National Institute for Health and Care Excellence

Draft for consultation

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

[E4] Evidence review for antibiotics for bacterial meningitis caused by Gram-negative bacilli

NICE guideline number tbc

Evidence review underpinning recommendations 1.6.4, 1.6.13 and 1.6.16 and research recommendation 3 in the NICE guideline

September 2023

Draft for consultation

This evidence review was developed by NICE

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Antibiotics for bacterial meningitis caused by Gram-negative bacilli

Review question

What antibiotic treatment regimens are effective in treating bacterial meningitis caused by Gram-negative bacilli?

Introduction

Bacterial meningitis is a rare but serious infection. The causative organism is usually confirmed by tests performed on cerebrospinal fluid or blood samples. Gram-negative bacilli (that is, bacterial species of the Enterobacterales order, such as E. coli) are an important cause of bacterial meningitis in neonates and younger babies, and very rarely in older adults.

The aim of this review is to determine what antibiotic treatment regimens are effective in treating bacterial meningitis caused by Gram-negative bacilli (Enterobacterales).

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	All adults, young people, children and babies (excluding neonates defined as aged 28 days old and younger) with confirmed bacterial meningitis caused by Gram-negative bacilli
Intervention	Antibiotic agent of interest: • Cefotaxime • Ceftriaxone • Ceftazidime • Gentamicin • Amikacin • Meropenem • Aztreonam • Ciprofloxacin • Moxifloxacin • Levofloxacin
Comparison	**Stage 1 (all antibiotic agents of interest):** • Antibiotic agent A (single or combination)* vs Antibiotic agent B (single or combination)* *Gentamycin and amikacin to be used in combination with other antibiotics not monotherapy. **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**

	Population: adults, children and infants • 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) Population: adults • Functional impairment (measured by any validated scale at any time point) Population: children and infants • Severe developmental delay (defined as score of >2 SD below normal on validated assessment scales, or MDI or PDI <70 on Bayleys assessment scale, or inability to assign a score due to cerebral palsy or severity of cognitive delay; measured at the oldest age reported unless there is substantially more data available at a younger age) **Important** Population: adults, children and infants • 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 • CSF sterilisation (defined as treatment failure, time-to-sterilisation or delay) Population: adults • Intracranial collections as a complication (defined as abscess or empyema) Population: children and infants • Functional impairment (measured by any validated scale at any time point) *For infants and children below school-age, cognitive and behavioural deficits will be assessed at school-age.

CSF: cerebrospinal fluid; MDI: mental development index; PDI: psychomotor development index; SD: standard deviation

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

One prospective cohort study was included for this review (Tauzin 2019).

The included study is summarised in Table 2.

The study (Tauzin 2019) compared third-generation cephalosporins (3GC alone) to third-generation cephalosporins with adjunct ciprofloxacin (3GC plus ciprofloxacin) in babies.

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.

Summary of included studies

Summary of the study that was included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Intervention	Comparison	Outcomes	Comments
Tauzin 2019 Prospective cohort study France	N=367 Babies aged <12 months, with a confirmed diagnosis of meningitis caused by E. coli Age in days (median): 15 (range, 1 - 318) Case-fatality: 10.4%	3GC alone group (n=166) Dose, route of administration, frequency and duration were not reported	3GC plus Ciprofloxacin group (n=201) IV Ciprofloxacin was given in 2 or 3 divided doses daily (Median 30 mg/kg per day; range, 10-60 mg/kg per day). Median duration of treatment was 6 days (range, 2-95 days)	• All-cause mortality • Any short-term neurological complication • CSF sterilisation failure	Population is indirect as it includes neonates (>50% of all participants) Any short-term neurological complication outcome is indirect as long-term neurological impairment is of interest for this review

3GC: third-generation cephalosporins; E. coli: Escherichia coli; IV: intravenous.

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no 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 insufficient information about the route of administration, dose, frequency, and duration of third-generation cephalosporin treatment, and the use of subjective measurement of outcome for short-term neurological impairment), inclusion of indirect populations and outcomes, and seriously imprecise findings.

No important difference in mortality or cerebrospinal fluid (CSF) sterilisation were shown between third-generation cephalosporin treatment with or without ciprofloxacin in the evidence reviewed, although the addition of ciprofloxacin was associated with a higher rate of short-term neurological complications.

No eligible studies were identified that reported on long-term neurological impairment, severe developmental delay, hearing impairment, functional impairment, or serious intervention-related adverse effects.

There was also no evidence available for the effectiveness of other antibiotic agents, dose, duration of antibiotic administration or length of infusion.

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.

