National Institute for Health and Care Excellence

Draft for consultation

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

[G1] Evidence review for fluid restriction in bacterial meningitis

NICE guideline number tbc

Evidence review underpinning recommendations 1.8.1 and 1.8.2 in the NICE guideline

September 2023

Draft for consultation

This evidence review was developed by NICE

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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ISBN:

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Review question

What is the effectiveness of fluid restriction in bacterial meningitis?

Introduction

Bacterial meningitis is a rare but serious infection, which can occur in any age group. Careful management of fluid and electrolyte balance is important in the treatment of meningitis. Fluid restriction in the initial management of bacterial meningitis has been advocated.

The aim of this review is to establish the effectiveness of fluid restriction in the early management of bacterial meningitis.

Summary of the protocol

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

Table 1: Summary of the protocol (PICO table)

Population	All adults, young people, children and babies (including neonates defined as aged 28 days old and younger) with confirmed bacterial meningitis.
Intervention	Restricted fluids (as defined in studies)
Comparison	Standard care (as defined in studies)
Outcome	**Critical** Population: adults, neonates, infants and children • All-cause mortality (measured up to 1 year after discharge) • Any long-term neurological impairment (defined as any motor deficits, sensory deficits [excluding hearing impairment], cognitive deficits*, or behavioural deficits*; measured from discharge up to 1 year after discharge) Population: adults • Functional impairment (measured by any validated scale at any time point) Population: neonates, 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) **Important** Population: adults, neonates, infants and children • Diagnosis of epilepsy or occurrence of seizures during hospitalisation • Hearing impairment (defined as any level of hearing impairment; measured from discharge up to 1 year after discharge) • Serious intervention-related adverse effects leading to death, disability or prolonged hospitalisation or that are life threatening or otherwise considered medically significant Population: adults • Length of hospitalisation Population: neonates, infants and children

	• Functional impairment (measured by any validated scale at any time point) *For infants and children below school-age, cognitive and behavioural deficits will be assessed at school-age.

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

Two randomised controlled trials were included in this review (Duke 2002, Singhi 1995).

The included studies are summarised in Table 2.

Both studies (Duke 2002, Singhi 1995) compared restricted fluids to maintenance fluids 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
Duke 2002 RCT Papua New Guinea	N=346 Children aged >1 month to <12 years with confirmed bacterial meningitis Age in months (median; IQR): Restricted fluids: 5.8 (4-9) Maintenance	Restricted fluids 60% of normal maintenance fluid of expressed breast milk or other milk feed through nasogastric tube for at least 48 hours	Maintenance fluids 100% of normal maintenance fluid as 0.45% normal saline with 5% dextrose and 10 mml/l of potassium chloride per litre for at least 48 hours	• All-cause mortality • Any long-term neurological impairment (severe motor deficit and major sensory deficit, persistent convulsions or coma) • Epilepsy • Serious intervention-related adverse effects (acute	2.6% and 0.3% of population had tuberculous meningitis and cryptococcal meningitis, respectively

Study	Population	Intervention	Comparison	Outcomes	Comments
	fluids: 7 (4-16) Malnourished population: 94 (27%) Case-fatality: 19%			hyponatraemia, acute pulmonary oedema, acute facial oedema, and hydrocephalus)	
Singhi 1995 RCT India	N=50 Children aged 2 months to 7 years with confirmed bacterial meningitis Age in months (mean; SD): 13 (18.1) Case-fatality: 18%	Restricted fluids 65% of normal maintenance fluid requirement as 0.18% normal saline in 5% dextrose solution for the first 24 hours	Maintenance fluids 100% of normal maintenance fluid requirement as 0.18% normal saline in 5% dextrose solution	• All-cause mortality	Trial stopped early due to an obvious trend toward poor outcome in the fluid-restricted group.

IQR: interquartile range; 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 low to very low quality due to risk of bias (arising from subjective outcome measurement), imprecision (due to low event rates), and the inclusion of indirect outcomes. All studies were conducted in lower middle-income countries, and 27% of participants were malnourished in 1 study (Duke 2002). See the GRADE tables in appendix F for the certainty of the evidence for each individual outcome.

The evidence showed no important difference between restricted fluids and maintenance fluids for all-cause mortality, acute hyponatraemia, acute pulmonary oedema, or hydrocephalus in babies and children. There was some evidence for a higher rate of neurological impairment and epilepsy associated with fluid restriction, and a higher rate of acute facial oedema associated with maintenance fluids, although all these effect estimates were seriously or very seriously imprecise.

No other outcomes in the protocol were reported by any studies.

See appendix F for full GRADE tables.

Economic evidence

Included studies

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

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation. This was because the committee did not expect their recommendations would change current NHS practice. Furthermore, there is other NICE guidance on fluid therapy in adults, young people, and children.

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. Fluid management may reduce mortality and morbidity in bacterial meningitis, and all-cause mortality and any long-term neurological impairment were prioritised as critical outcomes because of the severity of these outcomes. Functional impairment was also prioritised as a critical outcome in adults because of the potential long-term impact on the ability to carry out certain activities of daily life. Severe developmental delay was prioritised as a critical outcome in neonates, babies, and children as it is a more relevant and important outcome for this population.

Functional impairment (in neonates, babies, and children), 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 fluid management. In adults, length of hospitalisation was also chosen as an important outcome because this may be considered as an indicator of treatment effectiveness and was expected to be commonly reported in trials.

The quality of the evidence

The quality of the evidence was assessed using GRADE methodology. The evidence was rated as very low to low quality due to risk of bias (arising from subjective outcome measurement), imprecision (due to low event rates), and the inclusion of indirect populations and outcomes.

No evidence was found that reported functional impairment, severe developmental delay, hearing impairment, or length of hospitalisation.

Benefits and harms

The committee considered the evidence comparing fluid restriction and maintenance fluid in the treatment of bacterial meningitis in babies and children, that showed no important difference for mortality, and a higher rate of neurological impairment and epilepsy associated with fluid restriction. The committee acknowledged the low quality and limited evidence but were concerned that fluid restriction showed harm for a critical outcome. Based on this best available evidence, and their clinical knowledge and experience, the committee agreed to recommend that fluid intake is not routinely restricted (defined as a volume less than the person's maintenance requirements) in bacterial meningitis. The committee discussed that there are some situations in which fluid restriction should be considered. For example, if a patient had a lot of fluid resuscitation during an acute unstable phase, then fluid overload

could occur in recovery phase, in which case it would be clinically appropriate to restrict fluid intake. However, the committee agreed that fluid restriction should only be considered in certain cases and based on the individual clinical presentation and needs of the patient.

