians* 2019;**112**(12):900-6. [PMID: 31359051]

Werdan 2014

Werdan K, Dietz S, Loffler B, Niemann S, Bushnaq H, Silber RE, et al. Mechanisms of infective endocarditis: pathogen-host interaction and risk states. *Nature Reviews. Cardiology* 2014;**11**(1):35-50. [PMID: 24247105]

Widmer 2006

Widmer E, Que YA, Entenza JM, Moreillon P. New concepts in the pathophysiology of infective endocarditis. *Current Infectious Disease Reports* 2006;**8**(4):271-9. [PMID: 16822370]

Wong-Beringer 2011

Wong-Beringer A, Joo J, Tse E, Beringer P. Vancomycin-associated nephrotoxicity: a critical appraisal of risk with high-dose therapy. *International Journal of Antimicrobial Agents* 2011;**37**(2):95-101. [PMID: 21130609]

Yoshioka 2018

Yoshioka D, Toda K, Yokoyama JY, Matsuura R, Miyagawa S, Kainuma S, et al. Diabetes mellitus adversely affects mortality and recurrence after valve surgery for infective endocarditis. *Journal of Thoracic and Cardiovascular Surgery* 2018;**155**(3):1021-9.e5. [PMID: 28992971]

Yung 2007

Yung D, Kottachchi D, Neupane B, Haider S, Loeb M. Antimicrobials for right-sided endocarditis in intravenous drug users: a systematic review. *Journal of Antimicrobial Chemotherapy* 2007;**60**(5):921-8. [PMID: 17881630]

Şimşek-Yavuz 2020

Şimşek-Yavuz S, Akar AR, Aydoğdu S, Berzeg-Deniz D, Demir H, Hazırolan T, et al. Diagnosis, treatment and prevention of infective endocarditis: Turkish consensus report-2019. *Türk Kardiyoloji Derneği arşivi* 2020;**48**(2):187-226. [PMID: 32147661]

References to other published versions of this review

Marti-Carvajal 2016

Marti-Carvajal AJ, Dayer M, Conterno LO, Gonzalez Garay AG, Marti-Amarista CE, Simancas-Racines D. A comparison of different antibiotic regimens for the treatment of infective endocarditis. *Cochrane Database of Systematic Reviews* 2016, Issue 4. [DOI: 10.1002/14651858.CD009880.pub2] [PMID: 27092951]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

FINLEVO Trial 2006

Study characteristics	
Methods	Design: parallel (2 groups) Multicentre study: yes Country: Finland Follow-up period: at 28 days and 3 months Unit of randomisation: participants Unit of analysis: participants Duke's criteria for diagnosis of infective endocarditis: yes
Participants	People with *Staphylococcus aureus* bacteraemia with or without endocarditis Enrolled: 1226 Randomised: 381 • Levofloxacin: 191 • Standard treatment: 190 People with endocarditis: 70 • Levofloxacin: 31 • Standard treatment: 39 Age (mean) for overall participants • Levofloxacin: 58 (SD 19) years • Standard treatment: 58 (SD 17) years Gender (male) for overall participants • Levofloxacin: 61% • Standard treatment: 64% There was no information related solely to the baseline demographics of participants with endocarditis.

FINLEVO Trial 2006 *(Continued)*

Interventions	Experimental: levofloxacin (500 mg once daily for participants weighing < 60 kg and 500 mg twice daily for participants weighing > 60 kg, both IV and orally + standard treatment Control: standard treatment (cloxacillin or dicloxacillin (2 g every 4 hours), IV. Participants with a contraindication to penicillin use: cefuroxime (1.5 g every 6 hours), clindamycin (600 mg every 6 to 8 hours), or vancomycin (1 g twice daily). When oral treatment was indicated, cloxacillin (500 mg every 6 hours), cephalexin or cefadroxil (500 mg every 6 hours), or clindamycin (300 mg every 6 hours). Doses were adjusted according to renal function when required. Furthermore, aminoglycosides (tobramycin or netilmicin at 1 mg/kg/body weight 3 times daily) and rifampicin (450 mg once daily for participants weighing < 50 kg and 600 mg once daily for participants weighing > 50 kg, oral or IV) were used. Treatment duration: 14 days
Outcomes	Primary • Case fatality rate at 28 days and 3 months Secondary • Number of complications (e.g. deep infections) observed after the first week • Decrease in serum C-reactive protein concentration • Length of antibiotic treatment • Need for surgical intervention • Time to apyrexia (days until axillary temperature < 37.5 °C)
Notes	Conduction date: January 2000 to August 2002 A priori sample size estimation: yes Sponsor: Aventis Pharma, and Finnish governmental grant Role of sponsor: supplied experimental medication, but was not involved in the trial at any stage Conflict of interest: many primary researchers have been consulted by trial sponsor Identification number clinical trial: not reported The FINLEVO Trial 2006 specified treatment regimens for patients under 60/50 kg and patients over 60/50 kg, but does not specify the exact treatment pattern for people who are either 60 or 50 kg. We contacted the main author for clarification, but as of yet have received no answer.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was done blindly and separately at each study location..." (page 180) Comment: insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "...the treatments were open for the investigator and the patient" (page 180)
Blinding of outcome assessment (detection bias)	Unclear risk	Trial was designed to assess the efficacy of antibiotics in *Staphylococcus aureus* bacteraemia. There was no separate information on this outcome in peo-

FINLEVO Trial 2006 *(Continued)*

Cure		ple with endocarditis; insufficient information to permit judgement of 'low risk' or 'high risk'.
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	No blinding of outcome assessment, but the review authors judged that the outcome measurements were not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	Insufficient information about blinding outcome assessment process to permit judgement of 'low risk' or 'high risk' in participants with endocarditis.
Blinding of outcome assessment (detection bias) Incidence of septic embolism	Unclear risk	Trial was designed to assess the efficacy of antibiotics in *Staphylococcus aureus* bacteraemia. There was no separate information on the incidence of septic embolism in participants with endocarditis; insufficient information to permit judgement of 'low risk' or 'high risk'.
Blinding of outcome assessment (detection bias) Incidence of congestive heart failure	Unclear risk	Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) Quality of life	Unclear risk	Trial was designed for assessing efficacy of antibiotic in *Staphylococcus aureus* bacteraemia. There was no information on quality of life in participants with endocarditis; insufficient information to permit judgement of 'low risk' or 'high risk'.
Blinding of outcome assessment (detection bias) Need for cardiac surgical interventions	Unclear risk	Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) Indication of cardiac surgery	Unclear risk	Trial was designed to assess the efficacy of antibiotics in *Staphylococcus aureus* bacteraemia. There was no information on indication of cardiac surgery in participants with endocarditis; insufficient information to permit judgement of 'low risk' or 'high risk'.
Blinding of outcome assessment (detection bias) Uncontrolled infection	Unclear risk	Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) Relapse	Unclear risk	Trial was designed to assess the efficacy of antibiotics in *Staphylococcus aureus* bacteraemia. There was no information on relapse in participants with endocarditis; insufficient information to permit judgement of 'low risk' or 'high risk'.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Trial was designed to assess the efficacy of antibiotics in *Staphylococcus aureus* bacteraemia rather than in infective endocarditis, therefore there was insufficient information to permit judgement of 'low risk' or 'high risk'.
Selective reporting (reporting bias)	Unclear risk	Trial was designed to assess the efficacy of antibiotics in *Staphylococcus aureus* bacteraemia. There was no information on selective reporting in participants with endocarditis; insufficient information to permit judgement of 'low risk' or 'high risk'.
Other bias	High risk	Design bias

Fortún 2001

Study characteristics	
Methods	Design: parallel (3 groups) Multicentre study: no Country: Spain Follow-up period: at least 12 weeks after completion of therapy Unit of randomisation: participants Unit of analysis: participants Duke's criteria for diagnosis of infective endocarditis: yes
Participants	People with native valves Enrolled and randomised: 34 • Cloxacillin-gentamicin: 11 • Vancomycin-gentamicin: 11 • Teicoplanin-gentamicin: 12 Lost postrandomisation: 3 • Vancomycin-gentamicin: 1/11 (9%) by extrapulmonary foci • Teicoplanin-gentamicin: 2/12 (17%) by extrapulmonary foci, and voluntary withdrawal Analysed: 31/34 (91%) • Cloxacillin-gentamicin: 11 • Vancomycin-gentamicin: 10 • Teicoplanin-gentamicin: 10 Age (mean) • Overall: 30.5 (range 18 to 43) years • Cloxacillin-gentamicin: 28 (range 23 to 38) years • Vancomycin-gentamicin: 25 (range 18 to 31) years • Teicoplanin-gentamicin: 31 (range 21 to 43) years Gender (male) • Overall: 96.7% • Cloxacillin-gentamicin: 100% • Vancomycin-gentamicin: 90% • Teicoplanin-gentamicin: 100% Previous endocarditis (n/%) • Cloxacillin-gentamicin: 2 (18%) • Vancomycin-gentamicin: 2 (20%) • Teicoplanin-gentamicin: 1 (10%) HIV infection (n/%) • Cloxacillin-gentamicin: 8 (73%) • Vancomycin-gentamicin: 5 (71%) • Teicoplanin-gentamicin: 5 (62.5%) CD4 count (mean)

Fortún 2001 *(Continued)*

- Cloxacillin-gentamicin: 300 (range 129 to 600) cells/mm^3
- Vancomycin-gentamicin: 210 (range 120 to 500) cells/mm^3
- Teicoplanin-gentamicin: 243 (range 130 to 378) cells/mm^3

White blood cells count (mean)

- Cloxacillin-gentamicin: 7775 (range 3800 to 10,300) cells/mm^3
- Vancomycin-gentamicin: 6730 (range 2300 to 14,500) cells/mm^3
- Teicoplanin-gentamicin: 8160 (range 5400 to 16,300) cells/mm^3

Neutrophil count (mean)

- Cloxacillin-gentamicin: 5998 (range 4200 to 8100) cells/mm^3
- Vancomycin-gentamicin: 5040 (range 1400 to 11,730) cells/mm^3
- Teicoplanin-gentamicin: 6800 (range 4060 to 14,100) cells/mm^3

Inclusion criteria

- Parenteral drug abusers
- Fever
- Isolation of methicillin-susceptible *Staphylococcus aureus* from ≥ 2 cultures of blood samples
- Septic pulmonary embolisation
- Tricuspid regurgitation murmur
- Echocardiographic evidence of endocarditis (intracardiac mass on valve or supporting structures, abscess, or nodular tricuspid thickening)

Exclusion criteria

- Isolation of methicillin-resistant *Staphylococcus aureus* from cultures of blood samples
- Allergy to the antibiotics used
- Extrapulmonary metastatic focus at enrolment or developed within the first 48 hours of therapy
- Serum creatinine level > 220 nmol/L (> 2.5 mg/dL)
- Left-side endocarditis observed on an echocardiogram
- Presence of non-biological valvular prosthesis or long-term catheter
- Polymicrobial infections
- Pregnancy
- Receipt of effective antimicrobial treatment during the 72 hours prior to the study period

Interventions	Cloxacillin-gentamicin: cloxacillin: 2 g every 4 hours, IV + gentamicin 1.5 mg/kg every 8 hours Vancomycin-gentamicin: vancomycin: 500 mg every 6 hours, IV + gentamicin 1.5 mg/kg every 8 hours Teicoplanin-gentamicin: teicoplanin: 12 mg/kg every 24 hours, with a loading dose of 24 mg/kg on first day + gentamicin 1.5 mg/kg every 8 hours Treatment duration: 14 days

Outcomes	Outcomes were not classified as primary or secondary.
	
	• Efficacy (response to therapy) by:
	  * cure;
	  * clinical failure: definition;
	  * microbiological failure;
	  * microbiological relapse;
	  * duration of fever while receiving therapy.
	• Adverse effects

Notes	Conduction date: not reported

Fortún 2001 *(Continued)*

A priori sample size estimation: no

Sponsor: not reported

Role of sponsor: not reported

Conflict of interest: not declared

Identification number clinical trial: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: " ...randomized ..." (page 120) Comment: insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information about the allocation concealment process to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "...open..." (pages 120 and 123)
Blinding of outcome assessment (detection bias) Cure	Low risk	No blinding of outcome assessment, but the review authors judged that the outcome measure (cure) was not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	No blinding of outcome assessment, but the review authors judged that the outcome measure (all-cause mortality) was not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Adverse events	Low risk	No blinding of outcome assessment, but the review authors judged that the outcome measure (adverse events) was not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Incidence of septic embolism	Unclear risk	Trial did not assess incidence of septic embolism.
Blinding of outcome assessment (detection bias) Incidence of congestive heart failure	Unclear risk	Trial did not assess incidence of congestive heart failure.
Blinding of outcome assessment (detection bias) Quality of life	Unclear risk	Trial did not assess quality of life.
Blinding of outcome assessment (detection bias) Need for cardiac surgical interventions	Unclear risk	Trial did not assess need for cardiac surgical interventions.
Blinding of outcome assessment (detection bias)	Unclear risk	Trial did not assess indication of cardiac surgery.

