National Institute for Health and Care Excellence

Final

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

[G3] Evidence review for intracranial pressure monitoring in bacterial meningitis

NICE guideline NG240

Evidence review underpinning recommendations 1.9.6 and 1.9.7 and the recommendation for research on intracranial pressure monitoring in the NICE guideline

March 2024

Final

This evidence review was developed by NICE

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Contents

Intracranial pressure monitoring in bacterial meningitis

Review question

What is the effectiveness of intracranial pressure monitoring in bacterial meningitis?

Introduction

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

The aim of this review is to establish the role of intracranial pressure monitoring 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 (excluding neonates defined as aged 28 days old and younger) with confirmed bacterial meningitis.

Intervention	Intracranial pressure monitoring by any of the below methods:
	• Invasive methods
	  ○ Intraventricular catheter
	  ○ Epidural catheter
	  ○ Subarachnoid catheter
	  ○ Intraparenchymal catheter
	• Non-invasive methods
	  ○ Anterior Fontanelle Pressure
	  ○ Skull Elasticity
	  ○ Tympanic Membrane Displacement
	  ○ Tissue Resonance Analysis
	  ○ Transcranial Doppler
	  ○ Acoustoelasticity
	  ○ Venous Ophthalmodynamometer
	  ○ Optic Nerve Sheath Diameter
	  ○ Distortion-Product Otoacoustic Emissions
	  ○ Magnetic Resonance Imaging
	  ○ Computed Topography
	  ○ Electroencephalography
	  ○ Ophthalmoscopy
	  ○ Pupillometry
	  ○ Near Infrared Spectroscopy

Comparison	No intracranial pressure monitoring
Outcome	**Critical** Population: adults, 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, 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: 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, infants and children • Brain herniation (may be reported as herniation, loss of pupillary reactivity, significant drop on Glasgow Come Scale, coning) • Serious intervention-related adverse effects leading to death, disability or prolonged hospitalisation or that are life threatening or otherwise considered medically significant Population: adults • Quality of life (measured by any validated scale) • Diagnosis of epilepsy Population: infants and children • Functional impairment (measured by any validated scale at any time point) • Moderate developmental delay (defined as score of 1-2 SD below normal on validated assessment scales, or MDI or PDI 70-84 on Bayleys assessment scale; 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.

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 cohort studies were included in this review, 1 prospective (Glimaker 2014) and 1 retrospective (Odetola 2006).

The included studies are summarised in Table 2.

Both studies compared intracranial pressure monitoring to no intracranial pressure monitoring and did not adjust for confounding factors specified in the protocol. One study was conducted in babies and children (Odetola 2006), and 1 included adults (Glimaker 2014).

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
Glimaker 2014 Prospective cohort study with historical control Sweden	N=105 Adults 16 to 74 years with confirmed acute bacterial meningitis and severely impaired mental status at the point of admission Age in years (median, range): ICP monitoring: 55;16 to 74 No ICP monitoring: 58 (18 to 74) Case-fatality: 20%	ICP monitoring EVD-catheter or parenchymal ICP monitoring offered after CT-scanning of the brain. The aim was to reduce or maintain ICP below 20 mmHg.	No ICP monitoring No further details reported	• All-cause mortality • Any long-term neurological impairment (sensory deficit: hearing impairment) • Functional impairment with or without hearing impairment	Some of the participants were in an immunocompromised state due to alcoholism (33.3%), diabetes (5.7%), splenectomised, CSF leakage and malignancy /immunosuppression (14%), therefore, evidence from these participants is considered indirect as they do not meet the inclusion criteria of the review.
Odetola 2006 Retrospective cohort study USA	N=146 Children aged 0 to 17 years hospitalised with bacterial meningitis and receiving mechanical ventilation Age in years: <1: n=73; 1 to 4: n=27; 5 to 17: n=46 Case-fatality: 25.5%	ICP monitoring No further details reported	No ICP monitoring No further details reported	• All-cause mortality	

CSF: cerebrospinal fluid; CT: Computerised tomography; EVD: External ventricular drains; ICP: intracranial pressure

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 low to very low quality due to risk of bias (for example, due to selective reporting), imprecision (due to low event rates) and the inclusion of an indirect population and composite outcome. The evidence was stratified by age; however, there was insufficient evidence to stratify according to intracranial pressure monitoring method. See the GRADE tables in appendix F for the certainty of the evidence for each individual outcome.

The evidence showed no important differences between intracranial pressure monitoring and no intracranial pressure monitoring for all-cause mortality in babies and children, or for hearing impairment or functional impairment in adults. There was some evidence that intracranial pressure monitoring was associated with a lower mortality rate for adults, however, this finding was very seriously imprecise so cannot be taken as definitive evidence.

No other outcomes in the protocol were reported.

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. See the literature search strategy in appendix B and economic study selection flow chart in appendix G.

Economic model

No economic modelling was undertaken for this review because, although this question was originally prioritised, there was a lack of clinical evidence to inform any analysis.

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. These may be more likely in the instance of raised intracranial pressure (ICP); therefore, ICP monitoring may impact such outcomes by identifying instances of raised ICP that can then be responded to appropriately. Therefore, all-cause mortality and long-term neurological impairment were prioritised as critical outcomes due to the severity of these outcomes. Severe developmental delay was prioritised over functional impairment in children and babies, as it is a more relevant and important outcome for this population. Functional impairment was prioritised as a critical outcome in adults due to the concern about the

potential long-term limitations of bacterial meningitis, and complications of raised ICP, on the ability to carry out certain activities of daily life.

Brain herniation and serious intervention-related adverse effects were selected as important outcomes in babies, children, and adults. Brain herniation is a potentially life-threatening complication that can occur because of raised ICP, especially if a lumbar puncture is performed. It was chosen as an important, rather than critical outcome, despite its severity, because the committee agreed that the potential long-term impacts of brain herniation (those included as critical outcomes above) are more important in terms of the long-term impact on people's lives than the brain herniation itself. Serious intervention-related adverse effects were selected as an important outcome due to the invasive nature of some methods of ICP monitoring and potential risks associated with these. In addition to functional impairment, brain herniation and serious intervention-related adverse effects in children and babies, moderate developmental delay was also selected as an important outcome as it is a relevant and important outcome for this population. In adults, quality of life and diagnosis of epilepsy were selected as important outcomes; quality of life was selected because it is a global measure of wellbeing that takes into account both beneficial and adverse effects of interventions, and epilepsy was selected as it can be relatively common following bacterial meningitis and may be related to ICP.

