

Antibiotic prophylaxis for preventing meningitis in patients with basilar skull fractures (Review)

Ratilal BO, Costa J, Sampaio C, Pappamikail L



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Presented By: Yahya Fageeh



BACKGROUND

- The estimated incidence of BSF from nonpenetrating head trauma varies between 7%-15.8%.
- CSF leakage occur in 2% to 20.8%.*
- Clinical signs: otorrhoea/rhinorrhoea, bilateral periorbital ecchymosis, Battle's sign, VII palsy, haemotympanum or TM perforation, hearing loss, vestibular dysfunction and anosmia.
- High resolution CT. ^

*Buchanan 2004

^Leech 1973

BACKGROUND

- dura mater may be torn adjacent to the fracture site, placing CNS in contact with bacteria from the PNS, NP or ME.
- +/- CSF leakage
- BSF predispose the patient to meningitis.
- A greater associated risk if CSF leakage exists in particular if it persists for more than seven days.*

* Leech 1973

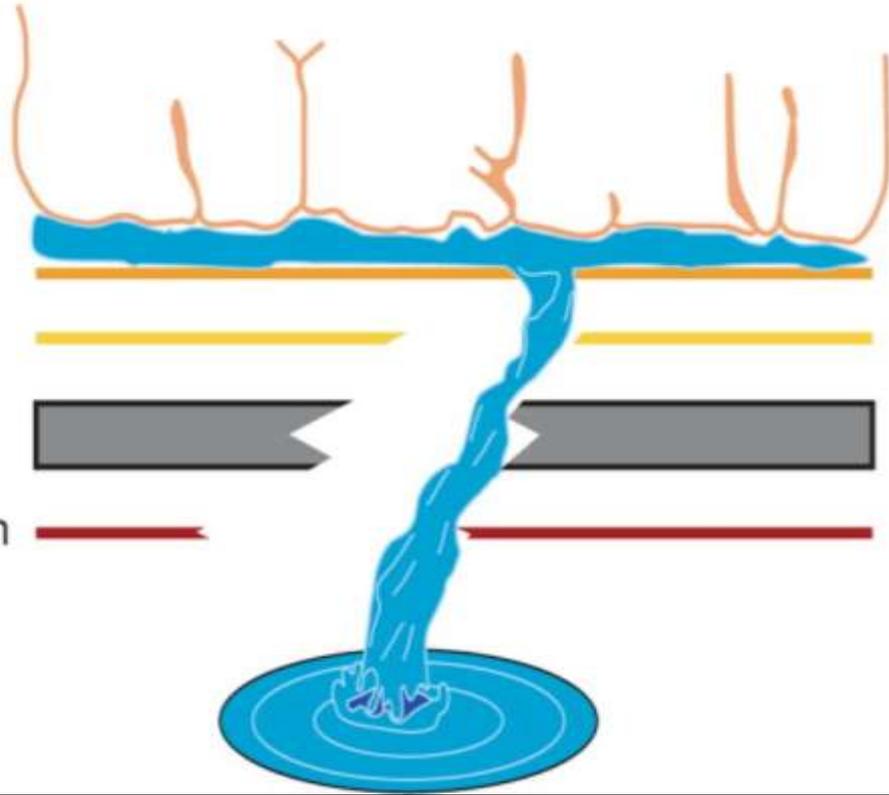
Pia/Brain

Arachnoid

Dura mater

Cranial bone

Mucoperiosteum



BACKGROUND

- The role of prophylactic antibiotics for preventing bacterial meningitis in patients with BSF is controversial.
- emergence of resistant organisms argues against their use.
- higher incidences of meningitis in patients with BSF who have received prophylactic antibiotics.*

* Choi 1996

How the intervention might work

- Chemoprophylaxis with antibiotics in basilar skull fractures may reduce the incidence of meningitis.