Fortún 2001 *(Continued)*

Indication of cardiac surgery		
Blinding of outcome assessment (detection bias) Uncontrolled infection	Unclear risk	Trial did not assess uncontrolled infection.
Blinding of outcome assessment (detection bias) Relapse	Low risk	No blinding of outcome assessment, but the review authors judged that the outcome measure (relapse) was not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data for primary outcome available for 31/34 (91%) of the randomised sample, with balanced reasons for withdrawals or losses to follow-up.
Selective reporting (reporting bias)	Unclear risk	All the outcomes listed in the Methods section were described in the Results section. Trial authors did not mention data of clinical key outcomes such as mortality and heart failure.
Other bias	High risk	Design bias

Fowler 2006

Study characteristics	
Methods	Design: parallel (2 arms) Multicentre: yes (44 sites) Countries: USA Follow-up period: 42 days Unit of randomisation: participants Unit of analysis: participants Duke's criteria for diagnosis of infective endocarditis: yes
Participants	People with native and prosthetic valve Enrolled and randomised: 246 • Daptomycin: 126 • Standard therapy: 120 Lost postrandomisation: 10 • Daptomycin: 6 • Standard therapy: 4 Analysed: 235/246 (96%) • Daptomycin: 120 • Standard therapy: 115 Age: not reported separately for the endocarditis group

Fowler 2006 *(Continued)*

Gender (male): not reported separately for the endocarditis group

Definitive endocarditis (baseline diagnosis) (n/%)

- Daptomycin: 17 (14.2%)
- Standard therapy: 20 (61.7%)

Left-sided endocarditis (final diagnosis) (n/%)

- Daptomycin: 9 (7.5%)
- Standard therapy: 9 (7.8%)

Inclusion criteria:

- ≥ 18 years of age
- ≥ 1 blood cultures that were positive for *Staphylococcus aureus* within 2 calendar days before initiating study medication

Exclusion criteria:

- Known osteomyelitis
- Polymicrobial bacteraemia
- Pneumonia
- Renal failure with creatinine clearance < 30 mL/minute
- Initial *Staphylococcus aureus* blood culture outside the 2-day window
- Inability to provide consent or unlikely to comply with study-related procedures
- Presence of an intravascular material (excluding cardiac stents) not intended to be removed within 4 calendar days
- Receipt of non-study antibiotics potentially effective against *Staphylococcus aureus*
- High likelihood of death or valve replacement surgery in the first 3 days following randomisation
- Refractory shock, significant hepatic insufficiency, or severe leukopenia
- Weight < 50 kg or > 150 kg
- Allergy to vancomycin or penicillin
- Infection with *Staphylococcus aureus* with reduced susceptibility to vancomycin (minimum inhibitory concentration > 4 µg/mL)

Interventions	Experimental: daptomycin: 6 mg/kg body weight, once daily, IV (1 participant also received gentamicin 1 mg/kg given every 8 hours for the first 4 days) Control: standard treatment with either: • vancomycin 1 g, every 12 hours with appropriate dose adjustment with gentamicin 1 mg/kg given every 8 hours for the first 4 days; OR • antistaphylococcal penicillin (nafcillin, oxacillin, or flucloxacillin) 2 g given every 4 hours, depending on the susceptibility of the causative strain to methicillin with gentamicin 1 mg/kg given every 8 hours for the first 4 days. Treatment duration: 4 to 6 weeks was determined by the investigator on the basis of the working group. Mean treatment durations were 14 days in daptomycin group and 15 days in standard treatment group.

Outcomes	Primary
	
	• Failure at this visit (42 days) was defined as:
	  • clinical failure: no response to the study drug on the basis of ongoing signs and symptoms of infection;
	  • microbiological failure: persistent or relapsing *Staphylococcus aureus* infection;
	  • death;
	  • failure to obtain blood culture;

Fowler 2006 *(Continued)*

- receipt of potentially effective non-study antibiotics (any antibiotic received during or after study drug therapy that may have influenced the outcome);
- premature discontinuation of the study medication because of clinical failure, microbiological failure, or an adverse event.

- Adverse events: coded using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 6.0)

Notes	Conduction date: 28 August 2002 to 16 February 2005 A priori sample size estimation: yes (page 655) Sponsor: Cubist Pharmaceuticals Role of sponsor: study was designed and analysed by the sponsor (page 656) Conflict of interest: many trials authors were consultants or employees of Cubist Pharmaceuticals (pages 654, 656) Identifier number: ClinicalTrials.gov ID NCT00093067 (page 653)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "... this centralized computer-generated schedule was designed to achieve a 1:1 ratio of patients, stratified according to investigative site" (page 655)
Allocation concealment (selection bias)	Low risk	Quote: "... this centralized computer-generated schedule ..." (page 655)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label" (page 654)
Blinding of outcome assessment (detection bias) Cure	Low risk	No blinding of outcome assessment, but the review authors judged that the outcome measure (cure) was not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) All-cause mortality	Unclear risk	Trial did not assess all-cause mortality.
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	Trial did not assess adverse events.
Blinding of outcome assessment (detection bias) Incidence of septic embolism	Unclear risk	Trial did not assess incidence of septic embolism.
Blinding of outcome assessment (detection bias) Incidence of congestive heart failure	Unclear risk	Trial did not assess incidence of congestive heart failure.
Blinding of outcome assessment (detection bias)	Unclear risk	Trial did not assess quality of life.

Fowler 2006 *(Continued)*

Quality of life		
Blinding of outcome assessment (detection bias) Need for cardiac surgical interventions	Unclear risk	Trial did not assess need for cardiac surgical interventions.
Blinding of outcome assessment (detection bias) Indication of cardiac surgery	Unclear risk	Trial did not assess indication of cardiac surgery.
Blinding of outcome assessment (detection bias) Uncontrolled infection	Low risk	No blinding of outcome assessment, but the review authors judged that the outcome measure (uncontrolled infection) was not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Relapse	Unclear risk	Trial did not assess relapse.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants lost postrandomisation not receiving treatment: 10/246 (4%) Participants lost receiving treatment: 1/236 (0.4%)
Selective reporting (reporting bias)	High risk	Trial did no report all-cause mortality and adverse events.
Other bias	High risk	Design bias

Pericas 2018

Study characteristics	
Methods	Design: parallel (2 arms) Multicentre: yes (10 sites) Countries: Spain Follow-up period: 6 weeks Unit of randomisation: participants Unit of analysis: participants
Participants	• Type: complicated bacteraemia and endocarditis due to methicillin-resistant *Staphylococcus aureus* • Randomised: 15 (The following data relate only to those participants with infective endocarditis (IE): 8) Fosfomycin plus imipenem: 4 (2 native valve IE, 2 prosthetic valve IE) Vancomycin: 4 (1 native valve IE, 3 pacemaker IE) Age (years, mean (SD)) • Fosfomycin plus imipenem: 84 (3.3) • Vancomycin: 78 (6.34)

Pericas 2018 *(Continued)*

Sex (male):

- Fosfomycin plus imipenem: 75% (3/4)
- Vancomycin: 25% (1/4)

Source

- Fosfomycin plus imipenem: vascular (1), urinary (1), cutaneous (1), unknown (1)
- Vancomycin: vascular (2) and unknown (2)

Acquisition

- Fosfomycin plus imipenem: non-nosocomial healthcare-associated (2) and nosocomial (2)
- Vancomycin: non-nosocomial healthcare-associated (2) and nosocomial (2)

Days of bacteraemia until study initiation (media)

- Fosfomycin plus imipenem: 3.25 (0.95)
- Vancomycin: 1 (all participants had 1 day)

Days of study treatment (mean (SD), median)

- Fosfomycin plus imipenem: 18.25 (22.02), 9
- Vancomycin: 35.75 (7.5), 37

Inclusion criteria: adults with suspected or confirmed methicillin-resistant *Staphylococcus aureus* infective endocarditis (IE; native or prosthetic valve, pacemaker/defibrillator) according to the modified Duke criteria, prosthetic vascular graft infection or complicated bacteraemia (septic thrombophlebitis, soft tissue-skin infection, pneumonia, osteomyelitis, or unknown source)

Excusion criteria:

- Aged under 18 years
- Antibiotics with anti-methicillin-resistant *Staphylococcus aureus* activity received for > 72 h
- Shock or hypotension
- Urgent surgery needed
- Active intravenous drug use
- Vancomycin trough levels > 15 µg/mL at 72 h in participants with chronic renal insufficiency or haemodialysis
- Methicillin-resistant *Staphylococcus aureus* strains with fosfomycin minimum inhibitory concentration (MIC) > 64 mg/L or vancomycin MIC ≥ 2 mg/L
- Known allergy to vancomycin, fosfomycin, or imipenem

Interventions	• Intervention: fosfomycin (2 g/6 h IV) plus imipenem (1 g/6 h IV), adjusted for renal function
	• Control: vancomycin (30 to 45 mg/kg daily IV divided into 2 to 3 doses, trough levels ≥ 15 mg/L)
	
	Note: if the participant developed either treatment failure or renal failure with vancomycin, he/she was switched to the other comparison group.
	
	• Treatment duration:
	  • Complicated bacteraemia with rapid control of the source and negative first control complicated bacteraemia: 2 weeks
	  • Non-complicated native valve infective endocarditis and pacemaker/defibrillator infective endocarditis or non-rapidly controlled complicated bacteraemia: 4 weeks
	  • Prosthetic valve infective endocarditis, complicated native infective endocarditis, and complicated bacteraemia with osteomyelitis: 6 weeks

Outcomes	Trial authors did not classify the outcomes as primary or secondary. However, the trial reported data on death, cure, adverse events including treatment-related adverse events, cardiac surgical interventions, uncontrolled infection, and relapse of endocarditis.

Pericas 2018 *(Continued)*

Notes	Conduction date: October 2009 to December 2014 A priori sample size estimation: yes This trial was stopped early due to difficulties in recruiting participants. Support: Ministerio de Sanidad y Consumo of Spain (Fondo de Investigaciones Sanitarias, Instituto de Salud Carlos III, Madrid, Spain, several grants from public Spanish entities). Role of support: not stated Conflict of interest: 1 author has received consulting honoraria or research grants, or both, from Abb-Vie, Bristol-Myers Squibb, Cubist, Novartis, Gilead Sciences, and ViiV. Identifier number: ClinicalTrials.gov ID NCT00871104

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote "...randomized clinical trial..." (page 673) Comment: insufficient information to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Quote "...randomized clinical trial..." (page 673) Comment: insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote "open-label" (page 673)
Blinding of outcome assessment (detection bias) Cure	Unclear risk	Comment: insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All-cause mortality	Unclear risk	Comment: insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	Comment: insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) Incidence of septic embolism	Unclear risk	Comment: insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) Incidence of congestive heart failure	Unclear risk	Comment: insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) Quality of life	Unclear risk	Trial did not assess quality of life.

Pericas 2018 *(Continued)*

Blinding of outcome assessment (detection bias) Need for cardiac surgical interventions	Unclear risk	Comment: insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) Indication of cardiac surgery	Unclear risk	Comment: insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) Uncontrolled infection	Unclear risk	Comment: insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) Relapse	Unclear risk	Comment: insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Trial authors reported data from 8 participants with IE.
Selective reporting (reporting bias)	Low risk	Trial authors reported relevant clinical endpoints.
Other bias	High risk	Bias in the presentation of the data

POET 2019

Study characteristics	
Methods	Design: parallel (2 arms) Multicentre: yes (15 sites) Countries: Denmark Follow-up period: 6 months Unit of randomisation: participants Unit of analysis: participants Type of randomised controlled trial: non-inferiority trial ("whether partial oral treatment was non-inferior to conventional intravenous treatment")

Participants	• Referred: 1954
	• Enrolled: 400 endocarditis on the left side of the heart
	• Randomised:
	  • Conventional intravenous treatment: 199
	  • To a shift to oral treatment: 201
	• Age (years, mean (SD)):
	  • Conventional intravenous treatment: 67.3 (12)
	  • To a shift to oral treatment: 67.6 (12.6)
	• Sex (male):
	  • Conventional intravenous treatment: 74.87% (149/199)