This review did not provide evidence on routes of fluid administration, however the committee felt that for patient safety, it was important to provide a recommendation on route of administration for maintenance fluids based on good clinical practice and their expert opinion. The committee agreed that people with bacterial meningitis do not need to have all their fluids as intravenous fluids and were aware of the risk of complications related to the intravenous route. Therefore, the committee agreed that maintenance fluid should be given orally or by enteral tube if tolerated to avoid unnecessary intravenous fluids.

Cost effectiveness and resource use

This review question was not prioritised for economic analysis and therefore the committee made a qualitative assessment of the likely cost-effectiveness of their recommendations. The committee considered that their recommendations with respect to fluid restriction were all very low cost and were therefore likely to be cost-effective as they were underpinned by the best available clinical evidence allied with their expertise and knowledge to maximise health related quality of life. The committee noted that their recommendations were in line with current NHS practice and that they would not have a significant resource impact.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.8.1 and 1.8.2.

References – included studies

Effectiveness

Duke 2002

Duke, T., Mokela, D., Frank, D., Michael, A., Paulo, T., Mgone, J., Kurubi, J., Management of meningitis in children with oral fluid restriction or intravenous fluid at maintenance volumes: a randomised trial, Annals of Tropical Paediatrics, 22, 145-57, 2002

Singhi 1995

Singhi, S. C., Singhi, P. D., Srinivas, B., Narakesri, H. P., Ganguli, N. K., Sialy, R., Walia, B. N., Fluid restriction does not improve the outcome of acute meningitis, Pediatric Infectious Disease Journal, 14, 495-503, 1995

Economic

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

Appendices

Appendix A Review protocols

Review protocol for review question: What is the effectiveness of fluid restriction in bacterial meningitis?

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42021264073
Review title	Fluid restriction in bacterial meningitis
Review question	What is the effectiveness of fluid restriction in bacterial meningitis?
Objective	To determine the effectiveness of fluid restriction 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: Date limitations: No date limit 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 (including neonates defined as

Field	Content
	aged 28 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, head trauma, 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	Restricted fluids (as defined in studies)
Comparator/Reference standard/Confounding factors	Standard care (as defined in studies)
Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs • RCTs • If insufficient RCTs: prospective 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 illness at presentation 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

Field	Content
	septicaemia in under 16s: recognition, diagnosis and management (CG102)
Primary outcomes (critical outcomes)	Population: adults • All-cause mortality (measured up to 1 year after discharge) • Any long-term neurological impairment (defined as any motor deficits, sensory deficits [excluding hearing impairment], cognitive deficits, or behavioural deficits; measured from discharge up to 1 year after discharge) • Functional impairment (measured by any validated scale at any time point) Population: neonates, infants and children: • All-cause mortality (measured up to 1 year after discharge) • Any long-term neurological impairment (defined as any motor deficits, sensory deficits [excluding hearing impairment], cognitive deficits*, or behavioural deficits*; measured from discharge up to 1 year after discharge) • Severe developmental delay (defined as score of >2 SD below normal on validated assessment scales, or MDI or PDI <70 on Bayleys assessment scale, or inability to assign a score due to cerebral palsy or severity of cognitive delay; measured at the oldest age reported unless there is substantially more data available at a younger age) *For infants and children below school-age, cognitive and behavioural deficits will be assessed at school-age.
Secondary outcomes (important outcomes)	Population: adults • Diagnosis of epilepsy or occurrence of seizures during hospitalisation • Hearing impairment (defined as any level of hearing impairment; measured from discharge up to 1 year after discharge) • Serious intervention-related adverse effects leading to death, disability or prolonged hospitalisation or that are life threatening or otherwise considered medically significant • Length of hospitalisation

Field	Content
	Population: neonates, infants and children: • 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	Evidence will be stratified by: Age: • Neonates and younger infants: 0 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.

Field	Content	
	Therefore, we will be guided by cut-offs used in the evidence when determining if 16 to 18 year olds should be treated as adults or children. Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes: Age: • Young and middle aged adults; • Older adults* *There is variation regarding the age at which adults should be considered older adults. Therefore, we will be guided by cut-offs used in the evidence when determining this threshold. Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.	
Type and method of review	☒	Intervention
	☐	Diagnostic
	☐	Prognostic
	☐	Qualitative
	☐	Epidemiologic
	☐	Service Delivery
	☐	Other (please specify)
Language	English	
Country	England	

Field	Content		
Anticipated or actual start date	24/06/2021		
Anticipated completion date	07/12/2023		
Stage of review at time of this submission	Review stage	Started	Completed
	Preliminary searches	☑	☑
	Piloting of the study selection process	☑	☑
	Formal screening of search results against eligibility criteria	☑	☑
	Data extraction	☑	☑
	Risk of bias (quality) assessment	☑	☑
	Data analysis	☑	☑
Named contact	Named contact: National Guideline Alliance Named contact e-mail: meningitis&meningococcal@nice.org.uk Organisational affiliation of the review: National Institute for Health and Care Excellence (NICE) and National Guideline Alliance		
Review team members	National Guideline Alliance		
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance which receives funding from NICE.		
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any 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		

Field	Content	
	published with the final guideline.	
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10149.	
Other registration details	None	
Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021264073	
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, fluid restriction, 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 is the effectiveness of fluid restriction in bacterial meningitis?

Clinical Search

Database(s): Medline & Embase (Multifile) – OVID interface
Embase Classic+Embase 1947 to 2022 November 09, **Ovid MEDLINE(R) ALL** 1946 to November 09, 2022
Date of last search: 10 November 2022
Multifile database codes: emczd = Embase Classic+Embase; medall= MEDLINE(R) ALL

#	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 exp Neisseria Meningitidis/
2	1 use medall
3	meningitis/ or bacterial meningitis/ or haemophilus meningitis/ or hemophilus influenzae meningitis/ or listeria meningitis/ or meningococcal meningitis/ or pneumococcal meningitis/ or meningoencephalitis/ 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* or mening* encephalitis*).ti,ab.
9	(Neisseria* mening* or n mening*).ti,ab.
10	or/2,4-9
11	Fluid Therapy/ or Solutions/ or exp Hypertonic solutions/ or Isotonic Solutions/ or Rehydration Solutions/ or Water Deprivation/
12	11 use medall
13	fluid therapy/ or "solution and solubility"/ or hypertonic solution/ or isotonic solution/ or oral rehydration solution/ or water deprivation/
14	13 use emczd
15	(fluid* adj3 (therap* or restrict* or unrestrict* or un-restrict* or limit* or reduc* or maint* or replacement or manage* or balance* or volume* or regimen* or intravenous* or iv)).ti,ab.
16	(fluid* adj (intake* or regulat* or administ*)).ti,ab.
17	((fluid* or volume) adj3 resuscitation?).ti,ab.
18	((liquid or water) adj3 (restrict* or unrestrict* or un-restrict* or limit* or reduc* or maint*)).ti,ab.
19	or/12,14-18
20	10 and 19
21	(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.
22	21 use medall
23	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.
24	23 use emczd
25	meta-analysis/
26	meta-analysis as topic/
27	systematic review/
28	meta-analysis/
29	(meta analy* or metanaly* or metaanaly*).ti,ab.
30	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
31	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
32	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.

