

# Osmotic therapies added to antibiotics for acute bacterial meningitis (Review)

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## TABLE OF CONTENTS

HEADER . . . . .	1
ABSTRACT . . . . .	1
PLAIN LANGUAGE SUMMARY . . . . .	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON . . . . .	2
BACKGROUND . . . . .	5
OBJECTIVES . . . . .	6
METHODS . . . . .	6
RESULTS . . . . .	8
Figure 1. . . . .	9
Figure 2. . . . .	10
DISCUSSION . . . . .	12
AUTHORS' CONCLUSIONS . . . . .	13
ACKNOWLEDGEMENTS . . . . .	13
REFERENCES . . . . .	14
CHARACTERISTICS OF STUDIES . . . . .	16
DATA AND ANALYSES . . . . .	22
Analysis 1.1. Comparison 1 Glycerol versus no osmotic diuretic, Outcome 1 Death. . . . .	22
Analysis 1.2. Comparison 1 Glycerol versus no osmotic diuretic, Outcome 2 Death and neurological disability. . . . .	24
Analysis 1.3. Comparison 1 Glycerol versus no osmotic diuretic, Outcome 3 Seizures. . . . .	25
Analysis 1.4. Comparison 1 Glycerol versus no osmotic diuretic, Outcome 4 Hearing loss. . . . .	26
ADDITIONAL TABLES . . . . .	26
APPENDICES . . . . .	28
CONTRIBUTIONS OF AUTHORS . . . . .	29
DECLARATIONS OF INTEREST . . . . .	29
SOURCES OF SUPPORT . . . . .	30

[Intervention Review]

# Osmotic therapies added to antibiotics for acute bacterial meningitis

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## ABSTRACT

### Background

Every day children and adults throughout the world die from acute community-acquired bacterial meningitis, particularly in low-income countries. Survivors are at risk of deafness, epilepsy and neurological disabilities. Osmotic therapies have been proposed as an adjunct to improve mortality and morbidity from bacterial meningitis. The theory is that they will attract extra-vascular fluid by osmosis and thus reduce cerebral oedema by moving excess water from the brain into the blood. The intention is to thus reduce death and improve neurological outcomes.

### Objectives

To evaluate the effects on mortality, deafness and neurological disability of osmotic therapies added to antibiotics for acute bacterial meningitis in children and adults.

### Search methods

We searched CENTRAL 2012, Issue 11, MEDLINE (1950 to November week 3, 2012), EMBASE (1974 to November 2012), CINAHL (1981 to November 2012), LILACS (1982 to November 2012) and registers of ongoing clinical trials (April 2012). We also searched conference abstracts and contacted researchers in the field.

### Selection criteria

Randomised controlled trials testing any osmotic therapy in adults or children with acute bacterial meningitis.

### Data collection and analysis

Two review authors independently screened the search results and selected trials for inclusion. We collected data from each study for mortality, deafness, seizures and neurological disabilities. Results are presented using risk ratios (RR) and 95% confidence intervals (CI) and grouped according to whether the participants received steroids or not.

## Main results

Four trials were included comprising 1091 participants. All compared glycerol (a water-soluble sugar alcohol) with a control; in three trials this was a placebo, and in one a small amount of 50% dextrose. Three trials included comparators of dexamethasone alone or in combination with glycerol. As dexamethasone appeared to have no modifying effect, we aggregated results across arms where both treatment and control groups received corticosteroids and where both treatment and control groups did not.

Compared to placebo, glycerol may have little or no effect on death in people with bacterial meningitis (RR 1.09, 95% confidence interval (CI) 0.89 to 1.33, 1091 participants, four trials, low-quality evidence); or on death and neurological disability combined (RR 1.04, 95% CI 0.86 to 1.25).

Glycerol may have little or no effect on seizures during treatment for meningitis (RR 1.08, 95% CI 0.90 to 1.30, 909 participants, three trials, low-quality evidence).

Glycerol may reduce the risk of subsequent deafness (RR 0.60, 95% CI 0.38 to 0.93, 741 participants, four trials, low-quality evidence).

## Authors' conclusions

The only osmotic diuretic to have undergone randomised evaluation is glycerol. Data from trials to date have not demonstrated benefit on death, but it may reduce deafness. Osmotic diuretics, including glycerol, should not be given to adults and children with bacterial meningitis unless as part of carefully conducted randomised controlled trial.

## PLAIN LANGUAGE SUMMARY

### Osmotic therapies added to antibiotics for acute bacterial meningitis

Meningitis is a condition where bacteria, fungi or viruses spread from the blood and infect the membranes and fluid that surround the brain and spinal cord. All types of meningitis are very serious but acute bacterial meningitis has a rapid onset and is usually fatal within hours to days without treatment. Signs and symptoms usually include high fever, severe headache, convulsions, coma and mental confusion. Even with antibiotics the mortality rate is 10% to 15% in children with bacterial meningitis and 20% to 30% in adults in high-income countries, rising to 50% in adults in low-income countries. Increased swelling of the brain caused by the infection is thought to contribute to death and may lead to complications in survivors such as long-term brain damage, deafness, epilepsy and learning difficulties in children. Bacterial meningitis is relatively rare in well-resourced settings but is more common in low-income countries, particularly where the prevalence of HIV is high.

Osmotic therapies function by increasing the concentration of the blood and exerting an osmotic pressure across a semi-permeable membrane (such as a cell wall or blood vessel lining in the brain) drawing water from the brain into the blood, thereby reducing pressure in the brain. This is theoretically advantageous if brain swelling is causing a reduction in brain function. Osmotic therapies can reduce brain swelling and potentially increase the rate of survival, or they could do harm. Glycerol is an osmotic treatment that was tested in the four trials included in this review, with a total of 1091 participants. No other osmotic treatments have been tested in randomised trials to date. This review detected no benefit from glycerol relating to death or neurological disabilities and one study in adults in Malawi suggested it may do harm. Deafness was slightly less common in the osmotic group at follow-up but the effect was small. No effect on epileptic seizures at follow-up was noted. Glycerol was not associated with any severe adverse effects. The number of trials included was small and only two of the included studies tested a large number of participants. All trials were from differently resourced healthcare settings and examined either adults or children.

## SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [\[Explanation\]](#)

Glycerol for acute bacterial meningitis		Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
Outcomes	Assumed risk	Control	Corresponding risk				
<b>Patient or population:</b> acute bacterial meningitis <b>Settings:</b> Finland, India, South America, Malawi <b>Intervention:</b> glycerol							
<b>Death</b>	201 per 1000	220 per 1000 (179 to 268)		<b>RR 1.09</b> (0.89 to 1.33)	1091 (4 studies)	⊕⊕○○ <b>low</b> <sup>1,2,3,4</sup>	
<b>Neurological disability</b>	70 per 1000	56 per 1000 (32 to 97)		<b>RR 0.8</b> (0.46 to 1.38)	732 (3 studies)	⊕○○○ <b>very low</b> <sup>1,5,6</sup>	
<b>Seizures</b>	324 per 1000	350 per 1000 (291 to 421)		<b>RR 1.08</b> (0.9 to 1.3)	909 (3 studies)	⊕⊕○○ <b>low</b> <sup>1,2,3,4</sup>	
<b>Hearing loss</b>	130 per 1000	78 per 1000 (49 to 121)		<b>RR 0.6</b> (0.38 to 0.93)	741 (3 studies)	⊕⊕○○ <b>low</b> <sup>1,7</sup>	
<p>*The basis for the <b>assumed risk</b> (e.g. the median control group risk across studies) is provided in footnotes. The <b>corresponding risk</b> (and its 95% confidence interval (CI)) is based on the assumed risk in the comparison group and the <b>relative effect</b> of the intervention (and its 95% CI).</p> <p>CI: confidence interval  RR: risk ratio</p>							
<b>GRADE Working Group grades of evidence</b> <b>High quality:</b> Further research is very unlikely to change our confidence in the estimate of effect <b>Moderate quality:</b> Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate <b>Low quality:</b> Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate <b>Very low quality:</b> We are very uncertain about the estimate							

- <sup>1</sup> No serious risk of bias: allocation concealment was adequate in all trials.
- <sup>2</sup> Downgraded by 1 for inconsistency: one trial found a statistically significant harm with glycerol but this trial used 50% glucose as the placebo which is not an inert substance and could plausibly have exerted a positive benefit.
- <sup>3</sup> The four trials were conducted in Finland, Malawi, India and South America. Three were in children and one in adults. All included patients with suspected meningitis and CSF changes suggestive of bacterial infection.
- <sup>4</sup> Downgraded by 1 for imprecision: the 95% CI includes what might be a clinically important harm and no effect with glycerol.
- <sup>5</sup> Downgraded by 1 for indirectness: there was significant heterogeneity in the reporting of neurological disability across the studies and formal scoring systems were not used.
- <sup>6</sup> Downgraded by 2 for imprecision: the number of neurological disabilities in these studies was very low, and consequently the 95% CI is very wide. Larger trials would be necessary to have confidence in this result.
- <sup>7</sup> Downgraded by 2 for imprecision: the number of patients with reported hearing loss was low in these studies. Even though the result is statistically significant, larger studies would be necessary to have full confidence in this effect.