Importance

- A meta-analysis showed a statistically significant reduction in the incidence of meningitis with prophylactic antibiotic therapy for patients with post-traumatic CSF leakage.*
- Another meta-analysis concluded that antibiotic prophylaxis after a BSF does not appear to decrease the risk of meningitis, independent of whether or not CSF leakage has occurred.^
- did not include an extensive review of the literature.
- until 1995 and 1996.
- retrospective and observational studies.

*Brodie 1997

^ Villalobos 1998

OBJECTIVES

- determine evidence for the effectiveness of prophylactic antibiotics in BSF.
- primary hypothesis: the frequency of meningitis is lower when prophylactic antibiotics are administered as soon as a diagnosis of BSF is made, with or without CSF leakage, compared with no treatment or placebo.
- administration of prophylactic antibiotics may influence outcomes such as:
 - all-cause/meningitis-related mortality
 - need for surgical correction in patients with CSF leak
 - non-CNS infection

METHODS

- **Types of studies**
 - RCTs comparing any antibiotic vs. placebo or no intervention.
 - non-RCTs to perform a separate meta-analysis to compare results.
- **Types of participants**
 - any age
 - recent BSF
 - independent of the presence and severity of CSF leak

METHODS

- **Types of interventions**
 - Any antibiotic administered at the time of primary treatment of the BSF compared with placebo or no antibiotic.
 - Excluded:
 - trials comparing different antibiotics, different antibiotic dosages, routes of administration, or differences in timing or duration of administration.

METHODS

- **Primary outcomes**
 - Frequency of meningitis:
 - clinically: fever, neck stiffness, deterioration of neurological status, headache
 - confirmed by CSF analysis:
 - Biochemistry
 - Gram stains/cultures

METHODS

- **Secondary outcomes**
 - All-cause mortality/meningitis-related mortality.
 - Need for surgical correction in patients with CSF leak
 - Non-CNS infection

Search Methods

- Cochrane Central Register of Controlled Trials which contain:
 - MEDLINE (1966 to February 2011)
 - EMBASE (1974 to February 2011)
 - LILACS (1982 to February 2011).
- Electronic search of meeting proceedings from the American Association of Neurological Surgeons (1997 to September 2005)
- handsearched the abstracts of meeting proceedings of the European Association of Neurosurgical Societies (1995, 1999 and 2003).

Data collection and analysis

- **Selection of studies:**
 - according to the criteria
- **Data extraction and management**
 - type of participants, type and dose of antibiotic used, methodological quality, number of patients excluded or lost to follow up and the outcome
- **Assessment of risk of bias in included studies**
 - Risk of bias assessment tool

Data collection and analysis

- **Measures of treatment effect**
 - reported as odds ratios and 95% confidence intervals for dichotomous outcomes, using the Peto fixed-effect method.
- **Unit of analysis issues**
 - Statistical analysis: Review Manager software
 - Significance: (of any differences between ORs) Standard method

Data collection and analysis

- **Assessment of heterogeneity**
 - I² statistic
- **Assessment of reporting biases**
 - publication bias were assessed according to the recommendations on testing for funnel plot asymmetry
- **Data synthesis**
 - The results of meta-analysis reported as OR and 95% CI for dichotomous outcomes, using the Peto fixed-effect method.

Data collection and analysis

- **Subgroup analysis and investigation of heterogeneity**
 - by undertaking a subgroup analysis of patients with or without CSF leakage in the event of uncovering significant heterogeneity.
- **Sensitivity analysis**
 - meta-analysis of all the controlled, nonrandomised studies identified in order to evaluate the consistency of the results of the main meta-analysis

Included Studies

1. Demetriades et al 1992

- Role of prophylactic antibiotics in open and basilar fractures of the skull: a randomized study. *Injury* 1992;23 (6):377–80.

2. Eftekhar et al 2004

- Prophylactic administration of ceftriaxone for the prevention of meningitis after traumatic pneumocephalus: results of a clinical trial. *Journal of Neurosurgery* 2004

3. Hoff et al 1976

- Antibiotics for basilar skull fracture. *Journal of Neurosurgery* 1976

4. Ignelzi et al 1975a

- Analysis of the treatment of basilar skull fractures with and without antibiotics. *Journal of Neurosurgery* 1975;43(6):721–6.

