National Institute for Health and Care Excellence

Draft for consultation

Meningitis (bacterial) and meningococcal disease: recognition, diagnosis and management

[D3] Evidence review for antibiotics for bacterial meningitis before or in the absence of identifying causative infecting organism in adults

NICE guideline number tbc

Evidence review underpinning recommendations 1.6.4 to 1.6.9 and 1.6.16 in the NICE guideline

September 2023

Draft for consultation

This evidence review was developed by NICE

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Antibiotics for bacterial meningitis before or in the absence of identifying causative infecting organism in adults

Review question

What antibiotic treatment regimens are effective in treating suspected bacterial meningitis in adults before identifying the causative infecting organism, or in the absence of identifying the causative infecting organism?

Introduction

Bacterial meningitis is a rare but serious infection. As in older babies and children, the commonest causes of bacterial meningitis in adults are Streptococcus pneumoniae and Neisseria meningitidis. In older adults, however, additional bacterial aetiologies become relevant.

The aim of this review is to establish the appropriate empirical antibiotic treatment regimen(s) that are effective in treating suspected bacterial meningitis in adults, before, or in the absence of identifying, the causative infecting organism.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Adults with suspected bacterial meningitis.
Intervention	Antibiotic agent of interest: Amoxicillin, Ampicillin, Benzylpenicillin sodium, Cefotaxime, Ceftriaxone, Chloramphenicol, Gentamicin, Meropenem In cases of severe beta-lactam allergy: Fluoroquinolones (all licensed in the UK)
Comparison	**Stage 1 (all antibiotic agents of interest):** Comparison: • Cefotaxime or ceftriaxone vs amoxicillin, ampicillin or benzylpenicillin sodium alone • Cefotaxime or ceftriaxone vs amoxicillin, ampicillin or benzylpenicillin sodium plus chloramphenicol [with or without gentamicin] • Cefotaxime or ceftriaxone vs chloramphenicol alone • Cefotaxime vs ceftriaxone • Cefotaxime or ceftriaxone plus ampicillin or amoxicillin vs cefotaxime or ceftriaxone alone • Meropenem vs cefotaxime or ceftriaxone • Fluoroquinolones vs cefotaxime or ceftriaxone In cases of severe beta-lactam allergy: • Chloramphenicol vs fluoroquinolones **Stage 2 (antibiotic agents identified during stage 1 as most effective/for use where there are contraindications)** Comparisons: • Antibiotic agent A – Dose A vs Antibiotic agent A – Dose B • Antibiotic agent A – Duration of administration A vs Antibiotic agent A –

	Duration of administration B • Antibiotic agent A – Short infusion vs Antibiotic agent A – Extended infusion
Outcome	**Critical** • All-cause mortality (measured up to 1 year after discharge) • Any long-term neurological impairment (defined as any motor deficits, sensory deficits [excluding hearing impairment], cognitive deficits, or behavioural deficits; measured from discharge up to 1 year after discharge) • Functional impairment (measured by any validated scale at any time point) **Important** • Diagnosis of epilepsy or occurrence of seizures during hospitalisation • Hearing impairment (defined as any level of hearing impairment; measured from discharge up to 1 year after discharge) • Serious intervention-related adverse effects leading to death, disability or prolonged hospitalisation or that are life threatening or otherwise considered medically significant • Length of hospitalisation

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness evidence

Included studies

Three studies were included for this review: 1 Cochrane systematic review (SR: Prasad 2007), 1 randomised controlled trial (RCT: Schmutzhard 1995), and 1 prospective cohort study (Brink 2019).

The included studies are summarised in Table 2.

The Cochrane SR used data from 19 RCTs. However, 16 studies included in the Cochrane SR were in babies and children, therefore were included in the evidence review (D2) on antibiotics for bacterial meningitis before or in the absence of identifying causative infecting organism in older babies and children.

One RCT compared ceftriaxone to ampicillin (1 RCT included in Prasad 2007), 1 RCT compared ceftriaxone to benzylpenicillin sodium (1 RCT included in Prasad 2007), and 1 RCT compared ceftriaxone to ampicillin plus chloramphenicol (1 RCT included in Prasad 2007). Two studies compared meropenem to a cephalosporin [cefotaxime or ceftriaxone (Schmutzhard 1995); cefotaxime plus ampicillin (Brink 2019)].

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

1 Summary of included studies

2 Summaries of the studies that were included in this review are presented in Table 2.

3 **Table 2: Summary of included studies**

Study	Population	Comparison	Outcomes	Comments
Brink 2019 Prospective cohort study Sweden	N=444 Adults aged >16 years with bacterial meningitis Age in years (median; IQR): Meropenem: 61 (44-69) Cefotaxime plus ampicillin: 60 (42-66) Population treated with steroid therapy: 92% Case-fatality: 4.9%	Meropenem versus cefotaxime plus ampicillin Meropenem: empirical treatment regimens Cefotaxime plus ampicillin: empirical treatment regimens	• All-cause mortality • Any long-term neurological impairment	Route of administration, dose, frequency and duration were not described.
Prasad 2007 Systematic review	Number of adults (≥16 years old) N=76 Number of RCTs in adults N=3 Countries included in SR n=1 high income n=2 non-high income Case-fatality range: 0%-6.7%	Ceftriaxone (IV) versus ampicillin (IV) 1 RCT (Narciso 1983) Ceftriaxone (IM or IV) versus ampicillin (IV) plus chloramphenicol (IV) 1 RCT (Girgis 1987) Ceftriaxone (IV) versus benzylpenicillin sodium 1 RCT (Filali 1993)	• All-cause mortality • Hearing impairment	n=16 RCTs conducted in neonates, babies and children included in the evidence review on antibiotics for bacterial meningitis before or in the absence of identifying causative infecting organism in older babies and children Route of administration of benzylpenicillin sodium was not described.
Schmutzhard 1995 RCT	N=56 Adults with suspected	Meropenem versus cephalosporin (cefotaxime or ceftriaxone)	• All-cause mortality • Any long-term	

Study	Population	Comparison	Outcomes	Comments
Hungary, the Czech Republic, Portugal, France, Spain and Austria	bacterial meningitis Age (years in median): Meropenem: 46 Cephalosporin: 31 Population treated with steroid therapy: 70% Case-fatality: 7.1%	Meropenem: 40 mg/kg IV every 8 h, up to a maximum dose of 6 g/day for 10.6 days Cephalosporin: ceftriaxone (100 mg/kg IV followed by single daily doses of 80 mg/kg up to a maximum dose of 4 g/day) or cefotaxime 75-100 mg/kg IV every 8 h (225 to 300 mg/kg/day up to a maximum dose of 12 g/day) for 12.9 days	neurological impairment • Hearing impairment	

IM: intramuscular; IQR: interquartile range; IV: intravenous; RCT: randomised controlled trial; SR: systematic review

See the full evidence tables in appendix D and the forest plots in appendix E.

Summary of the evidence

This section is a narrative summary of the findings of the review, as presented in the GRADE tables in appendix F. For details of the committee's confidence in the evidence and how this affected recommendations, see The committee's discussion and interpretation of the evidence.

The evidence was assessed as being very low quality due to risk of bias (arising from the randomisation process, measurement of the outcome, selective reporting, non-blinding, and failure to adjust for confounding factors), serious imprecision (due to low event rates), and indirectness in terms of interventions and outcomes.

The Cochrane SR (Prasad 2007) included analyses on babies, children and adults; however, not all outcomes were stratified into babies, children and adults. Where babies, children and adults were combined in a meta-analysis for outcomes of interest in our review protocol, the data from RCTs were extracted separately from the SR for adults and meta-analysed.

The evidence showed no important differences between antibiotics for all-cause mortality (ceftriaxone versus ampicillin or benzylpenicillin sodium, ceftriaxone versus ampicillin plus chloramphenicol, meropenem versus cefotaxime or ceftriaxone, meropenem versus cefotaxime plus ampicillin); any long-term neurological impairment (meropenem versus cefotaxime or ceftriaxone, meropenem versus cefotaxime plus ampicillin); or hearing impairment (ceftriaxone versus benzylpenicillin sodium, meropenem versus cefotaxime or ceftriaxone). No eligible studies were identified that reported functional impairment, epilepsy or seizures, serious intervention-related adverse effects, or length of hospitalisation.

For stage 2 of this review, dose and duration comparisons for antibiotics identified as effective in stage 1 (see summary of the protocol in Table 1), no evidence was identified.

See appendix F for full GRADE tables.

Economic evidence

Included studies

A single economic search was undertaken for all topics included in the scope of this guideline, but no economic studies were identified which were applicable to this review question.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation. This was because the choice of antibiotics in this population is quite limited, and the costs are generally similar and relatively inexpensive. Furthermore, local patterns of antibiotic resistance and allergies can also constrain the decision set.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Bacterial meningitis is associated with high rates of mortality and morbidity, and antibiotics are the mainstay of treatment for bacterial meningitis. Therefore, all-cause mortality and long-term neurological impairment were prioritised as critical outcomes because of the severity of these outcomes. Functional impairment was also prioritised as a critical outcome because of the potential long-term impact on the ability to carry out certain daily life functions.

Epilepsy or seizures, hearing impairment and serious intervention-related adverse effects were chosen as important outcomes because these outcomes are relatively common after bacterial meningitis and may be related to antibiotic therapy. Length of hospitalisation was also chosen as an important outcome because this may be considered as an indicator of treatment effectiveness and was expected to be commonly reported in trials.

The quality of the evidence

The quality of the evidence was assessed using GRADE methodology. The evidence for all outcomes in this review was very low quality, and the main reasons evidence was downgraded were risk of bias (for example, bias arising from issues with allocation concealment, subjective measurement of outcome, selective reporting, non-blinding, and failure to adjust for confounding factors) and imprecision (wide confidence intervals and small number of events). For the comparison between meropenem and cephalosporin (cefotaxime or ceftriaxone), the evidence for any long-term neurological impairment was downgraded for indirectness (composite outcome). For the comparison between meropenem and cefotaxime plus ampicillin, the evidence for all-cause mortality and any long-term neurological impairment was also downgraded for indirectness (indirect intervention and/or composite outcome).

No evidence was found for functional impairment, epilepsy or seizures, serious intervention-related adverse effects, or length of hospitalisation.

Benefits and harms

The committee considered the evidence for antibiotic treatment before or in the absence of identifying a causative organism for adults and noted that the evidence showed no important differences in the effectiveness of antibiotic treatment regimens. However, given that the evidence was very low quality and largely very seriously imprecise, the committee agreed that this should not be taken as definitive evidence of equivalence. Given the limitations of

the evidence, the committee agreed to make recommendations based on their clinical knowledge and experience.

The committee discussed common infective organisms (for example, Streptococcus pneumoniae and Neisseria meningitidis) in adults and agreed to recommend intravenous ceftriaxone for suspected bacterial meningitis in adults in line with the British National Formulary (BNF; Joint Formulary Committee 2022). This is consistent with the recommendations made for babies and children (see evidence reviews D1 and D2). The committee highlighted the practical and resource-use advantages associated with ceftriaxone because it has a broad spectrum of activity, and the long half-life means that it can be given only once a day. The committee acknowledged some concerns with once daily administration in that a second dose might need to be delayed if the first dose of ceftriaxone was administered outside of routine working hours; however, they were aware that a second dose can be given earlier, to shift the administration time, if there is a minimum of 12 hours between doses (Gbesemete 2019).

The committee discussed some reasons why in clinical practice (particularly in intensive care units) cefotaxime might be given instead of ceftriaxone. For instance, to minimise the time that intravenous lines are being used for administering antibiotics, which might be needed for other medications, due to ceftriaxone typically being infused over 30 minutes intravenous and cefotaxime being given as a bolus. However, the committee agreed that this practice is not necessary, as ceftriaxone can be given as bolus. Sometimes there may be a reaction (for example, vomit reflex) if ceftriaxone is administered too quickly, but in the committee's experience this is relatively rare, which was supported by a recent study (Patel 2021). The committee discussed that another reason why cefotaxime may be preferred in intensive care units is the concern that calcium containing infusions may be needed and the potential incompatibility between ceftriaxone and solutions containing calcium. However, the committee agreed that ceftriaxone should not be avoided just in case calcium containing infusions are needed, as the antibiotic can be changed if needed.

