National Institute for Health and Care Excellence

Draft for consultation

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

[D2] Evidence review for antibiotics for bacterial meningitis before or in the absence of identifying causative infecting organism in older infants and children

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 older infants and children

Review question

What antibiotic treatment regimens are effective in treating suspected bacterial meningitis in older infants and children 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. In older infants and children, the commonest causes of bacterial meningitis are Streptococcus pneumoniae and Neisseria meningitidis.

The aim of this review is to establish appropriate empirical antibiotic treatment regimen(s) that are effective in treating suspected bacterial meningitis in older infants and children, 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	Older infants and children (>3 months to <18 years* of age) 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 • 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) • 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** • 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) • 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 *For infants and children below school-age, cognitive and behavioural deficits will be assessed at school-age.

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

For stage 1 of this review, all antibiotic agents of interest (see summary of the protocol in Table 1), 1 Cochrane systematic review (SR: Prasad 2007) was included, and 3 additional randomised controlled trials (RCTs; Klugman 1995, Odio 1999, Scholz 1998). The Cochrane SR included data from 19 RCTs. Three RCTs (Filali 1993; Girgis 1987; Narciso 1983) in the Cochrane SR were conducted in adults and were not included here but were included in the evidence review (D3) on antibiotics for bacterial meningitis before or in the absence of identifying causative infecting organism in adults. One RCT (Rodriguz 1985) included in the Cochrane SR was excluded from this review as it did not compare an antibiotic treatment regimen of interest. One 4-armed RCT (Peltola 1989) was included in the Cochrane SR; however, data was extracted from the original paper as not all data of interest for the evidence review was included in the Cochrane SR. The additional RCTs (Klugman 1995, Odio 1999, Scholz 1998) were not included in the Cochrane SR as the intervention or comparison were not relevant to that review but are within protocol here.

Two RCTs compared cefotaxime or ceftriaxone to ampicillin or benzylpenicillin sodium (2 RCTs included in Prasad 2007), 12 RCTs compared cefotaxime or ceftriaxone to ampicillin or benzylpenicillin sodium plus chloramphenicol (12 RCTs included in Prasad 2007), and 2

RCTs compared cefotaxime or ceftriaxone to chloramphenicol (2 RCTs included in Prasad 2007). Two RCTs compared cefotaxime to ceftriaxone (Peltola 1989, Scholz 1998), and 2 RCTs compared meropenem to cefotaxime (Klugman 1995, Odio 1999).

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), 3 RCTs (Kavaliotis 1989, Lin 1985, Singhi 2002) and 1 quasi-RCT (Roine 2000) were included.

Three RCTs and 1 quasi-RCT compared short course ceftriaxone therapy to long ceftriaxone course therapy (Kavaliotis 1989, Lin 1985, Roine 2000, Singhi 2002). One quasi-RCT compared 4-day ceftriaxone therapy to 7-day ceftriaxone therapy (Roine 2000). Two RCTs compared 7-day ceftriaxone therapy to 10-day ceftriaxone therapy (Lin 1985, Singhi 2002). One RCT compared 4, 6 or 7-day ceftriaxone therapy to 8, 12, or 14-day therapy (Kavaliotis 1989).

The included studies are summarised in Table 2.

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

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

Table 2: Summary of included studies.

Study	Population	Comparison	Outcomes	Comments
Kavaliotis 1989 RCT Greece	N=52 All cases of bacterial meningitis beyond the neonatal period Age in months (mean; SD): 30 (27) Case-fatality: 0%	<u>Short course vs standard length ceftriaxone (IV)</u> Short course therapy treatment durations of 4, 6 and 7 days for Neisseria meningitidis, Hemophilus influenzae and Streptococcus pneumoniae meningitis, respectively. Standard length therapy treatment durations of 8, 12 and 14 days (twice as long for each microorganism). All patients received ceftriaxone intravenously in an initial loading dose of 100 mg/kg (maximum 4.0 g). The prerequisites for continuation of treatment were a negative CSF culture after 24 h and a high susceptibility of the isolated pathogen to ceftriaxone. In this case the patients received ceftriaxone 60 mg/kg/24 h. If the short-	• All-cause mortality • Any long-term neurological impairment • Hearing impairment	

Study	Population	Comparison	Outcomes	Comments
		course therapy was unsuccessful, the antibiotic was continued for the same length of time again. If the infection persisted after therapy of standard duration, the antibiotic was changed.		
Klugman 1995 RCT Argentina, France, Israel and South Africa	N=190 Children aged 3 months to 14 years with signs and symptoms of bacterial meningitis Age in years (median): Meropenem: 1; Cefotaxime: 1.04 Population treated with steroid therapy: 97% Case-fatality: 1.6%	<u>Meropenem versus cefotaxime</u> Meropenem: 40 mg/kg IV every 8 h for 7-14 days Cefotaxime: 75-100 mg/kg IV every 8 h for 7-14 days	• All-cause mortality • Any long-term neurological impairment • Occurrence of seizures • Hearing impairment	
Lin 1985 RCT USA	N=70 Babies aged ≥1 month with meningitis caused by Streptococcus pneumoniae, H influenzae, or Streptococcus agalactiae (group B streptococcus) were assigned to receive either 7 or 10 days of therapy (n=70). Age in months (median; range): 7-day group: 11 (1.5-28) 10-day group:	<u>Ceftriaxone (IV):</u> <u>7 days vs 10 days</u> After an initial dose of 75 mg/kg of ceftriaxone, 50 mg/kg doses were administered every 12 hours.	• Any long-term neurological impairment • Hearing impairment • Occurrence of seizures	Duration of therapy was assigned after the etiologic agent was identified by the microbiology laboratory. All patients with meningitis caused by Neisseria meningitidis were treated for only seven days because this has been our practice for many years. Those with meningitis caused by Streptococcus pneumoniae, H influenzae, or Streptococcus

Study	Population	Comparison	Outcomes	Comments
	9 (3-56) Case-fatality: not reported			agalactiae (group B streptococcus) were assigned to receive either seven or ten days of therapy, using a computer-generated randomized number list.
Odio 1999 RCT Costa Rica, Dominican Republic and USA	N=154 Children aged 2 months to 2 years with suspected or documented bacterial meningitis Age in months (mean): 25 Population treated with steroid therapy: 100% Case-fatality: 4.5%	Meropenem versus cefotaxime Meropenem: 40 mg/kg IV every 8 h for 7-14 days Cefotaxime: 45 mg/kg IV every 6 h for 7-14 days	• All-cause mortality • Any long-term neurological impairment • Severe developmental delay • Hearing impairment	
Peltola 1989 RCT Finland	N=200 Children aged 3 months to 15 years with bacterial meningitis Age in months (mean; SD): 32 (35) Steroid therapy: Not reported Case-fatality: 4.5%	Cefotaxime or ceftriaxone versus ampicillin Cefotaxime or ceftriaxone (n=101) versus chloramphenicol (n=53) Cefotaxime versus ceftriaxone Cefotaxime: 150 mg/kg/day in 4 divided doses (IV) for 7 days Ceftriaxone: 100 mg/kg once daily (IV) for 7 days Ampicillin: 250 mg/kg/day in 4 divided doses (IV) for 7 days Chloramphenicol: 100 mg/kg/day in 4 divided doses (IV) for 7 days	• All-cause mortality • Hearing impairment	
Prasad 2007	Number of neonates, babies and	Ceftriaxone (IV) versus benzylpenicillin sodium (IV)	• All-cause mortality	n=3 RCTs conducted in adults included

Study	Population	Comparison	Outcomes	Comments
Systematic review	children N=1120 Number of RCTs in neonates, babies and children n=14 (n=13 0-17 years old; n=1 5 months to 28 years old) Countries included in SR n=7 high income n=7 non-high income Case-fatality range: 0%-19.4%	1 RCT (Tuncer 1988) <u>Cefotaxime (IM or IV) or ceftriaxone (IM or IV) versus ampicillin (IM or IV) or benzylpenicillin sodium (IM or IV) plus chloramphenicol (IM or IV or oral)</u> 12 RCTs (Aronoff 1984; Barson 1985; Bryan 1985; Congeni 1984*; Del Rio 1983; Girgis 1988; Haffejee 1988; Jacobs 1985*; Odio 1986; Sharma 1996; Steele 1983; Wells 1984*) <u>Ceftriaxone (IM) versus chloramphenicol (IM)</u> 1 RCT (Nathan 2005) *Neonates received gentamicin instead of chloramphenicol	• Hearing impairment • Serious intervention-related adverse effects - Neutropenia	in the evidence review on antibiotics for bacterial meningitis before or in the absence of identifying causative infecting organism in adults. For Peltola 1989, data was extracted from original paper. Rodriguz 1985 excluded as did not compare antibiotic treatment regimen of interest for review.
Roine, 2000 Quasi-RCT Chile	N=100 Children aged ≥3 months with bacterial meningitis Age in months (mean; SD): 39 (49) Case-fatality: not reported	<u>Ceftriaxone 100 mg/kg (IV): 4 days vs 7 days</u>	• Any long-term neurological impairment • Hearing impairment • Occurrence of seizures	
Scholz 1998 RCT Germany	N=82 Children aged 6 weeks to 16 years with signs and symptoms of bacterial meningitis Age in years (mean): 4 Population treated with	<u>Cefotaxime versus ceftriaxone</u> Cefotaxime: 200 mg/kg/day in 4 divided doses for 4–7 days Ceftriaxone: 100 mg/kg once daily, up to a maximum dose of 4 g/day, on day 1 and 75 mg/kg/day, up to a maximum dose of 3 g/day, from day 2 for 4-7 days	• Any long-term neurological impairment	Route of administration of drug was not described.

Study	Population	Comparison	Outcomes	Comments
	steroid therapy: 67% Case-fatality: Not reported			
Singhi, 2002 RCT India	N=69 Children aged 3 months to 12 years with bacterial meningitis Age in months (mean): 45 Case-fatality: 1.4%	Ceftriaxone (IV): 7 days vs 10 days All children were started on ceftriaxone 100 mg/kg/day in two divided doses and were monitored and evaluated every day for improvement as well as for any complications. Randomisation of children to group I (7 days of therapy) or group II (10 days of therapy) was done on the 7th day.	• All-cause mortality • Any long-term neurological impairment • Hearing impairment • Occurrence of seizures	

IM: intramuscular; IV: intravenous; RCT: randomised controlled trial; SD: standard deviation; 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 moderate to very low quality due to risk of bias (for example, bias arising from the randomisation process due to lack of allocation concealment, subjective measurement of the outcome, selective reporting, missing outcome data, and non-blinding), and imprecision (due to low event rates or small sample size). See the GRADE tables in appendix F for the certainty of the evidence for each individual outcome.

The evidence showed no important differences between third generation cephalosporins (cefotaxime or ceftriaxone) and ampicillin or benzylpenicillin sodium, or compared to ampicillin or benzylpenicillin sodium plus chloramphenicol, on all-cause mortality, hearing impairment, or intervention-related adverse effects.

Across all the comparisons identified in this review, the majority showed no important difference between the interventions compared for the outcomes identified (cefotaxime or ceftriaxone versus ampicillin or benzylpenicillin sodium, cefotaxime or ceftriaxone versus ampicillin or benzylpenicillin sodium plus chloramphenicol, cefotaxime or ceftriaxone versus chloramphenicol, cefotaxime versus ceftriaxone). However, as the findings were seriously or very seriously imprecise, they should not be taken as definitive evidence. A significant difference was found for the meropenem versus cefotaxime comparison, with a lower rate of neurological impairment shown for people receiving cefotaxime. Functional impairment was not reported by any studies.

