To Trick or Treat: Antimicrobial Prophylaxis for Prevention of Meningitis in Traumatic Skull Fractures Associated with CSF Leak

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Learning Objectives:
1. Recall anatomy and physiology of skull bones and intracranial components
2. Describe pathophysiology of skull fractures with associated cerebrospinal fluid (CSF) leak
3. Evaluate role of antibiotic prophylaxis in the setting of CSF leak
4. Indicate appropriate use of antibiotic prophylaxis with CSF leak
I) Why do we care?
A) CNS infections including meningitis can be associated with cerebrospinal fluid (CSF) leaks
B) Overall incidence is low
C) Associated with morbidity, mortality, and increased cost
D) Controversial role for antibiotic prophylaxis

Figure 1. Severity of Injuries

II) Traumatic skull fractures
A) Incidence
   i) 1.7 million traumatic brain injuries (TBI) annually\(^1\)
      (a) 275,000 hospitalizations for nonfatal TBI\(^2\)
      (b) 52,000 TBI-related deaths
      (c) 80,000-90,000 experience long-term disability
      (d) Mechanism of injury\(^1\)
         (1) Fall – 28%
         (2) Motor vehicle accident – 20%
         (3) Blunt force – 19%
         (4) Assault – 11%
         (5) Blast injuries
      (e) Severity of TBI based on Glasgow Coma Scale (GCS)
         (1) Presence of skull fractures is a prognostic factor for worse outcome\(^3\)
            (i) Greater force of impact with trauma
      ii) 30% of patients with TBI have associated skull fractures
         (a) Incidence of fracture by type
            (1) Basal skull fractures (BSF) 3.5-25%\(^4,5\)
               (i) Incidence lower in pediatric patients
                  1. Increased flexibility of skull base
                  2. Underdevelopment of ethmoid, frontal, and mastoid air cells
            (2) Maxillofacial fractures 23%\(^5\)
            (3) Cranial vault fractures 1%\(^5\)
B) Morbidity
   i) Severe TBI with skull fractures is associated with a moderate or poor outcome\textsuperscript{6,7}
      (a) Intensive care unit admission, ventilator support during recovery, increased risk for
          prolonged hospital length of stay\textsuperscript{8}
   ii) Permanent neurologic disorders\textsuperscript{6}
       (a) Epilepsy, blindness, deafness, diplopia, facial paralysis, other cranial nerve deficits\textsuperscript{9,10}
   iii) Traumatic encephalocele
       (a) Herniation of brain tissue
   iv) Pneumocephalus\textsuperscript{4,11}
       (a) Entrapment of air under pressure in intracranial cavity
   v) Cerebrospinal fluid leaks
       (a) Escape of fluid that surrounds the brain and spinal cord
   vi) Infectious complications\textsuperscript{12}
       (a) Meningitis, encephalitis, intracranial abscesses, subdural empyema
       (b) Head trauma is the most common cause of recurrent bacterial meningitis

C) Mortality
   i) Early mortality has substantially declined over time\textsuperscript{7}
   ii) 7% mortality in mild TBI with BSF\textsuperscript{13}
   iii) 22% mortality in patients with penetrating injury and CSF leak\textsuperscript{14}
   iv) 65% mortality in severe TBI with skull fractures\textsuperscript{3}
       (a) 30-54% mortality in severe TBI

D) Cost\textsuperscript{5}
   i) Average cost of hospital stay in TBI cohorts from 2005-2009
      (a) Without meningitis: $32,319
      (b) With meningitis: $42,808
   ii) Independent risk factors for escalating cost of hospitalization
      (a) Rhinorrhea OR 2.0 (CI 1.6-2.7) and otorrhea OR 2.3 (1.9-2.7)
      (b) Posttraumatic meningitis OR 3.1 (CI 2.5-3.8)
      (c) Surgical intervention

