Prevention and Management of Infections Associated With Combat-Related Central Nervous System Injuries

Glenn W. Wortmann, MD, Alex B. Valadka, MD, and Leon E. Moores, MD

Combat-related injuries to the central nervous system (CNS) are of critical importance because of potential catastrophic outcomes. Although the overall infection rate of combat-related CNS injuries is less than 5%, if an infection develops there is a very high associated morbidity and mortality. This review focuses on the management and prevention of infections related to injuries to the brain or the spinal cord. Management strategies emphasize the importance of expert evaluation and management by a neurosurgeon. This review provides evidence-based recommendations from military and civilian data to the management of combat-related CNS injuries. Areas of focus include bacteria cultures, antimicrobial therapy, irrigation and debridement, timing of surgical care, and wound coverage. Given these recommendations are not supported by randomized control trials or adequate cohorts studies in a military population, further efforts are needed to answer best treatment strategies.

Key Words: Combat, Trauma, Central nervous system, Infection

J Trauma. 2008;64:S252–S256.

The prevention and management of infections associated with central nervous system (CNS) trauma are topics of critical importance, as CNS infections are usually catastrophic events. Battle wounds involving the head were reported in 6% of 14,000 injuries treated at the US 5th Army hospitals in 1944, with one third of those classified as intracranial.1 War-related penetrating spinal cord injury, which perhaps most famously claimed the life of Admiral Horatio Nelson at the Battle of Trafalgar, was reported in which perhaps most famously claimed the life of Admiral Horatio Nelson at the Battle of Trafalgar, was reported in nearly 12% of World War II battlefield injuries.2,3 War-related CNS trauma is often associated with high-velocity weapons (which create substantial tissue destruction and devitalization) and blast injuries (which are often associated with in-driven foreign bodies).

Before the modern era, penetrating head injuries were considered uniformly fatal and were treated with expectant care. In a review of the historical treatment of head injuries, a mortality rate of 73.9% was reported in 898 cases of head wounds in the Crimean War and 71.7% in a series of 704 cases of penetrating head wounds from the American Civil War.4 During World War I, Cushing found that more than 60% of deaths after dural penetration were because of sepsis. Although antimicrobial agents were not available, he was able to reduce the mortality associated with CNS injuries from 54% to 29% simply by expediting surgical debridement.5 The introduction of penicillin during World War II further helped decrease the mortality associated with CNS trauma. Several reports from the 1940s report an infection rate of 21% to 31% with the use of local sulfa powder or parenteral sulfonamide therapy; this rate improved to 5.7% to 13% with the addition of penicillin.1,6–9 Further medical advances saw mortality decrease to approximately 10% in the Korean and Vietnam wars and to 4.5% during Operation Desert Storm.10–13 Similar to penetrating head injury, outcome from penetrating spinal cord injury experienced a marked improvement with the introduction of antibiotics.14

Epidemiology and Microbiology of Wound Colonization and Infection

There have been few studies reporting the bacteriologic culture of retained fragments or the identification of organisms associated with penetrating craniocerebral trauma. Ascroft et al.15 obtained systematic aerobic and anaerobic cultures from CNS traumatic injuries from the battle of El Alamein in 1942. Twenty-five cases of penetrating craniocerebral injury were studied, of which 6 cultures grew Clostridium, 22 grew Staphylococcus aureus, and 5 grew β-hemolytic streptococci in removed brain tissue; only two cases of sepsis resulted, both because of S. aureus.15 Ecker,16 in a study of brain wounds because of shell fragments in the Normandy campaign, performed bacteriologic studies for patients wounded 3 to 86 days previously and who received sulfadiazine and penicillin. Seventy-six percent (32 of 42) of cultures grew organisms reported as S. aureus (7 cases), Staphylococcus albus (17 cases), Streptococcus viridans (9 cases), nonhemolytic Streptococcus (9 cases), gram-negative bacilli (6 cases),...
Micrococcus tetragenus (4 cases), and Clostridium (2 cases).16

During the Vietnam War, Carey et al.17 performed cultures of skin wounds, brain, and in-driven bone fragments in 45 craniocerebral missile cases within 2 to 4 hours of occurrence. Skin wounds were contaminated in 98% of cases, with 70% of the contaminating organisms being gram-positive cocci (predominantly Staphylococcus) and 28% being various gram-negative rods. Only five (11%) brain wounds showed bacterial contamination, suggesting that many missile tracks within the brain were initially sterile. In-driven bone fragments were positive in 20% to 45% of samples (depending on the number of bone fragments cultured) and all grew Staphylococcus. Based on the predominance of gram-positive isolates recovered, the authors concluded that skin bacteria were the most important source of contamination for cranial wounds.