Four studies analysing the duration of the treatment (Kavaliotis 1989, Lin 1985, Roine 2000, Singhi 2002) showed no important difference between short course therapy and long course therapy in relevant outcomes: all-cause mortality, any long-term neurological impairment, hearing impairment and occurrence of seizures. However, the findings were very seriously imprecise, so they should not be taken as definitive evidence. The studies varied in the duration of short and long course therapies. Roine 2000 compared 4-day to 7-day therapy,

whereas Lin 1985 and Singhi 2002 compared 7-day to 10-day therapy, so the 7-day course was both a short course and long course treatment depending on the comparison. Finally, Kavaliotis 1989 compared 3 different short course durations (4-, 6- and 7-day) to 3 different long course durations (8-, 12- and 14-day). No studies were identified that compared different doses.

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. Severe developmental delay was prioritised as a critical outcome while functional impairment was chosen as an important outcome because severe developmental delay is a more relevant and important outcome in babies and children.

In addition to functional impairment, 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.

The quality of the evidence

The quality of the evidence was assessed using GRADE methodology. Evidence was rated as being moderate to very low quality, and the main reasons evidence was downgraded were risk of bias (bias arising from the randomisation process due to lack of information on allocation concealment, subjective measurement of outcome, selective reporting, missing outcome data due to attrition and non-blinding) and imprecision (wide confidence intervals and small number of events). The evidence for any long-term neurological impairment and severe developmental delay was also downgraded for indirectness (composite outcome).

No evidence was found that reported functional impairment.

Benefits and harms

The committee considered the evidence for antibiotic treatment before or in the absence of identifying a causative organism for older babies and children (aged between 3 months and 18 years) and noted that except for 1 outcome there was no evidence of important differences in the effectiveness of antibiotic treatment regimens. The single important

difference in the evidence reviewed showed a lower rate of neurological impairment for babies and children receiving cefotaxime relative to meropenem. However, this evidence was very low quality. Further, the committee highlighted that none of the included studies were published since the previous NICE guideline on meningitis (NICE 2010). Therefore, the included studies may be outdated due to changes in epidemiology and differences between the dosage of antibiotics used in some of the included studies and those used in current practice. 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 this age group and agreed to recommend intravenous ceftriaxone for suspected bacterial meningitis in older babies and children in line with the British National Formulary for Children (BNFC) (Paediatric Formulary Committee 2022). 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 agreed that ceftriaxone should be given as first-line treatment for suspected bacterial meningitis when the causative organism has not been identified, unless contraindicated in which case cefotaxime can be considered.

The committee highlighted the importance of considering the possibility of a cephalosporin-resistant pneumococcus causing bacterial meningitis. 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 sufficient evidence on the effectiveness and safety of rifampicin or linezolid in suspected (or confirmed) cephalosporin resistant bacterial meningitis. Therefore, the committee recommended that, clinicians should seek advice from an infection specialist (a microbiologist or infectious diseases specialist) if cephalosporin resistance is suspected in older babies and children 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 gram-negative infective organisms tend to be resistant to cephalosporins.

Therefore, the committee agreed that alternative antibiotics may be needed for older babies and children colonised with cephalosporin-resistant gram-negative organisms who develop bacterial meningitis. In the absence of evidence on the effectiveness of antibiotic regimens in this group, the committee recommended that infection specialist advice is sought where cephalosporin resistance is suspected.

There was no evidence found on antibiotic use for suspected bacterial meningitis in older babies and children 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 people 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 parents or guardians. 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 older babies and children with anaphylactic or severe allergic reactions to penicillin , the committee recommended chloramphenicol.

The committee noted that listeria is not susceptible to ceftriaxone or cefotaxime based on their clinical knowledge and experience, and whilst listeria is most common in older adults, risk factors for listeria should also be considered in older babies and children. The committee were aware that amoxicillin is recommended by the BNFC (Paediatric Formulary Committee 2022) for meningitis caused by listeria monocytogenes (in combination with another antibiotic). Therefore, the committee recommended that intravenous amoxicillin should be part of the first line treatment described above for older babies and children with risk factors for listeria.

The committee agreed it was important to make a recommendation about appropriate antibiotic treatment for older babies and children with risk factors for Listeria monocytogenes and a history of penicillin allergy. 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 older babies and children with a penicillin allergy who have risk factors for Listeria monocytogenes.

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 this age group, 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 older babies or children 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 differences in older babies and children for any of the antibiotics compared for most outcomes and therefore the committee reasoned that it would be cost-effective to recommend ceftriaxone, as it is potentially less resource intensive because 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 and updates made to the BNFC since the previous guideline, 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 older baby or child, 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 adults (see evidence reviews D1 and D3) and for specific causative organisms (see evidence reviews E1 to E6).

References – included studies

Effectiveness

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Prasad 2007

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Roine 2000

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

Scholz 1989

Scholz, H., Hofmann, T., Noack, R. et al. (1998). Prospective comparison of ceftriaxone and cefotaxime for the short-term treatment of bacterial meningitis in children. Chemotherapy 44(2): 142-147

Singhi 2002

Singhi, P., Kaushal, M., Singhi, S. et al. (2002). Seven days vs. 10 days ceftriaxone therapy in bacterial meningitis. Journal of tropical pediatrics 48(5): 273-279

Economic

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

Other

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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 older infants and children 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	CRD42021234210
Review title	Antibiotics for bacterial meningitis before or in the absence of identifying causative infecting organism in older infants and children
Review question	What antibiotic treatment regimens are effective in treating suspected bacterial meningitis in older infants and children 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 older infants and children 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	Suspected bacterial meningitis
Population	Inclusion: Older infants and children (>3 months to <18 years* of age) with suspected bacterial meningitis *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 such be treated as adults (and excluded from this question) or children (and included in this question). 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

Field	Content
	• Chloramphenicol • Gentamicin • Meropenem In cases of severe beta-lactam allergy: • Fluoroquinolones (all licensed in the UK)
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 • 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: 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

Field	Content
	• 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) • 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) • 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)

Field	Content
	*For infants and children below school-age, cognitive and behavioural deficits will be assessed at school-age.
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) • 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
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.

Field	Content
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 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*: • >3 months to <16 years

Field	Content			
	• ≥16 years to <18 years *If 16-18 year olds are included within this question Status of infective organism: • Before organism is identified • Absence of identified organism 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		☑	☑

Field	Content		
	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 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:		

Field	Content	
	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=CRD42021234210	
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; 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 suspected bacterial meningitis in older infants and children 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 (D2) and D1, D3, 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.

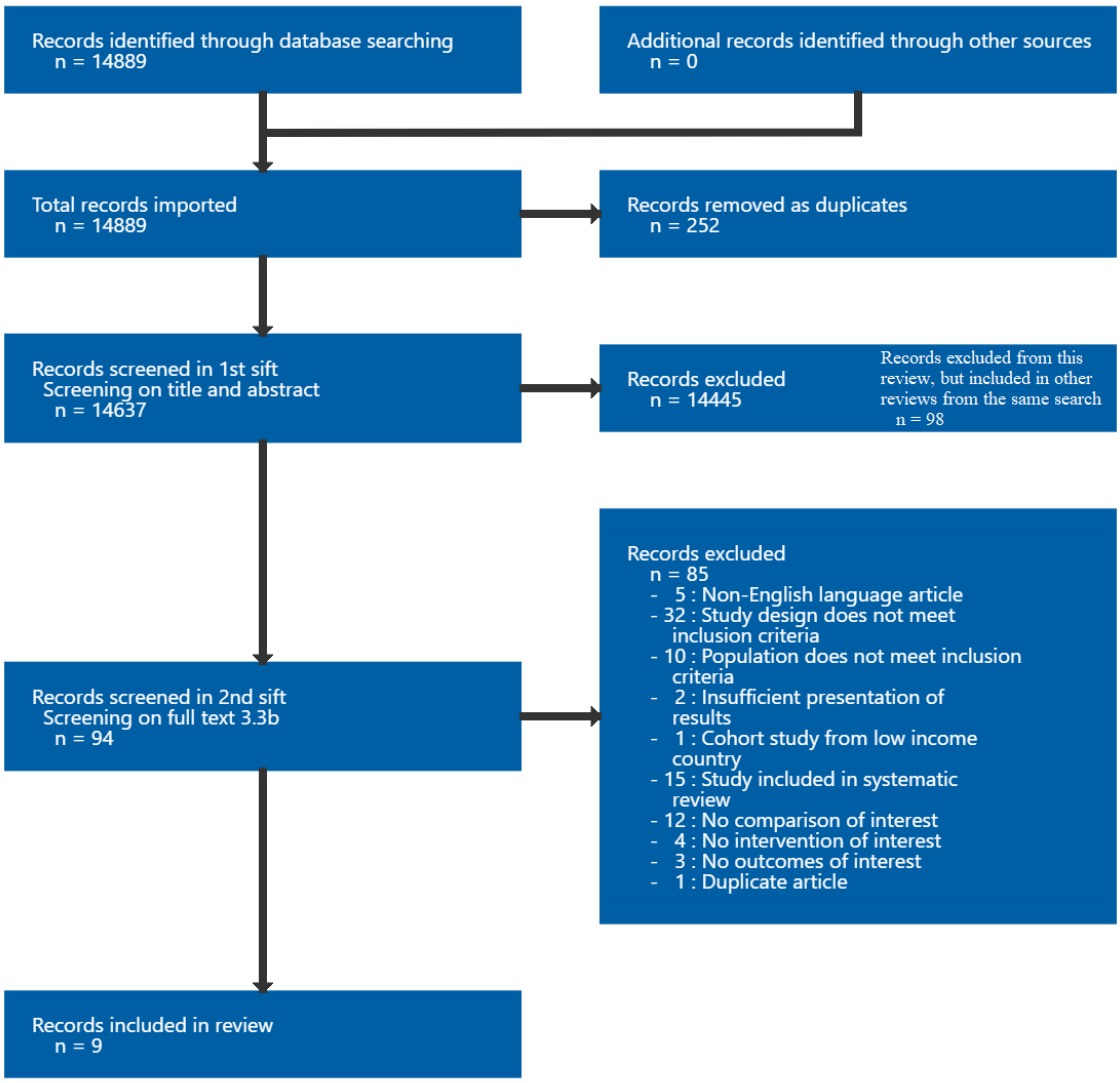
#	Searches
109	101 or 102 or 103 or 104 or 105 or 106 or 107 or 108
110	93 use ppez
111	109 use emczd
112	110 or 111
113	74 not 112
114	limit 113 to English language
115	75 not 112
116	limit 115 to English language
117	114 or 116

1
2
3
4

Appendix C Effectiveness evidence study selection

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

Table 4: Evidence tables – effectiveness evidence

Kavaliotis, 1989

Bibliographic Reference Kavaliotis, J.; Manios, S. G.; Kansouzidou, A.; Danielidis, V.; Treatment of childhood bacterial meningitis with ceftriaxone once daily: open, prospective, randomized, comparative study of short-course versus standard-length therapy; Chemotherapy; 1989; vol. 35 (no. 4); 296-303

Study details

Country/ies where study was carried out	Greece
Study type	Randomised controlled trial (RCT)
Study dates	July 1985 - December 1987
Inclusion criteria	All cases of bacterial meningitis beyond the neonatal period, with a positive CSF and/or blood culture, which were hospitalized.
Exclusion criteria	Patients with known or suspected sensitivity to cephalosporins, with renal or hepatobiliary diseases and patients who received other antibiotics prior to admission.

Patient characteristics	N=52 Age in months (mean ± SD): 30±27 Sex: male: 32 (62%); female: 20 (38%) Etiology: N. meningitidis: 27 (52%); H. influenzae: 21 (40%); S. pneumoniae: 4 (8%)
Intervention(s)/control	Short course ceftriaxone therapy vs standard length ceftriaxone therapy Short course therapy treatment durations of 4, 6 and 7 days for Neisseria meningitidis, Hemophilus influenzae and Streptococeus pneumoniae meningitis, respectively. Standard length therapy treatment durations of 8, 12 and 14 days (twice as long for each microorganism). All patients received ceftriaxone intravenously in an initial loading dose of 100 mg/kg (maximum 4.0 g). The prerequisites for continuation of treatment were a negative CSF culture after 24 h and a high susceptibility of the isolated pathogen to ceftriaxone. In this case the patients received ceftriaxone 60 mg/kg/24 h. If the short-course therapy was unsuccessful, the antibiotic was continued for the same length of time again. If the infection persisted after therapy of standard duration, the antibiotic was changed.
Duration of follow-up	Not reported
Sources of funding	Not reported
Sample size	N=52

Other information	Management without change of treatment schedule Short course therapy n=21/26 Standard length therapy n=25/26 Management with change of treatment schedule Short course therapy n=5/26 (Prolongation of ceftriaxone treatment. Causative pathogens N. meningitidis (3 cases), H. influenzae (2 cases)). Standard length therapy n=1/26 (Ceftriaxone was substituted by ampicillin after 8 days of treatment. Causative pathogen N. meningitidis).