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 non-comparable methods of outcome assessment across groups or selective reporting), imprecision (due to small numbers of events), and the inclusion of an indirect population and a composite outcome.

Benefits and harms

The committee considered the evidence comparing intracranial pressure (ICP) monitoring to no ICP, that showed no important differences for all-cause mortality in babies and children, or for hearing impairment or functional impairment in adults. There was some very low-quality evidence that intracranial pressure monitoring was associated with a lower mortality rate for adults, however, this finding was very seriously imprecise so cannot be taken as definitive evidence. Furthermore, the committee noted that, in the study that showed evidence of a mortality benefit, the ICP monitoring was part of a package of care that also included functional cerebrospinal fluid draining and care in a more specialist centre than where controls were cared for. Therefore, the committee did not think that the evidence of benefit could necessarily be attributed to the ICP monitoring itself. The population was also considered indirect as approximately one third of included participants were immunocompromised and outside the scope of this guideline. As ICP monitoring can be invasive, and an invasive method was used in the study that showed evidence of benefit, the committee agreed that the very limited evidence of benefit did not outweigh potential risks and that invasive ICP monitoring should not be routinely performed.

The committee acknowledged that if there are features of raised ICP or hydrocephalus, ICP monitoring may be more likely to be beneficial. However, the committee recommended that specialist advice should be sought on ICP monitoring in people with features of raised ICP or hydrocephalus.

The committee highlighted that people with bacterial meningitis and impaired consciousness are seriously unwell, often requiring treatment in intensive care units. While it is known that intracranial pressure is often high, it is not known whether monitoring and managing this improves outcomes, as the existing evidence on the effects of ICP monitoring on clinical outcomes is limited and of low quality. The committee agreed that ICP monitoring per se offers no direct benefit. It is only when ICP monitoring is used to guide other treatment decisions (for example, osmotic agents, ventilation targets, cerebrospinal fluid diversion) that

there are potential benefits in terms of clinical outcomes. The committee made a research recommendation that would test the effectiveness of using intracranial pressure monitoring (invasive or non-invasive) to guide treatment decisions in bacterial meningitis (see Appendix K).

Cost effectiveness and resource use

No economic modelling was undertaken for this review and therefore the committee made a qualitative assessment of the likely cost-effectiveness of their recommendations. Although the data was limited the committee agreed that it was not cost-effective to routinely recommend ICP monitoring for people with confirmed bacterial meningitis, as the procedure is expensive and invasive, and the committee were not persuaded that the very limited evidence of benefits outweighed the potential harms. It is not current practice to routinely offer ICP and therefore no significant cost savings are expected as a result of the committee's recommendations.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.9.6 and 1.9.7 and the recommendation for research on intracranial pressure monitoring.

References – included studies

Effectiveness

Glimaker 2014

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

Odetola 2006

Odetola, F. O., Tilford, J. M., Davis, M. M., Variation in the use of intracranial-pressure monitoring and mortality in critically ill children with meningitis in the United States, Pediatrics, 117, 1893-1900, 2006

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 intracranial monitoring agents in bacterial meningitis?

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42021231957
Review title	Intracranial pressure monitoring in bacterial meningitis
Review question	What is the effectiveness of intracranial pressure monitoring in bacterial meningitis?
Objective	To determine the effectiveness of intracranial pressure monitoring in bacterial meningitis
Searches	The following databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Searches will be restricted by: English language Human studies The full search strategies for MEDLINE database will be published in the final review. For each search, the principal database search strategy is quality assured by a second information scientist using an adaptation of the PRESS 2015 Guideline Evidence-Based Checklist.
Condition or domain being studied	Bacterial meningitis
Population	Inclusion: All adults, young people, children and babies (excluding neonates defined as aged 28

Field	Content
	days old and younger) with confirmed bacterial meningitis. Exclusion: People: • with known immunodeficiency. • who have brain tumours, pre-existing hydrocephalus, intracranial shunts, previous neurosurgical procedures, or known cranial or spinal anomalies that increase the risk of bacterial meningitis. • with confirmed viral meningitis or viral encephalitis. • with confirmed tuberculous meningitis. • with confirmed fungal meningitis.
Intervention/Exposure/Test	Intracranial pressure monitoring by any of the below methods • Invasive methods o Intraventricular catheter o Epidural catheter o Subarachnoid catheter o Intraparenchymal catheter • Non-invasive methods o Anterior Fontanelle Pressure o Skull Elasticity o Tympanic Membrane Displacement o Tissue Resonance Analysis o Transcranial Doppler o Acoustoelasticity o Venous Ophthalmodynamometr o Optic Nerve Sheath Diameter o Distortion-Product Otoacoustic Emissions o Magnetic Resonance Imaging o Computed Topography o Electroencephalography

Field	Content
	○ Ophthalmoscopy ○ Pupillometry ○ Near Infrared Spectroscopy
Comparator/Reference standard/Confounding factors	No intracranial pressure monitoring
Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs • Test–and-treat RCTs • If insufficient RCTs: prospective cohort studies • If insufficient prospective cohort studies: retrospective cohort studies Non-randomised studies will be downgraded for risk of bias if they do not adequately adjust for the following covariates, but will not be excluded for this reason: • Severity of illness at presentation • Infective organism, • Age (if data is not confined to one of the age groups of interest [see stratifications] or presented separately for different age groups) Exclude: • Conference abstracts
Other exclusion criteria	Cohort studies from low income countries. Studies conducted prior to 1980 as currently used antibiotics were not in common usage prior to this date. Studies published not in English language.
Context	This guidance will fully update the following: Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management (CG102)
Primary outcomes (critical outcomes)	Population: Adult • All-cause mortality (measured up to 1 year after discharge) • Any long-term neurological impairment (defined as any motor deficits, sensory deficits, cognitive

