The incidence of meningitis occurring after head trauma ranges from 0.2 to 17.8%. Several studies have shown that the incidence of bacterial meningitis following head trauma increases significantly in the presence of a skull base fracture or CSF leak. The reported incidence of meningitis after a basilar skull fracture varies from 9.2 to 17.8% and can be as high as 50% if CSF leakage is present.11,13,19

The incidence of pneumocephalus in cases of skull base fractures is also variable. Steudel and Hacker26 found evidence of intracranial air on 9.7% of CT scans in patients with acute head injury. In a study performed in our hospital (Ghodsi M, Nejat F, and Eftekhar B, unpublished data), 12% of patients with skull base fractures had pneumocephalus. Obviously, this rate partially depends on the resolution and quality of the CT scans.

The efficacy of prophylactic antibiotic agents in the setting of posttraumatic CSF leakage is controversial. Contrasting findings reported for two large studies in which metaanalyses were conducted reflect the general disagreement and lack of sufficient power of previous studies.3,27

It appears that some subsets of patients with traumatic CSF leakage are at greater risk for the development of meningitis. One possible reason for the inability of previous studies to demonstrate the efficacy of prophylactic antibiotic agents for the prevention of posttraumatic meningitis may have been related to these subsets of patients with specific risk factors.

To determine the efficacy of prophylactic antibiotic therapy in patients with CSF fistulae or skull base fractures, different risk factors should be considered. One of these risk factors may be the severity of the head injury. Some physicians prescribe prophylactic antibiotic agents for patients with severe head injury in whom immunosuppression is common and bacteremia frequently occurs.20

The risk of bacterial meningitis appears to be greater when the rhinorrhea or otorrhea continues beyond 7 days posttrauma.21,24 In their retrospective study, Friedman, et al.,8 concluded that prophylactic antibiotic therapy may be effective in those patients whose CSF leaks persist longer...
than 24 hours. Another factor that may increase the risk of meningitis is concomitant pneumocephalus (Ghodsi M, Nejat F, and Eftekhar B, unpublished data).20

Although there are some centers in which prophylactic antibiotic therapy is suggested in cases of intracranial pneumocephalus, there has been no published clinical trial that specifically addresses this issue.

The objective of this prospective study was to compare the efficacy of prophylactic antibiotic therapy for the prevention of meningitis in patients with acute traumatic pneumocephalus.

**Clinical Material and Methods**

**Patient Population**

This study was approved by the research ethics committee of Tehran University. We studied 109 patients with traumatic pneumocephalus who were admitted to Sina Hospital between June 2001 and September 2003.

The entry criterion for this study was traumatic pneumocephalus verified by a CT scan of the brain. Patients who received antibiotic therapy for other reasons; individuals with a penetrating traumatic brain injury or open skull fractures; patients who were surgically treated for any reason; patients with intradurally located air, intraparenchymal locations were not differentiated from extraparenchymal locations. Radiological findings of skull base fractures were not differentiated according to the exact location of the fracture.

The diagnosis of meningitis was based on CSF findings in patients with compatible clinical findings. In cases in which there were relative contraindications for lumbar puncture (accompanying intracranial hemorrhage and clinically suspected raised intracranial pressure), the diagnoses were based on clinical findings and ruling out other causes of infections. The clinical findings included fever, meningismus, and a concomitant decreased level of consciousness.

**Study Design**

This prospective randomized study was conducted at a single center. We observed our patients in the hospital until occurrence of meningitis or at least 5 days posttrauma. In the event a concomitant CSF leakage occurred requiring close observation in the hospital, the patient was hospitalized until recovery from the leakage. After discharge the patients were followed up until 1 month posttrauma.

The patients were divided into two groups: one in which prophylactic antibiotic therapy was given (PAT+ group) and another in which it was not (PAT− group), according to a list of on-call physicians. The list did not have any predictable sequence.

In the PAT+ group 53 patients were placed on a prophylactic antibiotic medication regimen (ceftriaxone, 1 g given twice a day). No placebos were given to the patients in control (PAT−) group and physicians caring for the patients were not blinded to the regimen in a particular patient. Corticosteroid agents were not prescribed for patients for any reason. The antibiotic therapy was continued for 5 days. In the case of meningitis, an appropriate course of antibiotics was continued until the patient’s recovery.

The volume of air was roughly calculated on the CT scan by using the formula ABC/2, in which A is the greatest diameter of the pneumatocele found on the CT scan, B is the diameter that is 90˚ to A, and C is the approximate number of CT slices in which the pneumatocele is seen multiplied by the slice thickness.15

Intracranial hemorrhages included subarachnoid hemorrhage, epidural and subdural hematomas, and cerebral contusion. Specific types of hemorrhages were not differentiated. In patients with intradurally located air, intraparenchymal locations were not differentiated from extraparenchymal locations. Radiological findings of skull base fractures were not differentiated according to the exact location of the fracture.