CSF: cerebrospinal fluid; RCT: randomised controlled trial; SD: standard deviation

Outcomes

Short course ceftriaxone therapy vs standard length ceftriaxone therapy

Outcome	**Short course therapy, N = 26**	**Standard length therapy, N = 26**
All-cause mortality No of events	n = 0	n = 0
Any long-term neurological impairment measured at discharge (ataxia) No of events	n = 0	n = 1
Hearing impairment measured at discharge No of events	n = 0	n = 3

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 *(Participants and intervention staff aware of intervention. Appropriate analysis was used. Treatment schedule has been changed for 6 patients: short course therapy n=5/26 and standard length therapy n=1/26.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Participants and intervention staff aware of intervention. No reason to believe deviations arose that could affect outcome.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(Low (all-cause mortality): Measurement did not differ between groups. Knowledge of the assigned intervention could not influence the outcome. High (any long-term neurological impairment, seizures 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	Some concerns *(No information provided on the methods of measuring neurological impairment outcome.)*
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

2 *RoB: risk of bias*

1 **Klugman, 1995**

Bibliographic Reference	Klugman, K. P.; Dagan, R.; Randomized comparison of meropenem with cefotaxime for treatment of bacterial meningitis. Meropenem Meningitis Study Group; Antimicrobial agents and chemotherapy; 1995; vol. 39 (no. 5); 1140-1146

2

3 **Study details**

Country/ies where study was carried out	Argentina, France, Israel, and South Africa
Study type	Randomised controlled trial (RCT)
Study dates	April 1992 - July 1993
Inclusion criteria	Children aged 3 months to 14 years with signs and symptoms of bacterial meningitis
Exclusion criteria	Hypersensitivity reaction to any β-lactam antibiotic, previous episode of meningitis, kidney function impairment, liver function impairment, previous history of abscess, severe illness that survival beyond 48 h was not likely, immunodeficiency, penetrating injury, foreign bodies (including shunts) in the central nervous system, skull fracture, and congenital spine abnormalities
Patient characteristics	N=190 Age (years in median): Meropenem: 1; Cefotaxime: 1.04 Sex: male: 118 (62%); female: 72 (38%) Etiology: Haemophilus influenzae: 66 (35%); Neisseria meningitidis: 50 (26%); Streptococcus pneumoniae: 21 (11%); Escherichia coli: 1 (0.5%); Salmonella species: 1 (0.5%); unknown: 51 (27%)
Intervention(s)/control	Meropenem: Intravenous meropenem (40 mg/kg every 8 h) for 7-14 days. In complicated cases, a longer duration of drug therapy was permitted. Cefotaxime: Intravenous cefotaxime (75-100 mg/kg every 8 h) for 7-14 days. In complicated cases, a longer duration of drug therapy was permitted.

Duration of follow-up	During hospitalisation, 6 weeks and 6 months after discharge.
Sources of funding	Industry funded
Sample size	N=190
Other information	95 patients in meropenem group and 90 patients in cefotaxime group received dexamethasone therapy (mean dose, 0.16 mg/kg)

RCT: randomised controlled trial

Outcomes

Meropenem versus cefotaxime: All-cause mortality, any long-term neurological impairment, seizures and hearing impairment

Outcome	Meropenem, N = 98	Cefotaxime, N = 92
All-cause mortality (up to 6 weeks after discharge) Custom value	1/98	2/92
Any long-term neurological impairment (motor deficit, sensory deficit, cranial nerve palsy, learning disability, cerebral palsy, cerebral infarction, and brain damage; at 6 months after discharge) Custom value	7/98	1/92
Occurrence of seizures (during hospitalisation) Custom value	6/98	3/92
Hearing impairment (at 6 months after discharge) Custom value	2/75	2/64

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 *(Computer generated randomisation and sealed envelopes were used. There is significant difference in baseline characteristic (16 participants in meropenem group had seizures compared with 6 participants in cefotaxime group))*
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)	Low *(No information on blinding. No reason to believe 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.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(Low (all-cause mortality): Measurement did not differ between groups. Knowledge of the assigned intervention could not influence the outcome. High (any long-term neurological impairment, seizures 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
Overall bias and Directness	Overall Directness	Directly applicable *(All-cause mortality, seizures and hearing impairment are directly applicable, but any long-term neurological impairment is indirect outcome as it is a composite outcome including cerebral infarction and brain damage.)*

Section	Question	Answer
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, seizures 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).

RoB: risk of bias

Lin, 1985

Bibliographic Reference	Lin, T. Y.; Chrane, D. F.; Nelson, J. D.; McCracken Jr, G. H.; Seven days of ceftriaxone therapy is as effective as ten days' treatment for bacterial meningitis; Journal of the American Medical Association; 1985; vol. 253 (no. 24); 3559-3563

Study details

Country/ies where study was carried out	USA (Dallas)
Study type	Randomised controlled trial (RCT)
Study dates	February to December 1983
Inclusion criteria	All babies older than 1 month of age and children with suspected or proved bacterial meningitis admitted to Parkland Memorial Hospital or Children's Medical Center.
Exclusion criteria	Patients with a history of allergy to β-lactam antibiotics.

Patient characteristics	N=70 Patients with meningitis caused by Streptococcus pneumoniae, H influenzae, or Streptococcus agalactiae (group B streptococcus) were assigned to receive either 7 or 10 days of therapy (n=70). Age (months in median; range in parentheses): 7-day group: 11 (1.5-28); 10-day group: 9 (3-56) Sex: male: 33 (47%); female: 37 (53%)
Intervention(s)/control	Intravenous Ceftriaxone therapy: 7 days vs 10 days After an initial dose of 75 mg/kg of ceftriaxone, 50mg/kg doses were administered every 12 hours.
Duration of follow-up	6 weeks
Sources of funding	This study was supported in part by a grant from Hoffmann-La Roche, Inc. Dr Christensen supplied the Morganella morgani strain from which the cephalosporinase was derived. Glaxo Laboratories, Inc, provided the nitrocefin.
Sample size	N=70
Other information	Antibiotic treatment before admission: 7-day group n=12 10-day group n=13 Duration of therapy was assigned after the etiologic agent was identified by the microbiology laboratory. All patients with meningitis caused by Neisseria meningitidis were treated for only seven days because this has been our practice for many years. Those with meningitis caused by Streptococcus pneumoniae, H influenzae, or Streptococcus agalactiae (group B streptococcus) were assigned to receive either seven or ten days of therapy, using a computer-generated randomized number list.

RCT: randomised controlled trial

Outcomes

7 days ceftriaxone therapy vs 10 days ceftriaxone therapy

Outcome	7-day group, N = 35	10-day group, N = 35
Any long-term neurological impairment measured 6 weeks after hospital discharge (Ataxia) Custom value	1/35	1/35
Occurrence of seizures during hospitalisation (>48 hr after admission) Custom value	5/35	3/35
Hearing impairment measured 6 weeks after hospital discharge Custom value	8/27	8/25

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 *(Participants and intervention staff aware of intervention. Appropriate analysis was used.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(More than 5% of participants lost-to-follow-up for hearing impairment outcome.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *High (any long-term neurological impairment, seizures and hearing impairment): Measurement did not differ between groups. Knowledge of the assigned intervention was likely to influence outcome assessment.)*

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No information provided on the methods of measuring neurological impairment outcome.)*
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

RoB: risk of bias

Odio, 1999

Bibliographic Reference	Odio, C. M.; Puig, J. R.; Feris, J. M.; Khan, W. N.; Rodriguez, W. J.; McCracken, G. H.; Bradley, J. S.; Prospective, randomized, investigator-blinded study of the efficacy and safety of meropenem vs. cefotaxime therapy in bacterial meningitis in children. Meropenem Meningitis Study Group; Pediatric infectious disease journal; 1999; vol. 18 (no. 7); 581-590

Study details

Country/ies where study was carried out	Costa Rica, Dominican Republic and USA
Study type	Randomised controlled trial (RCT)
Study dates	December 1992 - December 1996
Inclusion criteria	Children aged 2 months to 2 years with suspected or documented bacterial meningitis

Exclusion criteria	Polymicrobial meningitis, meningitis due to cefotaxime-resistant bacteria, history of previous bacterial meningitis and chronic seizure disorder, behavioural deficits, motor deficits, hearing impairment, developmental abnormality, viral hepatitis, HIV infection, cystic fibrosis, acquired or congenital anatomic abnormalities of the central nervous system, liver disease, renal function impairment, neutropenia, any underlying disease that could interfere with the assessment of the efficacy and safety of meropenem and cefotaxime, history of hypersensitivity reaction to any β-lactam antibiotic, and history of investigational drug therapy within 30 days of the study
Patient characteristics	N=154 Age (months in mean): 25 Sex: male: 94 (61%); female: 60 (39%)
Intervention(s)/control	Meropenem: 30-min intravenous infusion of meropenem (40 mg/kg every 8 h) for 7-14 days, but the duration of treatment decided based on the severity, clinical response, and microbiologic response Cefotaxime: 30-min intravenous infusion of cefotaxime (45 mg/kg every 6 h) for 7-14 days, but the duration of treatment decided based on the severity, clinical response, and microbiologic response
Duration of follow-up	During hospitalisation, 5-7 weeks and 5-7 months after discharge
Sources of funding	Industry funded
Sample size	N=154
Other information	Patients received intravenous dexamethasone therapy (0.15 mg/kg every 6 h for 4 days).

RCT: randomised controlled trial

Outcomes

Meropenem versus cefotaxime: All-cause mortality, any long-term neurological impairment, severe developmental delay and hearing impairment

Outcome	**Meropenem, N = 79**	**Cefotaxime, N = 75**

Outcome	Meropenem, N = 79	Cefotaxime, N = 75
All-cause mortality (up to 7 weeks after discharge) Custom value	3/79	4/75
Any long-term neurological impairment (neurological sequelae; at 5-7 months after discharge) Custom value	9/79	4/75
Severe developmental delay (severe developmental or behavioural sequelae that precluded performance of intellectual and physical tasks and assessed using the Bayley Scales, the McCarthy Scales of Children's Abilities or the Slosson Intelligence Test; at 5-7 months after discharge) Custom value	7/79	5/75
Hearing impairment (5-7 months after discharge) Custom value	25/77	20/71

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)	Low *(The investigators were not aware of the assigned intervention. No reason to believe deviations arose because of the trial context. Appropriate analysis was used.)*

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(About 16.2% of participants lost to follow-up at 5-7 weeks, but missingness in the outcome could not depend on its true value.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Measurement did not differ between groups, and outcome assessors were blinded to intervention status.)*
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	Some concerns *(The study is judged to raise some concerns in at least one domain (bias arising from the randomisation process).)*
Overall bias and Directness	Overall Directness	Directly applicable *(All-cause mortality, any long-term neurological impairment and hearing impariment are directly applicable. However, severe developmental delay is indirect outcome as it is a composite outcome including severe behavioural sequelae.)*
Overall bias and Directness	Risk of bias variation across outcomes	None

RoB: risk of bias

Peltola, 1989

Bibliographic Reference	Peltola, H.; Anttila, M.; Renkonen, O. V.; Randomised comparison of chloramphenicol, ampicillin, cefotaxime, and ceftriaxone for childhood bacterial meningitis. Finnish Study Group; Lancet (london, england); 1989; vol. 1 (no. 8650); 1281-1287

