National Institute for Health and Care Excellence

Draft for consultation

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

[B4] Evidence review for factors associated with brain herniation

NICE guideline number tbc

Evidence review underpinning recommendation 1.4.8 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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Factors associated with brain herniation

Review question

What factors (individually or in combination) are associated with an increased risk of brain herniation following lumbar puncture in people with suspected bacterial meningitis?

Introduction

Bacterial meningitis is a rare but serious infection, which can occur in any age group. Early recognition of the condition requires a high index of suspicion.

Cerebrospinal fluid (CSF) investigations are crucial for the diagnosis of bacterial meningitis, and obtaining CSF samples for urgent investigation should be prioritised whenever a diagnosis of bacterial meningitis is being considered.

Bacterial meningitis may cause raised intracranial pressure, which can represent a risk for brain herniation following lumbar puncture. The aim of this review is to evaluate what factors (individually or in combination) are associated with an increased risk of brain herniation following lumbar puncture in people with suspected bacterial meningitis.

Summary of the protocol

See Table 1 for a summary of the Population, Prognostic factors, Comparison and Outcome characteristics of this review.

Table 1: Summary of the protocol

Population	All adults, young people, children and babies (excluding neonates defined as aged 28 days old and younger) with suspected bacterial meningitis who have undergone a lumbar puncture
Prognostic factors	One or more of the following factors: • A new focal neurologic deficit • Papilloedema • Seizure • Continuous seizures/status epilepticus • Hypertension • Bradycardia • Reduced or fluctuating level of consciousness • Bulging fontanelle • Decorticate or decerebrate posturing • Irregular respiratory pattern/respiratory distress/Cheyne-Stokes breathing/apnoea • Shock
Comparison	Absence of risk factor
Outcome	**Critical** • Risk ratios for fatal brain herniation • Odds ratios for fatal brain herniation • Risk ratios for any brain herniation • Odds ratios for any brain herniation **Important** None

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.

Prognostic evidence

Included studies

Two studies were included for this review, 1 case-control study (Benjamin 1988) but only cases (children with meningitis that died) from that study included in this review, and 1 retrospective cohort study (Horwitz 1980).

Studies with univariate analyses were included as no studies with multivariate analyses were identified.

The included studies are summarised in Table 2.

One study reported fatal brain herniation based on post-mortem diagnosis of coning (Benjamin 1988), and 1 reported brain herniation using clinical diagnostic criteria (Horwitz 1980).

Both studies reported seizures and reduced consciousness as potential risk factors. One study used parental assessment of 'difficult to wake' to indicate reduced consciousness (Benjamin 1988), and 1 used coma for this risk factor (Horwitz 1980). One study was conducted in children (Benjamin 1988) and 1 study was conducted in babies and children (Horwitz 1980).

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	Risk factor	Outcomes	Comments
Benjamin 1988 Case-control study [only cases included in this review] UK	N=19 Cases: Children with meningitis that died [Matched controls were not of interest for this review as there was no data on brain herniation	• Seizure (fits on admission to hospital) • Reduced consciousness (parental report 'difficult to wake at home')	• Fatal brain herniation	No information on difference in age based on presence and absence of prognostic factor. Bacteria identified in 13 of the cases Post-mortem

Study	Population	Risk factor	Outcomes	Comments
	for this group] Age: NR			diagnosis.
Horwitz 1980 Retrospective cohort study USA	N=302 Babies and children aged 1 month to 16 years admitted to hospital with bacterial meningitis Age: NR	• Seizure • Reduced consciousness (defined as coma)	• Any brain herniation	No matching or adjustment for confounding factors. Clinical diagnosis based on review of case notes.

NR: not reported

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no forest plots in appendix E).

Summary of the evidence

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

The evidence was assessed as being very low quality due to high or moderate risk of bias in most domains (for example, bias arising from study participation due to lack of reporting of baseline characteristics and study confounding due to lack of adjustment for confounders), and imprecision due to the very low numbers of events. The evidence was stratified by age and definition of brain herniation. See the GRADE tables in appendix F for the certainty of the evidence for each individual outcome following lumbar puncture.

Presence of seizures and reduced consciousness increased the risk of brain herniation in babies and children, as measured by clinical diagnosis. There was no evidence of an increased risk of fatal brain herniation in children in the evidence reviewed, measured by post-mortem diagnosis, due to these same prognostic factors. However, as the findings were very seriously imprecise for all outcomes, they should not be taken as definitive evidence of association, or lack of association.

No studies reported data for the other prognostic factors in the protocol (new focal neurologic deficit, papilloedema, continuous seizures, hypertension, bradycardia, bulging fontanelle, decorticate or decerebrate posturing, irregular respiratory pattern, shock), and no evidence was available for adults.

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 this review does not involve a comparison of competing courses of action.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

This review aimed to identify factors associated with an increased risk of brain herniation following lumbar puncture in people with suspected bacterial meningitis; therefore, brain herniation was selected as the critical outcome. The committee included both any brain herniation and fatal brain herniation as outcomes as they agreed it was important to identify any differences in risk factors dependant on the outcome of the herniation.

The quality of the evidence

The quality of the evidence was assessed with GRADE methodology and was rated as very low quality for all reported outcomes. This was due to serious imprecision around the estimated effects due to small numbers of events and risk of bias arising from the selection of participants, and insufficient reporting of baseline characteristics or adjustment for confounding factors.

No evidence was identified for new focal neurologic deficit, papilloedema, continuous seizures, hypertension, bradycardia, bulging fontanelle, decorticate or decerebrate posturing, irregular respiratory pattern, or shock.

Benefits and harms

Based on their clinical knowledge, the committee highlighted that raised intracranial pressure is a contraindication for lumbar puncture due to the risk of brain herniation. The committee considered the evidence for factors associated with brain herniation and made recommendations based on risk factors identified in the evidence, and clinical consensus, to guide healthcare professionals about the circumstances in which neuroimaging should be performed prior to lumbar puncture to mitigate the risk of brain herniation.

The evidence showed that reduced consciousness and the presence of seizures increased the risk of any brain herniation in babies and children. These findings were consistent with the clinical expertise of the committee as they are recognised signs of raised intracranial pressure. The committee agreed that to mitigate these risks, neuroimaging should be considered before lumbar puncture if the person has a rapidly deteriorating level of consciousness or seizures. The committee noted that in the evidence reviewed, the study that examined reduced consciousness and seizures as risk factors for fatal brain herniation did not show significant associations, however as the findings were seriously imprecise, they agreed that this should not be taken as definitive evidence of absence of association.