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 due to the severity of these outcomes. Severe developmental delay was prioritised over functional impairment in children and babies, as it is a more relevant and important outcome for this population. Functional impairment was prioritised as a critical outcome in adults due to concern about the potential long-term limitations of bacterial meningitis on the ability to carry out certain activities of daily life.

In addition to functional impairment (in children and babies), hearing impairment, serious intervention-related adverse effects, and cerebrospinal fluid (CSF) sterilisation were selected as important outcomes in all age groups as these are relatively common after bacterial meningitis and may be related to antibiotic therapy. Intracranial collections as a complication was also included as an important outcome for adults as this is a rare but severe and life threatening complication of bacterial meningitis that may require prolonged antibiotic treatment.

The quality of the evidence

The quality of the evidence for outcomes was assessed with GRADE and was rated as very low. The evidence was downgraded for risk of bias (arising from insufficient information about the route of administration, dose, frequency, and duration of third-generation cephalosporin treatment, and the use of subjective measurement of outcome for short-term neurological impairment), imprecision (due to wide confidence intervals and small number of events) and indirectness of population (≥50% neonates) with or without indirectness of outcome (short-term instead of long-term neurological impairment).

No evidence was found for long-term neurological impairment, severe developmental delay, hearing impairment, functional impairment, or serious intervention-related adverse effects.

Benefits and harms

The committee considered the evidence comparing third-generation cephalosporin treatment with or without ciprofloxacin for the treatment of meningitis caused by Gram-negative bacilli, that showed no important difference for mortality or cerebrospinal fluid (CSF) sterilisation, but a higher rate of short-term neurological complications associated with the addition of ciprofloxacin. However, the committee noted that this evidence was very low quality. No

other evidence was identified comparing the effectiveness of different antibiotics for the treatment of meningitis caused by Gram-negative bacilli. Given the limitations of the evidence, the committee agreed to make recommendations based on their clinical knowledge and experience, and on current practice, and recommended ceftriaxone in line with the BNF (Joint Formulary Committee 2022) and BNFC (Paediatric Formulary Committee 2022), for the treatment of meningitis caused Gram-negative bacilli.

The committee highlighted the potential practical and resource-use advantages associated with ceftriaxone because 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 agreed that ceftriaxone should be given as first-line treatment for meningitis caused by Gram-negative bacilli, unless contraindicated in which case cefotaxime can be considered. The committee highlighted contraindications around pre-term babies less than 41 weeks corrected gestational age and included a reference to these in the BNFC in the recommendation in order to raise awareness.

The committee acknowledged that the clinical course of meningitis caused by Gram-negative bacilli can be complicated, particularly due to the ages of those likely to be affected, and the committee recommended that the treating clinician should consult an infection specialist (a microbiologist or infectious diseases specialist). The committee recommended that antibiotic treatment should continue for at least 21 days. This is in line with the cephalosporin treatment duration recommended in the previous NICE guideline on bacterial meningitis (NICE 2010). The committee noted that although treatment duration for at least 21 days is consistent with current practice, the evidence for this is minimal and it may well reflect a principle of providing 14 days of effective antibiotic therapy after sterilisation of CSF, and the historic use of antibiotics such as chloramphenicol that were associated with delayed sterilisation. Third generation cephalosporins are associated with more rapid sterilisation and may therefore allow a shorter duration of therapy. The committee agreed that research on the effectiveness of shorter duration courses of antibiotics (relative to standard duration courses) for the treatment of bacterial meningitis caused by Gram-negative bacilli was important and included this as a research recommendation (see Appendix K).

There was no evidence found on antibiotic use for meningitis caused by Gram-negative bacilli in people with a penicillin allergy, but the committee agreed it was important to make a recommendation for this population. Based on their clinical knowledge and experience, the committee agreed that cephalosporin-induced anaphylaxis is rare, and the risk-benefit balance of a cephalosporin (relative to chloramphenicol as an alternative) is favourable in most 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 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 a cephalosporin 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 or cefotaxime will be needed. The committee discussed that chloramphenicol is commonly used in the case of severe beta-lactam allergy. Further, 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. Based on clinical knowledge and experience, the committee recommended chloramphenicol for people with Gram-negative bacilli meningitis and anaphylactic or severe penicillin allergy.

The committee were aware that the previous NICE guideline on bacterial meningitis (NICE 2010) recommended to treat people who have travelled outside the UK with vancomycin (in addition to the cephalosporin). However, they discussed that practice has changed since the previous NICE guideline. 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 to support recommending them. Therefore, the committee recommended that, clinicians should seek advice from an infection specialist if cephalosporin resistance is suspected in people who have recently travelled abroad.

