Antibiotic Prophylaxis for Penetrating Brain Injury

I. RECOMMENDATIONS
A. Standards
The available data are not sufficient to support a treatment Standard for the role of prophylactic antibiotics after penetrating brain injury (PBI).

B. Guidelines
The available data are not sufficient to support a treatment Guideline for this topic.

C. Options
Use of prophylactic broad-spectrum antibiotics is recommended for patients with PBI.

II. OVERVIEW
The risk of intracranial infection among patients with PBI is high because of the presence of contaminated foreign objects, skin, hair, and bone fragments driven into the brain along the missile track. The presence of air sinus wounds or cerebrospinal fluid (CSF) fistulae may further increase the risk of infection. Since sulfa drugs were introduced just prior to World War II, all published studies have been of patients who received antibiotics after PBI. After World War II, the only studies of the infection rate in PBI are those in which all patients received prophylactic antibiotics. These data have been compared with preantibiotic series prior to World War II. Some conclusions may, in addition, be drawn from Class I and Class II studies that address the use of prophylactic antibiotics in clean elective neurosurgical procedures. Although the data on clean cases do not apply directly to the PBI population, their analysis can justifiably support recommendations for PBI patients at the level of Option.

This section of the Guidelines is directed exclusively at infection prophylaxis, meaning when antibiotics are begun early after injury before there is any evidence of clinical infection. The management of established infections (e.g., wound infection, meningitis, or cerebral abscess) is not specifically addressed here.

III. PROCESS
A MEDLINE search from January 1966 to January 2000, using the search terms wounds, gunshot, and brain injuries or head injuries, when limited to human subjects, identified 382 articles. Eighty-eight articles were rejected on the basis of clearly irrelevant titles. An additional 33 articles were then pulled from the bibliographies of reviewed articles. The primary selection process, therefore, identified 327 articles for further review. Two independent reviewers read the abstracts of all 327 and selected 65 for further inclusion. Articles were rejected on the basis of relevance to the topic (e.g., pediatric population, case reports, irrelevance to project, and series of less than 10 subjects with no other unique reasons for inclusion). The 65 articles were then read in detail. During this process, articles from the bibliographies of the 65 originally selected articles were considered and rejected or added to the active list using the above algorithm. Of these 65 articles, 14 were found appropriate and analyzed in detail for this section of the Guidelines. Because in these 14 articles, antibiotics were always given prophylactically, additional articles were selected from the World War I–era literature for comparison. These additional articles were selected, using the same criteria as stated in the introduction of the Office of the Surgeon General’s World War II neurosurgical text.

IV. SCIENTIFIC FOUNDATION

Historic Comparison
The infection rate in the preantibiotic era during World War I was reported by Whitaker to be 58.8%. In World War II, several articles compare the use of local sulfa powder alone and with the addition of penicillin, given either locally or systemically. The opportunity for these studies was created by the delayed availability of penicillin to different theaters of war throughout the conflict. The reported infection rate with local application of sulfa powder and/or parenteral sulfonamide therapy in these studies was 21% to 31%. When penicillin was added to this regimen in these studies, the clinical infection rate dropped to 5.7% to 13%. A single report challenges this assertion. In Maltby’s 200 patients, he states “as far as could be determined from the overseas records,” no overall difference in the drug therapy was apparent in the cases showing infection. However, no statistics or case numbers are offered in this article to defend the position taken. The most recent military and civilian series using a variety of more sophisticated antibiotic regimens report clinical infection rates between 4% and 11%. The reported risk of brain abscess has dropped from 8.5% in World War II to 1.6% to 3.1% in more recent series.

It is recognized that other factors, such as surgical and management advances, may be responsible for these improved infection rates. For example, in World War I Dr. Cushing emphasized closure of the galea. During World War II, this concept was extended to include a vigorous emphasis on dural closure. The World War II series, however, provides a direct comparison of the results when the...
only significant variable among groups appears to be the addition of penicillin. These data provide support for our recommendation to use antibiotics.

**Infection Rate**

The rate of infection reported in series of patients with PBI varies directly with the use of broad-spectrum antibiotics early in the management of these patients. It ranges from 1% to 59%, as seen in the reported infection rates in civilian and military series in Table 1 that tracks the rate to the introduction of antibiotics as used over the past six decades.