The committee noted there are other well documented signs of significant abnormal neurology, which could be features of brain herniation, including posturing and abnormal pupillary reactions, and the committee agreed that where these signs are present neuroimaging should be considered.

Cost effectiveness and resource use

This review question did not consider decisions between competing alternatives and therefore is not directly relevant to the tools of economic evaluation. The recommendations based on this review primarily provide advice to healthcare professionals on the

contraindications to lumbar puncture. The committee considered their recommendations would promote cost effective care by highlighting the circumstances when neuroimaging prior to lumbar puncture should be considered to avoid the potential harms when a person has features of brain herniation. A recent retrospective cohort study in the UK (Ellis 2022) in a population with community acquired meningitis reported that contraindications to immediate lumbar puncture were uncommon, being present for 20% of patients. The committee considered that the recommendations largely reinforce current best practice and knowledge and therefore they did not believe they would have a significant resource impact.

Commented [PJ1]: Response to RAG row 207 - probably some clinical check to agree that this statement is ok/helpful in this context.

Recommendations supported by this evidence review

This evidence review supports recommendation 1.4.8. Other evidence supporting this recommendation can be found in the evidence review on the role of neuroimaging prior to lumbar puncture (see evidence review B5).

References – included studies

Prognostic

Benjamin 1988

Benjamin, C. M., Newton, R. W., Clarke, M. A., Risk factors for death from meningitis, British Medical Journal Clinical Research Ed.Br Med J (Clin Res Ed), 296, 20, 1988

Horwitz 1980

Horwitz, S. J., Boxerbaum, B., O'Bell, J., Cerebral herniation in bacterial meningitis in childhood, Annals of Neurology, 7, 524-8, 1980

Economic

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

Other

Ellis 2022

Ellis, J., Harvey, D., Defres, S., et al. Clinical management of community acquired meningitis in adults in the UK and Ireland in 2017: a retrospective cohort study on behalf of the National Infection Trainees Collaborative for Audit and Research (NITCAR). BMJ Open 2022;12: e062698. doi:10.1136/bmjopen-2022-062698

Appendices

Appendix A Review protocols

Review protocol for review question: What factors (individually or in combination) are associated with an increased risk of brain herniation following lumbar puncture in people with suspected bacterial meningitis?

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42021245997
Review title	Factors associated with brain herniation
Review question	What factors (individually or in combination) are associated with an increased risk of brain herniation following lumbar puncture in people with suspected bacterial meningitis?
Objective	To determine what factors (individually or in combination) are associated with an increased risk of brain herniation following lumbar puncture in people with suspected 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	Brain herniation in people with suspected bacterial meningitis who have undergone lumbar puncture

Field	Content
Population	Inclusion: All adults, young people, children and babies (excluding neonates defined as aged 28 days old and younger) with suspected bacterial meningitis who have undergone a lumbar puncture 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.
Exposure/prognostic factors	One or more of the following factors: • A new focal neurologic deficit (for example, cranial nerve palsy, extremity weakness or drift, dysarthria, aphasia, abnormal 'doll's eye' movements, unequal, dilated or poorly responsive pupils, abnormal posture or posturing) • Papilloedema • Seizure • Continuous seizures/status epilepticus • Hypertension • Bradycardia • Reduced or fluctuating level of consciousness (for example, decrease of changes in Glasgow Coma Scale score) • Bulging fontanelle (relevant for young children only) • Decorticate or decerebrate posturing • Irregular respiratory pattern/respiratory distress/Cheyne-Stokes breathing/apnoea • Shock
Comparator/Reference standard/Confounding factors	Absence of risk factor
Types of study to be included	Include published full text papers:

Field	Content
	• Systematic reviews of cohort studies • Prospective cohort studies with multivariate analyses • If insufficient prospective cohort studies: retrospective cohort studies with multivariate analyses Studies with univariate analyses will only be included if there are insufficient studies with multivariate analyses. 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: age (if not possible to stratify. Conference abstracts will not be considered.
Other exclusion criteria	Countries other than OECD high 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)	• Risk ratios for fatal brain herniation* • Odds ratios** for fatal brain herniation* • Risk ratios for any brain herniation* • Odds ratios** for any brain herniation* * Brain herniation as reported by papers (for example, herniation/fatal herniation, loss of pupillary reactivity, significant drop on Glasgow Coma Scale, coning) **adjusted odds ratios will be included where multivariate analyses are available
Secondary outcomes (important outcomes)	N/A
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. 5% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third

Field	Content
	independent reviewer. 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 risk factors, 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 checklist: • ROBIS tool for systematic reviews • Quality in Prognostic Studies (QUIPS) tool for prognostic studies The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Where multiple studies report on the same definition of the outcome of interest for the same factor and handle adjusting for covariates in a similar way, 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). 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:**

Field	Content
	• Strong association: <0.5 and >2.00 • Moderate association: <0.80 and >1.25 • Small association: any statistically significant association • No association: no statistically significant association
Analysis of sub-groups	Evidence will be stratified by: Age: • Younger Infants: >28 days to ≤3 months of age • Older infants: >3 months to <1 year of age • Children: ≥1 year to <18 years of age • Adults: ≥18 years of age Definition of brain herniation: • Clinical diagnosis (based on one or more of: loss of pupillary reflexes; significant drop in GCS; loss of regular spontaneous respiratory drive; or decorticate or decerbrate posturing) • Radiological diagnosis (of trans-tentorial uncal herniation, trans-tentorial central herniation, or cerebellar tonsillar herniation) • Post-mortem diagnosis (of trans-tentorial uncal herniation, trans-tentorial central herniation, or cerebellar tonsillar herniation) 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 Corticosteroid use

Field	Content		
	Glasgow coma scale scores Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.		
Type and method of review	☐	Intervention	
	☐	Diagnostic	
	☒	Prognostic	
	☐	Qualitative	
	☐	Epidemiologic	
	☐	Service Delivery	
	☐	Other (please specify)	
Language	English		
Country	England		
Anticipated or actual start date	11/03/2021		
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	☑	☑

Field	Content		
	Data extraction	☑	☑
	Risk of bias (quality) assessment	☑	☑
Named contact	Named contact: National Guideline Alliance Named contact e-mail: meningitis&meningococcal@nice.org.uk Organisational affiliation of the review: National Institute for Health and Care Excellence (NICE) and National Guideline Alliance		
Review team members	National Guideline Alliance		
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance which receives funding from NICE.		
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: 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=CRD42021245997		
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		

Field	Content	
	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, lumbar puncture, brain herniation, sensitivity, specificity	
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; GCS: Glasgow Coma Score; GRADE: Grading of Recommendations Assessment, Development and Evaluation; N/A: not applicable; NGA: National Guideline Alliance; NICE: National Institute for Health and Care Excellence; OECD: Organisation for Economic Co-operation and Development; PRESS: Peer Review of Electronic Search Strategies; QUIPS: Quality in Prognosis Studies; ROBIS: Risk of Bias in Systematic Reviews

Appendix B Literature search strategies

Literature search strategies for review question: What factors (individually or in combination) are associated with an increased risk of brain herniation following lumbar puncture in people with suspected bacterial meningitis?