## BACKGROUND

### Description of the condition

Community-acquired acute bacterial meningitis is a devastating infection with associated rates of death and disability that have changed little over the last 10 to 15 years. In high-income countries, 5% to 30% of adult patients die, rising to 50% to 60% in low-income countries, despite highly effective antibiotics against the causative pathogens (de Gans 2002; Nguyen 2007; Scarborough 2007). The high mortality is predominately seen in *Streptococcus pneumoniae* (*S. pneumoniae*) infections; meningitis caused by *Neisseria meningitidis* (*N. meningitidis*) carries a lower mortality. In children, a wider range of pathogens are noted and the case fatality rate is lower (Harnden 2006; Molyneux 2006; Pelkonen 2009; Peltola 2009; Roine 2009). Nevertheless, some survivors develop neurological problems that may be permanent. The most common meningitis sequelae are deafness, epilepsy and poor cognitive development (Molyneux 2002; Nguyen 2007; van de Beek 2009), thought to be caused by infection-induced inflammation, thrombosis and brain oedema (swelling). The outcome from bacterial meningitis is influenced by the pathogen, the geographical area, the patient's access to health care and the quality of the healthcare system. There are very few data on risk factors for poor outcomes in low-income countries. However, anaemia and delayed presentation to hospital are probably important (McCormick 2012; Sudarsanam 2011). HIV may influence outcomes but the role of the virus in pathogenesis is not yet clearly understood (Domingo 2009). High mortality rates, despite effective antibiotics, have led investigators to try and minimise neurological inflammation with adjunctive therapies.

Increasing understanding of the pathways of cerebral inflammation in meningitis has led several investigators to try treatments that aim to reduce brain oedema and inflammation and improve brain perfusion. The intervention most extensively tested in clinical trials has been corticosteroids. A Cochrane Review (Brouwer 2010) shows a mortality benefit in adults in Europe with meningitis due to *S. pneumoniae* and an overall reduction in deafness in adults and children. A another systematic review, of individual patient data from five randomised studies suggests that the effect of dexamethasone on outcomes for bacterial meningitis in these countries is limited to reducing the incidence of hearing loss in survivors (van de Beek 2010). A long-held concern exists over excessive fluids contributing to brain oedema; a further Cochrane Review suggests that judicious fluid resuscitation guided by the clinical condition is appropriate to maximise brain perfusion without contributing to brain oedema (Maconochie 2011).

### Description of the intervention

Osmotic therapies work by increasing the concentration of the blood. They exert an osmotic pressure across a semi-permeable

membrane (such as a cell wall or blood vessel lining in the brain) which draws water from the brain into the blood and reduces pressure in the brain. This is theoretically advantageous if brain swelling is causing reduction in brain function.

Osmotic therapies have long been used in acute brain trauma (BTF 2000) and their use has been postulated in other forms of acute brain injury, particularly stroke (Bereczki 2010; Yu 1992; Yu 1993) and cerebral malaria (Namutangula 2007; Okoromah 2011). Mannitol and hypertonic saline are the most commonly used osmotic therapies (Wakai 2008) but glycerol, sorbitol and sodium lactate have also been investigated (Righetti 2005; Stoll 1998). Details of all these therapies have been reported in Table 1. Glycerol has been studied in animals with meningitis, where no effect was noted. Conclusions from these studies are limited by the applicability of animal models of meningitis, where set doses of pathogenic bacteria are introduced directly into the animal's central nervous system, to the complex host pathogen interactions in human disease (Blaser 2010; Schmidt 1998). The excellent safety profile of glycerol in previous studies (Righetti 2005), combined with its low cost and easy administration and availability, has led investigators to look for efficacy as adjuvant treatment in acute bacterial meningitis in both adults and children, particularly in low-income countries.

### How the intervention might work

All osmotic therapies have slightly different and poorly understood mechanisms of action. The osmotic drug's mechanism of action causes dehydration of central nervous system (CNS) cells, lowering intracranial pressure (ICP). However this effect may only be temporary and lead to a rebound phenomenon where cells subsequently draw in too much water, increasing the oedema. Mannitol has this mechanism of action but acts primarily through a rheological action causing erythrocyte deformity through increases in intravascular water, allowing increased tissue oxygenation in the CNS. Mannitol produces a large diuresis through this effect, which causes a reflex cerebral vaso-constriction, temporarily reducing ICP. However, there is a significant risk of subsequent rebound raised ICP and mannitol is now used sparingly due to this concern. The main mechanism of action of glycerol in humans is unknown but there are some data to suggest that the addition of glycerol in meningitis could potentially improve cerebral blood flow and metabolism (Mathew 1972; Meyer 1972). Glycerol also has a mild effect on serum osmolality (Singhi 2008).

Hypertonic saline and sodium lactate appear to have direct osmotic actions on cells and they do not cause diuresis. These drugs may therefore be better than mannitol in reducing ICP (Ichai 2009). Osmotic diuretics such as mannitol and sorbitol could potentially also have a clinical benefit in meningitis through reduction in ICP but may risk volume depletion in the febrile patient. All osmotic therapies ideally require an intact blood brain barrier to exert their effects. Bacterial meningitis causes disruption of the barrier due

to intense inflammation in the sub-arachnoid space and therefore it cannot be assumed that osmotic therapies would be beneficial. [Table 1](#) gives details of all the properties of currently available osmotic therapies.

## Why it is important to do this review

To date, there have been a few placebo-controlled studies using osmotic therapies in meningitis published in different settings in children and adults. A systematic review and meta-analysis would help to decide if these studies have demonstrated clinical benefit either by improvement in mortality or long-term neurological disabilities from the use of these treatments. This review will therefore encompass all types of osmotic therapies to investigate whether the principle of osmotic pressure change in the CNS is of benefit in meningitis and will demonstrate whether osmotic therapies should be recommended in principle, or if a particular therapy should be recommended in the treatment of acute bacterial meningitis.

## OBJECTIVES

To evaluate the effects on death, deafness and neurological disability of osmotic therapies added to antibiotics for acute bacterial meningitis in children and adults.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised controlled trials (RCTs).

#### Types of participants

Adults and children diagnosed with acute community-acquired bacterial meningitis, as defined by the trial authors, on the basis of cerebral-spinal fluid (CSF) culture, white cell count, biochemical composition and clinical presentation.

#### Types of interventions

**Intervention:** osmotic therapy, including at least one of the following: glycerol per oral (PO) administration, intravenous (IV) hypertonic saline, sodium lactate and osmotic diuretics including IV mannitol and sorbitol.

**Control:** standard IV therapy or matched placebo.

All participants receive broad-spectrum intravenous antibiotic treatment.

### Types of outcome measures

#### Primary outcomes

All-cause mortality.

#### Secondary outcomes

Mortality combined with residual neurological deficit at the end of the follow-up period, including focal neurological deficit, epilepsy and deafness. Deafness was defined as hearing loss at greater than 40 decibels bilaterally.

### Search methods for identification of studies

#### Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 11, part of *The Cochrane Library*, [www.thecochranelibrary.com](http://www.thecochranelibrary.com) (accessed 30 November 2012), which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE (1950 to November week 3, 2012), EMBASE (1974 to November 2012), LILACS (1982 to November 2012) and CINAHL (1981 to November 2012).

We used the following search terms to search MEDLINE and CENTRAL. We combined the MEDLINE search strategy with the Cochrane highly sensitive search strategy for identifying randomised trials in MEDLINE: sensitivity-maximising version (2008 revision); Ovid format [Lefebvre 2011](#). We adapted the search strategy to search EMBASE (See [Appendix 1](#)), CINAHL (see [Appendix 2](#)) and LILACS (see [Appendix 3](#)).

#### MEDLINE (Ovid)

- 1 exp Meningitis/
- 2 meningit\*.tw.
- 3 1 or 2
- 4 Osmosis/
- 5 Osmotic Pressure/
- 6 exp Diuretics, Osmotic/
- 7 (osmos\* or osmot\* or osmol\*).tw.
- 8 exp Sugar Alcohols/
- 9 glycer\*.tw,nm.
- 10 1,2,3-propanetrio\*.tw,nm.
- 11 mannitol\*.tw,nm.
- 12 sorbit\*.tw,nm.
- 13 Sodium Lactate/
- 14 (sodium adj2 lactat\*).tw,nm.



15 Saline Solution, Hypertonic/  
16 (hypertonic adj2 saline\*).tw,nm.  
17 or/4-16  
18 3 and 17

### Searching other resources

We searched the following clinical trials registers in April 2012.

1. [www.clinicaltrials.gov](http://www.clinicaltrials.gov).
2. Meningitis research charities trial registers; the Meningitis Research Foundation ([www.meningitis.org](http://www.meningitis.org)).
3. Wellcome Trust and Medical Research Council trial registers.
4. World Health Organization (WHO) trial registers.