The committee discussed that Listeria monocytogenes is a common infective organism in older adults based on their clinical knowledge and experience. The committee were aware that there is variation in practice regarding the threshold for classifying someone as an older adult, but they were aware that the 2018 Public Health England (PHE) report on Listeriosis in England and Wales (PHE 2018, updated 2021) considered people aged over 60 years at risk for invasive listeriosis. This report identified the following additional risk factors that may occur in people aged under 60 years: pregnancy, malignancy, kidney disease, liver disease, diabetes, alcoholism, and immunocompromising treatment. The committee agreed that Listeria monocytogenes coverage should be provided as part of empiric treatment for suspected bacterial meningitis in these high-risk groups and were aware that amoxicillin is recommended by the BNF (Joint Formulary Committee 2022) for Listerial meningitis (in combination with another antibiotic). Therefore, the committee recommended that intravenous amoxicillin should be part of the first line treatment described above for adults with risk factors for Listeria.

There was no evidence found on antibiotic use for suspected bacterial meningitis in adults with a penicillin allergy, but the committee agreed it was important to make a recommendation for this population. Based on their knowledge and experience, the committee agreed that cephalosporin-induced anaphylaxis is rare, and the risk-benefit balance of cephalosporin relative to chloramphenicol is favourable in the majority of patients with non-anaphylactic penicillin allergy. Therefore, the committee agreed that clinicians should seek information about the nature of the allergy and advice from an infection specialist (a microbiologist or infectious diseases specialist) before making a treatment decision. The committee acknowledged that it is important that treatment is not delayed; however, they agreed that information about the nature of allergy is often readily available from the patient's family. The committee agreed that ceftriaxone should still be considered if the nature of the allergic reaction they get is non-anaphylactic or non-severe, in accordance

with the first line treatment recommended above. However, if the allergic reaction is anaphylactic or severe, alternatives to ceftriaxone will be needed. The committee discussed that chloramphenicol is commonly used in the case of severe beta-lactam allergy, but they were aware that its spectrum of activity does not cover gram-negative bacilli. However, the committee acknowledged that meningitis caused by gram-negative bacilli is rare and typically happens only in the first weeks of life where you would not see an anaphylactic reaction, so in practice this situation would rarely occur. For adults with anaphylactic allergic reactions to penicillin, the committee recommended chloramphenicol.

The committee agreed it was important to make a recommendation about appropriate antibiotic treatment for adults with risk factors for Listeria monocytogenes and a history of penicillin allergy as Listeria monocytogenes is a common infective organism in older adults. The committee were aware that current practice would be to consider the use of co-trimoxazole for both non-anaphylactic and anaphylactic reactions, rather than amoxicillin, in addition to the first line treatment recommended above for people with a history of penicillin allergy and, in line with current practice, recommended co-trimoxazole (in addition to cephalosporin for non-anaphylaxis or in addition to chloramphenicol for anaphylaxis) for adults with a penicillin allergy who have risk factors for Listeria monocytogenes.

The committee highlighted the importance of considering the possibility of a cephalosporin-resistant pneumococcus causing bacterial meningitis. The committee also noted that gram-negative infective organisms are relatively common in older adults and tend to be resistant to cephalosporins. The committee were aware that the previous NICE guideline on bacterial meningitis (NICE 2010) recommended to treat people who have travelled outside the UK or had prolonged or multiple exposure to antibiotics within the last 3 months with vancomycin (in addition to the cephalosporin). However, they discussed that practice has changed since the previous NICE guideline and agreed that changes to this recommendation were required. Firstly, the committee were aware that current practice is to use rifampicin or linezolid in addition to a cephalosporin where the cephalosporin itself might be insufficient due to resistance. However, the committee highlighted that there is not enough evidence about the effectiveness and safety of rifampicin or linezolid in suspected (or confirmed) cephalosporin resistant bacterial meningitis to support recommending them. Therefore, the committee recommended that, clinicians should seek advice from an infection specialist if cephalosporin resistance is suspected in adults who have recently travelled abroad. Secondly, the committee noted that the evidence used to inform the recommendation about prolonged or multiple exposure to antibiotics in the previous guideline came from Canada (Vanderkooi 2005), which has a higher prevalence of cephalosporin resistance than the UK. The committee discussed that there was insufficient evidence that prolonged or multiple exposure to antibiotics on an individual level causes people to be colonised with resistant organisms. Rather, the committee agreed that it is antibiotic use at a population level that contributes to cephalosporin resistant bacteria. Therefore, the committee agreed that the evidence did not warrant recommending different treatment for these people. Moreover, the committee noted that, in their experience, such people are not currently treated differently.

The committee were aware that the previous NICE guideline on bacterial meningitis made recommendations about the use of antibiotics for herpes simplex encephalitis. The committee acknowledged that this condition was not included in the scope for the current guideline. The committee were aware that prescribing aciclovir has become routine practice in cases of suspected bacterial meningitis (Hagen 2020) and were concerned about the overuse of aciclovir. Therefore, the committee made a recommendation to clarify that aciclovir should only be given when herpes simplex encephalitis is strongly suspected.

The committee agreed that there should be a recommendation about duration of antibiotic treatment. The committee were aware that the results of confirmatory tests could be available within 48 to 72 hours and recommended that empirical antibiotic treatment should be continued until results suggest an alternative treatment is needed, or there is an alternative diagnosis, which is in line with current practice. The committee agreed that it was

necessary to specify a duration of antibiotic treatment for cases where the CSF parameters are consistent with bacterial meningitis, but the blood culture and whole-blood diagnostic PCR are negative. The committee acknowledged that different durations of antibiotic therapy are needed for different causative organisms. Given that Streptococcus pneumoniae and Neisseria meningitidis are the most common causes of bacterial meningitis in adults, the committee agreed that the duration of antibiotic treatment should be consistent with the treatment recommended for these causative organisms and as 10 days is the longer duration of treatment prior to review (recommended for Streptococcus pneumoniae meningitis) this was considered the most appropriate default duration to recommend in culture negative cases. The committee also agreed that advice from an infection specialist should be sought if adults have not recovered after 10 days.

Cost effectiveness and resource use

This review question was not prioritised for economic analysis and therefore the committee made a qualitative assessment of the likely cost-effectiveness of their recommendations. The clinical evidence reviewed did not show important difference in adults for any of the antibiotics compared and therefore the committee reasoned that it would be cost-effective to recommend ceftriaxone, as it is potentially less resource intensive as it can be given once a day compared to cefotaxime which is given 3 times daily. As these recommendations were in line with current NHS practice no significant resource impact is anticipated.

The committee also made recommendations outlining when infection specialist advice should be sought reflecting their view that the cost-effective choice of antibiotic would depend on the specific individualised characteristics of the presenting person, such as a penicillin allergy or travel outside of the UK.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.6.4 to 1.6.9 and 1.6.16. Other evidence supporting these recommendations can be found in evidence reviews on antibiotic regimens for bacterial meningitis before or in the absence of identifying causative infecting organism in younger infants, and older infants and children (see evidence reviews D1 and D2) and for specific causative organisms (see evidence reviews E1 to E6).

References – included studies

Effectiveness

Brink 2019

Brink, M., Glimaker, M., Sjolin, J. et al. (2019). Meropenem versus cefotaxime and ampicillin as empirical antibiotic treatment in adult bacterial meningitis: a quality registry study, 2008 to 2016, Antimicrobial Agents and Chemotherapy 63(11), e00883-19

Prasad 2007

Prasad, K., Kumar, A., Singhal, T. et al. (2007). Third generation cephalosporins versus conventional antibiotics for treating acute bacterial meningitis, Cochrane Database of Systematic Reviews

Schmutzhard 1995

Schmutzhard, E., Williams, K. J., Vukmirovits, G. et al. (1995). A randomised comparison of meropenem with cefotaxime or ceftriaxone for the treatment of bacterial meningitis in adults. Meropenem Meningitis Study Group, Journal of Antimicrobial Chemotherapy 36(Suppl. A), 85-97

Economic

No studies were identified which were applicable to this review question.

Other

Gbesemete 2019

Gbesemete, D., Faust, S. (2019). Prescribing in infection: antibacterials. In. Barker, C., Turner, M., Sharland, M. (Eds.) Prescribing Medicines for Children: From drug development to practical administration, Pharmaceutical Press, London: UK

Hagen 2020

Hagen, A., Eichinger, A., Meyer-Buehn, M. et al. (2020). Comparison of antibiotic and acyclovir usage before and after the implementation of an on-site FilmArray meningitis/ encephalitis panel in an academic tertiary pediatric hospital: a retrospective observational study, BMC Pediatrics 20(1), 56

Joint Formulary Committee 2022

Joint Formulary Committee. British National Formulary (online). London: BMJ Group and Pharmaceutical Press. Available at: http://www.medicinescomplete.com [Accessed 04/04/2022]

NICE 2010

National Institute for Health and Care Excellence (2010). Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management. Available at: https://www.nice.org.uk/guidance/cg102 [Accessed 04/04/2022]

PHE 2018 (updated 2021)

Public Health England (2018, updated 2021). Listeriosis in England and Wales: summary for 2018. Available at: https://www.gov.uk/government/publications/listeria-monocytogenes-surveillance-reports/listeriosis-in-england-and-wales-summary-for-2018 [Accessed 04/04/2022]

Patel 2021

Patel, S., Green. H., Gray, J., Rutter, M., Bevan, A., Hand, K., Jones, C. E., Faust, S. N. (2021). Evaluating Ceftriaxone 80 mg/kg Administration by Rapid Intravenous Infusion—A Clinical Service Evaluation. The Pediatric Infectious Disease Journal, 40(2), 128-129

Vanderkooi 2005

Vanderkooi, O. G., Low, E. D., Green, K. et al. (2005). Predicting antimicrobial resistance in invasive pneumococcal infections, Clinical Infectious Diseases 40(9), 1288-1297

Appendices

Appendix A Review protocols

Review protocol for review question: What antibiotic treatment regimens are effective in treating suspected bacterial meningitis in adults before identifying the causative infecting organism, or in the absence of identifying the causative infecting organism?

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42021234211
Review title	Antibiotics for bacterial meningitis before or in the absence of identifying causative infecting organism in adults
Review question	What antibiotic treatment regimens are effective in treating suspected bacterial meningitis in adults before identifying the causative infecting organism, or in the absence of identifying the causative infecting organism?
Objective	This review aims to find out what is the optimal antibiotic treatment regimen in improving outcomes for adults with suspected bacterial meningitis before identifying the causative infecting organism, or in the absence of identifying the causative infecting organism
Searches	The following databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Searches will be restricted by: Date limitations: 1980 English language Human studies

Field	Content
	The full search strategies for MEDLINE database will be published in the final review. For each search, the principal database search strategy is quality assured by a second information scientist using an adaptation of the PRESS 2015 Guideline Evidence-Based Checklist.
Condition or domain being studied	Bacterial meningitis
Population	Inclusion: Adults with suspected bacterial meningitis. Exclusion: People: • with known immunodeficiency. • who have brain tumours, pre-existing hydrocephalus, intracranial shunts, previous neurosurgical procedures, or known cranial or spinal anomalies that increase the risk of bacterial meningitis. • with confirmed viral meningitis or viral encephalitis. • with confirmed tuberculous meningitis. • with confirmed fungal meningitis.
Intervention/Exposure/Test	Antibiotic agent of interest: • Amoxicillin • Ampicillin • Benzylpenicillin sodium • Cefotaxime • Ceftriaxone • Chloramphenicol • Gentamicin • Meropenem In cases of severe beta-lactam allergy: • Fluoroquinolones (all licensed in the UK)

Field	Content
Comparator/Reference standard/Confounding factors	Stage 1 (all antibiotic agents of interest): Comparison: • Cefotaxime or ceftriaxone vs amoxicillin, ampicillin or benzylpenicillin sodium alone • Cefotaxime or ceftriaxone vs amoxicillin, ampicillin or benzylpenicillin sodium plus chloramphenicol [with or without gentamicin] • Cefotaxime or ceftriaxone vs chloramphenicol alone • Cefotaxime vs ceftriaxone • Cefotaxime or ceftriaxone plus ampicillin or amoxicillin vs cefotaxime or ceftriaxone alone • Meropenem vs 3rd cefotaxime or ceftriaxone • Fluoroquinolones vs cefotaxime or ceftriaxone In cases of severe beta-lactam allergy: • Chloramphenicol vs fluoroquinolones Stage 2 (antibiotic agents identified during stage 1 as most effective/for use where there are contraindications) Comparisons: 1. Antibiotic agent A – Dose A vs Antibiotic agent A – Dose B 2. Antibiotic agent A – Duration of administration A vs Antibiotic agent A – Duration of administration B 3. Antibiotic agent A – Short infusion vs Antibiotic agent A – Extended infusion
Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs • RCTs • If insufficient RCTs: prospective cohort studies • If insufficient prospective cohort studies: retrospective cohort studies Non-randomised studies will be downgraded for risk of bias if they do not adequately