#	Searches
33	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
34	(search* adj4 literature).ab.
35	(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.
36	cochrane.jw.
37	((pool* or combined) adj2 (data or trials or studies or results)).ab.
38	(or/25-26,29,31-36) use medall
39	(or/27-30,32-37) use emczd
40	or/22,24,38-39
41	20 and 40
42	20 not 41
43	((letter/ or editorial/ or news/ or exp historical article/ or anecdotes as topic/ or comment/ or case report/ or (letter or comment*).ti.) not (randomized controlled trial/ or random*.ti,ab.)) or (animals not humans).sh. or exp animals, laboratory/ or exp animal experimentation/ or exp models, animal/ or exp rodentia/ or (rat or rats or mouse or mice).ti.
44	43 use medall
45	((letter.pt. or letter/ or note.pt. or editorial.pt. or case report/ or case study/ or (letter or comment*).ti.) not (randomized controlled trial/ or random*.ti,ab.)) or ((animal/ not human/) or nonhuman/ or exp animal experiment/ or exp experimental animal/ or animal model/ or exp rodent/ or (rat or rats or mouse or mice).ti.)
46	45 use emczd
47	44 or 46
48	41 not 47
49	42 not 47
50	limit 48 to English language
51	limit 49 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: [Fluid Therapy] this term only
#18	MeSH descriptor: [Solutions] this term only
#19	MeSH descriptor: [Hypertonic Solutions] explode all trees
#20	MeSH descriptor: [Isotonic Solutions] this term only
#21	MeSH descriptor: [Rehydration Solutions] this term only
#22	MeSH descriptor: [Water Deprivation] this term only
#23	((fluid* near/3 (therap* or restrict* or unrestrict* or "un restrict*" or limit* or reduc* or maint* or replace* or manag* or balanc* or volume* or regimen* or intravenous* or iv))):ti,ab,kw

#	Searches
#24	((fluid* next (intake* or regulat* or administ*))):ti,ab,kw
#25	(((fluid* or volume) near/3 resuscitation*)):ti,ab,kw
#26	(((liquid or water) near/3 (restrict* or unrestrict* or "un restrict*" or limit* or reduc* or maint* or manag*))):ti,ab,kw
#27	{or #17-#26}
#28	#16 and #27
#29	"conference":pt or (clinicaltrials or trialsearch):so
#30	#28 not #29

Database(s): Database of Abstracts of Reviews of Effects (DARE); HTA Database – CRD interface

Date of last search: 26 May 2021

#	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 EXPLODE ALL TREES 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 Neisseria meningitidis EXPLODE ALL TREES IN DARE,HTA
10	(((((bacter* or infect*) NEAR3 (meningit* or meninges* or leptomeninges* or "subarachnoid space*"))))) IN DARE, HTA
11	((((((meningencephalitis* or meningoencephalitis* or meningit*)))))) IN DARE, HTA
12	((((Neisseria* NEXT mening*)))) IN DARE, HTA
13	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
14	MeSH DESCRIPTOR Fluid Therapy IN DARE,HTA
15	MeSH DESCRIPTOR Solutions IN DARE,HTA
16	MeSH DESCRIPTOR Hypertonic solutions EXPLODE ALL TREES IN DARE,HTA
17	MeSH DESCRIPTOR Isotonic Solutions IN DARE,HTA
18	MeSH DESCRIPTOR Rehydration Solutions IN DARE,HTA
19	MeSH DESCRIPTOR Water Deprivation IN DARE,HTA
20	((fluid* NEAR3 (therap* or restrict* or unrestrict* or un-restrict* or limit$ or reduc* or maint* or replacement or manage* or balance* or volume* or regimen* or intravenous* or iv))) IN DARE, HTA
21	((fluid* NEAR1 (intake* or regulat* or administ*))) IN DARE, HTA
22	(((fluid* or volume) NEAR3 resuscitation*)) IN DARE, HTA
23	(((liquid or water) NEAR3 (restrict* or unrestrict* or un-restrict* or limit* or reduc* or maint*))) IN DARE, HTA
24	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
25	#13 AND #24

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

#	Searches
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
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.

#	Searches
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
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/

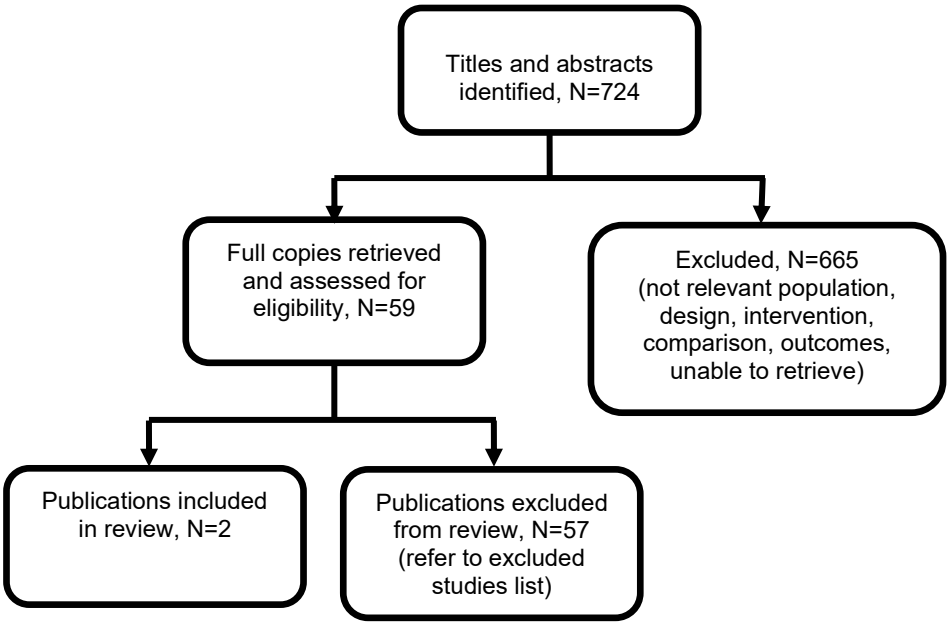
#	Searches
105	exp Experimental Animal/
106	animal model/
107	exp Rodent/
108	(rat or rats or mouse or mice).ti.
109	101 or 102 or 103 or 104 or 105 or 106 or 107 or 108
110	93 use ppez
111	109 use emczd
112	110 or 111
113	74 not 112
114	limit 113 to English language
115	75 not 112
116	limit 115 to English language
117	114 or 116