It should be noted that in all these series subsequent to 1945, the patients routinely received antibiotic prophylaxis. In a study of data collected on 1,221 patients from the Vietnam Head Injury Study, 37 cases of abscess were found (3%), 6 of which were incidentally discovered during postmortem examinations of patients dying of unrelated causes.5

A retrospective study of 600 cases from the Lebanese conflict between 1981 and 1988 found intracranial infection in 30 patients (5%). Aarabi,11 reporting on the final postsurgical outcome in 435 patients who sustained missile head wounds during the Iran-Iraq War, report the presence of meningitis in 25 of 71 patients who died from their injuries. A comparative study of bacteriologic contamination and infection rates between primary and secondary exploration in 161 patients with missile head wounds reports meningitis in six cases and the development of a cerebral abscess in two cases. Brandvold et al.19 and Levi et al.,20 reporting on penetrating cranial injuries sustained during the Lebanese conflict, report meningitis in 8% of patients and the development of an abscess in 1%.

The incidence of intracranial infection is lower (between 1% and 5%) in series of patients with civilian PBI. Benzel et al.12 reported no deep intracranial infections such as meningitis or abscess in a series of 120 civilian gunshot wounds to the head with penetration of the dura. Three superficial wound infections were noted in the 54 survivors from this series, all of whom received prophylactic antibiotics. The reports in the civilian literature commonly report the development of brain abscesses after rare causes of injury, such as pool or snooker cues,21,22 pencils,23–26 or a tree branch,27 which may represent a different bacteriologic or fungal risk.

The majority of intracranial infections after PBI occur within a relatively short period after injury (55% within 3 weeks; 90% within 6 weeks).28 However, in rarer instances, the development of a cerebral abscess may occur after many years, even 15 years after injury.29

**Bacteriologic Culture**

Relatively few published studies30 report on the results of bacteriologic studies of removed fragments or on studies of causative agents of infection in PBI. In Vietnam, Carey et al.31 reported that 45% of the fragments removed and cultured were positive, mainly with gram-positive bacteria. Similarly, Hagan,32 in a study of 506 patients with penetrating brain wounds in the Vietnam War, showed isolation of *Staphylococcus epidermidis* from removed fragments in two thirds of the patients, the others showing a variety of gram-positive and gram-negative organisms. Aarabi,10 reporting on data from the Iran-Iraq War in 1983 to 1984, found positive cultures in approximately 20% of samples, which included swabs from the scalp wound, brain, and bone fragments. Cultures from the wound mainly demonstrated *Staphylococcus*, *Acinetobacter*, and *Streptococcus*. Cultures from removed bone fragments mainly demonstrated *Staphylococcus*, and cultures from removed brain tissue grew *Staphylococcus*, *Acinetobacter*, *Escherichia coli*, *Klebsiella*, and *Enterobacter*. A subsequent investigation of 105 patients with proven intracranial infections from the same conflict yielded positive cultures for gram-negative organisms in 45% and gram-positive organisms in 15%. *Klebsiella pneumoniae* and *Staphylococcus aureus* were the predominant organisms.4 Notably, none of these authors describe results of standardized anaerobic culture studies and do not
Staphylococcus aureus was cultured in 22 cases, β-hemolytic streptococci in 5, and Clostridium in 6 cases, but only a few patients developed signs of intracranial infection. In the civilian literature, data on causative organisms are less commonly reported. Case reports on patients with brain abscesses attributable to rare causes mention Staphylococcus aureus, Clostridium, Bacteroides, and Moraxella catarrhalis.

Although the main causative agent appears to be Staphylococcus, gram-negative bacteria also frequently cause intracranial infection after PBI. When investigated appropriately, Clostridium or other anaerobic organisms may be found. The data from the microbiologic studies would support the administration of broad-spectrum antibiotics, if antibiotics are given.

**Risk Factors**

The risk factors for infection were identified as CSF leaks, air sinus wounds, or wound dehiscence. Arendall and Meirowsky report an intracranial infection rate of 29% in the presence of air sinus wounds, and Meirowsky et al. report an infection rate of 49% in 101 patients with CSF fistulae (Table 2). Taha et al. further point out a relation between CSF leaks with and without retained bone fragments and intracranial infection. In a recent study of 964 casualties from the Iran-Iraq War performed retrospectively, multivariate analysis strongly implicated CSF leaks, involvement of air sinuses, injuries crossing the midline, and transventricular injury as independent predictors of infectious complications. A suspected causal relationship between retained bone or metal fragments and infection has been one of the main reasons for advocating extensive debridement. This has been challenged by reports from foreign military services, which have chosen less aggressive surgical procedures without removal of all foreign objects. They report an incidence of intracranial infections not notably different from earlier reports in which extensive debridement was performed. One prospective study was conducted of 148 patients from the Southeastern Anatolia conflict (1992–1994) for whom there was no vigorous search for fragments at the time of initial surgery and no reoperations for retained fragments (as revealed on routine follow-up computed tomographic scan evaluations). The overall infection rate in that study was 9%. Four percent of patients with retained bone fragments became infected versus 7% without fragments. Data on the relationship between infection and CSF leaks and retained bone (Table 3) suggest that other associated risk factors, such as the presence of a CSF leak, are probably much more predictive of subsequent infection. Since 70% of infections in this series occurred around retained bone fragments, it is more likely that the retained bone became clinically infected as a result of a CSF leak.