POET 2019 *(Continued)*

- To a shift to oral treatment: 79.10% (159/201)
- Pathogen:
  - Conventional intravenous treatment: *Streptococcus* (52.3%), *Enterococcus faecalis* (23.1%), *Staphylococcus aureus* (20.1%), and coagulase-negative staphylococci (5.0%)
  - To a shift to oral treatment: *Streptococcus* (45.8%), *Enterococcus faecalis* (25.4%), *Staphylococcus aureus* (23.4%), and coagulase-negative staphylococci (6.5%)
- Pre-existing prosthesis, implant, or cardiac disease:
  - Conventional intravenous treatment: prosthetic heart valve (26.6%), pacemaker (7.5%), other known valve disease (41.2%)
  - To a shift to oral treatment: prosthetic heart valve (26.9%), pacemaker (10%), other known valve disease (44.8%)
- Cardiac involvement at randomisation:
  - Conventional intravenous treatment: mitral-valve endocarditis (32.7%), aortic-valve endocarditis (54.8%), mitral-valve and aortic-valve endocarditis (11.6%), pacemaker endocarditis (3.0%), and vegetation size > 9 mm (3.5%)
  - To a shift to oral treatment: mitral-valve endocarditis (35.8%), aortic-valve endocarditis (54.2%), mitral-valve and aortic-valve endocarditis (10.0%), pacemaker endocarditis (4.0%), and vegetation size > 9 mm (5.5%)
- Coexisting condition or risk factor:
  - Conventional intravenous treatment: diabetes (18.1%), renal failure (12.6%), dialysis (6.5%), COPD (8.5%), liver disease (3.5%), cancer (7.0%), and intravenous drug use (1.5%)
  - To a shift to oral treatment: diabetes (15.4%), renal failure (10.4%), dialysis (7.5%), COPD (4.5%), liver disease (3.0%), cancer (9.0%), and intravenous drug use (1.0%)
- Inclusion criteria:
  - Left-sided endocarditis based on the Duke criteria
  - Infected with 1 of the following micro-organisms: streptococci, *Enterococcus faecalis*, *Staphylococcus aureus*, coagulase-negative staphylococci
  - Adult participants (≥ 18 years)
  - At least ≥ 10 days of appropriate parenteral antibiotic treatment overall, and at least 1 week of appropriate parenteral treatment after valve surgery
  - Temperature < 38.0 °C > 2 days
  - C-reactive protein dropped to less than 25% of peak value or < 20 mg/L, and white blood cell count less than 15 x 10^9/L during antibiotic treatment
  - No sign of abscess formation revealed by echocardiography
  - Transthoracic and trans-oesophageal echocardiography performed within 48 hours of randomisation
- Exclusion criteria:
  - Body mass index > 40
  - Concomitant infection requiring intravenous antibiotic therapy
  - Inability to give informed consent to participation
  - Suspicion of reduced absorption of oral treatment due to abdominal disorder
  - Reduced compliance

Interventions	• Oral treatment: the composition, doses, and duration of different oral regimens is shown in Appendix 6. • Conventional intravenous treatment: based on the guidelines of the European Society of Cardiology (Habib 2015), with modifications endorsed by the Danish Society of Cardiology (Moser 2017) No details were provided regarding the conventional intravenous therapy regimens.
Outcomes	Primary: composite of all-cause mortality, unplanned cardiac surgery, clinically evident embolic events, or relapse of bacteraemia with the primary pathogen (detected in blood cultures obtained during follow-up or for clinical reasons) from randomisation through 6 months after antibiotic treatment was completed

POET 2019 *(Continued)*

	Trial assessed and reported adverse events.
Notes	Identifier number: ClinicalTrials.gov ID NCT01375257 Conduction date: 15 July 2011 to 30 August 2017 A priori sample size estimation: yes Support: the Danish Heart Foundation and the Capital Regions Research Council, the Hartmann's Foundation, Svend Aage Andersens Foundation, and the Novo Nordisk Foundation Role of support: not stated Conflict of interest: 1 author has received consulting honoraria or research grants, or both, from Bayer.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote "Randomization was performed with the use of a Web-based system, in permuted blocks of 2 to 6, with stratification according to randomization site." (page 417)
Allocation concealment (selection bias)	Low risk	Quote "Randomization was performed with the use of a Web-based system, in permuted blocks of 2 to 6, with stratification according to randomization site." (page 417)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote "...unblinded..." (page 416)
Blinding of outcome assessment (detection bias) Cure	Unclear risk	This outcome was not mentioned.
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	Quote "A clinical-event adjudication committee, whose members were unaware of the treatment assignments, adjudicated the prespecified clinical outcomes. The committee consisted of experienced cardiologists and a specialist in infectious diseases." (page 417)
Blinding of outcome assessment (detection bias) Adverse events	Low risk	Quote "A clinical-event adjudication committee, whose members were unaware of the treatment assignments, adjudicated the prespecified clinical outcomes. The committee consisted of experienced cardiologists and a specialist in infectious diseases." (page 417)
Blinding of outcome assessment (detection bias) Incidence of septic embolism	Low risk	Quote "A clinical-event adjudication committee, whose members were unaware of the treatment assignments, adjudicated the prespecified clinical outcomes. The committee consisted of experienced cardiologists and a specialist in infectious diseases." (page 417)
Blinding of outcome assessment (detection bias) Incidence of congestive heart failure	Low risk	Quote "A clinical-event adjudication committee, whose members were unaware of the treatment assignments, adjudicated the prespecified clinical outcomes. The committee consisted of experienced cardiologists and a specialist in infectious diseases." (page 417)
Blinding of outcome assessment (detection bias) Quality of life	Unclear risk	This outcome was not mentioned.

POET 2019 *(Continued)*

Blinding of outcome assessment (detection bias) Need for cardiac surgical interventions	Low risk	Quote "A clinical-event adjudication committee, whose members were unaware of the treatment assignments, adjudicated the prespecified clinical outcomes. The committee consisted of experienced cardiologists and a specialist in infectious diseases." (page 417)
Blinding of outcome assessment (detection bias) Indication of cardiac surgery	Low risk	Quote "A clinical-event adjudication committee, whose members were unaware of the treatment assignments, adjudicated the prespecified clinical outcomes. The committee consisted of experienced cardiologists and a specialist in infectious diseases." (page 417)
Blinding of outcome assessment (detection bias) Uncontrolled infection	Unclear risk	This outcome was not mentioned.
Blinding of outcome assessment (detection bias) Relapse	Low risk	Quote "A clinical-event adjudication committee, whose members were unaware of the treatment assignments, adjudicated the prespecified clinical outcomes. The committee consisted of experienced cardiologists and a specialist in infectious diseases." (page 417)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants were lost to follow-up.
Selective reporting (reporting bias)	Low risk	Trial reported relevant clinical outcomes.
Other bias	Low risk	-

Sexton 1998

Study characteristics	
Methods	Design: parallel (2 groups) Multicentre study: yes (9 sites) Country: USA Follow-up period: 3 months Unit of randomisation: participants Unit of analysis: participants Duke's criteria for diagnosis of infective endocarditis: yes
Participants	People with ceftriaxone-susceptible *Streptococcus viridans* or *Streptococcus bovis* endocarditis People with native valve Enrolled and randomised: 67 • Ceftriaxone: 33 • Ceftriaxone + gentamicin: 3 Analysed for clinical efficacy: 51 • Ceftriaxone: 26 • Ceftriaxone + gentamicin: 25

Sexton 1998 *(Continued)*

Age (mean)

- Ceftriaxone: 52.5 (SD 17.8) (range 18 to 87) years
- Ceftriaxone + gentamicin: 59.5 (SD 15.5) (range 27 to 92) years

Gender (male)

- Ceftriaxone: not reported
- Ceftriaxone + gentamicin: not reported
- Total group: 41 (80.3%)

Previous endocarditis

- Ceftriaxone: 4 (15.3%)
- Ceftriaxone + gentamicin: 1 (4%)

History of rheumatic heart disease

- Ceftriaxone: 3 (11.5%)
- Ceftriaxone + gentamicin: 3 (12%)

Inclusion criteria

- Aged ≥ 18 years
- Received < 72 hours of parenteral antibiotic therapy before enrolment
- Provided written informed consent

Exclusion criteria

- Presence of aetiological agents other than ceftriaxone-susceptible viridans streptococci or *S bovis*
- Hypersensitivity to cephalosporins or aminoglycosides
- Prior treatment with antibiotics for > 72 hours
- New York Heart Association class IV heart failure
- Need for therapy for > 2 weeks
- Moderate-to-severe renal dysfunction (serum creatinine clearance of < 20 mL/minute)
- Prosthetic valve endocarditis
- Clinically apparent moderate-to-severe hearing loss or vestibular dysfunction
- Neutropenia (absolute neutrophil count < 1000/mm^3)

Interventions	Experimental: ceftriaxone 2 g once daily for 4 weeks, IV + gentamicin 3 mg/kg IV once daily for 2 weeks Control: ceftriaxone 2 g once daily, IV Infusion time: 30 to 60 minutes Co-intervention: not reported Treatment duration: 2 to 4 weeks
Outcomes	Outcomes were not classified as primary or secondary. • Cure with or without surgery • Re-infection • Treatment failure • Adverse events
Notes	Conduction date: 29 January 1992 to 22 December 1996 A priori sample size estimation: no Sponsor: Roche

Sexton 1998 *(Continued)*

Role of sponsor: not reported

Conflict of interest: not declared

Identification number clinical trial: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were assigned randomly" (page 1471) Comment: insufficient information to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "This randomised, multicenter, open-label study" (page 1470)
Blinding of outcome assessment (detection bias) Cure	Low risk	The review authors judged that the outcome measure (cure) was not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) All-cause mortality	Unclear risk	The trial did not assess all-cause mortality.
Blinding of outcome assessment (detection bias) Adverse events	Low risk	The review authors judged that the outcome measure (adverse events) was not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Incidence of septic embolism	Unclear risk	The trial did not assess incidence of septic embolism.
Blinding of outcome assessment (detection bias) Incidence of congestive heart failure	Unclear risk	The trial did not assess incidence of congestive heart failure.
Blinding of outcome assessment (detection bias) Quality of life	Unclear risk	The trial did not assess quality of life.
Blinding of outcome assessment (detection bias) Need for cardiac surgical interventions	Low risk	The review authors judged that the outcome measure (need for cardiac surgical interventions) was not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Indication of cardiac surgery	Low risk	The review authors judged that the outcome measure (indication of cardiac surgery) was not likely to be influenced by lack of blinding.

Sexton 1998 *(Continued)*

Blinding of outcome assessment (detection bias) Uncontrolled infection	Low risk	The review authors judged that the outcome measure (uncontrolled infection) was not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Relapse	Unclear risk	The review authors judged that the outcome measure (relapse) was not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss postrandomisation: 51/67 (24%) • Ceftriaxone: 7 (21.2%) • Ceftriaxone + gentamicin: 9 (26.47%)
Selective reporting (reporting bias)	High risk	Trial did not mention all-cause mortality and other clinically relevant outcomes.
Other bias	High risk	Design bias

COPD: chronic obstructive pulmonary disease
IV: intravenous
n: number of participants
SD: standard deviation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abrams 1979	Randomised clinical trial did not use Duke's criteria for diagnosis of infective endocarditis. It used Von Reyn 1981 criteria.
Fortún 1995	Randomised clinical trial that did not use Duke's criteria for diagnosis of infective endocarditis
Gilbert 1991	Randomised clinical trial that did not use Duke's criteria for diagnosis of infective endocarditis
Greenman 1984	Randomised clinical trial that did not use Duke's criteria for diagnosis of infective endocarditis
Heldman 1996	Randomised clinical trial that did not use Duke's criteria for diagnosis of infective endocarditis
Korzeniowski 1982	Randomised clinical trial that did not use Duke's criteria for diagnosis of infective endocarditis
Levine 1991	Randomised clinical trial that did not use Duke's criteria for diagnosis of infective endocarditis
Markowitz 1992	Randomised clinical trial that did not use Duke's criteria for diagnosis of infective endocarditis
Ribera 1996	Randomised clinical trial that did not use Duke's criteria for diagnosis of infective endocarditis
Stamboulian 1991	Randomised clinical trial that did not use Duke's criteria for diagnosis of infective endocarditis

Characteristics of ongoing studies *[ordered by study ID]*

CTRI/2008/091/000060

Study name	An open labelled, double arm, randomized, multicentric, prospective and comparative, phase-III trial to evaluate the safety and efficacy of fixed dose combination of ceftriaxone and vancomycin injection versus vancomycin injection in subjects with various bacterial infections
Methods	Randomised, parallel-group, active-controlled trial Method of generating randomisation sequence: computer-generated randomisation Method of allocation concealment: not applicable Blinding and masking: not applicable Phase 3

Participants	• Age minimum: not reported
	• Age maximum: not reported
	• Gender: not reported
	• Inclusion criteria: all participants aged between 18 and 70 years
	  • Diagnosed participants of infectious disease (on clinical evaluation)
	  • Participants willing to give informed consent
	  • Participant suffering from any of the following infections: lower respiratory tract infections, skin and skin structure infections, endocarditis, bacterial meningitis, and bone infection
	• Exclusion criteria:
	  • History of hypersensitivity reaction or any specific contraindication to penicillin group of drugs or ceftriaxone or vancomycin
	  • Presence of hepatic or renal disorder
	  • Pregnancy and/or lactation