One review author (EW) contacted the authors of all identified ongoing and published trials for details of other studies and contacts for other researchers in the field, particularly for details of abstracts presented at conferences not yet published in November 2010. We handsearched relevant conference abstracts. We searched the references of all identified trials for additional studies or information.

### Data collection and analysis

#### Selection of studies

One author (EW) screened all search results (title and abstract) and selected relevant studies according to the review inclusion criteria. Two authors (EW, KA) screened all selected studies by reading the published full text to ensure each study met the inclusion criteria. The same two authors then agreed which studies were to be included in the review. We emailed trial authors to clarify duplication and study numbers.

#### Data extraction and management

Two review authors (EW, KA) independently extracted all data from the selected studies using a data extraction form. They discussed all trial data which was then included only when the data matched that extracted by both review authors. We contacted one trial author regarding duplication and we excluded one study from the analysis as a result. No further discrepancies arose during data extraction. We entered data for analysis using Review Manager 5.1 software ([RevMan 2011](#)).

#### Assessment of risk of bias in included studies

The data extraction form included a 'Risk of bias' collection tool. Two review authors (EW, KA) independently judged the potential risk of bias for each included study as low, uncertain or high for the following parameters ([Higgins 2011](#)). Both review authors then discussed and agreed the final judgements. One review author

(EW) synthesised these judgements into a standard 'Risk of bias' table for each study. See [Characteristics of included studies](#).

1. Random sequence generation.
2. Allocation concealment.
3. Blinding.
4. Incomplete outcome data.
5. Selective reporting of outcome data.
6. Other identified areas of bias particular to that study (for example, if the principal investigator was employed by the pharmaceutical company manufacturing the drug under investigation, or if the study is sponsored by a pharmaceutical company).

### Measures of treatment effect

The primary outcome of this review was binary and the studies included were all RCTs, therefore we used risk ratio (RR) as the most appropriate statistical tool to express the results of the treatment effect in a meta-analysis. We displayed results as forest plots. All included studies had outcomes defined by the trial authors using standardised measurements. Hearing loss of greater than 40 dB was counted as significant where measured. If a formal neurological score was used to define neurological disability this was used. However, where only a description was given, a described deficit that results in the participant not being able to work or attend school was counted as significant. As the number of studies was small we were not able to analyse mortality by continental geographical area and resource setting as secondary outcomes, as planned in the protocol.

Due to the small number of studies retrieved, we were not able to group results for both primary and secondary outcomes by the follow-up period: acute phase, less than three months since inclusion in the study and longer-term up to one year of follow-up.

### Unit of analysis issues

We did not anticipate any cluster-randomised trials on this topic. However, within the trials included a four parallel arm design was employed. Data were separated into groups comparing the intervention alone with placebo, and the intervention plus a second intervention with the second intervention alone. These results are expressed in [Analysis 1.1](#) and [Analysis 1.4](#).

### Dealing with missing data

We found some relevant data to be missing from [Kilpi 1995](#) and [Sankar 2007](#). We contacted the authors of both studies for clarification but no further data were supplied. We proceeded with the analysis despite this missing data.

### Assessment of heterogeneity

We intended to use the  $I^2$  statistic and to explore explanations for heterogeneity by subgroup analysis as outlined in the protocol, but data were insufficient.

### Assessment of reporting biases

We assessed each study for reporting bias. Where it was suspected that selected results had been presented, we contacted the authors for clarification (see [Dealing with missing data](#)).

### Data synthesis

We entered all extracted data into [RevMan 2011](#) and performed all analyses using this software. We expressed all results using forest plots. We used a fixed-effect model for analysis and found minimal heterogeneity between the studies, so a random-effects model was not required.

## RESULTS

### Description of studies

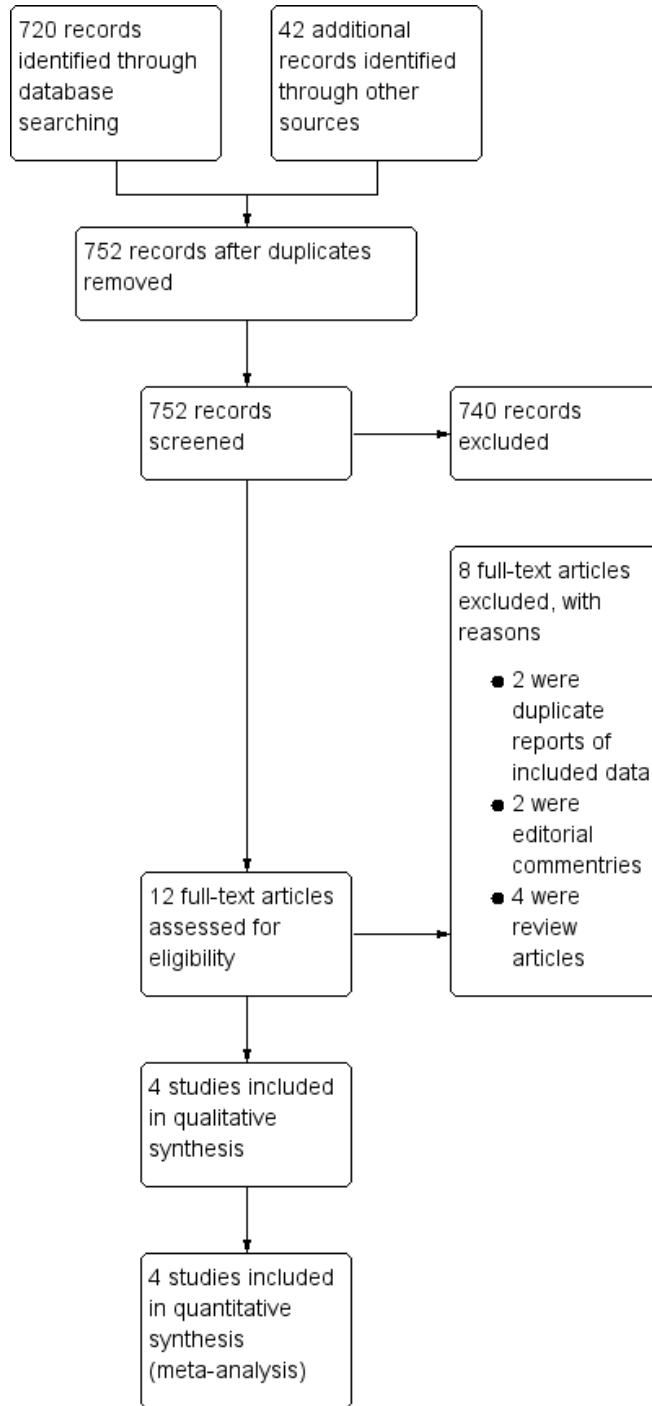
See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of ongoing studies](#).

All included studies found by the search strategy tested glycerol compared to matched placebo, with some studies including a dexamethasone arm. One excluded study investigated mannitol. No studies were found testing any other osmotic therapy or diuretic.

### Results of the search

See [Figure 1](#).

**Figure 1. Study screening flow diagram.**



We screened a total of 752 abstracts following the initial search in November 2010. An update search in November 2012 identified a further 35 records from the search of the electronic databases. One ongoing trial is testing high-dose paracetamol and glycerol compared with placebo in children with acute bacterial meningitis aged 6 to 60 months in Malawi (Molyneux 2012).

### Included studies

We included four trials with a total of 1091 participants meeting the inclusion criteria (Ajdukiewicz 2011; Kilpi 1995; Peltola 2007; Sankar 2007). One trial reported different outcomes from the same trial in two separate publications (Sankar 2007; Singhi 2008). Data from Sankar 2007 are presented in this analysis. Data from Singhi 2008 were not included in the analysis as that paper reported osmolarity data exclusively and no mortality data were presented.

### Participants

Three trials were conducted in children under 16 years (Kilpi 1995; Peltola 2007; Sankar 2007). The other trial was conducted in adults and adolescents older than 14 years (Ajdukiewicz 2011).

### Interventions

All included studies used oral glycerol as the primary intervention. The potential mechanism of action of glycerol is detailed in Table 1. The three trials in children evaluated glycerol alone, dexamethasone alone and glycerol combined with dexamethasone. These studies used IV placebo to 'blind' the dexamethasone treatment

group. No placebo for oral glycerol was used in Kilpi 1995 and Sankar 2007, and Peltola 2007 used oral carboxymethylcellulose as a placebo for glycerol.

The adult study used 50% dextrose as an oral placebo agent to compare to glycerol diluted in water or 50% dextrose (Ajdukiewicz 2011).

### Location

Kilpi 1995 took place in Finland, Peltola 2007 in South America (multiple sites), Sankar 2007 in India and Ajdukiewicz 2011 in Malawi.

### Outcomes

Death was the primary outcome in all included studies.