E) Fracture classifications\textsuperscript{1}
   i) Characteristics
      (a) Linear
      (b) Depressed
      (c) Compound
      (d) Open
      (e) Closed
      (f) Penetrating
ii) BSF
   (a) Characteristics
      (1) Thin and more vulnerable to trauma
      (2) Air-filled sinuses and multiple foramen render skull base more vulnerable to trauma
   (b) Anterior BSF
      (1) Type I, cribriform
      (2) Type II, frontoethmoidal
      (3) Type III, lateral frontal
      (4) Type IV, complex
   (c) Middle BSF
      (1) Longitudinal - parallel to petrous portion of temporal bone
      (2) Transverse - perpendicular to petrous portion of temporal bone
      (3) Sella turcica fractures
   (d) Posterior BSF
      (1) Clivus
         (i) Transverse, oblique, longitudinal
      (2) Occipital
         (i) Ring fracture- encircles foramen magnum at skull base
         (ii) Occipital condyle- type I – IV
   iii) Facial fractures\(^{15}\)
      (a) Le Fort I
         (1) Horizontal maxillary fracture, separating the teeth from upper face, fracture line passes through alveolar ridge, lateral nose and inferior wall of maxillary sinus
      (b) Le Fort II
         (1) Pyramidal fracture, passes through posterior alveolar ridge, lateral walls of maxillary sinuses, inferior orbital rim and nasal bones
      (c) Le Fort III
         (1) Craniofacial disjunction, fracture line passes through nasofrontal suture, maxillo-frontal suture, orbital wall and zygomatic arch

\textbf{Figure 2. Le Fort Fracture Classifications}
III) CSF
A) Function\textsuperscript{16}
   i) Provide physical support and buoyancy for brain/spinal elements
   ii) Remove by-products of metabolism from neural tissues and regulates chemical environment of brain
B) Production and circulation\textsuperscript{16,17}
   i) Produced by choroid plexus in the lateral, third, and fourth ventricles at a rate of 20-30 mL/h
      (a) Approximately 90-150 mL total volume
   ii) Flows from: lateral ventricles to third ventricle to fourth ventricle through subarachnoid space and circulates through meninges before being reabsorbed via arachnoid granulations

IV) CSF leaks
A) CSF fistula\textsuperscript{5}
   i) A fracture involving skull or facial structures may produce a breach in dura
   ii) Abnormal passageway allowing escape of CSF from subarachnoid space
   iii) Can be associated with CSF leak
B) Types of CSF leaks
   i) Rhinorrhea\textsuperscript{18,19}
      (a) 72\% of CSF leaks
      (b) CSF leak through nares
      (c) Origins of leak\textsuperscript{19,20}
         (1) Fistula of anterior cranial fossa
         (2) Fistula of temporal bone
         (3) Fistula of middle cranial fossa through sphenoid sinus
      (d) Presentation\textsuperscript{19,20}
         (1) Fluid initially may appear sanguineous
         (2) Unilateral or bilateral clear fluid
         (3) Discharge amount varies from drops to stream-like flow
         (4) Reservoir sign
            (i) Rush of fluid when patient brought from supine to upright with neck flexed
            (ii) Useful for collection of diagnostic samples
      (5) Anosmia\textsuperscript{19}
         (i) Inability to perceive odor
         (ii) Present in 80\% of cases or rhinorrhea and only 5\% in TBIs
      (6) Target sign or halo effect\textsuperscript{19,21}
         (i) CSF will migrate further when CSF/blood applied to filter paper
            1. Apparent on pillowcase or sheets
         (ii) Bull’s eye stain appearance
      (7) Battles sign
         (i) Periorbital ecchymosis
ii) Otorrhea
(a) 28% of CSF leaks\textsuperscript{18}
(b) CSF leak through ear
   (1) Tympanic membrane may be intact or ruptured\textsuperscript{22}
      (i) Healing of tympanic membrane occurs within 1 week in \textasciitilde{80}\%\textsuperscript{23}
(c) Origins of leak
   (1) BSF involving temporal bone\textsuperscript{22}
(d) Presentation\textsuperscript{21,23}
   (1) Clear fluid draining from ear
   (2) Conductive hearing loss
      (i) 20% still present 7 years post trauma
   (3) Sensation of fluid or bubbles in ear
   (4) Hemotympanum
      (i) Presence of blood in tympanic cavity of middle ear
   (5) Battles sign
      (i) Retroauricular ecchymosis

