National Institute for Health and Care Excellence

Draft for consultation

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

[G2] Evidence review for osmotic agents in bacterial meningitis

NICE guideline number tbc

Evidence review underpinning recommendations 1.8.3 to 1.8.5 in the NICE guideline

September 2023

Draft for consultation

This evidence review was developed by NICE

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ISBN:

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Osmotic agents for bacterial meningitis

Review question

What is the effectiveness of osmotic agents in bacterial meningitis?

Introduction

Bacterial meningitis is a rare but serious infection, which can occur in any age group. Raised intracranial pressure is known to complicate bacterial meningitis and may impair cerebral perfusion or cause death due to global ischaemia and intracranial herniation. Osmotic agents are widely used to control raised intracranial pressure.

The aim of this review is to determine the effectiveness of using osmotic agents in bacterial meningitis.

Summary of the protocol

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

1 **Table 1: Summary of the protocol (PICO table)**

Population	All adults, young people, children and babies (excluding neonates defined as aged 28 days old and younger) with confirmed bacterial meningitis.

Intervention	Osmotic therapy: • Orally administered glycerol • IV hypertonic saline • IV mannitol

Comparison	• Head-to-head comparisons between the above osmotic therapies • Isotonic fluid • Placebo • No intervention for raised ICP
Outcome	**Critical** Population: adults, infants and children • All-cause mortality (measured up to 1 year after discharge) • Brain herniation (may be reported as herniation, loss of pupillary reactivity, significant drop on Glasgow Come Scale, coning) • Serious intervention-related adverse effects leading to death, disability or prolonged hospitalisation or that are life threatening or otherwise considered medically significant **Important** Population: adults, infants and children • Reduction in intracranial pressure (measured either continuously or dichotomously based on study-defined cut-off) • Any long-term neurological impairment (defined as any motor deficits, sensory deficits, cognitive deficits*, or behavioural deficits*; measured from discharge up to 1 year after discharge) • Functional impairment (measured by any validated scale at any time point) Population: infants and children • Severe developmental delay (defined as score of >2 SD below normal on validated assessment scales, or MDI or PDI <70 on Bayleys assessment scale, or inability to assign a score due to cerebral palsy or severity of cognitive delay; measured at the oldest age reported unless there is substantially more data available at a younger age) *For infants and children below school-age, cognitive and behavioural deficits will be assessed at school-age.

ICP: intracranial pressure; IV: intravenous; 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

Four randomised controlled trials were included in this review (Kilpi 1995, Molyneux 2014, Peltola 2007, Sankar 2007).

The included studies are summarised in Table 2.

Three studies compared oral glycerol to placebo (Molyneux 2014, Peltola 2007, Sankar 2007) and 1 study compared oral glycerol to no intervention for raised intracranial pressure (Kilpi 1995). All studies were conducted in babies and children.

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	Intervention	Comparison	Outcomes	Comments
Kilpi 1995 RCT Finland	N=122 Children 3 months to 15 years with suspected or confirmed bacterial meningitis Age in years (mean; SD): 3.5; 3.7 Population treated with pre-admission antibiotics: 14%	Oral glycerol (n=64) 4.5g/kg/day glycerol given orally/via nasogastric tube for 3 days	No intervention for raised ICP (n=58) No further details reported	• All-cause mortality • Any long-term neurological impairment	Population is indirect as it included suspected and confirmed bacterial meningitis All children received ceftriaxone 100mg/kg/day IV for 4 days, followed by IM for 3 days. Those receiving dexamethasone received 1.5mg/kg/day IV

Study	Population	Intervention	Comparison	Outcomes	Comments
	Case-fatality: 2%				
Molyneux 2014 RCT Malawi	N=360 Children ≥2 months with confirmed bacterial meningitis Age: NR Population treated with pre-admission antibiotics: 46% Case-fatality: 26%	Oral glycerol (n=182) 6g/kg/day 85% glycerol given orally/via nasogastric tube	Placebo (n=178) 6ml/kg/day carboxymethylcellulose placebo	• All-cause mortality • Composite outcome: Any long-term neurological impairment, developmental delay or seizures	Population is indirect as 36% were HIV+ All children received 100mg/kg/day IV ceftriaxone for 5 days. Those receiving paracetamol received 20mg/kg/6h suppository for 42 hours
Peltola 2007 RCT Argentina, Brazil, Dominican Republic, Ecuador, Paraguay and Venezuela	N=654 Children 2 months to 16 years with confirmed bacterial meningitis Age in months (median; range): glycerol + dexamethasone: 12 (2 – 184); glycerol + placebo: 10 (2-152); placebo + dexamethasone: 13 (2-178); placebo + placebo: 10 (2-168) Population treated with antibiotics before diagnosis (unclear if pre-admission): 214/589 (36%) Case-fatality: 13%	Oral glycerol (n=325) 1.5g/kg/6h 85% glycerol given orally/via nasogastric tube	Placebo (n=329) Oral placebo. No further details reported	• All-cause mortality • Any long-term neurological impairment	All children received 80-100mg/kg/day IV ceftriaxone for 7 - 10 days. Those receiving dexamethasone received 0.15mg/kg/6h IV

Study	Population	Intervention	Comparison	Outcomes	Comments
Sankar 2007 RCT India	N=58 Children 2 months to 12 years with confirmed bacterial meningitis Age in months (mean; SD): 50; 41 Population treated with pre-admission antibiotics: 40% Case-fatality: 5%	Oral glycerol (n=33) 1.5g/kg/6h glycerol given orally/via nasogastric tube	Placebo (n=25) 2% carboxymethylcellulose solution given orally/via nasogastric tube	• All-cause mortality • Any long-term neurological impairment	All children received 100mg/kg/day IV ceftriaxone for minimum of 7 days. Those receiving dexamethasone received 0.15mg/kg/6h IV

HIV+: human immunodeficiency virus positive; ICP: intracranial pressure; IM: intramuscular; IV: intravenous; NR: not reported: RCT: randomised controlled trial; SD: standard deviation

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 (arising from selective reporting, missing outcome data and the randomisation process), imprecision (due to low event rates), and the inclusion of indirect populations and outcomes. See the GRADE tables in appendix F for the certainty of the evidence for each individual outcome.

The evidence showed no important differences between oral glycerol and placebo for all-cause mortality or any long-term neurological impairment in babies and children. There was also no important difference between oral glycerol and no treatment for all-cause mortality, although a lower rate of any long-term neurological impairment was associated with oral glycerol relative to no treatment for raised intracranial pressure.

No eligible studies were identified that reported on other osmotic therapies or other outcomes defined in the protocol.

See appendix F for full GRADE tables.

Economic evidence

Included studies

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

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation. This was because intervention is not expensive, and the committee did not expect their recommendations would change current NHS practice.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Bacterial meningitis is associated with inflammation and swelling of the brain and high rates of mortality and morbidity. The aim of osmotic agents is to reduce brain swelling, and therefore pressure and distortion that may cause secondary brain injury. Therefore, all-cause mortality and brain herniation were chosen as critical outcomes due to the severity of these outcomes and the potential for osmotic agents to reduce intracranial pressure. Brain herniation was prioritised over reduction in intracranial pressure as is a more direct measure of the effectiveness of the intervention. Serious intervention-related adverse effects was also prioritised as a critical outcome due to concern about the potential for rebound raised intracranial pressure and the safety of osmotic agents.

In addition to reduction in intracranial pressure, long-term neurological impairment and functional impairment were selected as important outcomes as these are relatively common after bacterial meningitis and may be related to inflammation and swelling of the brain. Severe developmental delay was also included as an important outcome for children as this may be more commonly reported than neurological and functional impairment in this population.

The quality of the evidence

The quality of the evidence was assessed using GRADE methodology. The evidence was rated as moderate to very low quality, and reasons for downgrading the evidence included risk of bias (arising from selective reporting, missing outcome data and the randomisation process), imprecision (due to low event rates), and the inclusion of indirect populations and outcomes.

No evidence was found that reported brain herniation, serious intervention-related adverse effects, reduction in intracranial pressure, functional impairment, or severe developmental delay. There was no evidence identified for other osmotic therapies defined in the protocol (IV hypertonic saline and IV mannitol), or head-to-head comparisons between the osmotic therapies or IV Isotonic fluid.

Benefits and harms

The committee considered the evidence comparing oral glycerol to placebo or no treatment in babies and children with bacterial meningitis. The evidence showed no important differences between oral glycerol and placebo for all-cause mortality or any long-term neurological impairment, and no important difference between oral glycerol and no treatment for all-cause mortality. There was some evidence for a lower rate of any long-term neurological impairment associated with oral glycerol relative to no treatment for raised intracranial pressure. However, the committee noted that this finding was at odds to the placebo comparison, and this evidence was from a single study with an indirect population (included those with suspected as well as confirmed meningitis).