1

Appendix C Effectiveness evidence study selection

Study selection for review question: What is the effectiveness of fluid restriction in bacterial meningitis?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What is the effectiveness of fluid restriction in bacterial meningitis?

Table 4: Evidence tables – effectiveness evidence

Study details	Results and risk of bias assessment using Cochrane RoB 2
Full citation Duke, T., Mokela, D., Frank, D., Michael, A., Paulo, T., Mgone, J., Kurubi, J., Management of meningitis in children with oral fluid restriction or intravenous fluid at maintenance volumes: a randomised trial, Annals of Tropical Paediatrics, 22, 145-57, 2002 **Ref Id** 1135462 **Country/ies where the study was carried out** Papua New Guinea **Study type** RCT **Study dates** September 1997 - October 2000 **Inclusion criteria** Children aged >1 month to <12 years with confirmed bacterial meningitis (clinical signs and characteristic CSF findings) **Exclusion criteria** Congenital heart disease, renal failure, septic or hypovolaemic shock and history of parenteral antibiotics treatment for 48 hours or more in the week prior to presentation **Patient characteristics**	**Results** Outcome: All-cause mortality (3 months after discharge) Restricted fluids: 34/172 Maintenance fluids: 31/174 Composite outcome[1]: Any long-term neurological impairment (severe motor deficit and major sensory deficit, persistent convulsions or coma; 3 months after discharge) Restricted fluids: 21/172 Maintenance fluids: 9/174 Outcome: Epilepsy (during hospitalisation) Restricted fluids: 10/172 Maintenance fluids: 2/174 Outcome: Serious intervention-related adverse effects (acute hyponatraemia; serum sodium <130 mmol/l at 72 hours; during hospitalisation) Restricted fluids: 13/123 Maintenance fluids: 11/144 Outcome: Serious intervention-related adverse effects (acute pulmonary oedema; during hospitalisation) Restricted fluids: 0/172 Maintenance fluids: 4/174 Outcome: Serious intervention-related adverse effects (acute facial oedema at 48 hours; during hospitalisation)

Study details	Results and risk of bias assessment using Cochrane RoB 2
N=346 Age (months in median; IQR in parentheses): Restricted fluids: 5.8 (4-9); Maintenance fluids: 7 (4-16) Sex: male: 185 (53%); female: 161 (47%) Malnourished: 94 (27%) Etiology: Streptococcus pneumoniae: 124 (36%); Haemophilus influenzae type b: 110 (32%); Streptococcus pneumoniae and Haemophilus influenzae type b: 2 (0.5%); Non-type b H. influenzae: 5 (1%); Enteric gram-negative bacteria: 7 (2%); other gram-positive bacteria: 10 (3%); Proteus mirabilis and streptococci: 1 (0.3%); Neisseria meningitidis: 1 (0.3%); likely Mycobacterium tuberculosis: 9 (2.6%); Cryptococcus neoformans: 1 (0.3%); other: 76 (22%). Hyponatraemia (serum sodium <130 mmol/l): 61 (19% of 326) **Interventions** Restricted fluids: Children received 60% of normal maintenance fluid* of expressed breast milk or other milk feed through nasogastric tube for at least 48 hours. Maintenance fluids: Children received 100% of normal maintenance fluid[1] as 0.45% normal saline with 5% dextrose and 10 mml/l of potassium chloride per litre for at least 48 hours. [1]Normal maintenance fluid requirement was defined as 100 ml/kg/day for the first 10 kg, 50 ml/kg for next 10 kg and 20 ml/kg for over 20 kg. **Follow-up** Infants and children were assessed during hospitalisation and 3 months after discharge.	Restricted fluids: 8/172 Maintenance fluids: 45/174 Outcome: Serious intervention-related adverse effects (hydrocephalus at 14 days; during hospitalisation) Restricted fluids: 7/172 Maintenance fluids: 2/174 [1]It is a composite of outcomes included in the protocol (and persistent convulsions and coma are not included in the protocol). **1. Bias arising from the randomisation process (Low/High/Some concerns)** Low risk: Computer generated randomisation and sealed envelopes were used. 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 there is no reason to believe deviations arose because of the trial context. Appropriate analysis was used. **3. Bias due to missing outcome data (Low/High/Some concerns)** Low risk: About 11.3% of participants lost to follow-up at 3 months, but missingness in the outcome could not depend on its true value. **4. Bias in measurement of the outcome (Low/High/Some concerns)** Low risk (all-cause mortality and acute hyponatraemia): Measurement did not differ between groups. Knowledge of the assigned intervention could not influence the outcome. High risk (any long-term neurological impairment, epilepsy, acute pulmonary oedema, acute facial oedema and hydrocephalus):

Study details	Results and risk of bias assessment using Cochrane RoB 2
	Measurement did not differ between groups. Knowledge of the assigned intervention was likely to influence outcome assessment. **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 (all-cause mortality and acute hyponatraemia): The study is judged to be at low risk of bias for all domains. High risk (any long-term neurological impairment, epilepsy, acute pulmonary oedema, acute facial oedema and hydrocephalus): The study is judged to be at high risk of bias in at least one domain (bias in measurement of the outcome). **Source of funding** Part-industry funded. **Other information** Population is not indirect because only 2.6% (n=9) and 0.3% (n=1) of total participants (N=346) have tuberculous meningitis and cryptococcal meningitis, respectively.
Full citation Singhi, S. C., Singhi, P. D., Srinivas, B., Narakesri, H. P., Ganguli, N. K., Sialy, R., Walia, B. N., Fluid restriction does not improve the outcome of acute meningitis, Pediatric Infectious Disease Journal, 14, 495-503, 1995 **Ref Id** 1136531 **Country/ies where the study was carried out** India	**Results** Outcome: All-cause mortality (during hospitalisation) Restricted fluids: 7/28 Maintenance fluids: 2/22 **1. Bias arising from the randomisation process (Low/High/Some concerns)** Some concerns: Randomisation list was prepared using a random number table, but no information about allocation concealment was provided. No significant differences between groups at baseline.