Field	Content
	adjust for the following covariates, but will not be excluded for this reason: • Co-morbidity • Severity of infection at presentation (including sepsis) • Antibiotics administered pre or post lumbar puncture • Infective organisms Exclude: • Conference abstracts
Other exclusion criteria	Cohort studies from low income countries. Studies conducted prior to 1980 as currently used antibiotics were not in common usage prior to this date. Studies published not in English-language
Context	This guidance will fully update the following: Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management (CG102)
Primary outcomes (critical outcomes)	• All-cause mortality (measured up to 1 year after discharge) • Any long-term neurological impairment (defined as any motor deficits, sensory deficits [excluding hearing impairment], cognitive deficits, or behavioural deficits; measured from discharge up to 1 year after discharge) • Functional impairment (measured by any validated scale at any time point)
Secondary outcomes (important outcomes)	• Diagnosis of epilepsy or occurrence of seizures during hospitalisation • Hearing impairment (defined as any level of hearing impairment; measured from discharge up to 1 year after discharge) • Serious intervention-related adverse effects leading to death, disability or prolonged hospitalisation or that are life threatening or otherwise considered medically significant • Length of hospitalisation
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated. Titles and abstracts of the retrieved citations will be screened

Field	Content
	to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will not be undertaken for this question. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs and quasi-RCTs • Cochrane ROBINS-I tool for non-randomised (clinical) controlled trials and cohort studies The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Quantitative findings will be formally summarised in the review. Where multiple studies report on the same outcome for the same comparison, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios if possible or odds ratios when required (for example if only available in this form in included studies) for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed by visual inspection of the forest plots and consideration of the I2 statistic. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled if the random effects model does not adequately address heterogeneity. The confidence in the findings across all available evidence will be evaluated for each

Field	Content
	outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ **Minimally important differences:** • All-cause mortality: statistical significance • Serious intervention-related adverse effects: statistical significance • Length of hospitalisation: 1 day • Validated scales: Published MIDs where available; if not GRADE default MIDs • All other outcomes: GRADE default MIDs
Analysis of sub-groups	No preplanned stratifications. Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes: Age: • ≥16 years to <18 years* • Young and middle aged adults (aged ≥18 years) • Older adults** Status of infective organism: • Before organism is identified • Absence of identified organism *If 16-18 year olds are included within this question **There is variation regarding the age at which adults should be considered older adults. Therefore, we will be guided by cut-offs used in the evidence when determining this threshold.

Field	Content			
	Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.			
Type and method of review	☒	Intervention		
	☐	Diagnostic		
	☐	Prognostic		
	☐	Qualitative		
	☐	Epidemiologic		
	☐	Service Delivery		
	☐	Other (please specify)		
Language	English			
Country	England			
Anticipated or actual start date	12/01/2021			
Anticipated completion date	07/12/2023			
Stage of review at time of this submission	Review stage		Started	Completed
	Preliminary searches		☑	☑
	Piloting of the study selection process		☑	☑
	Formal screening of search results against eligibility criteria		☑	☑
	Data extraction		☑	☑
	Risk of bias (quality) assessment		☑	☑
	Data analysis		☑	☑
Named contact	Named contact: National Guideline Alliance			

Field	Content
	Named contact e-mail: meningitis&meningococcal@nice.org.uk Organisational affiliation of the review: National Institute for Health and Care Excellence (NICE) and National Guideline Alliance
Review team members	National Guideline Alliance
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance which receives funding from NICE.
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10149.
Other registration details	None
Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021234211
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE

Field	Content	
	website, using social media channels, and publicising the guideline within NICE.	
Keywords	Bacterial meningitis, antibiotic, anti-bacterial, mortality, impairments	
Details of existing review of same topic by same authors	None	
Current review status	☐	Ongoing
	☒	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	None	
Details of final publication	www.nice.org.uk	

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MEDLINE: Medical Literature Analysis and Retrieval System Online; MID: minimally important difference; NICE: National Institute for Health and Care Excellence; PRESS: Peer Review of Electronic Search Strategies; RCT: randomised controlled trial; RoB: risk of bias; ROBINS-I: risk of bias in non-randomised studies – of interventions; ROBIS: risk of bias in systematic reviews

Appendix B Literature search strategies

Literature search strategies for review question: What antibiotic treatment regimens are effective in treating suspected bacterial meningitis in adults before identifying the causative infecting organism, or in the absence of identifying the causative infecting organism?

Clinical Search

This was a combined search to cover both this review (D3) and D1, D2, E1, E2, E3, E4, E5, E6 and F1 on antibiotic regimens for bacterial meningitis (before or in the absence of identifying causative infecting organism and for specific causative organisms) and meningococcal disease.

Database(s): Medline & Embase (Multifile) – OVID interface
Embase Classic+Embase 1947 to 2022 November 09, **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to November 09, 2022
Date of last search: 10 November 2022
Multifile database codes: emczd = Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	Meningitis/ or Meningitis, Bacterial/ or Meningitis, Escherichia Coli/ or Meningitis, Haemophilus/ or Meningitis, Listeria/ or Meningitis, Meningococcal/ or Meningitis, Pneumococcal/ or Meningoencephalitis/
2	1 use ppez
3	meningitis/ or bacterial meningitis/ or haemophilus meningitis/ or hemophilus influenzae meningitis/ or listeria meningitis/ or meningococcal meningitis/ or pneumococcal meningitis/ or meningoencephalitis/
4	3 use emczd
5	((bacter* or infect*) adj3 (meningit* or meninges* or leptomeninges* or subarachnoid space?)).ti,ab.
6	(meningit* adj3 (e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon* or septic* or sepsis* or bacter?emi?)).ti,ab.
7	((e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon*) adj3 (septic* or sepsis* or bacter?emi?)).ti,ab.
8	(meningit* or mening?encephalitis*).ti,ab.
9	exp Neisseria meningitidis/ use ppez
10	neisseria meningitidis/ use emczd
11	(Neisseria* mening* or n mening*).ti,ab.
12	or/2,4-11
13	Meningococcal Infections/ use ppez
14	meningococcosis/ or meningococcemia/
15	14 use emczd
16	(meningococc* adj3 (sepsis* or septic* or toxic* or endotoxic* or disease? or infection?)).ti,ab.
17	(meningococcus* or meningococci* or meningococc?emi?).ti,ab.
18	or/13,15-17
19	exp Anti-Bacterial Agents/ or exp Penicillins/ or exp Cephalosporins/ or exp Cefotaxime/ or exp Amoxicillin/ or exp Ampicillin/
20	19 use ppez
21	exp antibiotic agent/ or antibiotic therapy/ or exp penicillin derivative/ or exp cephalosporin derivative/
22	21 use emczd
23	(anti?biotic* or anti?bacterial* or anti?biotherap*).ti,ab.
24	(empiric* adj2 (therap* or treatment*)).ti,ab.
25	(abbocillin or adimicin or alcomicin or alpen or amblosin or amcill or amfipen or aminobenzylpenicillin* or aminoglycosid* or amox?cillin* or amoxil* or ampicillin* or ancef or anticepim or apogen or axepim* or ayercillin or azithrom?cin* or benzo?penicillin* or benzyl?penicillin* or bicillin or binotal or biomox or bmy 28142 or bmy?28142 or bristagen or bristamox or carbapenem* or cedax or ceftazidim* or cefatriaxon* or cefepim* or cefixim* or cefizox or cefobid* or cefotan or cefotaxim* or ceftaroline* or ceftin or ceftolozane* or ceftriaxon* or ceftriazon* or cefuroxim* or cefzil or cepazin* or cephalosporin* or cephotaxim* or cephuroxim* or cepim?x or chloramphenicol* or ciprofloxacin* or claforan or clamoxyl or clarithromycin* or clindamycin* or colistin* or compocillin or cosmopen or cotrimoxazol* or co trimoxazol* or crysticillin or delafloxacin* or deripen or dexamethasone or diatracin or doktacillin or duricef or elobact or erythromycin* or flucloxacillin* or fluoroquinolon* or fosfomycin* or gelacillin or gentam?cin* or gent?mycin* or gentamyl* or gentamytrex or gentaplus or gentarad or gentaso* or gentasporin or gentatrim or gent?cin* or gent?cyn* or geocillin* or geomycin* or glycopeptid* or guicitrin* or hexam?cin* or hiconcil or histocillin or ibiamox or imacillin or jenamicin or kefurox or kefzol or klaforan or lendacin or levofloxacin* or linezolid* or longacef or longaceph or lyphocin

#	Searches
	or macrolide* or mandol or maxcef or maxipim* or mefoxin or megacillin or meropen* or miram?cin* or monocid or moxacin or moxifloxacin* or ofloxacin* or oftagen* or omnipen or optigen* or pefloxacin* or penbritin* or penbrock or penicillin? or penicline or pentids or pentrex or pentrexl or pentrexyl or permapen or pfizerpen or polycillin or polymox or polymyxin*or primafen or principen or quinolon* or refobacin* or ribom?cin* or rifampicin or rifampin* or rocefalin or rocefin or rocephin* or roscillin or rufloxacin* or sagestam* or spectrobid or sulm?cin* or supen or tazobactam* or terram?cin* or tetracycline* or tobramycin* or totacillin or totapen or trimox or u?gencin* or ukapen or ultrabion or vamysin or vancam* or vanccostacin or vancin or vancom* or vancomycin* or vankom* or velosef or vetramox* or viccillin or voncon* or wycillin or zimox or zinacef or zin?at).mp.
26	or/20,22-25
27	(12 or 18) and 26
28	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
29	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
30	meta-analysis/
31	meta-analysis as topic/
32	systematic review/
33	meta-analysis/
34	(meta analy* or metanaly* or metaanaly*).ti,ab.
35	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
36	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
37	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
38	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
39	(search* adj4 literature).ab.
40	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
41	cochrane.jw.
42	((pool* or combined) adj2 (data or trials or studies or results)).ab.
43	letter/
44	editorial/
45	news/
46	exp historical article/
47	Anecdotes as Topic/
48	comment/
49	case report/
50	(letter or comment*).ti.
51	43 or 44 or 45 or 46 or 47 or 48 or 49 or 50
52	randomized controlled trial/ or random*.ti,ab.
53	51 not 52
54	animals/ not humans/
55	exp Animals, Laboratory/
56	exp Animal Experimentation/
57	exp Models, Animal/
58	exp Rodentia/
59	(rat or rats or mouse or mice).ti.
60	53 or 54 or 55 or 56 or 57 or 58 or 59
61	letter.pt. or letter/
62	note.pt.
63	editorial.pt.
64	case report/ or case study/
65	(letter or comment*).ti.
66	61 or 62 or 63 or 64 or 65
67	randomized controlled trial/ or random*.ti,ab.
68	66 not 67
69	animal/ not human/
70	nonhuman/
71	exp Animal Experiment/
72	exp Experimental Animal/
73	animal model/
74	exp Rodent/
75	(rat or rats or mouse or mice).ti.
76	68 or 69 or 70 or 71 or 72 or 73 or 74 or 75
77	60 use ppez
78	76 use emczd
79	77 or 78
80	28 use ppez
81	29 use emczd
82	80 or 81
83	(or/30-31,34,36-41) use ppez
84	(or/32-35,37-42) use emczd

#	Searches
85	83 or 84
86	27 not 79
87	limit 86 to English language
88	limit 87 to yr="1980 -Current"
89	limit 88 to (conference abstract or conference paper or conference review or conference proceeding) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]
90	89 use emczd
91	88 not 90
92	82 or 85
93	91 and 92
94	91 not 93

Database(s): Cochrane Library – Wiley interface
Cochrane Database of Systematic Reviews, Issue 11 of 12, November 2022, **Cochrane Central Register of Controlled Trials**, Issue 11 of 12, November 2022
Date of last search: 10 November 2022