The committee considered this evidence alongside additional evidence that they were aware of, which is outlined in the 'other factors the committee took into account' section below. The committee agreed, based on their experience, that osmotic agents have only a transient

effect on intracranial pressure. They are used to avert impending brain herniation and secondary brain injury while other measures with a more durable effect on intracranial pressure (such as intubation and ventilation or decompressive craniectomy) are considered and implemented, or until the underlying condition improves. In bacterial meningitis, definitive treatments for raised intracranial pressure are limited, and the disease process generally outlasts the effect of osmotic agents. Therefore, based on the evidence that it is unclear if glycerol reduces long-term neurological impairment, it may be associated with harm (see other factors the committee took into account), and the limited clinical rationale, the committee recommended that oral glycerol should not be used in the management of bacterial meningitis. The committee also recommended to avoid using other osmotic agents such as mannitol or hypertonic sodium chloride as part of routine management of bacterial meningitis due to an absence of evidence in these areas.

Based on their clinical knowledge and experience, the committee agreed that if there were signs of brain herniation, such as rapid change in level of consciousness, bradycardia, hypertension, or loss of pupillary reaction, it may be appropriate to use osmotic agents in the short-term to provide temporary control of intracranial pressure while other options are considered. Therefore, they recommended that osmotic agents (other than glycerol) could be considered if there are signs of brain herniation as they did not want to preclude this as an option, but they recommended that urgent advice should be sought from critical care clinicians.

Cost effectiveness and resource use

This review question was not prioritised for economic analysis and therefore the committee made a qualitative assessment of the likely cost-effectiveness of their recommendations. The committee did not recommend the use of osmotic agents as part of the routine management of bacterial meningitis. They recommended that they could be considered in the context of raised intracranial pressure when there are signs of brain herniation where they reasoned that an inexpensive intervention to mitigate catastrophic consequences of brain injury would be cost-effective. They noted that their recommendations reinforce current practice and would not have a significant resource impact.

Other factors the committee took into account

The committee were aware of an RCT (Ajdukiewicz 2011) conducted in adults that was stopped early due to a higher rate of mortality in those receiving oral glycerol compared with those receiving placebo. This study was excluded from the current review as 83% of the population had immunodeficiency due to HIV. However, the committee agreed that the rationale for excluding people with HIV from the current guideline is related to differences in aetiology, rather than an impact of HIV on response to treatment. As this paper excluded people with cryptococcal or lymphocytic meningitis and the most common cause of bacterial meningitis was Streptococcus pneumoniae*,* the committee agreed that the study should be considered relevant to the population of interest for this guideline. Further, the committee were aware of further studies that showed that HIV was not associated with mortality (Wall 2013, Wall 2017) or white cell count (Wall 2014) in people with bacterial meningitis. Therefore, the committee agreed that they could not exclude the possibility of harm associated with glycerol treatment in those without HIV.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.8.3 to 1.8.5 in the NICE guideline.

References – included studies

Effectiveness

Kilpi 1995

Kilpi, T., Peltola, H., Jauhiainen, T., Kallio, M. J. Oral glycerol and intravenous dexamethasone in preventing neurologic and audiologic sequelae of childhood bacterial meningitis. The Finnish Study Group, Pediatric Infectious Disease Journal, 14, 270-8, 1995

Molyneux 2014

Molyneux, E. M., Kawaza, K., Phiri, A., Chimalizeni, Y., Mankhambo, L., Schwalbe, E., Kataja, M., Pensulo, P., Chilton, L., Peltola, H. Glycerol and acetaminophen as adjuvant therapy did not affect the outcome of bacterial meningitis in Malawian children. Pediatric Infectious Disease Journal, 33, 214-6, 2014

Peltola 2007

Peltola, H., Roine, I., Fernandez, J., Zavala, I., Ayala, S.G., Mata, A.G., Arbo, A., Bologna, R., Mino, G., Goyo, J., Lopez, E., de Andrade, S.D. Sarna, S., Adjuvant glycerol and/or dexamethasone to improve the outcomes of childhood bacterial meningitis: a prospective, randomized, double-blind, placebo-controlled trial. Clinical Infectious Diseases, 45, 1277-1286, 2007

Sankar 2007

Sankar, J., Singhi, P., Bansal, A., Ray, P., Singhi, S. Role of dexamethasone and oral glycerol in reducing hearing and neurological sequelae in children with bacterial meningitis. Indian Pediatrics, 44, 649-656, 2007

Economic

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

Other

Ajdukiewicz 2011

Ajdukiewicz, K. M., Cartwright, K. E., Scarborough, M., Mwambene, J. B., Goodson, P., Molyneux, M. E., Zijlstra, E. E., French, N., Whitty, C. J., Lalloo, D. G. Glycerol adjuvant therapy in adults with bacterial meningitis in a high HIV seroprevalence setting in Malawi: a double-blind, randomised controlled trial. The Lancet Infectious Diseases, 11, 293-300, 2011

Wall 2013

Wall, C. E., Catwright, K., Scarborough, M., Ajdukiewicz, K. M., Goodson, P., Mwambene, J., Zijlstra, E. E., Gordon, S. B., French, N., Fragher, B., Heyderman, R. S., Lalloo. D. G. High mortality amongst adolescents and adults with bacterial meningitis in Sub-Saharan Africa: an analysis of 715 cases from Malawi. PLoS ONE, 8, e69783, 2013

Wall 2014

Wall, C. E., Everett, D. B., Mukaka, M., Bar-Zeev, N., Feasey, N., Jahn, A., Moore, M., van Oosterhout, J. J., Pensalo, P., Baguimira, K., Gordon, S. B., Molyneux, E. M., Carrol, E. D., French, N., Molyneux, M. E., Heyderman, R. S. Bacterial meningitis in Malawian adults, adolescents, and children during the era of antiretroviral scale-up and *Haemophilus influenzae* type b vaccination, 2000–2012. Clinical Infectious Diseases, 58, e137-45, 2014

Wall 2017

Wall, C. E., Mukaka, M., Scarborough, M., Ajdukiewicz, K. M. A., Cartwright, K. E., Nyirenda, M., Denis, B., Allain, T. J., Faragher, B., Lalloo, D. G., Heyderman, R. S. Prediction of outcome from adult bacterial meningitis in a high-HIV-seroprevalence, resource-poor setting using the Malawi Adult Meningitis Score (MAMS). Clinical Infectious Diseases, 64, 413-9, 2017

Appendices

Appendix A Review protocols

Review protocol for review question: What is the effectiveness of osmotic agents in bacterial meningitis?

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42020225147
Review title	Osmotic agents in bacterial meningitis
Review question	What is the effectiveness of osmotic agents in bacterial meningitis?
Objective	To determine the effectiveness of osmotic agents in bacterial meningitis
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: English language Human studies The full search strategies for MEDLINE database will be published in the final review. For each search, the principal database search strategy is quality assured by a second information scientist using an adaptation of the PRESS 2015 Guideline Evidence-Based Checklist.
Condition or domain being studied	Bacterial meningitis
Population	Inclusion: All adults, young people, children and babies (excluding neonates defined as aged 28

Field	Content
	days old and younger) with confirmed bacterial meningitis. Exclusion: People: • with known immunodeficiency. • who have brain tumours, pre-existing hydrocephalus, intracranial shunts, previous neurosurgical procedures, or known cranial or spinal anomalies that increase the risk of bacterial meningitis. • with confirmed viral meningitis or viral encephalitis. • with confirmed tuberculous meningitis. • with confirmed fungal meningitis.
Intervention/Exposure/Test	Osmotic therapy: • Orally administered glycerol • IV hypertonic saline • IV mannitol
Comparator/Reference standard/Confounding factors	• Head-to-head comparisons between the above osmotic therapies • IV Isotonic fluid • Placebo • No intervention for raised ICP
Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs • RCTs • If insufficient RCTs: prospective cohort studies • If insufficient prospective cohort studies: retrospective cohort studies Non-randomised studies will be downgraded for risk of bias if they do not adequately adjust for the following covariates, but will not be excluded for this reason: • Severity of infection at presentation (including sepsis) • Infective organism, • Use of invasive ventilation