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 committee considered that in the absence of evidence it would be cost-effective to recommend ceftriaxone instead of cefotaxime in people with meningitis caused by Gram-negative bacilli. This is because ceftriaxone can be administered once daily making it more practical and less resource intensive. The committee believed that this change from previous NICE guidance (NICE 2010) could result in some small cost savings for the NHS although the population affected would be small.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.6.4, 1.6.13 and 1.6.16 and the research recommendation on duration of antibiotic treatment for meningitis caused by gram-negative bacteria. Other evidence supporting the recommendations 1.6.4 and 1.6.16 can be found in evidence reviews on antibiotic regimens for bacterial meningitis before or in the absence of identifying causative infecting organism (see evidence reviews D1 to D3) and for specific causative organisms (see evidence reviews E1 to E3, E5 and E6).

References – included studies

Effectiveness

Tauzin 2019

Tauzin, M., Ouldali, N., Levy, C. et al., Combination therapy with ciprofloxacin and third-generation cephalosporin versus third-generation cephalosporin monotherapy in Escherichia coli meningitis in infants: a multicentre propensity score-matched observational study. Clinical Microbiology and Infection 25(8), 1006-1012, 2019

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

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

Paediatric Formulary Committee 2022

Paediatric Formulary Committee. BNF for Children (online). London: BMJ Group, Pharmaceutical Press, and RCPCH Publications. Available at: http://www.medicinescomplete.com [Accessed 29/03/2022]

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

Appendices

Appendix A Review protocols

Review protocol for review question: What antibiotic treatment regimens are effective in treating bacterial meningitis caused by Gram-negative bacilli?

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42021276578
Review title	Antibiotics for bacterial meningitis caused by Gram-negative bacilli
Review question	What antibiotic treatment regimens are effective in treating bacterial meningitis caused by Gram-negative bacilli?
Objective	This review aims to find out what is the optimal antibiotic treatment regimen in improving outcomes for people with bacterial meningitis caused by Gram-negative bacilli
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 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.

Field	Content
Condition or domain being studied	Bacterial meningitis caused by Gram-negative bacilli
Population	Inclusion: All adults, young people, children and babies (excluding neonates defined as aged 28 days old and younger) with confirmed bacterial meningitis caused by Gram-negative bacilli 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: • Cefotaxime • Ceftriaxone • Ceftazidime • Gentamicin • Amikacin • Meropenem • Aztreonam • Ciprofloxacin • Moxifloxacin • Levofloxacin
Comparator/Reference standard/Confounding factors	**Stage 1 (all antibiotic agents of interest):** • Antibiotic agent A (single or combination)* vs Antibiotic agent B (single or combination)*

Field	Content
	* Gentamycin and amikacin to be used in combination with other antibiotics not monotherapy. **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 adjust for the following covariates, but will not be excluded for this reason: • Co-morbidity • Severity of infection at presentation (including sepsis) 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

Field	Content
	septicaemia in under 16s: recognition, diagnosis and management (CG102)
Primary outcomes (critical outcomes)	**Adults** • 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) **Children and infants** • 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) • Severe developmental delay (defined as score of >2 SD below normal on validated assessment scales, or MDI or PDI <70 on Bayleys assessment scale, or inability to assign a score due to cerebral palsy or severity of cognitive delay; measured at the oldest age reported unless there is substantially more data available at a younger age) *For infants and children below school-age, cognitive and behavioural deficits will be assessed at school-age.
Secondary outcomes (important outcomes)	**Adults** • 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 • CSF sterilisation (defined as treatment failure, time-to-sterilisation or delay). • Intracranial collections as a complication (defined as abscess or empyema)

Field	Content
	Children and infants • Hearing impairment (defined as any level of hearing impairment; measured from discharge up to 1 year after discharge) • Functional impairment (measured by any validated scale at any time point) • Serious intervention-related adverse effects leading to death, disability or prolonged hospitalisation or that are life threatening or otherwise considered medically significant • CSF sterilisation (defined as treatment failure, time to sterilisation or delay)
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 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

Field	Content
	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 I^2 statistic. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through sensitivity 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 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 • CSF sterilization: statistical significance • Intracranial collections: statistical significance • Validated scales: Published MIDs where available; if not GRADE default MIDs • All other outcomes: GRADE default MIDs
Analysis of sub-groups	Evidence will be stratified by: **Stage 1** Age: • Younger Infants, older infants and children: >28 days to <18* years of age • Adults: ≥18* years of age **Stage 2**