1 **Study details**

Country/ies where study was carried out	Finland
Study type	Randomised controlled trial (RCT)
Study dates	1984 - 1985
Inclusion criteria	Children aged 3 months to 15 years with bacterial meningitis
Exclusion criteria	Children who did not receive the scheduled antibiotics and without bacterial meningitis
Patient characteristics	N=200 Age (months in mean; SD in parentheses): 32 (35) Sex: male: 118 (59%); female: 82 (41%) Etiology: Haemophilus influenzae type b: 146 (73%); Neisseria meningitidis: 32 (16%); Streptococcus pneumoniae: 13 (6.5%); other: 2 (1%); unknown: 7 (3.5%)
Intervention(s)/control	Cefotaxime: Intravenous infusion of cefotaxime (150 mg/kg/day in 4 divided doses) for 7 days Ceftriaxone: Intravenous infusion of ceftriaxone (100 mg/kg once daily) for 7 days Ampicillin: Intravenous infusion of ampicillin (250 mg/kg/day in 4 divided doses) for 7 days Chloramphenicol: Intravenous infusion of chloramphenicol (100 mg/kg/day in 4 divided doses) for 7 days
Duration of follow-up	During hospitalisation and at discharge, 2 weeks, 3 months, 6 months and 12 months after discharge
Sources of funding	Not industry funded
Sample size	N=200
Other information	

RCT: randomised controlled trial; SD: standard deviation

Outcomes

Cefotaxime versus ceftriaxone versus ampicillin versus chloramphenicol: All-cause mortality and hearing impairment

Outcome	Cefotaxime, N = 51	Ceftriaxone, N = 50	Ampicillin, N = 46	Chloramphenicol, N = 53
All-cause mortality (during hospitalisation) Custom value	4/51	1/50	1/46	3/53
Hearing impairment (6 months after discharge) Custom value	0/47	4/49	2/45	2/50

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 (all-cause mortality): Measurement did not differ between groups. Knowledge of the assigned intervention could not influence the outcome. High (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 (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
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 (hearing impairment): The study is judged to be at high risk of bias in at least one domain (bias in measurement of the outcome).

RoB: risk of bias

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	Not reported
Sample size	N=1496
Other information	3 studies conducted in adults and 1 study that did not compare the effectiveness of antibiotic treatment regimens of interest were excluded from review. For Peltola 1989, data was extracted from original paper.

1 *RCT: randomised controlled trial*

Outcomes

Ceftriaxone versus benzylpenicillin sodium: All-cause mortality and serious intervention-related adverse effects - neutropenia

Outcome	Cephalosporins, N = 20	Conventional antibiotics, N = 22
All-cause mortality (up to 6 months after discharge) Data from 1 RCT (Tuncer 1988) extracted from analysis 1.1 in SR (Prasad 2007); see Cochrane review https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001832.pub3/full Custom value	1/20	2/22
Serious intervention-related adverse effects - Neutropenia (up to 6 months after discharge) Data from 1 RCT (Tuncer 1988) extracted from analysis 1.5 in SR (Prasad 2007); see Cochrane review https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001832.pub3/full Custom value	0/15	0/13

RCT: randomised controlled trial; SR: systematic review

Cefotaxime or ceftriaxone versus ampicillin or benzylpenicillin sodium plus chloramphenicol: All-cause mortality, hearing impairment and serious intervention-related adverse effects - neutropenia

Outcome	Cephalosporins, N = 285	Conventional antibiotics, N = 290

Outcome	Cephalosporins, N = 285	Conventional antibiotics, N = 290
All-cause mortality (up to 27 months after discharge) Data from 12 RCTs (Aronoff 1984; Barson 1985; Bryan 1985; Congeni 1984; Del Rio 1983; Girgis 1988; Haffejee 1988; Jacobs 1985; Odio 1986; Sharma 1996; Steele 1983; Wells 1984) extracted from analysis 1.1 in SR (Prasad 2007); see Cochrane review https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001832.pub3/full Custom value	18/285	22/290
Hearing impairment (severe deafness; up to 27 months after discharge) Data from 8 RCTs (Aronoff 1984; Barson 1985; Bryan 1985; Del Rio 1983; Haffejee 1988; Jacobs 1985; Steele 1983; Wells 1984) extracted from analysis 1.2 in SR (Prasad 2007); see Cochrane review https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001832.pub3/full Custom value	17/136	26/140
Serious intervention-related adverse effects - Neutropenia (up to 27 months after discharge) Data from 8 RCTs (Aronoff 1984; Barson 1985; Bryan 1985; Congeni 1984; Haffejee 1988; Jacobs 1985; Odio 1986; Steele 1983) extracted from analysis 1.5 in SR (Prasad 2007); see Cochrane review https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001832.pub3/full Custom value	7/173	11/171

RCT: randomised controlled trial; SR: systematic review

Ceftriaxone versus chloramphenicol: All-cause mortality

Outcome	Cephalosporins, N = 247	Conventional antibiotics, N = 256

Outcome	Cephalosporins, N = 247	Conventional antibiotics, N = 256
All-cause mortality (during hospitalisation) Data from 1 RCT (Nathan 2005) 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 = 14	n = 12

RCT: randomised controlled trial; SR: systematic review

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

RoB: risk of bias; ROBIS: risk of bias in systematic reviews; SR: systematic review

Roine, 2000

Bibliographic Reference	Roine, I.; Ledermann, W.; Foncea, L. M.; Banfi, A.; Cohen, J.; Peltola, H.; Randomized trial of four vs. seven days of ceftriaxone treatment for bacterial meningitis in children with rapid initial recovery; Pediatric infectious disease journal; 2000; vol. 19 (no. 3); 219-222

Study details

Country/ies where study was carried out	Chile (Santiago)
Study type	Quasi-randomised controlled trial

Study dates	Due to temporary absence of the main investigator patients were included in the study during two periods: 01/03/1988 - 30/09/1993, and 01/08/1996 - 31/12/1996
Inclusion criteria	All children with bacterial meningitis who were at least 3 months old.
Exclusion criteria	Patients with: previous developmental abnormality (n=26); fatal outcome before day 4 (n=4); unknown etiology of meningitis (n=7, this criterion was valid only in 1988); not fulfilling the criteria for rapid initial recovery during the first 4 days of treatment (n=77).
Patient characteristics	N=100 Age (months in mean; SD in parentheses): 39 (49) Etiology: H. influenzae: 26 (26%); S. pneumonia: 13 (13%); N. meningitidis: 34 (34%); Other: 2 (2%); Unknown: 25 (25%)
Intervention(s)/control	Intravenous Ceftriaxone therapy 100 mg/kg: 4 days (4 injections) vs 7 days
Duration of follow-up	1 to 3 months after discharge
Sources of funding	Financial support during 4 years from the Academy of Finland. Orion Diagnostica donated the reagents and the equipment for CRP analysis and Hoffmann La Roche - ceftriaxone.
Sample size	N=100

Other information	Adjunct 0.15 mg/kg Dexamethasone n=21 (4-day group), n=12 (7-day group) every 6 h for a total of 8 doses; the first dose was administered 5 to 10 min before the first dose of Ceftriaxone. None of the Dexamethasone recipients had neurologic or audiologic sequelae, but the differences between them and the children who had not received dexamethasone did not reach significance (P>0.05).

SD: standard deviation

Outcomes

4 days ceftriaxone therapy vs 7 days ceftriaxone therapy

Outcome	**4-day group, N = 53**	**7-day group, N = 47**
Any long-term neurological impairment measured 1 to 3 months after hospital discharge 4-day group 0/47 7-day group 2/39 (n=1 hemiparesis, n=1 moderate retardation of motor development) Custom value	0/47	2/39
Occurrence of seizures measured 1 to 3 months after hospital discharge Custom value	0/47	1/40
Hearing impairment measured 1 to 3 months after hospital discharge 4-day group 1/38 (moderate unilateral hearing loss (threshold 70 dB)) 7-day group 3/32 (n=2 severe (hearing threshold 100 dB) and n=1 moderate (threshold 60 dB) unilateral hearing loss) Custom value	1/38	3/32

dB: decibel

Critical appraisal – Cochrane RoB 2

Section	**Question**	**Answer**
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(Randomisation process based on dates of birth and no details on allocation concealment.)*

Section	Question	Answer
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)	Low *(Participants and intervention staff were aware of intervention. No reason to believe 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	Some concerns *(Nearly half of the participants were excluded because they did not fulfill criteria for rapid initial recovery during the first 4 days of treatment. More than 5% of participants lost-to-follow-up.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(High (any long-term neurological impairment, seizures 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	Some concerns *(No information provided on the methods of measuring neurological impairment outcome.)*
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

RoB: risk of bias

Scholz, 1998

Bibliographic Reference	Scholz, H.; Hofmann, T.; Noack, R.; Edwards, D. J.; Stoeckel, K.; Prospective comparison of ceftriaxone and cefotaxime for the short-term treatment of bacterial meningitis in children; Chemotherapy; 1998; vol. 44 (no. 2); 142-147

1 **Study details**

Country/ies where study was carried out	Germany
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	Children aged 6 weeks to 16 years with signs and symptoms of bacterial meningitis
Exclusion criteria	Children without bacterial meningitis
Patient characteristics	N=82 Age (years in mean): 4 Sex: male: 38 (46%); female: 44 (64%) Etiology: Neisseria meningitidis: 41 (50%); Streptococcus pneumoniae: 16 (20%); Haemophilus influenzae: 15 (18%); Streptococcus agalactiae: 1 (1%); Unidentified: 9 (11%)
Intervention(s)/control	Cefotaxime: Cefotaxime as four divided doses daily (200 mg/kg/day) for 4–7 days Ceftriaxone: Ceftriaxone as a single daily dose (100 mg/kg/day, up to a maximum dose of 4 g/day, on day 1 and 75 mg/kg/day, up to a maximum dose of 3 g/day, from day 2) for 4-7 days
Duration of follow-up	During hospitalisation and 90 days after discharge
Sources of funding	Not reported
Sample size	N=82
Other information	Route of administration of drug was not described. 23 patients in cefotaxime group and 32 patients in ceftriaxone group received dexamethasone therapy.