Field	Content
	• Age (if data is not confined to one of the age groups of interest [see stratifications] or presented separately for different age groups) Exclude: • Conference abstracts
Other exclusion criteria	Cohort studies from low income countries. 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)	Population: Adult • All-cause mortality (measured up to 1 year after discharge) • Brain herniation (may be reported as herniation, loss of pupillary reactivity, significant drop on Glasgow Come Scale, coning) • Serious intervention-related adverse effects leading to death, disability or prolonged hospitalisation or that are life threatening or otherwise considered medically significant Population: Children • All-cause mortality (measured up to 1 year after discharge) • Brain herniation (reactivity, significant drop on Glasgow Come Scale, coning) • Serious intervention-related adverse effects leading to death, disability or prolonged hospitalisation or that are life threatening or otherwise considered medically significant
Secondary outcomes (important outcomes)	Population: Adults • Reduction in intracranial pressure (measured either continuously or dichotomously based on study-defined cut-off) • Any long-term neurological impairment (defined as any motor deficits, sensory deficits, cognitive deficits, or behavioural deficits; measured from discharge up to 1 year after discharge) • Functional impairment (measured by any validated scale at any time point) Population: Children

Field	Content
	• Reduction in intracranial pressure (measured either continuously or dichotomously based on study-defined cut-off) • Any long-term neurological impairment (defined as any motor deficits, sensory deficits, cognitive deficits*, or behavioural deficits*; measured from discharge up to 1 year after discharge) • Functional impairment (measured by any validated scale at any time point) • Severe developmental delay (defined as score of >2 SD below normal on validated assessment scales, or MDI or PDI <70 on Bayleys assessment scale, or inability to assign a score due to cerebral palsy or severity of cognitive delay; measured at the oldest age reported unless there is substantially more data available at a younger age) *For infants and children below school-age, cognitive and behavioural deficits will be assessed at school-age.
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will not be undertaken for this question. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs and quasi-RCTs • Cochrane ROBINS-I tool for non-randomised (clinical) controlled trials and cohort studies. The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Quantitative findings will be formally summarised in the review. Where multiple studies report on the same outcome for the same comparison, meta-analyses will be conducted using Cochrane Review

Field	Content
	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 • Brain herniation – statistical significance • Intracranial pressure – published MIDs if available or 5mmHg for continuous outcomes; default MIDs for dichotomous outcomes • Validated scales: Published MIDs where available; if not GRADE default MIDs • All other outcomes: GRADE default MIDs
Analysis of sub-groups	Evidence will be stratified by: Age: • Younger Infants: >28 days to ≤3 months of age • Older infants and children: >3 months to <18* years of age • Adults: ≥18* years of age *There is variation in clinical practice regarding the treatment of 16 to 18 year olds. Therefore, we

Field	Content	
	will be guided by cut-offs used in the evidence when determining if 16 to 18 year olds should be treated as adults or children Evidence will be sub-grouped by the following only in the event that there is significant heterogeneity in outcomes: Age: • Young and middle aged adults • Older adults* *There is variation regarding the age at which adults should be considered older adults. Therefore, we will be guided by cut-offs used in the evidence when determining this threshold. Concentration of osmotic agent Where evidence is stratified or sub-grouped 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)

Field	Content		
Language	English		
Country	England		
Anticipated or actual start date	30/11/2020		
Anticipated completion date	07/12/2023		
Stage of review at time of this submission	Review stage	Started	Completed
	Preliminary searches	☑	☑
	Piloting of the study selection process	☑	☑
	Formal screening of search results against eligibility criteria	☑	☑
	Data extraction	☑	☑
	Risk of bias (quality) assessment	☑	☑
	Data analysis	☑	☑
Named contact	Named contact: National Guideline Alliance Named contact e-mail: meningitis&meningococcal@nice.org.uk Organisational affiliation of the review: National Institute for Health and Care Excellence (NICE) and National Guideline Alliance		
Review team members	National Guideline Alliance		
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance which receives funding from NICE.		
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude		

Field	Content	
	a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10149.	
Other registration details	None	
Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=225147	
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, osmotic agents, intracranial pressure, glycerol, hypertonic saline, mannitol, 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; ICP: intracranial pressure; IV: intravenous; MDI: mental development index; 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 is the effectiveness of osmotic agents in bacterial meningitis?

Clinical Search

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

#	Searches
1	Meningitis/ or Meningitis, Bacterial/ or Meningitis, Escherichia Coli/ or Meningitis, Haemophilus/ or Meningitis, Listeria/ or Meningitis, Meningococcal/ or Meningitis, Pneumococcal/ or Meningoencephalitis/ or *Meningococcal Infections/ or Neisseria meningitidis/
2	1 use ppez
3	meningitis/ or bacterial meningitis/ or haemophilus meningitis/ or hemophilus influenzae meningitis/ or listeria meningitis/ or pneumococcal meningitis/ or meningoencephalitis/ or meningococcal meningitis/ or *meningococcosis/ or *meningococcemia/ or neisseria meningitidis/
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	(Neisseria* mening* or n mening*).ti,ab.
10	or/2,4-9
11	Osmosis/ use ppez
12	exp Diuretics, Osmotic/ use ppez
13	exp osmotic agent/ use emczd
14	(osmotic* adj2 (therap* or treatment* or agent*)).ti,ab.
15	Glycerol/ use ppez
16	glycerol/ use emczd
17	(glycerol or glycerine or glycerin).mp.
18	Mannitol/ use ppez
19	mannitol/ use emczd
20	(mannitol or osmitrol or bronchitol or d-Mannitol or mannite or "manna sugar").mp.
21	Saline Solution, Hypertonic/ use ppez
22	sodium chloride/ use emczd
23	((hyperton* or hypoton*) adj3 (saline or fluid*)).mp.
24	or/11-23
25	10 and 24
26	letter/
27	editorial/
28	news/
29	exp historical article/
30	Anecdotes as Topic/
31	comment/
32	case report/
33	(letter or comment*).ti.
34	26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35	randomized controlled trial/ or random*.ti,ab.
36	34 not 35
37	animals/ not humans/
38	exp Animals, Laboratory/
39	exp Animal Experimentation/
40	exp Models, Animal/
41	exp Rodentia/
42	(rat or rats or mouse or mice).ti.
43	36 or 37 or 38 or 39 or 40 or 41 or 42
44	letter.pt. or letter/

#	Searches
45	note.pt.
46	editorial.pt.
47	case report/ or case study/
48	(letter or comment*).ti.
49	44 or 45 or 46 or 47 or 48
50	randomized controlled trial/ or random*.ti,ab.
51	49 not 50
52	animal/ not human/
53	nonhuman/
54	exp Animal Experiment/
55	exp Experimental Animal/
56	animal model/
57	exp Rodent/
58	(rat or rats or mouse or mice).ti.
59	51 or 52 or 53 or 54 or 55 or 56 or 57 or 58
60	43 use ppez
61	59 use emczd
62	60 or 61
63	25 and 62
64	25 not 63
65	limit 64 to English language

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: [Osmosis] this term only
#18	MeSH descriptor: [Diuretics, Osmotic] explode all trees
#19	(osmo* near/2 (agent* or intervention* or therap* or treatment*)):ti,ab,kw
#20	MeSH descriptor: [Glycerol] this term only
#21	MeSH descriptor: [Mannitol] this term only
#22	MeSH descriptor: [Saline Solution, Hypertonic] this term only
#23	((glycerol or glycerine or glycerin or mannitol or osmitrol or bronchitol or d-Mannitol or mannite or "manna sugar")):ti,ab,kw
#24	((hyperton* or "hyper ton*" or hypoton* or "hypo ton*") near/3 (saline or fluid*)):ti,ab,kw
#25	{or #17-#24}
#26	#16 and #25
#27	"conference":pt or (clinicaltrials or trialsearch):so
#28	#26 not #27

Database(s): Database of Abstracts of Reviews of Effects (DARE); HTA Database – CRD interface
Date of last search: 16 November 2020

#	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

#	Searches
6	MeSH DESCRIPTOR Meningitis, Meningococcal IN DARE,HTA
7	MeSH DESCRIPTOR Meningitis, Pneumococcal EXPLODE ALL TREES IN DARE,HTA
8	MeSH DESCRIPTOR Meningoencephalitis IN DARE,HTA
9	((((bacter* or infect*) NEAR3 (meningit* or meninges* or leptomeninges* or "subarachnoid space*"))))) IN DARE, HTA
10	(((((meningencephalitis* or meningoencephalitis* or meningit*))))) IN DARE, HTA
11	MeSH DESCRIPTOR Meningococcal Infections IN DARE,HTA
12	MeSH DESCRIPTOR Neisseria meningitidis 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* NEXT 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 Osmosis IN DARE,HTA
18	MeSH DESCRIPTOR Diuretics, Osmotic IN DARE,HTA
19	(((osmotic* NEAR2 (therap* or treatment* or agent*)))) IN DARE, HTA
20	MeSH DESCRIPTOR Mannitol IN DARE,HTA
21	MeSH DESCRIPTOR Saline Solution, Hypertonic IN DARE,HTA
22	(((glycerol or glycerine or glycerin or mannitol or osmitrol or bronchitol or d-Mannitol or mannite or "manna sugar"))) IN DARE, HTA
23	((((hyperton* or hypoton*) NEAR3 (saline or fluid*)))) IN DARE, HTA
24	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
25	#16 AND #24