5. Klastersky et al 1976

- Antimicrobial prophylaxis in patients with rhinorrhea or otorrhea: a double blind study. *Surgical Neurology* 1976;6(2):111–4.

Included studies

- All had a parallel design and were stated by the trial authors to be randomised, although the method of randomisation was not clearly described in any trial report.
- All trials included participants with a clinical or radiological diagnosis of BSF.
- Hoff 1976 trial: CSF leakage was an exclusion
- Criterion
- Klastersky 1976 trial: in which the participants had to have evidence of CSF leakage to be included.

Included studies

- The primary outcome for all trials included the occurrence of meningitis.
- In three trials* the primary outcome also included extracranial infection, bacterial colonisations of bronchial secretions or urine, change in the posterior nasopharyngeal flora, or death from brain damage.
- None of the studies reported data on outcomes of safety and tolerability of prophylactic antibiotics.

*Demetriades 1992; Ignelzi 1975a; Klastersky 1976

Included studies

- Ignelzi 1975a:
 - small controlled trial with 10 participants with BSF that was included in a report of a larger retrospective study.
 - The presence of CSF was not described
 - Group1: received prophylactic ampicillin or cephalothin 1 g six-hourly for 10 days
 - Group2: did not.

Included studies

- Klastersky 1976
 - a double-blind controlled trial that enrolled 52 participants.
 - Group1: five mega units of penicillin G given IV six-hourly for a mean duration of 7.7 days
 - Group2: Placebo was given under identical conditions.

Included studies

- Hoff 1976
 - enrolled 160 participants assigned randomly and blindly to one of three groups:
 - Group1: no antibiotic
 - Group2: 1.2million units of penicillin IV daily for three days
 - Group3: 20 million units of penicillin IV daily for three days
 - No cases of meningitis were found
 - numbers of participants enrolled in each group were not provided.

Included studies

- Demetriades 1992
 - randomised 37 participants to three groups
 - Group1: no antibiotic
 - Group2: 1 g ceftriaxone IV daily for three days
 - Group3: combined ampicillin (1 g IV six-hourly)/sulphadiazine (0.5g IV six-hourly)

Included studies

- Eftekhar 2004
 - studied 109 participants with acute traumatic pneumocephalus verified by a CT scan, who were followed until occurrence of meningitis or at least for five days post-trauma.
 - Group1: PAT given, in which ceftriaxone was administered at a dose of 1 g twice a day for five days
 - Group2: NO PAT