### Excluded studies

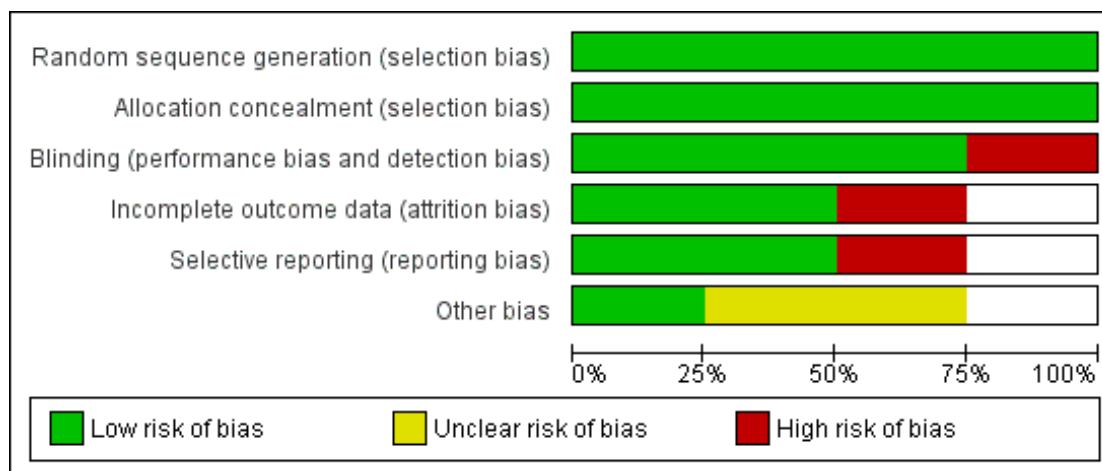
We found that six studies, which each used or mentioned the use of osmotic therapies, were not randomised controlled trials (RCTs) and these were excluded (Figure 1).

### Risk of bias in included studies

#### Allocation

The risk of bias was low for generation of allocation concealment across all studies (Figure 2).

**Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.**



## Blinding

The risk of bias was low for blinding across three studies. We judged [Kilpi 1995](#) at high risk of performance and detection bias, as no details of any concealment were given, so we assumed that the allocations were not blinded ([Figure 2](#)).

## Incomplete outcome data

Two studies reported complete data and we judged them to have a low risk of attrition bias ([Ajdukiewicz 2011](#); [Peltola 2007](#)). Data on two participants were missing from [Kilpi 1995](#) and we judged this study to have a high risk of attrition bias. Outcome data were complete for [Sankar 2007](#) but no data were given for important outcomes including adverse effects or early cessation of treatment and we assigned an unclear risk of attrition bias to this study.

## Selective reporting

We judged [Ajdukiewicz 2011](#) and [Peltola 2007](#) to have a low risk of reporting bias as all data appeared to be presented clearly and completely. [Kilpi 1995](#) presented selected data as there was significant attrition bias, so we judged it to have a high risk of reporting bias. We judged [Sankar 2007](#) to have an unclear risk of reporting bias as no adverse effects nor time of stopping treatment were presented.

## Other potential sources of bias

No trials were sponsored by pharmaceutical companies, nor were the authors declared to have significant conflicts of interest. [Peltola 2007](#) was partly funded by a pharmaceutical company but this supplied the dexamethasone for the trial and not the glycerol, so we did not judge this to have a significant bias effect on this analysis.

## Effects of interventions

See: [Summary of findings for the main comparison Glycerol for acute bacterial meningitis](#)

Four trials were included, all evaluating glycerol. Three of the trials had four arms, which also compared glycerol plus dexamethasone with dexamethasone alone. We carried out the initial analysis comparing participants who received glycerol or placebo only, labelled 'no steroids', and carried out a subgroup analysis with the remaining trial participants who received either glycerol plus dexamethasone or dexamethasone plus placebo, labelled 'with steroids'. All trial participants received the antibiotic ceftriaxone, so no antibiotic subgroup analysis was necessary. Due to the small number of

included studies, a subgroup analysis of purely paediatric data was not required.

## Glycerol

### All-cause death

In the adult study, there were more deaths in the glycerol group and this led to the study being stopped by the data monitoring committee (risk ratio (RR) 1.30, 95% confidence interval (CI) 1.04 to 1.62) ([Ajdukiewicz 2011](#)). None of the other studies detected harm with glycerol and the meta-analysis did not detect an effect on mortality (RR 1.09, 95% CI 0.89 to 1.33, 1091 participants, four trials, [Analysis 1.1](#)). The stratified analysis found no significant difference whether dexamethasone was administered or not.

### Deaths plus long-term disability

Overall, 21 cases of neurological disability were reported in the glycerol group and 25 cases in the placebo group. All-cause mortality was combined with neurological disability and no effect of glycerol was detected (RR 1.04, 95% CI 0.86 to 1.25, 1091 participants, four trials, [Analysis 1.2](#)) with no pattern evidence on stratification by whether steroids were received or not.

### Seizures, convulsions and epilepsy

Convulsions on admission and during treatment were reported in all studies but none of the studies reported data for persistent epileptic seizures post discharge. In the adult study, risk of seizures was higher with glycerol (RR 1.62, 95% CI 1.18 to 2.23) ([Ajdukiewicz 2011](#)). However, this was not found in the other studies and the meta-analysis did not detect a difference (RR 1.08, 95% CI 0.90 to 1.30, 909 participants, three trials ([Analysis 1.3](#))).

### Deafness

Fewer surviving participants given glycerol were reported as deaf at four to eight weeks of follow-up compared to placebo (RR 0.60, 95% CI 0.38 to 0.93, four trials, 741 participants, low-quality evidence ([Analysis 1.4](#))).

## Adverse effects

Neither glycerol nor dexamethasone were associated with significant adverse effects in the included studies but systematic recording of adverse events was not reported. Common adverse effects were nausea and vomiting, with small numbers of cases of gastro-intestinal bleeding reported in [Sankar 2007](#), [Kilpi 1995](#) and [Peltola 2007](#), all in the dexamethasone groups.

## DISCUSSION

### Summary of main results

We only identified four trials evaluating glycerol in acute bacterial meningitis. Other osmotic diuretics, such as mannitol and hypertonic saline, have not yet been tested.

Glycerol was tested in adults and children with acute bacterial meningitis in a variety of different clinical settings and in three of the four included trials, glycerol was evaluated in a complex trial design including dexamethasone. The review and meta-analysis did not detect an overall effect of glycerol on mortality from acute bacterial meningitis in children and adults. However, in the single trial in adults, glycerol was associated with increased mortality. The quality of the evidence using GRADE criteria ([GRADEpro 2008](#)) was low ([Summary of findings for the main comparison](#)). This meta-analysis of low-quality evidence suggests that glycerol may reduce hearing loss ([Summary of findings for the main comparison](#)).

The small numbers seen overall in the paediatric studies are not sufficient to fully exclude the impact of dexamethasone, particularly on neurological disabilities and deafness in children, as this has been shown to be effective elsewhere ([van de Beek 2010](#)). The results of the ongoing study of glycerol in children in Malawi ([Molyneux 2012](#)) will add to the data when we update our review and provide larger numbers for more rigorous analysis.

The overall numbers in this analysis were small and there is a significant degree of bias present in the two smaller studies. The weighting of the analysis is mainly on [Ajdukiewicz 2011](#) and [Peltola 2007](#), two large studies which were both well conducted but limited in their population demographics and follow-up data. Data from [Peltola 2007](#) have been subject to systematic reviews investigating the effect of dexamethasone, and some methodological concerns were raised regarding the randomisation schedule ([van de Beek 2010](#)).

Each study was undertaken in a very different environment and the population for each has its own particular issues. The HIV prevalence in [Ajdukiewicz 2011](#) was 83.5% and the impact of this on mortality and other outcomes has not been measured and may be significant. This study was conducted in a severely resource-limited environment in Malawi, with no access to advanced resuscitation or intensive care units (ICUs) ([UNDP 2009](#)). All the

other studies were carried out in hospitals with ICUs and paediatric specialist teams, which is not necessarily representative of most hospitals in low-income countries and this may introduce a degree of confounding, particularly regarding lower mortality rates in children.

The study by [Peltola 2007](#) was conducted across multiple sites and excluded participants who had received parenteral antibiotics but not oral antibiotics before the first dose of glycerol and/or dexamethasone. The authors of this study do not include these data in the analysis, so it is unclear if prior antibiotic treatment had an effect on outcomes, particularly deafness.

The doses and duration of glycerol used varied across the included studies, introducing further inconsistencies between the studies, outlined in [Table 2](#). We were unable to control for this in the analysis, which may have introduced further heterogeneity ([Brouwer 2011](#); [Saez-Llorens 2007](#)). Prolonged use of osmotic agents, such as the four-day courses of glycerol used in [Ajdukiewicz 2011](#), have been suggested to be harmful. [Peltola 2007](#) and [Sankar 2007](#) both utilised two-day courses due to this concern. However, the majority of seizures and deaths in [Ajdukiewicz 2011](#) occurred in the first two days, and therefore an association between mortality and glycerol duration is unlikely.