1
2

Economic Search

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

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

Date of last search: 11 March 2021

#	Searches
1	MeSH DESCRIPTOR meningitis IN NHSEED,HTA
2	MeSH DESCRIPTOR Meningitis, Bacterial IN NHSEED,HTA
3	MeSH DESCRIPTOR Meningitis, Escherichia coli IN NHSEED,HTA
4	MeSH DESCRIPTOR Meningitis, Haemophilus EXPLODE ALL TREES IN NHSEED,HTA
5	MeSH DESCRIPTOR Meningitis, Listeria IN NHSEED,HTA
6	MeSH DESCRIPTOR Meningitis, Meningococcal IN NHSEED,HTA
7	MeSH DESCRIPTOR Meningitis, Pneumococcal IN NHSEED,HTA
8	MeSH DESCRIPTOR Meningoencephalitis IN NHSEED,HTA
9	(((bacter* or infect*) NEAR3 (meningit* or meninges* or leptomeninges* or subarachnoid space*))) IN NHSEED, HTA
10	((meningit* NEAR3 (e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon* or septic* or sepsis* or bacter?emi?))) IN NHSEED, HTA
11	(((e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon*) NEAR3 (septic* or sepsis* or bacter?emi?))) IN NHSEED, HTA
12	((meningencephalitis* or meningoencephalitis* or meningit*)) IN NHSEED, HTA
13	MeSH DESCRIPTOR Meningococcal Infections IN NHSEED,HTA
14	MeSH DESCRIPTOR Neisseria meningitidis EXPLODE ALL TREES IN NHSEED,HTA
15	((meningococc* NEAR3 (sepsis* or septic* or toxic* or endotoxic* or disease* or infection*))) IN NHSEED, HTA
16	((meningococcus* or meningococci* or meningococcaemia* or meningococcemia*)) IN NHSEED, HTA
17	((Neisseria* NEXT mening*)) IN NHSEED, HTA
18	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17

Database(s): Medline & Embase (Multifile) – OVID interface

Embase Classic+Embase 1947 to 2022 November 09, **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to November 09, 2022

Date of last search: 10 November 2022

Multifile database codes: emczd = Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	Meningitis/ or Meningitis, Bacterial/ or Meningitis, Escherichia Coli/ or Meningitis, Haemophilus/ or Meningitis, Listeria/ or Meningitis, Meningococcal/ or Meningitis, Pneumococcal/ or Meningoencephalitis/
2	1 use ppez
3	meningitis/ or bacterial meningitis/ or haemophilus meningitis/ or listeria meningitis/ or pneumococcal meningitis/ or meningoencephalitis/
4	3 use emczd
5	((bacter* or infect*) adj3 (meningit* or meninges* or leptomeninges* or subarachnoid space?)).ti,ab.
6	(meningit* adj3 (e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon* or septic* or sepsis* or bacter?emi?)).ti,ab.
7	((e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon*) adj3 (septic* or sepsis* or bacter?emi?)).ti,ab.
8	(mening?encephalitis* or meningit*).ti,ab.
9	or/2,4-8
10	Meningococcal Infections/ or exp Neisseria meningitidis/
11	10 use ppez
12	Meningococcosis/ or Meningococcemia/ or Neisseria Meningitidis/
13	12 use emczd
14	(meningococc* adj3 (sepsis* or septic* or toxic* or endotoxic* or disease? or infection?)).ti,ab.
15	(meningococcus* or meningococci* or meningococc?emi?).ti,ab.
16	(Neisseria* mening* or n mening*).ti,ab.
17	or/11,13-16
18	Economics/ use ppez
19	Value of life/ use ppez

#	Searches
20	exp "Costs and Cost Analysis"/ use ppez
21	exp Economics, Hospital/ use ppez
22	exp Economics, Medical/ use ppez
23	Economics, Nursing/ use ppez
24	Economics, Pharmaceutical/ use ppez
25	exp "Fees and Charges"/ use ppez
26	exp Budgets/ use ppez
27	health economics/ use emczd
28	exp economic evaluation/ use emczd
29	exp health care cost/ use emczd
30	exp fee/ use emczd
31	budget/ use emczd
32	funding/ use emczd
33	budget*.ti,ab.
34	cost*.ti.
35	(economic* or pharmaco?economic*).ti.
36	(price* or pricing*).ti,ab.
37	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
38	(financ* or fee or fees).ti,ab.
39	(value adj2 (money or monetary)).ti,ab.
40	or/18-39
41	Quality-Adjusted Life Years/ use ppez
42	Sickness Impact Profile/
43	quality adjusted life year/ use emczd
44	"quality of life index"/ use emczd
45	(quality adjusted or quality adjusted life year*).tw.
46	(qaly* or qal or qald* or qale* or qtime* or qwb* or daly).tw.
47	(illness state* or health state*).tw.
48	(hui or hui2 or hui3).tw.
49	(multiattibute* or multi attribute*).tw.
50	(utilit* adj3 (score*1 or valu* or health* or cost* or measur* or disease* or mean or gain or gains or index*)).tw.
51	utilities.tw.
52	(eq-5d* or eq5d* or eq-5* or eq5* or euroqual* or euro qual* or euroqual 5d* or euro qual 5d* or euro qol* or euroqol*or euro quol* or euroquol* or euro quol5d* or euroquol5d* or eur qol* or eurqol* or eur qol5d* or eurqol5d* or eur?qul* or eur?qul5d* or euro* quality of life or european qol).tw.
53	(euro* adj3 (5 d* or 5d* or 5 dimension* or 5dimension* or 5 domain* or 5domain*)).tw.
54	(sf36 or sf 36 or sf thirty six or sf thirtysix).tw.
55	(time trade off*1 or time tradeoff*1 or tto or timetradeoff*1).tw.
56	Quality of Life/ and ((quality of life or qol) adj (score*1 or measure*1)).tw.
57	Quality of Life/ and ec.fs.
58	Quality of Life/ and (health adj3 status).tw.
59	(quality of life or qol).tw. and Cost-Benefit Analysis/ use ppez
60	(quality of life or qol).tw. and cost benefit analysis/ use emczd
61	((qol or hrqol or quality of life).tw. or *quality of life/) and ((qol or hrqol* or quality of life) adj2 (increas* or decreas* or improv* or declin* or reduc* or high* or low* or effect or effects or worse or score or scores or change*1 or impact*1 or impacted or deteriorat*)).ab.
62	Cost-Benefit Analysis/ use ppez and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
63	cost benefit analysis/ use emczd and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
64	*quality of life/ and (quality of life or qol).ti.
65	quality of life/ and ((quality of life or qol) adj3 (improv* or chang*)).tw.
66	quality of life/ and health-related quality of life.tw.
67	Models, Economic/ use ppez
68	economic model/ use emczd
69	care-related quality of life.tw,kw.
70	((capability$ or capability-based$) adj (measure$ or index or instrument$)).tw,kw.
71	social care outcome$.tw,kw.
72	(social care and (utility or utilities)).tw,kw.
73	or/41-72
74	(9 or 17) and 40
75	(9 or 17) and 73
76	letter/
77	editorial/
78	news/
79	exp historical article/
80	Anecdotes as Topic/
81	comment/
82	case report/
83	(letter or comment*).ti.
84	76 or 77 or 78 or 79 or 80 or 81 or 82 or 83