Field	Content
	deficits, or behavioural deficits; measured from discharge up to 1 year after discharge) • Functional impairment (measured by any validated scale at any time point) Population: Children • All-cause mortality (measured up to 1 year after discharge) • Any long-term neurological impairment (defined as any motor deficits, sensory deficits, cognitive deficits*, or behavioural deficits*; measured from discharge up to 1 year after discharge) • 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 • Brain herniation (may be reported as herniation, loss of pupillary reactivity, significant drop on Glasgow Come Scale, coning) • Serious intervention-related adverse effects leading to death, disability or prolonged hospitalisation or that are life threatening or otherwise considered medically significant • Quality of life (measured by any validated scale) • Diagnosis of epilepsy Population: Children • Functional impairment (measured by any validated scale at any time point) • Brain herniation (may be reported as herniation, loss of pupillary reactivity, significant drop on Glasgow Come Scale, coning) • Serious intervention-related adverse effects leading to death, disability or prolonged hospitalisation or that are life threatening or otherwise considered medically significant • Moderate developmental delay (defined as score of 1-2 SD below normal on validated assessment scales, or MDI or PDI 70-84 on Bayleys assessment scale; measured at the oldest age reported

Field	Content
	unless there is substantially more data available at a younger age)
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. 5% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third 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 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. • CASP case control checklist for case-control studies The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Quantitative findings will be formally summarised in the review. Where multiple studies report on the same outcome for the same comparison, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios if possible or odds ratios when required (for example if only available in this form in included studies) for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed by visual inspection of the forest plots and consideration of the I^2 statistic. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through 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

Field	Content
	not adequately address heterogeneity. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ **Minimally important differences:** • All-cause mortality: statistical significance • Serious intervention-related adverse effects: statistical significance • Brain herniation – statistical significance • Validated scales: Published MIDs where available; if not GRADE default MIDs • All other outcomes: GRADE default MIDs
Analysis of sub-groups	Evidence will be stratified by: Age: • Younger Infants: >28 days to ≤3 months of age • Older infants and children: >3 months to <18* years of age • Adults: ≥18* years of age *There is variation in clinical practice regarding the treatment of 16 to 18 year olds. Therefore, we 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 Intracranial pressure monitoring method: • Invasive • Non-invasive Evidence will be sub-grouped by the following only in the event that there is significant heterogeneity in outcomes: Age: • Young and middle aged adults

Field	Content			
	• 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 sub-grouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.			
Type and method of review	☒	Intervention		
	☐	Diagnostic		
	☐	Prognostic		
	☐	Qualitative		
	☐	Epidemiologic		
	☐	Service Delivery		
	☐	Other (please specify)		
Language	English			
Country	England			
Anticipated or actual start date	14/01/2021			
Anticipated completion date	07/12/2023			
Stage of review at time of this submission	Review stage		Started	Completed
	Preliminary searches		☑	☑
	Piloting of the study selection process		☑	☑
	Formal screening of search results against		☑	☑

Field	Content		
	eligibility criteria		
	Data extraction	☑	☑
	Risk of bias (quality) assessment	☑	☑
	Data analysis	☑	☑
Named contact	Named contact: National Guideline Alliance Named contact e-mail: meningitis&meningococcal@nice.org.uk Organisational affiliation of the review: National Institute for Health and Care Excellence (NICE) and National Guideline Alliance		
Review team members	National Guideline Alliance		
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance which receives funding from NICE.		
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: 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=CRD42021231957		
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include		

Field	Content	
	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, intracranial pressure monitoring, intraventricular catheter, 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	

CASP: Critical Appraisals Skills Programme; 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; MID: minimally important difference; NICE: National Institute for Health and Care Excellence; PDI: psychomotor development index; 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 intracranial pressure monitoring in bacterial meningitis?

Clinical Search

Database(s): Medline & Embase (Multifile) – OVID interface
Embase Classic+Embase 1947 to 2020 December 15, **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to December 15, 2020
Date of last search: 17 December 2020
Multifile database codes: emczd = Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	Meningitis/ or Meningitis, Bacterial/ or Meningitis, Escherichia Coli/ or Meningitis, Haemophilus/ or Meningitis, Listeria/ or Meningitis, Meningococcal/ or Meningitis, Pneumococcal/ or Meningoencephalitis/ or exp Neisseria meningitidis/
2	1 use ppez
3	meningitis/ or bacterial meningitis/ or haemophilus meningitis/ or hemophilus influenzae meningitis/ or listeria meningitis/ or pneumococcal meningitis/ or meningoencephalitis/ or meningococcal meningitis/ or neisseria meningitidis/
4	3 use emczd
5	((bacter* or infect*) adj3 (meningit* or meninges* or leptomeninges* or subarachnoid space?)).ti,ab.
6	(meningit* adj3 (e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon* or septic* or sepsis* or bacter?emi?)).ti,ab.
7	((e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon*) adj3 (septic* or sepsis* or bacter?emi?)).ti,ab.
8	(meningit* or mening?encephalitis*).ti,ab.
9	(Neisseria* mening* or n mening*).ti,ab.
10	or/2,4-9
11	Intracranial Pressure/ use ppez
12	intracranial pressure/ use emczd
13	((intracran* or intra-cran* or intracerebr* or intra-cerebr* or craniospin* or cranio-spin* or compartment*) adj3 press*).ti,ab.
14	((intraparenchym* or intra-parenchym* or parenchym* or intracran* press* or intra-cran* press* or ICP) adj3 monitor*).ti,ab.
15	((intracran* or intra-cran*) adj monitor*).ti,ab.
16	((rais* or rise or high or elevat* or increas* or alter* or manag* or measure* or pressure*) adj3 ICP).ti,ab.
17	intraventricular catheter/ use emczd
18	((intraventricular or intra-ventricular) adj catheter*).ti,ab.
19	or/11-18
20	10 and 19
21	Cerebrospinal Fluid/
22	Drainage/ use ppez
23	Monitoring, Physiologic/ use ppez
24	cerebrospinal fluid drainage system/ use emczd
25	physiologic monitoring/ use emczd
26	or/22-25
27	10 and 21 and 26
28	20 or 27
29	letter/
30	editorial/
31	news/
32	exp historical article/
33	Anecdotes as Topic/
34	comment/
35	case report/
36	(letter or comment*).ti.
37	29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
38	randomized controlled trial/ or random*.ti,ab.
39	37 not 38
40	animals/ not humans/
41	exp Animals, Laboratory/
42	exp Animal Experimentation/