**Statistical Analysis**

Categorical variables were compared using a chi-square test, and the Student t-test was used to compare continuous variables between groups. A logistic regression with an adjustment for other possible risk factors for meningi-
Antibiotic prophylaxis for traumatic pneumocephalus

### Consideration of factors that might lead to the development of meningitis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio</th>
<th>p Value</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>prophylactic antibiotics therapy</td>
<td>0.853</td>
<td>0.739</td>
<td>0.340–2.143</td>
</tr>
<tr>
<td>CSF rhinorrhea</td>
<td>13.067</td>
<td>0.000</td>
<td>3.257–51.732</td>
</tr>
<tr>
<td>CSF rhinorrhea (adjusted for air &gt;10 ml)</td>
<td>11.178</td>
<td>0.003</td>
<td>2.293–54.485</td>
</tr>
<tr>
<td>CSF rhinorrhea (adjusted for intradural air)</td>
<td>7.293</td>
<td>0.015</td>
<td>1.465–36.297</td>
</tr>
<tr>
<td>CSF rhinorrhea (adjusted for intracranial hemorrhage)</td>
<td>12.955</td>
<td>0.002</td>
<td>2.526–66.442</td>
</tr>
<tr>
<td>CSF rhinorrhea (adjusted for intradural air, air &gt;10 ml &amp; intracranial hemorrhage)</td>
<td>7.082</td>
<td>0.030</td>
<td>1.214–41.316</td>
</tr>
<tr>
<td>intradural air (adjusted for air &gt;10 ml)</td>
<td>9.125</td>
<td>0.000</td>
<td>3.225–25.816</td>
</tr>
<tr>
<td>intradural air (adjusted for rhinorrhea)</td>
<td>4.375</td>
<td>0.015</td>
<td>1.332–14.369</td>
</tr>
<tr>
<td>intradural air (adjusted for intracranial hemorrhage)</td>
<td>6.777</td>
<td>0.001</td>
<td>2.261–20.316</td>
</tr>
<tr>
<td>intradural air (adjusted for intracranial hemorrhage)</td>
<td>7.247</td>
<td>0.001</td>
<td>2.352–22.324</td>
</tr>
<tr>
<td>intradural air (adjusted for air &gt;10 ml, intracranial hemorrhage, &amp; rhinorrhea)</td>
<td>2.069</td>
<td>0.302</td>
<td>0.520–8.231</td>
</tr>
<tr>
<td>air &gt;10 ml (adjusted for intradural air)</td>
<td>4.873</td>
<td>0.004</td>
<td>1.622–14.747</td>
</tr>
<tr>
<td>air &gt;10 ml (adjusted for rhinorrhea)</td>
<td>2.900</td>
<td>0.160</td>
<td>0.695–8.987</td>
</tr>
<tr>
<td>air &gt;10 ml (adjusted for intracranial hemorrhage)</td>
<td>4.788</td>
<td>0.012</td>
<td>1.412–16.234</td>
</tr>
<tr>
<td>air &gt;10 ml (adjusted for intracranial hemorrhage, intradural air, &amp; air &gt;10 ml)</td>
<td>5.062</td>
<td>0.016</td>
<td>1.349–18.992</td>
</tr>
<tr>
<td>intracranial hemorrhage</td>
<td>3.590</td>
<td>0.084</td>
<td>0.840–15.332</td>
</tr>
<tr>
<td>intracranial hemorrhage (adjusted for rhinorrhea)</td>
<td>8.400</td>
<td>0.000</td>
<td>3.047–23.158</td>
</tr>
<tr>
<td>intracranial hemorrhage (adjusted for intradural air)</td>
<td>8.356</td>
<td>0.000</td>
<td>2.713–25.733</td>
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<tr>
<td>intracranial hemorrhage (adjusted for intradural air, air &gt;10 ml)</td>
<td>6.620</td>
<td>0.001</td>
<td>2.151–20.372</td>
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<tr>
<td>intracranial hemorrhage (adjusted for air &gt;10 ml)</td>
<td>10.903</td>
<td>0.000</td>
<td>3.265–36.401</td>
</tr>
<tr>
<td>intracranial hemorrhage (adjusted for rhinorrhea, intradural air, &amp; air &gt;10 ml)</td>
<td>9.084</td>
<td>0.001</td>
<td>2.502–32.984</td>
</tr>
</tbody>
</table>

*Statistical significance was set at a probability value less than 0.05.

The data were analyzed using Intercooled STATA for Windows, Version 6 (STATA Corp., College Station, TX).

## Results

The mean age of the study population was 34.2 ± 13.6 years; 93.6% of patients were male and the overall meningitis rate was 20.1%. In all cases of meningitis the patients were older than 15 years.