C) Diagnosis of CSF leaks
i) High clinical suspicion of CSF leak in patients with skull fractures\textsuperscript{24}
   (a) Prompt recognition is key for instituting treatment and preventative measures\textsuperscript{9,21}
   (b) Potential to be overlooked due to nature of concomitant issues
ii) Diagnostic markers can confirm presence of CSF leak\textsuperscript{25}
   (a) Produced in CSF and when present in sample indicate presence of CSF
      (1) Beta-2 transferrrin
      (2) Beta-trace protein
iii) Confirm presence of concomitant fractures with imaging
   (a) Computed tomography (CT) scan
   (b) Formerly, X-ray

D) Incidence of CSF leak
i) 1-3\% of all TBIs\textsuperscript{5,16,22}
ii) 9 - 11\% of penetrating head injuries\textsuperscript{4,20}
iii) 10-30\% of BSF\textsuperscript{5,25}
iv) 36\% of Le Fort fractures\textsuperscript{20}

E) Time to presentation of CSF leak\textsuperscript{25}
   i) Acute
      (a) Within 2 days following injury – 50\%
   ii) Delayed
      (a) Within 1 week – 70\%
      (b) Within 3 months – 99\%
   iii) Sources of delayed presentation\textsuperscript{19,20}
      (a) Edema, inflammation, hematoma obstructing flow
      (b) May appear in times of increased intracranial pressure (ICP)
F) Duration of CSF leak
   i) Temporary
      (a) Less than 24 hours
   ii) Persistent
      (a) Present greater than 7 days
      (b) Characteristics of injury which prevent arachnoid mesh from sealing to dura
          (1) Fracture site mobility
          (2) Disrupted blood supply
          (3) Infections
   iii) Intermittent
      (a) Soft tissue or brain can obstruct flow

G) Treatment of CSF leak with skull fractures
   i) Reduction and fixation of facial fractures as appropriate
      (a) Stabilize fracture and prevents disruption of dura by reducing movement of facial skeleton
      (b) Facilitate body’s natural repair of anterior fossa CSF leak
   ii) Conservative treatment
      (a) Facilitate spontaneous resolution of CSF leak
          (1) Adhesion formation and granulation from local inflamed meninges
          (2) Mucosal swelling, local fibrosis, regenerated nasal mucosa
          (3) Dura mater dose not regenerate
      (b) Strict CSF precautions
          (i) Bed rest
          (ii) Avoid: nose blowing, Valsalva maneuvers, straws, incentive spirometer
              1. To prevent increase intracranial pressure
          (2) Head elevation
              (i) At least 15º
              (ii) To prevent negative gradient allowing ascending path for bacteria between intracranial and paranasal sinus cavities
   (c) Duration of treatment is controversial
      (1) Typically pursued for 1 week
   (d) Spontaneous resolution outcomes
      (1) Within 3 days in 40% of all cases
      (2) Within 1 week in 70% of rhinorrhea
      (3) Within 10 days in 85% of rhinorrhea
      (4) Ultimately in 98% of rhinorrhea
      (5) Otorrhea ceases spontaneously in nearly all cases
      (6) Spontaneous closure higher with temporal bone fractures than BSF
iii) CSF diversion
(a) If conservative treatment fails\textsuperscript{25}
   (i) Typically after 1 week\textsuperscript{29}
(b) Treatment options
   (1) Temporary CSF drainage device placed
      (i) Lumbar drain
      (ii) External ventricular drain (EVD)
      (iii) Duration less than 7 days due to increased infection risk
iv) Surgical management\textsuperscript{4,16}
(a) Employed for definitive closure of CSF leak
   (1) Failure of conservative management and CSF diversion
(b) Approaches
   (1) Advances in neurosurgical approaches from open craniotomies to endoscopic procedures
   (2) Surgical approach and graft type used to repair leak depends on individual clinical scenario
      (i) Based on force of impact, location of fistula, temporal relationship between the leak and traumatic event
      (ii) Endoscopic endonasal approach preferred
      (iii) Transcranial approach, extracranial approach, suprasinus transfrontal approach also available
(c) Outcomes\textsuperscript{25}
   (1) 75-100% success rate
V) CNS Infections\textsuperscript{4,20,22,30}
A) CSF fistulas allow direct access of nasopharyngeal and middle ear flora to the subarachnoid space
B) Pathogens\textsuperscript{30,31}
   i) Most common: \textit{Streptococcus pneumoniae, Haemophilus influenzae}
   ii) Less common: gram-negative, more resistant pathogens
C) Can appear within hours or up to years after injury\textsuperscript{4,19,24}
   i) Median onset 5-13 day
D) Risk factors for meningitis
   i) CSF leaks
      (a) Not associated with severity of leak or size of dural tear\textsuperscript{19,20}
      (b) Rhinorrhea increases risk 23-fold\textsuperscript{5}
      (c) Otorrhea increases risk 9-fold
      (d) Persistent leaks increase risk 9-fold\textsuperscript{16,24,28,32,33}
         (1) Improper healing or traumatic encephalocele
   ii) Pneumocephalus increase risk up to 4-fold\textsuperscript{11,16}
iii) Fracture types
(a) Penetrating fractures\textsuperscript{14}
   (1) Compound fractures with skull depressed deeper than thickness of cranium\textsuperscript{12}
   (2) Incidence of infection \( \sim \) 10\%\textsuperscript{34}
(b) Frontobasilar fractures proximal to midline\textsuperscript{33}
(c) Fracture displacement > 1 cm
iv) GCS < 8\textsuperscript{29}
(a) Associated with severity of injury and increased utilization of invasive interventions
v) Surgical interventions are associated with a 5-fold increase risk retrospectively\textsuperscript{5}
(a) Craniotomies\textsuperscript{12}
   (1) Incidence 0.8-1.5\%
      (i) Risk associated with concomitant infection at site of incision and duration of surgery greater than 4 hours
(b) EVDs
   (1) Incidence 4-17\%
      (i) Increased risk associated with colonization of catheter at time of surgery