#	Searches
43	exp Models, Animal/
44	exp Rodentia/
45	(rat or rats or mouse or mice).ti.
46	39 or 40 or 41 or 42 or 43 or 44 or 45
47	letter.pt. or letter/
48	note.pt.
49	editorial.pt.
50	case report/ or case study/
51	(letter or comment*).ti.
52	47 or 48 or 49 or 50 or 51
53	randomized controlled trial/ or random*.ti,ab.
54	52 not 53
55	animal/ not human/
56	nonhuman/ not human/
57	exp Animal Experiment/
58	exp Experimental Animal/
59	animal model/
60	exp Rodent/
61	(rat or rats or mouse or mice).ti.
62	54 or 55 or 56 or 57 or 58 or 59 or 60 or 61
63	46 use ppez
64	62 use emczd
65	63 or 64
66	28 not 65
67	limit 66 to English language
68	limit 67 to yr="1980 -Current"

Database(s): Cochrane Library – Wiley interface
Cochrane Database of Systematic Reviews, Issue 12 of 12, December 2020, **Cochrane Central Register of Controlled Trials**, Issue 12 of 12, December 2020
Date of last search: 17 December 2020

#	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	(((bacter* or infect*) NEAR/3 (meningit* or meninges* or leptomeninges* or "subarachnoid space*"))):ti,ab,kw
#10	((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 “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
#11	((“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*))
#12	(meningencephalitis* or meningoencephalitis* or meningit*)
#13	MeSH descriptor: [Neisseria meningitidis] explode all trees
#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 #13 #14
#16	MeSH descriptor: [Intracranial Pressure] this term only
#17	(((intracran* or intra-cran* or intracerebr* or intra-cerebr* or craniospin* or cranio-spin* or compartment*) NEAR/3 press*)):ti,ab,kw
#18	(((intraparenchym* or intra-parenchym* or parenchym* or intracran* press* or intra-cran* press* or ICP) NEAR/3 monitor*)):ti,ab,kw
#19	(((intracran* or intra-cran*) NEXT monitor*)):ti,ab,kw
#20	(((rais* or rise or high or elevat* or increas* or alter* or manag* or measure* or pressure*) NEAR/3 ICP)):ti,ab,kw
#21	(((intraventricular or intra-ventricular) NEXT catheter*)):ti,ab,kw
#22	#16 OR #17 OR #18 OR #19 OR #20 OR #21
#23	#15 AND #22
#24	MeSH descriptor: [Cerebrospinal Fluid] this term only
#25	MeSH descriptor: [Drainage] this term only
#26	MeSH descriptor: [Monitoring, Physiologic] this term only
#27	#25 OR #26
#28	#15 AND #24 AND #27
#29	#23 OR #28

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

Date of last search: 17 December 2020

#	Searches
1	MeSH DESCRIPTOR Meningitis IN DARE,HTA
2	MeSH DESCRIPTOR Meningitis, Bacterial IN DARE,HTA
3	MeSH DESCRIPTOR Meningitis, Escherichia coli IN DARE,HTA
4	MeSH DESCRIPTOR Meningitis, Haemophilus IN DARE,HTA
5	MeSH DESCRIPTOR Meningitis, Listeria IN DARE,HTA
6	MeSH DESCRIPTOR Meningitis, Meningococcal IN DARE,HTA
7	MeSH DESCRIPTOR Meningitis, Pneumococcal IN DARE,HTA
8	MeSH DESCRIPTOR Meningoencephalitis IN DARE,HTA
9	(((bacter* or infect*) NEAR3 (meningit* or meninges* or leptomeninges* or "subarachnoid space*"))) IN DARE, HTA
10	((meningencephalitis* or meningoencephalitis* or meningit*)) IN DARE, HTA
11	MeSH DESCRIPTOR Neisseria meningitidis 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 Intracranial Pressure IN DARE,HTA
15	(((intracran* or intra-cran* or intracerebr* or intra-cerebr* or craniospin* or cranio-spin* or compartment*) NEAR3 press*)) IN DARE, HTA
16	(((intraparenchym* or intra-parenchym* or parenchym* or intracran* press* or intra-cran* press* or ICP) NEAR3 monitor*)) IN DARE, HTA
17	(((intracran* or intra-cran*) NEXT monitor*)) IN DARE, HTA
18	(((rais* or rise or high or elevat* or increas* or alter* or manag* or measure* or pressure*) NEAR3 ICP)) IN DARE, HTA
19	(((intraventricular or intra-ventricular) NEXT catheter*)) IN DARE, HTA
20	#14 OR #15 OR #16 OR #17 OR #18 OR #19
21	#13 AND #20
22	MeSH DESCRIPTOR cerebrospinal fluid IN DARE,HTA
23	MeSH DESCRIPTOR drainage IN DARE,HTA
24	MeSH DESCRIPTOR monitoring, physiologic IN DARE,HTA
25	#23 OR #24
26	#13 AND #22 AND #25
27	#21 OR #26

Economic Search

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

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

Date of last search: 11 March 2021

#	Searches
1	MeSH DESCRIPTOR meningitis IN NHSEED,HTA
2	MeSH DESCRIPTOR Meningitis, Bacterial IN NHSEED,HTA
3	MeSH DESCRIPTOR Meningitis, Escherichia coli IN NHSEED,HTA
4	MeSH DESCRIPTOR Meningitis, Haemophilus EXPLODE ALL TREES IN NHSEED,HTA
5	MeSH DESCRIPTOR Meningitis, Listeria IN NHSEED,HTA
6	MeSH DESCRIPTOR Meningitis, Meningococcal IN NHSEED,HTA
7	MeSH DESCRIPTOR Meningitis, Pneumococcal IN NHSEED,HTA
8	MeSH DESCRIPTOR Meningoencephalitis IN NHSEED,HTA
9	(((bacter* or infect*) NEAR3 (meningit* or meninges* or leptomeninges* or subarachnoid space*))) IN NHSEED, HTA
10	((meningit* NEAR3 (e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon* or septic* or sepsis* or bacter?emi?))) IN NHSEED, HTA
11	(((e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or 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