Field	Content	
	Age: • Younger Infants: >28 days to ≤3 months of age • Older infants and children: >3 months to <18* years of age • Adults: ≥18* years of age *There is variation in clinical practice regarding the treatment of 16 to 18 year olds. Therefore, we will be guided by cut-offs used in the evidence when determining if 16 to 18 year olds should be treated as adults or children. Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes: Age: • Young and middle aged adults • Older adults* *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. 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

Field	Content		
	☐	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 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		

Field	Content	
	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?RecordID=276578	
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 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; CSF: cerebrospinal fluid; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MDI: mental development index; MEDLINE: Medical Literature Analysis and Retrieval System Online; MID: minimally important difference; NICE: National Institute for Health and Care Excellence; PDI: psychomotor development index; 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; SD: standard deviation

Appendix B Literature search strategies

Literature search strategies for review question: What antibiotic treatment regimens are effective in treating bacterial meningitis caused Gram-negative bacilli?

This was a combined search to cover both this review and D1, D2, D3, E1, E2, E3, 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.

Clinical Search

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 or macrolide* or mandol or maxcef or maxipim* or mefoxin or megacillin or meropen* or miram?cin* or monocid or

#	Searches
	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
85	83 or 84

#	Searches
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 [SR/RCT data]
94	91 not 93 [Non-RCT data]

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
1	MeSH DESCRIPTOR meningitis IN DARE,HTA
2	MeSH DESCRIPTOR meningitis, bacterial IN DARE,HTA

#	Searches
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

1
2

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 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

#	Searches
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
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

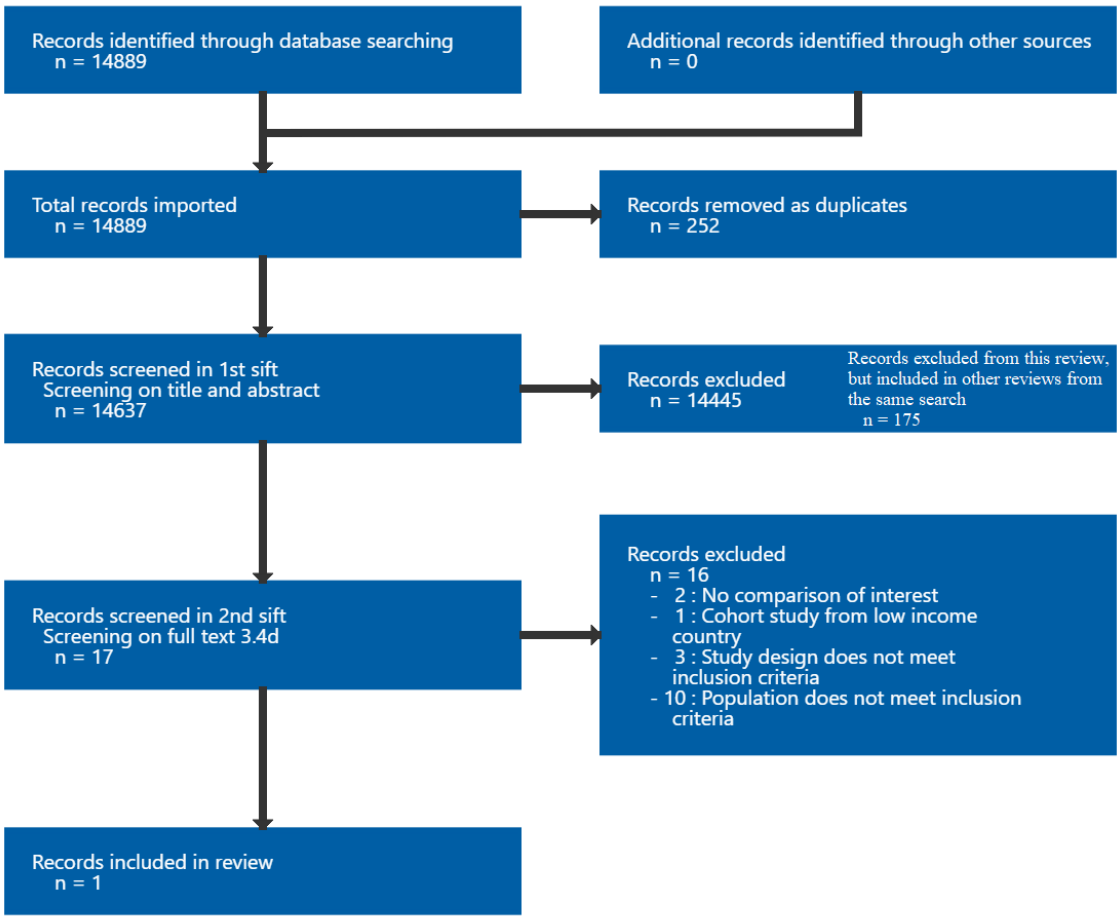
#	Searches
85	randomized controlled trial/ or random*.ti,ab.
86	84 not 85
87	animals/ not humans/
88	exp Animals, Laboratory/
89	exp Animal Experimentation/
90	exp Models, Animal/
91	exp Rodentia/
92	(rat or rats or mouse or mice).ti.
93	86 or 87 or 88 or 89 or 90 or 91 or 92
94	letter.pt. or letter/
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.
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 bacterial meningitis caused by Gram-negative bacilli?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What antibiotic treatment regimens are effective in treating bacterial meningitis caused by Gram-negative bacilli?