**Figure 3. Incidence of Meningitis Associated with CSF Leaks in Literature**\textsuperscript{10,17,22,24, 26,27,30-43,46,49,50}
E) Incidence
   i) 0.2-17.8% of TBI \textsuperscript{5,11}
   ii) When CSF leak is present\textsuperscript{5,25}
      (a) Range: 0-52%
      (b) Median: 4.24%,
      (c) Rhinorrhea: 7-38%
      (d) Otorrhea: 2.6%
   iii) Penetrating injury with CSF leak: 36\%\textsuperscript{22}
      (a) 1.7\% without CSF leak
   iv) 12-50\% of cases are associated with recurrence\textsuperscript{35}
F) Mortality\textsuperscript{6,20}
   i) Early studies found morbidity and mortality rates of 50\% and 25\% respectively for intracranial infections following CSF rhinorrhea
   ii) Recent literature suggests posttraumatic meningitis is associated with \sim 10\% mortality rate
VI) Role of antibiotic prophylaxis\textsuperscript{24}
   A) Early publications emphasized importance of antibiotic use as a means of reducing meningitis
      i) Advocated for patients who presented with CSF leak or pneumocephalus
      ii) Recommended duration of prophylaxis 5-7 days after cessation of CSF leak
      iii) Recommendation was based on perceived or theoretical risk of infection and experience of authors
   B) Proposed mechanism of benefit\textsuperscript{48,49}
      i) Antibiotics maintain sterility of CSF until defect in dura closes spontaneously or is surgically corrected
      ii) Antibiotics may eradicate bacterial colonization in nasopharynx, nasal sinuses, and aural canal

\underline{Literature Review}

C) 24 studies evaluating incidence of meningitis in patients with CSF leak
   i) 19 evaluate the role of antibiotic prophylaxis
   ii) Literature dating back to 1942