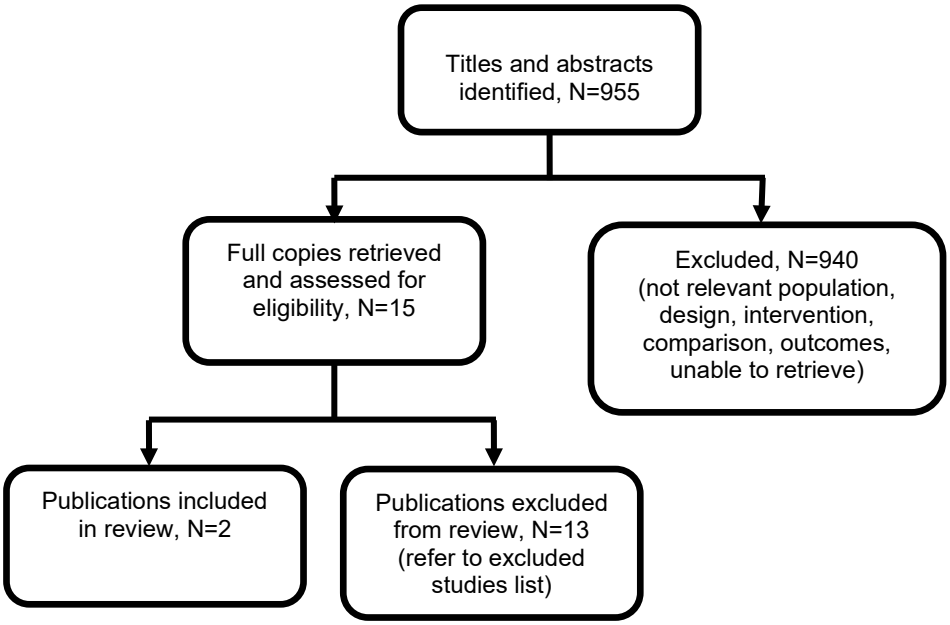
#	Searches
1	Meningitis/ or Meningitis, Bacterial/ or Meningitis, Escherichia Coli/ or Meningitis, Haemophilus/ or Meningitis, Listeria/ or Meningitis, Meningococcal/ or Meningitis, Pneumococcal/ or Meningoencephalitis/
2	1 use ppez
3	meningitis/ or bacterial meningitis/ or haemophilus meningitis/ or 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.

#	Searches
55	(time trade off*1 or time tradeoff*1 or tto or timetradeoff*1).tw.
56	Quality of Life/ and ((quality of life or qol) adj (score*1 or measure*1)).tw.
57	Quality of Life/ and ec.fs.
58	Quality of Life/ and (health adj3 status).tw.
59	(quality of life or qol).tw. and Cost-Benefit Analysis/ use ppez
60	(quality of life or qol).tw. and cost benefit analysis/ use emczd
61	((qol or hrqol or quality of life).tw. or *quality of life/) and ((qol or hrqol* or quality of life) adj2 (increas* or decreas* or improv* or declin* or reduc* or high* or low* or effect or effects or worse or score or scores or change*1 or impact*1 or impacted or deteriorat*)).ab.
62	Cost-Benefit Analysis/ use ppez and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
63	cost benefit analysis/ use emczd and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
64	*quality of life/ and (quality of life or qol).ti.
65	quality of life/ and ((quality of life or qol) adj3 (improv* or chang*)).tw.
66	quality of life/ and health-related quality of life.tw.
67	Models, Economic/ use ppez
68	economic model/ use emczd
69	care-related quality of life.tw,kw.
70	((capability$ or capability-based$) adj (measure$ or index or instrument$)).tw,kw.
71	social care outcome$.tw,kw.
72	(social care and (utility or utilities)).tw,kw.
73	or/41-72
74	(9 or 17) and 40
75	(9 or 17) and 73
76	letter/
77	editorial/
78	news/
79	exp historical article/
80	Anecdotes as Topic/
81	comment/
82	case report/
83	(letter or comment*).ti.
84	76 or 77 or 78 or 79 or 80 or 81 or 82 or 83
85	randomized controlled trial/ or random*.ti,ab.
86	84 not 85
87	animals/ not humans/
88	exp Animals, Laboratory/
89	exp Animal Experimentation/
90	exp Models, Animal/
91	exp Rodentia/
92	(rat or rats or mouse or mice).ti.
93	86 or 87 or 88 or 89 or 90 or 91 or 92
94	letter.pt. or letter/
95	note.pt.
96	editorial.pt.
97	case report/ or case study/
98	(letter or comment*).ti.
99	94 or 95 or 96 or 97 or 98
100	randomized controlled trial/ or random*.ti,ab.
101	99 not 100
102	animal/ not human/
103	nonhuman/
104	exp Animal Experiment/
105	exp Experimental Animal/
106	animal model/
107	exp Rodent/
108	(rat or rats or mouse or mice).ti.
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

Appendix C Effectiveness evidence study selection

Study selection for: What is the effectiveness of intracranial pressure monitoring in bacterial meningitis?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What is the effectiveness of intracranial pressure monitoring in bacterial meningitis?

Table 4: Evidence tables – effectiveness evidence

Study details	Results and risk of bias assessment using ROBINS-I
Full citation 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 **Ref Id** 1283516 **Country/ies where the study was carried out** Sweden **Study type** Prospective cohort with historical control **Study dates** September 2004 - January 2012 **Inclusion criteria** Adults aged 16 to 75 years; confirmed acute bacterial meningitis (ABM); severely impaired mental status at the point of admission. The intervention group were recruited prospectively while. controls were included retrospectively from admission data in the registry. **Exclusion criteria** No additional criteria reported for the intervention group. However, controls who were not treated according to national guidelines for corticosteroids and antibiotics, in ICU with assisted ventilation and sedation, whose physicians missed to contact NICU for inclusion and those that received ICP-targeted treatment in a NICU outside Stockholm	**Results** Outcome: All-cause mortality (GOS 1) at 2 months ICP monitoring: 5/52 No ICP monitoring: 16/53 Any long-term neurological impairment (sensory deficit: hearing impairment at 2 to 6 months) ICP monitoring: 4/52 No ICP monitoring: 6/53 [1]Functional impairment (GOS 2 to 4) with or without hearing impairment at 2 to 6 months ICP monitoring: 15/52 No ICP monitoring: 14/53 [1]Outcome is indirect as it is a composite of outcomes included in the protocol **1. Bias due to confounding (Low/Moderate/Serious/Critical/No information)** Low: None of the confounding factors of interest were adjusted for, however, there was no difference between the intervention and the control group in any of these factors. **2. Bias in selection of participants into the study (Low/Moderate/Serious/Critical/No information)** Low: Independent observers excluded a number of participants from the control group to avoid selection bias,