Different agents were used as placebo comparators across the studies. [Ajdukiewicz 2011](#) used 50% dextrose, [Peltola 2007](#) and [Sankar 2007](#) used carboxymethylcellulose and [Kilpi 1995](#) did not use a placebo agent. It may be argued that the placebo agents used were not wholly inert and may exert an independent osmotic action. All authors designed control agents that had a similar taste and texture to glycerol for concealment purposes, and it is untested if any of the substances used exerted an independent osmotic action. However, the higher mortality in [Ajdukiewicz 2011](#) in the glycerol group suggests glycerol had an action beyond any osmotic effect exerted by the dextrose placebo, particularly as the glycerol was diluted in dextrose for some participants ([Brouwer 2011](#)).

The reduction in hearing loss observed suggests that glycerol may be acting to reduce oedema or improve cerebral blood flow in particular areas of the brain, either the nucleus or length of the vestibular-cochlear nerve (which is encased in a bony canal). There is some evidence to suggest that glycerol is required for bacterial metabolic pathways in the central nervous system (CNS) ([Mahdi 2012](#)). Genetic susceptibility to hearing loss following meningitis has been suggested and the presence of glycerol may attenuate the production of free radicals that may affect CNS damage leading to hearing loss ([van Well 2012](#)). We selected greater than 40 dB as the cut-off for hearing loss to capture all clinically significant deficits; the effect of glycerol on more severe hearing loss was not evaluated. Currently there are no clear data showing the mechanistic effects of glycerol on either hearing or mortality in humans and more research is needed. Experimental animal work has shown no effect of glycerol in a bacterial meningitis model ([Blaser 2010](#)). The cause of increased mortality with glycerol in adults is unclear but may relate to enhanced virulence of pneumococci in the CNS in the

presence of glycerol (Mahdi 2012).

The use of dexamethasone did not have any impact on the outcomes studied when used with or without glycerol. Other larger reviews have found an impact of dexamethasone in reduction of hearing loss in children with meningitis (van de Beek 2010). The data in this review are much smaller than were analysed in the other studies and therefore no conclusion as to the utility of dexamethasone in meningitis can be drawn from this review.

### **Overall completeness and applicability of evidence**

This is the first Cochrane Review examining the evidence for the use of osmotic therapies in acute bacterial meningitis. To date the evidence is incomplete and therefore we cannot recommend the use of glycerol in meningitis. Data from further ongoing studies are required, particularly in children to assess the impact of glycerol on meningitis-induced hearing loss. There is no evidence testing any other osmotic therapy apart from glycerol for meningitis and therefore the overall use of osmotic therapies in acute bacterial meningitis cannot be recommended. The high-quality evidence from Ajdukiewicz 2011 demonstrates harm from glycerol in adults with bacterial meningitis in Malawi and no further testing or clinical use of glycerol in adults is currently warranted.

### **Quality of the evidence**

We have assessed the quality of evidence provided by this review using the GRADE methods, and this is presented in [Summary of findings for the main comparison](#). The evidence is generally considered to be of low or very low quality, which indicates that further research is very likely to change these estimates of effect. The main reason for downgrading quality was the small size of the trials, and the low number of events and substantial differences between the locations, sizes and patient populations studied in the included studies. Much larger trials would be necessary to prove or exclude significant benefits or harms.

We also downgraded the evidence for mortality and seizures for inconsistency. The single trial in adults (Ajdukiewicz 2011) was stopped early due to small but statistically significant harm, while the three trials in children have so far not demonstrated statistically significant effects.

### **Potential biases in the review process**

Dr Katherine Ajdukiewicz is an author of this review and was the principal investigator for one of the studies included in this review. To minimise bias she did not extract any data from her study to include in the analysis or perform any of the analysis.

### **Agreements and disagreements with other studies or reviews**

There are no current systematic reviews examining glycerol or other osmotic agents for use in acute bacterial meningitis.

## **AUTHORS' CONCLUSIONS**

### **Implications for practice**

There is no evidence to support the use of glycerol as adjunctive treatment for acute bacterial meningitis. Glycerol may have a small beneficial effect on reducing deafness in surviving children but further data are needed and the quality of the overall evidence is low. When the results of the paediatric study in Malawi are available (Molyneux 2012) they will be added to the analysis.

### **Implications for research**

Trials testing other osmotic interventions in acute bacterial meningitis may be considered, particularly in children.

## **ACKNOWLEDGEMENTS**

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- \* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Ajdukiewicz 2011

Methods	Randomised controlled trial	
Participants	Adults with bacterial meningitis (clinical suspicion of meningitis plus CSF evidence of infection: > 100 white cells/mm <sup>3</sup> , predominately neutrophils, a positive gram stain or cloudy CSF)	
Interventions	Oral glycerol 75 mg in 135 ml Oral glucose 50% solution 135 ml	
Outcomes	Primary outcome: mortality Secondary outcomes: epilepsy, deafness, residual neurological deficit	
Notes	Placebo is not potentially completely inactive and 50% glucose may exert a neurological effect in meningitis	
<b><i>Risk of bias</i></b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	"A randomisation number list in blocks of 12 was produced by an independent statistician using Stata version 9.0"
Allocation concealment (selection bias)	Low risk	"Numbers and allocation were placed into sealed envelopes. Envelopes were opened sequentially by an independent person not involved in the clinical care or assessment of trial participants"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Triple blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis, all patients included in the analysis
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	No other biases apparent

## Kilpi 1995

Methods	Randomised controlled trial with 4 arms
Participants	Children from 3 months to 15 years of age with bacterial meningitis (CSF culture positive; CSF leucocytes > 100/mm <sup>2</sup> ; positive blood culture in a patient with signs and symptoms of bacterial meningitis)
Interventions	Glycerol 4.5 g/kg to a maximum 180 g/day divided into 3 doses/24 hours. Increased by 50% for dose 1 and decreased by 50% for dose 2. No details of placebo given. 3 days treatment given Dexamethasone 1.5 mg/kg od IV divided into 3 doses/24 hours. 50% dose adjustments as per glycerol also used. 3 days treatment given 4 groups used, glycerol, glycerol + dexamethasone, dexamethasone and 'neither'
Outcomes	Primary outcome: mortality Secondary outcomes: epilepsy, deafness, residual neurological deficit
Notes	No details given if any placebo agent was used

### *Risk of bias*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A computer generated list of random therapy assignments was kept at the children's hospital"
Allocation concealment (selection bias)	Low risk	"The next adjunctive treatment regimen was obtainable by telephone 24 hours a day" It is not clear if this person giving the assignments was part of the study team or independent
Blinding (performance bias and detection bias) All outcomes	High risk	No details of blinding are given, so we assumed that the study was unblinded
Incomplete outcome data (attrition bias) All outcomes	High risk	134 children enrolled, 12 excluded, 122 in the final series but 120 only analysed. Details of the missing data are not present in the text
Selective reporting (reporting bias)	High risk	No details of the missing data given, so it is not clear if selective cases only are presented
Other bias	Unclear risk	Groups not completely matched, increased females in the dexamethasone group and increased meningitis due to <i>S. pneumoniae</i> in the control group

**Peltola 2007**

Methods	Randomised controlled trial with 4 arms, multicentre in South America	
Participants	Children aged 2 months to 16 years with bacterial meningitis (CSF culture positive, “characteristic CSF findings” with a positive blood culture or CSF positive with latex antigen test; symptoms and signs of bacterial meningitis with at least 3 of the following: CSF white cell count > 1000 cells/mm <sup>3</sup> , CSF glucose < 40 mg/dL, CSF protein > 40 mg/dL, blood white cell count >15000 cells/mm <sup>3</sup> )	
Interventions	Glycerol 1.5 g/kg in an 85% solution divided into 3 doses/24 hours. 2 days treatment given. Placebo saline plus carboxy methylcellulose. Doses and volumes of placebo not given in the paper Dexamethasone 0.15 mg/kg od IV divided into 3 doses/24 hours. 2 days treatment given 4 groups used, GLY + placebo, GLY + Dex, Dex + placebo and placebo + placebo	
Outcomes	Primary mortality. No secondary mortality at the end of follow up given Secondary outcomes: epilepsy, deafness and residual neurological deficit	
Notes		
<b><i>Risk of bias</i></b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	“Stratified block randomisation took place in blocks of 20”
Allocation concealment (selection bias)	Low risk	“All treatment kits were packaged according to the randomisation lists in Santiago, Chile. Saline and carboxymethylcellulose were the placebo preparations for dexamethasone and glycerol, respectively The agents were provided in identical ampoules or bottles and were labelled only with a study code”
Blinding (performance bias and detection bias) All outcomes	Low risk	The placebos and blinding are described above
Incomplete outcome data (attrition bias) All outcomes	Low risk	None identified
Selective reporting (reporting bias)	Low risk	No missing data identified
Other bias	Unclear risk	Drugs were supplied by GlaxoSmithKline and Famacia Ahumada. GSK partially funded the study