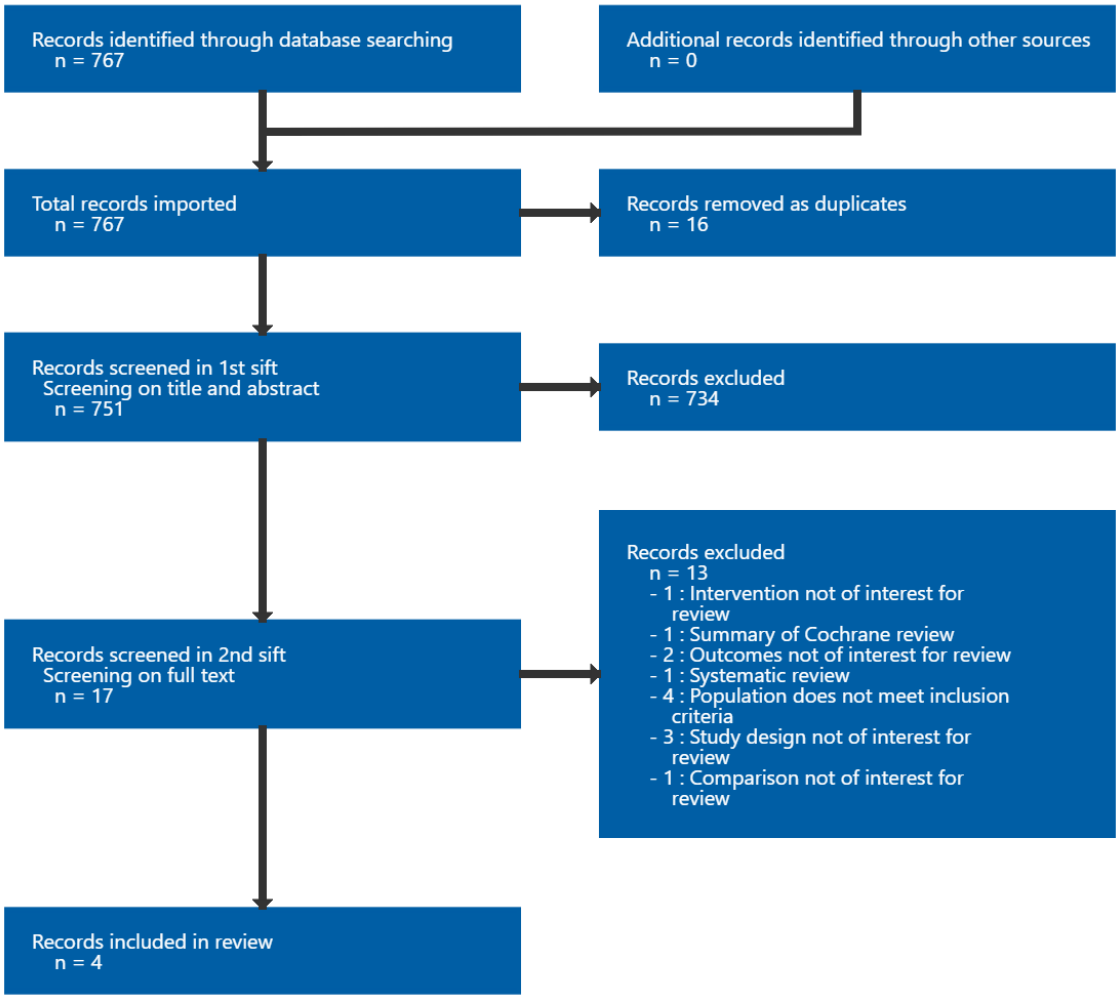
#	Searches
85	randomized controlled trial/ or random*.ti,ab.
86	84 not 85
87	animals/ not humans/
88	exp Animals, Laboratory/
89	exp Animal Experimentation/
90	exp Models, Animal/
91	exp Rodentia/
92	(rat or rats or mouse or mice).ti.
93	86 or 87 or 88 or 89 or 90 or 91 or 92
94	letter.pt. or letter/
95	note.pt.
96	editorial.pt.
97	case report/ or case study/
98	(letter or comment*).ti.
99	94 or 95 or 96 or 97 or 98
100	randomized controlled trial/ or random*.ti,ab.
101	99 not 100
102	animal/ not human/
103	nonhuman/
104	exp Animal Experiment/
105	exp Experimental Animal/
106	animal model/
107	exp Rodent/
108	(rat or rats or mouse or mice).ti.
109	101 or 102 or 103 or 104 or 105 or 106 or 107 or 108
110	93 use ppez
111	109 use emczd
112	110 or 111
113	74 not 112
114	limit 113 to English language
115	75 not 112
116	limit 115 to English language
117	114 or 116

1
2

Appendix C Effectiveness evidence study selection

Study selection for: What is the effectiveness of osmotic agents in bacterial meningitis?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What is the effectiveness of osmotic agents in bacterial meningitis?

Table 4: Evidence tables – effectiveness evidence

Study details	Results and risk of bias assessment using Cochrane RoB 2
Full citation Kilpi, T., Peltola, H., Jauhiainen, T., Kallio, M. J., Oral glycerol and intravenous dexamethasone in preventing neurologic and audiologic sequelae of childhood bacterial meningitis. The Finnish Study Group, Pediatric Infectious Disease JournalPediatr Infect Dis J, 14, 270-8, 1995 **Ref Id** 1135819 **Country/ies where the study was carried out** Finland **Study type** RCT **Study dates** March 1987 - February 1991 **Inclusion criteria** Children aged 3 months to 15 years with suspected or confirmed bacterial meningitis. **Exclusion criteria** Children who were immunocomprised, had a prosthetic device such as a ventriculoperitoneal shunt, or had received more than one dose of IV antibiotics before diagnosis. **Patient characteristics** N=122	**Results** Outcome: All-cause mortality (during hospitalisation) Oral glycerol: 2/64 No intervention for raised ICP: 0/58 Outcome: Any long-term neurological impairment at 3 or 6 months (any neurologic or audiologic abnormality) Oral glycerol: 4/61 No intervention for raised ICP: 11/57 **1. Bias arising from the randomisation process (Low/High/Some concerns)** Low risk: Centrally allocated, computer generated randomisation. No significant differences between groups at baseline **2. Bias arising due to deviations from intended interventions (Low/High/Some concerns)** Low risk: Participants and personnel were aware of interventions but outcomes were objective. No reason to believe deviations arose because of the trial context and appropriate analyses used **3. Bias due to missing outcome data (Low/High/Some concerns)** Low risk: Outcome data available for 97% of participants **4. Bias in measurement of the outcome (Low/High/Some concerns)** Low risk: Outcomes are objective and measurement did not differ between groups

Study details	Results and risk of bias assessment using Cochrane RoB 2
Age (years in mean; SD in parentheses): 3.5 (3.7) Sex: male: 59 (48%); female: 63 (52%) Etiology: Haemophilus influenza: 65 (53%); Neisseria meningitides: 41 (34%); Streptococcus pneumonia: 12 (10%); other: 4 (3%) Pre-treatment antibiotics: 17 (14%) Consciousness: normal: 36 (30%); slightly impaired: 41 (33%); moderately impaired: 41 (33%); unconscious: 3 (3%) Case-fatality: 2% **Interventions** n=64 (52%) oral glycerol (glycerol only and glycerol + dexamethasone groups combined): 4.5g/kg/day of glycerol was given orally, divided into 3 doses (maximum dose 180g/day), for 3 days. If children were unable or unwilling to swallow glycerol, they received it through a nasogastric tube. Those receiving dexamethasone received 1.5mg/kg/day IV, divided into three doses (maximum dose 60mg/day). For both medications, the first dose was increased by 50% and administered alongside ceftriaxone and the last three doses were reduced by 50%. n=58 (48%) no intervention for raised ICP (neither glycerol or dexamethasone and dexamethasone only groups combined): No further details reported. **Follow-up** Neurological examinations were performed every day during hospitalisation, before discharge and at 2 weeks, 3 months and 6 months after discharge. Hearing impairment was assessment 2 months or more after discharge.	**5. Bias in selection of the reported result (Low/High/Some concerns)** Low risk: There is clear evidence that all eligible reported results for the outcome correspond to all intended outcome measurements and analyses. **Overall risk of bias (Low/High/Some concerns)** Low risk: The study is judged to be at low risk of bias for all domains **Source of funding** Not industry funded **Other information** Population is indirect as it included suspected and confirmed bacterial meningitis. All groups received ceftriaxone 100mg/kg/day IV for 4 days, followed by IM for 3 days (maximum dose 4g/day).
Full citation Molyneux, E. M., Kawaza, K., Phiri, A., Chimalizeni, Y., Mankhambo, L., Schwalbe, E., Kataja, M., Pensulo, P., Chilton, L., Peltola, H., Glycerol and acetaminophen as adjuvant therapy did not affect the outcome of bacterial meningitis in Malawian children, Pediatric Infectious Disease JournalPediatr Infect Dis J, 33, 214-6, 2014 **Ref Id** 1136101 **Country/ies where the study was carried out**	**Results** All-cause mortality (during hospitalisation) Oral glycerol: 49/182 Placebo: 44/178 Composite outcome[1]: Any long-term neurological impairment, developmental delay or seizures (up to 180 days after discharge) Oral glycerol: 64/182 Placebo: 63/178