#	Searches
#1	MeSH descriptor: [Meningitis] this term only
#2	MeSH descriptor: [Meningitis, Bacterial] this term only
#3	MeSH descriptor: [Meningitis, Escherichia coli] this term only
#4	MeSH descriptor: [Meningitis, Haemophilus] this term only
#5	MeSH descriptor: [Meningitis, Listeria] this term only
#6	MeSH descriptor: [Meningitis, Meningococcal] this term only
#7	MeSH descriptor: [Meningitis, Pneumococcal] this term only
#8	MeSH descriptor: [Meningoencephalitis] this term only
#9	MeSH descriptor: [Neisseria meningitidis] explode all trees
#10	((bacter* or infect*) near/3 (mening* or leptomening* or subarachnoid space*)):ti,ab,kw
#11	(("e coli" or "escherichia coli" or haemophilus or hemophilus or hib or (h next influenz*) or listeria* or pneumococc* or (gram next negativ* next bacill*) or streptococc* or GBS or (s next pneumon*)) near/3 (septic* or sepsis* or bacteraemi* or bacteremi* or infect*)):ti,ab,kw
#12	(meningit* or mening?encephalitis* or (mening* next encephalitis*)).:ti,ab,kw
#13	((neisseria* next mening*) or (n next mening*)):ti,ab,kw
#14	MeSH descriptor: [Meningococcal Infections] this term only
#15	meningococc*:ti,ab,kw
#16	{or #1-#15}
#17	MeSH descriptor: [Anti-Bacterial Agents] explode all trees
#18	((antibiotic* or antibacterial* or antibiotherap* or "anti biotic*" or "anti bacterial*" or "anti biotherap*")):ti,ab,kw
#19	((empiric* near/2 (therap* or treatment*))):ti,ab,kw
#20	((abbocillin or adimicin or alcomicin or alpen or amblosin or amcill or amfipen or aminobenzylpenicillin* or aminoglycosid* or amox?cillin* or amoxil* or ampicillin* or ancef or anticepim or apogen or axepim* or ayercillin or azithrom?cin* or benzo?penicillin* or benzyl?penicillin* or bicillin or binotal or biomox or bmy 28142 or bmy?28142 or bristagen or bristamox or carbapenem* or cedax or ceftazidim* or cefatriaxon* or cefepim* or cefixim* or cefizox or cefobid* or cefotan or cefotaxim* or ceftaroline* or ceftin or ceftolozane* or ceftriaxon* or ceftriazon* or cefuroxim* or cefzil or cepazin* or cephalosporin* or cephotaxim* or cephuroxim* or cepim?x or chloramphenicol* or ciprofloxacin* or claforan or clamoxyl or clarithromycin* or clindamycin* or colistin* or compocillin or cosmopen or cotrimoxazol* or co trimoxazol* or crysticillin or delafloxacin* or deripen or dexamethasone or diatracin or doktacillin or duricef or elobact or erythromycin* or flucloxacillin* or fluoroquinolon* or fosfomycin* or gelacillin or gentam?cin* or gent?mycin* or gentamyl* or gentamytrex or gentaplus or gentarad or gentaso* or gentasporin or gentatrim or gent?cin* or gent?cyn* or geocillin* or geomycin* or glycopeptid* or guicitrin* or hexam?cin* or hiconcil or histocillin or ibiamox or imacillin or jenamicin or kefurox or kefzol or klaforan or lendacin or levofloxacin* or linezolid* or longacef or longaceph or lyphocin or macrolide* or mandol or maxcef or maxipim* or mefoxin or megacillin or meropen* or miram?cin* or monocid or moxacin or moxifloxacin* or ofloxacin* or oftagen* or omnipen or optigen* or pefloxacin* or penbritin* or penbrock or penicillin? or penicline or pentids or pentrex or pentrexl or pentrexyl or permapen or pfizerpen or polycillin or polymox or polymyxin*or primafen or principen or quinolon* or refobacin* or ribom?cin* or rifampicin or rifampin* or rocefalin or rocefin or rocephin* or roscillin or rufloxacin* or sagestam* or spectrobid or sulm?cin* or supen or tazobactam* or terram?cin* or tetracycline* or tobramycin* or totacillin or totapen or trimox or u?gencin* or ukapen or ultrabion or vamysin or vancam* or vanccostacin or vancin or vancom* or vancomycin* or vankom* or velosef or vetramox* or viccillin or voncon* or wycillin or zimox or zinacef or zin?at)):ti,ab,kw
#21	{or #17-#20}
#22	#16 and #21
#23	"conference":pt or (clinicaltrials or trialsearch):so
#24	#22 not #23

Database(s): Database of Abstracts of Reviews of Effects (DARE); HTA Database – CRD interface
Date of last search: 12 February 2021

#	Searches

#	Searches
1	MeSH DESCRIPTOR meningitis IN DARE,HTA
2	MeSH DESCRIPTOR meningitis, bacterial IN DARE,HTA
3	MeSH DESCRIPTOR Meningitis, Escherichia coli IN DARE,HTA
4	MeSH DESCRIPTOR Meningitis, Haemophilus IN DARE,HTA
5	MeSH DESCRIPTOR Meningitis, Listeria IN DARE,HTA
6	MeSH DESCRIPTOR Meningitis, Meningococcal IN DARE,HTA
7	MeSH DESCRIPTOR Meningitis, Pneumococcal IN DARE,HTA
8	MeSH DESCRIPTOR Meningoencephalitis IN DARE,HTA
9	MeSH DESCRIPTOR Meningococcal infections IN DARE,HTA
10	(((((bacter* or infect*) NEAR3 (meningit* or meninges* or leptomeninges* or "subarachnoid space*"))))) IN DARE, HTA
11	(meningit*) IN DARE, HTA
12	((((meningencephalitis* or meningoencephalitis*)))) IN DARE, HTA
13	((((meningococc* NEAR3 (sepsis* or septic* or toxic* or endotoxic* or disease or diseases or infection or infections))))) IN DARE, HTA
14	((((meningococcus* or meningococci* or meningococcaemia* or meningococcemia*)))) IN DARE, HTA
15	((Neisseria* NEAR1 mening*)) IN DARE, HTA
16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
17	MeSH DESCRIPTOR Anti-Bacterial Agents EXPLODE ALL TREES IN DARE,HTA
18	MeSH DESCRIPTOR Penicillins EXPLODE ALL TREES IN DARE,HTA
19	MeSH DESCRIPTOR Cephalosporins EXPLODE ALL TREES IN DARE,HTA
20	MeSH DESCRIPTOR Cefotaxime EXPLODE ALL TREES IN DARE,HTA
21	MeSH DESCRIPTOR Amoxicillin EXPLODE ALL TREES IN DARE,HTA
22	MeSH DESCRIPTOR Ampicillin EXPLODE ALL TREES IN DARE,HTA
23	(((antibiotic* or antibacterial* or antibiotherap* or anti-biotic* or anti-bacterial* or anti-biotherap* or "anti biotic*" or "anti bacterial*" or "anti biotherap*"))) IN DARE, HTA
24	(((empiric* NEAR2 (therap* or treatment*)))) IN DARE, HTA
25	(((abbbocillin or adimicin or alcomicin or alpen or amblosin or amcill or amfipen or aminobenzylpenicillin or amox?cillin or amoxil* or ampicillin or ancef or anticepim or apogen or axepim* or ayercillin or benzo?penicillin* or benzyl?penicillin* or bicillin or binotal or biomox or bmy 28142 or bmy-28142 or bmy28142 or bristagen or bristamox or cedax or cefatriaxon* or cefepim* or cefixim* or cefizox or cefobid* or cefotan or cefotaxim* or ceftin or ceftriaxon* or ceftriazon* or cefuroxim* or cefzil or cepazin* or cephotaxim* or cephuroxim* or cepim?x or chloramphenicol or claforan or clamoxyl or compocillin or cosmopen or cotrimoxazol* or co trimoxazol* or co-trimoxazol or crysticillin or deripen or dexamethasone or diatracin or doktacillin or duricef or elobact or gelacillin or gentam?cin* or gent?mycin* or gentamyl* or gentamytrex or gentaplus or gentarad or gentaso* or gentasporin or gentatrim or gent?cin* or gent?cyn* or geocillin* or geomycin* or guicitrin* or hexam?cin* or hiconcil or histocillin or ibiamox or imacillin or jenamicin or kefurox or kefzol or klaforan or lendacin or longacef or longaceph or lyphocin or mandol or maxcef or maxipim* or mefoxin or megacillin or meropen* or miram?cin* or monocid or moxacin or oftagen* or omnipen or optigen* or penbritin* or penbrock or penicillin? or penicline or pentids or pentrex or pentrexl or pentrexyl or permapen or pfizerpen or polycillin or polymox or primafen or principen or refobacin* or ribom?cin* or rifampicin or rocefalin or rocefin or rocephin* or roscillin or sagestam* or spectrobid or sulm?cin* or supen or terram?cin* or totacillin or totapen or trimox or u?gencin* or ukapen or ultrabion or vamysin or vancam* or vanccostacin or vancin or vancom* or vancomycin or vankom* or velosef or vetramox* or viccillin or voncon* or wycillin or zimox or zinacef or zin?at))) IN DARE, HTA
26	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25
27	#16 AND #26

Economic Search

One global search was conducted for economic evidence across the guideline.

Database(s): NHS Economic Evaluation Database (NHS EED), HTA Database – CRD interface

Date of last search: 11 March 2021

#	Searches
1	MeSH DESCRIPTOR meningitis IN NHSEED,HTA
2	MeSH DESCRIPTOR Meningitis, Bacterial IN NHSEED,HTA
3	MeSH DESCRIPTOR Meningitis, Escherichia coli IN NHSEED,HTA
4	MeSH DESCRIPTOR Meningitis, Haemophilus EXPLODE ALL TREES IN NHSEED,HTA
5	MeSH DESCRIPTOR Meningitis, Listeria IN NHSEED,HTA
6	MeSH DESCRIPTOR Meningitis, Meningococcal IN NHSEED,HTA
7	MeSH DESCRIPTOR Meningitis, Pneumococcal IN NHSEED,HTA
8	MeSH DESCRIPTOR Meningoencephalitis IN NHSEED,HTA
9	(((bacter* or infect*) NEAR3 (meningit* or meninges* or leptomeninges* or subarachnoid space*))) IN NHSEED, HTA
10	((meningit* NEAR3 (e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon* or septic* or sepsis* or bacter?emi?))) IN NHSEED, HTA
11	(((e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or

#	Searches
	pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon*) NEAR3 (septic* or sepsis* or bacter?emi?))) IN NHSEED, HTA
12	((meningencephalitis* or meningoencephalitis* or meningit*)) IN NHSEED, HTA
13	MeSH DESCRIPTOR Meningococcal Infections IN NHSEED,HTA
14	MeSH DESCRIPTOR Neisseria meningitidis EXPLODE ALL TREES IN NHSEED,HTA
15	((meningococc* NEAR3 (sepsis* or septic* or toxic* or endotoxic* or disease* or infection*))) IN NHSEED, HTA
16	((meningococcus* or meningococci* or meningococcaemia* or meningococcemia*)) IN NHSEED, HTA
17	((Neisseria* NEXT mening*)) IN NHSEED, HTA
18	#1 OR #2 OR #3 OR #4 OR #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