**Use of Antibiotics**

Considerable variability exists in the antimicrobial agents used as prophylaxis in PBI. In a survey on American neurosurgical practice by Kaufman et al., 87% of responding surgeons used a cephalosporin, 24% used chloramphenicol, 16% used penicillin, 12% used an aminoglycoside, and 6% used vancomycin and, less frequently, erythromycin, mitomycin, and tetracycline.

For clean elective neurosurgical procedures, a number of Class I and Class II studies have been performed on the use of prophylactic antibiotics. These studies, summarized by Haines, showed a statistically significant reduction in postoperative infections with the use of perioperative antibiotics.

**Table 2** Risk Factors for Infection

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Authors, Year</th>
<th>Treatment</th>
<th>Rate of Infection (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF Leak</td>
<td>Taha et al., 1991</td>
<td>Broad-spectrum antibiotics</td>
<td>49</td>
</tr>
<tr>
<td>Air sinus penetration</td>
<td>Arendall and Meirowsky, 1983</td>
<td>Broad-spectrum antibiotics</td>
<td>29</td>
</tr>
<tr>
<td>Retained bone fragments</td>
<td>Taha et al., 1991</td>
<td>Broad-spectrum antibiotics</td>
<td>2</td>
</tr>
</tbody>
</table>

**Table 3** Rate and Number of Patients with Clinical Infection with Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>+ Bone %</th>
<th>− Bone %</th>
<th>Total Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ CSF leak</td>
<td>85</td>
<td>21</td>
<td>15 of 32</td>
</tr>
<tr>
<td>− CSF leak</td>
<td>4</td>
<td>0.6</td>
<td>4 of 371</td>
</tr>
</tbody>
</table>

+, with; −, without.
antibiotic prophylaxis. Similar results have been shown in a meta-analysis by Velanovich. If Class I and II evidence supports the use of antibiotics in a clean wound made under controlled conditions, the use of antibiotics in a grossly contaminated penetrating wound appears justified. In contrast to the clean wounds in operative procedures that use only perioperative prophylactic antimicrobial treatment, the presence of potentially contaminated debris in PBI favors a treatment of longer duration.

V. SUMMARY

Although there is a paucity of evidence regarding causative agents of infection in PBI, those data that are available suggest a wide variety of organisms may act as agents of infection in these patients. This diversity supports the use of a broad-spectrum antibiotic regimen. The significantly lower rate of infection in later series, as compared with earlier studies during World War II and prior to World War II, supports the indication for routine prophylactic antibiotics.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

A randomized, controlled trial of antibiotics versus no antibiotics is not likely to be performed because the use of antibiotics in PBI has become routine practice. However, a randomized controlled trial of specific antibiotics and the