**Sankar 2007**

Methods	Randomised controlled trial. Single centre
Participants	Children aged 2 months to 12 years with bacterial meningitis (positive CSF culture or CSF latex agglutination positive, or CSF cytology with a suggestive biochemical profile with fever and signs of CNS involvement)
Interventions	Glycerol 1.5 g/kg IV or PO 6-hourly. Placebo carboxymethyl cellulose 2% solution IV. Total dose of placebo not given just documented "matched". Dexamethasone 0.15 mg/kg 6-hourly. Duration of treatment not given in the text
Outcomes	Primary mortality. No secondary mortality at the end of follow-up given Secondary outcomes: epilepsy, deafness and residual neurological deficit
Notes	This study was published twice, with a preliminary analysis of the osmotic effects published as <a href="#">Singhi 2008</a> . Study funding, the source of drugs or co-infection documented

***Risk of bias***

<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Randomisation list prepared with simple random numbers table
Allocation concealment (selection bias)	Low risk	Serially numbered, sealed packets prepared, kept readily available
Blinding (performance bias and detection bias) All outcomes	Low risk	Clinicians and patients blinded. It is not clear from the text if the investigators were fully blinded but the packets were prepared by a separate person from the investigating team

CSF: cerebral spinal fluid

CNS: central nervous system

Dex: dexamethasone

GLY: glycerol

IV: intravenous

od: once daily

PO: per-oral

### Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alimarante 1995	Case series of mannitol used for bacterial meningitis. No randomisation or placebo use documented
Herson 1977	Not a randomised controlled trial. Glycerol use discussed
Pecco 1991	Literature review and documented personal experience of the use of mannitol in meningitis
Pelegrin 2012	Retrospective cohort study examining patients with bacterial meningitis 1987 to 2009 who were treated with dexamethasone, mannitol and phenytoin. No data were collected prospectively and participants were not randomised to receive any of the interventions
Peltola 2010	This is not a new trial, but is a specific analysis of <a href="#">Peltola 2007</a> trial looking at deafness in more detail
Singhi 2004	Review article not randomised controlled trial
Singhi 2007	Letter in response to the journal editorial summary of the trial <a href="#">Peltola 2007</a>
Singhi 2008	Duplicated trial of <a href="#">Sankar 2007</a> . This was a subset of the data published in <a href="#">Sankar 2007</a> , an included study. <a href="#">Singhi 2008</a> reports osmolality effects of glycerol rather than mortality outcome
Urciuoli 1963	Mannitol tested for neurosurgical infections and not acute bacterial meningitis. Not a randomised controlled trial

### Characteristics of ongoing studies *[ordered by study ID]*

#### Molyneux 2012

Trial name or title	Glycerol and high dose paracetamol for paediatric meningitis
Methods	Randomised controlled trial with 4 arms
Participants	Children under 12 years with acute bacterial meningitis
Interventions	Oral glycerol and oral paracetamol
Outcomes	Death, hearing loss, neurological disability, cognitive ability
Starting date	2010
Contact information	Professor Elizabeth Molyneux, Queen Elizabeth Central Hospital, Blantyre, Malawi
Notes	Trial due to complete 2012

## DATA AND ANALYSES

### Comparison 1. Glycerol versus no osmotic diuretic

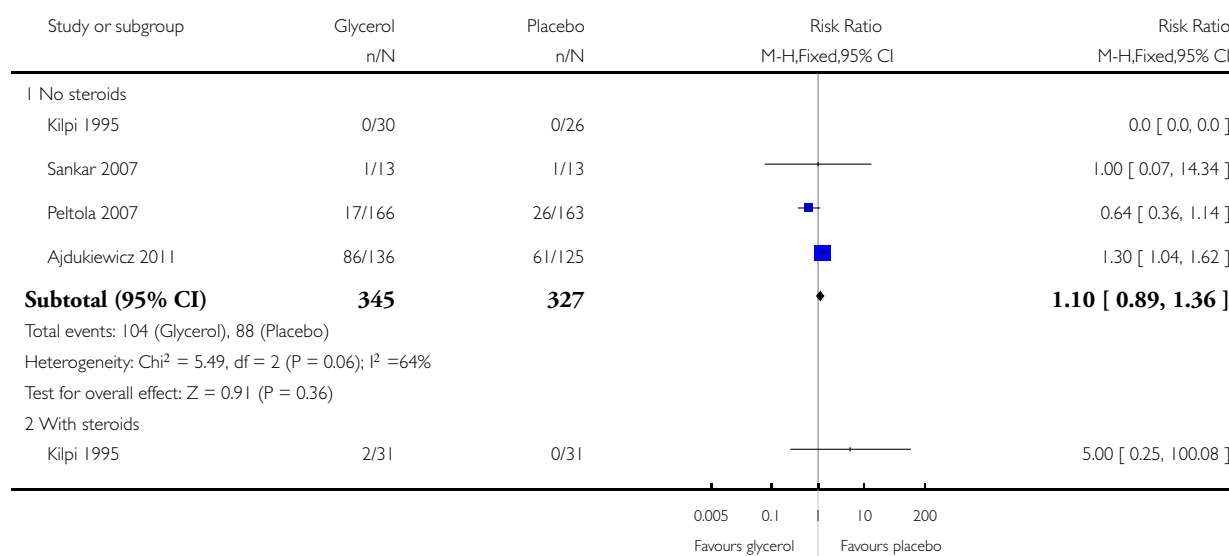
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	4	1091	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.89, 1.33]
1.1 No steroids	4	672	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.89, 1.36]
1.2 With steroids	3	419	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.60, 1.74]
2 Death and neurological disability	4	1091	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.86, 1.25]
2.1 No steroids	4	672	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.87, 1.31]
2.2 With steroids	3	419	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.62, 1.46]
3 Seizures	3	909	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.90, 1.30]
3.1 No steroids	3	574	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.91, 1.43]
3.2 With steroids	2	335	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.70, 1.33]
4 Hearing loss	4	741	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.38, 0.93]
4.1 No steroids	3	391	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.32, 0.98]
4.2 With steroids	3	350	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.32, 1.35]

#### Analysis 1.1. Comparison 1 Glycerol versus no osmotic diuretic, Outcome 1 Death.

Review: Osmotic therapies added to antibiotics for acute bacterial meningitis

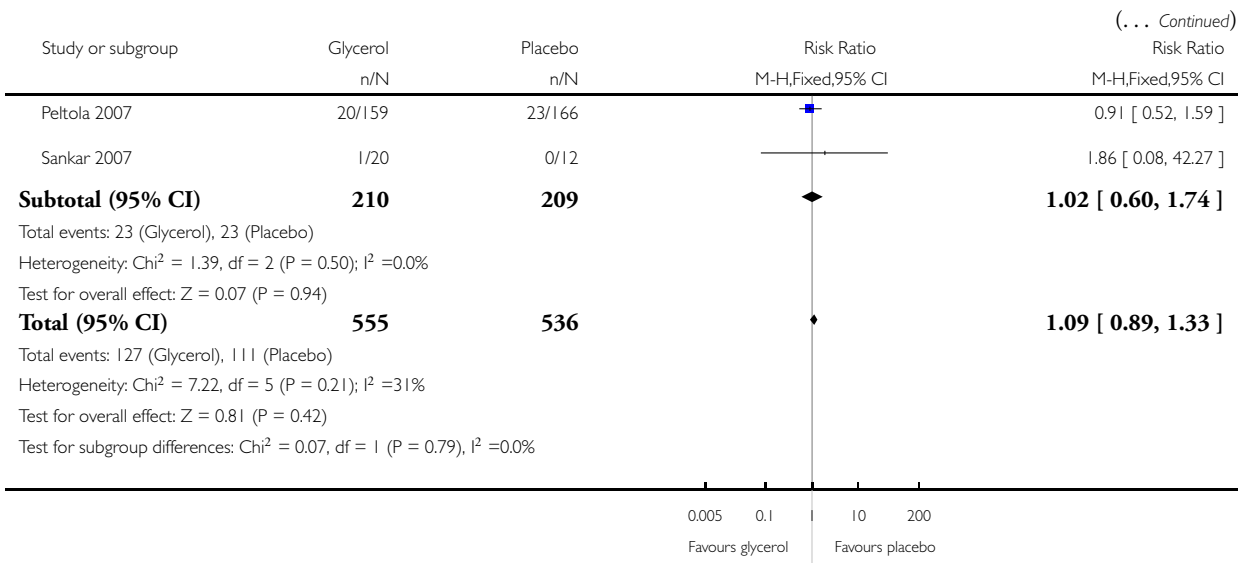
Comparison: 1 Glycerol versus no osmotic diuretic

Outcome: 1 Death



(Continued ...)