Clinical Search

Database(s): Medline & Embase (Multifile) – OVID interface
Database(s): Embase Classic+Embase 1947 to 2021 April 21 , **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily** 1946 to April 21, 2021
Date of last search: 20 April 2021
Multifile database codes: emczd = Embase Classic+Embase; ppez = MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	Meningitis/ or Meningitis, Bacterial/ or Meningitis, Escherichia Coli/ or Meningitis, Haemophilus/ or Meningitis, Listeria/ or Meningitis, Meningococcal/ or Meningitis, Pneumococcal/ or Meningoencephalitis/
2	1 use ppez
3	meningitis/ or bacterial meningitis/ or haemophilus meningitis/ or hemophilus influenzae meningitis/ or listeria meningitis/ or meningococcal meningitis/ or pneumococcal meningitis/ or meningoencephalitis/
4	3 use emczd
5	((bacter* or infect*) adj3 (meningit* or meninges* or leptomeninges* or subarachnoid space?)).ti,ab.
6	(meningit* adj3 (e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon* or septic* or sepsis* or bacter?emi?)).ti,ab.
7	((e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon*) adj3 (septic* or sepsis* or bacter?emi?)).ti,ab.
8	(meningit* or mening?encephalitis* or mening* encephalitis*).ti,ab.
9	exp Neisseria meningitidis/ use ppez
10	neisseria meningitidis/ use emczd
11	(Neisseria* mening* or n mening*).ti,ab.
12	or/2,4-11
13	Encephalocele/ use ppez
14	brain hernia/ use emczd
15	((brain* or cerebral* or cerebell* or uncal or transtentorial or suspect* or suspicious* or risk* or impend*) adj3 hernia*).ti,ab.
16	(craniocel* or notoencephalocele* or encephalocel* or exencephalocel* or encephalocystocel* or hydroencephalocel* or cranioschisis*).ti,ab.
17	(pressure adj cone).ti,ab.
18	or/13-17
19	Spinal Puncture/ use ppez
20	lumbar puncture/ use emczd
21	((spin* or lumbar* or dural* or thecal*) adj3 (punctur* or tap*)).ti,ab.
22	LP.ti,ab.
23	or/19-22
24	Papilledema/ or Seizures/ or Seizures, Febrile/ or Status Epilepticus/ or exp Hypertension/ or Bradycardia/ or Glasgow Coma Scale/ or Dysarthria/ or Aphasia/ or *Eye Movements/ or *Posture/ or exp Shock/ or Cheyne-Stokes Respiration/ or exp Apnea/
25	24 use ppez
26	papilledema/ or seizure/ or febrile convulsion/ or epileptic state/ or exp hypertension/ or bradycardia/ or glasgow coma scale/ or dysarthria/ or aphasia/ or *eye movement/ or *body posture/ or exp shock/ or Cheyne Stokes breathing/ or exp apnea/
27	26 use emczd
28	(papill?edem* or seizure or seizures or epilep* or hypertens* or hypotens* or bradycard* or dysarthr* or aphas* or drift or shock or Cheyn* or apn?ea*).ti,ab.
29	((elevat* or high or increas* or rais*) adj3 blood adj pressur*).ti,ab.
30	((decreas* or slow* or reduc*) adj3 heart adj (rate* or beat*)).ti,ab.
31	((Glasgow or Rankin) adj2 scale).ti,ab.
32	((decreas* or reduc* or fluctuat* or disturb*) adj3 consciousness).ti,ab.
33	(neurolog* adj deficit*).mp.
34	(nerve adj (palsy or paralysis)).mp.
35	(doll* adj2 eye*).ti,ab.
36	((abnormal* or extensor* or decorticat* or decerebrat*) adj3 postur*).ti,ab.
37	((unequal or dilated or "poorly responsive") adj pupils).ti,ab.
38	(extremity adj weakness).ti,ab.

#	Searches
39	((deteriorat* or decreas* or reduc*) adj3 alertness).ti,ab.
40	(bulg* adj fontanel*).ti,ab.
41	((respirat* or breath*) adj3 (distress* or irregular*)).ti,ab.
42	or/25,27-41
43	Risk Assessment/ use ppez
44	risk assessment/ use emczd
45	Risk Factors/ use ppez
46	risk factor/ use emczd
47	(safety adj (checklist* or check-list* or indicator*)).ti,ab.
48	(risk adj factor*).ti,ab.
49	Medical History Taking/ use ppez
50	anamnesis/ use emczd
51	Physical Examination/ use ppez
52	physical examination/ use emczd
53	(medical adj history).ti,ab.
54	(physical adj exam*).ti,ab.
55	or/43-54
56	12 and 18 and 23
57	18 and 23 and 42
58	18 and 23 and 55
59	45 or 46 or 48
60	12 and 23 and 59
61	Contraindications, Procedure/ use ppez
62	treatment contraindication/ use emczd
63	61 or 62
64	23 and 63
65	Spinal Puncture/ae, co or *Punctures/ae, co
66	herniat*.mp.
67	65 and 66
68	or/56-58,60,64,67
69	((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.
70	69 use ppez
71	((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.)
72	71 use emczd
73	70 or 72
74	68 not 73
75	limit 74 to English language
76	((spin* or lumbar* or dural* or thecal*) adj3 (punctur* or tap*)).m_titl.
77	18 and 76
78	77 not 68
79	78 not 73
80	limit 79 to English language
81	75 or 80
82	12 and 18
83	82 not 73
84	limit 83 to English language
85	81 or 84