Study details	Results and risk of bias assessment using Cochrane RoB 2
Malawi **Study type** RCT **Study dates** Not reported **Inclusion criteria** Children aged ≥2 months with confirmed bacterial meningitis (positive CSF culture; characteristic CSF findings with positive blood culture; or signs and symptoms combatable with bacterial meningitis and CSF containing ≥100 polymorphonuclear leucocytes/mm3 **Exclusion criteria** Trauma, previous neurological disease or previous permanent, nonconductive hearing loss. **Patient characteristics** N=360 Etiology: Streptococcus pneumonia: 190 (53%); Haemophilus influenza: 30 (9%); other bacteria: 25 (6%); no bacteria cultured: 115 (32%) Pre-admission antibiotics: 165 (46%) Blantyre Coma Score ≤2 (=Glasgow coma score ≤8): 109 (30%) Case-fatality: 26% **Interventions** n=182 oral glycerol (Glycerol + placebo and glycerol + paracetamol groups combined): 6g/kg/day 85% glycerol was given orally, divided into 4 equal doses (6g/kg/day=6ml; maximum 25ml per dose). If children were unable or unwilling to swallow glycerol, they received it through a nasogastric tube. Children also received either an initial dose of 35mg/kg paracetamol suppository, followed by 20mg/kg every 6 hours for 42 hours, or a cocoa butter-based placebo suppository. n=178 placebo (placebo + placebo and placebo + paracetamol groups combined):	[1]Outcome is indirect as it is a composite of outcomes included in the protocol (and seizures is not included in the protocol) **1. Bias arising from the randomisation process (Low/High/Some concerns)** High risk: No information about allocation concealment and there is a substantial excess in statistically significant differences in baseline characteristics between intervention groups (49% of the no intervention for raised ICP group received preadmission antibiotics compared with 37% of the oral glycerol group) **2. Bias arising due to deviations from intended interventions (Low/High/Some concerns)** Low risk: Double-blind trial and appropriate analyses used **3. Bias due to missing outcome data (Low/High/Some concerns)** Low risk: Outcome data available for 99% of participants **4. Bias in measurement of the outcome (Low/High/Some concerns)** Low risk: Double-blind trial and measurement did not differ between groups **5. Bias in selection of the reported result (Low/High/Some concerns)** Some concerns: Analysis intentions are not available **Overall risk of bias (Low/High/Some concerns)** High risk: The study is judged to be at high risk of bias in at least one domain (bias arising from the randomisation process) **Source of funding** Not industry funded

Study details	Results and risk of bias assessment using Cochrane RoB 2
Children received 6ml/kg/day carboxymethycellulose placebo. Children also received wither an initial dose of 35mg/kg paracetamol suppository, followed by 20mg/kg every 6 hours for 42 hours, or a cocoa butter-based placebo suppository. **Follow-up** Children were assessed for hearing, visual, developmental and neurological outcomes at hospital discharge, and 30 and 180 days after discharge.	**Other information** All groups received 100mg/kg/day IV ceftriaxone for 5 days. Children with salmonella meningitis were treated with 14 days of ceftriaxone followed by 14 days of oral ciprofloxacin. Population is seriously indirect as 36% were HIV+
Full citation Peltola, H., Roine, I., Fernandez, J., Zavala, I., Ayala, S.G., Mata, A.G., Arbo, A., Bologna, R., Mino, G., Goyo, J., Lopez, E., de Andrade, S.D., Sarna, S., Adjuvant glycerol and/or dexamethasone to improve the outcomes of childhood bacterial meningitis: a prospective, randomized, double-blind, placebo-controlled trial, Clinical Infectious Diseases, 45, 1277-1286, 2007 **Ref Id** 137418 **Country/ies where the study was carried out** Argentina, Brazil, Dominican Republic, Ecuador, Paraguay and Venezuela **Study type** RCT **Study dates** 1996 - 2003 **Inclusion criteria** Children aged 2 months - 16 years with bacterial meningitis (CSF culture positive; characteristic CSF findings and positive blood culture; characteristic CSF findings and positive latex agglutination test; or signs and symptoms of bacterial meningitis and at least 3 of WBC count ≥1000 cells/mm3, CSF glucose level <40mg/dL, CSF protein concentration ≥40mg/dL, C-reactive protein level ≥40mg/L or blood leukocyte count >15,000 cell/mm3). **Exclusion criteria**	**Results** Outcome: All-cause mortality (2 months after discharge) Oral glycerol: 37/325 Placebo: 49/329 Outcome: Long-term neurological impairment (Severe neurological sequelae and profound hearing loss combined; 2 months after discharge) Oral glycerol: 36/281 Placebo: 51/275 **1. Bias arising from the randomisation process (Low/High/Some concerns)** Low risk: Centrally allocated, computer generated randomisation. No significant differences between groups at baseline **2. Bias arising due to deviations from intended interventions (Low/High/Some concerns)** Low risk: Double-blind trial and appropriate analyses used **3. Bias due to missing outcome data (Low/High/Some concerns)** Low risk: Mortality, severe neurological sequelae and profound hearing loss outcome data available for 100%, 98% and 94% of participants, respectively **4. Bias in measurement of the outcome (Low/High/Some concerns)**

Study details	Results and risk of bias assessment using Cochrane RoB 2
Recent head injury, previous neurosurgical procedure, previous neurological disease, immunosuppression or known hearing impairment. **Patient characteristics** N=654 Age (months in median; range in parentheses): glycerol + dexamethasone: 12 (2-184); glycerol + placebo: 10 (2-152); placebo + dexamethasone: 13 (2-178); placebo + placebo: 10 (2-168) Sex: male: 377 (58%); female: 277 (42%) Etiology: Haemophilus influenza: 221 (34%); Streptococcus pneumonia: 132 (20%); Neisseria meningitides: 110 (17%); other: 21 (3%); unknown: 170 (26%) Use of antibiotics before diagnosis (unclear if pre-admission): 214/589 (36%) Glasgow Coma Scale <13: 252/612 (41%) Case-fatality: 13% **Interventions** n=325 oral glycerol (glycerol + dexamethasone and glycerol + placebo groups combined): 1.5g/kg/6h 85% glycerol given orally (1.5g/kg/6h=1.5ml; maximum 25ml per dose). Most centres inserted a nasogastric tube as standard. Doses were repeated if children vomited within 30 minutes of a dose. Children also received 0.15mg/kg/6h of IV dexamethasone or IV placebo. n=329 placebo (placebo + dexamethasone and placebo + placebo groups combined): Children received either oral and intravenous placebo, or oral placebo and 0.15mg/kg/6h of IV dexamethasone. **Follow-up** Children were assessed for neurological, developmental and hearing sequelae on discharge, and after 1-2 months if sequelae were found.	Low risk: Double-blind trial and measurement did not differ between groups **5. Bias in selection of the reported result (Low/High/Some concerns)** Low risk: There is clear evidence that all eligible reported results for the outcome correspond to all intended outcome measurements and analyses **Overall risk of bias (Low/High/Some concerns)** Low risk: The study is judged to be at low risk of bias for all domains **Source of funding** Industry funded. **Other information** All children received 80-100mg/kg/day IV ceftriaxone for 7 - 10 days.
Full citation Sankar, J., Singhi, P., Bansal, A., Ray, P., Singhi, S., Role of dexamethasone and oral glycerol in reducing hearing and neurological sequelae in children with bacterial meningitis, Indian Pediatrics, 44, 649-656, 2007 **Ref Id** 139676	**Results** Outcome: All-cause mortality (up to 1 month after discharge) Oral glycerol: 2/33 Placebo: 1/25 Outcome: Any long-term neurological impairment (neurological sequelae or hearing sequelae*; up to 1 month after discharge)