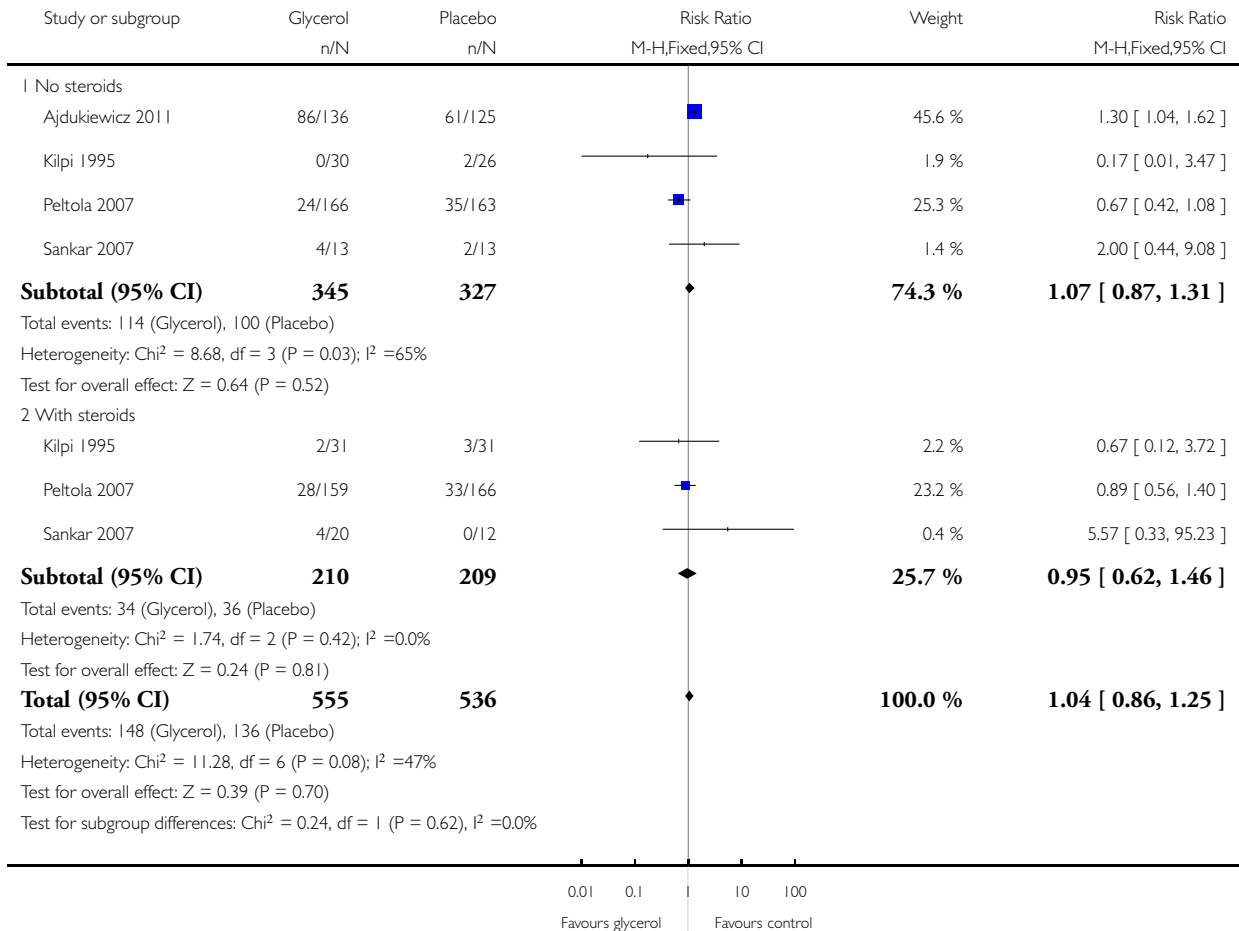


## Analysis 1.2. Comparison 1 Glycerol versus no osmotic diuretic, Outcome 2 Death and neurological disability.

Review: Osmotic therapies added to antibiotics for acute bacterial meningitis

Comparison: 1 Glycerol versus no osmotic diuretic

Outcome: 2 Death and neurological disability

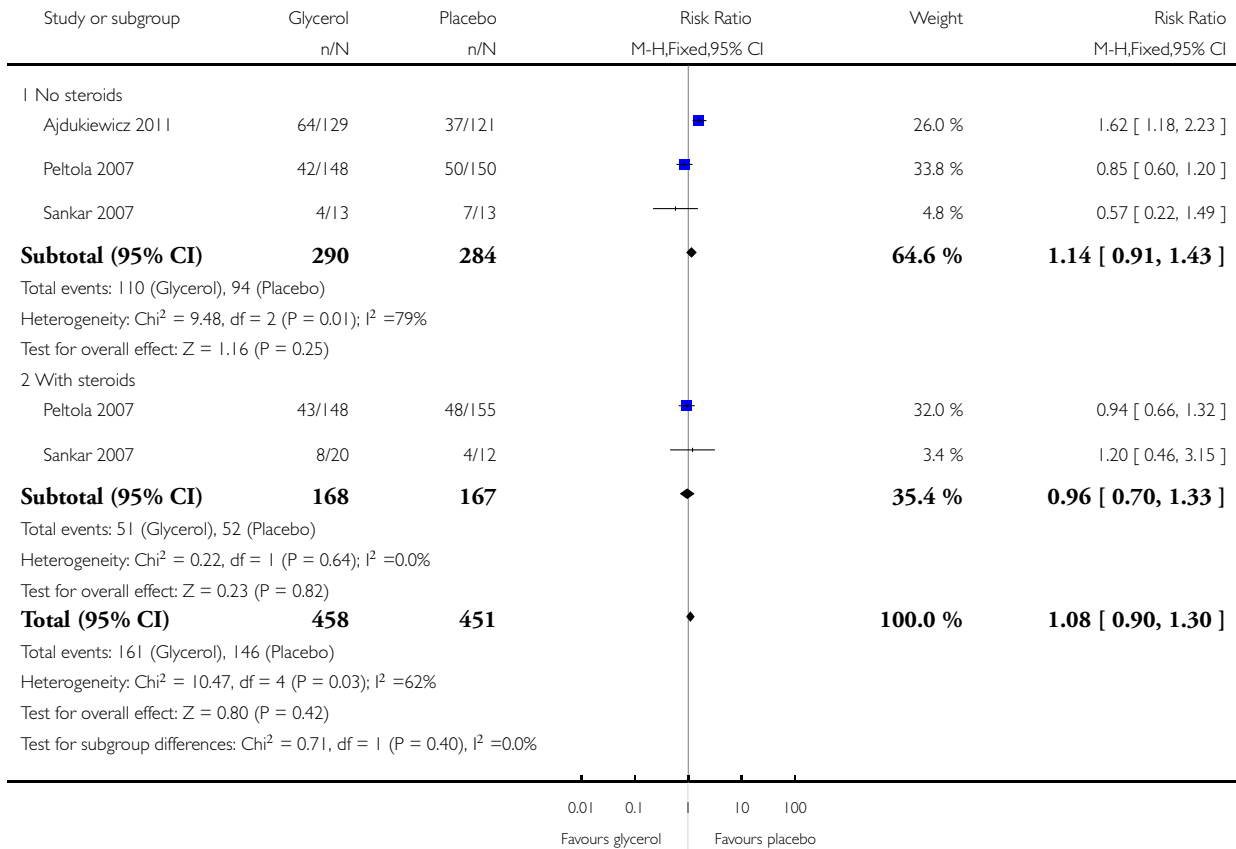


### Analysis 1.3. Comparison 1 Glycerol versus no osmotic diuretic, Outcome 3 Seizures.

Review: Osmotic therapies added to antibiotics for acute bacterial meningitis

Comparison: 1 Glycerol versus no osmotic diuretic

Outcome: 3 Seizures

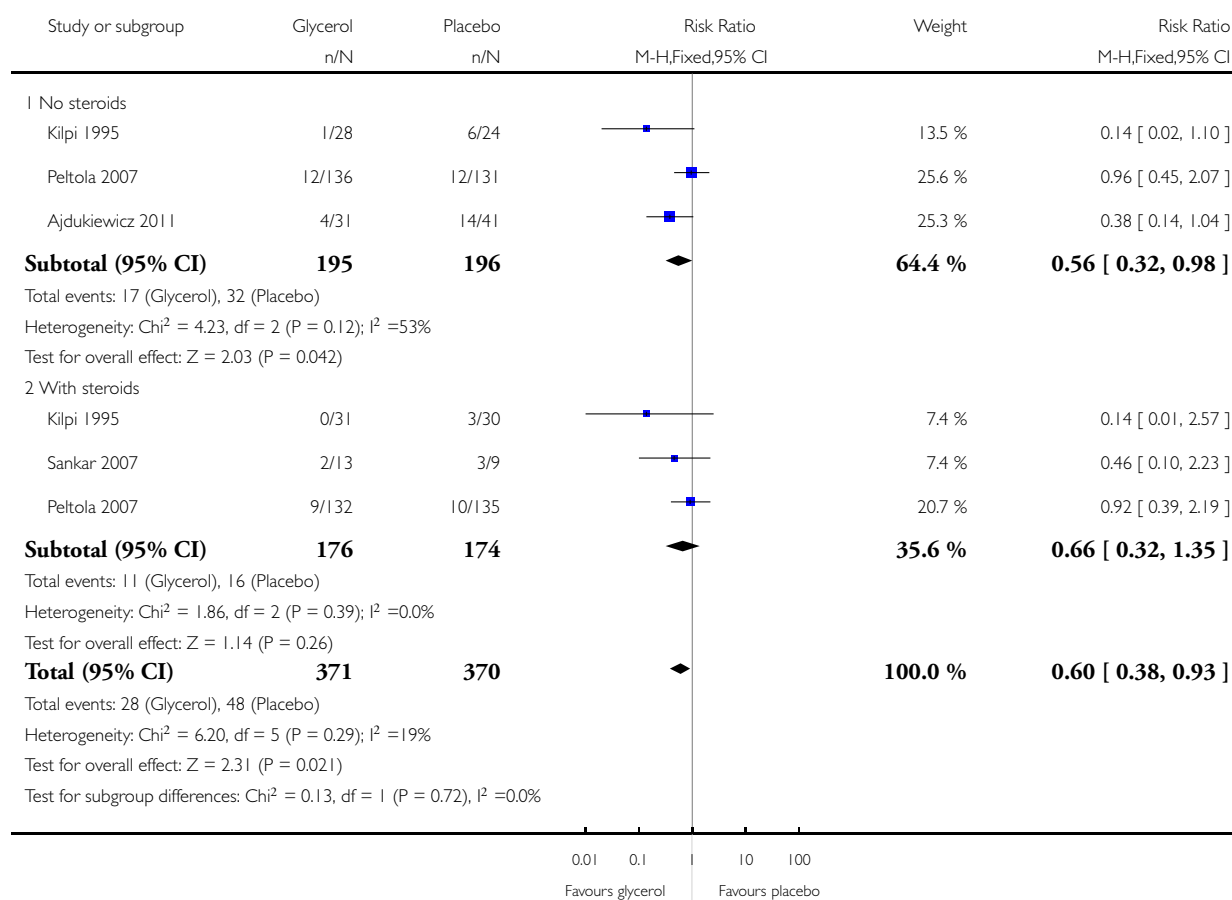


## Analysis 1.4. Comparison 1 Glycerol versus no osmotic diuretic, Outcome 4 Hearing loss.

Review: Osmotic therapies added to antibiotics for acute bacterial meningitis

Comparison: 1 Glycerol versus no osmotic diuretic

Outcome: 4 Hearing loss



## ADDITIONAL TABLES

Table 1. Available osmotic therapies

Drug	Class	Mechanism of action	Dose range and route	Studied/used in
Glycerol	Sugar alcohol	Probably osmosis plus possible vascular and metabolic benefit	IV 5% to 10% solution or 50 g PO 1.5 g/kg	Meningitis (Peltola 2007), stroke (Righetti 2005)

**Table 1. Available osmotic therapies** (Continued)

Mannitol	Sugar alcohol	Osmotic diuretic	IV 20% solution 1 ml/kg to 10 ml/kg or 1 g/kg	Brain trauma (Wakai 2008), cerebral malaria (Namutangula 2007), stroke (Bereczki 2010)
Sorbitol	Sugar alcohol	Osmotic diuretic (weak)	PO, IV	Experimental brain perfusion, stroke
Hypertonic saline	Hypertonic solutions	Osmosis	IV	Brain trauma (Choi 2005), stroke (Schwarz 2002)
Sodium lactate	Hydroxy acids	Osmosis (weak)	IV	Brain trauma (Ichai 2009)

IV: intravenous  
PO: per oral

**Table 2. Comparison of included study interventions**

Name of study	Population	Intervention and dose	Control used	Treatment duration	Study arms
Kilpi 1995	Children in Finland	Glycerol (gly) PO 4.5 g/kg max 180 g/24 hrs in 3 divided doses  Dexamethasone (dex) 1.5 mg/kg max 60 mg/day	No oral placebo IV saline	3 days	4 arms IV dex + gly, PO gly, IV dex, and neither treatment
Sankar 2007	Children in India	Glycerol PO 1.5 g/kg 3 x daily  Dex 0.15 mg/kg 3 x daily	Oral carboxymethylcellulose 2% IV saline	Not detailed	4 arms placebo PO and IV, IV dex + PO gly, IV placebo + PO gly, IV dex + PO placebo
Peltola 2007	Children in South America	Glycerol PO 1.5 g/kg 3 x daily  Dex 0.15 mg/kg 3 x daily	Oral carboxymethylcellulose 2% IV saline	2 days	4 arms placebo PO and IV, IV dex + PO gly, IV placebo + PO gly, IV dex + PO placebo
Ajdkiewicz 2011	Adults in Malawi, Southern Africa	Glycerol PO 75 mg 4 x daily diluted in water or 50% dex-	Oral 50% dextrose solution	4 days	PO gly versus PO 50% dextrose

**Table 2. Comparison of included study interventions** (Continued)

	trose solution			
IV: intravenous				
PO: per oral				
gly: glycerol				
dex: dexamethasone				

## APPENDICES

### Appendix I. EMBASE search strategy

#### Embase.com

#20 #16 AND #19

#19 #17 OR #18