Table 4: Evidence tables – effectiveness evidence

Tauzin, 2019

Bibliographic Reference Tauzin, M.; Ouldali, N.; Levy, C.; Bechet, S.; Cohen, R.; Caeymaex, L.; Combination therapy with ciprofloxacin and third-generation cephalosporin versus third-generation cephalosporin monotherapy in Escherichia coli meningitis in infants: a multicentre propensity score-matched observational study; Clinical Microbiology and Infection; 2019; vol. 25 (no. 8); 1006-1012

Study details

Country/ies where study was carried out	France
Study type	Prospective cohort study
Study dates	2001 - 2016
Inclusion criteria	All neonates and babies, aged <12 months of age, with a confirmed diagnosis of meningitis caused by E. coli. Diagnosis was based on at least one of the following: positive CSF culture or PCR result, presence of positive soluble antigens in CSF, and/or positive blood culture associated with pleocytosis (≥30 cells/μL) in CSF.
Exclusion criteria	Patients were excluded if they: were missing data for disease severity at diagnosis, outcome or treatment; did not receive antimicrobial therapy with a 3rd generation cephalosporin (3GC); and were infected with E. coli producing an extended-spectrum β-lactamase.
Patient characteristics	N=367

	n=166 3GC alone group n=201 3GC plus Ciprofloxacin group Median age (days): 15 (range, 1 - 318) Sex (missing data: 9 (2%)): male: 206 (57.5%); female: 152 (42.5%) Initial severity*: non-severe disease: 197 (53.7%); severe disease: 170 (46.3%) * Babies considered having severe form of disease if they were presenting with any of the following symptoms before treatment: seizures, coma, mechanical ventilation, shock and/or extensive purpura; non-severe: none of these signs present at diagnosis.
Intervention(s)/control	3GCs were reported for the whole cohort, not separately for each arm. 3GC received: cefotaxime: 251 (68.4%), ceftriaxone: 38 (10.4%), ceftriaxone: 76 (20.7%) and ceftazidime: 2 (0.5%). 3GC alone: no further information reported 3GC plus Ciprofloxacin: IV Ciprofloxacin was given in two or three divided doses daily (Median 30 mg/kg per day; range, 10-60 mg/kg per day). Median duration of treatment was 6 days (range, 2-95 days). Delay of adjunct ciprofloxacin therapy (missing data: 23 (11.4%)): ≤2 days after lumbar puncture 158 (78.6%) ≥2 days after lumbar puncture 20 (10%)
Duration of follow-up	Not reported

Sources of funding	Industry funding
Sample size	N=367
Other information	An aminoglycoside was prescribed for n=329 (89.6%) babies: 3GC alone group n=152/166 3GC plus Ciprofloxacin group n=177/201 Neurologic complications were assessed by clinician using questionnaire with open-ended questions. Case-fatality: 10.4%

3GC: third-generation cephalosporins; CSF: cerebrospinal fluid; E. coli: Escherichia coli; IV: intravenous; PCR: Polymerase Chain Reaction

Outcomes

3GCs alone vs 3GC plus Ciprofloxacin: All-cause mortality, any short-term neurological complication, CSF sterilisation failure

Outcome	3GC alone, N = 166	3GC plus Ciprofloxacin, N = 201
All-cause mortality (during hospitalisation) **Custom value**	16/166	22/201
Any short-term neurological complication (empyema, hydrocephalus, seizures, strokes, abscesses, arachnoiditis, during hospitalisation) **Custom value**	29/166	57/201
CSF sterilisation failure (during hospitalisation) **Custom value**	15/105	17/150