Study details	Results and risk of bias assessment using ROBINS-I
were excluded. **Patient characteristics** N=105 adults Age in years (median range): ICP monitoring: 55;16 to 74 No ICP monitoring: 58; 18 to 74. Sex: male 53 (50.5%); female 52 (49.5%) Mental status on admission: Glasgow Coma Scale score ≤7/RLS ≥5: 48/105 (45.7%) Glasgow Coma Scale score ≤4/RLS = 8 : 8/105 (7.6%) Aetiology: S. pneumoniae: 77/105 (73.3%) N. meningitidis: 16/105 (15.2%) Other bacteria: 12/105 (11.4%) **Interventions** EVD-catheter or parenchymal ICP monitoring: EVD-catheter (n = 48) or parenchymal ICP monitor (n = 4): Participants underwent CT-scanning of the brain and ICP monitoring. ICP was continuously registered in a computerised patient monitoring system with the aim of reducing or maintaining pressure below 20mmHg. The treatment for increased ICP was CSF-drainage through the EVD. Additional treatment targeting ICP was provided if needed. No ICP monitoring: no further details reported. **Follow-up** 2 to 6 months after discharge	**3. Bias in classification of interventions (Low/Moderate/Serious/Critical/No information)** Low: There was no apparent bias in classification of interventions **4. Bias due to deviations from intended interventions (Low/Moderate/Serious/Critical/No information)** Low: Deviations from the intended intervention were not related to the intervention/outcome. **5. Bias due to missing data (Low/Moderate/Serious/Critical/No information)** Low: All participants were included in an ITT analysis **6. Bias in measurement of outcomes (Low/Moderate/Serious/Critical/No information)** Serious: Results from controls were retrospectively included, therefore, unlikely. It is likely that the results for intervention group were not obtained in a similar way. **7. Bias in selection of the reported result (Low/Moderate/Serious/Critical/No information)** Low: All specified outcomes appear to have been reported **Overall risk of bias (Low/Moderate/Serious/Critical/No information)** Serious **Source of funding** Not reported **Other information** *All deaths occurred within one month after admission. S pneumonia was the infective agent in all fatal cases of the ICP monitoring group and in 9/16 fatality cases in the control group.

Study details	Results and risk of bias assessment using ROBINS-I
	35/105 (33.3%) are reported to have been in an immunocompromised state for due to alcoholism; diabetes (6/105: 5.7%); splenectomised; CSF leakage and malignancy/immunosuppression (15/105: 14%). Therefore, they do not meet the inclusion criteria of the review leading to indirectness of population. There is no overlap between the hearing impairment and functional impairment with or without hearing impairment outcomes as those included in the former outcome were reported to otherwise have recovered (GOS of 5).
Full citation Odetola, F. O., Tilford, J. M., Davis, M. M., Variation in the use of intracranial-pressure monitoring and mortality in critically ill children with meningitis in the United States, Pediatrics, 117, 1893-1900, 2006 **Ref Id** 668749 **Country/ies where the study was carried out** United States **Study type** Retrospective cohort study **Study dates** Not reported **Inclusion criteria** Aged 0 to 17 years; hospitalised with meningitis (bacterial, viral and fungal) and receiving mechanical ventilation **Exclusion criteria** Traumatic brain injury; pretransfer hospitalisations; hospitalisation for ventriculoperitoneal shunts and other indwelling shunts	**Results** Outcome: All-cause mortality (during hospitalisation) ICP monitoring: 13/49 No ICP monitoring: 13/53 **1. Bias due to confounding (Low/Moderate/Serious/Critical/No information)** Low: To assess the effectiveness of ICP monitoring, patients with the same probability of receiving ICP monitors were matched based on their clinical characteristics to ensure that the decision to treat with the use of ICP monitors or not was balanced. **2. Bias in selection of participants into the study (Low/Moderate/Serious/Critical/No information)** Low: Participants were selected from a database of childhood meningitis requiring mechanical ventilation and all eligible participants identified from the database were included. **3. Bias in classification of interventions (Low/Moderate/Serious/Critical/No information)** Low: Intervention groups were clearly defined - there is no ambiguity in the monitoring versus non-monitoring of ICP. **4. Bias due to deviations from intended interventions (Low/Moderate/Serious/Critical/No information)**

Study details	Results and risk of bias assessment using ROBINS-I
Patient characteristics N=146 children (102 children with bacterial meningitis) Age (years): <1: 73/146 (50%) 1 to 4: 27/146 (18.5%) 5 to 17: 46/146 (31.5%) Sex: male 89 (61%); female 57 (39%) Aetiology: Pneumococcal: 35/146 (24%) Streptococcal: 19/146 (13%) Staphylococcal: 22/146 (15%) Gram-negative organisms: 26/146 (17.8%) Meningitis not otherwise specified (NOS): 29/146 (19.9%) Other aetiology: 15/146 (10.3%) **Interventions** ICP monitoring: No further details reported. No ICP monitoring: No further details reported. **Follow-up** In-hospital	No information: The study information was retrospectively extracted from a database. It is not possible to determine whether there were any deviations from the interventions of interest, from the coding used or how deviations were handled in the database. **5. Bias due to missing data (Low/Moderate/Serious/Critical/No information)** Low: Outcome data were available for those eligible for inclusion in the sample that was matched according to the use of ICP monitoring **6. Bias in measurement of outcomes (Low/Moderate/Serious/Critical/No information)** Low: The outcome is an objective outcome and is unlikely to have been influenced by knowledge of the intervention received. **7. Bias in selection of the reported result (Low/Moderate/Serious/Critical/No information)** Moderate: Length of hospital stay was measured, however, was merely reported as being 'higher in the monitored group versus the non-monitored group' (page 1897). This was also the case for 'log transformed total charges' outcome but this outcome was not of interest to the review. **Overall risk of bias (Low/Moderate/Serious/Critical/No information)** Moderate **Source of funding** Not reported **Other information** Results from people with meningitis not otherwise specified infections were not extracted (29/157:18%) as it was not of interest for the current review and would amount to indirectness of the evidence,

ABM: acute bacterial meningitis; CSF: cerebrospinal fluid; CT-scanning: computerised tomography scanning; EVD-catheter: external ventricular drainage-catheter; GOS: Glasgow outcome score; ICP: intracranial pressure; ICU: intensive care unit; ITT: intention to treat; ; N: number; N. meningitidis; Neisseria.meningitidis: NICU: neonatal intensive care unit; NOS: not otherwise specified; RLS: reaction level scale; ROBINS-I: Risk Of Bias in Non-randomized Studies – of Interventions; S.pneumoniae: Streptococcus pneumonia.