\textbf{Figure 4. Role of Antibiotics}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{antibiotics.png}
\caption{Position on Antibiotic Prophylaxis in Literature}
\end{figure}
D) Conflicting meta-analysis published\textsuperscript{18,49}

i) Brodie et al. 1997
   (a) Objective: determine efficacy of antibiotic prophylaxis in CSF leaks
   (b) Population: 6 studies involving 324 patients
      (1) Included all articles with case series and sufficient data to allow evaluation
      (2) Findings
         (i) 237 patients received prophylactic antibiotics and 87 did not
         (ii) Overall incidence of meningitis: 15/234 (6.4%)
            1. Antibiotic prophylaxis: 6/237 (2.5%)
            2. Inadequate/no antibiotic prophylaxis: 9/87 (10%)
            3. Associated with p value=0.006
      (3) Conclusion: meningitis rate was significantly lower in patients who received antibiotic prophylaxis

ii) Villalobos et al. 1998
   (a) Objective: determine efficacy of antibiotic prophylaxis in patients with BSF
      (1) Evaluated CSF leaks as a secondary endpoint
   (b) Population: 12 studies involving 1241 patients
      (1) CSF leak: 9 studies involving 547 patients
   (c) Findings in patients with CSF leaks
      (1) 297 received prophylactic antibiotics and 250 did not
         (i) 6 studies with 179 patients with either rhinorrhea or otorrhea were evaluated
         (ii) Overall incidence of meningitis 63/547 (11.5%)
            1. Antibiotic prophylaxis: 29/297 (9.7%)
            2. Inadequate/no antibiotics: 34/250 (13.6%)
            3. Common OR 1.34 (CI 0.75-2.41)
      (d) Concluded antibiotic prophylaxis after BSF does not appear to decrease risk of meningitis

VII) Primary Literature

<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Objective</strong></td>
<td>Investigate incidence of meningitis, morbidity and mortality with adequate and inadequate antibiotic prophylaxis</td>
</tr>
<tr>
<td><strong>Trial design</strong></td>
<td>Retrospective, single center review at teaching hospital in Glasgow</td>
</tr>
</tbody>
</table>
| **Patients** | Inclusion: skull fracture with associated CSF leak from 1943-1972  
Exclusion: not specified |
| **Outcomes** | Incidence of meningitis, morbidity and mortality |
| **Methods** | Adequate prophylaxis: penicillin 500 mg PO QID and sulfadimidine 500 mg PO Q6H from time of injury until 1 week after CSF leak cessation  
Inadequate prophylaxis: those not meeting above criteria  
Diagnostic criteria: not specified for skull fractures, CSF leak, or meningitis  
Follow up: clinic visits, postal query, reviewing cases of meningitis at hospital; for up to ten years |
n=155
- Referred for neurosurgical care: 141/155
- CSF leak associated with fracture: 108/155
- Surgical repair of rhinorrhea: 65/118
- Le Fort fractures: all received antibiotic prophylaxis, incidence not specified

<table>
<thead>
<tr>
<th></th>
<th>Adequate Prophylaxis n=95</th>
<th>No Adequate Prophylaxis n=54</th>
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</thead>
<tbody>
<tr>
<td>Rhinorrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>76</td>
<td>42</td>
</tr>
<tr>
<td>Meningitis leak ≤ 1 week</td>
<td>0 (0%)</td>
<td>7 (17%)*</td>
</tr>
<tr>
<td>Otorrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>Meningitis</td>
<td>1 (5%)</td>
<td>5 (41.7%)*</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>2/155 (3%)</td>
<td></td>
</tr>
<tr>
<td>Attributable</td>
<td>0/15 (0%)</td>
<td></td>
</tr>
<tr>
<td>Morbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anosmia</td>
<td>Majority</td>
<td></td>
</tr>
<tr>
<td>Recurrent rhinorrhea</td>
<td>4/124</td>
<td></td>
</tr>
<tr>
<td>Pathogens</td>
<td>Streptococcus pneumonia n=5, coliforms n=1, no growth n=5</td>
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</table>

* p ≤0.05
- Increased incidence of meningitis associated with otorrhea if fracture was associated with middle fossa (p=0.01)
- All patients with meningitis recovered satisfactorily

**Authors’ conclusions**
- The inference is clear: all cases of CSF otorrhea should receive adequate antibiotic prophylaxis from time of injury until 1 week after the leak has ceased.
- The benefit of adequate chemotherapy in protecting patients from meningitis in patients with rhinorrhea has been demonstrated.