Database(s): Medline & Embase (Multifile) – OVID interface
Embase Classic+Embase 1947 to 2022 November 09, **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to November 09, 2022
Date of last search: 10 November 2022
Multifile database codes: emczd = Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	Meningitis/ or Meningitis, Bacterial/ or Meningitis, Escherichia Coli/ or Meningitis, Haemophilus/ or Meningitis, Listeria/ or Meningitis, Meningococcal/ or Meningitis, Pneumococcal/ or Meningoencephalitis/
2	1 use ppez
3	meningitis/ or bacterial meningitis/ or haemophilus meningitis/ or listeria meningitis/ or pneumococcal meningitis/ or meningoencephalitis/
4	3 use emczd
5	((bacter* or infect*) adj3 (meningit* or meninges* or leptomeninges* or subarachnoid space?)).ti,ab.
6	(meningit* adj3 (e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon* or septic* or sepsis* or bacter?emi?)).ti,ab.
7	((e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon*) adj3 (septic* or sepsis* or bacter?emi?)).ti,ab.
8	(mening?encephalitis* or meningit*).ti,ab.
9	or/2,4-8
10	Meningococcal Infections/ or exp Neisseria meningitidis/
11	10 use ppez
12	Meningococcosis/ or Meningococcemia/ or Neisseria Meningitidis/
13	12 use emczd
14	(meningococc* adj3 (sepsis* or septic* or toxic* or endotoxic* or disease? or infection?)).ti,ab.
15	(meningococcus* or meningococci* or meningococc?emi?).ti,ab.
16	(Neisseria* mening* or n mening*).ti,ab.
17	or/11,13-16
18	Economics/ use ppez
19	Value of life/ use ppez
20	exp "Costs and Cost Analysis"/ use ppez
21	exp Economics, Hospital/ use ppez
22	exp Economics, Medical/ use ppez
23	Economics, Nursing/ use ppez
24	Economics, Pharmaceutical/ use ppez
25	exp "Fees and Charges"/ use ppez
26	exp Budgets/ use ppez
27	health economics/ use emczd
28	exp economic evaluation/ use emczd
29	exp health care cost/ use emczd
30	exp fee/ use emczd
31	budget/ use emczd
32	funding/ use emczd
33	budget*.ti,ab.
34	cost*.ti.
35	(economic* or pharmaco?economic*).ti.
36	(price* or pricing*).ti,ab.
37	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
38	(financ* or fee or fees).ti,ab.
39	(value adj2 (money or monetary)).ti,ab.
40	or/18-39
41	Quality-Adjusted Life Years/ use ppez
42	Sickness Impact Profile/
43	quality adjusted life year/ use emczd

#	Searches
44	"quality of life index"/ use emczd
45	(quality adjusted or quality adjusted life year*).tw.
46	(qaly* or qal or qald* or qale* or qtime* or qwb* or daly).tw.
47	(illness state* or health state*).tw.
48	(hui or hui2 or hui3).tw.
49	(multiattibute* or multi attribute*).tw.
50	(utilit* adj3 (score*1 or valu* or health* or cost* or measur* or disease* or mean or gain or gains or index*)).tw.
51	utilities.tw.
52	(eq-5d* or eq5d* or eq-5* or eq5* or euroqual* or euro qual* or euroqual 5d* or euro qual 5d* or euro qol* or euroqol*or euro quol* or euroquol* or euro quol5d* or euroquol5d* or eur qol* or eurqol* or eur qol5d* or eurqol5d* or eur?qul* or eur?qul5d* or euro* quality of life or european qol).tw.
53	(euro* adj3 (5 d* or 5d* or 5 dimension* or 5dimension* or 5 domain* or 5domain*)).tw.
54	(sf36 or sf 36 or sf thirty six or sf thirtysix).tw.
55	(time trade off*1 or time tradeoff*1 or tto or timetradeoff*1).tw.
56	Quality of Life/ and ((quality of life or qol) adj (score*1 or measure*1)).tw.
57	Quality of Life/ and ec.fs.
58	Quality of Life/ and (health adj3 status).tw.
59	(quality of life or qol).tw. and Cost-Benefit Analysis/ use ppez
60	(quality of life or qol).tw. and cost benefit analysis/ use emczd
61	((qol or hrqol or quality of life).tw. or *quality of life/) and ((qol or hrqol* or quality of life) adj2 (increas* or decreas* or improv* or declin* or reduc* or high* or low* or effect or effects or worse or score or scores or change*1 or impact*1 or impacted or deteriorat*)).ab.
62	Cost-Benefit Analysis/ use ppez and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
63	cost benefit analysis/ use emczd and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
64	*quality of life/ and (quality of life or qol).ti.
65	quality of life/ and ((quality of life or qol) adj3 (improv* or chang*)).tw.
66	quality of life/ and health-related quality of life.tw.
67	Models, Economic/ use ppez
68	economic model/ use emczd
69	care-related quality of life.tw,kw.
70	((capability$ or capability-based$) adj (measure$ or index or instrument$)).tw,kw.
71	social care outcome$.tw,kw.
72	(social care and (utility or utilities)).tw,kw.
73	or/41-72
74	(9 or 17) and 40
75	(9 or 17) and 73
76	letter/
77	editorial/
78	news/
79	exp historical article/
80	Anecdotes as Topic/
81	comment/
82	case report/
83	(letter or comment*).ti.
84	76 or 77 or 78 or 79 or 80 or 81 or 82 or 83
85	randomized controlled trial/ or random*.ti,ab.
86	84 not 85
87	animals/ not humans/
88	exp Animals, Laboratory/
89	exp Animal Experimentation/
90	exp Models, Animal/
91	exp Rodentia/
92	(rat or rats or mouse or mice).ti.
93	86 or 87 or 88 or 89 or 90 or 91 or 92
94	letter.pt. or letter/
95	note.pt.
96	editorial.pt.
97	case report/ or case study/
98	(letter or comment*).ti.
99	94 or 95 or 96 or 97 or 98
100	randomized controlled trial/ or random*.ti,ab.
101	99 not 100
102	animal/ not human/
103	nonhuman/
104	exp Animal Experiment/
105	exp Experimental Animal/
106	animal model/
107	exp Rodent/
108	(rat or rats or mouse or mice).ti.

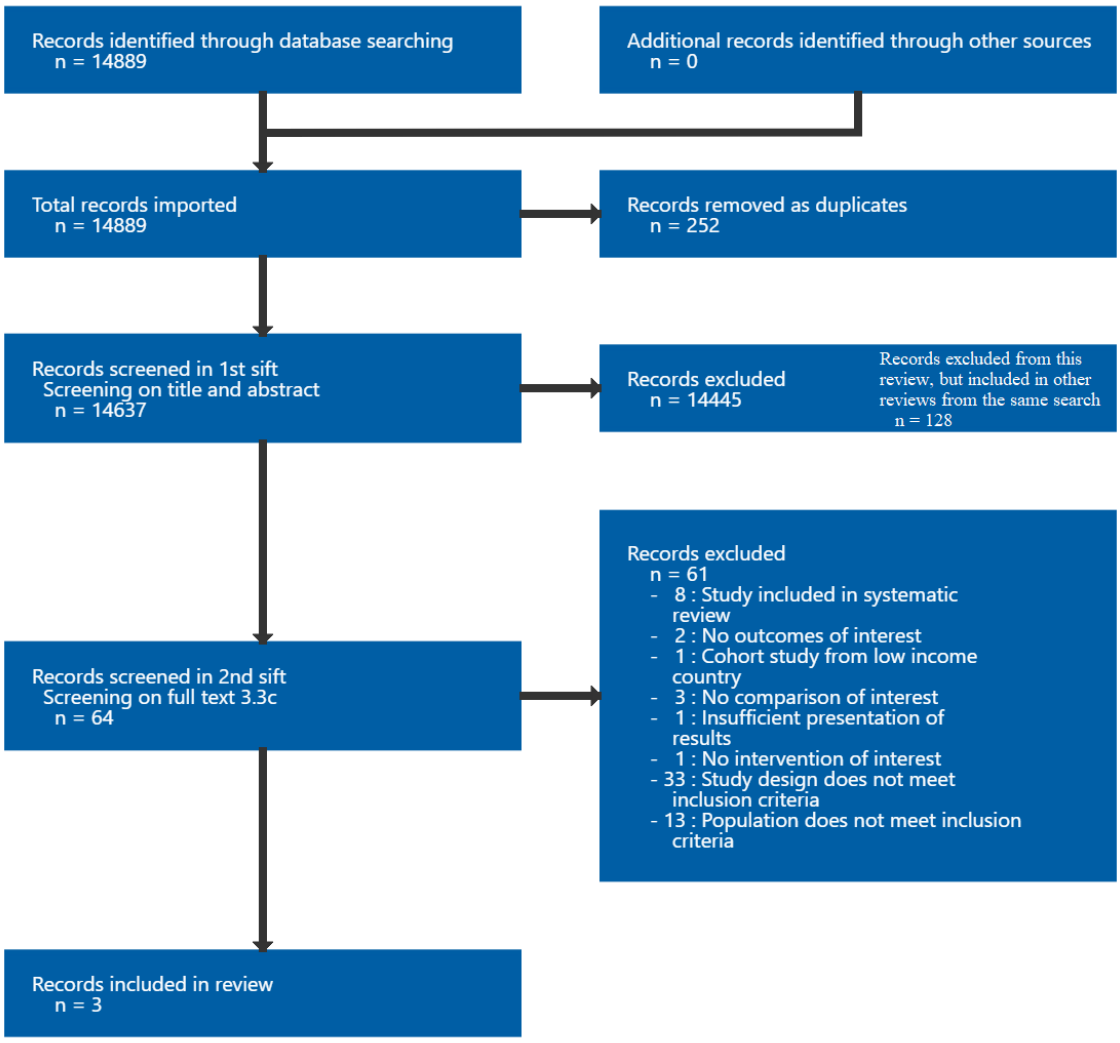
#	Searches
109	101 or 102 or 103 or 104 or 105 or 106 or 107 or 108
110	93 use ppez
111	109 use emczd
112	110 or 111
113	74 not 112
114	limit 113 to English language
115	75 not 112
116	limit 115 to English language
117	114 or 116

1
2

Appendix C Effectiveness evidence study selection

Study selection for: What antibiotic treatment regimens are effective in treating suspected bacterial meningitis in adults before identifying the causative infecting organism, or in the absence of identifying the causative infecting organism?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What antibiotic treatment regimens are effective in treating suspected bacterial meningitis in adults before identifying the causative infecting organism, or in the absence of identifying the causative infecting organism?

Table 4: Evidence tables – effectiveness evidence

Brink, 2019

Bibliographic Reference	Brink, Magnus; Glimaker, Martin; Sjolin, Jan; Naucler, Pontus; Meropenem versus Cefotaxime and Ampicillin as Empirical Antibiotic Treatment in Adult Bacterial Meningitis: a Quality Registry Study, 2008 to 2016; Antimicrobial agents and chemotherapy; 2019; vol. 63 (no. 11)

Study details

Country/ies where study was carried out	Sweden
Study type	Prospective cohort study
Study dates	January 2008 - December 2016
Inclusion criteria	Adults aged >16 years with bacterial meningitis (clinical criteria, characteristic CSF findings, and CSF and blood microbiological tests)
Exclusion criteria	Infections associated with cerebrospinal shunts or devices and patients treated with other antibiotics before study antibiotics

Patient characteristics	N=444 Age (years in median; IQR in parentheses): Meropenem: 61 (44-69); Cefotaxime plus ampicillin: 60 (42-66) Etiology: Streptococcus pneumoniae: 245 (55.2%); Neisseria meningitidis: 46 (10.4%); other: 117 (26.4%); unknown: 36 (8%)
Intervention(s)/control	Meropenem: Empirical treatment regimens of meropenem Cefotaxime plus ampicillin: Empirical treatment regimens of cefotaxime plus ampicillin
Duration of follow-up	Patients were assessed from 1 month to 6 months after discharge.
Sources of funding	Not industry funded
Sample size	N=444 (propensity matched patients)
Other information	Route of administration, dose, frequency and duration were not described. 202 patients in meropenem group and 206 patients in cefotaxime plus ampicillin group received adequate corticosteroid therapy.