Appendix E Forest plots

Forest plots for review question: What is the effectiveness of intracranial pressure monitoring in 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 is the effectiveness of intracranial pressure monitoring in bacterial meningitis?

Table 5: Clinical evidence profile for comparison intracranial pressure monitoring versus no intracranial pressure monitoring

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intracranial pressure monitoring	No intracranial pressure monitoring	Relative (95% CI)	Absolute		
All-cause mortality: babies and children (during hospitalisation)												
1 (Odetola 2006)	observational study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	13/49 (26.5%)	13/53 (24.5%)	RR 1.08 (0.56 to 2.1)	20 more per 1000 (from 108 fewer to 270 more)	LOW	CRITICAL
All-cause mortality: adults (follow-up 2 to 6 months)												
1 (Glimaker 2014)	observational study	serious[2]	no serious inconsistency	serious [3]	very serious[1]	none	5/52 (9.6%)	16/53 (30.2%)	RR 0.32 (0.13 to 0.81)	205 fewer per 1000 (from 57 fewer to 263 fewer)	VERY LOW	CRITICAL
Any long-term neurological impairment (hearing impairment): adults (follow-up 2 to 6 months)												
1 (Glimaker 2014)	observational study	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	4/52 (7.7%)	6/53 (11.3%)	RR 0.68 (0.2 to 2.27)	36 fewer per 1000 (from 91 fewer to 144 more)	VERY LOW	CRITICAL
Functional impairment (with or without hearing impairment): adults - (follow-up 1-2 months)												
1 (Glimaker 2014)	observational study	serious[2]	no serious inconsistency	very serious[5]	very serious[6]	none	15/52 (28.8%)	14/53 (26.4%)	RR 1.09 (0.59 to 2.03)	24 more per 1000 (from 108 fewer to 272 more)	VERY LOW	IMPORTANT

CI: confidence interval; RR: risk ratio
[1] <150 events
[2] Serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I
[3] Population is indirect as it includes people that were immunocompromised

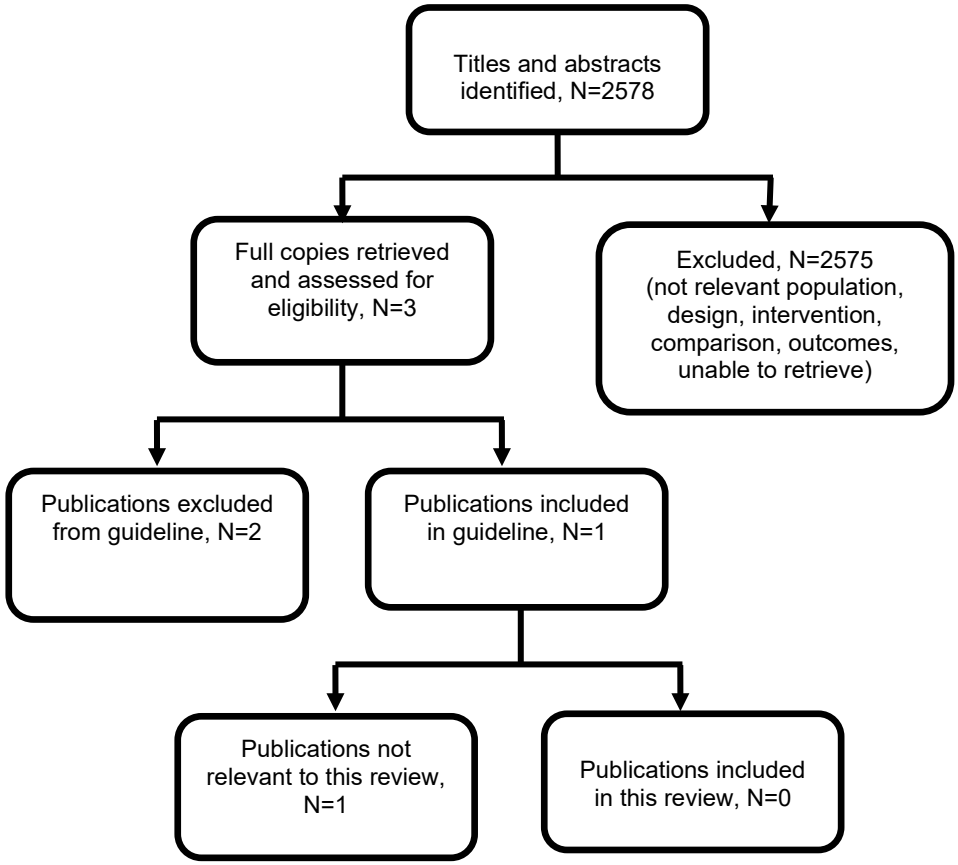
[4] 95%CI crosses 1 MID
[5] Population is indirect as it includes people that were immunocompromised; outcome is indirect as it is a composite outcome including functional impairment with or without hearing impairment;
[6] 95%CI crosses 2 MIDs

Appendix G Economic evidence study selection

Study selection for: What is the effectiveness of intracranial pressure monitoring 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 2: Study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: What is the effectiveness of intracranial pressure monitoring 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 intracranial pressure monitoring 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 intracranial pressure monitoring in bacterial meningitis?