Database(s): Cochrane Library – Wiley interface
Cochrane Database of Systematic Reviews, Issue 4 of 12, April 2021, **Cochrane Central Register of Controlled Trials**, Issue 4 of 12, April 2021
Date of last search: 22 April 2021

#	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 (meningit* or meninges* or leptomeninges* or "subarachnoid space*"))):ti,ab,kw
#11	((meningit* NEAR/3 (“e coli” or “escherichia coli” or haemophilus or hemophilus or hib or “haemophilus influenz*” or “hemophilus influenz*” or “h influenz*” or listeria* or meningococc* or pneumococc* or “gram-negativ* bacill*” or

#	Searches
	"gram negativ* bacill*" or streptococc* or "group B streptococc*" or GBS or "streptococcus pneumon*" or "s pneumon*" or septic* or sepsis* or bacteraemia* or bacteremia*))):ti,ab,kw
#12	(("e coli" or "escherichia coli" or haemophilus or hemophilus or hib or "haemophilus influenz*" or "hemophilus 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*") NEAR/3 (septic* or sepsis* or bacteraemia* or bacteremia*))):ti,ab,kw
#13	((meningit* or meningencephalitis* or meningoencephalitis* or "mening* encephalitis*")):ti,ab,kw
#14	((Neisseria* NEXT mening*)):ti,ab,kw
#15	#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
#16	MeSH descriptor: [Encephalocele] explode all trees
#17	(((brain* or cerebral* or cerebell* or uncal or transtentorial or suspect* or suspicious* or risk* or impend*) NEAR/3 hernia*)):ti,ab,kw
#18	((craniocel* or notoencephalocele* or encephalocel* or exencephalocel* or encephalocystocel* or hydroencephalocel* or cranioschisis*)):ti,ab,kw
#19	((pressure NEXT cone)):ti,ab,kw
#20	#16 OR #17 OR #18 OR #19
#21	MeSH descriptor: [Spinal Puncture] this term only
#22	(((spin* or lumbar* or dural* or thecal*) NEAR/3 (punctur* or tap*))):ti,ab,kw
#23	(LP):ti,ab,kw
#24	#21 OR #22 OR #23
#25	MeSH descriptor: [Papilledema] this term only
#26	MeSH descriptor: [Seizures] this term only
#27	MeSH descriptor: [Seizures, Febrile] this term only
#28	MeSH descriptor: [Status Epilepticus] this term only
#29	MeSH descriptor: [Hypertension] explode all trees
#30	MeSH descriptor: [Bradycardia] this term only
#31	MeSH descriptor: [Glasgow Coma Scale] this term only
#32	MeSH descriptor: [Dysarthria] this term only
#33	MeSH descriptor: [Aphasia] this term only
#34	MeSH descriptor: [Eye Movements] this term only
#35	MeSH descriptor: [Posture] this term only
#36	MeSH descriptor: [Shock] explode all trees
#37	MeSH descriptor: [Cheyne-Stokes Respiration] this term only
#38	MeSH descriptor: [Apnea] explode all trees
#39	((papilledem* or papilloedem* or seizure or seizures or epilep* or hypertens* or hypotens* or bradycard* or dysarthr* or aphas* or drift or shock or Cheyn* or apnea* or apnoea*)):ti,ab,kw
#40	(((elevat* or high or increas* or rais*) NEAR/3 blood NEXT pressur*)):ti,ab,kw
#41	(((decreas* or slow* or reduc*) NEAR/3 heart NEXT (rate* or beat*))):ti,ab,kw
#42	(((Glasgow or Rankin) NEAR/2 scale)):ti,ab,kw
#43	(((decreas* or reduc* or fluctuat* or disturb*) NEAR/3 consciousness)):ti,ab,kw
#44	((neurolog* NEXT deficit*)):ti,ab,kw
#45	((nerve NEXT (palsy or paralysis))):ti,ab,kw
#46	((doll* NEAR/2 eye*)):ti,ab,kw
#47	(((abnormal* or extensor* or decorticat* or decerebrat*) NEAR/3 postur*)):ti,ab,kw
#48	(((unequal or dilated or "poorly responsive") NEXT pupils)):ti,ab,kw
#49	((extremity NEXT weakness)):ti,ab,kw
#50	(((deteriorat* or decreas* or reduc*) NEAR/3 alertness)):ti,ab,kw
#51	((bulg* NEXT fontanel*)):ti,ab,kw
#52	(((respirat* or breath*) NEAR/3 (distress* or irregular*))):ti,ab,kw
#53	#25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52
#54	MeSH descriptor: [Risk Assessment] this term only
#55	MeSH descriptor: [Risk Factors] this term only
#56	((safety NEXT (checklist* or check-list* or indicator*))):ti,ab,kw
#57	((risk NEXT factor*)):ti,ab,kw
#58	MeSH descriptor: [Medical History Taking] this term only
#59	MeSH descriptor: [Physical Examination] this term only
#60	((medical NEXT history)):ti,ab,kw
#61	((physical NEXT exam*)):ti,ab,kw
#62	#54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61
#63	#15 AND #20 AND #24
#64	#20 AND #24 AND #53
#65	#20 AND #24 AND #62
#66	#55 OR #57
#67	#15 AND #24 AND #66
#68	MeSH descriptor: [Contraindications, Procedure] this term only
#69	#24 AND #68
#70	MeSH descriptor: [Spinal Puncture] this term only and with qualifier(s): [adverse effects - AE]
#71	MeSH descriptor: [Punctures] this term only and with qualifier(s): [adverse effects - AE]
#72	(herniat*):ti,ab,kw

#	Searches
#73	(#70 OR #71) AND #72
#74	#63 OR #64 OR #65 OR #67 OR #69 OR #73
#75	#15 AND #20
#76	#74 OR #75

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

Date of last search: 30 March 2021

#	Searches
1	MeSH DESCRIPTOR Encephalocele IN DARE,HTA
2	(((brain* or cerebral* or cerebell* or uncal or transtentorial or suspect* or suspicious* or risk* or impend*) NEAR3 hernia*)) IN DARE, HTA
3	((craniocel* or notoencephalocele* or encephalocel* or exencephalocel* or encephalocystocel* or hydroencephalocel* or cranioschisis*)) IN DARE, HTA
4	((pressure NEXT cone)) IN DARE, HTA
5	#1 OR #2 OR #3 OR #4
6	MeSH DESCRIPTOR Spinal Puncture IN DARE,HTA
7	(((spin* or lumbar* or dural* or thecal*) NEAR3 (punctur* or tap*))) IN DARE, HTA
8	(LP) IN DARE, HTA
9	#6 OR #7 OR #8
10	#5 AND #9