2 *RCT: randomised controlled trial*

3

1 **Outcomes**

2 **Cefotaxime versus ceftriaxone: Any long-term neurological impairment**

Outcome	Cefotaxime, N = 38	Ceftriaxone, N = 44
Any long-term neurological impairment (neurological sequelae, primarily hearing impairment; up to 90 days after discharge) No of events	n = 5	n = 2

3

4 **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 *(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)	Low *(Participants and personnel were aware of interventions, but there is no reason to believe 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 all participants.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(Measurement did not differ between groups. Knowledge of the assigned intervention was likely to influence outcome assessment.)*

Section	Question	Answer
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 *(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	Indirectly applicable *(Any long-term neurological impairment is indirect outcome as it is a composite outcome including hearing impairment.)*
Overall bias and Directness	Risk of bias variation across outcomes	None

Singhi, 2002

Bibliographic Reference Singhi, P.; Kaushal, M.; Singhi, S.; Ray, P.; Seven days vs. 10 days ceftriaxone therapy in bacterial meningitis; Journal of tropical pediatrics; 2002; vol. 48 (no. 5); 273-279

Study details

Country/ies where study was carried out	India
Study type	Randomised controlled trial (RCT)
Study dates	July 1998 - October 1999

Inclusion criteria	Children aged between 3 months to 12 years with suspected bacterial meningitis and admitted to Pediatric Emergency, PGIMER. Patients had to fulfil the diagnostic criteria for acute bacterial meningitis: to have clinical signs suggestive of meningitis (fever, headache, altered sensorium and meningeal irritation along with any of the following: CSF culture positive for bacteria, or positive latex agglutination test for N. meningitides, H. influenzae or S pneumoniae (Welcogen, Span Diagnostics, Surat), CSF Gram stain positive and a positive blood culture, or at least two of the following three abnormalities in CSF: total leukocytes >100/mm3 with polymorphonuclear leukocytes >60 per cent, CSF to blood glucose ratio <60 per cent or CSF glucose <40mg/dl, and protein more than 40mg/dl.
Exclusion criteria	Exclusion: children less than 3 months of age, those with prior intravenous antibiotic treatment for more than 48 hours after onset of symptoms, recurrent meningitis and identification of a micro-organism different from the above three.
Patient characteristics	N=69 Age (months in mean): 45 Sex: male: 50 (72%); female: 19 (28%) Etiology: S. pneumoniae or H. influenzae or N. meningitidis: 26 (38%); unknown: 43 (62%)
Intervention(s)/control	Ceftriaxone therapy: 7 days vs 10 days All children were started on ceftriaxone 100 mg/kg/day in two divided doses and were monitored and evaluated every day for improvement as well as for any complications. Randomization of children to group I (7 days of therapy) or group II (10 days of therapy) was done on the 7th day.
Duration of follow-up	1 month
Sources of funding	Not reported
Sample size	N=69

Other information	n=15 in 7-day therapy group and n=10 in 10-day therapy group had received oral antibiotics before coming to the hospital. N=2 Death/Left against medical advice

CSF: cerebrospinal fluid; RCT: randomised controlled trial

Outcomes

7 days ceftriaxone therapy vs 10 days ceftriaxone therapy

Outcome	**7-day therapy, N = 35**	**10-day therapy, N = 34**
All-cause mortality Custom value	1/35	0/34
Any long-term neurological impairment measured at 1 month follow-up 7-day therapy n=8/33 (n=1 Cranial nerve palsy, n=1 Spastic quadriplegia, n=0 Hemiplegia, n=0 Monoplegia, n=1 Hypotonia, n=5 Extra pyramidal symptoms) 10-day therapy n=11/34 (n=1 Cranial nerve palsy, n=0 Spastic quadriplegia, n=1 Hemiplegia, n=1 Monoplegia, n=0 Hypotonia, n=8 Extra pyramidal symptoms) Custom value	8/33	11/34
Occurrence of seizures during hospitalisation Custom value	8/35	8/34
Hearing impairment measured at 1 month follow-up Custom value	6/33	8/34

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(No information about randomisation process was provided. Sealed envelopes were used for allocation sequence concealment. 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)	Low *(Participants and intervention staff were aware of intervention. No reason to believe 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.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(Low (all-cause mortality): Measurement did not differ between groups. Knowledge of the assigned intervention could not influence the outcome. High (any long-term neurological impairment, seizures 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
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

RoB: risk of bias

Appendix E Forest plots

Forest plots for review question: What antibiotic treatment regimens are effective in treating suspected bacterial meningitis in older infants and children 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.

Cefotaxime or ceftriaxone versus ampicillin or benzylpenicillin sodium

Figure 2: All-cause mortality*

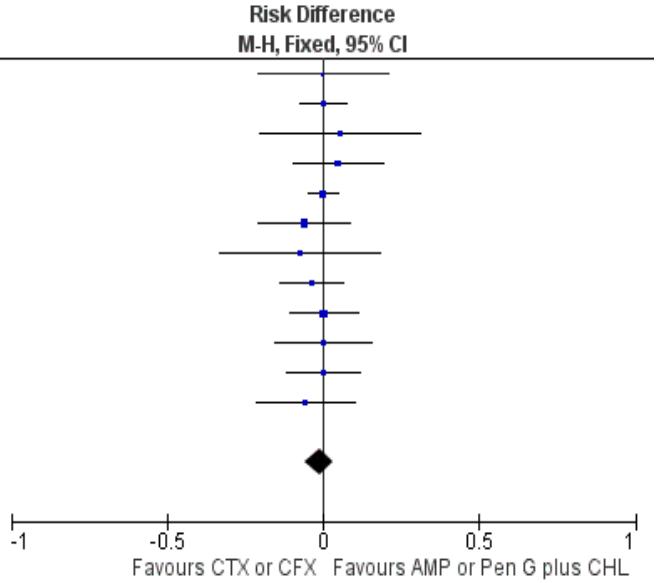
1 RCT (Tuncer 1988) extracted from Cochrane SR (Prasad 2007)
AMP: ampicillin; CTX: cefotaxime; CFX: ceftriaxone; CI: confidence interval; M-H: Mantel-Haenszel; Pen G: benzylpenicillin sodium; SR: systematic review

Cefotaxime or ceftriaxone versus ampicillin or benzylpenicillin sodium plus chloramphenicol

Figure 3: All-cause mortality*

Study or Subgroup	CTX or CFX Events	CTX or CFX Total	AMP or Pen G plus CHL Events	AMP or Pen G plus CHL Total	Weight	Risk Difference M-H, Fixed, 95% CI
Aronoff 1984	0	10	0	7	2.9%	0.00 [-0.21, 0.21]
Barson 1985	0	27	0	23	8.7%	0.00 [-0.08, 0.08]
Bryan 1985	4	18	3	18	6.3%	0.06 [-0.20, 0.31]
Congeni 1984	2	22	1	23	7.9%	0.05 [-0.10, 0.19]
Del Rio 1983	0	39	0	39	13.6%	0.00 [-0.05, 0.05]
Girgis 1988	7	50	10	50	17.5%	-0.06 [-0.21, 0.09]
Haffejee 1988	2	16	3	15	5.4%	-0.08 [-0.33, 0.18]
Jacobs 1985	0	23	1	27	8.7%	-0.04 [-0.14, 0.06]
Odio 1986	3	42	3	43	14.8%	0.00 [-0.11, 0.11]
Sharma 1996	0	11	0	12	4.0%	0.00 [-0.15, 0.15]
Steele 1983	0	15	0	15	5.2%	0.00 [-0.12, 0.12]
Wells 1984	0	12	1	18	5.0%	-0.06 [-0.22, 0.10]
Total (95% CI)		**285**		**290**	**100.0%**	**-0.01 [-0.06, 0.03]**
Total events	18		22			

Heterogeneity: Chi² = 2.58, df = 11 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.59 (P = 0.56)

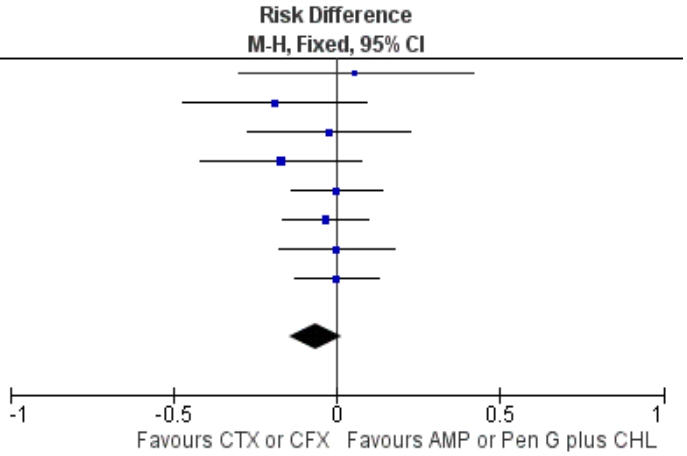


**All RCTs extracted from Cochrane SR (Prasad 2007)*
AMP: ampicillin; CHL: chloramphenicol; CTX: cefotaxime; CFX: ceftriaxone; CI: confidence interval; M-H: Mantel-Haenszel; Pen G: benzylpenicillin sodium; SR: systematic review

Figure 4: Hearing impairment*

Study or Subgroup	CTX or CFX Events	CTX or CFX Total	AMP or Pen G plus CHL Events	AMP or Pen G plus CHL Total	Weight	Risk Difference M-H, Fixed, 95% CI
Aronoff 1984	2	10	1	7	6.0%	0.06 [-0.30, 0.42]
Barson 1985	3	21	5	15	12.8%	-0.19 [-0.47, 0.09]
Bryan 1985	2	14	3	18	11.6%	-0.02 [-0.28, 0.23]
Del Rio 1983	8	27	14	30	20.9%	-0.17 [-0.42, 0.08]
Haffejee 1988	0	14	0	12	9.5%	0.00 [-0.14, 0.14]
Jacobs 1985	1	23	2	26	17.9%	-0.03 [-0.17, 0.10]
Steele 1983	1	15	1	15	11.0%	0.00 [-0.18, 0.18]
Wells 1984	0	12	0	17	10.3%	0.00 [-0.13, 0.13]
Total (95% CI)		**136**		**140**	**100.0%**	**-0.07 [-0.15, 0.02]**
Total events	17		26			

Heterogeneity: Chi² = 4.57, df = 7 (P = 0.71); I² = 0%
Test for overall effect: Z = 1.57 (P = 0.12)

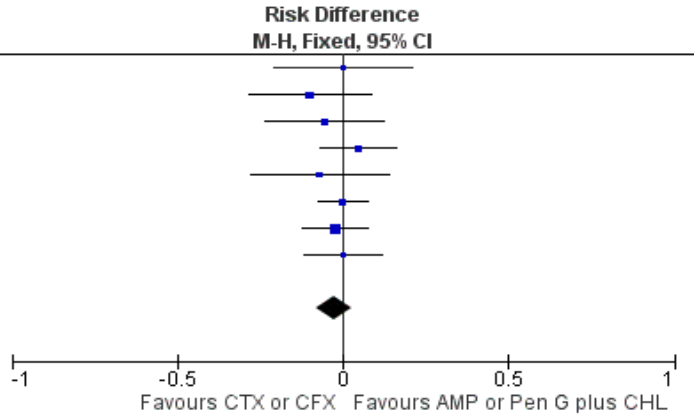


**All RCTs extracted from Cochrane SR (Prasad 2007)*
AMP: ampicillin; CHL: chloramphenicol; CTX: cefotaxime; CFX: ceftriaxone; CI: confidence interval; M-H: Mantel-Haenszel; Pen G: benzylpenicillin sodium; SR: systematic review

Figure 5: Serious intervention-related adverse effects - Neutropenia*

Study or Subgroup	CTX or CFX Events	CTX or CFX Total	AMP or Pen G plus CHL Events	AMP or Pen G plus CHL Total	Weight	Risk Difference M-H, Fixed, 95% CI
Aronoff 1984	0	10	0	7	4.8%	0.00 [-0.21, 0.21]
Barson 1985	2	27	4	23	14.5%	-0.10 [-0.28, 0.08]
Bryan 1985	1	18	2	18	10.5%	-0.06 [-0.24, 0.12]
Congeni 1984	1	22	0	23	13.1%	0.05 [-0.07, 0.16]
Haffejee 1988	1	16	2	15	9.0%	-0.07 [-0.28, 0.14]
Jacobs 1985	0	23	0	27	14.5%	0.00 [-0.08, 0.08]
Odio 1986	2	42	3	43	24.8%	-0.02 [-0.12, 0.08]
Steele 1983	0	15	0	15	8.8%	0.00 [-0.12, 0.12]
Total (95% CI)		**173**		**171**	**100.0%**	**-0.03 [-0.08, 0.03]**
Total events	7		11			

Heterogeneity: Chi² = 3.08, df = 7 (P = 0.88); I² = 0%
Test for overall effect: Z = 1.00 (P = 0.32)



**All RCTs extracted from Cochrane SR (Prasad 2007)*
AMP: ampicillin; CHL: chloramphenicol; CTX: cefotaxime; CFX: ceftriaxone; CI: confidence interval; M-H: Mantel-Haenszel; Pen G: benzylpenicillin sodium; SR: systematic review