Interventions	• Intervention: vancomycin (2 g divided either as 500 mg every 6 hours or 1 g every 12 hours) and ceftriaxone combined (6 g IV in 2 equally divided slow doses, depending on the severity of disease) • Control intervention: vancomycin (2 g divided either as 500 mg every 6 hours or 1 g every 12 hours)
Outcomes	Primary: efficacy of a 3.0 g ceftriaxone and vancomycin injection versus 1.0 g vancomycin injection in participants with mild-to-severe bacterial infections Secondary: safety of the test and comparative product Note: the protocol authors did not report primary outcomes, instead reporting a primary objective rather than a measurement of efficacy.
Starting date	7 May 2008
Contact information	Dr Namit Saraf (Senior Doctor) (drnamitsaraf@rediffmail.com). Orthopaedics Department, Ansari Road AIIMS 110029, New Delhi, DELHI, India Mahesh Mudgal: Flat No: 90, Pocket A Sector - 14, Dwarka 110029 New Delhi, DELHI, India
Notes	Primary sponsor: Venus Remedies Limited (Venus Remedies Limited 51-52, Industrial Area, Phase 1, Panchkula, 134112 Haryana)

EUCTR 2016-003059-31

Study name	A multicenter, double-blind, randomized, comparative study of the safety, tolerability, efficacy, and pharmacokinetics of CF-301 versus placebo in addition to standard-of-care antibacterial therapy for the treatment of adult patients with *Staphylococcus aureus* bloodstream infections (bacteremia) including endocarditis
Methods	Controlled, randomised, double-blind, parallel group, placebo

EUCTR 2016-003059-31 *(Continued)*

	Arms: 2 Phase: phase II
Participants	• Male or female • Age: ≥ 18 years or older • Inclusion criteria: known or suspected endocarditis by modified Duke criteria and/or known or suspected complicated *Staphylococcus aureus*, and several other inclusion criteria • Exclusion criteria: several
Interventions	CF-301, solution for infusion Placebo: solution for infusion, intravenous use Standard-of-care antibacterial therapy
Outcomes	Primary: • Safety and tolerability of CF-301 versus placebo in addition to standard-of-care antibacterial therapy • Clinical outcome at Day 14 after CF-301/placebo administration • Pharmacokinetic parameters of CF-301 Secondary endpoint(s): • Clinical outcome at Day 7 after CF301/placebo administration • Clinical outcome at the end of standard-of-care antibacterial therapy, and at test of cure, and 28 days after test of cure • Microbiological response • Microbiological outcome
Starting date	27 October 2017
Contact information	Clinical Development Corporation
Notes	Primary sponsor: ContraFect Corporation (28 Wells Ave 10701 Yonkers, NY, USA) clinicalstudies@contrafect.com

EUCTR 2017-001699-43

Study name	A randomized, double-blind, multi-center study to establish the efficacy and safety of ceftobiprole medocaril compared to daptomycin in the treatment of *Staphylococcus aureus* bacteremia, including infective endocarditis
Methods	Controlled, randomised, double-blind, parallel group Phase: phase III International multicentre
Participants	Age minimum: 18 years Age maximum: not reported Female: yes Male: yes Several inclusion and exclusion criteria

EUCTR 2017-001699-43 *(Continued)*

Interventions	Ceftobiprole medocaril: infusion Daptomycin: infusion Aztreonam: infusion Doses: not reported
Outcomes	• Primary endpoint(s): overall success at the PTE visit (Day 70 ± 5 days postrandomisation): the primary endpoint will be tested for the non-inferiority of ceftobiprole versus daptomycin using a non-inferiority margin of 15%. Several criteria for assessing overall success. • Secondary objective: to compare ceftobiprole with daptomycin with respect to several criteria
Starting date	13 December 2018
Contact information	Alain Bobillier (alain.bobillier@basilea.com) Affiliation: Basilea Pharmaceutica International Ltd
Notes	Primary sponsor: Basilea Pharmaceutica International Ltd

EudraCT 2008-008683-28

Study name	Evaluación de la eficacia y la seguridad de la combinación de fosfomicina (F) e imipenem (I) para el tratamiento de la endocarditis infecciosa (EI) sobre válvula nativa o protésica por *Staphylococcus aureus* resistente a meticilina (SARM)
Methods	Not reported
Participants	Age: adults, elderly Sex: male or female
Interventions	Not reported
Outcomes	Not reported
Starting date	23 September 2009
Contact information	Sponsor: Fundació Privada Clínic per a la Recerca Biomèdica, Barcelona, Spain
Notes	www.clinicaltrialsregister.eu/ctr-search/search?query=2008-008683-28

JPRN-UMIN 000032006

Study name	An open-label randomized controlled trial of ampicillin/cloxacillin and ceftriaxone for empirical treatment of infective endocarditis
Methods	Interventional Parallel, randomised
Participants	• Inclusion criteria: • Patients with confirmed or suspected diagnosis of infective endocarditis based on modified Duke's criteria, who need to start empirical treatment waiting for the result of blood cultures • Exclusion criteria:

JPRN-UMIN 000032006 *(Continued)*

	• Causative micro-organism already confirmed • History of allergy or contraindication of penicillin, cephalosporins, and aminoglycoside • History of prosthetic valve replacement within 1 year • eGFR less than 50 mL/min • White blood cells less than 1000/μL, when physicians in charge chose another treatment regimen • Age minimum: 20 years • Age maximum: not applicable • Gender: male and female
Interventions	• Intervention: ampicillin/cloxacillin 4 g every 4 hours IV maximum for 6 weeks plus gentamicin 3 mg/kg every 4 hours IV maximum for 2 weeks • Control: ceftriaxone 2 g every 4 hours IV maximum for 6 weeks plus gentamicin 3 mg/kg every 4 hours IV maximum for 2 weeks
Outcomes	Primary: • Outcome of infective endocarditis at the end of antimicrobial treatment Secondary: • Days for defervescence less than 37 °C • Days of hospitalisation • Outcome at discharge • Necessity of surgery during hospitalisation • Outcome of infective endocarditis 3 months after the end of antimicrobial treatment • Adverse events on skin, blood, liver, and kidney
Starting date	2 April 2018
Contact information	Primary sponsor: Juntendo University Contacts: Toshio Naito (naito@juntendo.ac.jp) and Yuki Uehara (yuuehara@juntendo.ac.jp) Affiliation Juntendo University Faculty of Medicine Department of General Medicine
Notes	upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000036524 Date of first enrolment: 2 April 2018

NCT00638157

Study name	A phase 4 multicenter, randomized, double blind study to describe the efficacy and safety of cubicin (Daptomycin for Injection) with and without initial gentamicin combination therapy in the treatment of *Staphylococcus aureus* infective endocarditis
Methods	Interventional, randomised, parallel assignment, and double-blind (participant, investigator) Phase IV
Participants	Estimated enrolment: 24 Inclusion criteria: • Written informed consent has been obtained • Men or women ≥ 18 years • History of drug abuse within the past 3 months or recent needle track marks • Definite or possible infective endocarditis according to the modified Duke's criteria

NCT00638157 *(Continued)*

	• 2 blood cultures positive for *Staphylococcus aureus* obtained within 96 hours prior to first dose of study medication acquired by fresh venepuncture using aseptic technique and analysed at the local laboratory Exclusion criteria: • Intravascular foreign material in place at the time that the positive blood culture was drawn • High likelihood of left infective endocarditis as indicate • Prosthetic heart valve • Baseline creatinine clearance of < 30 mL/minute • Baseline creatinine phosphokinase value 5 x upper limit of normal in conjunction with symptoms of myalgia or baseline creatine phosphokinase value 10 x upper limit of normal without symptoms • Alanine aminotransferase > 5 x upper limit of normal • Aspartate aminotransferase > 5 x upper limit of normal • Moribund clinical condition • Shock or hypotension • Known pneumonia or osteomyelitis • Polymicrobial infection or bacteraemia due to a pathogen other than *Staphylococcus aureus* • Neutropenia (absolute neutrophil count < 0.5 x 10^3/µL) or lymphopenia (CD4 lymphocytes < 0.2 x 10^3/µL), or both • Anticipated to require non-study antibiotics that may potentially be effective against *Staphylococcus aureus* • Prior gentamicin therapy > 1 day • Documented history of significant allergy or intolerance to any of the study medications • Unlikely to comply with study procedures • Pregnant or nursing • Female of childbearing potential and not willing to practice barrier methods of contraception
Interventions	Experimental: daptomycin 6 mg/kg every 24 hours with concomitant initial gentamicin dosed for the first 2 days of therapy Control: daptomycin 6 mg/kg every 24 hours Treatment duration: daptomycin will be 28 days. The duration of treatment for gentamicin will be 3 days.
Outcomes	Primary: • Clinically significant increases in serum creatinine by visit Secondary: • Clinical response
Starting date	13 February 2009
Contact information	Sponsors and collaborators: Cubist Pharmaceuticals LLC (NCT00638157)
Notes	Status: terminated due to "(commitment completed)" (accessed: 21 January 2016) Primary completion date: November 2011 (final data collection date for primary outcome measure) Sponsors and collaborators: Cubist Pharmaceuticals LLC No publications provided. Results first received: 4 March 2013 Last updated: 5 January 2016

NCT00638157 *(Continued)*

	Organisation: Cubist Pharmaceuticals Telephone: 781-860-8318 Email: ed.campanaro@cubist.com

NCT00695903

Study name	Official title: A phase 2 multicenter, randomized, double-blinded, study to describe the safety, efficacy, and pharmacokinetics of daptomycin 10 mg/kg/day and vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* bacteraemia
Methods	Interventional, randomised, parallel assignment, and double-blind (participant, investigator) Phase II
Participants	Enrolment: 38 Inclusion criteria: • Written informed consent has been obtained • ≥ 18 years • Suspected methicillin-resistant *Staphylococcus aureus* bacteraemia determined by clinical judgement or 2 sets of positive blood cultures • Increased risk for a methicillin-resistant *Staphylococcus aureus* infection Exclusion criteria: • Received > 48 hours of vancomycin therapy in the 7 days prior to enrolment • Received any systemic antibacterial agents potentially effective against methicillin-resistant *Staphylococcus aureus* in the 7 days prior to enrolment • Anticipated requirement of antibiotics potentially effective against methicillin-resistant *Staphylococcus aureus* • High likelihood of left-sided infective endocarditis • Known/suspected polymicrobial bacteraemia or infection including gram-negative infections • Known pneumonia, osteomyelitis, or meningitis • Intravascular foreign material unless material intended removed within 3 days • Prosthetic heart valve • Cardiac decompensation, valve damage, or both, such that high likelihood of valve replacement surgery within first 3 days of study drug treatment • Moribund clinical condition such that death likely within first 3 days of study drug treatment • Shock or hypotension or oliguria unresponsive to fluids after 4 hours • Received investigational drug within 30 days of study entry • Received statins or other therapy associated with rhabdomyolysis within 2 days of study entry • History of significant allergy or intolerance to vancomycin or daptomycin • Infecting pathogen with confirmed reduced susceptibility to vancomycin • Infecting pathogen with confirmed reduced susceptibility to daptomycin • Creatinine clearance < 30 mL/minute • Serum creatine phosphokinase ≥ 500 U/L • Alanine transaminase or aspartate aminotransferase > 5 x upper limit of normal • Total bilirubin ≥ 3.0 mg/dL • Severe neutropenia or expected development of severe neutropenia during study • Known or suspected HIV infection with a CD4+ T-cell count < 200/µL • Unlikely to comply with study procedures or return for evaluations • Body mass index ≥ 40 kg/m^2

NCT00695903 *(Continued)*

	• Pregnant or nursing • Woman of childbearing potential not willing to practice barrier methods of contraception
Interventions	Experimental: daptomycin 10 mg/kg IV every 24 hours Control: vancomycin 15 mg/kg IV, dosed to maintain trough serum concentrations of 15 to 20 µg/mL
Outcomes	Primary: • Number of participants with treatment-emergent creatine phosphokinase elevations • Number of participants with elevated serum creatinine Secondary: • Number of participants with treatment cure at end of therapy visit • Number of participants with treatment cure at test of cure/safety visit
Starting date	17 September 2008
Contact information	Sponsors and collaborators: Cubist Pharmaceuticals LLC Study director: Peter Pertel, MD; Cubist Pharmaceuticals LLC Organisation: Cubist Pharmaceuticals Email: ellie.hershberger@cubist.com
Notes	Status: terminated due to lack of enrolment (accessed: 21 January 2016) Study completion date: October 2010

NCT02208063

Study name	A Phase 3 multicenter, randomized, open-label, clinical trial of telavancin versus standard intravenous therapy in the treatment of subjects with *Staphylococcus aureus* bacteremia Including *Staphylococcus aureus* right-sided infective endocarditis
Methods	Interventional, randomised, parallel assignment and open-label Phase III
Participants	Estimated enrolment: 248 Age: ≥ 18 years Gender: men and women Inclusion criteria: • ≥ 18 years with ≥ 1 blood culture positive for S. aureus within 48 hours before randomisation • ≥ 1 of the following signs or symptoms of bacteraemia: temperature ≥ 38.0 °C, white blood cells > 10,000 or < 4000 cells/µL or > 10% immature neutrophils (bands), tachycardia (heart rate > 90 beats/minute), tachypnoea (respiratory rate > 20 breaths/minute), hypotension (systolic blood pressure < 90 mmHg), signs or symptoms of localised catheter-related infection

NCT02208063 *(Continued)*

	• At enrolment, participants must have:
	  * known right-sided infective endocarditis by modified Duke's criteria;
	  * known complicated bacteraemia, demonstrated as signs or symptoms of metastatic foci of *Staphylococcus aureus* infection; or
	  * ≥ 1 risk factor for complicated bacteraemia.
	