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 2021 March 10, **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to March 09, 2021

Date of last search: 11 March 2021

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

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

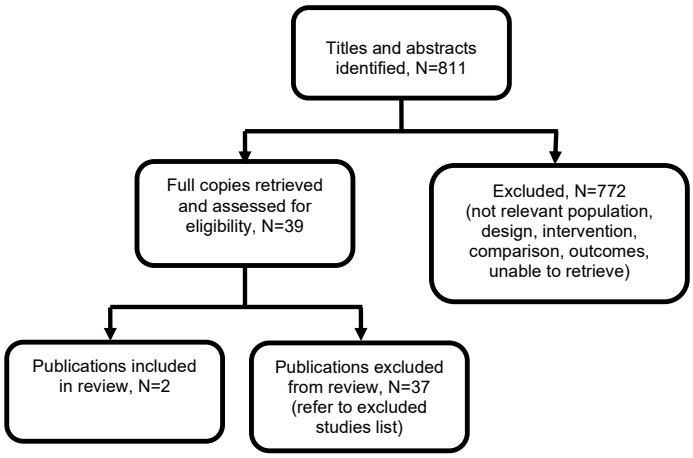
#	Searches
	life expectanc*)).tw.
64	*quality of life/ and (quality of life or qol).ti.
65	quality of life/ and ((quality of life or qol) adj3 (improv* or chang*)).tw.
66	quality of life/ and health-related quality of life.tw.
67	Models, Economic/ use ppez
68	economic model/ use emczd
69	care-related quality of life.tw,kw.
70	((capability$ or capability-based$) adj (measure$ or index or instrument$)).tw,kw.
71	social care outcome$.tw,kw.
72	(social care and (utility or utilities)).tw,kw.
73	or/41-72
74	(9 or 17) and 40
75	(9 or 17) and 73
76	letter/
77	editorial/
78	news/
79	exp historical article/
80	Anecdotes as Topic/
81	comment/
82	case report/
83	(letter or comment*).ti.
84	76 or 77 or 78 or 79 or 80 or 81 or 82 or 83
85	randomized controlled trial/ or random*.ti,ab.
86	84 not 85
87	animals/ not humans/
88	exp Animals, Laboratory/
89	exp Animal Experimentation/
90	exp Models, Animal/
91	exp Rodentia/
92	(rat or rats or mouse or mice).ti.
93	86 or 87 or 88 or 89 or 90 or 91 or 92
94	letter.pt. or letter/
95	note.pt.
96	editorial.pt.
97	case report/ or case study/
98	(letter or comment*).ti.
99	94 or 95 or 96 or 97 or 98
100	randomized controlled trial/ or random*.ti,ab.
101	99 not 100
102	animal/ not human/
103	nonhuman/
104	exp Animal Experiment/
105	exp Experimental Animal/
106	animal model/
107	exp Rodent/
108	(rat or rats or mouse or mice).ti.
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 Prognostic evidence study selection

Study selection for review question: What factors (individually or in combination) are associated with an increased risk of brain herniation following lumbar puncture in people with suspected bacterial meningitis?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What factors (individually or in combination) are associated with an increased risk of brain herniation following lumbar puncture in people with suspected bacterial meningitis?

Table 4: Evidence tables – prognostic evidence

Study details	Results and risk of bias assessment using the QUIPs checklist
Full citation Benjamin, C. M., Newton, R. W., Clarke, M. A., Risk factors for death from meningitis, British Medical Journal Clinical Research Ed.Br Med J (Clin Res Ed), 296, 20, 1988 **Ref Id** 1301378 **Country/ies where the study was carried out** UK **Study type** Case-control study [only cases included in this review] **Study dates** 1974 to 1985 **Inclusion criteria** Diagnosis on discharge of meningitis. Study cases were children who died. Matched controls were not of interest for this review as there was no data on brain herniation for this group. **Exclusion criteria** Children with malformations of the central nervous system; neonates who had suffered complications of prematurity or low birth weight.	**Results** **Prognostic factor: seizure; outcome: fatal brain herniation (defined as coning present at necropsy) in children** | | fatal brain herniation | no fatal brain herniation | total | | --- | --- | --- | --- | | seizure | 1 | 1 | 2 | | no seizure | 3 | 6 | 9 | | total | 4 | 7 | 11 | **Prognostic factor: reduced consciousness; outcome: fatal brain herniation (defined as coning present at necropsy) in children** | | fatal brain herniation | no fatal brain herniation | total | | --- | --- | --- | --- | | difficult to wake at home | 4 | 4 | 8 | | not difficult to wake at home | 0 | 3 | 3 | | total | 4 | 7 | 11 | **1. Risk of bias: Study participation (High/Moderate/Low)** High: only 13 of the 19 children who died had necropsy data available and were included in the comparison of interest. No baseline characteristics presented. **2. Risk of bias: Study attrition (High/Moderate/Low)** Moderate: data on seizures and level of consciousness only presented for 11 of the 13 children who had necropsy data. Two of the 9 children without brain herniation are

Study details	Results and risk of bias assessment using the QUIPs checklist
Patient characteristics N=19 study children. Necropsies were performed on 13/19 children [N=19 pair-matched controls - not relevant to assessment of brain herniation risk] No further information in paper Bacteria identified in 13/19 study children **Risk factor(s) of interest** Seizures (fits on admission to hospital) Reduced level of consciousness (parental report 'difficult to wake at home') **Confounding factor(s)** The matching was not on our comparison of interest, so there is no information on whether there were any differences in age based on presence/absence of prognostic factor. **Setting** Royal Manchester and Booth Hall Children's Hospitals	missing from the analysis, with no explanation given. **3. Risk of bias: Prognostic factor measurement (High/Moderate/Low)** For seizures: low risk (recorded on admission to hospital). For decreased level of consciousness: moderate (parental assessment of 'difficult to wake' may be quite variable and could be related to outcome). **4. Risk of bias: Outcome measurement (High/Moderate/Low)** Low: brain herniation measured in an objective way. **5. Risk of bias: Study confounding (High/Moderate/Low)** High: study was case-matched for main comparison (death versus no death), but not to control for confounders in the comparison of risk factors for brain herniation. **6. Risk of bias: Statistical analysis and reporting (High/Moderate/Low)** Low: statistical analysis used was adequate for the design of the study and there was no evidence of selective reporting of the results. **Source of funding** No sources of funding reported
Full citation Horwitz, S. J., Boxerbaum, B., O'Bell, J., Cerebral herniation in bacterial meningitis in childhood, Annals of Neurology, 7, 524-8, 1980 **Ref Id** 1286793 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study	**Results** **Prognostic factor: seizure; outcome: any brain herniation in babies and children** | | brain herniation | no brain herniation | total | | --- | --- | --- | --- | | seizures | 9 | 53 | 62 | | no seizures | 9 | 231 | 240 | | totals | 18 | 284 | 302 | **Prognostic factor: Reduced consciousness (defined as coma) at time of admission; outcome: any brain herniation in babies and children**