VII. Evidentiary Table: Antibiotic Prophylaxis

<table>
<thead>
<tr>
<th>Authors, Year</th>
<th>Description of Study</th>
<th>Data Class</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aarabi et al., 1987</td>
<td>Case series of 125 patients with dural penetration: 123 had operative intervention; 64 had primary and 53 had secondary explorations; sporadic wound, tract, and bone cultures in both groups. Antibiotics (ampicillin and chloromyocetin or penicillin G and chloromyocetin) given to all. Average follow-up, 73 wk.</td>
<td>III</td>
<td>Clinical infection rate primarily surgical series is 6.4%. Abscess, 1.6% Meningitis, 4.7%</td>
</tr>
<tr>
<td>Aarabi, 1990</td>
<td>Military case series of 435 surgical patients. All patients received broad-spectrum antibiotics. Follow-up period: at least 6 mo.</td>
<td>III</td>
<td>Clinical infection rate in this surgical series is 8.1%</td>
</tr>
<tr>
<td>Aarabi et al., 1998</td>
<td>Military (n = 964). Surgical experience with casualties from the Iran-Iraq War. Retrospective study of infectious complications among 105 patients with univariate and multivariate analysis of predictors of intracranial infection in the entire group, including projectile type, injury mode, air sinus involvement, number of involved lobes, transventricular injuries, location of exploration, CSF leak, GCS score, retained bone, and retained metal.</td>
<td>III</td>
<td>Clinical infection in 10.9% (105 patients), 82 meningitis, 20 abscess. Causative organisms, 45% gram-negative and 15% gram-positive. Multivariate analysis showed each of the following associated with increased risk of CNS infection: CSF leaks, transventricular injury, and paranasal sinus injury.</td>
</tr>
<tr>
<td>Arendall and Meirowsky, 1983</td>
<td>Military case series of 147 surgical and 16 nonsurgical cases with air sinus penetration. Delay in debridement over 12 h results in marked increase in infection rate from 5% to 43%. Antibiotics used for all cases. No clear follow-up period stated but 20-y follow-up is suggested.</td>
<td>III</td>
<td>Clinical infection in this mixed series is 29%. Abscess, &lt;1% Empyema, 2%</td>
</tr>
<tr>
<td>Benzel et al., 1991</td>
<td>Civilian (n = 120). Victims of civilian gunshot wounds to the head were evaluated 3–4 mo after surgical and nonsurgical management for their outcome on the basis of the state of consciousness. Antibiotics used for all cases.</td>
<td>III</td>
<td>No abscess or meningitis in 54 survivors. Three superficial wound infections.</td>
</tr>
<tr>
<td>Brandvold et al., 1990</td>
<td>Military case series on 85 surgical and 28 nonsurgical patients (10 of whom died early). All received antibiotics (clexacin or chloramphenicol). Surgical treatment was limited debridement. Follow-up on all patients was initial hospitalization only. Subsequent follow-up on 46 patients obtained at mean 5.9 y.</td>
<td>III</td>
<td>Acute clinical infection rate in this mixed series is 9%. Abscess, 0.9% Meningitis, 8% Delayed clinical infection rate, 1 of 46 (meningitis), 2.2%.</td>
</tr>
<tr>
<td>Carey et al., 1974</td>
<td>Prognostic military case series of 103 patients. All patients assumed to have received antibiotics (penicillin and chloromyocetin or ampicillin) on the basis of previous report. Follow-up extrapolated to be −2 y.</td>
<td>III</td>
<td>Clinical infection rate in this surgical series is 15%. Abscess, 1.9% Meningitis, 9.7% Empyema, 1.9%</td>
</tr>
<tr>
<td>Authors, Year</td>
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<tr>
<td>Chaudhri et al., 1994</td>
<td>Military case series of 20 patients. All received antibiotics (gentamicin, ceftriaxone, metronidazole). 15 patients had limited debridement, 5 had skin closure only. Follow-up approximately 6 mo.</td>
<td>III</td>
<td>Clinical infection rate in this small mixed series is 10%. Abscess, 5% GCS, Glasgow Coma Scale.</td>
</tr>
<tr>
<td>Gonul et al., 1997</td>
<td>Military case series of 148 surgical patients. All received antibiotics (ceftriaxone and/or nidazol for 10–14 days). Average follow-up, 12 mo. Primary purpose of article is to show relationship with CSF leak and dispel relationship with retained bone fragments.</td>
<td>III</td>
<td>Clinical infection rate in this surgical series is 6%. Abscess, 2.7% Meningitis, 1.3% Empyema, 1.4% Ventriculitis, 0.7%</td>
</tr>
<tr>
<td>Haynes, 1945</td>
<td>Military case series of 342 surgical patients. First 161 patients received local sulfanilamide powder and parenteral sulfadiazine; second 161 patients received local sulfadiazine and penicillin powder and parenteral sulfadiazine (99 in this group also received parenteral penicillin). Follow-up is 10 days for these groups.</td>
<td>III</td>
<td>Clinical infection in first group is 21.1%. Clinical infection in second group with penicillin addition is 6.8%. Overall infection rate is 13.9%.</td>
</tr>
<tr>
<td>Levi et al., 1990</td>
<td>Military case series of 96 surgical and 20 nonsurgical patients. All received antibiotics (cloxacillin and chloromycetin). Average follow-up, 3–6 y.</td>
<td>III</td>
<td>Clinical infection in this mixed series is 4%.</td>
</tr>
<tr>
<td>Maltby, 1946</td>
<td>Military case series of 200 surgical patients; all had either sulfa drug and/or penicillin locally and/or parenterally. Follow-up is at time of disposition from army state side hospital (exact time unclear).</td>
<td>III</td>
<td>Overall clinical infection rate is 23.5%. Abscess, 8.5% Author states no difference between antibiotic regimens was apparent.</td>
</tr>
<tr>
<td>Martin and Campbell, 1946</td>
<td>Military case series of 426 surgical patients. First group of 158 cases had parenteral sulfonamide therapy. The second group of 268 had the added parenteral and local penicillin therapy. Follow-up period not clearly stated.</td>
<td>III</td>
<td>Deep infection incidence in sulfa only group is 23%. Deep infection rate after addition of penicillin is 13%. Author points out that better debridement and improved use of blood products also accompanied use of penicillin.</td>
</tr>
<tr>
<td>Meirowsky et al., 1981</td>
<td>Military (n = 101). Review of patients in the Caveness-Rish database from Vietnam with missile head wounds complicated by CSF fistulas.</td>
<td>III</td>
<td>Only 50% of CSF leaks at wound site, the remainder being rhinorrhea or otorrhea from remote basal skull fractures. 44% of leaks closed spontaneously. 72% of leaks appeared =2 wk after injury. Mortality with CSF leaks was 22.8% vs. 5.1% without leaks. Infection incidence was 49.5% vs. 4.6% in the 1,032 casualties without CSF leaks. Stressed vigilance for leaks and definitive treatment when found. The variable most highly correlated with intracranial infection was the presence of an acute or delayed CSF leak, which had a 49.5% infection rate.</td>
</tr>
<tr>
<td>Munslow, 1946</td>
<td>Military case series of 140 surgical patients. Use of local sulfa or penicillin powder was sporadic. First 53 patients received parenteral sulfa drugs only; last 42 patients received parenteral penicillin only. Of note, first group was evacuated sooner. Postoperative and epidural drains were only used for the first group. Follow-up obtained on 103 of 116 survivors after evacuation to rear. Time of follow-up unclear.</td>
<td>III</td>
<td>Clinical infection in group with sulfa only is 21%. Clinical infection in group with penicillin only is 5.7%. Overall infection rate is 11.6%.</td>
</tr>
<tr>
<td>Rish et al., 1981</td>
<td>Military case series of 37 patients with brain abscess in total population of 1,221. All patients received antibiotics (penicillin and chloromycetin). Follow-up, 5 y, but vague. 37 patients form basis for this retrospective analysis evaluating etiologic factors for abscess development.</td>
<td>III</td>
<td>Brain abscess in this mixed series is 3%.</td>
</tr>
<tr>
<td>Rish et al., 1983</td>
<td>Military case series evaluating mortality at 15-y follow-up of Vietnam Head Injury cohort.</td>
<td>III</td>
<td>Clinical infection in this mixed series is 6.2%. Abscess, 3.2%</td>
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GCS, Glasgow Coma Scale.
effect of length of treatment should be performed to answer the following questions: (1) What is the optimum duration of prophylactic antibiotic treatment in PBI and PBI subgroups? (2) What is the optimum prophylactic antibiotic regimen in PBI, and does it depend on the environment in which the injury is sustained?