Study details	Results and risk of bias assessment using Cochrane RoB 2
Study type RCT **Study dates** Not reported **Inclusion criteria** Children aged 2 months to 7 years with confirmed bacterial meningitis (history, physical examination and characteristic CSF findings with or without a positive CSF culture or blood culture or counterimmunoelectrophoresis for bacterial antigens). **Exclusion criteria** Respiratory disease, heart disease, gastrointestinal disease, renal disease, other central nervous system disease, endocrine disorder, cancer, immunocompromisation, malnutrition and history of anticonvulsant treatment. **Patient characteristics** N=50 Age (months in mean; SD in parentheses): 13 (18.1) Sex: male: 32 (64%); female: 18 (36%) Etiology: Streptococcus pneumoniae: 8 (16%); Haemophilus influenzae: 6 (12%); Staphylococcus aureus: 3 (6%); other: 8 (16%); unknown: 25 (50%) Hyponatraemia (serum sodium ≤130 mq/l): No hyponatraemia: 24 (48%); Hyponatraemia: 26 (52%) **Interventions** Restricted fluids: Children received 65% of normal maintenance fluid requirement* as 0.18% normal saline in 5% dextrose solution for the first 24 hours, with a gradual liberalisation at a rate of 10 ml/kg over 8 hours after 24 hours and full amount of normal maintenance fluid after 48 hours. Maintenance fluids: Children received 100% of normal maintenance fluid requirement[1] as 0.18% normal saline in 5% dextrose solution.	**2. Bias arising due to deviations from intended interventions (Low/High/Some concerns)** Low risk: No information on blinding. No reason to believe deviations arose because of the trial context. Appropriate analysis was used. **3. Bias due to missing outcome data (Low/High/Some concerns)** Low risk: Outcome data was available for 100% of participants. **4. Bias in measurement of the outcome (Low/High/Some concerns)** Low risk: Measurement did not differ between groups. No information on blinding of investigator. Knowledge of the assigned intervention could not influence the outcome (all-cause mortality). **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)** Some concerns: The study is judged to raise some concerns in at least one domain (bias arising from the randomisation process). **Source of funding** Not reported **Other information** Trial stopped early due to an obvious trend toward poor outcome in the fluid-restricted group.

Study details	Results and risk of bias assessment using Cochrane RoB 2
[1]Normal maintenance fluid requirement was defined as 110 ml/kg/day for the first 10 kg, 50 ml/kg for next 10 kg and 25 ml/kg for over 20 kg. **Follow-up** Babies and children were assessed during hospitalisation.	

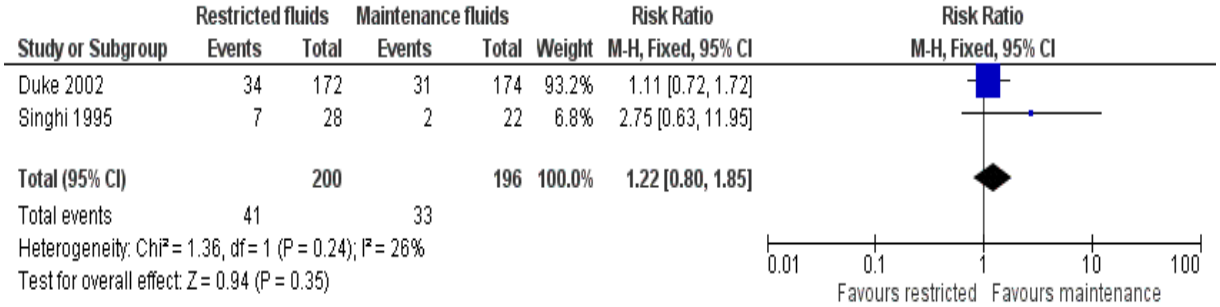
CSF: cerebrospinal fluid; IQR: interquartile range; RCT: randomised controlled trial; SD: standard deviation

Appendix E Forest plots

Forest plots for review question: What is the effectiveness of fluid restriction 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: Restricted fluids versus maintenance fluids: All-cause mortality (babies and children)



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

Appendix F GRADE tables

GRADE tables for review question: What is the effectiveness of fluid restriction in bacterial meningitis?

Table 5: Evidence profile for comparison restricted fluids versus maintenance fluids

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Restricted fluids	Maintenance fluids	Relative (95% CI)	Absolute		
All-cause mortality: babies and children (follow-up 0-3 months)												
2*	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	41/200 (20.5%)	33/196 (16.8%)	RR 1.22 (0.8 to 1.85)	37 more per 1000 (from 34 fewer to 143 more)	LOW	CRITICAL
Any long-term neurological impairment (severe motor deficit and major sensory deficit, persistent convulsions or coma): babies and children (follow-up 3 months)												
1 (Duke 2002)	randomised trials	very serious[2]	no serious inconsistency	serious[3]	serious[4]	none	21/172 (12.2%)	9/174 (5.2%)	RR 2.36 (1.11 to 5.01)	70 more per 1000 (from 6 more to 207 more)	VERY LOW	CRITICAL
Epilepsy: babies and children (during hospitalisation)												
1 (Duke 2002)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	10/172 (5.8%)	2/174 (1.1%)	RR 5.06 (1.12 to 22.75)	47 more per 1000 (from 1 more to 250 more)	VERY LOW	IMPORTANT
Serious intervention-related adverse effects (acute hyponatraemia): babies and children (during hospitalisation)												
1 (Duke 2002)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	13/123 (10.6%)	11/144 (7.6%)	RR 1.38 (0.64 to 2.98)	29 more per 1000 (from 28 fewer to 151 more)	LOW	IMPORTANT
Serious intervention-related adverse effects (acute pulmonary oedema): babies and children (during hospitalisation)												
1 (Duke 2002)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	0/172 (0%)	4/174 (2.3%)	RR 0.11 (0.01 to 2.07)	20 fewer per 1000 (from 23 fewer to 25 more)	VERY LOW	IMPORTANT