3GC: third-generation cephalosporins; CSF: cerebrospinal fluid

Critical appraisal – ROBINS-I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(A propensity score was calculated based on the following covariates: gestational age at birth, postnatal age at diagnosis, birth weight, weight at diagnosis, sex, seizures before treatment, coma, mechanical ventilation, shock, CSF/blood glucose ratio <0.1, CSF cell count and CSF protein value. Those receiving 3GC alone were matched 1:1 to those receiving 3GC plus ciprofloxacin using the propensity score)*
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 and for each participant, start of follow up and start of intervention coincided)*
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 defined for 3GCs treatment)*
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 *(Proportions of and reasons for missing outcome data were similar across intervention groups and the analysis addressed missing data and is likely to have removed any risk of bias.)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Serious *(Low (all-cause mortality and CSF sterilization failure): The outcome measure was not influenced by knowledge of the intervention received. Serious (any short-term neurological impairment): The outcome measure was subjective)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of	Low *(There is no indication of selection of the cohort or*

Section	Question	Answer
	the reported result	*subgroups for analysis and reporting on the basis of the results)*
Overall bias	Risk of bias judgement	Serious

3GC: third-generation cephalosporins; CSF: cerebrospinal fluid; ROBINS-I: risk of bias in non-randomised studies – of interventions

Appendix E Forest plots

Forest plots for review question: What antibiotic treatment regimens are effective in treating bacterial meningitis caused by Gram-negative bacilli?

No meta-analysis was conducted for this review question and so there are no forest plots.

Appendix F GRADE tables

GRADE tables for review question: What antibiotic treatment regimens are effective in treating bacterial meningitis caused by Gram-negative bacilli?

Table 5: Evidence profile for comparison: 3GC alone therapy versus 3GC plus ciprofloxacin therapy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3GC alone	3GC plus Ciprofloxacin	Relative (95% CI)	Absolute		
All-cause mortality: neonates and babies (during hospitalisation)												
1 Tauzin, 2019	observational studies	serious[1]	no serious inconsistency	very serious[2]	very serious[3]	none	16/166 (9.6%)	22/201 (10.9%)	RR 0.88 (0.48 to 1.62)	13 fewer per 1000 (from 57 fewer to 68 more)	VERY LOW	CRITICAL
Any short-term neurological complication: neonates and babies (empyema, hydrocephalus, seizures, strokes, abscesses, arachnoiditis, during hospitalisation)												
1 Tauzin, 2019	observational studies	serious[1]	no serious inconsistency	very serious[4]	serious[5]	none	29/166 (17.5%)	57/201 (28.4%)	RR 0.62 (0.41 to 0.92)	108 fewer per 1000 (from 23 fewer to 167 fewer)	VERY LOW	CRITICAL
CSF sterilisation: neonates and babies (during hospitalisation)												
1 Tauzin, 2019	observational studies	serious[1]	no serious inconsistency	very serious[2]	very serious[3]	none	15/105 (14.3%)	17/150 (11.3%)	RR 1.26 (0.66 to 2.41)	29 more per 1000 (from 39 fewer to 160 more)	VERY LOW	IMPORTANT

3GC: third-generation cephalosporins; CI: confidence interval; CSF: cerebrospinal fluid; RR: risk ratio

[1] Serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I

[2] Population is very indirect as it is likely that ≥50% of the population were neonates

[3] <150 events

[4] Outcome is very indirect due to outcome measured short-term complication instead of long-term, and population is very indirect as it is likely that ≥50% of the population were neonates