	Exclusion criteria:
	
	• Treatment with any potentially effective (antistaphylococcal) systemic antibiotic for > 48 hours within 7 days before randomisation. Exception: documented resistance to the prior systemic antibacterial therapy
	• Presence of any removable infection source (e.g. IV line, abscess) that will not be removed or debrided within 3 days after randomisation
	• Presence of prosthetic joint or cardiac device (e.g. implantable cardioverter defibrillator, permanent pacemaker, or prosthetic valve or cardiac valve support ring)
	• Known or suspected left-sided infective endocarditis, by modified Duke's criteria
	• Known or suspected osteomyelitis (primary or embolic), or meningitis (primary). Note: evidence of metastatic complications related to the primary infection such as right-sided endocarditis, septic arthritis, and septic pulmonary infarcts will be allowed.

Interventions	Experimental: telavancin Control: standard of care (vancomycin, daptomycin, synthetic penicillin or cefazolin)
Outcomes	Primary: • Clinical response (success or failure) Secondary: • Development of new metastatic foci of infection • Clearance of bacteraemia
Starting date	December 2014
Contact information	Peter St Wecker, email: PStwecker@theravance.com; telephone: 650-808-6000 USA
Notes	Estimated study completion date: April 2017 Sponsors: Theravance Biopharma Antibiotics Inc

NCT02701595

Study name	Oral switch during treatment of left-sided endocarditis due to multi-susceptible *Streptococcus*
Methods	Interventional (clinical trial) Randomised Parallel assignment Open-label
Participants	Male or female at least 18 years old Inclusion criteria: several

NCT02701595 *(Continued)*

	Exclusion criteria: several
Interventions	Experimental: oral switch treatment. Oral switch to amoxicillin Active comparator: conventional IV treatment according to European guidelines. Conventional IV treatment of streptococci/enterococci infective disease (European guidelines 2015)
Outcomes	Primary: • Failure is a composite outcome defined by death from all causes and/or symptomatic embolic events and/or unplanned valvular surgery and/or a microbiological relapse (with the primary pathogen). Secondary: several endpoints
Starting date	29 February 2016
Contact information	Louis Bernard (L.BERNARD@chu-tours.fr) Elodie Mousset (e.mousset@chu-tours.fr)
Notes	Sponsor: University Hospital, Tours Principal Investigator: Louis Bernard, MD, PHD

NCT02701608

Study name	Oral switch during treatment of left-sided endocarditis due to multi-susceptible *Staphylococcus*
Methods	Interventional (clinical trial) Randomised Parallel assignment Open-label
Participants	Male or female at least 18 years old Inclusion criteria: several Exclusion criteria: several
Interventions	Experimental: oral switch treatment. Oral switch to combination levofloxacin and rifampicin Active comparator: conventional IV treatment according to European guidelines. Conventional IV treatment of staphylococci infective endocarditis (European guidelines 2015)
Outcomes	Primary: • Failure is a composite outcome defined by death from all causes and/or symptomatic embolic events and/or unplanned valvular surgery and/or a microbiological relapse (with the primary pathogen). Secondary: several endpoints
Starting date	29 February 2016
Contact information	Louis Bernard (L.BERNARD@chu-tours.fr)

NCT02701608 *(Continued)*

	Elodie Mousset (e.mousset@chu-tours.fr)
Notes	Sponsor: University Hospital, Tours Principal Investigator: Louis Bernard, MD, PHD

NCT03138733

Study name	A randomized, double-blind, multi-center study to establish the efficacy and safety of ceftobiprole medocaril compared to daptomycin in the treatment of *Staphylococcus aureus* bacteremia, including infective endocarditis
Methods	Interventional (clinical trial), randomised, parallel assignment, quadruple masking (participant, care provider, investigator, outcomes assessor)

Participants	Inclusion criteria:
	
	• Male or female ≥ 18 years of age
	• *Staphylococcus aureus* bacteraemia, based on at least 1 positive blood culture obtained within the 72 h prior to randomisation
	• At least 2 of the following signs or symptoms of bacteraemia:
	  • fever ≥ 38 °C/100.4 °F
	  • white blood cell count > 10,000 or < 4000 cells/µL, or > 10% immature neutrophils (bands)
	  • tachycardia (heart rate > 90 beats per minute)
	  • hypotension (systolic blood pressure < 90 mmHg)
	• At least 1 of the following:
	  • *Staphylococcus aureus* bacteraemia in patients undergoing chronic intermittent haemodialysis or peritoneal dialysis
	  • Persistent *Staphylococcus aureus* bacteraemia
	  • Definite native-valve right-sided infective endocarditis by modified Duke's criteria
	  • Other forms of complicated *Staphylococcus aureus* bacteraemia
	
	Exclusion criteria:
	
	• Treatment with potentially effective (antistaphylococcal) systemic antibacterial treatment for more than 48 h within the 7 days prior to randomisation. Exception: documented failure of bloodstream clearance
	• Bloodstream or non-bloodstream concomitant infections with gram-negative bacteria that are known to be non-susceptible to either ceftobiprole or aztreonam
	• Left-sided infective endocarditis
	• Prosthetic cardiac valves or valve support rings, cardiac pacemakers, automatic implantable cardioverter-defibrillator, or left-ventricular assist devices
	• Community- or hospital-acquired pneumonia
	• Opportunistic infections within 30 days prior to randomisation, where the underlying cause of these infections is still active
	• Requirement for continuous renal-replacement therapy
	• Women who are pregnant or nursing
	• Other exclusion criteria may apply

Interventions	Experimental: ceftobiprole medocaril (ceftobiprole medocaril 500 mg) Active comparator: daptomycin (daptomycin 6 mg/kg, with or without aztreonam)
Outcomes	Primary outcome measures:

NCT03138733 *(Continued)*

	• Overall success at the PTE Secondary outcome measures: • All-cause mortality at the PTE visit • Microbiological eradication at the PTE visit • Overall success at the PTE visit • Development of new metastatic foci or other complications of *Staphylococcus aureus* bacteraemia after day 7 • Time to *Staphylococcus aureus* bloodstream clearance • Incidence, type, severity, and relationship to study medication of adverse events; and changes in laboratory tests • Ceftobiprole maximum plasma concentration Ceftobiprole area under the concentration-time curve
Starting date	1 June 2018
Contact information	Kamal Hamed, MD, MPH (+41 61 567 15 88) (kamal.hamed@basilea.com) Marc Engelhardt, MD (+41 61 567 15 46) (marc.engelhardt@basilea.com) Sponsors and collaborators: Basilea Pharmaceutica
Notes	International, multicentre (56 sites) Estimated study completion date: August 2021

NCT03148756

Study name	Efficacy and safety of dalbavancin compared to standard of care antibiotic therapy for the completion of treatment of patients with complicated bacteremia or infective endocarditis
Methods	Interventional (clinical trial), randomised parallel assignment, single-masking (outcomes assessor), treatment
Participants	Male or female ≥ 18 years of age Inclusion criteria: • Diagnosis of complicated bacteraemia or infective endocarditis • Gram-positive bacteraemia at screening with MSSA, MRSA, or streptococci • Treatment with standard-of-care antibiotics for 72 h - 10 days • Defervescence for at least 24 h and clearance of bacteraemia from screening pathogen Exclusion criteria: • Embolic events • History of prosthetic valve surgery, cardiac device, or prosthetic joint • Left-sided endocarditis due to *Staphylococcus aureus* • Large mobile vegetations (> 10 mm) on mitral valves • Perivalvular abscess • Several other exclusion criteria: see clinicaltrials.gov/ct2/show/NCT03148756 for details
Interventions	Experimental: dalbavancin. Dalbavancin 1500 mg, IV administration over 30 minutes on days 1 and 8

NCT03148756 *(Continued)*

	Active comparator: standard of care. Antibiotic consistent with standard of care, based on baseline pathogen, for 4 to 6 weeks
Outcomes	Primary outcome measures: • Number of participants with clinical response at day 84 in the ITT population Secondary outcome measures: • Clinical outcome of success at day 42 in the ITT population • Clinical outcome of success at day 42 in the clinically evaluable population • Number of participants with day 84 mortality in the safety population • Clinical outcome of success at day 84 in the clinically evaluable population • Clinical outcome of success by pathogen at day 42 in the ITT population • Note: total number of secondary outcome measures: 12. See clinicaltrials.gov/ct2/show/NCT03148756 for details.
Starting date	12 May 2017
Contact information	Sponsor: Allergan Study Director: Urania Rappo, MD
Notes	Midway Immunology and Research Center (Fort Pierce, Florida, USA, 34982)

NCT04222257

Study name	Short-course antibiotic regimen compared to conventional antibiotic treatment for Gram-positive Cocci infective endocarditis: randomized clinical trial
Methods	Randomised, parallel assignment, open-label Phase IV
Participants	Male or female at least 18 years old Inclusion criteria: several Exclusion criteria: several
Interventions	Experimental group: • Participants allocated to this group will receive a short course of antibiotic therapy for 2 weeks. Control group: • Those participants allocated to continue with standard parenteral treatment will maintain the same antibiotic treatment for 4 to 6 weeks.
Outcomes	Primary: • Composite endpoint: all-cause mortality, unplanned cardiac surgery, symptomatic embolisms, and relapses within 6 months after inclusion into the study, between participants with infective endocarditis caused by gram-positive cocci receiving a short course of 2 weeks of antibiotic therapy and those participants receiving conventional antibiotic therapy for 4 to 6 weeks Secondary: • Perceived quality of life: SF-12

NCT04222257 *(Continued)*

	• Determination of functional performance according to the short performance physical battery test • Clinical complications: nosocomial infections, intravascular catheter-related infections • Total hospital length of stay
Starting date	1 March 2020
Contact information	Carmen Olmos Blanco, MD +0034-913303149 carmen.olmosblanco@gmail.com Cardiovascular Institute. Hospital Clínico San Carlos
Notes	apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2019-003358-10-ES apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT04222257

RBR-3p8g7n 2016

Study name	A phase 3 multicenter, randomized, open-label, clinical trial of telavancin versus standard intravenous therapy in the treatment of subjects with *Staphylococcus aureus* bacteremia including infective endocarditis
Methods	Randomised controlled, parallel, open-label Arms: 2 Phase: III International multicentre study
Participants	Male or female at least 18 years old Inclusion criteria: several Exclusion criteria: several
Interventions	Experimental group: • Telavancin, 7.5 mg/kg, IV in 100 to 250 mL over 60 (+/- 10) minutes, once every 24 hours for 2 to 6 weeks Control group: • Standard IV therapy, administered for 2 to 6 weeks: vancomycin (recommended dose of 15 mg/kg IV every 12 hours); daptomycin (recommended dose of 6 mg/kg IV every 24 hours); antistaphylococcal penicillin (i.e. nafcillin, oxacillin, or cloxacillin) recommended dose of 2 g IV every 4 hours or 12 g IV continuous infusion over 24 hours; or cefazolin (recommended dose of 2 g IV every 8 hours)
Outcomes	Primary: clinical success or failure at test of cure Secondary: reported as "not applicable"
Starting date	03 August 2016
Contact information	Anna Carolina Coimbra (Rua da passagem, 123 / 6º andar, Botafogo 22290-030 Rio de Janeiro, Brazil) annacarolina.coimbra@increasearch.com INC Research BR Serviços de Pesquisas Clínicas Ltda

RBR-3p8g7n 2016 *(Continued)*

Notes	There is inconsistency regarding 'date of registration' (03 August 2016) and 'date of first enrolment' (01 June 2015). Status: discontinued (27 Feb 2018). Source: https://adisinsight.springer.com/trials/700248032 (6 May 2020).

eGFR: estimated Glomerular Filtration Rate
ITT: intention-to-treat
IV: intravenous
MIC: minimum inhibitory concentration
MRSA: methicillin-resistant *Staphylococcus aureus*
MSSA: methicillin-susceptible *Staphylococcus aureus*
PTE: post-treatment evaluation
SF-12: 12-item Short Form Health Survey
U: unit

APPENDICES

Appendix 1. Types of infective endocarditis

- According to localisation of infection and presence or absence of intracardiac material (left-sided native valve, left-sided prosthetic valve, right-sided and device-related (permanent pacemaker or cardioverter-defibrillator)).
- According to the mode of acquisition (healthcare associated (nosocomial and non-nosocomial), community-acquired, and intravenous drug abusers).
- Active (infective endocarditis with persistent fever, and positive blood culture or active inflammatory morphology found at surgery or person still under antibiotic therapy or histopathological evidence of active infective endocarditis).
- Recurrent (relapse or reinfection).

From Habib 2019.