Serious intervention-related adverse effects (acute facial oedema): babies and children (during hospitalisation)												
1 (Duke 2002)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	8/172 (4.7%)	45/174 (25.9%)	RR 0.18 (0.09 to 0.37)	212 fewer per 1000 (from 163 fewer to 235 fewer)	VERY LOW	IMPORTANT
Serious intervention-related adverse effects (hydrocephalus): babies and children (during hospitalisation)												
1 (Duke 2002)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	7/172 (4.1%)	2/174 (1.1%)	RR 3.54 (0.75 to 16.8)	29 more per 1000 (from 3 fewer to 182 more)	VERY LOW	IMPORTANT

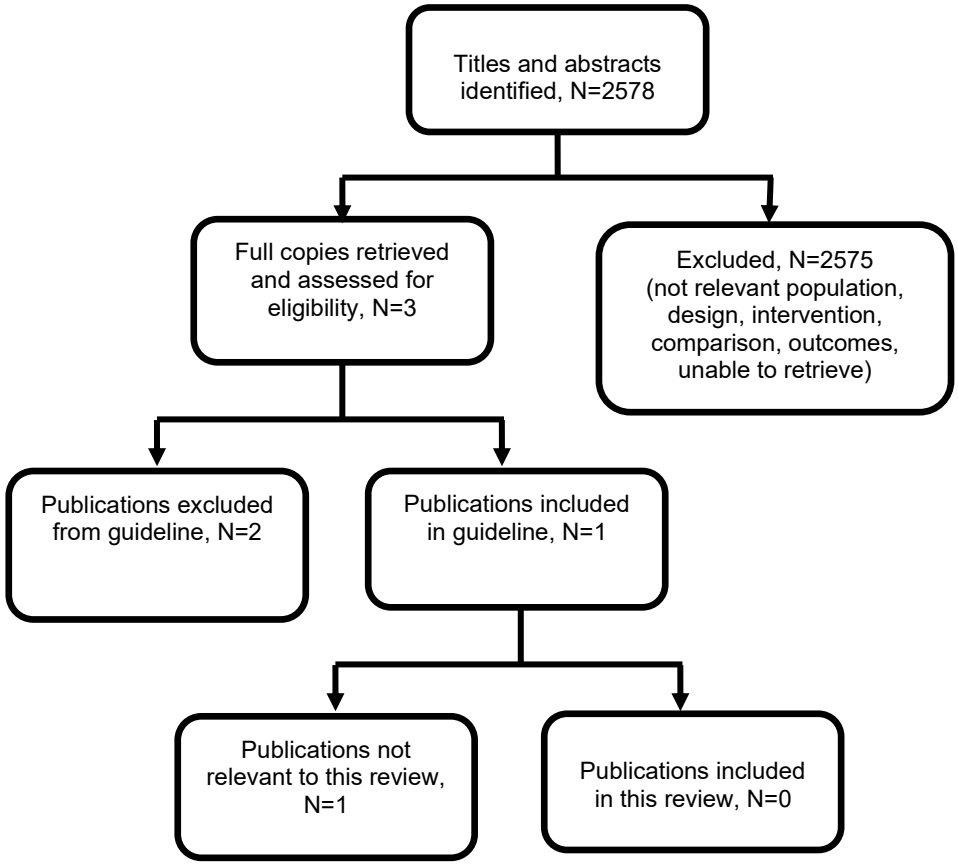
CI: confidence interval; RR: risk ratio
**See corresponding forest plot*
[1] <150 events
[2] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[3] Outcome is indirect as it is a composite outcome including persistent convulsions and coma
[4] 95% CI crosses 1 MID

Appendix G Economic evidence study selection

Study selection for: What is the effectiveness of fluid restriction 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 3).

Figure 3: Study selection flow chart



Appendix H Economic evidence tables

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

Excluded effectiveness studies

Table 6: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Ackerman, A. D., Singhi, S., Pediatric infectious diseases: 2009 update for the Rogers' Textbook of Pediatric Intensive Care, Pediatric Critical Care Medicine, 11, 117-23, 2010	Study design does not meet inclusion criteria: narrative review
Bradshaw, J., The infant with meningitis, Nursing - OxfordNursing (Lond), 2, 473-5, 1983	Study design does not meet inclusion criteria
Brouwer, M. C., van de Beek, D., Heckenberg, S. G., Spanjaard, L., de Gans, J., Hyponatraemia in adults with community-acquired bacterial meningitis, Qjm, 100, 37-40, 2007	Comparison does not meet inclusion criteria: hyponatraemia present vs. hyponatraemia absent
Brown, L. W., Feigin, R. D., Bacterial meningitis: fluid balance and therapy, Pediatric Annals, 23, 93-8, 1994	Study design does not meet inclusion criteria: narrative review
Charlier, C., Kermorvant-Duchemin, E., Perrodeau, E., Moura, A., Maury, M. M., Bracq-Dieye, H., Thouvenot, P., Vales, G., Leclercq, A., Ravaud, P., Lecuit, M., neonatal, Monalisa study group, Neonatal listeriosis presentation and outcome: a prospective study of 189 cases, Clinical Infectious Diseases, 20, 20, 2021	Study intervention/exposure does not meet inclusion criteria: no fluid restriction
Craft, J. C., Feldman, W. E., Nelson, J. D., Clinicopharmacological evaluation of amoxicillin and probenecid against bacterial meningitis, Antimicrobial Agents & Chemotherapy, 16, 346-52, 1979	Intervention does not meet inclusion criteria: drug intervention
Di Mauro, A., Cortese, F., Laforgia, N., Pantaleo, B., Giuliani, R., Bonifazi, D., Ciccone, M. M., Giordano, P., Neonatal bacterial meningitis: a systematic review of European available data, Minerva Pediatrica, 71, 201-208, 2019	Study design does not meet inclusion criteria: systematic review does not report the evidence from RCTs investigating the effectiveness of fluid restriction in bacterial meningitis
El Bashir, H., Laundy, M., Booy, R., Diagnosis and treatment of bacterial meningitis, Archives of Disease in Childhood, 88, 615-620, 2003	Study design does not meet inclusion criteria: narrative review
English, M., Berkley, J., Mwangi, I., Mohammed, S., Ahmed, M., Osier, F., Muturi, N., Ogutu, B., Marsh, K., Newton, C. R. J. C., Hypothetical performance of syndrome-based management of acute paediatric admissions of children aged more than 60 days in a Kenyan district hospital, Bulletin of the World Health Organization, 81, 166-173, 2003	Study intervention/exposure does not meet inclusion criteria: no fluid restriction
Esteban, E., Ferrer, R., Segura, S., Felipe, A., Perez-Baena, L., Bustinza, A., Gomezo, F., Concha, A., Septic children in pediatric intensive care: Descriptive analysis of the preintervention	Conference paper