**Critique**

**Strengths**
- Large patient population
- Majority of fractures associated with middle or anterior fossa
- Morbidity and mortality were examined as endpoints

**Limitations**
- Temporal bias: variations in surgical procedures, CSF precautions, antibiotic selection, prevalence of resistant organisms
- Included pre-existing cases of meningitis
- High incidence of meningitis with otorrhea
- Unknown exposure to antibiotics in patients receiving inadequate prophylaxis
- Incidence of meningitis in rhinorrhea arm no longer associated with adequate or inadequate prophylaxis following first week
- Extensive referral from outside hospitals
- Unknown baseline characteristics
- Statistical analysis used not specified
- Lack of specification of diagnostic techniques for fractures, CSF leak, meningitis

**Take home points**
- Results favored use of antibiotic prophylaxis
- Questionable validity
- Broad spectrum of antibiotics and extended duration of treatment
**Objectives**

Primary: determine efficacy of antibiotic prophylaxis in treatment of BSF  
Post hoc: determine effect of prophylactic antibiotics on nasopharyngeal flora

**Trial design**

Combined retrospective and observational prospective at Denver General Hospital  
**Retrospective arm:** patients admitted with BSF, initiated on antibiotic prophylaxis (ampicillin, cephalothin, or other)  
**Prospective arm:** withheld antibiotic prophylaxis for BSF; antibiotic treatment was indicated if fever, neck stiffness, clinical deterioration

**Patients**

**Retrospective arm:** Adult patients with traumatic BSF who survived > 10 days  
**Prospective arm:** Adult patients with BSF admitted for 10 day observation, excluded patients who received antibiotics for other indications

**Outcomes**

Rates of CNS and other other infections, nasopharyngeal cultures on admission, day 5 and 10

**Methods**

First year: Antibiotic prophylaxis (ampicillin or cephalothin 1 g Q6H IV x 3 days or until 2 days after cessation of CSF leak then IM or PO antibiotics for duration of hospitalization  
**Posterior nasopharynx cultures:** Post hoc endpoint, randomized to receive either no antibiotic, ampicillin or cephalothin; obtained at hospital admission, day 5 and day 10  
**Follow up:** method unspecified

**Statistics**

- ANOVA  
- Fisher’s exact test  
- Chi-square

**Results**

<table>
<thead>
<tr>
<th>Prophylaxis (Retrospective)</th>
<th>No Prophylaxis (Prospective)</th>
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<tbody>
<tr>
<td>CNS infections</td>
<td>2 (12%)</td>
</tr>
<tr>
<td>Pathogens isolated</td>
<td>Resistant <em>E. coli</em> n=1, no growth n=1</td>
</tr>
<tr>
<td>Attributable mortality</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>Attributable morbidity</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>Mortality, overall</td>
<td>7.2%</td>
</tr>
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</table>

- n=129 with 136 BSF  
- n=40 with CSF leak  
- Follow up: 3-24 months  

Baseline characteristics:

- Treated group had increased incidence facial fractures and one compound depressed fracture  
- No antibiotic prophylaxis group had more patients unconscious for > 24 hours, CNS operations, prior medical illness  
- Prophylaxis: ampicillin: n=41 cephalothin: n=9 other: n=4
### Nasopharyngeal Cultures Results

<table>
<thead>
<tr>
<th>Antibiotic Exposure</th>
<th>Day 0</th>
<th>Day 5</th>
<th>Day 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (n=5)</td>
<td>Normal</td>
<td>Unchanged</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Cephalothin (n=3)</td>
<td>Normal</td>
<td>Gram-negative (n=2)</td>
<td>Gram-negative (n=2)</td>
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<tr>
<td></td>
<td></td>
<td>Increased normal (n=1)</td>
<td>Increased normal (n=1)</td>
</tr>
<tr>
<td>Ampicillin (n=2)</td>
<td>Normal</td>
<td>Gram-negative</td>
<td>Gram-negative</td>
</tr>
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</table>

Normal: *Streptococcus* and *Staphylococcus* sp.