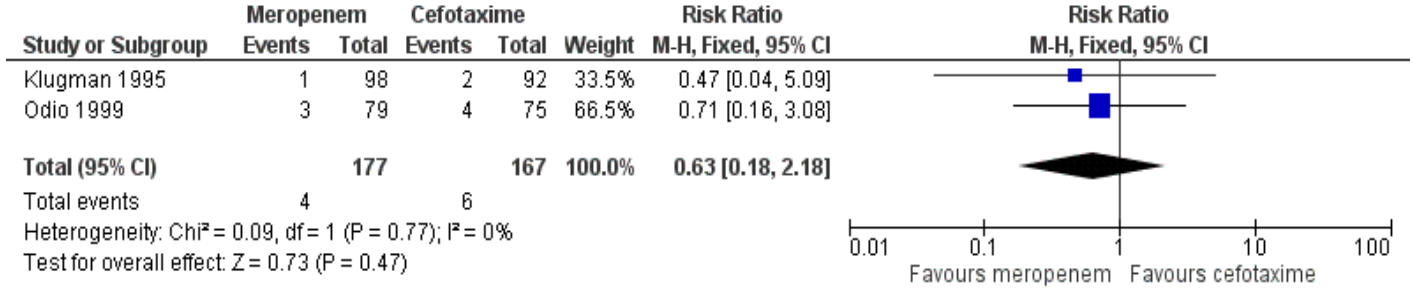
Cefotaxime or ceftriaxone versus chloramphenicol

Figure 6: All-cause mortality*

**1RCT (Nathan 2005) extracted from Cochrane SR (Prasad 2007)*
CHL: chloramphenicol; CTX: cefotaxime; CFX: ceftriaxone; CI: confidence interval; M-H: Mantel-Haenszel; SR: systematic review

Meropenem versus cefotaxime

Figure 7: All-cause mortality



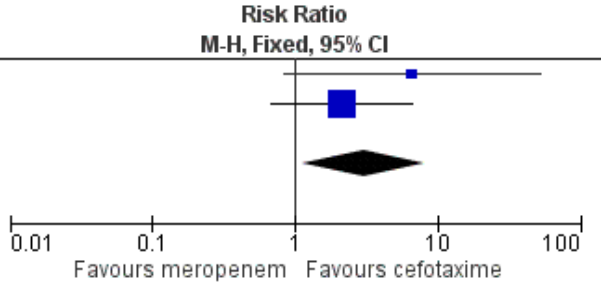
CI: confidence interval; M-H: Mantel-Haenszel

1

Figure 8: Any long-term neurological impairment

Study or Subgroup	Meropenem Events	Meropenem Total	Cefotaxime Events	Cefotaxime Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Klugman 1995	7	98	1	92	20.1%	6.57 [0.82, 52.38]
Odio 1999	9	79	4	75	79.9%	2.14 [0.69, 6.64]
Total (95% CI)		**177**		**167**	**100.0%**	**3.03 [1.14, 8.05]**
Total events	16		5			

Heterogeneity: Chi² = 0.90, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 2.22 (P = 0.03)

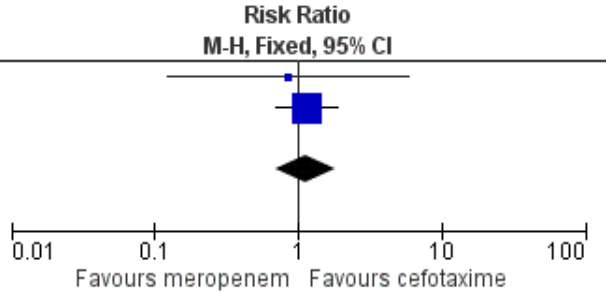


CI: confidence interval; M-H: Mantel-Haenszel

Figure 9: Hearing impairment

Study or Subgroup	Meropenem Events	Meropenem Total	Cefotaxime Events	Cefotaxime Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Klugman 1995	2	75	2	64	9.4%	0.85 [0.12, 5.89]
Odio 1999	25	77	20	71	90.6%	1.15 [0.70, 1.88]
Total (95% CI)		**152**		**135**	**100.0%**	**1.12 [0.70, 1.81]**
Total events	27		22			

Heterogeneity: Chi² = 0.09, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.48 (P = 0.63)

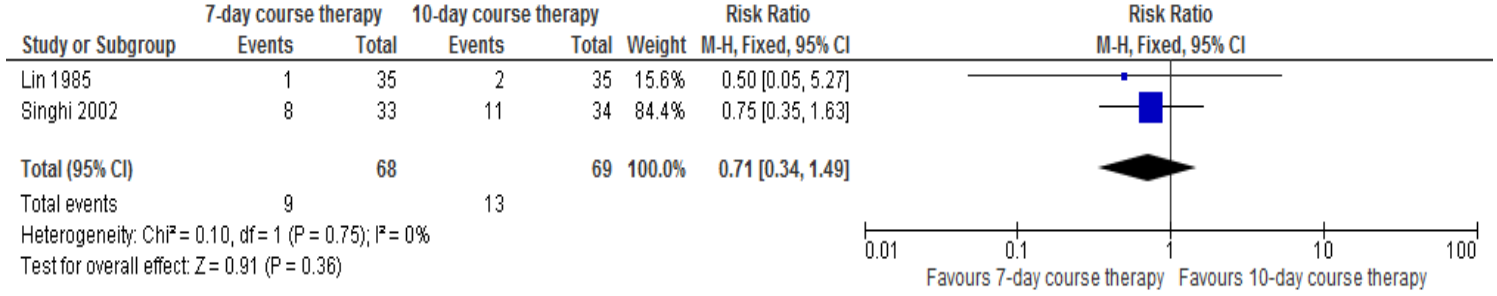


CI: confidence interval; M-H: Mantel-Haenszel

2
3

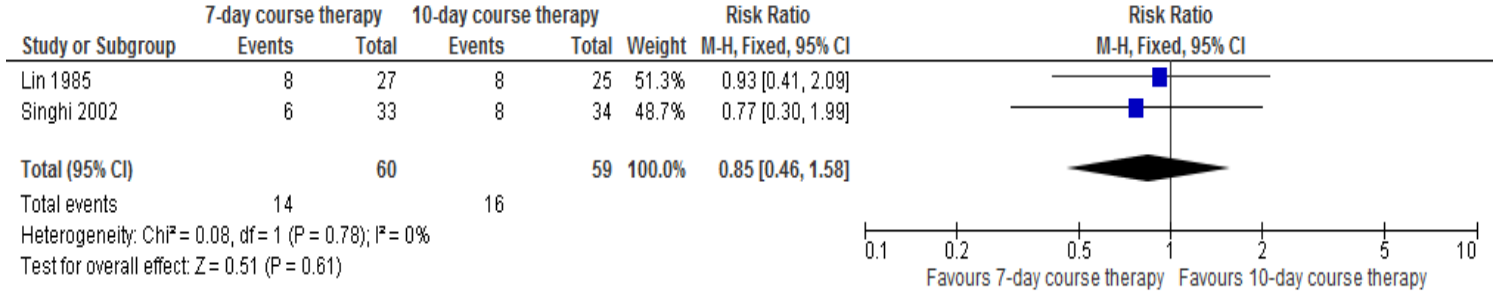
7-day ceftriaxone therapy versus 10-day ceftriaxone therapy

Figure 10: Any long-term neurological impairment



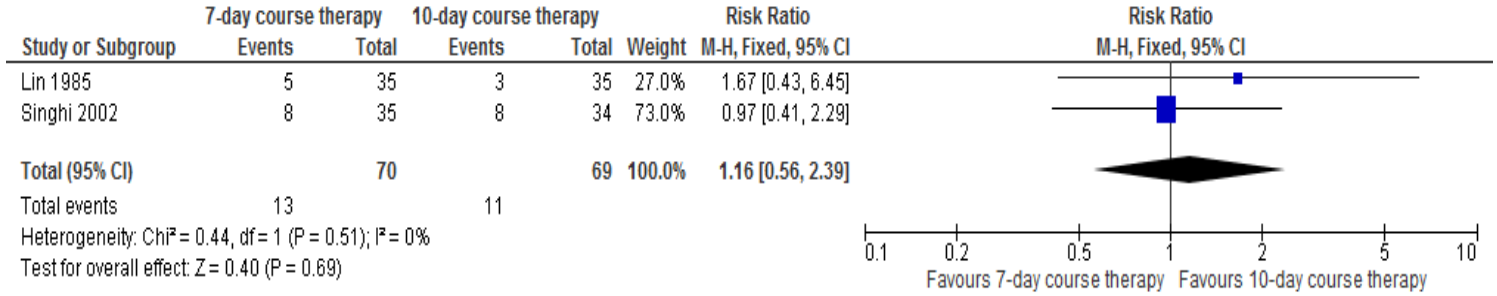
CI: confidence interval; M-H: Mantel-Haenszel

Figure 11: Hearing impairment



CI: confidence interval; M-H: Mantel-Haenszel

Figure 12: Occurrence of seizures



CI: confidence interval; M-H: Mantel-Haenszel

Appendix F GRADE tables

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

Table 5: Evidence profile for comparison: cefotaxime or 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	Cefotaxime or ceftriaxone	Ampicillin or benzylpenicillin sodium	Relative (95% CI)	Absolute		
All-cause mortality												
2*	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/121 (5%)	3/68 (4.4%)	RR 1.27 (0.29 to 5.61)	12 more per 1000 (from 31 fewer to 203 more)	VERY LOW	CRITICAL
Hearing impairment (follow-up 6 months)												
1 (Peltola 1989)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	4/96 (4.2%)	2/45 (4.4%)	RR 0.94 (0.18 to 4.93)	3 fewer per 1000 (from 36 fewer to 175 more)	VERY LOW	IMPORTANT
Serious intervention-related adverse effects - Neutropenia												
1 (Tuncer 1988 extracted from SR Prasad 2007)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	0/15 (0%)	0/13 (0%)	RD 0 (-0.13 to 0.13)	0 fewer per 1000 (from 130 fewer to 130 more)[6]	VERY LOW	IMPORTANT

CI: confidence interval; RD: risk difference; RR: risk ratio; SR: systematic review
**See corresponding forest plot*
[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
[3] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[4] 95% CI crosses 2 MIDs
[5] Sample size <200

[6] *Absolute effect calculated based on risk difference*

Table 6: Evidence profile for comparison: cefotaxime or ceftriaxone versus ampicillin or benzylpenicillin sodium plus chloramphenicol

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cefotaxime or ceftriaxone	Ampicillin or benzylpenicillin sodium plus chloramphenicol	Relative (95% CI)	Absolute		
All-cause mortality												
12*	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/285 (6.3%)	22/290 (7.6%)	RD -0.01 (-0.06 to 0.03)	13 fewer per 1000 (from 60 fewer to 30 more)	MODERATE	CRITICAL
Hearing impairment (follow-up 0-27 months)												
8*	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	17/136 (12.5%)	26/140 (18.6%)	RD -0.07 (-0.15 to 0.02)	65 fewer per 1000 (from 150 fewer to 20 more)	LOW	IMPORTANT
Serious intervention-related adverse effects - Neutropenia												
8*	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	7/173 (4%)	11/171 (6.4%)	RD -0.03 (-0.08 to 0.03)	26 fewer per 1000 (from 80 fewer to 30 more)	LOW	IMPORTANT

CI: confidence interval; RD: risk difference; SR: systematic review
**See corresponding forest plot*
[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] *Sample size <400*

Table 7: Evidence profile for comparison: cefotaxime or ceftriaxone versus chloramphenicol

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cefotaxime or ceftriaxone	Chloramphenicol	Relative (95% CI)	Absolute		

All-cause mortality												
2*	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	19/348 (5.5%)	15/309 (4.9%)	RR 1.13 (0.58 to 2.18)	6 more per 1000 (from 20 fewer to 57 more)	VERY LOW	CRITICAL
Hearing impairment (follow-up 6 months)												
1 (Peltola 1989)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	4/96 (4.2%)	2/50 (4%)	RR 1.04 (0.2 to 5.49)	2 more per 1000 (from 32 fewer to 180 more)	VERY LOW	IMPORTANT

CI: confidence interval; RR: risk ratio; SR: systematic review
**See corresponding forest plot*
[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
[3] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[4] 95% CI crosses 2 MIDs