Study	Reason for exclusion
period of the abiss-edusepsis pediatric study, Intensive Care Medicine, 2), S231-S232, 2013	
Feigin, R. D., Kaplan, S., Inappropriate secretion of antidiuretic hormone in children with bacterial meningitis, American Journal of Clinical Nutrition, 30, 1482-4, 1977	Study design does not meet inclusion criteria: non-comparative
Galiza,E.P., Heath,P.T., Improving the outcome of neonatal meningitis, Current Opinion in Infectious Diseases, 22, 229-234, 2009	Study design does not meet inclusion criteria: narrative review
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	Study design and intervention do not meet inclusion criteria: no randomisation and no fluid restriction
Grimwood, K., Dawson, K. P., Management of acute bacterial meningitis in childhood, New Zealand Medical Journal, 95, 545-548, 1982	Study design does not meet inclusion criteria: narrative review
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 Pediatrics, 10, 23, 2010	Study population and intervention do not meet inclusion criteria: children with acute encephalopathies and osmotic agents
Hadgu, P., Tafari, N., Results of current therapy for pyogenic meningitis in childhood, Ethiopian Medical Journal, 11, 67-73, 1973	Study design does not meet inclusion criteria: retrospective study
Heyman, S. N., Ginosar, Y., Shapiro, M., Kluger, Y., Marx, N., Maayan, S., Diarrheal epidemics among Rwandan refugees in 1994: Management and outcome in a field hospital, Journal of Clinical Gastroenterology, 25, 595-601, 1997	Study design and intervention/exposure do not meet inclusion criteria: retrospective study, and no fluid restriction
Holliday, M. A., Friedman, A. L., Segar, W. E., Chesney, R., Finberg, L., Acute hospital-induced hyponatremia in children: A physiologic approach, Journal of Pediatrics, 145, 584-587, 2004	Study design does not meet inclusion criteria: narrative review and case report
Hoorn, E. J., Spasovski, G., Recent developments in the management of acute and chronic hyponatremia, Current Opinion in Nephrology & Hypertension, 28, 424-432, 2019	Study design does not meet inclusion criteria: narrative review
Jacobs, L. G., Infectious disease emergencies in the geriatric population, Clinics in Geriatric Medicine, 9, 559-575, 1993	Study design does not meet inclusion criteria: narrative review
Jenson, A., Rao, A., Mda, P., Cawe, B., Iruedo, J., Dubula, T., Stead, D., Rothman, R., Hansoti, B., One in four die from acute infectious illness in an emergency department in Eastern Cape Province, South Africa, South African Medical Journal, 111, 129-136, 2021	Population does not meet inclusion criteria: 90% with lung infection, abdominal infection, UTI, TB and PUO
Johnsen,S.D., Some important pitfalls in the diagnosis and treatment of bacterial meningitis in children, Clinical Pediatrics, 14, 191-200, 1975	Study design does not meet inclusion criteria: narrative review
Juntunen, A., Ritvanen, O., Herrgard, E., Korppi, M., Fluid balance in bacterial meningitis in	Comparison does not meet inclusion criteria: comparison between different fluid disorders

Study	Reason for exclusion
children, Current Paediatric Research, 2, 11-16, 1998	
Kanakriyeh, M., Carvajal, H. F., Vallone, A. M., Initial fluid therapy for children with meningitis with consideration of the syndrome of inappropriate anti-diuretic hormone, Clinical Pediatrics, 26, 126-30, 1987	Study design does not meet inclusion criteria: retrospective study
Kaplan, S. L., Feigin, R. D., Treatment of meningitis in children, Pediatric Clinics of North America, 30, 259-269, 1983	Study design does not meet inclusion criteria: narrative review/symposium paper
Kaplan, S. L., O'Brian Smith, E., Wills, C., Feigin, R. D., Associated between preadmission oral antibiotic therapy and cerebrospinal fluid findings and sequlae caused by Haemophilus influenzae type b meningitis, Pediatric Infectious Disease, 5, 626-632, 1986	Study intervention/exposure does not meet inclusion criteria: oral antibiotic therapy
Kauhtio, J., Rantasalo, J., Acute bacterial meningitis in children. III. Treatment of the 257 cases admitted to Children's Hospital, University of Helsinki, in 1946-55, Annales Paediatriae Fenniae, 4, 174-180, 1958	Study design and intervention/exposure do not meet inclusion criteria: case series, and no fluid restriction
Kumar, M., Mitra, K., Jain, R., Isotonic versus hypotonic saline as maintenance intravenous fluid therapy in children under 5 years of age admitted to general paediatric wards: a randomised controlled trial, Paediatrics & international Child Health, 40, 44-49, 2020	Study population and comparison do not meet inclusion criteria: children with an anticipated requirement for IVF (for example, respiratory disease, GI disease, CNS disease and metabolic disease), and Isotonic fluid vs. Hypo tonic fluid
Kumar, V., Singhi, P., Singhi, S., Changes in body water compartments in children with acute meningitis, Pediatric Infectious Disease Journal, 13, 299-305, 1994	≥50% of population not of interest for review: comparison group without meningitis
Laine, J., Holmberg, C., Anttila, M., Peltola, H., Perheentupa, J., Types of fluid disorder in children with bacterial meningitis, Acta Paediatrica Scandinavica, 80, 1031-6, 1991	Comparison does not meet inclusion criteria: comparison between different fluid disorders
Lunoe, M., Overgaard-Steensen, C., Prevention of hospital-acquired hyponatraemia: individualised fluid therapy, Acta Anaesthesiologica Scandinavica, 59, 975-85, 2015	Study design does not meet inclusion criteria: narrative review
Maconochie, I. K., Bhaumik, S., Fluid therapy for acute bacterial meningitis, Cochrane Database of Systematic Reviews, 2016	Discrepancy between the data presented in the review and the primary paper for mortality, therefore data extracted from primary papers (Duke 2002 and Singhi 1995)
Martos-Benitez, F. D., Guzman-Breff, B. I., Volume expansion and variation in haemodynamic parameters, Emergencias, 31, 177-181, 2019	Population and outcomes do not meet inclusion criteria: individuals without bacterial meningitis, and haemodynamic parameters
Nahata, M.C., Arnoto, R.T., Powell, D.A., Management of pediatric patients with bacterial meningitis in the emergency department, Drug Intelligence and Clinical Pharmacy, 20, 796-798, 1986	Study design does not meet inclusion criteria: non RCT
Nathavitharana, K. A., Tarlow, M. J., Current trends in the management of bacterial meningitis, British Journal of Hospital Medicine,	Study design does not meet inclusion criteria: narrative review