Outcomes

Meropenem versus cefotaxime plus ampicillin: All-cause mortality and any long-term neurological impairment

Outcome	**Meropenem, N = 222**	**Cefotaxime plus ampicillin, N = 222**
All-cause mortality (3 months after discharge) Custom value	13/222	9/222

Outcome	Meropenem, N = 222	Cefotaxime plus ampicillin, N = 222
Any long-term neurological impairment (neurological sequelae and/or Glasgow outcome score of <5 and/or hearing deficits; 2-6 months after discharge) Custom value	99/201	94/201

1

2 **Critical appraisal - ROBINS-I**

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(The study controlled for the estimated propensity score (age, sex, immunocompromised state, septic shock, new-onset seizures, mental status, time from admission to adequate antibiotic treatment, corticosteroid treatment, etiology and calendar year).)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low *(All eligible participants were included and followed up in the trial.)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Serious *(Intervention status (for example., route of administration, dose, frequency and duration) is not well defined.)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low *(No deviations from intended interventions)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(Outcome data was available for all participants)*

Section	Question	Answer
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Serious *(Low (all-cause mortality): The outcome measure was not influenced by knowledge of the intervention received. Serious (any long-term neurological impairment): The outcome measure was subjective.)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate *(No indication of selection of the reported analysis from among multiple analyses)*
Overall bias	Risk of bias judgement	Serious
Overall bias	Risk of bias variation across outcomes	Serious
Overall bias	Directness	Directly applicable *(All-cause mortality is directly applicable, but any long-term neurological impairment is indirect outcome as it is a composite outcome including Glasgow outcome score and hearing deficits.)*

Prasad, 2007

Bibliographic Reference Prasad, K.; Kumar, A.; Singhal, T.; Gupta, P. K.; Third generation cephalosporins versus conventional antibiotics for treating acute bacterial meningitis; Cochrane Database of Systematic Reviews; 2007; (no. 4)

Study details

Country/ies where study was carried out	• Brazil (Bryan 1985) • Costa Rica (Odio 1986) • Dominican Republic (Rodriguz 1985) • Egypt (Girgis 1987; Girgis 1988) • Finland (Peltola 1989) • Italy (Narciso 1983) • USA (Aronoff 1984; Barson 1985; Congeni 1984; Del Rio 1983; Jacobs 1985; Steele 1983; Wells 1984) • Morocco (Filali 1993) • Nepal (Sharma 1996) • Niger (Nathan 2005) • South Africa (Haffejee 1988) • Turkey (Tuncer 1988)
Study type	Systematic review of RCTs
Study dates	1983 to 2005
Inclusion criteria	RCTs with participants of any age or sex with bacterial meningitis (clinical features and characteristic of CSF findings)
Exclusion criteria	Meningitis after lumbar puncture, meningitis related to head injury, neurosurgical procedures, CSF leak, known para-meningeal focus of infection (for example., brain abscess, otitis media or cranial osteomyelitis), and known immunodeficiency

Patient characteristics	Age: • 0 to 17 years: 15 studies (Aronoff 1984; Barson 1985; Bryan 1985; Congeni 1984; Del Rio 1983; Haffejee 1988; Jacobs 1985; Nathan 2005; Odio 1986; Peltola 1989; Rodriguz 1985; Sharma 1996; Steele 1983; Tuncer 1988; Wells 1984) • 5 months to 28 years (mean age: 9.8 years): 1 study (Girgis 1988) • ≥16 years: 3 studies (Filali 1993; Girgis 1987; Narciso 1983)
Intervention(s)/control	Cephalosporins: Ceftriaxone (IM or IV) for 2-21 days in 14 studies (Aronoff 1984; Barson 1985; Bryan 1985; Congeni 1984; Del Rio 1983; Filali 1993; Girgis 1987; Girgis 1988; Narciso 1983; Nathan 2005; Peltola 1989; Sharma 1996; Steele 1983; Tuncer 1988), cefotaxime (IM or IV) for 10-14 days in 5 studies (Haffejee 1988; Jacobs 1985; Odio 1986; Peltola 1989; Wells 1984), and ceftazidime (IV) for 10.2 days in 1 study (Rodriguz 1985) Conventional antibiotics: Ampicillin plus chloramphenicol (IM or IV +/- oral dose) for 7-21 days in 9 studies (Aronoff 1984; Barson 1985; Bryan 1985; Del Rio 1983; Girgis 1987; Girgis 1988; Odio 1986; Rodriguz 1985; Steele 1983), ampicillin plus chloramphenicol or gentamicin (IV) for 11-14 days in 3 studies (Congeni 1984; Jacobs 1985; Wells 1984), benzylpenicillin sodium (IM or IV) plus chloramphenicol (IV or oral dose) for up to 14 days in 2 studies (Haffejee 1988; Sharma 1996), ampicillin (IV) alone in 2 studies (Narciso 1983; Peltola 1989), benzylpenicillin sodium (IV) alone for 5-6 days in 2 studies (Filali 1993; Tuncer 1988), and chloramphenicol alone (IM or IV) for 2-7 days in 2 studies (Nathan 2005; Peltola1989)
Duration of follow-up	During hospitalisation (Congeni 1984) to 27 months (Haffejee 1988)
Sources of funding	Non reported
Sample size	N=1496
Other information	16 studies conducted in neonates, babies and children were excluded from this review

Outcomes

1 **Ceftriaxone versus ampicillin or benzylpenicillin sodium: All-cause mortality**

Outcome	Cephalosporins, N = 21	Conventional antibiotics, N = 25
All-cause mortality (up to 2 months after discharge) Data from 2 RCTs (Filali 1993; Narciso 1983) extracted from analysis 1.1 in SR (Prasad 2007); see Cochrane review https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001832.pub3/full No of events	n = 1	n = 1

2

3 **Ceftriaxone versus benzylpenicillin sodium: Hearing impairment**

Outcome	Cephalosporins, N = 15	Conventional antibiotics, N = 19
Hearing impairment (severe deafness; 2 months after discharge) Data from 1 RCT (Filali 1993) extracted from analysis 1.2 in SR (Prasad 2007); see Cochrane review https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001832.pub3/full No of events	n = 0	n = 0

4

5 **Ceftriaxone versus ampicillin plus chloramphenicol: All-cause mortality**

Outcome	Cephalosporins, N = 15	Conventional antibiotics, N = 15

Outcome	Cephalosporins, N = 15	Conventional antibiotics, N = 15
All-cause mortality Data from 1 RCT (Girgis 1987) extracted from analysis 1.1 in SR (Prasad 2007); see Cochrane review https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001832.pub3/full No of events	n = 1	n = 1

Critical appraisal - NGA Critical appraisal - ROBIS checklist

Section	Question	Answer
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low *(Objectives and eligibility criteria were pre-specified and they were adhered to throughout the review)*
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Unclear *(The search was restricted by date; however, this was not justified. There were no restrictions on publication format and language.)*
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low *(There are no concerns regarding methods used to collect data and appraise studies. However, the reviewers could not extract the analysable data on disability or neurological sequelae (other than hearing impairment) because the number of participants involved was unclear and participants had more than one sequela.)*

Section	Question	Answer
Synthesis and findings	Concerns regarding the synthesis and findings	Low *(The synthesis is unlikely to produce biased results. Between-study variation (heterogeneity) was minimal for most outcomes, and subgroup analyses, sensitivity analyses and random effect models were used. The findings were convincing that the limitations would have little impact.)*
Overall study ratings	Overall risk of bias	Unclear **Risk of bias rating for RCTs in SR using RoB** See Cochrane review https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001832.pub3/full
Overall study ratings	Applicability as a source of data	Fully applicable

Schmutzhard, 1995

Bibliographic Reference	Schmutzhard, E.; Williams, K. J.; Vukmirovits, G.; Chmelik, V.; Pfausler, B.; Featherstone, A.; A randomised comparison of meropenem with cefotaxime or ceftriaxone for the treatment of bacterial meningitis in adults. Meropenem Meningitis Study Group; Journal of antimicrobial chemotherapy; 1995; vol. 36suppla; 85-97

Study details

Country/ies where study was carried out	Hungary, the Czech Republic, Portugal, France, Spain and Austria
Study type	Randomised controlled trial (RCT)
Study dates	April 1992 - June 1993

Inclusion criteria	Adults with signs and symptoms of bacterial meningitis, who needed an intravenous antibiotic therapy and had a CSF pathogen likely to be susceptible to meropenem and cephalosporin
Exclusion criteria	Adults with a history of hypersensitivity reaction to any β-lactam antibiotic, previous episode of meningitis, renal impairment (creatinine clearance <50L/min), liver failure or hepatic coma, congenital or acquired immunodeficiency, congenital spine abnormalities, abscesses of central nervous system, penetrating trauma, fracture or foreign bodies (including shunts) in central nervous system
Patient characteristics	N=56 Age (years in median): Meropenem: 46; Cephalosporin: 31 Sex: male: 28 (50%); female: 28 (50%) Etiology: Neisseria meningitidis: 8 (14%); Streptococcus pneumoniae: 14 (25%); Haemophilus influenzae: 1 (3%); other: 7 (12%); unknown: 26 (46%)
Intervention(s)/control	Meropenem: Intravenous meropenem (40 mg/kg every 8 h, up to a maximum dose of 6 g/day) for average duration of 10.6 days Cephalosporin: Intravenous ceftriaxone (an initial dose of 100 mg/kg followed by single daily doses of 80 mg/kg up to a maximum dose of 4 g/day) or cefotaxime 75 to 100 mg/kg every 8 h (225 to 300 mg/kg/day up to a maximum dose of 12 g/day) for average duration of 12.9 days
Duration of follow-up	Patients were assessed during hospitalisation, 6 weeks and 6 months after discharge.
Sources of funding	Industry funded
Sample size	N=56
Other information	39 patients (meropenem: 19; ceftriaxone: 10; cefotaxime: 10) received dexamethasone therapy (average dose 0.16 mg/kg).

Outcomes

Meropenem versus cephalosporin (cefotaxime or ceftriaxone): All-cause mortality, any long-term neurological impairment and hearing impairment

Outcome	Meropenem, N = 28	Cephalosporin, N = 28
All-cause mortality (during hospitalisation) No of events	n = 3	n = 1
Any long-term neurological impairment (sensory deficit, motor deficit, cerebral oedema and coma; at 6 weeks after discharge) No of events	n = 3	n = 4
Hearing impairment (6 months after discharge) No of events	n = 5	n = 1

Critical appraisal - Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information about allocation concealment was provided. No significant differences between groups at baseline.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(No information on blinding. No information on whether deviations arose because of the trial context. Appropriate analysis was used.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data was available for nearly all participants.)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(Low risk (all-cause mortality): Measurement did not differ between groups. Knowledge of the assigned intervention could not influence the outcome. High risk (any long-term neurological impairment and hearing impairment): Measurement did not differ between groups. Knowledge of the assigned intervention was likely to influence outcome assessment.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(There is clear evidence that all eligible reported results for the outcome correspond to all intended outcome measurements and analyses.)*
Overall bias and Directness	Risk of bias judgement	High *(Some concerns (all-cause mortality): The study is judged to raise some concerns in at least one domain (bias arising from the randomisation process). High risk (any long-term neurological impairment and hearing impairment): The study is judged to be at high risk of bias in at least one domain (bias in measurement of the outcome).)*
Overall bias and Directness	Overall Directness	Directly applicable *(All-cause mortality and hearing impairment are directly applicable, but any long-term neurological impairment is indirect outcome as it is a composite outcome including cerebral oedema, otitis externa and coma.)*
Overall bias and Directness	Risk of bias variation across outcomes	Some concerns (all-cause mortality): The study is judged to raise some concerns in at least one domain (bias arising from the randomisation process). High risk (any long-term neurological impairment and hearing impairment): The study is judged to be at high risk of bias in at least one domain (bias in measurement of the outcome).

CSF: cerebrospinal fluid; IM: intramuscular; IV: intravenous; RCT: randomised controlled trial; RoB: risk of bias; ROBINS-I: risk of bias in non-randomised studies – of interventions; ROBIS: risk of bias in systematic reviews; SR: systematic review

Appendix E Forest plots

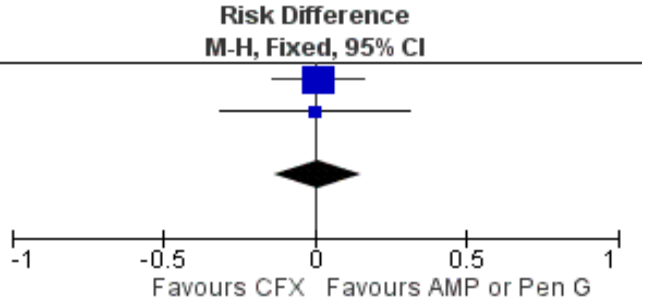
Forest plots for review question: What antibiotic treatment regimens are effective in treating suspected bacterial meningitis in adults before identifying the causative infecting organism, or in the absence of identifying the causative infecting organism?

This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Figure 2: Ceftriaxone versus ampicillin or benzylpenicillin sodium: All-cause mortality*

	CFX		AMP or Pen G			Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Filali 1993	1	16	1	20	78.0%	0.01 [-0.14, 0.16]
Narciso 1983	0	5	0	5	22.0%	0.00 [-0.31, 0.31]
Total (95% CI)		**21**		**25**	**100.0%**	**0.01 [-0.13, 0.15]**
Total events	1		1			

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.13 (P = 0.89)



2 RCTs (Filali 1993; Narciso 1983) extracted from Cochrane SR (Prasad 2007)
AMP: ampicillin; CFX: ceftriaxone; CI: confidence interval; M-H: Mantel-Haenszel; Pen G: benzylpenicillin sodium; SR: systematic review

Appendix F GRADE tables

GRADE tables for review question: What antibiotic treatment regimens are effective in treating suspected bacterial meningitis in adults before identifying the causative infecting organism, or in the absence of identifying the causative infecting organism?