In the majority of patients, there were clinical signs of the skull base fracture, including CSF rhinorrhea, rhinorrhagia, CSF otorrhea, otorrhagia, periorbital hematoma, or battle sign (retromastoid hematoma). There was one patient in whom there was a radiological sign of a skull base fracture, or intracranial hemorrhage. Even if we put aside cases in which there was a clinical diagnosis of the skull base fracture, or air volume, presence of CSF rhinorrhea, or CSF otorrhea, radiological sign of a skull base fracture, or intracranial hemorrhage. Even if we put aside cases in which there was a clinical diagnosis of meningitis, the difference between the rates of meningitis in the PAT+ and PAT− groups were not statistically significant (p = 0.9).

As shown in Table 3, the odds of developing meningitis in patients with CSF rhinorrhea, intradural air, air volume greater than 10 ml, or intracranial hemorrhage, relative to patients without these signs, were statistically significant. When we adjusted for these factors, altogether the odds of developing meningitis in patients with CSF rhinorrhea or intracranial hemorrhage remained statistically significant.

The odds ratios for the risk of meningitis, when adjusted for the length of hospitalization, was not statistically significant for variables other than the presence of CSF rhinorrhea.

Leakage of CSF stopped in less than 6 days in patients who received conservative treatment and there was no need for further surgical intervention for the control of CSF leakage.

## Discussion

### Pneumocephalus and the Mechanism of Meningitis

Pneumocephalus should be considered the equivalent of a CSF fistula. Although it is often difficult to identify an actual leak, the open communication that the air repre-
sent indicates that the patient is at risk for a central nervous system infection. A relatively minute quantity of air is not infrequently seen in patients suffering head injury, and the site of the leak may never be identified.20

Most cases of pneumocephalus are traumatic. When there is a skull base fracture and, particularly, when such a fracture involves the paranasal sinuses, mastoid air cells, or petrous temporal regions, air can enter the cranium. Lacerations of the dura mater enable the air to pass into the subarachnoid space or even into the ventricles without direct brain laceration.21

Although it is rational that the risk of developing meningitis should be higher in cases of skull base fractures or obvious CSF leakage with simultaneous pneumocephalus, there is no publication in which this issue is specifically addressed, and the role of prophylactic antibiotic mediation in the prevention of meningitis in these patients remains controversial.

Previous Studies

In a review of the pertinent literature we found that almost all the studies focused on CSF leakage and skull base fractures, and not on pneumocephalus. Patients with posttraumatic pneumocephalus are a subset of patients with an increased risk of meningitis, and the results of previous studies may not be completely applicable to them.

Another point in the interpretation and comparison of previous studies is the choice of antibiotic regimen (dosage and duration) and whether any regimen provides adequate prophylaxis. Considering the epidemiology of causative bacteria in cases of posttraumatic meningitis, the antibiotic regimen used in the present study appears to be suitable, although the results are not completely comparable to any previously used or other regimens.

One problem we encountered in our review of previous studies is the presence of confounding factors. One of the advantages of the present study is that the two groups were well balanced with respect to different characteristics.

Limitations of the Study

The nondiagnostic culture results in the PAT+ group seem to be acceptable, but such results in the PAT− group should be attributed to inefficient microbiological techniques and is one of the weaknesses of the present study. No antibiograms were obtained and thus we cannot comment on the sensitivity of the causative microorganisms to ceftriaxone in cases of meningitis. Use of classic methods of randomization could have enhanced the reliability of this study.

Analysis of the Results

This study shows that a prophylactic antibiotic agent (ceftriaxone, 1 g given twice a day) does not prevent the occurrence of meningitis in cases of traumatic pneumocephalus. The study also shows that we cannot claim that this regimen has any prophylactic effect in any subset of patients with traumatic pneumocephalus separated on the basis of GCS score, sex, age, intradural location of air, air volume, presence of rhinorrhea or otorrhea, radiological sign of skull base fracture, or intracranial hemorrhage.

The timing of the prescription of prophylactic antibiot-
Antibiotic prophylaxis for traumatic pneumocephalus

1st week posttrauma. One patient in whom meningitis developed 2 weeks after trauma was in the PAT group. This finding is partially in agreement with the results of Klastersky, et al., who described four of five patients in whom posttraumatic meningitis developed within 6 days posttrauma and one patient in whom it did not develop until 10 days postinjury; the latter patient had received prophylactic antibiotic therapy. Obviously, we cannot extrapolate the results of the present study to delayed posttraumatic meningitis occurring long after our follow-up period.

This study does not disclose any indication for keeping patients with traumatic pneumocephalus in the hospital for a longer period of close observation.

Conclusions

This study does not provide a basis to approve the efficacy of a prophylactic antibiotic agent (ceftriaxone) in the prevention of meningitis in patients with traumatic pneumocephalus after mild head injury. Cerebrospinal fluid rhinorrhea and intracranial hemorrhage may be considered primary risk factors and, in their absence, intradural location of air and air volume greater than 10 ml may be secondary risk factors for the development of meningitis in patients with posttraumatic pneumocephalus. Further studies in this area are warranted.

References

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