Study	Reason for exclusion
50, 403-7, 1993	
Nishizawa, Y., Spinal fluid therapy in purulent meningitis, Archives of Pediatrics, 70, 351-63, 1953	Study design and intervention/exposure do not meet inclusion criteria: case report and no fluid restriction
Opiyo, N., Molyneux, E., Sinclair, D., Garner, P., English, M., Immediate fluid management of children with severe febrile illness and signs of impaired circulation in low-income settings: A contextualised systematic review, BMJ Open, 4 (4) (no pagination), 2014	Study population and intervention do not meet inclusion criteria: individuals with other severe febrile illness (but not bacterial meningitis), and fluid bolus vs. maintenance fluid
Pecco, P., Pavesio, D., Peisino,M.G., Rational basis of modern therapy of bacterial meningitis. Review of the literature and our clinical experience of 122 pediatric cases, Panminerva Medica, 33, 185-190, 1991	Study design does not meet inclusion criteria: non RCT and no systematic review of RCT
Powell, K. R., Sugarman, L. I., Eskenazi, A. E., Woodin, K. A., Kays, M. A., McCormick, K. L., Miller, M. E., Sladek, C. D., Normalization of plasma arginine vasopressin concentrations when children with meningitis are given maintenance plus replacement fluid therapy, Journal of Pediatrics, 117, 515-22, 1990	Study outcomes do not meet inclusion criteria: serum arginine vasopressin, osmolality and sodium levels
Prasad, K., Karlupia, N., Kumar, A., Treatment of bacterial meningitis: an overview of Cochrane systematic reviews, Respiratory Medicine, 103, 945-50, 2009	Study design does not meet inclusion criteria: review of Cochrane systematic reviews
Prince, A. S., Neu, H. C., Fluid management in Haemophilus influenzae meningitis, Infection, 8, 5-7, 1980	Study design and outcomes do not meet inclusion criteria: retrospective study
Rantasalo, I., Kauhtio, J., Acute bacterial meningitis in children. II. Some aspects of 257 cases admitted to Children's Hospital, University of Helsinki, in 1946-55. III. Treatment of the 257 cases admitted to Children's Hospital, University of Helsinki, in 1946-55, Annales Paediatriae Fenniae, 4, 80-180, 1958	Study design does not meet inclusion criteria: case series
Shann, F., Germer, S., Hyponatraemia associated with pneumonia or bacterial meningitis, Archives of Disease in Childhood, 60, 963-6, 1985	Study outcome and exposure do not meet inclusion criteria: hyponatraemia and no fluid restriction
Shann, F., Germer, S., Treatment of bacterial meningitis in children without intravenous fluids, Medical Journal of Australia, 1, 577-8, 1981	Study design and intervention do not meet inclusion criteria: non RCT and drug intervention (IM vs. IV)
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	Population and exposure do not meet inclusion criteria: 70% of participants with encephalitis and no fluid restriction
Singhi, S., Effective adjuvant therapies for meningitis, International Journal of Infectious Diseases, 1), e331-e332, 2010	Conference abstract
Singhi, S., Jayashree, M., Free water excess is not the main cause for hyponatremia in critically ill children receiving conventional maintenance fluids, Indian Pediatrics, 46, 577-583, 2009	Study population, exposure and outcome do not meet inclusion criteria: 84% with pneumonia, myocarditis, CHD, pericardial effusion and others

Study	Reason for exclusion
Singhi, S., Singhi, P., Baranwal, A.K., Bacterial meningitis in children: Critical care needs, Indian Journal of Pediatrics, 68, 737-747, 2001	Study design does not meet inclusion criteria: narrative review
Smith, A., Fluid management during bacterial meningitis, Report on Pediatric Infectious Diseases, 3, 10-11, 1993	Study design does not meet inclusion criteria
Srivastava, G., Pyogenic meningitis, Indian Journal of Pediatrics, 36, 307-313, 1969	Study design and exposure do not meet inclusion criteria: case series and no fluid restriction
Therapeutic management of purulent meningitis in children. Report of 101 cases, Archives francaises de pediatrie, 47, 491-495, 1990	Study intervention does not meet inclusion criteria: drug intervention. Not in English
Tsolia, M.N., Theodoridou, M., Tzanakaki, G., Vlachou, V., Mostrou, G., Stripeli, F., Kalabalikis, P., Pangalis, A., Kafetzis, D., Kremastinou, J., Konstantopoulos, A., Invasive meningococcal disease in children in Greece: Comparison of serogroup A disease with disease caused by other serogroups, European Journal of Clinical Microbiology and Infectious Diseases, 25, 449-456, 2006	Study design and exposure do not meet inclusion criteria: case series and no fluid restriction
Tuomanen, E., Mediators of inflammation and the treatment of bacterial meningitis, Current Opinion in Infectious Diseases, 8, 218-223, 1995	Study design does not meet inclusion criteria: narrative review
van Paridon, B. M., Sheppard, C., G, G. G., Joffe, A. R., Alberta Sepsis, Network, Timing of antibiotics, volume, and vasoactive infusions in children with sepsis admitted to intensive care, Critical Care (London, England), 19, 293, 2015	Study design and population do not meet inclusion criteria: non RCT and children with sepsis (meningitis is one of the causes)
VanDemark, M., Acute bacterial meningitis: Current review and treatment update, Critical Care Nursing Clinics of North America, 25, 351-361, 2013	Study design does not meet inclusion criteria: narrative review
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	Study intervention does not meet inclusion criteria: osmotic therapies
Williams, C. P., Swanson, A. G., Chapman, J. T., Brain Swelling with Acute Purulent Meningitis. Report of Treatment with Hypertonic Intravenous Urea, Pediatrics, 34, 220-7, 1964	Study design does not meet inclusion criteria: case report

CHD: congenital heart disease; CNS: central nervous system; GI: gastrointestinal; IM: intramuscular; IV: intravenous; IVF: intravenous fluid; PUO: pyrexia of unknown origin; RCT: randomised controlled trial; TB: tuberculosis; UTI: urinary tract infection

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 fluid restriction in bacterial meningitis?

No research recommendation was made for this review.