Included studies

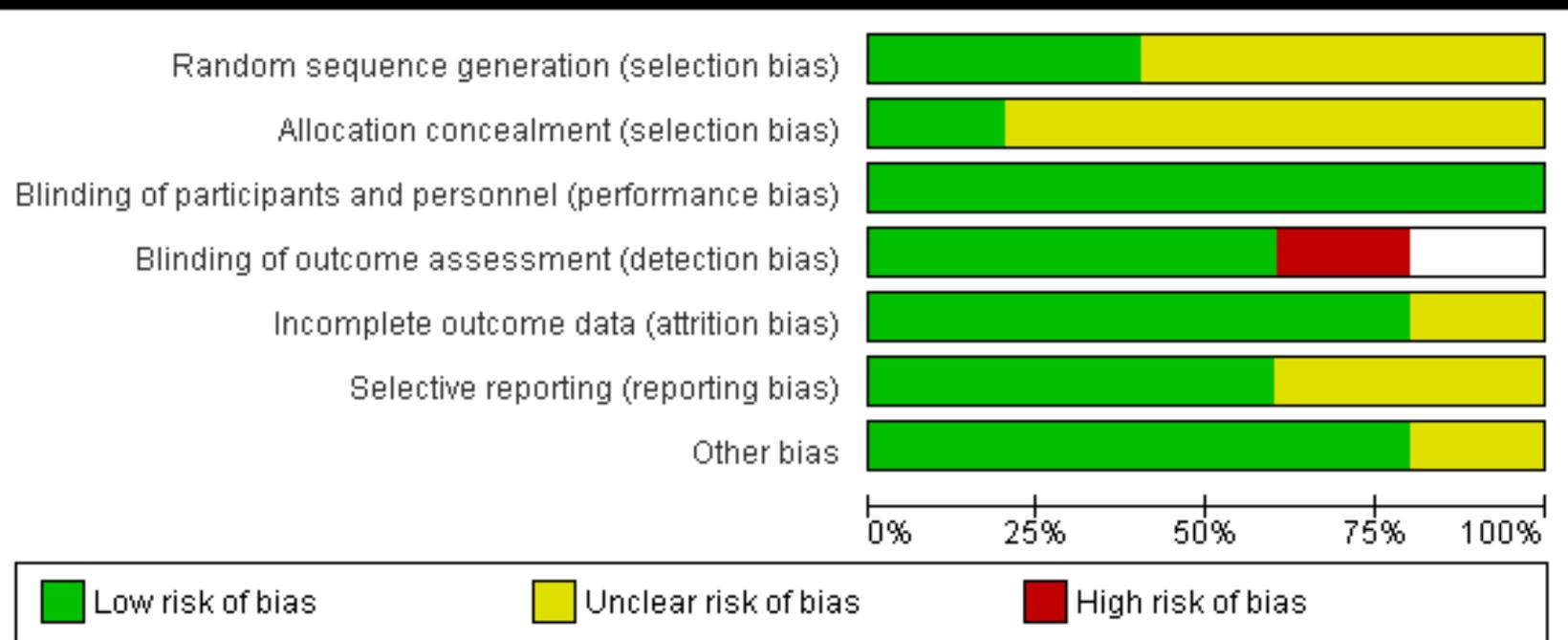
- 368 participants were enrolled in these five studies.
- Two of them (Eftekhar 2004; Hoff 1976) enrolled 73% of these participants.
- the number included in the meta-analysis (208)
- 109 participants in the treatment group
- 99 in the control group.

Included studies

- In three trials (Demetriades 1992; Eftekhar 2004; Klastersky 1976) participants were well-matched between the treatment and control arms for demographics, clinical status at admission and presence of rhinorrhoea or otorrhoea.
- The other trials (Hoff 1976; Ignelzi 1975a) did not describe the characteristics of the population included in each group.

Included studies

- There was only one study in which the presence of CSF leakage was not specified (Ignelzi 1975a).
- CSF leakage was an exclusion criteria in the Hoff 1976 study.
- Traumatic rhinorrhoea or otorrhoea had to be present in the participants included in the Klastersky 1976 study.
- The other two trials (Demetriades 1992; Eftekhar 2004) included participants with and without CSF leakage.



Demetriades 1992	?	?	?	?	?	?	?
Eftekhar 2004	+	?	+	-	+	+	+
Hoff 1976	?	?	+		+	?	?
Ignelzi 1975a	?	?	+	+	+	+	+
Klasterky 1976	+	+	+	+	+	+	+

Random sequence generation (selection bias)

Allocation concealment (selection bias)

Blinding of participants and personnel (performance bias)

Blinding of outcome assessment (detection bias)

Incomplete outcome data (attrition bias)

Selective reporting (reporting bias)

Other bias

Risk of bias in included studies

- **Allocation**

- The precise method of randomisation and details of concealment of allocation were not explained in any trial.
- the method of allocation considered to be unclear in all trials.

- **Blinding**

- Only one study ([Klastersky 1976](#)) was double-blinded throughout, using identical appearance interventions (antibiotics or placebo).
- only two studies ([Demetriades 1992](#); [Klastersky 1976](#)) reported the number of and reasons for patients leaving the trials.