REFERENCES

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<td>Slemon, 1945&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Military case series of 217 patients. First group of 32 cases received local sulfathiazole powder. Second group of 184 patients received local penicillin and sulfa powder. Both groups received systemic sulfadiazine without parenteral penicillin. Single patient received no local application. Average follow-up was 42 days.</td>
<td>III</td>
<td>Clinical infection in the first group with sulfa only is 31.2%. Clinical infection in the second group with penicillin added is 9.2%. Single patient with no local antibiotic treatment became infected. Overall clinical infection rate is 12.9%.</td>
</tr>
<tr>
<td>Taha et al., 1991&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Military case series of 600 patients. 30 developed intracranial infection. All received antibiotics (methicillin or ampicillin). Average follow-up, 2.5 y. Only 6 of 340 patients with retained bone fragments developed infection. 15 of 32 patients with CSF leak developed infection.</td>
<td>III</td>
<td>Clinical infection in this mixed series is 5%. Abscess, 3% Meningitis, 0.8% Cerebritis, 1.5% Infection in patients with retained bone fragments, 1.8% Infection in patients with CSF leak, 46.9%</td>
</tr>
<tr>
<td>Taha et al., 1991&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Military case series of 32 patients with rigid entry criteria treated with scalp closure only. All received antibiotics (methicillin for 2 wk). 3.5-y average follow-up.</td>
<td>III</td>
<td>Brain abscess in this mixed series is 3.1%.</td>
</tr>
<tr>
<td>Vrankovic et al., 1992</td>
<td>Military case series of 62 surgical and 7 nonsurgical patients. All received antibiotics (penicillin and gentamicin, sometimes metronidazole). Main focus of article is comparison of grafting techniques. Follow-up only during acute hospitalization.</td>
<td>III</td>
<td>Clinical infection in this small mixed series is 10.1%. Meningitis, 5.8%</td>
</tr>
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</table>


SUGGESTED READINGS