Table 5: Evidence profile for comparison: ceftriaxone versus ampicillin or benzylpenicillin sodium

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone	Ampicillin or benzylpenicillin sodium	Relative (95% CI)	Absolute		
All-cause mortality												
2*	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/21 (4.8%)	1/25 (4%)	RD 0.01 (-0.13 to 0.15)	10 more per 1000 (from 130 fewer to 150 more)	VERY LOW	CRITICAL

CI: confidence interval; RD: risk difference; SR: systematic review
**See corresponding forest plot*
[1] SR assessed as unclear risk of bias using ROBIS; very serious risk of bias in the evidence contributing to the outcomes as per Cochrane RoB in SR (Prasad 2007)
[2] Sample size <200

Table 6: Evidence profile for comparison: ceftriaxone versus ampicillin plus chloramphenicol

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone	Ampicillin plus chloramphenicol	Relative (95% CI)	Absolute		
All-cause mortality												

1 (Girgis 1987 extracted from SR Prasad 2007)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/15 (6.7%)	1/15 (6.7%)	RR 1 (0.07 to 14.55)	0 fewer per 1000 (from 62 fewer to 903 more)	VERY LOW	CRITICAL

CI: confidence interval; RR: risk ratio; SR systematic review
[1] SR assessed as unclear risk of bias using ROBIS; serious risk of bias in the evidence contributing to the outcomes as per Cochrane RoB in SR (Prasad 2007)
[2] <150 events

Table 7: Evidence profile for comparison: ceftriaxone versus benzylpenicillin sodium

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ceftriaxone**	**Benzylpenicillin sodium**	**Relative (95% CI)**	**Absolute**		
Hearing impairment (follow-up 2 months)												
1 (Filali 1993 extracted from SR Prasad 2007)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/15 (0%)	0/19 (0%)	RD 0 (-0.11 to 0.11)	0 fewer per 1000 (from 110 fewer to 110 more)[3]	VERY LOW	IMPORTANT

CI: confidence interval; RD: risk difference; RR: risk ratio; SR: systematic review
[1] SR assessed as unclear risk of bias using ROBIS; very serious risk of bias in the evidence contributing to the outcomes as per Cochrane RoB in SR (Prasad 2007)
[2] Sample size <200
[3] Absolute effect calculated based on risk difference

Table 8: Evidence profile for comparison: meropenem versus cephalosporin (cefotaxime or ceftriaxone)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Meropenem**	**Cephalosporin (cefotaxime or ceftriaxone)**	**Relative (95% CI)**	**Absolute**		
All-cause mortality												
1 (Schmutzhard 1995)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/28 (10.7%)	1/28 (3.6%)	RR 3 (0.33 to 27.12)	71 more per 1000 (from 24 fewer to 933 more)	VERY LOW	CRITICAL
Any long-term neurological impairment (sensory deficit, motor deficit, cerebral oedema and coma) (follow-up 6 weeks)												

1 (Schmutzhard 1995)	randomised trials	very serious[3]	no serious inconsistency	serious[4]	very serious[5]	none	3/28 (10.7%)	4/28 (14.3%)	RR 0.75 (0.18 to 3.05)	36 fewer per 1000 (from 117 fewer to 293 more)	VERY LOW	CRITICAL
Hearing impairment (follow-up 6 months)												
1 (Schmutzhard 1995)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[5]	none	5/28 (17.9%)	1/28 (3.6%)	RR 5 (0.62 to 40.11)	143 more per 1000 (from 14 fewer to 1000 more)	VERY LOW	IMPORTANT

CI: confidence interval; RR: risk ratio
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] <150 events
[3] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[4] Outcome is indirect as it is a composite outcome including cerebral oedema and coma
[5] 95% CI crosses 2 MIDs

Table 9: Evidence profile for comparison: meropenem versus cefotaxime plus ampicillin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Meropenem**	**Cefotaxime plus ampicillin**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (adjusted analyses)												
1 (Brink, 2019)	observational studies	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	13/222 (5.9%)	9/222 (4.1%)	RR 1.44 (0.63 to 3.31)	18 more per 1000 (from 15 fewer to 94 more)	VERY LOW	CRITICAL
Any long-term neurological impairment (neurological sequelae and/or Glasgow outcome score of <5 and/or hearing deficits; adjusted analyses) (follow-up 2-6 months)												
1 (Brink, 2019)	observational studies	serious[1]	no serious inconsistency	very serious[4]	serious[5]	none	99/201 (49.3%)	94/201 (46.8%)	RR 1.05 (0.86 to 1.29)	23 more per 1000 (from 65 fewer to 136 more)	VERY LOW	CRITICAL

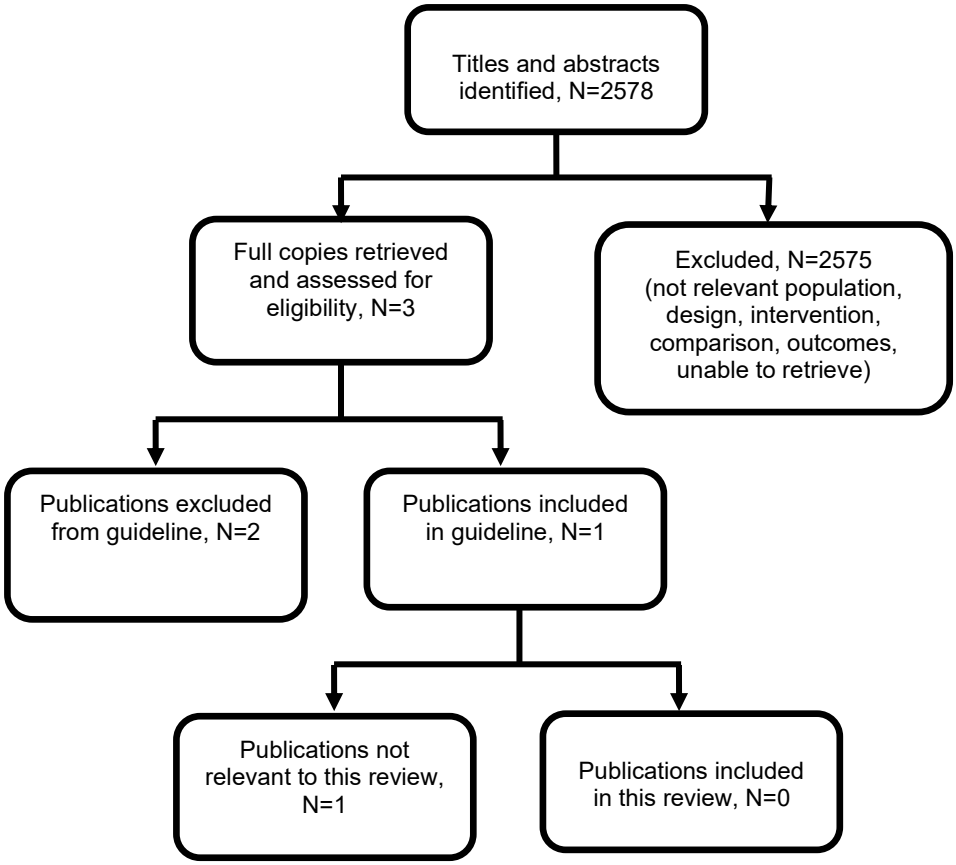
CI: confidence interval; RR: risk ratio
[1] Serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I
[2] Intervention is indirect due to combination of cefotaxime and ampicillin
[3] <150 events
[4] Intervention and outcome are indirect due to combination of cefotaxime and ampicillin, and a composite outcome including Glasgow outcome score and hearing deficit
[5] 95% CI crosses 1 MID

Appendix G Economic evidence study selection

Study selection for: What antibiotic treatment regimens are effective in treating suspected bacterial meningitis in adults before identifying the causative infecting organism, or in the absence of identifying the causative infecting organism?

A global economic search was undertaken for the whole guideline, but no economic evidence was identified which was applicable to this review question (see Figure 3).

Figure 3: Study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: What antibiotic treatment regimens are effective in treating suspected bacterial meningitis in adults before identifying the causative infecting organism, or in the absence of identifying the causative infecting organism?

No evidence was identified which was applicable to this review question.

Appendix I Economic model

Economic model for review question: What antibiotic treatment regimens are effective in treating suspected bacterial meningitis in adults before identifying the causative infecting organism, or in the absence of identifying the causative infecting organism?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What antibiotic treatment regimens are effective in treating suspected bacterial meningitis in adults before identifying the causative infecting organism, or in the absence of identifying the causative infecting organism?

Excluded effectiveness studies

The excluded studies table only lists the studies that were considered and then excluded at the full-text stage for this review (N=61) and not studies (N=128) that were considered and then excluded from the search at the full-text stage as per the PRISMA diagram in Appendix C for the other review questions in the same search.

Table 10: Excluded studies and reasons for their exclusion

Study	Code [Reason]
(1993) Long-acting chloramphenicol for bacterial meningitis. Bulletin of the World Health Organization 71(1): 117-8, 123	- Study design does not meet inclusion criteria
Anonymous (1998) Antimicrobial therapy in the management of bacterial meningitis. WHO Drug Information 12(2): 70-72	- Study design does not meet inclusion criteria
Anonymous (1995) Meropenem: A new carbapenem with potential for treating bacterial meningitis. Drugs and Therapy Perspectives 6(10): 1-5	- Study design does not meet inclusion criteria
Anonymous (1988) American Academy of Pediatrics Committee on Infectious Diseases: Treatment of bacterial meningitis. Pediatrics 81(6): 904-907	- Study design does not meet inclusion criteria
Anonymous (2010) Initiate appropriate antibacterial and adjunctive therapies when treating bacterial meningitis. Drugs and Therapy Perspectives 26(8): 19-22	- Study design does not meet inclusion criteria
Bass, J. W.; Person, D. A.; Fonseca, R. J. (1990) Cefuroxime versus ceftriaxone for bacterial meningitis (I). Journal of pediatrics 116(3): 488	- Study design does not meet inclusion criteria
Begue, P., Astruc, J., Francois, P. et al. (1998) Comparison of ceftriaxone and cefotaxime in severe pediatric bacterial infection: a multicentric study. Medecine ET maladies infectieuses 28(4): 300-306	- Population does not meet inclusion criteria
Bijlsma, Merijn W., Brouwer, Matthijs C., Kasanmoentalib, E. Soemirien et al. (2016) Community-acquired bacterial meningitis in adults in the Netherlands, 2006-14: a prospective cohort study. The Lancet. Infectious diseases 16(3): 339-47	- Study design does not meet inclusion criteria

Study	Code [Reason]
Bretonniere, Cedric, Jozwiak, Mathieu, Girault, Christophe et al. (2015) Rifampin use in acute community-acquired meningitis in intensive care units: the French retrospective cohort ACAM-ICU study. Critical care (London, England) 19: 303	- Study design does not meet inclusion criteria
Bryan, J. P., Rocha, H., da Silva, H. R. et al. (1985) Comparison of ceftriaxone and ampicillin plus chloramphenicol for the therapy of acute bacterial meningitis. Antimicrobial agents and chemotherapy 28(3): 361-368	- Study included in systematic review- Prasad 2007 (included in evidence review 3.3b)
Chaudhary, M.; Shrivastava, S. M.; Sehgal, R. (2008) Efficacy and safety study of fixed-dose combination of ceftriaxone-vancomycin injection in patients with various infections. Current drug safety 3(1): 82-85	- Study design does not meet inclusion criteria - Population does not meet inclusion criteria
del Rio, M. A., Chrane, D., Shelton, S. et al. (1983) Ceftriaxone versus ampicillin and chloramphenicol for treatment of bacterial meningitis in children. Lancet (london, england) 1(8336): 1241-1244	- Population does not meet inclusion criteria
Dzupova, O., Rozsypal, H., Prochazka, B. et al. (2009) Acute bacterial meningitis in adults: Predictors of outcome. Scandinavian Journal of Infectious Diseases 41(5): 348-354	- Study design does not meet inclusion criteria
Eisen, Damon P, Hamilton, Elizabeth, Bodilsen, Jacob et al. (2022) Longer than 2 hours to antibiotics is associated with doubling of mortality in a multinational community-acquired bacterial meningitis cohort. Scientific reports 12(1): 672	- Study design does not meet inclusion criteria
Eliakim-Raz, N., Lador, A., Leibovici-Weissman, Y. et al. (2014) Efficacy and safety of chloramphenicol: Joining the revival of old antibiotics? Systematic review and meta-analysis of randomized controlled trials. Journal of Antimicrobial Chemotherapy 70(4): 979-996	- All studies that meet inclusion criteria are included in systematic review – Prasad 2007
Ellis, Jayne, Harvey, David, Defres, Sylviane et al. (2022) Clinical management of community-acquired meningitis in adults in the UK and Ireland in 2017: a retrospective cohort study on behalf of the National Infection Trainees Collaborative for Audit and Research (NITCAR). BMJ open 12(7): e062698	- Study design does not meet inclusion criteria
Elyasi, S., Khalili, H., Dashti-Khavidaki, S. et al. (2015) Conventional- versus high-dose vancomycin regimen in patients with acute bacterial meningitis: a randomized clinical trial. Expert opinion on pharmacotherapy 16(3): 297-304	- No outcomes of interest for review
Erdem, H., Kilic, S., Coskun, O. et al. (2010) Community-acquired acute bacterial meningitis in	- Study design does not meet inclusion criteria