Study details	Results and risk of bias assessment using the QUIPs checklist
Study dates 1967 to 1976 **Inclusion criteria** General study: Babies and children aged 1 month to 16 years admitted to hospital with bacterial meningitis, with positive cerebrospinal fluid cultures for H. influenzae type B, Streptococcus pneumoniae, or Neisseria meningitidis. Diagnosis of brain herniation based on two or more of the following, present simultaneously: (1) pupillary abnormalities restricted to unilateral or bilateral dilatation with absence of reaction to light; (2) decorticate or decerebrate posture or development of hemiparesis; (3) Cheyne-Stokes respiration, hyperventilation, or apnea; (4) loss of oculocephalic response or fixed oculomotor deviation; (5) clonic convulsive activity ceased before the signs of brain herniation were recorded. **Exclusion criteria** previously placed ventricular shunts for hydrocephalus. **Patient characteristics** Total N = 302 with bacterial meningitis (no baseline data presented) 27 patients with suspected cerebral herniation, of whom n = 18 were diagnosed and included in the study. Level of consciousness: coma on admission 4/18; not comatose on admission but later deteriorated 13/18 Pupils: fixed in 6/18, bilateral fixed in 10/18, unequal or large in 0/18 Respiration: hyperventilation 9/18; Cheyne-Stokes 2/18; apnea 1/18; not recorded 4/18 Motor function: hemiparesis 4/18; decorticate 4/18; decerebrate 4/18; not recorded 1/18 Oculocephalic reflexes: absent 3/18; fixed deviation 2/18; not recorded 10/18	<table><tr><td></td><td>brain herniation</td><td>no brain herniation</td><td>total</td></tr><tr><td>coma at time of admission</td><td>4</td><td>11</td><td>15</td></tr><tr><td>no coma at time of admission</td><td>14</td><td>273</td><td>287</td></tr><tr><td>totals</td><td>18</td><td>284</td><td>302</td></tr></table> **1. Risk of bias: Study participation (High/Moderate/Low)** Moderate: study appears to have included all relevant children admitted to the hospital. Baseline characteristics only presented for the 18 children with brain herniation. **2. Risk of bias: Study attrition (High/Moderate/Low)** Low: data presented for all children. **3. Risk of bias: Prognostic factor measurement (High/Moderate/Low)** Moderate: objective outcome measurement assumed, but possible that seizures unobserved or reported less completely for some children in these historical records. Measurement of prognostic factor may be different for children who did/did not have brain herniation. "The occurrence of any seizures within 10 minutes prior to the suspected episode of herniation was recorded." **4. Risk of bias: Outcome measurement (High/Moderate/Low)** Moderate: strict criteria used to diagnose herniation, but only retrospectively from hospital records. 9 of the 27 with suspected herniation were excluded from the diagnosis because they did not have at least 2 or the researchers' required physical signs, and one was not diagnosed because he/she showed seizure activity at the time of mannitol treatment. **5. Risk of bias: Study confounding (High/Moderate/Low)** High: data were not adjusted for any confounders. **6. Risk of bias: Statistical analysis and reporting (High/Moderate/Low)** Moderate: risk of selective reporting. Factors of interest are only reported for those

Study details	Results and risk of bias assessment using the QUIPs checklist
Risk factor(s) of interest Seizure Reduced consciousness (defined as coma) **Confounding factor(s)** No matching or adjustment for confounding factors. **Setting** Rainbow Babies and Children's Hospital, Cleveland OH.	with suspected or diagnosed herniation, not for the full cohort. **Source of funding** No sources of funding reported

1 *QUIPS: quality in prognostic studie*

Appendix E Forest plots

Forest plots for review question: What factors (individually or in combination) are associated with an increased risk of brain herniation following lumbar puncture in people with suspected bacterial meningitis?

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

Appendix F GRADE tables

GRADE tables for review question: What factors (individually or in combination) are associated with an increased risk of brain herniation following lumbar puncture in people with suspected bacterial meningitis?

Table 5: Evidence profile for seizure as a prognostic factor for brain herniation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Presence of seizures	Absence of seizures	Relative (95% CI)	Absolute		
Any brain herniation as measured by clinical diagnosis in babies and children												
1 (Horwitz 1980)	observational study	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/62 (14.5%)	9/240 (3.8%)	RR 3.87 (1.6 to 9.34)	108 more per 1000 (from 23 more to 313 more)	VERY LOW	CRITICAL
Fatal brain herniation as measured by post-mortem diagnosis in children												
1 (Benjamin 1988)	observational study	very serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/2 (50%)	3/9 (33.3%)	RR 1.5 (0.28 to 7.93)	167 more per 1000 (from 240 fewer to 1000 more)	VERY LOW	CRITICAL

[1] *Serious risk of bias in the evidence contributing to the outcomes as per QUIPS*
[2] *Evidence downgraded by 2 levels due to risk of very serious imprecision. Number of events < 150*
[3] *Very serious risk of bias in the evidence contributing to the outcomes as per QUIPS*

Table 6: Evidence profile for reduced consciousness as a prognostic factor for brain herniation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Presence of reduced consciousness	Absence of reduced consciousness	Relative (95% CI)	Absolute		
Any brain herniation as measured by clinical diagnosis in babies and children												
1 (Horwitz 1980)	observational study	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/15 (26.7%)	14/287 (4.9%)	RR 5.47 (2.05 to 14.6)	218 more per 1000 (from 51 more to 663 more)	VERY LOW	CRITICAL