Table 8: Evidence profile for comparison: cefotaxime versus ceftriaxone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cefotaxime**	**Ceftriaxone**	**Relative (95% CI)**	**Absolute**		
All-cause mortality												
1 (Peltola 1989)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/51 (7.8%)	1/50 (2%)	RR 3.92 (0.45 to 33.88)	58 more per 1000 (from 11 fewer to 658 more)	VERY LOW	CRITICAL
Any long-term neurological impairment (neurological sequelae, primarily hearing impairment) (follow-up 0-90 days)												
1 (Scholz 1998)	randomised trials	very serious[3]	no serious inconsistency	serious[4]	very serious[5]	none	5/38 (13.2%)	2/44 (4.5%)	RR 2.89 (0.6 to 14.07)	86 more per 1000 (from 18 fewer to 594 more)	VERY LOW	CRITICAL
Hearing impairment (follow-up 6 months)												

1 (Peltola 1989)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[5]	none	0/47 (0%)	4/49 (8.2%)	RR 0.12 (0.01 to 2.09)	72 fewer per 1000 (from 81 fewer to 89 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 hearing impairment
[5] 95% CI crosses 2 MIDs

Table 9: Evidence profile for comparison: meropenem versus cefotaxime

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Meropenem**	**Cefotaxime**	**Relative (95% CI)**	**Absolute**		
All-cause mortality												
2*	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/177 (2.3%)	6/167 (3.6%)	RR 0.63 (0.18 to 2.18)	13 fewer per 1000 (from 29 fewer to 42 more)	VERY LOW	CRITICAL
Any long-term neurological impairment (motor deficit, sensory deficit, cranial nerve palsy, learning disability, cerebral palsy, cerebral infarction and brain damage) (follow-up 5-7 months)												
2*	randomised trials	serious[1]	no serious inconsistency	serious[3]	serious[4]	none	16/177 (9%)	5/167 (3%)	RR 3.03 (1.14 to 8.05)	61 more per 1000 (from 4 more to 211 more)	VERY LOW	CRITICAL
Severe developmental delay (severe developmental or behavioural sequelae) (follow-up 5-7 months)												
1 (Odio 1999)	randomised trials	serious[1]	no serious inconsistency	serious[5]	very serious[6]	none	7/79 (8.9%)	5/75 (6.7%)	RR 1.33 (0.44 to 4.01)	22 more per 1000 (from 37 fewer to 201 more)	VERY LOW	CRITICAL
Seizures (during hospitalisation)												
1 (Klugman 1995)	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	very serious[6]	none	6/98 (6.1%)	3/92 (3.3%)	RR 1.88 (0.48 to 7.29)	29 more per 1000 (from 17 fewer to 205 more)	VERY LOW	IMPORTANT

Hearing impairment (follow-up 5-7 months)												
2*	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[6]	none	27/152 (17.8%)	22/135 (16.3%)	RR 1.12 (0.7 to 1.81)	20 more per 1000 (from 49 fewer to 132 more)	VERY LOW	IMPORTANT

CI: confidence interval; RR: risk ratio
**See corresponding forest plot*
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] <150 events
[3] Outcome is indirect as it is a composite outcome including cerebral infarction and brain damage
[4] 95% CI crosses 1 MID
[5] Outcome is indirect as it is a composite outcome including severe behavioural sequelae
[6] 95% CI crosses 2 MIDs
[7] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2

Table 10: Evidence profile for comparison: 4-day ceftriaxone therapy vs 7-day ceftriaxone therapy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**4-day ceftriaxone therapy**	**7-day ceftriaxone therapy**	**Relative (95% CI)**	**Absolute**		
Any long-term neurological impairment measured 1 to 3 months after hospital discharge												
1 (Roine 2000)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/47 (0%)	2/39 (5.1%)	RR 0.17 (0.01 to 3.37)	43 fewer per 1000 (from 51 fewer to 122 more)	VERY LOW	CRITICAL
Occurrence of seizures measured 1 to 3 months after hospital discharge												
1 (Roine 2000)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/47 (0%)	1/40 (2.5%)	RR 0.28 (0.01 to 6.80)	18 fewer per 1000 (from 25 fewer to 145 more)	VERY LOW	IMPORTANT
Hearing impairment measured 1 to 3 months after hospital discharge												
1 (Roine 2000)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/38 (2.6%)	3/32 (9.4%)	RR 0.28 (0.03 to 2.57)	68 fewer per 1000 (from 91 fewer to 147 more)	VERY LOW	IMPORTANT

CI: confidence interval; RR: risk ratio
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 2 MIDs

Table 11: Evidence profile for comparison: 7-day ceftriaxone therapy vs 10-day ceftriaxone therapy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	7-day ceftriaxone therapy	10-day ceftriaxone therapy	Relative (95% CI)	Absolute		
All-cause mortality												
1 (Singhi 2002)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/35 (2.9%)	0/34 (0%)	RR 2.92 (0.12to 69.20)	10 more per 1000 (from 50 more to 100 more)[3]	VERY LOW	CRITICAL
Any long-term neurological impairment measured 1 month after hospital discharge												
2*	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	9/68 (13.2%)	13/69 (18.8%)	RR 0.71 (0.34 to 1.49)	55 fewer per 1000 (from 124 fewer to 92 more)	VERY LOW	CRITICAL
Occurrence of seizures during hospitalisation												
2*	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	13/70 (18.6%)	11/69 (15.9%)	RR 1.16 (0.56 to 2.39)	26 more per 1000 (from 70 fewer to 222 more)	VERY LOW	IMPORTANT
Hearing impairment measured 6 weeks after hospital discharge												
2*	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	14/60 (23.3%)	16/59 (27.1%)	RR 0.85 (0.46 to 1.58)	41 fewer per 1000 (from 146 fewer to 157 more)	VERY LOW	IMPORTANT

CI: confidence interval; RR: risk ratio
*See corresponding forest plot
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] <150 events
[3] Absolute effect calculated based on risk difference
[4] 95% CI crosses 2 MIDs

Table 12: Evidence profile for comparison: 4, 6 or 7-day ceftriaxone therapy vs 8, 12 or 14-day ceftriaxone therapy

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	4, 6 or 7-day ceftriaxone therapy	8, 12 or 14-day ceftriaxone therapy	Relative (95% CI)	Absolute		
All-cause mortality												
1 (Kavaliotis 1989)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/26 (0%)	0/26 (0%)	RD 0.00 (-0.07 to 0.07)	0 fewer per 1000 (from 70 more to 70 more) [3]	VERY LOW	CRITICAL
Any long-term neurological impairment measured at discharge												
1 (Kavaliotis 1989)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/26 (0%)	1/26 (3.8%)	RR 0.33 (0.01 to 7.82)	26 fewer per 1000 (from 38 fewer to 262 more)	VERY LOW	CRITICAL
Hearing impairment measured at discharge												
1 (Kavaliotis 1989)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/26 (0%)	3/26 (11.5%)	RR 0.14 (0.01 to 2.63)	99 fewer per 1000 (from 114 fewer to 188 more)	VERY LOW	IMPORTANT

CI: confidence interval; RR: risk ratio

[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2

[2] Sample size <200

[3] Absolute effect calculated based on risk difference

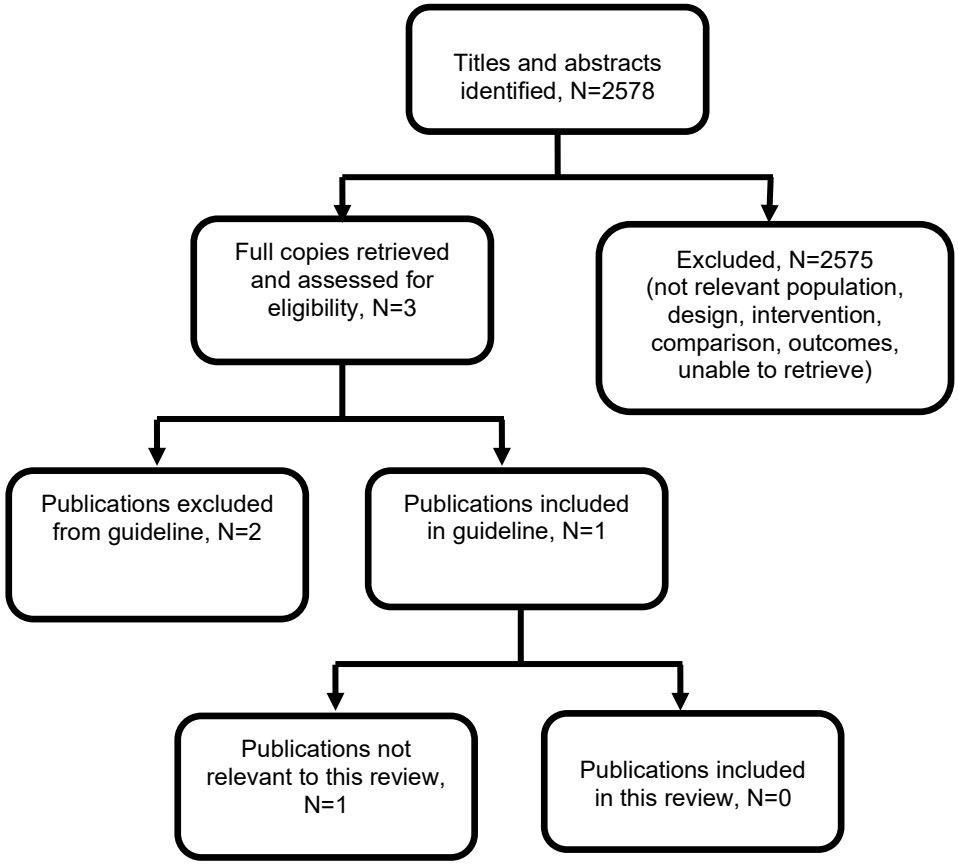
[4] 95% CI crosses 2 MIDs

Appendix G Economic evidence study selection

Study selection for: What antibiotic treatment regimens are effective in treating suspected bacterial meningitis in older infants and children 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 13).

Figure 13: 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 older infants and children 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 older infants and children 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 older infants and children 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=85) and not studies (N=98) 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 13: 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
Adderson, E. E.; Flynn, P. M.; Hoffman, J. M. (2010) Efficacy and safety of cefepime in pediatric patients: A systematic review and meta-analysis. Journal of Pediatrics 157(3): 490	- No intervention of interest for review
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 (1990) Ceftriaxone in the treatment of meningitis, gonococcal infections and other serious bacterial infections. Infectious Diseases and Immunization Committee, Canadian Paediatric Society. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 142(5): 450-2	- Study design does not meet inclusion criteria
Anonymous (1986) Initial antibiotic treatment of bacterial meningitis in children. Infectious Diseases and Immunization Committee, Canadian Paediatric Society. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 135(10): 1085-6	- Study design does not meet inclusion criteria
Anonymous (1997) Therapy for children with invasive pneumococcal infections. American Academy of Pediatrics Committee on Infectious Diseases. Pediatrics 99(2): 289-99	- 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	- Study design does not meet inclusion criteria

Study	Code [Reason]
Pediatrics Committee on Infectious Diseases: Treatment of bacterial meningitis. Pediatrics 81(6): 904-907	
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
Anttila, M., Anttolainen, I., Ellmén, J. et al. (1991) (Antibiotics for bacterial meningitis in children - results of a Finnish multicentre trial). Duodecim; laaketieteellinen aikakauskirja 107: 149-157	- Non-English language article
Anttila, M., Anttolainen, I., Ellmén, J. et al. (1991) Antibiotic treatment of bacterial meningitis in children--results from a Finnish multicenter study. Duodecim; laaketieteellinen aikakauskirja 107(3): 149-157	- Non-English language article
Aronoff, S. C., Reed, M. D., O'Brien, C. A. et al. (1984) Comparison of the efficacy and safety of ceftriaxone to ampicillin/chloramphenicol in the treatment of childhood meningitis. Journal of antimicrobial chemotherapy 13(2): 143-151	- Study included in systematic review – Prasad 2007
Arrieta, A. (1997) Use of meropenem in the treatment of serious infections in children: review of the current literature. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 24suppl2: S207-12	- Study design does not meet inclusion criteria
Barson, W. J., Miller, M. A., Brady, M. T. et al. (1985) Prospective comparative trial of ceftriaxone vs. conventional therapy for treatment of bacterial meningitis in children. Pediatric infectious disease 4(4): 362-368	- Study included in systematic review – Prasad 2007
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	- Non-English language article
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
Bingen, Edouard, Levy, Corinne, de la Rocque, France et al. (2005) Bacterial meningitis in children: a French prospective study. Clinical infectious diseases : an official publication of the	- Study design does not meet inclusion criteria