Hagan, in another study from the Vietnam War, reported that 56% (35 of 62) patients operated on for retained intracranial bone fragments had positive microbial cultures of the fragment.18 Most of these patients had undergone previous craniectomy and had been on antibiotics for an average of 2 weeks. Staphylococcus epidermidis was the most common organism isolated, with a variety of gram-negative and gram-positive bacteria also reported.

Aarabi19 reported on 161 patients with missile head wounds injured in the Iran-Iraq war who underwent culture of wound edges and brain tracks as well as all in-driven bone fragments. All patients in that study had received ampicillin and chloramphenicol or penicillin G and chloramphenicol after field evacuation, and before culture sampling. Wound cultures grew predominately coagulase-negative Staphylococcus, whereas the brain tract cultures grew coagulase-negative Staphylococcus, Acinetobacter, and S. aureus. Cultures of bone fragments grew mostly coagulase-negative Staphylococcus and S. aureus. In this study, there were six cases of meningitis (secondary to Klebsiella pneumoniae, Pseudomonas aeruginosa, Herellea vaginicola, Enterobacter, α-streptococci, and coagulase-negative Staphylococcus) and two cases of brain abscess (coagulase-negative Staphylococcus and Escherichia coli). Of interest, there was no relationship between the contaminating bacteria and postdebridement infective organisms. Furthermore, no patient with positive early wound, bone or brain culture, with or without bone or metal fragments retained, developed either meningitis or deep infection during follow-up.

Infection after penetrating brain injury is most commonly because of osteomyelitis of the skull, meningitis, and early or late abscess formation.20 Several studies from the Vietnam War era included large numbers of patients in their analyses. Hammon11 published a series of 2,187 consecutive penetrating wounds of the brain and reported a meningitis rate of 0.63%, whereas Hagan18 reported 506 patients with penetrating brain injury, of whom culture-proven meningitis occurred in 3.56% of cases. Brain abscess formation after penetrating injury has been reported in 2% to 3% of patients.21,22 In one of these studies, 37 of 1221 patients developed a brain abscess after penetrating craniocerebral injuries in Vietnam, with culture of gram-positive cocci (predominantly S. aureus and S. epidermidis) in 43% and gram-negative rods (a variety of organisms) in 56%.21 Of note, anaerobic culture data were not routinely used.

In a publication on intracranial infections after missile brain wounds in the war in Croatia, Hecimovic et al.23 reported infectious complications occurring in 15 of 88 patients after missile brain injury (17%). In 14 of 15 patients, infection developed within the first 2 months, and in one case, 5 months after wounding. Four cases of isolated bacterial meningitis, nine cases of brain abscess, one local cerebritis, and one subdural empyema with concomitant meningitis were reported. The most commonly isolated organism was S. aureus, and most patients developed a cerebrospinal fluid fistula or dehiscence in association with infection. Vrankovic et al.24 have reported their experience of 127 war-related missile brain injuries sustained in northeastern Croatia, and noted a 10% intracranial (meningitis, abscess) infection rate. In reporting complications of missile craniocerebral injuries during the Croatian Homeland War, Tudor et al.25 found a 8.5% intracranial infection (meningitis, meningoencephalitis, or ventriculitis) rate in 176 patients. Splavski et al.,26 also in Croatia, reported three cases of brain abscess and one bacterial meningitis among 21 patients with skull base missile injuries (19%).

An intracranial infection rate of 4.7% (19 of 403) was reported as a result of missile injuries to the brain during the Lebanese Conflict by Taha et al.27 Ninety percent of infections occurred within 6 weeks of injury, and the mortality rate was 43%. Gram-positive organisms were responsible for 36% of infections, gram-negative organisms accounted for 40%, mixed infections occurred in 7%, and 17% of cultures were negative. The relatively high rate of gram-negative infections was attributed to the use of antibiotics before surgery. In reporting the surgical outcome in 435 patients who sustained missile head wounds during the Iran-Iraq War, Aarabi28 found that 35 of 71 (49%) patients who died had an infection as a contributory factor (25 cases with meningitis and 10 with sepsis). Levi et al.29 in their report on the wartime neurosurgical experience in Lebanon, reported a 4% intracranial infection rate in 116 patients, whereas Brandvold et al.30 reported that 8% of their patients, injured in the same conflict, developed meningitis. Although most studies report that intracranial infection occurs within 1 to 5 weeks after injury, delayed infection, sometime occurring years after the initial trauma, is well reported.31,32