Study	Code [Reason]
the elderly in Turkey. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 16(8): 1223-9	
Fisher, Jane, Linder, Adam, Calevo, Maria Grazia et al. (2021) Non-corticosteroid adjuvant therapies for acute bacterial meningitis. The Cochrane database of systematic reviews 11: cd013437	- No intervention of interest
Girgis, N. I., Abu el Ella, A. H., Farid, Z. et al. (1987) Ceftriaxone compared with a combination of ampicillin and chloramphenicol in the treatment of bacterial meningitis in adults. Drugs under experimental and clinical research 13(8): 497-500	- Study included in systematic review – Prasad 2007 (included in evidence review 3.3b)
Girgis, N. I., Abu el-Ella, A. H., Farid, Z. et al. (1988) Ceftriaxone alone compared to ampicillin and chloramphenicol in the treatment of bacterial meningitis. Chemotherapy 34suppl1: 16-20	- Study included in systematic review - Prasad 2007
Gregoire, M., Dailly, E., Le Turnier, P. et al. (2019) High-dose ceftriaxone for bacterial meningitis and optimization of administration scheme based on nomogram. Antimicrobial Agents and Chemotherapy 63(9): e00634-19	- No comparison of interest for review
Haffejee, I. E. (1988) Cefotaxime versus penicillin-chloramphenicol in purulent meningitis: a controlled single-blind clinical trial. Annals of tropical paediatrics 8(4): 225-9	- Study included in systematic review - Prasad 2007 (included in evidence review 3.3b)
Heffernan, Aaron J and Roberts, Jason A (2021) Dose optimisation of antibiotics used for meningitis. Current opinion in infectious diseases 34(6): 581-590	- Study design does not meet inclusion criteria
Hofinger, Diedre and Davis, Larry E. (2013) Bacterial meningitis in older adults. Current treatment options in neurology 15(4): 477-91	- Study design does not meet inclusion criteria
Johansson, O.; Cronberg, S.; Hoffstedt, B. (1982) Cefuroxime versus ampicillin and chloramphenicol for the treatment of bacterial meningitis. Report from a Swedish study group. Lancet 1(8267): 295-299	- Population does not meet inclusion criteria
Kasiakou, S. K., Sermaides, G. J., Michalopoulos, A. et al. (2005) Continuous versus intermittent intravenous administration of antibiotics: A meta-analysis of randomised controlled trials. Lancet Infectious Diseases 5(9): 581-589	- Population does not meet inclusion criteria
Kecmanovic, M.; Pavlovic, M.; Kostic, A. (1982) Cefotaxime in the treatment of suppurative meningitis. Chemioterapia 1(4suppl): 85	- Study design does not meet inclusion criteria
Korbila, I. P., Tansarli, G. S., Karageorgopoulos,	- Population does not meet inclusion criteria

Study	Code [Reason]
D. E. et al. (2013) Extended or continuous versus short-term intravenous infusion of cephalosporins: A meta-analysis. Expert Review of Anti-Infective Therapy 11(6): 585-595	
Le Terrier, Christophe, Vinetti, Marco, Bonjean, Paul et al. (2021) Impact of a restrictive antibiotic policy on the acquisition of extended-spectrum beta-lactamase-producing Enterobacteriaceae in an endemic region: a before-and-after, propensity-matched cohort study in a Caribbean intensive care unit. Critical care (London, England) 25(1): 261	- Study design does not meet inclusion criteria
Le Turnier, P., Vandamme, Y. M., Pere, M. et al. (2019) Tolerability of high-dose ceftriaxone in CNS infections: A prospective multicentre cohort study. Journal of Antimicrobial Chemotherapy 74(4): 1078-1085	- Study design does not meet inclusion criteria
Levine, D. P.; McNeil, P.; Lerner, S. A. (1989) Randomized, double-blind comparative study of intravenous ciprofloxacin versus ceftazidime in the treatment of serious infections. American journal of medicine 87(5a): 160S-163S	- Population does not meet inclusion criteria
Li, Yajuan, Liu, Tingting, Shi, Cuixiao et al. (2022) Epidemiological, clinical, and laboratory features of patients infected with Elizabethkingia meningoseptica at a tertiary hospital in Hefei City, China. Frontiers in public health 10: 964046	- Population does not meet inclusion criteria
Madson, L. and Grose, C. (1990) Ceftriaxone vs cefotaxime for treatment of Haemophilus influenzae meningitis (I). Pediatrics 85(4): 622-623	- Study design does not meet inclusion criteria
McGill, F., Heyderman, R. S., Michael, B. D. et al. (2016) The UK joint specialist societies guideline on the diagnosis and management of acute meningitis and meningococcal sepsis in immunocompetent adults. The Journal of infection 72(4): 405-38	- Study design does not meet inclusion criteria
Moayedi, Yasbanoo and Gold, Wayne L. (2012) Acute bacterial meningitis in adults. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 184(9): 1060	- Study design does not meet inclusion criteria
Narciso, P.; De Mori, P.; Giannuzzi, R. (1983) Ceftriaxon versus ampicillin therapy for purulent meningitis in adults. Drugs under Experimental and Clinical Research 9(10): 717-719	- Study included in systematic review – Prasad 2007
Norrby, S. R. and Gildon, K. M. (1999) Safety profile of meropenem: A review of nearly 5000 patients treated with meropenem. Scandinavian Journal of Infectious Diseases 31(1): 3-10	- Population does not meet inclusion criteria

Study	Code [Reason]
O'Neill, P. (1993) How long to treat bacterial meningitis. Lancet (London, England) 341(8844): 530	- Study design does not meet inclusion criteria
Okike, I. O., Awofisayo, A., Adak, B. et al. (2015) Empirical antibiotic cover for Listeria monocytogenes infection beyond the neonatal period: A time for change?. Archives of Disease in Childhood 100(5): 423-425	- Study design does not meet inclusion criteria
Olarte, Liset (2019) Vancomycin Should Be Part of Empiric Therapy for Suspected Bacterial Meningitis. Journal of the Pediatric Infectious Diseases Society 8(2): 187-188	- Study design does not meet inclusion criteria
Onakpoya, Igho J., Walker, A. Sarah, Tan, Pui S. et al. (2018) Overview of systematic reviews assessing the evidence for shorter versus longer duration antibiotic treatment for bacterial infections in secondary care. PloS one 13(3): e0194858	- Insufficient presentation of results
Paul, M., Shani, V., Muchtar, E. et al. (2010) Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. Antimicrobial Agents and Chemotherapy 54(11): 4851-4863	- Population does not meet inclusion criteria
Pichler, H., Diridl, G., Jeschko, E. et al. (1989) Ceftriaxone vs. piperacillin in patients with bacterial meningitis. Journal of chemotherapy (Florence, Italy) 1(4suppl): 682-683	- No comparison of interest
Pécoul, B., Varaine, F., Keita, M. et al. (1991) Long-acting chloramphenicol versus intravenous ampicillin for treatment of bacterial meningitis. Lancet (london, england) 338(8771): 862-866	- Study included in systematic review - Prasad 2007 (included in evidence review 3.3b)
Rafailidis, P. I.; Pitsounis, A. I.; Falagas, M. E. (2009) Meta-analyses on the Optimization of the Duration of Antimicrobial Treatment for Various Infections. Infectious Disease Clinics of North America 23(2): 269-276	- Study design does not meet inclusion criteria
Rayanakorn, Ajaree, Ser, Hooi-Leng, Pusparajah, Priyia et al. (2020) Comparative efficacy of antibiotic(s) alone or in combination of corticosteroids in adults with acute bacterial meningitis: A systematic review and network meta-analysis. PloS one 15(5): e0232947	- No comparison of interest for review
Steele, R. W. (1984) Ceftriaxone therapy of meningitis and serious infections. American Journal of Medicine 77(4c): 50-53	- Study included in systematic review - Prasad 2007 (included in evidence review 3.3b)
Steele, R. W.; Steele, A. J.; Gelzine, A. L. (1992) Ceftriaxone and bacterial meningitis. A ten-year follow-up. Antibiotics and chemotherapy 45: 161-168	- Study design does not meet inclusion criteria

Study	Code [Reason]
Tunkel, A. R. and Scheld, W. M. (1996) Acute bacterial meningitis in adults. Current clinical topics in infectious diseases 16: 215-39	- Study design does not meet inclusion criteria
Tunkel, Allan R. (2006) Use of ceftriaxone during epidemics in patients with suspected meningococcal meningitis. Current infectious disease reports 8(4): 291-2	- No outcomes of interest for review
van de Beek, D., Cabellos, C., Dzupova, O. et al. (2016) ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 22suppl3: S37-62	- Study design does not meet inclusion criteria
van de Beek, D., de Gans, J., Spanjaard, L. et al. (2002) Antibiotic guidelines and antibiotic use in adult bacterial meningitis in The Netherlands. Journal of Antimicrobial Chemotherapy 49(4): 661-666	- Study design does not meet inclusion criteria
van Soest, Thijs M, Chekrouni, Nora, van Sorge, Nina M et al. (2022) Community-acquired bacterial meningitis in patients of 80 years and older. Journal of the American Geriatrics Society 70(7): 2060-2069	- Study design does not meet inclusion criteria
Vasikasin, Vasin and Changpradub, Dhitiwat (2021) Clinical manifestations and prognostic factors for Streptococcus agalactiae bacteremia among nonpregnant adults in Thailand. Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy 27(7): 967-971	- Population does not meet inclusion criteria
Waheed, A. and Gardezi, S. A. A. (2008) Comparison of three antibiotics regimens in the treatment of acute pyogenic meningitis. Pak armed forces med j 58(2): 120-124	- Cohort study from low income country
Watanakunakorn, C., Greifenstein, A., Stroh, K. et al. (1993) Pneumococcal bacteremia in three community teaching hospitals from 1980 to 1989. Chest 103(4): 1152-6	- Population does not meet inclusion criteria
Weisfelt, Martijn; de Gans, Jan; van de Beek, Diederik (2007) Bacterial meningitis: a review of effective pharmacotherapy. Expert opinion on pharmacotherapy 8(10): 1493-504	- Study design does not meet inclusion criteria
Weiss, D. and Glaser, J. H. (1990) Ceftriaxone versus cefuroxime for treatment of bacterial meningitis. Journal of pediatrics 116(3): 492	- Study design does not meet inclusion criteria
Wintenberger, C., Guery, B., Bonnet, E. et al. (2017) Proposal for shorter antibiotic therapies. Medecine et maladies infectieuses 47(2): 92-141	- Study design does not meet inclusion criteria
Zavala, I.; Barrera, E.; Nava, A. (1988)	- Population does not meet inclusion criteria

Study	Code [Reason]
Ceftriaxone in the treatment of bacterial meningitis in adults. Chemotherapy 34suppl1: 47-52	

1

2 **Excluded economic studies**

3 No studies were identified which were applicable to this review question.

4

Appendix K Research recommendations – full details

Research recommendations for review question: What antibiotic treatment regimens are effective in treating suspected bacterial meningitis in adults before identifying the causative infecting organism, or in the absence of identifying the causative infecting organism?

No research recommendation was made for this review.