Fatal brain herniation as measured by post-mortem diagnosis in children												
1 (Benjamin 1988)	observational study	very serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/8 (50%)	0/3 (0%)	RR 4 (0.28 to 57.98)	500 more per 1000 (from 40 more to 960 more)[4]	VERY LOW	CRITICAL

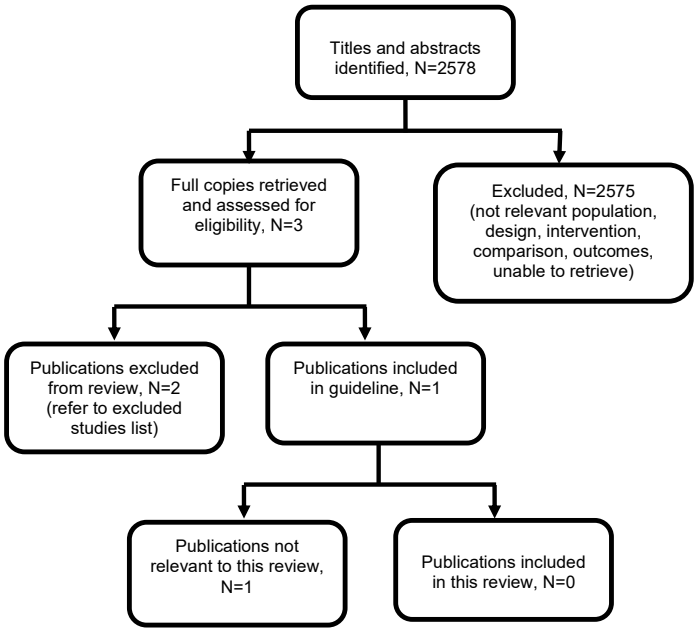
CI: confidence interval; RR: risk ratio
[1] Serious risk of bias in the evidence contributing to the outcomes as per QUIPS
[2] Evidence downgraded by 2 levels due to risk of very serious imprecision. Number of events < 150
[3] Very serious risk of bias in the evidence contributing to the outcomes as per QUIPS
[4] Calculated based on risk difference due to zero events in the control group

Appendix G Economic evidence study selection

Study selection for review question: What factors (individually or in combination) are associated with an increased risk of brain herniation following lumbar puncture in people with suspected 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 2).

Figure 2: Study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: What factors (individually or in combination) are associated with an increased risk of brain herniation following lumbar puncture in people with suspected bacterial meningitis?

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

Appendix I Economic model

Economic model for review question: What factors (individually or in combination) are associated with an increased risk of brain herniation following lumbar puncture in people with suspected bacterial meningitis?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What factors (individually or in combination) are associated with an increased risk of brain herniation following lumbar puncture in people with suspected bacterial meningitis?

Excluded prognostic studies

Table 7: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Adriani, K. S., Brouwer, M. C., van der Ende, A., van de Beek, D., Bacterial meningitis in pregnancy: Report of six cases and review of the literature, Clinical Microbiology and Infection, 18, 345-351, 2012	Study design not of interest for review: case reports from clinical practice and a non-systematic literature review
Adriani, K. S., van de Beek, D., Brouwer, M. C., Spanjaard, L., de Gans, J., Community-acquired recurrent bacterial meningitis in adults, Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 45, e46-51, 2007	No outcomes of interest for review
Beg, M., Ali, S., Ahmad, S., Akhtar, N., A study of computed tomography of head before lumbar puncture in patients with suspected meningitis, Journal, Indian Academy of Clinical Medicine, 8, 355-359, 2007	Country not of interest for review: not an OECD high-income country. Study investigated whether clinical features predict CT abnormalities.
Bouvier, G., Cour-Andlauer, F., Mottolese, C., Teyssedre, S., Javouhey, E., Incidence of raised intracranial pressure in children<2 years admitted for severe brain injury, Intensive Care Medicine, 2), S379, 2011	Conference paper
Costerus, J. M., Brouwer, M. C., Van Der Ende, A., Van De Beek, D., Community-acquired bacterial meningitis in adults with cancer or a history of cancer, NeurologyNeurology, 86, 860-866, 2016	Population does not meet the inclusion criteria
Costerus, J., Brouwer, M., Sprengers, M., Roosendaal, S., Van Der Ende, A., Van De Beek, D., Cerebral herniation after lumbar puncture in adults with bacterial meningitis, European Journal of Neurology, 24, 38, 2017	Conference abstract
Costerus, Joost M., Brouwer, Matthijs C., Sprengers, Marieke E. S., Roosendaal, Stefan D., van der Ende, Arie, van de Beek, Diederik, Cranial Computed Tomography, Lumbar Puncture, and Clinical Deterioration in Bacterial Meningitis: A Nationwide Cohort Study, Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 67, 920-926, 2018	Data on prognostic factors of interest only presented for patients with deterioration; no comparative data for those without deterioration
Durand, M. L., Calderwood, S. B., Weber, D. J., Miller, S. I., Southwick, F. S., Caviness Jr, V. S., Swartz, M. N., Acute bacterial meningitis in adults - A review of 493 episodes, New England Journal of Medicine, 328, 21-28, 1993	Paper does not identify risk factors for brain herniation