In summary, for penetrating brain injuries, study differences in culture techniques, prophylactic antibiotic use, and time of culture acquisition make definitive statements regarding the epidemiology of wound colonization after injury difficult to conclude with certainty. However, based on the available data, it appears that the most common organisms associated with wound colonization are of dermal origin.
(predominantly coagulase-negative *Staphylococcus*). For intracranial infections, most result from *S. aureus* or gram-negative facultative aerobic organisms, and, although most occur within several weeks of injury, delayed presentation must be considered.

Infectious complications occurring after spinal cord injury vary markedly from study to study. Meningitis is probably the most common infection, and a report from the US military experience in Vietnam reported this complication in 6 of 19 (32%) patients sustaining a spinal cord injury secondary to a transcolonic gunshot injury. A similar high rate of infection was reported by Romanick et al. in a series of low-velocity missile wounds to the abdomen in a civilian institution. In this study, although no patients without gastrointestinal tract perforation sustained infection, seven of eight patients with colonic perforation developed infectious complications. Despite receiving broad-spectrum antibiotics for a minimum of 4 days after the injury, there was one case of meningitis, three cases of abscesses, and three cases of osteomyelitis. Cultures from three patients grew *E. coli*, *Enterococcus*, and *Proteus mirabilis*, which would be consistent with a colonic source of infection. Heary et al. in a series of penetrating wounds to the spine at a civilian hospital, reported seven spinal infections occurring in five patients (2% of the entire cohort). There were three occurrences of meningitis (2 of these patients had bowel injuries), two paravertebral abscesses, one vertebral osteomyelitis, and one epidural abscess.

Other studies have reported contradictory results as to the risk of infection occurring after spinal injury. Waters and Adkins reported no cases of meningitis or spine infection in 19 cases of spine injury associated with bowel injury and Kihtir et al. reported no spinal or paraspinal infectious complications in five cases of spine injury with colonic injury. Roffi et al. compiled a series of 42 patients with low-velocity gunshot wounds to the spine with an associated perforated viscus, and found that only three patients developed spinal or paraspinal infections. One patient with a stomach perforation developed *E. coli* meningitis, and 2 of 14 patients with colonic perforations developed psoas abscesses. A more recent publication of 114 patients with low-velocity gunshot wounds to the spine with an associated perforated viscus, and found that only three patients developed spinal or paraspinal infections. One patient with a stomach perforation developed *E. coli* meningitis, and 2 of 14 patients with colonic perforations developed psoas abscesses.

**Prevention of Infection**

Several recent, complete reviews have addressed the issue of preemptive antibiotics after penetrating brain injury and have concluded that, although available data are not sufficient to support a treatment standard, the use of preemptive antibiotics is recommended. For craniocerebral injuries, prevention of infection requires the use of antibiotics which treat *S. aureus* and gram-negative bacteria. For penetrating brain injury, cefazolin 1 g i.v. every 8 hours is recommended with consideration of extending coverage with the addition of gentamicin and penicillin if gross contamination is present (BIII) (grading outlined in this supplement of *Journal of Trauma*: “Guidelines for the Prevention of Infection After Combat-Related Injuries”). Alternative therapy includes ceftriaxone 2 g i.v. every 24 hours with consideration of extending coverage with the addition of gentamicin and penicillin if gross contamination is present. If the patient is allergic to penicillin then vancomycin 1 g i.v. every 12 hours and ciprofloxacin 400 mg i.v. every 8 hours to 12 hours is recommended.

The relationship between retained bone and metal fragments and subsequent infection is debated. Although extensive debridement has classically been recommended, some reports suggest less aggressive surgical intervention may be successful with preservation of brain function. At this time, it is recommended to only remove easily accessible foreign bodies and grossly devitalized tissue (BII). Certain complications including cerebrospinal fluid leaks, air sinus wounds, or wound dehiscence have all been identified as risk factors for infection and necessitate more aggressive surgical interventions.