Appendix 2. Clinical presentation of infective endocarditis

Infective endocarditis should be suspected in the following situations.

- New regurgitant heart murmur.
- Embolic events of unknown origin.
- Sepsis of unknown origin (especially if it is associated with an organism recognised as causing infective endocarditis).
- Fever: the most frequent sign of infective endocarditis. Fever may be absent in older people, after antibiotic pre-treatment, in immunocompromised people, and in infective endocarditis involving less virulent or atypical organisms.

Infective endocarditis should be suspected if fever is associated with the following.

- Intracardiac prosthetic material (e.g. prosthetic valve, pacemaker or implantable defibrillator, surgical baffle/conduit).
- Previous history of infective endocarditis.
- Known valvular or congenital heart disease.
- Other predisposition for infective endocarditis (e.g. immunocompromised state, intravenous drug abusers).
- Recent intervention with associated bacteraemia.
- Evidence of congestive heart failure.
- New conduction disturbance.
- Positive blood cultures with typical infective endocarditis causative organism or positive serology for chronic Q fever (microbiological findings may precede cardiac manifestations).
- Vascular or immunological phenomena: embolic event, Roth spots, splinter haemorrhages, Janeway lesions, Osler's nodes.
- Focal or non-specific neurological symptoms and signs.
- Evidence of pulmonary embolism/infiltration (right-sided infective endocarditis).
- Peripheral abscesses (renal, splenic, cerebral, vertebral) of unknown cause.

From Habib 2019.

Appendix 3. Antibiotic therapy for the treatment of infective endocarditis: recommended dosages of the main antibiotics

- Crystalline penicillin G 12 to 18 million U/24 h IV either continuously or in 4 or 6 equally divided doses.
- Ampicillin sodium 12 g/24 h IV in 6 equally divided doses.
- Flucloxacillin 12 g/24 h IV in 6 equally divided doses.
- Nafcillin or oxacillin 12 g/24 h IV in 6 equally divided doses.
- Ceftriaxone 2 g/24 h IV/IM in 1 dose.
- Vancomycin 30 mg/kg per 24 h IV in 2 equally divided doses.
- Teicoplanin 10 mg/kg per 24 h.
- Gentamicin 3 mg/kg per 24 h IV/IM in 1 dose.
- Daptomycin 6 mg/kg per 24 h.
- Levofloxacin 500 mg/daily either IV or orally.

Abbreviations: IM: intramuscular; IV: intravenous U: unit

Sources: Baddour 2015; FINLEVO Trial 2006..

A description of the various classes of antibiotics and their adverse reactions follows below.

Clinical pharmacology and microbiological spectrum

Many antimicrobial drugs have been used alone or in combination in the treatment of infective endocarditis (Vinh 2016). They include beta-lactam antibiotics, aminoglycosides, glycopeptides, oxazolidinones, and complex macrocyclic antibiotics (Drees 2006; Frank 2009).

- **Beta-lactam antibiotics:** includes penicillins, cephalosporins, and carbapenems (Petri 2001a). The penicillins consist of penicillins G and V, which are highly active against susceptible gram-positive cocci, and ampicillin and other agents with an improved gram-negative spectrum. This group also includes the cephalosporin antibiotics, which are classified by generation: first-generation agents with excellent gram-positive and modest gram-negative activity; second-generation agents with somewhat better activity against gram-negative organisms and some have additional anti-anaerobe activity; third-generation agents have activity against gram-positive organisms and more activity against the Enterobacteriaceae, with a subset active against *Pseudomonas aeruginosa*; and fourth-generation agents encompass the antimicrobial spectrum of all the third-generation agents but have increased stability to hydrolysis by inducible chromosomal beta-lactamases (Petri 2001a).
- **Aminoglycosides:** gentamicin is the most studied drug of this pharmacological antibiotic class (Chambers 2001a), and was once widely used as a primary agent for treating gram-negative infections. However, because of their toxicity and the availability of newer effective agents, systemic aminoglycosides have been primarily relegated to a role as companion drugs, either to broaden coverage against gram-negative aerobic bacilli, or to provide synergistic effects against gram-positive cocci or certain gram-negative bacilli (Chen 2009). Aminoglycosides are poorly absorbed orally, and the excretion of aminoglycosides is primarily by glomerular filtration; clearance is decreased with renal insufficiency, but increased in children and pregnant women (Chen 2009). In addition to gentamicin, amikacin and streptomycin are aminoglycosides that have been used to treat infective endocarditis.
- **Glycopeptides:** includes vancomycin and teicoplanin, which have been widely used for treating serious gram-positive infections, particularly those involving methicillin-resistant *Staphylococcus aureus* (Nailor 2009).
- **Oxazolidinones:** linezolid is a synthetic class of antimicrobial agent. Linezolid has both parenteral and oral preparations with 100% bioavailability, and penetrates well into tissues (Dryden 2011). The antimicrobial spectrum of the oxazolidinedione is similar to that of vancomycin, with activity against most gram-positive organisms, including methicillin-resistant *S aureus* and penicillin-resistant pneumococci (Leach 2011; Muñoz 2007; Nailor 2009).
- **Complex macrocyclic antibiotics (rifamycins):** rifampicin is highly active against both coagulase-positive and -negative staphylococci and other gram-positive cocci, such as *Streptococcus pyogenes* and *Streptococcus pneumoniae* (Chen 2009; Petri 2001b). Enterococci are only moderately susceptible. Among gram-negative organisms, *Neisseria meningitidis*, *Neisseria gonorrhoeae*, and *Hemophilus influenzae* are the most susceptible. Rifampicin is well absorbed when given orally. An intravenous preparation is available when the oral route cannot be used. It penetrates well into body fluids, achieving therapeutic levels in saliva, bile, bone, pleural fluid, prostate, and cerebrospinal fluid. Moreover, rifampicin readily enters phagocytic cells and can kill micro-organisms in the cells (Chen 2009).
- **Lipopeptide antibiotics (daptomycin):** an antibiotic with bactericidal activity against *S aureus* bacteraemia and endocarditis, and infections caused by *Enterococcus* spp., especially if vancomycin-resistant (Warren 2008). There are reports of an increasing of daptomycin non-susceptibility in *S aureus, Enterococcus faecium*, and *Enterococcus faecalis* (Humphries 2013).
- **Fluoroquinolone (levofloxacin):** a synthetic antimicrobial agent of third-generation fluoroquinolone that is quickly absorbed by oral administration (Leyva 2008; Liu 2010). This property is important because the intravenous formulation can be changed to oral route. This drug has a broad-spectrum antibacterial profile (Anderson 2008).

Antibiotic adverse reactions

The major antibiotic adverse reactions associated with the main antimicrobial drugs for treating infective endocarditis have been widely described (Granowitz 2008). Briefly, untoward reactions of these drugs are as follows.

- **Beta-lactam antibiotics:** although this group of antibiotics commonly causes drug hypersensitivity reactions (Chambers 2001b; Torres 2010), beta-lactams are generally safe (Lagace-Wiens 2012; Petri 2001a), and serious adverse events are rare and allergy is overdiagnosed (Lagace-Wiens 2012). One publication suggests that amoxicillin given as endocarditis prophylaxis is associated with a very low rate of adverse events (Thornhill 2015).
- **Aminoglycosides:** gentamicin: the major adverse effects of the aminoglycosides are nephrotoxicity and oto-vestibular toxicity (Chen 2009). Furthermore, aminoglycosides can cause neuromuscular blockade due to interference with neurotransmission at the neuromuscular junction (Chen 2009; Cosgrove 2009).
- **Glycopeptides:** vancomycin: there are three major adverse events associated with this drug. First, the 'red man' syndrome is a non-immunologically mediated histamine release associated with rapid infusion of vancomycin. Clinical signs and symptoms include pruritus, erythema, and flushing of the upper torso, angio-oedema, and occasionally, hypotension (Nailor 2009). Second, nephrotoxicity is well described, but rare when vancomycin is used alone and at conventional dosages (e.g. 1 g every 12 hours) (Nailor 2009). The risk increases in people who are critically ill and on vasopressor support or when used with concomitant nephrotoxic agents, or both; who have deranged renal function at baseline; who are undergoing prolonged duration of therapy; or who are obese (Gupta 2011; Wong-Beringer 2011). Third, deafness may occur, usually preceded by tinnitus and high-tone hearing loss (Nailor 2009).
- **Oxazolidinones:** linezolid: the major adverse events associated with the use of this drug include hepatic dysfunction (Gould 2011), peripheral neuropathies (Gould 2011; Vinh 2016), with or without optic neuropathy in people receiving therapy for more than 28 days (Gould 2011), haematological abnormalities (anaemia and thrombocytopenia) (Gould 2011), gastrointestinal disturbances (Gould 2011; Vinh 2016), and lactic acidosis, generally in people with numerous comorbidities, such as thiamine deficiency or cirrhosis (Gould 2011).
- **Complex macrocyclic antibiotics:** rifampicin: the administration of this drug frequently results in urine and sweat developing an orange tinge; soft contact lenses may be stained. An influenza-like syndrome can occur in up to 5% of people who have had prolonged intermittent use of rifampicin. Rash and gastrointestinal adverse effects (e.g. nausea, vomiting, diarrhoea, heartburn) may occur in up to 5% of people. Abnormal liver function tests are common, but frank hepatitis is uncommon (< 1%) (Chen 2009).
- **Lipopeptide antibiotics:** daptomycin: Shrestha and colleagues have reported that people receiving daptomycin at home have fewer antimicrobial adverse events than similar people receiving vancomycin (Shrestha 2014). One meta-analysis assessing the safety and efficacy of daptomycin versus other antibiotics for skin and soft-tissue infections showed higher creatine phosphokinase elevation in the daptomycin group than in the control group (Wang 2014), as reported by Falagas and colleagues in people with endocarditis and treated with daptomycin (Falagas 2007).
- **Fluoroquinolone:** levofloxacin: this drug is relatively well tolerated, with low rates of clinically important adverse events such as central nervous system toxicity (headache and dizziness), cardiovascular toxicity (QT interval prolongation), and metabolism glucose disruption (Liu 2010).

How the intervention might work

Appropriate antibiotic treatment is important to control local infection, eradicate the organisms from the vegetations, and reduce the risk of complications such as septic embolisation (Baddour 2015).

The pharmacodynamics of the most frequent antimicrobial drugs used for treating infective endocarditis include the following.

- **Beta-lactam antibiotics:** the beta-lactam antibiotics share a common mechanism of action, i.e. inhibition of synthesis of the bacterial peptidoglycan cell wall (Petri 2001a).
- **Aminoglycosides:** gentamicin is the most studied aminoglycoside, and acts in part by impairing bacterial protein synthesis through irreversible binding to the 30S subunit of the bacterial ribosome (Chen 2009).
- **Glycopeptides:** vancomycin exhibits concentration-independent bactericidal activity by the inhibition of bacterial cell wall synthesis. Vancomycin requires actively growing bacteria to exert its effect (Nailor 2009).
- **Oxazolidinones:** linezolid exerts its effect early in protein synthesis by inhibiting the initiation complex at the 30S ribosome (Nailor 2009; Vinh 2016).
- **Complex macrocyclic antibiotics:** rifampicin acts by inhibiting deoxyribonucleic acid-dependent ribonucleic acid polymerase, after binding to the beta subunit of the enzyme. This interaction interferes with protein synthesis by preventing chain initiation (Chen 2009).
- **Lipopeptide antibiotics:** daptomycin affects the membrane of the micro-organism through a calcium-dependent dissipation of membrane potential that leads to the release of intracellular ions from the cell and bacteria death (Vilhena 2012).
- **Fluoroquinolone:** levofloxacin acts by inhibition of deoxyribonucleic acid gyrase or topoisomerase IV (Leyva 2008).

Appendix 4. Search strategies

CENTRAL

#1 MeSH descriptor: [Endocarditis] explode all trees

#2 endocarditi*

#3 (infect* near/2 endocard*)

#4 #1 or #2 or #3

#5 MeSH descriptor: [Anti-Infective Agents] explode all trees

#6 ((antimycobacterial or (anti next mycobacterial) or antibacterial or (anti next bacterial) or antibiotic*) near/2 (drug* or agent* or treatment* or medicat* or therap*))

#7 (((anti next infect*) or antiinfect* or antimicrobial or (anti next microbial)) near/2 (drug* or agent* or treatment* or medicat* or therap*))

#8 bacteriocid*

#9 ampicillin or amcill or ukapen or polycillin or omnipen or aminobenzylpenicillin or (aminobenzyl next penicillin) or pentrexyl or amoxicillin or azlocillin

#10 mezlocillin or piperacillin or pivampicillin or talampicillin or aminopenicillin* or (Penicillin next g) or penilevel or pekamin or penibiot or ursopen or van-pen-g

#11 pfizerpen or sodiopen or benpen or peniroger or or-pen or pengesod or (sodium next penicillin) or parcillin or unicilina or (benzylpenicillin next potassium)

#12 sodipen or crystapen or coliriocilina or benzylpenicillin or Sulbenicillin or Carbenicillin or flucloxacillin or floxacillin or fluorochloroxacillin or cefazolin or cephazolin or cephamezine

#13 cefamedin or totacef or cefamezine or gramaxin or ancef or kefzol or cephalosporin* or ceftriaxon* or terbac or rocefalin or longacef or rocephine or lendacin or rocephin

#14 cefaxona or ceftrex or longaceph or rocefin or tacex or benaxona

#15 MeSH descriptor: [Aminoglycosides] explode all trees

#16 gentam?cin* or gentavet or genticin or garamycin or gentacycol or gmyticin or (g next myticin) or aminoglycoside* or vancom?cin* or vanco-saar or (vanco next azupharma)

#17 diatracin or (vancocin next hcl) or ab-vancomycin or vanco-cell or vancocin* or linezolid* or benemycin or rimactane or tubocin or rifampicin or rimactan or rifadin or rifampin

#18 MeSH descriptor: [Glycopeptides] explode all trees

#19 Bleomycin or Peptidoglycan or Ristocetin or Teicoplanin

#20 MeSH descriptor: [beta-Lactams] this term only

#21 (beta-lactam* near/2 antibiot*) or betalactam

#22 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21

#23 #4 and #22

MEDLINE Ovid

1. exp Endocarditis/

2. endocarditi*.tw.