[5] 95% CI crosses 1 MID

1

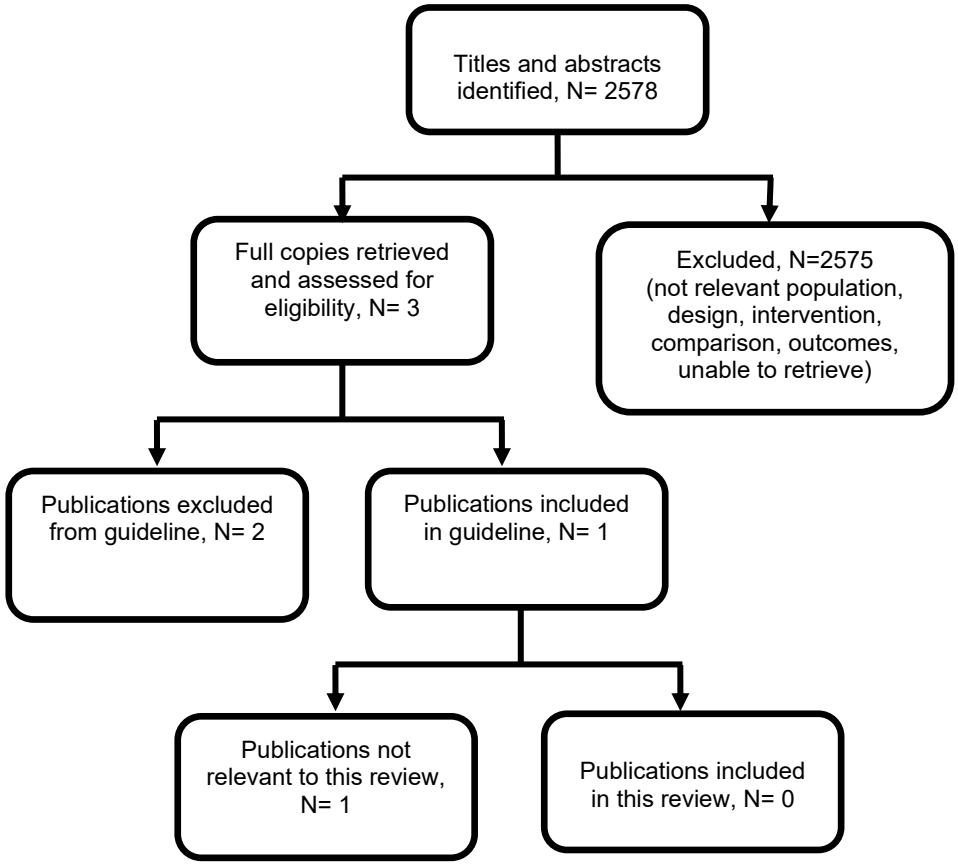
2

Appendix G Economic evidence study selection

Study selection for: What antibiotic treatment regimens are effective in treating bacterial meningitis caused by Gram-negative bacilli?

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 2).

Figure 2: Study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: What antibiotic treatment regimens are effective in treating bacterial meningitis caused by Gram-negative bacilli?

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 bacterial meningitis caused by Gram-negative bacilli?

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 bacterial meningitis caused by Gram-negative bacilli?

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=16) and not studies (N=175) 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 6: Excluded studies and reasons for their exclusion

Study	Code [Reason]
Al-Hasan, Majdi N., Wilson, John W., Lahr, Brian D. et al. (2009) Beta-lactam and fluoroquinolone combination antibiotic therapy for bacteremia caused by gram-negative bacilli. Antimicrobial agents and chemotherapy 53(4): 1386-94	Population does not meet inclusion criteria
Aryee, A., Rockenschaub, P., Gill, M. J. et al. (2020) The relationship between clinical outcomes and empirical antibiotic therapy in patients with community-onset Gram-negative bloodstream infections: a cohort study from a large teaching hospital. Epidemiology and infection 148: e225	Population does not meet inclusion criteria
Isani, Z., Rehman, N., Adil, N. et al. (1987) Aztreonam in the treatment of gram-negative meningitis in children. Chemioterapia : international journal of the Mediterranean Society of Chemotherapy 6(2suppl): 428-430	Cohort study from low income country
Kato, T., Ono, E., Hiroshima, Y. et al. (2020) Comparison of the efficacy of cefmetazole and meropenem for patients with extended-spectrum beta-lactamase-producing Escherichia coli bacteremia: A single-center experience. International Medicine 2(1): 1-6	Population does not meet inclusion criteria
Lagast, H.; Klastersky, J.; Kains, J. P. (1986) Empiric antimicrobial therapy with aztreonam or ceftazidime in gram-negative septicemia. American Journal of Medicine 80(5c): 79-84	Population does not meet inclusion criteria
Le Fevre, Lucie and Timsit, Jean-Francois (2020) Duration of antimicrobial therapy for Gram-negative infections. Current opinion in infectious diseases 33(6): 511-516	Study design does not meet inclusion criteria
Li, Yuming, Hu, Dakang, Ma, Xiaobo et al. (2021) Convergence of carbapenem resistance and hypervirulence leads to high mortality in patients with postoperative Klebsiella pneumoniae meningitis. Journal of global antimicrobial	Study design does not meet inclusion criteria