Gram negative: resistant to antibiotic therapy

### Outcomes Associated with Antibiotic Administration

- Antibiotic administered
- Nasopharyngeal flora not sterilized
- Alteration of flora to resistant bacteria
- Alteration of potential pathogen

### Authors’ conclusions
- Antibiotics are ineffective in preventing CNS infections and in some cases, harmful.
- Antibiotics associated with more resistant, invasive and potentially pathogenic organisms in nasopharynx.
- Recommend close observation for early signs of meningitis and if present, start appropriate antibiotics.

### Critiques

**Strengths**
- Included observational prospective arm
- Post hoc investigation of antibiotic impact on nasopharyngeal flora

**Limitations**
- Not specific to those with CSF leak, x-ray confirmation of fracture was present in 14/129 patients
- Not adequately powered to determine no difference exists or more harm associated with antibiotics, limited number of patients with CSF leak in 2 year time frame
- Unknown demographic information; epidemiologic, fracture specific, time to onset/duration of CSF, role of CSF precautions, duration of leak, duration of antibiotics or length of hospitalization
- More selective criteria for the prospective portion

**Take home points**
- No benefit demonstrated with antibiotic prophylaxis
- Nasopharyngeal cultures demonstrated no sterilization of site
- Change from usual nasopharyngeal flora to gram-negative/resistant bacteria
Eljamel MS. Br J Neurosurg. 1993;7:501-505

**Objective**
Evaluate efficacy of antibiotic prophylaxis in patients with CSF leak prior to surgical dural repair

**Trial design**
Retrospective analysis of patients with CSF leaks who received adequate or inadequate antibiotic prophylaxis prior to surgical dural repair at Mersey Regional

**Patients**
**Inclusion:** adult patients with CSF fistula  
**Exclusion:** patients who received antibiotics for reasons other than CSF leak, from time of surgical dural repair forward

**Outcomes**
Meningitis, mortality, and pathogens isolated

**Methods**
Similar age, CSF leak type, duration of leak, presence/absence of skull fractures  
**Adequate antibiotic prophylaxis:** if started within 3 days of onset of CSF leak; penicillin 500 mg Q6H and sulphonamide 500 mg Q6H and continued for at least one week after CSF leak cessation  
**Meningitis diagnosis:** based on clinical signs and symptoms, confirmed by isolating pathogen or cytology of CSF  
**CSF leak:** confirmed surgically or post-mortem  
**Follow-up:** until surgical dural repair, death or 1990

**Statistics**
- Chi-square test with Yate’s correction  
- Two-tailed p values  
- Log rank  
- Kaplan-Meier

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<tr>
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<th>Adequate Prophylaxis</th>
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<tbody>
<tr>
<td></td>
<td>n=106</td>
<td>n=109</td>
</tr>
<tr>
<td>Facial fractures</td>
<td>52</td>
<td>26</td>
</tr>
<tr>
<td>Skull fractures</td>
<td>76</td>
<td>75</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>99</td>
<td>97</td>
</tr>
<tr>
<td>Duration CSF leak, mean</td>
<td>17 days</td>
<td>20 days</td>
</tr>
<tr>
<td>Pneumocephalus</td>
<td>31 (29%)</td>
<td>12 (11%)*</td>
</tr>
<tr>
<td>Meningitis, first week</td>
<td>7 (6%)</td>
<td>10 (9%)</td>
</tr>
<tr>
<td>Meningitis, per year</td>
<td>8 (8%)</td>
<td>13 (12%)</td>
</tr>
<tr>
<td>Meningitis, total</td>
<td>20 (19%)</td>
<td>36 (33%)</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>6</td>
<td>22</td>
</tr>
<tr>
<td>Gram-negative</td>
<td>3</td>
<td>0*</td>
</tr>
<tr>
<td>No pathogen isolated</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Survival free from meningitis, 1 month</td>
<td>86 (81%)</td>
<td>84 (77%)*</td>
</tr>
<tr>
<td>Mortality</td>
<td>20 (19%)</td>
<td>25 (22%)</td>
</tr>
</tbody>
</table>