Effects of interventions

- meta-analysis
- to compare prophylactic antibiotics with no antibiotic or placebo in patients with BSF
- (sub groups analysis) identify the influence of CSF leakage in the frequency of meningitis in patients with BSF
- no evidence of heterogeneity in any of the outcomes measured
- NO significant differences between treatment and control groups in any of the included trials

Effects of interventions

- **Frequency of meningitis**
 - no significant differences for this outcome (Peto OR 0.69; 95% CI 0.29 to 1.61) (Analysis 1.2).
 - no differences in the subgroups of patients with CSF leakage (Peto OR 0.44; 95% CI 0.09 to 2.15) (Analysis 1.1.1)
 - no differences in the subgroups of patients without CSF leakage (Peto OR 0.77; 95% CI 0.25 to 2.41) (Analysis 1.1.2).

Effects of interventions

- **All-cause mortality/meningitis-related mortality**
 - no significant differences for all-cause mortality (Peto OR 1.68; 95% CI 0.41 to 6.95) (Analysis 2.1)
 - no significant differences for meningitis-related mortality (Peto OR 1.03; 95% CI 0.14 to 7.40) (Analysis 3.1).

Effects of interventions

- **Need for surgical correction in patients with CSF leakage**
- Only one study (Eftekhar 2004) provided data for this secondary outcome and no participants in either treatment or control groups underwent surgical correction for CSF leakage in this trial

Effects of interventions

- **Non-CNS infection**
- Only one study (Klastersky 1976) provided data for this outcome. No significant differences were found (Peto OR 0.61; 95% CI 0.15 to 2.46) (Analysis 5.1).

Summary of main results

- The frequency of meningitis in the Eftekhar 2004 trial was significantly higher than in the other trials.
- The diagnosis of meningitis was based on CSF analysis in participants with compatible clinical findings and was comparable with the other trials.
- included only the subset of patients with BSF and pneumocephalus that is associated with a dural tear with an open communication with air in the paranasal sinuses, mastoid air cells or petrous temporal regions and the CNS.
- These participants might have had an additional risk factor for developing meningitis that may have been independent of CSF leakage.
- Further investigations are necessary to clarify this issue.

Summary of main results

- not possible to recommend the use of prophylactic antibiotics in patients with BSF.
- This study did not show that the administration of antibiotics had an effect on the frequency of meningitis.
- No significant difference was found in the subgroup of participants with CSF leakage
- no significant difference was found for all-cause or meningitis-related mortality.
- The study could not exclude the possibility that antibiotic prophylaxis is either better or worse than the control. This is partially explained by the relatively small number of participants enrolled and the small number of events
- recorded.

Overall completeness and applicability

- There is no support for routine prophylactic antibiotics in all patients with basilar skull fracture.
- Further RCTs are needed to assess its benefits and risks clearly.

Quality of the evidence

- The quality of the evidence was indicated by the identification of only five RCTs that we considered suitable for this review.
- In general, the quality of the included trials was poor, as assessed by the 'Risk of bias' tool (Higgins 2011).

AUTHORS' CONCLUSIONS

- **Implications for practice**
 - This systematic review did not show that prophylactic antibiotics had an effect on the prevention of meningitis in patients with BSF, regardless of CSF leakage.
 - Currently available evidence from RCTs does not support the use of prophylactic antibiotics in patients with BSF.
 - The risk of adverse reactions and financial costs are factors that should be taken into account when deciding if antibiotic therapy is appropriate.

AUTHORS' CONCLUSIONS

- **Implications for research**
 - More appropriately designed RCTs to test the effectiveness of prophylactic antibiotic use following the diagnosis of BSF are needed in order to establish whether or not there is a net benefit from this intervention.
 - Until more research results are available, firm conclusions regarding the efficacy of this treatment cannot be provided.
 - Future trials should evaluate all clinically relevant outcomes (all-cause mortality, need for surgical correction in patients with CSF leakage, disability),
 - should pay attention to subgroups of patients, such as those with CSF leakage or pneumocephalus (or both).

THANK YOU