Study	Code [Reason]
resistance 27: 95-100	
Rodriguez, W. J., Khan, W. N., Gold, B. et al. (1985) Ceftazidime in the treatment of meningitis in infants and children over one month of age. American journal of medicine 79(2a): 52-55	No comparison of interest
Rodriguez, W. J., Puig, J. R., Khan, W. N. et al. (1986) Ceftazidime vs. standard therapy for pediatric meningitis: therapeutic, pharmacologic and epidemiologic observations. Pediatric infectious disease 5(4): 408-15	No comparison of interest
Roine, I., Ledermann, W., Foncea, L. M. et al. (2000) Randomized trial of four vs. seven days of ceftriaxone treatment for bacterial meningitis in children with rapid initial recovery. Pediatric infectious disease journal 19(3): 219-222	Population does not meet inclusion criteria
Ruiz-Ruigomez, Maria and Aguado, Jose Maria (2021) Duration of antibiotic therapy in central venous catheter-related bloodstream infection due to Gram-negative bacilli. Current opinion in infectious diseases 34(6): 681-685	Study design does not meet inclusion criteria
Ruiz-Ruigomez, Maria, Fernandez-Ruiz, Mario, San-Juan, Rafael et al. (2020) Impact of duration of antibiotic therapy in central venous catheter-related bloodstream infection due to Gram-negative bacilli. The Journal of antimicrobial chemotherapy 75(10): 3049-3055	Population does not meet inclusion criteria
Safdar, N.; Handelsman, J.; Maki, D. G. (2004) Does combination antimicrobial therapy reduce mortality in Gram-negative bacteraemia? A meta-analysis. Lancet Infectious Diseases 4(8): 519-527	Population does not meet inclusion criteria
Scheetz, Marc H., Bolon, Maureen K., Esterly, John S. et al. (2011) Life-years gained with meropenem over ciprofloxacin in penicillin-allergic patients with gram-negative bacilli sepsis: results of a probabilistic model. Pharmacotherapy 31(5): 469-79	Population does not meet inclusion criteria
Shabaan, A. E., Nour, I., Elsayed Eldegla, H. et al. (2017) Conventional Versus Prolonged Infusion of Meropenem in Neonates With Gram-negative Late-onset Sepsis: a Randomized Controlled Trial. Pediatric infectious disease journal 36(4): 358-363	Population does not meet inclusion criteria
Sousa, Adrian, Perez-Rodriguez, Maria Teresa, Suarez, Milagros et al. (2019) Short- versus long-course therapy in gram-negative bacilli bloodstream infections. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology 38(5): 851-857	Population does not meet inclusion criteria

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 bacterial meningitis caused by Gram-negative bacilli?

Research question

What is the effectiveness of shorter courses of antibiotics (compared with standard duration courses) for treating bacterial meningitis caused by gram-negative bacilli, particularly in newborn babies?

Why this is important

The duration of antibiotic treatment for bacterial meningitis due to Gram negative bacilli is traditionally at least 21 days. The evidence for this is minimal and may well reflect a principle of providing 14 days of effective antibiotic therapy after sterilisation of cerebrospinal fluid (CSF), and the historic use of antibiotics such as chloramphenicol that were associated with delayed sterilisation. Third generation cephalosporins are associated with more rapid sterilisation and may therefore allow a shorter duration of therapy. The benefit for patients of a shorter duration of antibiotic therapy would include a shorter duration of hospitalisation and potentially fewer drug-related and line-related complications. No RCTs have evaluated the optimal duration of antibiotic regimens for the treatment of meningitis caused by Gram-negative bacilli.

Table 3: Research recommendation rationale

Research question	**What is the effectiveness of shorter courses of antibiotics (compared with standard duration courses) for treating bacterial meningitis caused by gram-negative bacilli, particularly in newborn babies?**
Why is this needed	
Importance to 'patients' or the population	Shorter duration of antibiotic therapy may allow earlier discharge from hospital and fewer complications associated with antibiotic therapy.
Relevance to NICE guidance	No RCTs were found that evaluated the optimal duration of antibiotic regimens for the treatment of meningitis caused by Gram-negative bacilli
Relevance to the NHS	Appropriate use of NHS resources
National priorities	Antimicrobial stewardship
Current evidence base	No RCTs of different antibiotic durations are available
Equality	Bacterial meningitis is more common in certain ethnic groups and in families of lower socioeconomic background
Feasibility	Given that third generation cephalosporins are associated with more rapid CSF sterilisation, a shorter duration of antibiotic treatment was considered to be feasible
Other comments	None

RCT: randomised controlled trial

Table 4: Research recommendation modified PICO table

Criterion	Explanation
Population	People with meningitis caused by Gram-negative bacilli, particularly neonates
Intervention	Short duration course of third generation cephalosporins
Comparator	Standard duration course of third generation cephalosporins
Outcomes	Mortality, length of hospital stay, relapse, neurodevelopmental sequelae
Study design	RCT (non-inferiority)
Timeframe	12-month post-intervention follow-up
Additional information	None

RCT: randomised controlled trial