Study details	Results and risk of bias assessment using Cochrane RoB 2
Country/ies where the study was carried out India **Study type** RCT **Study dates** June 2002 - September 2003 **Inclusion criteria** Children aged 2 months to 12 years with fever <1-week duration and signs of CNS involvement (for example, irritability, lethargy, convulsion, neck stiffness). Diagnosis of bacterial meningitis based on: positive CSF or blood culture, positive latex agglutination or suggestive CSF cytology and biochemical profile. **Exclusion criteria** Neurological disability, ventriculoperitoneal shunt, weight for age <60%, immunosuppressed, chronic illness, trauma or >1 dose of IV antibiotics before diagnosis. **Patient characteristics** N=58 Age (months in mean; SD in parentheses): 50 (41) Sex: male: 48 (83%); female: 10 (17%) Etiology: Hemophilus influenza: 7 (12%); Streptococcus pneumonia: 10 (17%); Staphylococcus aureus: 5 (9%); other: 2 (3%) Pre-admission antibiotics: 23 (40%) Glasgow Coma Scale <8: 10 (17%) Case-fatality: 5% **Interventions** n=33 oral glycerol (glycerol + dexamethasone and glycerol + placebo groups combined): 1.5g/kg/6h glycerol given orally or via nasogastric tube. Children also	Oral glycerol: 10/33 Placebo: 7/25 Outcome: Any long-term neurological impairment (neurological sequelae only; up to 1 month after discharge) Oral glycerol: 6/33 Placebo: 1/25 *Calculated by adding the events for both outcomes; unclear if this has led to double counting of any participants. **1. Bias arising from the randomisation process (Low/High/Some concerns)** Low risk: Generated by independent personnel using a random number table **2. Bias arising due to deviations from intended interventions (Low/High/Some concerns)** Low risk: Double-blind trial and appropriate analyses used **3. Bias due to missing outcome data (Low/High/Some concerns)** Some concerns: Loss to follow up greater in the glycerol + dexamethasone arm compared with other arms and could be related to participants' health status **4. Bias in measurement of the outcome (Low/High/Some concerns)** Low risk: Double-blind trial and appropriate analyses used **5. Bias in selection of the reported result (Low/High/Some concerns)** Some concerns: Analysis intentions are not available

Study details	Results and risk of bias assessment using Cochrane RoB 2
received 0.15mg/kg/6h IV dexamethasone or IV saline placebo. n=25 placebo (placebo + dexamethasone and placebo + placebo groups combined): 2% carboxymethylcellulose solution oral or nasogastric placebo. Children also received 0.15mg/kg/6h IV dexamethasone or IV saline placebo. **Follow-up** Daily during hospitalisation, at discharge from hospital and 1 month after discharge.	**Overall risk of bias (Low/High/Some concerns)** Some concerns: The study is judged to raise some concerns in at least one domain **Source of funding** Not industry funded **Other information** All children received 100mg/kg/day IV ceftriaxone for minimum of 7 days. Study underpowered to detect small differences in outcomes.

CNS: central nervous system; CSF: cerebrospinal fluid; ICP: intracranial pressure; HIV+: human immunodeficiency virus positive; IM: intramuscular; IV: intravenous; RCT: randomised controlled trial; SD: standard deviation; WBC: whole blood count

Appendix E Forest plots

Forest plots for review question: What is the effectiveness of osmotic agents in bacterial meningitis?

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

Figure 2: Oral glycerol versus placebo: All-cause mortality (older babies and children)

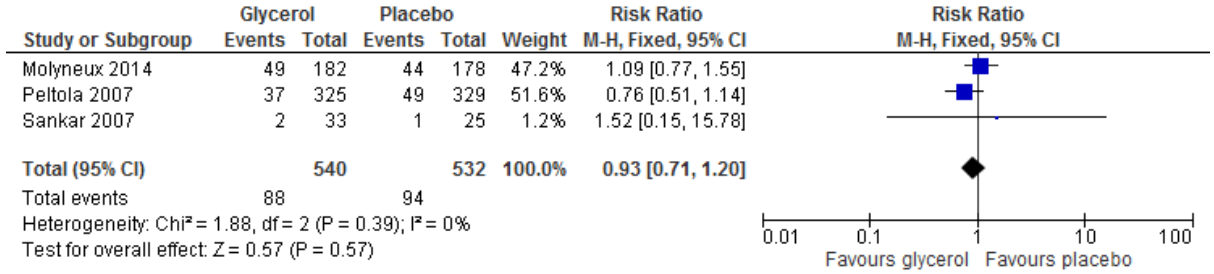
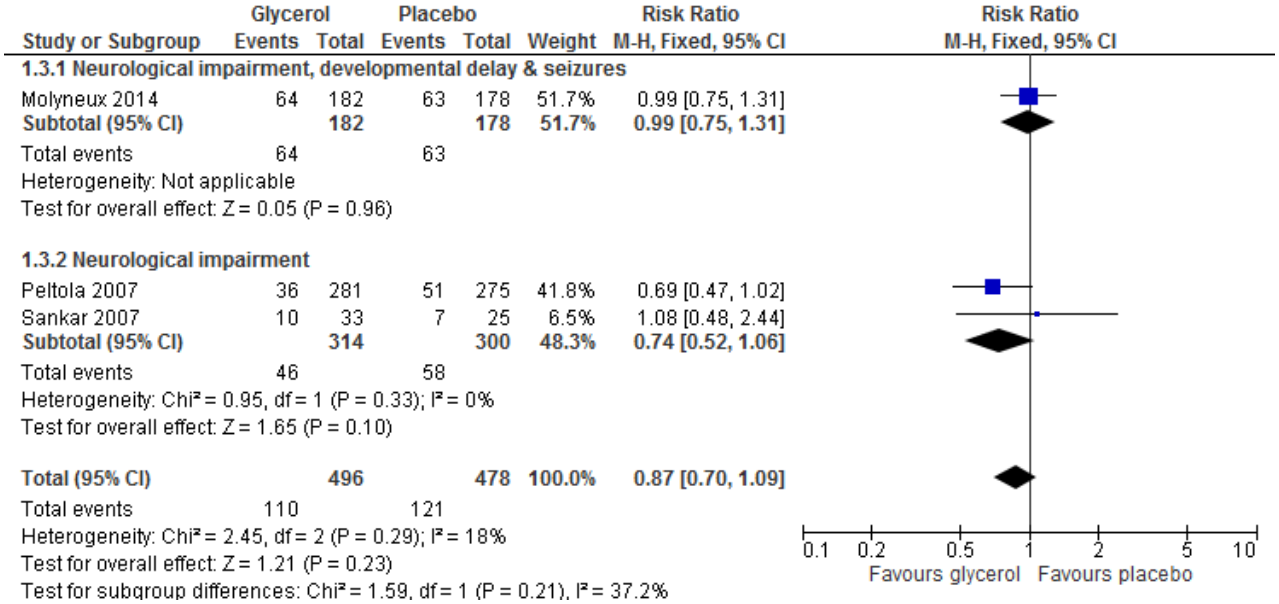


Figure 3: Oral glycerol versus placebo: Any long-term neurological impairment (older babies and children)



1 Appendix F GRADE tables

2 GRADE tables for review question: What is the effectiveness of osmotic agents in bacterial meningitis?

3 Table 5: Clinical evidence profile for comparison oral glycerol versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral glycerol	Placebo	Relative (95% CI)	Absolute		
All-cause mortality: older babies and children (follow-up 0-2 months)												
3*	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	88/540 (16.3%)	94/532 (17.7%)	RR 0.93 (0.71 to 1.2)	12 fewer per 1000 (from 51 fewer to 35 more)	VERY LOW	CRITICAL

Any long-term neurological impairment: older babies and children - Neurological impairment, developmental delay & seizures (follow-up 0-180 days)											
1 (Molyneux 2014)	randomised trials	very serious[4]	no serious inconsistency	very serious[5]	very serious[6]	none	64/182 (35.2%)	63/178 (35.4%)	RR 0.99 (0.75 to 1.31)	4 fewer per 1000 (from 88 fewer to 110 more)	VERY LOW	IMPORTANT
Any long-term neurological impairment: older babies and children - Neurological impairment (follow-up 1-2 months)											
2*	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	46/314 (14.6%)	58/300 (19.3%)	RR 0.74 (0.52 to 1.06)	50 fewer per 1000 (from 93 fewer to 12 more)	MODERATE	IMPORTANT
Any long-term neurological impairment: older babies and children (follow-up 0-6 months)											
3*	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[7]	none	110/496 (22.2%)	121/478 (25.3%)	RR 0.87 (0.7 to 1.09)	33 fewer per 1000 (from 76 fewer to 23 more)	VERY LOW	IMPORTANT

**See corresponding forest plot*
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] Population is indirect due to 36% of population in Molyneux 2014 being HIV+
[3] <300 events
[4] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[5] Outcome is indirect as it is a composite outcome including developmental delay and seizures and population is indirect due to 36% of population being HIV+
[6] 95% CI crosses 2 MIDs
[7]95% CI crosses 1 MID

Table 6: Clinical evidence profile for comparison oral glycerol versus no intervention for raised ICP

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oral glycerol**	**No intervention for raised ICP**	**Relative (95% CI)**	**Absolute**		
All-cause mortality during hospitalisation: meningitis in older babies or children												
1 (Kilpi 1995)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	2/64 (3.1%)	0/58 (0%)	OR 6.84 (0.42 to 110.92)	30 more per 1000 (from 20 fewer to 80 more)[3]	VERY LOW	CRITICAL
Any long-term neurological impairment: babies and children (follow-up 3-6 months)												
1 (Kilpi 1995)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[4]	none	4/61 (6.6%)	11/57 (19.3%)	RR 0.34 (0.14 to 0.85)	127 fewer per 1000 (from 29 fewer to 166 fewer)	LOW	IMPORTANT