*p value <0.05

**Baseline characteristics**
- Mean age 35 years old, majority male, with rhinorrhea and skull fractures  
- More patients in the prophylaxis arm had facial fractures and pneumocephalus  
- Majority of patients received antibiotic prophylaxis within 24 hours of injury  
- Mean follow-up 2.5 years
Critiques

**Strengths**
- Large population
- Specific to CSF leaks
- Fracture type specified
- Primary endpoint examining efficacy of antimicrobial prophylaxis
- Excluded patients receiving antibiotics for other indications

**Limitations**
- More pneumocephalus and facial fractures in antibiotic prophylaxis arm
- Mean duration of CSF leak 17-20 days
- Broad antibiotic coverage and extended duration of prophylaxis
- Unknown demographic information, mode of injury, incidence of penetrating or other fracture characteristics, number of patients receiving CSF diversion

**Authors’ conclusions**
- These data do not support routine use of antibiotic prophylaxis in patients with CSF leak
- It is ethically justifiable to withhold antibiotic prophylaxis in patients with CSF fistula until a prospective controlled double-blind trial has settled the question

**Take home points**
- No statistically significant in incidence of meningitis in a well-designed retrospective review

VIII) Limitations in literature

A) Lack of power of individual studies
   i) Infrequent incidence of CSF leaks
   ii) Even lower incidence of post-traumatic meningitis

B) Confounding factors in studies
   i) Retrospective
   ii) Lack of randomization

C) Temporal bias
   i) Treatment of CSF leak
      (a) CSF precautions
      (b) CSF diversions and surgical management
   ii) Antibiotic availability
   iii) Alteration in pathogens

IX) Conclusions

A) Overall the data supporting the use of antibiotic prophylaxis to prevent meningitis in post traumatic CSF leaks is of poor quality

B) Convincing evidence to support antibiotic prophylaxis is lacking

C) Randomized, prospective, multicenter trials are needed to provide further evidence

D) Harm has been demonstrated with administration of prophylactic antibiotics
X) Recommendation
   i) Antibiotic prophylaxis in skull fractures with CSF leak not recommended to prevent meningitis
      (a) Closed fractures of basilar skull or skull vault
   ii) Concomitant conditions may benefit from antibiotic prophylaxis
      (a) Le Fort facial fractures, open/penetrating fractures, compound/depressed skull fractures
      (b) Potential benefit in high-risk subsets of patients with multiple risk factors cannot be fully excluded based on current level of evidence
         (1) Lack of randomization
         (2) High risk patients typically received antibiotic prophylaxis
      (c) Antibiotic prophylaxis when selected should cover pathogens most likely to colonize patient’s nasopharynx
      (d) Duration should be one week after CSF leak resolution
   iii) Regardless of presence of antibiotic prophylaxis, patients should be monitored for signs and symptoms associated with meningitis
      (a) If suspected, empiric treatment of meningitis should be promptly initiated
         (1) Obtain cultures
         (2) Vancomycin + cefepime
References

### Appendix A

#### Glasgow Coma Scale (GCS)

<table>
<thead>
<tr>
<th>Score</th>
<th>Eye opening</th>
<th>Verbal response</th>
<th>Motor response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>None</td>
<td>No movements</td>
</tr>
<tr>
<td>2</td>
<td>Open to painful stimulation</td>
<td>Incomprehensible sounds</td>
<td>Extends to pain</td>
</tr>
<tr>
<td>3</td>
<td>Open to voice</td>
<td>Inappropriate words</td>
<td>Abnormal flexion to pain</td>
</tr>
<tr>
<td>4</td>
<td>Open spontaneously</td>
<td>Confused, disoriented</td>
<td>Withdrawals to pain</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>Oriented, converses</td>
<td>Localizes to painful stimulus</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>Obeys commands</td>
</tr>
</tbody>
</table>

#### Severity of TBI based on GCS

<table>
<thead>
<tr>
<th>Severity</th>
<th>GCS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>13-15</td>
</tr>
<tr>
<td>Moderate</td>
<td>9-12</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;8</td>
</tr>
</tbody>
</table>