3. (infect* adj2 endocard*).tw.

4. or/1-3

5. exp Anti-Infective Agents/

6. ((antimycobacterial or anti mycobacterial or antibacterial or anti bacterial or antibiotic*) adj (drug* or agent* or treatment* or medicat* or therap*)).tw.

7. ((anti infect* or antiinfect* or antimicrobial or anti microbial) adj (drug* or agent* or treatment* or medicat* or therap*)).tw.

8. bacteriocid*.tw.

9. ampicillin.tw.

10. amcill.tw.

11. (ksr1 or ks-r1).tw.

12. ukapen.tw.

13. polycillin.tw.

14. omnipen.tw.

15. (aminobenzylpenicillin or aminobenzyl penicillin).tw.

16. pentrexyl.tw.

17. amoxicillin.tw.

18. azlocillin.tw.

19. mezlocillin.tw.

20. piperacillin.tw.

21. pivampicillin.tw.

22. talampicillin.tw.

23. aminopenicillin*.tw.

24. Penicillin G.tw.

25. penilevel.tw.

26. pekamin.tw.

27. penibiot.tw.

28. ursopen.tw.

29. van-pen-g.tw.

30. pfizerpen.tw.

31. sodiopen.tw.

32. benpen.tw.

33. peniroger.tw.

34. or-pen.tw.

35. pengesod.tw.

36. sodium penicillin.tw.

37. parcillin.tw.

38. unicilina.tw.

39. benzylpenicillin potassium.tw.

40. sodipen.tw.

41. crystapen.tw.

42. coliriocilina.tw.

43. benzylpenicillin.tw.

44. Sulbenicillin.tw.

45. Carbenicillin.tw.

46. flucloxacillin.tw.

47. floxacillin.tw.

48. fluorochloroxacillin.tw.

49. cefazolin.tw.

50. cephazolin.tw.

51. cephamezine.tw.

52. cefamedin.tw.

53. totacef.tw.

54. cefamezine.tw.

55. gramaxin.tw.

56. ancef.tw.

57. kefzol.tw.

58. cephalosporin*.tw.

59. ceftriaxon*.tw.

60. terbac.tw.

61. rocefalin.tw.

62. longacef.tw.

63. rocephine.tw.

64. (ro13 9904 or ro 139904 or ro139904 or ro 13 9904).tw.

65. lendacin.tw.

66. rocephin.tw.

67. cefaxona.tw.

68. ceftrex.tw.

69. longaceph.tw.

70. rocefin.tw.

71. tacex.tw.

72. benaxona.tw.

73. exp Aminoglycosides/

74. gentam?cin*.tw.

75. gentavet.tw.

76. genticin.tw.

77. garamycin.tw.

78. gentacycol.tw.

79. (g myticin or gmyticin).tw.

80. aminoglycoside*.tw.

81. vancom?cin*.tw.

82. vanco-saar.tw.

83. vanco azupharma.tw.

84. diatracin.tw.

85. vancocin hcl.tw.

86. ab-vancomycin.tw.

87. vanco-cell.tw.

88. vancocin*.tw.

89. linezolid*.tw.

90. benemycin.tw.

91. rimactane.tw.

92. tubocin.tw.

93. rifampicin.tw.

94. rimactan.tw.

95. rifadin.tw.

96. rifampin.tw.

97. exp Glycopeptides/

98. Bleomycin.tw.

99. Peptidoglycan.tw.

100. Ristocetin.tw.

101. Teicoplanin.tw.

102. beta-Lactams/

103. (beta-lactam* adj2 antibiot*).tw.

104. betalactam.tw.

105. or/5-104

106. 4 and 105

107. randomized controlled trial.pt.

108. controlled clinical trial.pt.

109. randomized.ab.

110. placebo.ab.

111. clinical trials as topic.sh.

112. randomly.ab.

113. trial.ti.

114. 107 or 108 or 109 or 110 or 111 or 112 or 113

115. exp animals/ not humans.sh.

116. 114 not 115

117. 106 and 116

EMBASE Ovid

1. exp endocarditis/

2. endocarditi*.tw.

3. (infect* adj2 endocard*).tw.

4. or/1-3

5. exp antiinfective agent/

6. ((antimycobacterial or anti mycobacterial or antibacterial or anti bacterial or antibiotic*) adj (drug* or agent* or treatment* or medicat* or therap*)).tw.

7. ((anti infect* or antiinfect* or antimicrobial or anti microbial) adj (drug* or agent* or treatment* or medicat* or therap*)).tw.

8. bacteriocid*.tw.

9. ampicillin.tw.

10. amcill.tw.

11. (ksr1 or ks-r1).tw.

12. ukapen.tw.

13. polycillin.tw.

14. omnipen.tw.

15. (aminobenzylpenicillin or aminobenzyl penicillin).tw.

16. pentrexyl.tw.

17. amoxicillin.tw.

18. azlocillin.tw.

19. mezlocillin.tw.

20. piperacillin.tw.

21. pivampicillin.tw.

22. talampicillin.tw.

23. aminopenicillin*.tw.

24. Penicillin G.tw.

25. penilevel.tw.

26. pekamin.tw.

27. penibiot.tw.

28. ursopen.tw.

29. van-pen-g.tw.

30. pfizerpen.tw.

31. sodiopen.tw.

32. benpen.tw.

33. peniroger.tw.

34. or-pen.tw.

35. pengesod.tw.

36. sodium penicillin.tw.

37. parcillin.tw.

38. unicilina.tw.

39. benzylpenicillin potassium.tw.

40. sodipen.tw.

41. crystapen.tw.

42. coliriocilina.tw.

43. benzylpenicillin.tw.

44. Sulbenicillin.tw.

45. Carbenicillin.tw.

46. flucloxacillin.tw.

47. floxacillin.tw.

48. fluorochloroxacillin.tw.

49. cefazolin.tw.

50. cephazolin.tw.

51. cephamezine.tw.

52. cefamedin.tw.

53. totacef.tw.

54. cefamezine.tw.

55. gramaxin.tw.

56. ancef.tw.

57. kefzol.tw.

58. cephalosporin*.tw.

59. ceftriaxon*.tw.

60. terbac.tw.

61. rocefalin.tw.

62. longacef.tw.

63. rocephine.tw.

64. (ro13 9904 or ro 139904 or ro139904 or ro 13 9904).tw.

65. lendacin.tw.

66. rocephin.tw.

67. cefaxona.tw.

68. ceftrex.tw.

69. longaceph.tw.

70. rocefin.tw.

71. tacex.tw.

72. benaxona.tw.

73. exp aminoglycoside/

74. gentam?cin*.tw.

75. gentavet.tw.

76. genticin.tw.

77. garamycin.tw.

78. gentacycol.tw.

79. (g myticin or gmyticin).tw.

80. aminoglycoside*.tw.

81. vancom?cin*.tw.

82. vanco-saar.tw.

83. vanco azupharma.tw.

84. diatracin.tw.

85. vancocin hcl.tw.

86. ab-vancomycin.tw.

87. vanco-cell.tw.

88. vancocin*.tw.

89. linezolid*.tw.

90. benemycin.tw.

91. rimactane.tw.

92. tubocin.tw.

93. rifampicin.tw.

94. rimactan.tw.

95. rifadin.tw.

96. rifampin.tw.

97. exp glycopeptide/

98. Bleomycin.tw.

99. Peptidoglycan.tw.

100. Ristocetin.tw.

101. Teicoplanin.tw.

102. beta lactam/

103. (beta-lactam* adj2 antibiot*).tw.

104. betalactam.tw.

105. or/5-104

106. 4 and 105

107. random$.tw.

108. factorial$.tw.

109. crossover$.tw.

110. cross over$.tw.

111. cross-over$.tw.

112. placebo$.tw.

113. (doubl$ adj blind$).tw.

114. (singl$ adj blind$).tw.

115. assign$.tw.

116. allocat$.tw.

117. volunteer$.tw.

118. crossover procedure/

119. double blind procedure/

120. randomized controlled trial/

121. single blind procedure/

122. 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121

123. (animal/ or nonhuman/) not human/

124. 122 not 123

125. 106 and 124

126. limit 125 to embase

LILACS

"antibiotics" [Subject descriptor] or (antibiotic$ OR antiinfect$ OR anti-infect$ OR antibacter$ OR anti-bacter$) [Words] and (endocarditis) or "endocarditis" [Words]

CINAHL

S51 S32 AND S50

S50 S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49

S49 cross-over*

S48 crossover*

S47 volunteer*

S46 (MH "Crossover Design")

S45 allocat*

S44 control*

S43 assign*

S42 placebo*

S41 (MH "Placebos")

S40 random*

S39 (doubl* N1 mask*)

S38 (singl* N1 mask*)

S37 (doubl* N1 blind*)

S36 (singl* N1 blind)

S35 (clinic* N1 trial?)

S34 PT clinical trial

S33 (MH "Clinical Trials")

S32 S4 and S31

S31 S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30

S30 AB (gentam?cin* or gentavet or genticin or garamycin or gentacycol or gmyticin or "g myticin" or aminoglycoside* or vancom?cin* or vanco-saar or "vanco azupharma")

S29 TI (gentam?cin* or gentavet or genticin or garamycin or gentacycol or gmyticin or "g myticin" or aminoglycoside* or vancom?cin* or vanco-saar or "vanco azupharma")

S28 AB ((beta-lactam* N2 antibiot*) or betalactam)

S27 TI ((beta-lactam* N2 antibiot*) or betalactam)

S26 AB (Bleomycin or Peptidoglycan or Ristocetin or Teicoplanin or glycopeptid*)

S25 TI (Bleomycin or Peptidoglycan or Ristocetin or Teicoplanin or glycopeptid*)

S24 AB (diatracin or "vancocin hcl" or ab-vancomycin or vanco-cell or vancocin* or linezolid* or benemycin or rimactane or tubocin or rifampicin or rimactan or rifadin or rifampin)

S23 TI (diatracin or "vancocin hcl" or ab-vancomycin or vanco-cell or vancocin* or linezolid* or benemycin or rimactane or tubocin or rifampicin or rimactan or rifadin or rifampin)

S22 (MH "Aminoglycosides+")

S21 TI (cefaxona or ceftrex or longaceph or rocefin or tacex or benaxona) or AB (cefaxona or ceftrex or longaceph or rocefin or tacex or benaxona)

S20 AB (cefamedin or totacef or cefamezine or gramaxin or ancef or kefzol or cephalosporin* or ceftriaxon* or terbac or rocefalin or longacef or rocephine or lendacin or rocephin)

S19 TI (cefamedin or totacef or cefamezine or gramaxin or ancef or kefzol or cephalosporin* or ceftriaxon* or terbac or rocefalin or longacef or rocephine or lendacin or rocephin)

S18 AB (sodipen or crystapen or coliriocilina or benzylpenicillin or Sulbenicillin or Carbenicillin or flucloxacillin or floxacillin or fluorochloroxacillin or cefazolin or cephazolin or cephamezine)

S17 TI (sodipen or crystapen or coliriocilina or benzylpenicillin or Sulbenicillin or Carbenicillin or flucloxacillin or floxacillin or fluorochloroxacillin or cefazolin or cephazolin or cephamezine)

S16 AB (pfizerpen or sodiopen or benpen or peniroger or or-pen or pengesod or "sodium penicillin" or parcillin or unicilina or "benzylpenicillin potassium")

S15 TI (pfizerpen or sodiopen or benpen or peniroger or or-pen or pengesod or "sodium penicillin" or parcillin or unicilina or "benzylpenicillin potassium")

S14 AB (mezlocillin or piperacillin or pivampicillin or talampicillin or aminopenicillin* or "Penicillin g" or penilevel or pekamin or penibiot or ursopen or van-pen-g)