Study	Code [Reason]
Infectious Diseases Society of America 41(7): 1059-63	
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
Bulloch, B.; Craig, W. R.; Klassen, T. P. (1997) The use of antibiotics to prevent serious sequelae in children at risk for occult bacteremia: a meta-analysis. Academic Emergency Medicine 4(7): 679-683	- Population does not meet inclusion criteria
Cantey, Joseph B., Lopez-Medina, Eduardo, Nguyen, Sean et al. (2015) Empiric Antibiotics for Serious Bacterial Infection in Young Infants: Opportunities for Stewardship. Pediatric emergency care 31(8): 568-71	- Population does not meet inclusion criteria
Chadwick, E. G., Connor, E. M., Shulman, S. T. et al. (1983) Efficacy of ceftriaxone in treatment of serious childhood infections. Journal of Pediatrics 103(1): 141-145	- Study design does not meet inclusion criteria
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	- Population does not meet inclusion criteria
Congeni, B. L. (1984) Comparison of ceftriaxone and traditional therapy of bacterial meningitis. Antimicrobial agents and chemotherapy 25(1): 40-44	- Study included in systematic review
De Gaudio, M., Chiappini, E., Galli, L. et al. (2010) Therapeutic management of bacterial meningitis in children: a systematic review and comparison of published guidelines from a European perspective. Journal of chemotherapy (Florence, Italy) 22(4): 226-37	- Study design 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	- Study included in systematic review
Donma, M. M. and Donma, O. (1992) Cephalosporins in childhood bacterial meningitis. Journal of the Singapore Paediatric Society 34(34): 141-147	- 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	- Study included in systematic review – Prasad 2007

Study	Code [Reason]
of randomized controlled trials. Journal of Antimicrobial Chemotherapy 70(4): 979-996	
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
Feldman, E. A., McCulloh, R. J., Myers, A. L. et al. (2017) Empiric antibiotic use and susceptibility in infants with bacterial infections: A multicenter retrospective cohort study. Hospital Pediatrics 7(8): 427-435	- No outcomes of interest for review
Feldstein, T. J.; Uden, D.; Larson, T. A. (1987) Cefotaxime for treatment of Gram-negative bacterial meningitis in infants and children. Pediatric Infectious Disease Journal 6(5): 471-475	- Study design does not meet inclusion criteria
Girgis, N. I., Abu el Ella, A. H., Farid, Z. et al. (1988) Intramuscular ceftriaxone versus ampicillin-chloramphenicol in childhood bacterial meningitis. Scandinavian journal of infectious diseases 20(6): 613-617	- Study included in systematic review – Prasad 2007
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. (1984) A therapeutic trial of cefotaxime versus penicillin-gentamicin for severe infections in children. Journal of antimicrobial chemotherapy 14supplb: 147-152	- Population does not meet inclusion criteria
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
Helwig, H., Tosberg, P., Peller, P. et al. (1990) Ceftriaxone versus conventional therapy in bacterial meningitis of childhood. Zac zeitschrift fur antimikrobielle antineoplastische chemotherapie 8(34): 43-49	- Non-English language article
Hsieh, Dong-Yi, Lai, Yun-Ru, Lien, Chia-Yi et al. (2021) Nationwide Population-Based Epidemiological Study for Outcomes of Adjunctive Steroid Therapy in Pediatric Patients with	- No intervention of interest

Study	Code [Reason]
Bacterial Meningitis in Taiwan. International journal of environmental research and public health 18(12)	
Jacobs, R. F., Wells, T. G., Steele, R. W. et al. (1985) A prospective randomized comparison of cefotaxime vs ampicillin and chloramphenicol for bacterial meningitis in children. Journal of pediatrics 107(1): 129-133	- Study included in systematic review – Prasad 2007
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	- No comparison of interest for review
Karageorgopoulos, D. E., Valkimadi, P. E., Kapaskelis, A. et al. (2009) Short versus long duration of antibiotic therapy for bacterial meningitis: a meta-analysis of randomised controlled trials in children. Archives of Disease in Childhood 94(8): 607-614	- Insufficient presentation of results
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
Kobayashi, Y., Morikawa, Y., Haruta, T. et al. (1981) Clinical evaluation of cefotaxime in the treatment of purulent meningitis in children. The Japanese journal of antibiotics 34(6): 946-54	- No comparison of interest for review
Korbila, I. P., Tansarli, G. S., Karageorgopoulos, 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	- Population does not meet inclusion criteria
Kovacs, J. E. and Ryan, M. E. (1987) Initial treatment of purulent meningitis in infants 1 to 3 months of age. The Journal of the American Osteopathic Association 87(8): 566-8	- Study design does not meet inclusion criteria
Kumar, P. and Verma, I. C. (1993) Antibiotic therapy for bacterial meningitis in children in developing countries. Bulletin of the World Health Organization 71(2): 183-188	- No comparison of interest for review
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

Study	Code [Reason]
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
Mallet, E.; Leroy, A.; Lemeland, J. P. (1987) Pharmacokinetics and clinical evaluation of ceftriaxone (CRO) in children with purulent meningitis. Chemioterapia : international journal of the Mediterranean Society of Chemotherapy 6(2suppl): 427	- Study design does not meet inclusion criteria
Marks, W. A., Stutman, H. R., Marks, M. I. et al. (1986) Cefuroxime versus ampicillin plus chloramphenicol in childhood bacterial meningitis: a multicenter randomized controlled trial. Journal of pediatrics 109(1): 123-130	- No comparison of interest for review
Martin, E., Hohl, P., Guggi, T. et al. (1990) Short course single daily ceftriaxone monotherapy for acute bacterial meningitis in children: results of a Swiss multicenter study. Part I: clinical results. Infection 18(2): 70-77	- No intervention of interest for review *Change in route and dose without sub-group analysis to account for conflicting factors*
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
Ngu, J. and Youmbissi, T. (1987) A comparative study with ceftriaxone (Rocephin) versus ampicillin and chloramphenicol in children with bacterial meningitis. Chemioterapia 6(2suppl): 417-418	- Cohort study from low income country
Noack, R. and Hobusch, D. (1994) Cerebrospinal fluid findings in antibiotic short term therapy for bacterial meningitis in childhood. Pediatrics and related topics 32(46): 341-346	- Non-English language article
O'Neill, P. (1993) How long to treat bacterial meningitis. Lancet (London, England) 341(8844): 530	- Study design does not meet inclusion criteria
Odio, C., Faingezicht, I., Salas, J. et al. (1986) Cefotaxime versus conventional therapy for the treatment of bacterial meningitis of infants and children. Pediatric infectious disease 5: 402-407	- Study included in systematic review – Prasad 2007
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	- Study design does not meet inclusion criteria

Study	Code [Reason]
Meningitis. Journal of the Pediatric Infectious Diseases Society 8(2): 187-188	
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
Peltola, H.; Vuori-Holopainen, E.; Kallio, M. J. (2001) Successful shortening from seven to four days of parenteral beta-lactam treatment for common childhood infections: a prospective and randomized study. International journal of infectious diseases 5(1): 3-8	- Population does not meet inclusion criteria
Pintado, Vicente, Cabellos, Carmen, Moreno, Santiago et al. (2003) Enterococcal meningitis: a clinical study of 39 cases and review of the literature. Medicine 82(5): 346-64	- Study design does not meet inclusion criteria
Posadas, Emerson and Fisher, Jay (2018) Pediatric bacterial meningitis: an update on early identification and management. Pediatric emergency medicine practice 15(11): 1-20	- Study design does not meet inclusion criteria
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
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
Renevey, F., Martin, E., Froscher, F. et al. (1989) Treatment of pediatric bacterial meningitis with a 7-day regimen of once-daily ceftriaxone injections. Multicentre study carried out in non-university pediatric departments in the French and Italian-speaking regions of Switzerland. Journal of chemotherapy (Florence, Italy) 1(4suppl): 678-9	- No comparison of interest for review
Savonius, Okko, Rugemalira, Emilie, Roine, Irmeli et al. (2020) Extended Continuous beta-Lactam Infusion with Oral Acetaminophen in Childhood Bacterial Meningitis: A Randomized, Double-Blind Clinical Trial. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America	- No comparison of interest for review
Schaad, U. B., Suter, S., Gianella-Borradori, A. et al. (1990) A comparison of ceftriaxone and cefuroxime for the treatment of bacterial meningitis in children. New England journal of	- No comparison of interest for review

Study	Code [Reason]
medicine 322(3): 141-147	
Schroeder, Alan R. and Ralston, Shawn L. (2014) Intravenous antibiotic durations for common bacterial infections in children: when is enough enough?. Journal of hospital medicine 9(9): 604-9	- Study design does not meet inclusion criteria
Shann, F.; Barker, J.; Poore, P. (1985) Chloramphenicol alone versus chloramphenicol plus penicillin for bacterial meningitis in children. Lancet (london, england) 2(8457): 681-684	- No comparison of interest for review
Sharma, P. R., Adhikari, R. K., Joshi, M. P. et al. (1996) Intravenous chloramphenicol plus penicillin versus intramuscular ceftriaxone for the treatment of pyogenic meningitis in Nepalese children [1]. Tropical Doctor 26(2): 84-85	- Study included in systematic review – Prasad 2007
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
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
Sáez-Llorens, X., McCoig, C., Feris, J. M. et al. (2002) Quinolone treatment for pediatric bacterial meningitis: a comparative study of trovafloxacin and ceftriaxone with or without vancomycin. Pediatric infectious disease journal 21(1): 14-22	- No comparison of interest for review
Tetanye, E., Yondo, D., Bernard-Bonnin, A. C. et al. (1990) Initial treatment of bacterial meningitis in Yaounde, Cameroon: theoretical benefits of the ampicillin-chloramphenicol combination versus chloramphenicol alone. Annals of tropical paediatrics 10(3): 285-291	- No comparison of interest for review
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
Uppal, L., Singhi, S., Singhi, P. et al. (2017) Role of Rifampin in Reducing Inflammation and Neuronal Damage in Childhood Bacterial Meningitis: a Pilot Randomized Controlled Trial. Pediatric infectious disease journal 36(6): 556-559	- No comparison 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

Study	Code [Reason]
Vaswani, N D, Gupta, Nishu, Yadav, Ravi et al. (2021) Seven versus Ten Days Antibiotics Course for Acute Pyogenic Meningitis in Children: A Randomized Controlled Trial. Indian journal of pediatrics 88(3): 246-251	- No intervention of interest
Vaswani, N. D., Gupta, N., Yadav, R. et al. (2020) Seven versus Ten Days Antibiotics Course for Acute Pyogenic Meningitis in Children: a Randomized Controlled Trial. Indian journal of pediatrics	- Duplicate article
Walker, M. C.; Lam, W. M.; Manasco, K. B. (2012) Continuous and extended infusions of beta-Lactam antibiotics in the pediatric population. Annals of Pharmacotherapy 46(11): 1537-1546	- Population does not meet inclusion criteria
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
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
Wells, T. G., Trang, J. M., Brown, A. L. et al. (1984) Cefotaxime therapy of bacterial meningitis in children. Journal of Antimicrobial Chemotherapy 14(supplb): 181-189	- Study included in systematic review – Prasad 2007
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

Excluded economic studies

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

Appendix K Research recommendations – full details

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

No research recommendation was made for this review.