Study	Reason for exclusion
Ellis, Jayne, Luintel, Akish, Chandna, Arjun, Heyderman, Robert S., Community-acquired acute bacterial meningitis in adults: a clinical update, British medical bulletin, 131, 57-70, 2019	Study design not of interest for review: description of clinical features and management guide
Evans, R. W., Complications of lumbar puncture, Neurologic Clinics, 16, 83-105, 1998	Study design not of interest for review: non-systematic review
Glimaker, M., Johansson, B., Grindborg, O., Bottai, M., Lindquist, L., Sjolin, J., Adult bacterial meningitis: earlier treatment and improved outcome following guideline revision promoting prompt lumbar puncture, Clinical Infectious DiseasesClin Infect Dis, 60, 1162-9, 2015	Study design and outcomes do not meet inclusion criteria: registry study with focus on timing of treatment
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	No comparison or outcome of interest for this review
Grande, P. O., Myhre, E. B., Nordstrom, C. H., Schliamser, S., Treatment of intracranial hypertension and aspects on lumbar dural puncture in severe bacterial meningitis, Acta Anaesthesiologica Scandinavica, 46, 264-70, 2002	No outcomes of interest for review
Hasbun, R., Abrahams, J., Jekel, J., Quagliarello, V. J., Computed tomography of the head before lumbar puncture in adults with suspected meningitis, New England Journal of Medicine, 345, 1727-1733, 2001	No outcomes of interest for review. Study investigated Whether clinical features predict CT abnormalities
Heckenberg, Sebastiaan G. B., de Gans, Jan, Brouwer, Matthijs C., Weisfelt, Martijn, Piet, Jurgen R., Spanjaard, Lodewijk, van der Ende, Arie, van de Beek, Diederik, Clinical features, outcome, and meningococcal genotype in 258 adults with meningococcal meningitis: a prospective cohort study, Medicine, 87, 185-192, 2008	No outcomes of interest for review
Heyderman, R. S., Klein, N. J., Emergency management of meningitis, Journal of the Royal Society of Medicine, 93, 225-229, 2000	Study design not of interest for review: non-systematic review and management
Joffe, Ari R., Lumbar puncture and brain herniation in acute bacterial meningitis: a review, Journal of intensive care medicine, 22, 194-207, 2007	Review paper that includes population/review questions that are not relevant for the review
Kellner, James D., Scheifele, David W., Halperin, Scott A., Lebel, Marc H., Moore, Dorothy, Le Saux, Nicolle, Ford-Jones, E. Lee, Law, Barbara, Vaudry, Wendy, Canadian Paediatric Society/Centre for Infectious Disease, Prevention, Control Immunization Monitoring, Program, Outcome of penicillin-nonsusceptible Streptococcus pneumoniae meningitis: a nested case-control study, The Pediatric infectious disease journal, 21, 903-10, 2002	No outcomes of interest for the review
Koelman, D., Brouwer, M. C., Ter Horst, L.,	Conference Abstract

Study	Reason for exclusion
Bijlsma, M., Van Der Ende, A., Van De Beek, D., Clinical characteristics, prognostic factors, and causes of death in adults with community-acquired pneumococcal meningitis, European Journal of Neurology, 27 (Supplement 1), 449, 2020	
Kwong, K. L., Chiu, W. K., Potential risk of fatal cerebral herniation after lumbar puncture in suspected CNS infection, Hong Kong Journal of Paediatrics, 14, 22-28, 2009	Study design not of interest for review: non-systematic review
Mellor, D. H., The place of computed tomography and lumbar puncture in suspected bacterial meningitis, Archives of Disease in Childhood, 67, 1417-1419, 1992	Study design not of interest for review: non-systematic review
Meyer, C. N., Augustesen, S., Models of predicting the risk of brain herniation in bacterial meningitis, Clinical Microbiology and Infection, 15, S335-S336, 2009	Conference abstract
Meyer, C. N., Augustesen, S., Brain herniation and the use of CT-scanning in acute bacterial meningitis, Clinical microbiology and infection, 15 (S4), S336, 2009	Conference abstract
Oliver, W. J., Shope, T. C., Kuhns, L. R., Fatal lumbar puncture: fact versus fiction--an approach to a clinical dilemma, Pediatrics, 112, e174-6, 2003	Study design not of interest for review: non-systematic review
Petheram, K. R. C., Neurology on the acute take, Clinical Medicine, Journal of the Royal College of Physicians of London, 10, 148-150, 2010	Study type not of interest for review: summary of a conference
Pfister, H. W., Feiden, W., Einhaupl, K. M., Spectrum of complications during bacterial meningitis in adults. Results of a prospective clinical study, Archives of Neurology, 50, 575-81, 1993	No comparison of interest for this review. No risk factors for brain herniation assessed
Pingree, E. W., Kimia, A. A., Nigrovic, L. E., The effect of traumatic lumbar puncture on hospitalization rate for febrile infants 28 to 60 days of age, Academic emergency medicine, 22, 240-3, 2015	Study design not of interest for review: non-systematic review
Radetsky, M., Fulminant bacterial meningitis, Pediatric infectious disease journal, 33, 204-207, 2014	Study design not of interest for review: non-systematic review
Rennick, G., Shann, F., De Campo, J., Cerebral herniation during bacterial meningitis in children, British medical journal, 306, 953-955, 1993	Comparison not of interest for review: no comparison between presence/absence of factors in those that did and did not have brain herniation
Sharew, A., Bodilsen, J., Hansen, B. R., Nielsen, H., Brandt, C. T., The cause of death in bacterial meningitis, BMC Infectious Diseases, 20, 182, 2020	Population not relevant for this review: not clear how many patients had lumber puncture
Swanson, D., Meningitis, Pediatrics in Review, 36, 514-524, 2015	Study type not of relevance for this review: guidance on diagnosis and management of meningitis
Tubiana, S., Varon, E., Biron, C., Ploy, M. C., Mourvillier, B., Taha, M. K., et al. Community-	No outcomes of interest for review

Study	Reason for exclusion
acquired bacterial meningitis in adults: in-hospital prognosis, long-term disability and determinants of outcome in a multicentre prospective cohort, Clinical Microbiology and Infection, 26, 1192-1200, 2020	
Turner, T., Risk of cerebral herniation due to lumbar puncture in children with suspected meningitis, 28, 2003	Study design not of interest to this review: systematic review with no relevant research questions
Van De Beek, D., De Gans, J., Tunkel, A. R., Wijdicks, E. F. M., Community-acquired bacterial meningitis in adults, New England Journal of Medicine, 354, 44-53, 2006	Study design not of interest for review: non-systematic review
Van De Beek, D., Drake, J. M., Tunkel, A. R., Nosocomial bacterial meningitis, New England journal of medicine, 362, 146-154+100, 2010	Study design not of interest for review: non-systematic review
Weisfelt, M., Van De Beek, D., Spanjaard, L., Reitsma, J. B., De Gans, J., Community-acquired bacterial meningitis in older people, Journal of the American Geriatrics Society, 54, 1500-1507, 2006	No comparison of interest for this review: paper compares outcomes for people aged 60 or over versus people under 60 years old
Williams, J., Lye, D. C. B., Umapathi, T., Diagnostic lumbar puncture: Minimizing complications, Internal Medicine Journal, 38, 587-591, 2008	Systematic review with no relevant questions for the current review

CT: computed tomography; OECD: Organisation for Economic Co-operation and Development

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 factors (individually or in combination) are associated with an increased risk of brain herniation following lumbar puncture in people with suspected bacterial meningitis?

No research recommendation was made for this review.