S13 TI (mezlocillin or piperacillin or pivampicillin or talampicillin or aminopenicillin* or "Penicillin g" or penilevel or pekamin or penibiot or ursopen or van-pen-g)

S12 AB (ampicillin or amcill or ukapen or polycillin or omnipen or aminobenzylpenicillin or "aminobenzyl penicillin" or pentrexyl or amoxicillin or azlocillin)

S11 TI (ampicillin or amcill or ukapen or polycillin or omnipen or aminobenzylpenicillin or "aminobenzyl penicillin" or pentrexyl or amoxicillin or azlocillin)

S10 TI bacteriocid* or AB bacteriocid*

S9 AB (("anti infect*" or antiinfect* or antimicrobial or "anti microbial") N2 (drug* or agent* or treatment* or medicat* or therap*))

S8 TI (("anti infect*" or antiinfect* or antimicrobial or "anti microbial") N2 (drug* or agent* or treatment* or medicat* or therap*))

S7 AB ((antimycobacterial or "anti mycobacterial" or antibacterial or "anti bacterial" or antibiotic*) N2 (drug* or agent* or treatment* or medicat* or therap*))

S6 TI ((antimycobacterial or "anti mycobacterial" or antibacterial or "anti bacterial" or antibiotic*) N2 (drug* or agent* or treatment* or medicat* or therap*))

S5 (MH "Antiinfective Agents+")

S4 S1 or S2 or S3

S3 TI (infect* N2 endocard*) or AB (infect* N2 endocard*)

S2 TI endocarditi* or AB endocarditi*

S1 (MH "Endocarditis+")

Web of Science

#14 #13 AND #12

#13 TS=(random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*)

#12 #11 AND #1

#11 #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2

#10 TS=(Bleomycin or Peptidoglycan or Ristocetin or Teicoplanin or (beta-lactam* NEAR/2 antibiot*) or betalactam)

#9 TS=(cefaxona or ceftrex or longaceph or rocefin or tacex or benaxona or Glycopeptide*)

#8 TS=(cefamedin or totacef or cefamezine or gramaxin or ancef or kefzol or cephalosporin* or ceftriaxon* or terbac or rocefalin or longacef or rocephine or lendacin or rocephin)

#7 TS=(sodipen or crystapen or coliriocilina or benzylpenicillin or Sulbenicillin or Carbenicillin or flucloxacillin or floxacillin or fluorochloroxacillin or cefazolin or cephazolin or cephamezine)

#6 TS=(pfizerpen or sodiopen or benpen or peniroger or or-pen or pengesod or "sodium penicillin" or parcillin or unicilina or "benzylpenicillin potassium")

#5 TS=(mezlocillin or piperacillin or pivampicillin or talampicillin or aminopenicillin* or "Penicillin g" or penilevel or pekamin or penibiot or ursopen or van- pen-g)

#4 TS=(bacteriocid* or ampicillin or amcill or ukapen or polycillin or omnipen or aminobenzylpenicillin or "aminobenzyl penicillin" or pentrexyl or amoxicillin or azlocillin)

#3 TS=(("anti infect*" or antiinfect* or antimicrobial or "anti microbial") NEAR/2 (drug* or agent* or treatment* or medicat* or therap*))

#2 TS=((antibiotic* or antimycobacterial or "anti mycobacterial" or antibacterial or "anti bacterial") NEAR/2 (drug* or agent* or treatment* or medicat* or therap*))

#1 TS=endocard*

clinicaltrials.gov

infective endocarditis plus randomized and recruiting OR not yet recruiting

International Clinical Trials Registry Platform Search Portal

infective endocarditis AND randomized

ISRCTN registry

infective endocarditis AND randomized

Appendix 5. Assessment of risk of bias in included studies

Generation of allocation sequence (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk (any truly random process, e.g. random number table; computer random number generator);
- high risk (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear, if the trial was described as randomised, but the method used for the allocation sequence generation was not described.

Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear, if the trial was described as randomised, but the method used to conceal the allocation was not described.

Blinding or masking (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from the knowledge of which intervention a participant received. We judged studies to be at low risk of bias if they were blinded, or if we judged that the lack of blinding could not have affected the results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low risk, high risk, or unclear risk for participants;
- low risk, high risk, or unclear risk for personnel;
- low risk, high risk, or unclear risk for outcome assessors.

Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

- Low risk (any one of the following): no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome

data, plausible effect size (difference in means or standardised difference in means) amongst missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data were imputed using appropriate methods.

- High risk (any one of the following): reason for missing outcome data likely to be related to true outcome, with either an imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) amongst missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
- Unclear risk (any one of the following): insufficient reporting of attrition/exclusions to permit judgement of 'low risk' or 'high risk' (e.g. number randomised not stated, no reasons for missing data provided); the study did not address this outcome.

Selective reporting bias (reporting bias due to selective outcome reporting)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

- low risk (any one of the following): the study protocol was available, and all of the study's prespecified (primary and secondary) outcomes that were of interest in the review were reported in the prespecified way, or the study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon);
- high risk (any one of the following): not all of the study's prespecified primary outcomes were reported; one or more primary outcomes were reported using measurements, analysis methods, or subsets of the data (e.g. subscales) that were not prespecified; one or more reported primary outcomes were not prespecified (unless clear justification for their reporting was provided, such as an unexpected adverse effect); one or more outcomes of interest in the review were reported incompletely so that they could not be entered in a meta-analysis; the study report did not include results for a key outcome that would be expected to have been reported for such a study;
- unclear risk: insufficient information to permit judgement of 'low risk' or 'high risk'.

Free of other bias (bias due to problems not covered elsewhere)

We described for each included study any important concerns we had about other possible sources of bias (sponsorship bias, confirmation bias, bias of the presentation data, etc.).

- Low risk: the trial appears to be free of other components that could put it at risk of bias.
- High risk: there are other factors in the trial that could put it at risk of bias (e.g. no sample size calculation made).
- Unclear risk: the trial may or may not be free of other components that could put it at risk of bias.

Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings.

Appendix 6. Oral regimens recommended in POET 2019

Penicillin and methicillin-sensitive *Staphylococcus aureus* and coagulase-negative staphylococci

- Amoxicillin 1 g x 4 and fusidic acid 0.75 g x 2
- Amoxicillin 1 g x 4 and rifampicin 0.6 g x 2
- Linezolid 0.6 g x 2 and fusidic acid 0.75 g x 2
- Linezolid 0.6 g x 2 and rifampicin 0.6 g x 2

Methicillin-sensitive *Staphylococcus aureus* and coagulase-negative staphylococci

- Dicloxacillin 1 g x 4 and fusidic acid 0.75 g x 2
- Dicloxacillin 1 g x 4 and rifampicin 0.6 g x 2
- Linezolid 0.6 g x 2 and fusidic acid 0.75 g x 2
- Linezolid 0.6 g x 2 and rifampicin 0.6 g x 2

Methicillin-resistant coagulase-negative staphylococci

- Linezolid 0.6 g x 2 and fusidic acid
- Linezolid 0.6 g x 2 and rifampicin 0.6 g x 2

Enterococcus faecalis

- Amoxicillin 1 g x 4 and rifampicin 0.6 g x 2
- Amoxicillin 1 g x 4 and moxifloxacin 0.4 g x 1
- Linezolid 0.6 g x 2 and rifampicin 0.6 g x 2
- Linezolid 0.6 g x 2 and moxifloxacin 0.4 g x 1

Streptococci with a minimal inhibitory concentration for penicillin of < 1 mg/L

- Amoxicillin 1 g x 4 and rifampicin 0.6 g x 2
- Linezolid 0.6 g x 2 and rifampicin 0.6 g x 2
- Linezolid 0.6 g x 2 and moxifloxacin 0.4 g x 1

Streptococci with a minimal inhibitory concentration for penicillin of ≥ 1 mg/L

- Linezolid 0.6 g x 2 and rifampicin 0.6 g x 2
- Moxifloxacin 0.4 g x 1 and rifampicin 0.6 g x 2
- Moxifloxacin 0.4 g x 1 and clindamycin 0.6 g x 3

Source: POET 2019 (Supplementary Appendix).

Appendix 7. Oral antibiotic regimens in POET 2019

Micro-organism	Regimens	Frequency (%)
Staphylococcus aureus	Dicloxacillin and rifampicin	33
	Amoxicillin and rifampicin	29
Enterococcus faecalis	Amoxicillin and moxifloxacin	47
	Amoxicillin and linezolid	25
	Amoxicillin and rifampicin	12
	Moxifloxacin and linezolid	10
Streptococci	Amoxicillin and rifampicin	52
	Amoxicillin and moxifloxacin	13
Coagulase-negative staphylococci	Fusidic acid and linezolid	38
	Rifampicin and linezolid	31

Source: POET 2019 (Supplementary Appendix)

WHAT'S NEW

Date	Event	Description
5 February 2020	New citation required but conclusions have not changed	Conclusion: This first update confirms the findings of the original version: current evidence does not support or reject any regimen of antibiotic therapy for the treatment of infective endocarditis.

Date	Event	Description
6 January 2020	New search has been performed	This update is based on a search from 6 January 2020 and includes two new randomised controlled trials. The review has a total of six included trials.

HISTORY

Protocol first published: Issue 5, 2012
Review first published: Issue 4, 2016

CONTRIBUTIONS OF AUTHORS

Arturo Martí-Carvajal is the lead author of the protocol and review, and acts as guarantor of the review.

Mark Dayer reviewed and contributed to the manuscript.

Lucieni Oliveira Conterno contributed to the review conception and design; screened the studies for inclusion; assessed the risk of bias; interpreted the results providing a clinical perspective; revised and commented on the draft; and approved the final version.

Alejandro González Garay and Cristina Martí-Amarista checked the search results and data, and contributed to the manuscript.

DECLARATIONS OF INTEREST

Arturo Martí-Carvajal: in 2004 Arturo Martí-Carvajal was employed by Eli Lilly to run a four-hour workshop on 'How to critically appraise clinical trials on osteoporosis and how to teach this'. This activity was not related to his work with Cochrane or any Cochrane Review. In 2007, Arturo Martí-Carvajal was employed by Merck to run a four-hour workshop on 'How to critically appraise clinical trials and how to teach this'. This activity was not related to his work with Cochrane or any Cochrane Review.

Mark Dayer is currently undertaking clinical trials, sponsored by Novartis, in the field of heart failure. He has received no direct funding from Novartis since 2008, when the company sponsored his attendance at the European Society of Cardiology. Novartis is the manufacturer of daptomycin. In 2015, Dr Dayer received educational sponsorship from Bayer. He received advisory board fees from Res-Med (2014 to 2015), Daiichi-Sankyo (2015), and St Jude (2015 to 2016). Between 2007 and 2015, Dr Dayer also received educational sponsorship/speaker fees from Boehringer-Ingelheim, Pfizer, Boston Scientific, Medtronic, Biotronik, and Sorin.

Lucieni Oliveira Conterno, Alejandro González Garay, and Cristina Martí-Amarista have no known conflicts of interest.

None of the authors of this review were authors on the studies considered by this review.

SOURCES OF SUPPORT

Internal sources

- Cochrane Ecuador, Ecuador

  Financial

External sources

- Iberoamerican Cochrane Center, Spain

  Academic
- NIHR Cochrane Infrastructure Funding, UK

  This project was supported by the National Institute for Health Research, via Cochrane Infrastructure, Cochrane Programme Grant or Cochrane Incentive funding to the Heart Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health and Social Care.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We added:

- lipopeptide antibiotics (daptomycin) into the Background and Types of interventions due to the inclusion of a trial assessing that drug (Fowler 2006);
- quinolone antibiotics (levofloxacin) into the Background and Types of interventions due to the inclusion of a trial assessing that drug (FINLEVO Trial 2006).

- We changed:

  - the initial review question, which was to assess the effect of antibiotic treatment versus no antibiotic treatment, as no suitable studies were identified;
  - the number of authors who extracted data. We had planned for three review authors to independently extract data, but only two extracted the data, as only two review authors were available at the time of the data extraction;
  - the presentation of data. We added a 'Summary of findings' table and GRADE assessments;
  - the search strategy. We did not search the Scientific Electronic Library Online (SciELO) because of more recent concerns over the quality of some open access studies;
  - we removed the following sentence: "...we will consider there to be substantial statistical heterogeneity if the I^2 statistic is greater than 50% (Higgins 2011), and will explore this by pre-specified subgroup analysis". We did this to adapt this Cochrane Review to statistical issues and common analysis queries of the Cochrane Heart Group;
  - we removed those studies that were not randomised controlled trials from the Excluded studies section.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [adverse effects] [*therapeutic use]; Endocarditis, Bacterial [*drug therapy] [microbiology] [mortality]; Fosfomycin [adverse effects] [therapeutic use]; Imipenem [adverse effects] [therapeutic use]; Levofloxacin [adverse effects] [therapeutic use]; Penicillins [adverse effects] [therapeutic use]; Randomized Controlled Trials as Topic; Vancomycin [adverse effects] [therapeutic use]

MeSH check words

Female; Humans; Male