For penetrating injuries of the spine, one published review has suggested broad-spectrum antibiotic use for a minimum of 48 hours, with extension to a minimum of 7 days if the alimentary tract has been violated (BII). Retained bullets are not thought to be a significant risk factor for the development of infectious complications from low-velocity civilian gunshot wounds, and that tenet presumably extends to shrapnel and high-velocity gunshot wounds. Removal of foreign bodies in the spine should be immediately preformed for neurologic compromise but otherwise can remain in place until evaluation by a neurosurgeon (CIII). However if the casualty’s injury is associated with gross contamination or associated with a tract from the peritoneal cavity into the spinal canal then exploration and irrigation are recommended. The optimum timing for spinal fracture fixation is debated. Although studies have shown that fixation within 3 days can reduce the incidence of pneumonia, length of stay, number of ventilator days, and hospital charges, another study demonstrated poorer outcomes in some groups with early spine stabilization. The timing of fixation should be individualized, especially in those patients with other catastrophic injuries (CIII).

There have been no studies assessing the ideal irrigation fluid for CNS combat-related injuries. Typically room temperature normal saline is used. It is also important to close the injury site as quickly as possible, but there is often inadequate dura present for closure with penetrating trauma. Autologous tissue graft or a commercially available dural substitute may be needed in such cases. A high importance is placed on at least closing the skin if it is not possible to close the skin and dura (a watertight skin closure is emphasized) (CIII). If para-
nasal sinuses are involved, dural closure or reconstruction becomes essential (BIII).

**Diagnosis of Infection**

The diagnosis of infection after penetrating brain injury can be difficult, as the patient usually has a depressed sensorium, and may have other wounds, which complicate the clinical picture. Computed tomographic (CT) scanning of the head has been strongly recommended to evaluate the patient with penetrating brain injury, and repeat imaging in the event of delayed clinical improvement (to assess for abscess) is recommended (BIII). MRI is usually not suggested, as there is a concern for retained ferromagnetic fragments, which can cause artifact and image distortion, and potentially rotate and deflect in response to magnetic torque. A clinical concern for meningitis warrants sampling of the cerebrospinal fluid for cell count, protein, glucose, and culture.

As with penetrating brain injury, infection after penetrating spine injury can be subtle, a follow-up CT scanning of the spine and abdomen/pelvis to assess for abscess formation is recommended for patients who present with signs or symptoms consistent with an infection (BIII).

**Treatment and Outcome of Infection**

Specific treatment for posttraumatic CNS infections is beyond the scope of this review, and readers are directed to practice guidelines and current textbooks for the management of intracranial infections. In general, antibiotic therapy in posttraumatic meningitis will be directed by the antibiotic susceptibilities determined from the culture of cerebrospinal fluid. Abscesses (intracranial, paravertebral, intraperitoneal, etc.) usually require drainage (either surgical or CT-guided aspiration). Again, antibiotic therapy will be guided by the results of microbiologic culture, with some clinicians opting to add coverage for anaerobic bacteria, as these organisms can be difficult to isolate from clinical samples.

In general, the estimated mortality for posttraumatic meningitis appears to be approximately 10%, for epidural and subdural abscesses from 10% to 40%, and for brain abscess approximately 5%. Several studies have addressed the overall outcome of penetrating brain injuries in military injuries. Aarabi analyzed 435 patients injured in the Iran-Iraq War, and reported 71 dead, 0 vegetative, 22 severe disability, 203 moderate disability, and 139 with good recovery. Levi et al. and Brandvold et al. reporting on 229 patients injured in Lebanon, with 60 dead, 12 vegetative, 14 severe disability, 48 moderate disability, and 95 good recovery. Military penetrating brain injury surviving to reach medical care is predominantly caused by shell and shrapnel injuries, which skews the surviving population toward lower velocity shrapnel wounds. Mortality rates from civilian penetrating brain injury tend to be much higher, as most wounds are as a result of gunshots and suicides.

Data on the outcome of infection in wartime penetrating spine injuries are also scarce. A report of 96 patients with spine and spinal cord war injuries from the War in Croatia has been published, with a 4% in-hospital mortality and a 43% survival rate.

**Unresolved Issues and Potential Future Research Topics**

Although the use of antibiotics after penetrating brain and spine injuries has become standard-of-care, questions regarding the optimum choice of antibiotics and length of therapy are still unresolved. The impact of the rising incidence of bacteria (such as community-acquired methicillin-resistant S. aureus and multidrug resistant Acinetobacter baumannii) needs to be tracked closely, and changes to the current recommendations may be needed if these bacteria emerge as common postinjury pathogens.

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