#18 random\*:ab,ti OR placebo\*:ab,ti OR factorial\*:ab,ti OR crossover\*:ab,ti OR 'cross over':ab,ti OR 'cross-over':ab,ti OR assign\*:ab,ti OR allocat\*:ab,ti OR volunteer\*:ab,ti OR ((doubl\* OR singl\*) NEAR/2 (blind\* OR mask\*)):ab,ti

#17 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp

#16 #3 AND #15

#15 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14

#14 (hypertonic NEAR/2 saline):ab,ti

#13 'sodium chloride'/de

#12 (lactat\* NEAR/2 sodium):ab,ti

#11 'lactate sodium'/de

#10 sorbit\*:ab,ti

#9 mannitol\*:ab,ti

#8 '1,2,3-propanetriol':ab,ti OR propanetrio\*:ab,ti

#7 glycer\*:ab,ti

#6 'sugar alcohol'/exp

#5 osmotic\*:ab,ti

#4 'osmotic diuretic agent'/exp

#3 #1 OR #2

#2 meningit\*:ab,ti

#1 'meningitis'/exp

## Appendix 2. CINAHL search strategy

### CINAHL (Ebsco)

S12 S3 and S11

S11 S4 or S5 or S6 or S7 or S8 or S9 or S10

S10 TI hypertonic N2 saline or AB hypertonic N2 saline

S9 (MH "Saline Solution, Hypertonic")

S8 TI sodium N2 lactat\* or AB sodium N2 lactat\*

S7 TI ( glycerol\* or 1,2,3-propanetriol or propanetriol\* or mannitol\* or sorbit\* ) or AB ( glycerol\* or 1,2,3-propanetriol or propanetriol\* or mannitol\* or sorbit\* )

S6 AB sugar alcohol\* or TI sugar alcohol\*

S5 (MH "Sugar Alcohols+")

S4 TI osmotic\* or AB osmotic\*

S3 S1 or S2

S2 TI meningit\* or AB meningit\*

S1 (MH "Meningitis+")

## Appendix 3. LILACS search strategy

### LILACS (BIREME)

> Search > MH:Meningitis OR Meningite OR MH:C10.228.228.507\$ OR C10.228.566\$ OR MH:C01 252.200\$ OR C10.228.228.180.500\$ OR meningit\$ AND MH:"Diuretics, Osmotic" OR "Diuréticos Osmóticos" OR "Diuréticos Osmóticos" OR "Osmotic Diuretics" OR MH:D27.505.696.560.500.453\$ OR osmot\$ OR osmos\$ OR osmol\$ OR MH:"Sugar Alcohols" OR "Alcoholes del Azúcar" OR "Álcoois de Açúcar" OR MH:D02.033.800\$ OR MH:D09.853\$ OR "sugar alcohols" OR glycer\$ OR "1,2,3-propanetriol" OR mannitol\$ OR sorbit\$ OR MH:"Sodium Lactate" OR "Lactato de Sodio" OR "Lactato de Sódio" OR MH:D02.241.511.459.500\$ OR "sodium lactate" OR MH:"Saline Solution, Hypertonic" OR "Solución Salina Hipertónica" OR "Solução Salina Hipertônica" OR "Hypertonic Saline Solution" OR "Sodium Chloride Solution, Hypertonic" OR "Hypertonic Solution, Saline" OR "Solución Hipertónica de Cloruro de Sodio" OR "Solução Hipertônica de Cloreto de Sódio" OR "hypertonic saline" > clinical trials

## CONTRIBUTIONS OF AUTHORS

Emma Wall (EW) was responsible for writing the main text, extracting data from studies and performing the analyses.

Paul Garner (PG) was responsible for methodological input, help with interpretation and writing the review.

Katherine Ajdukiewicz (KA) extracted data from the studies and commented on the text.

Robert Heyderman (RH) provided comments on the text.

## **DECLARATIONS OF INTEREST**

KA is the principal investigator of a trial she conducted in Malawi investigating oral glycerol for acute bacterial meningitis in adults.

RH was a co-investigator on that study and is the director of the host institution.

EW and PG declare no conflict of interest.

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