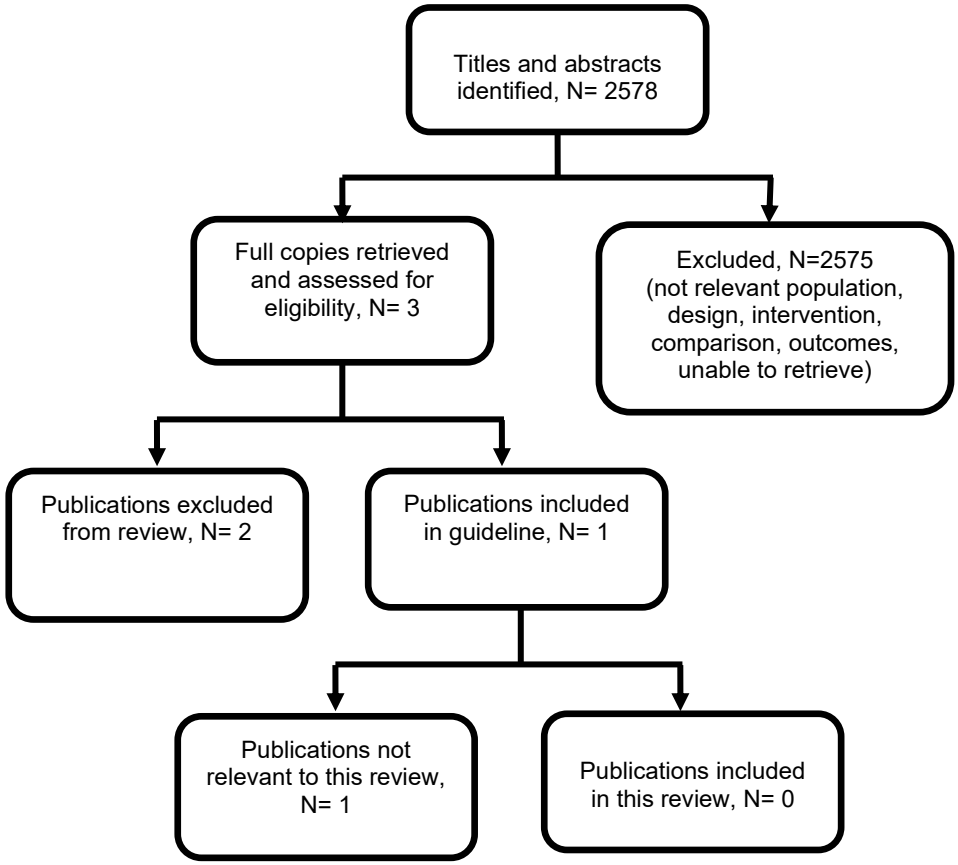
[1] *Population is indirect as it included suspected and confirmed bacterial meningitis*
[2] *<300 events and confidence interval is very large*
[3] *Absolute effect calculated based on risk difference*
[4] *95% CI crosses 1 MID*

Appendix G Economic evidence study selection

Study selection for: What is the effectiveness of osmotic agents in bacterial meningitis?

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 4).

Figure 4: Study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: What is the effectiveness of osmotic agents in bacterial meningitis?

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

Appendix I Economic model

Economic model for review question: What is the effectiveness of osmotic agents in bacterial meningitis?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What is the effectiveness of osmotic agents in bacterial meningitis?

Excluded effectiveness studies

Table 7: Excluded studies and reasons for their exclusion

Study	Reason for Exclusion
Ajdukiewicz, K. M., Cartwright, K. E., Scarborough, M., Mwambene, J. B., Goodson, P., Molyneux, M. E., Zijlstra, E. E., French, N., Whitty, C. J., Lalloo, D. G., Glycerol adjuvant therapy in adults with bacterial meningitis in a high HIV seroprevalence setting in Malawi: a double-blind, randomised controlled trial, The Lancet Infectious DiseasesLancet Infect Dis, 11, 293-300, 2011	Population not of interest for review: 83% had immunodeficiency due to HIV
Bhat, Smitha, How does glycerol compare with placebo for people with acute bacterial meningitis treated with antibiotics?, Cochrane Clinical Answers, 2018	Summary of Cochrane review (Wall 2018)
Glimaker, M., Johansson, B., Halldorsdottir, H., Wanecek, M., Elmi-Terander, A., Ghatan, P. H., Lindquist, L., Bellander, B. M., Neuro-intensive treatment targeting intracranial hypertension improves outcome in severe bacterial meningitis: an intervention-control study, Plos one, 9, 2014	Intervention not of interest for review: intracranial pressure-targeted treatment (treatment based on ICP monitoring)
Gwer, S., Gatakaa, H., Mwai, L., Idro, R., Newton, C. R., The Role for Osmotic Agents in Children with Acute Encephalopathies: A Systematic Review, JBI Library of Systematic ReviewisJBI Libr Syst Rev, 7, 154-174, 2009	Systematic review updated by Gwer 2010
Gwer, S., Gatakaa, H., Mwai, L., Idro, R., Newton, C. R., The role for osmotic agents in children with acute encephalopathies: a systematic review, BMC PediatricsBMC Pediatr, 10, 23, 2010	Includes populations not of interest for review: cerebral malaria, traumatic injury, cerebral oedema (not due to meningitis)
Kumar, R., Singhi, S., Singhi, P., Jayashree, M., Bansal, A., Bhatti, A., Randomized controlled trial comparing cerebral perfusion pressure-targeted therapy versus intracranial pressure-targeted therapy for raised intracranial pressure due to acute CNS infections in children, Critical Care Medicine, 42, 1775-1787, 2014	Population not of interest for review: only 30% had diagnosis of bacterial meningitis (remaining diagnoses: aseptic meningitis, fungal meningitis and viral encephalitis)
Peltola, H., Roine, I., Improving the outcomes in children with bacterial meningitis, Current Opinion in Infectious DiseasesCurr Opin Infect Dis, 22, 250-5, 2009	Study design not of interest for review: narrative review
Peltola, H., Roine, I., Fernandez, J., Gonzalez Mata, A., Zavala, I., Gonzalez Ayala, S., Arbo, A., Bologna, R., Goyo, J., Lopez, E., Mino, G., Dourado de Andrade, S., Sarna, S., Jauhiainen,	Outcomes and analysis not of interest for review: secondary analysis of Peltola 2007 examining the effect of interventions and presenting status on different thresholds of

Study	Reason for Exclusion
T., Hearing impairment in childhood bacterial meningitis is little relieved by dexamethasone or glycerol, PediatricsPediatrics, 125, e1-8, 2010	hearing loss
Shetty, R., Singhi, S., Singhi, P., Jayashree, M., Cerebral perfusion pressure--targeted approach in children with central nervous system infections and raised intracranial pressure: is it feasible?, Journal of Child Neurology, 23, 192-8, 2008	Study design and country combination not of interest for review: cohort study conducted in India
Singhi, S., Jarvinen, A., Peltola, H., Increase in serum osmolality is possible mechanism for the beneficial effects of glycerol in childhood bacterial meningitis, Pediatric Infectious Disease JournalPediatr Infect Dis J, 27, 892-6, 2008	Outcomes not of interest for review: comparative outcome data only available for plasma osmolality and urine output
van de Beek, D., Brouwer, M. C., Randomised controlled trial: Hearing loss after bacterial meningitis is predicted by presenting status and young age; effectiveness of adjuvant dexamethasone or glycerol unclear, Evidence Based MedicineEvid Based Med, 15, 39-40, 2010	Study design not of interest for review: commentary
Vaziri, S., Mansouri, F., Sayad, B., Ghadiri, K., Torkashvand, E., Rezaei, M., Najafi, F., Azizi, M., Meta-analysis of studies comparing adjuvant dexamethasone to glycerol to improve clinical outcome of bacterial meningitis, Journal of Research in Medical SciencesJ, 21, 22, 2016	Comparison not of interest for review: Dexamethasone versus glycerol
Wall, E. C. B., Ajdukiewicz, K. M. B., Bergman, H., Heyderman, R. S., Garner, P., Osmotic therapies added to antibiotics for acute bacterial meningitis, Cochrane Database of Systematic Reviews, 2018	Includes populations not of interest for review: immunodeficiency due to HIV

HIV: human immunodeficiency virus; ICP: intracranial pressure

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 is the effectiveness of osmotic agents in bacterial meningitis?

No research recommendation was made for this review.