Excluded effectiveness studies

Table 6: Excluded studies and reasons for their exclusion

Study	Reason for Exclusion
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
Depreitere, B., Bruyninckx, D., Guiza, F., Monitoring of Intracranial Pressure in Meningitis, Acta Neurochirurgica - SupplementActa Neurochir Suppl, 122, 101-4, 2016	Study design not of interest for review: Non-comparative study
Di Rocco, F., Vanel, B., Szathmari, A., Berthon, M., Landzberg, P., Javouhey, E., Mottolese, C., Management of pneumococcal meningitis in infants associated to acute intracranial pressure, Child's Nervous System, 32 (5), 956-957, 2016	Conference Paper
Dubourg, J., Javouhey, E., Geeraerts, T., Messerer, M., Kassai, B., Ultrasonography of optic nerve sheath diameter for detection of raised intracranial pressure: a systematic review and meta-analysis, Intensive Care Medicine, 37, 1059-1068, 2011	Systematic review which includes population not of interest for review: traumatic brain injury, intracranial/intracerebral haemorrhage, stroke
Glimåker, M., Johansson, B., Halldorsdottir, H., Wanecek, M., Elmi-Terander, A., Bellander, B. M., Intracranial pressure targeted treatment in acute bacterial meningitis increased survival, Lakartidningen, 111, 2288â□□2291, 2014	Article in Swedish
Goitein, K. J., Amit, Y., Mussaffi, H., Intracranial pressure in central nervous system infections and cerebral ischaemia of infancy, Archives of Disease in Childhood, 58, 184-6, 1983	Study design not of interest for review: Non-comparative study
Helbok, R., Olson, D. M., Le Roux, P. D., Vespa, P., Participants in the International Multidisciplinary Consensus Conference on Multimodality, Monitoring, Intracranial pressure and cerebral perfusion pressure monitoring in non-TBI patients: special considerations, Neurocritical CareNeurocrit Care, 21 Suppl 2, S85-94, 2014	Study design not of interest for review: Narrative review
Larsen, L., Poulsen, F. R., Nielsen, T. H., Nordstrom, C. H., Schulz, M. K., Andersen, A. B., Use of intracranial pressure monitoring in bacterial meningitis: a 10-year follow up on outcome and intracranial pressure versus head CT scans, Infectious Diseases, 49, 356-364, 2017	Study design not of interest for review: Non-comparative study
Le Roux,P.D., Jardine,D.S., Kanev,P.M.,	Study design not of interest for review: Non-

Study	Reason for Exclusion
Loeser,J.D., Pediatric intracranial pressure monitoring in hypoxic and nonhypoxic brain injury, Childs Nervous System, 7, 34-39, 1991meningitis is little relieved by dexamethasone or glycerol, PediatricsPediatrics, 125, e1-8, 2010	comparative study
Lindvall, P., Ahlm, C., Ericsson, M., Gothefors, L., Naredi, S., Koskinen, L. O. D., Reducing Intracranial Pressure May Increase Survival among Patients with Bacterial Meningitis, Clinical Infectious Diseases, 38, 384-390, 2004	Study design not of interest for review: Non-comparative study
Pople, I. K., Muhlbauer, M. S., Sanford, R. A., Kirk, E., Results and complications of intracranial pressure monitoring in 303 children, Pediatric Neurosurgery, 23, 64-7, 1995	Study design not of interest for review: Non-comparative study
Singhi, S., Bansal, A., Kumar, R., Bhatti, A., Randomized comparison of cerebral perfusion pressure (CPP) with intracranial pressure (ICP) targeted therapy in children with acute CNS infections, Pediatric Critical Care Medicine, 1), A15, 2011	Conference Paper
Singhi, S., Bansal, A., Kumar, R., Bhatti, A., Randomized comparison of cerebral perfusion pressure (CPP) with intracranial pressure (ICP) targeted therapy in children with acute CNS infections, Critical Care Medicine, 12), A90, 2010	Conference Paper

Excluded economic studies

No economic evidence was identified for this review.

Appendix K Research recommendations – full details

Research recommendations for review question: What is the effectiveness of intracranial pressure monitoring in bacterial meningitis?

Research question

In people with bacterial meningitis and impaired consciousness, are clinical outcomes improved if invasive or non-invasive intracranial pressure monitoring is used to guide treatment decisions?

Why this is important

Bacterial meningitis commonly causes raised intracranial pressure, and it is likely that this mediates some of the adverse outcomes of the condition. It is possible to lower intracranial pressure, at least temporarily, if this is known to be high. But the conventional methods for monitoring intracranial pressure are invasive, associated with important risks, and usually only available in specialist hospitals. Very little evidence exists on the effects that intracranial pressure monitoring has on outcomes in bacterial meningitis, and it is of low or very low quality.

Table 7: Research recommendation rationale

Research question	**In people with bacterial meningitis and impaired consciousness, are clinical outcomes improved if invasive or non-invasive intracranial pressure monitoring is used to guide treatment decisions?**
Why is this needed	
Importance to 'patients' or the population	Bacterial meningitis is a serious condition, from which people may die or suffer life-changing effects. If used to guide relevant treatment decisions, intracranial pressure monitoring offers the potential to improve survival and outcomes.
Relevance to NICE guidance	The committee were unable to recommend intracranial pressure monitoring in bacterial meningitis because the evidence was too limited and of too low quality.
Relevance to the NHS	People with bacterial meningitis and impaired consciousness are seriously unwell, often requiring treatment in intensive care units. While it is known that intracranial pressure is often high, it is not known whether monitoring and managing this improves outcomes. Also, intracranial pressure monitoring by conventional methods is invasive, costly, carries risks, and can only be performed in specialist centres. Clinicians do not know whether or how this intervention should be offered.
National priorities	This does not align with any specific NHS priority but reliable non-invasive methods to measure intracranial pressure could have clinical and cost benefits
Current evidence base	The existing evidence is very limited and is of low quality

Research question	In people with bacterial meningitis and impaired consciousness, are clinical outcomes improved if invasive or non-invasive intracranial pressure monitoring is used to guide treatment decisions?
Equality	People with meningitis treated in specialist neuroscience centres may be considered for intracranial pressure monitoring, which would not be available to people treated in non-specialist centres.
Feasibility	Conventional methods to measure intracranial pressure are well established, and most treatments to manage intracranial hypertension are simple to administer. However, intracranial pressure monitoring is generally only available in specialist centres. The identification of reliable non-invasive methods to measure intracranial pressure would enable this to be offered to a broader population, potentially with lower risks and costs.
Other comments	It must be understood that ICP monitoring per se offers no direct benefit. It is only when ICP monitoring is used to guide other treatment decisions (for example, osmotic agents, ventilation targets, cerebrospinal fluid diversion) that it may positively influence outcomes.

ICP: intracranial pressure monitoring

Table 8: Research recommendation modified PICO table

Criterion	Explanation
Population	People with bacterial meningitis and impaired consciousness
Intervention	• Clinical management guided by conventional/invasive methods • Clinical management guided by novel/non-invasive intracranial pressure monitoring
Comparators	Clinical management without intracranial pressure monitoring
Outcomes	All-cause mortality Long-term neurological impairment Functional impairment Brain herniation Serious intervention-related adverse effects Developmental delay [children] Quality of life [adults]
Study design	Randomised controlled trial
Timeframe	12 months post-intervention follow-up
Additional information	Studies may involve preliminary work to validate novel/non-invasive methods for intracranial pressure monitoring in bacterial meningitis