Presumptive antibiotic therapy for civilian trauma injuries

Teri L. Hopkins, PharmD, Mitchell J. Daley, PharmD, Dusten T. Rose, PharmD, Theresa C. Jaso, PharmD, *and* **Carlos V.R. Brown, MD***, Austin, Texas*

AAST Continuing Medical Education Article

Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint providership of the American College of Surgeons and the American Association for the Surgery of Trauma. The American College Surgeons is accredited by the ACCME to provide continuing medical education for physicians.

AMA PRA Category 1 Credits™

The American College of Surgeons designates this journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Of the *AMA PRA Category 1 Credit*™ listed above, a maximum of 1 credit meets the requirements for self-assessment.

Credits can only be claimed online

AMERICAN COLLEGE OF SURGEONS

Inspiring Quality: Highest Standards, Better Outcomes

100+*years*

Objectives

After reading the featured articles published in the *Journal of Trauma and Acute Care Surgery*, participants should be able to demonstrate increased understanding of the material specific to the article. Objectives for each article are featured at the beginning of each article and online. Test questions are at the end of the article, with a critique and specific location in the article referencing the question topic.

Claiming Credit

To claim credit, please visit the AAST website at http://www.aast.org/ and click on the "e-Learning/MOC" tab. You must read the article, successfully complete the post-test and evaluation. Your CME certificate will be available immediately upon receiving a passing score of 75% or higher on the post-test. Post-tests receiving a score of below 75% will require a retake of the test to receive credit.

Disclosure Information

In accordance with the ACCME Accreditation Criteria, the American College of Surgeons, as the accredited provider of this journal activity, must ensure that anyone in a position to control the content of *J Trauma Acute Care Surg* articles selected for CME credit has disclosed all relevant financial relationships with any commercial interest. Disclosure forms are completed by the editorial staff, associate editors, reviewers, and all authors. The ACCME defines a `commercial interest' as "any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients." "Relevant" financial relationships are those (in any amount) that may create a conflict of interest and occur within the 12'months preceding and during the time that the individual is engaged in writing the article. All reported conflicts are thoroughly managed in order to ensure any potential bias within the content is eliminated. However, if you'perceive a bias within the article, please report the circumstances on the evaluation form.

Please note we have advised the authors that it is their responsibility to disclose within the article if they are describing the use of a device, product, or drug that is not FDA approved or the off-label use of an approved device, product, or drug or unapproved usage.

Disclosures of Significant Relationships with Relevant Commercial Companies/Organizations by the Editorial Staff

Ernest E. Moore, Editor: PI, research support and shared U.S. patents Haemonetics; PI, research support, TEM Systems, Inc. Ronald V. Maier, Associate editor: consultant, consulting fee, LFB Biotechnologies. Associate editors: David Hoyt and Steven Shackford have nothing to disclose. Editorial staff: Jennifer Crebs, Jo Fields, and Angela Sauaia have nothing to disclose.

Author Disclosures

The authors have nothing to disclose.

Reviewer Disclosures

The reviewers have nothing to disclose.

Cost

For AAST members and *Journal of Trauma and Acute Care Surgery* subscribers there is no charge to participate in this activity. For those who are not a member or subscriber, the cost for each credit is $25.

System Requirements

The system requirements are as follows: Adobe® Reader 7.0 or above installed; Internet Explorer® 7 and above; Firefox® 3.0 and above, Chrome® 8.0 and above, or Safari™ 4.0 and above.

Questions

If you have any questions, please contact AAST at 800-789-4006. Paper test and evaluations will not be accepted.

Submitted: February 29, 2016, Revised: May 2, 2016, Accepted: May 3, 2016, Published online: July 6, 2016.

From the Department of Pharmaceutical Services (T.L.H., M.D., D.T.R.), University Medical Center Brackenridge, Austin, Texas; College of Pharmacy at the University of Texas (M.D., T.L.H.,D.T.R.,T.C.J.), Austin, Texas; Department of Pharmaceutical Services (T.C.J.), Seton Medical Center Austin, Austin, Texas; Department of Trauma Services (C.V.R.B.), University Medical Center Brackenridge, Austin, Texas; and Department of Surgery and Perioperative Services (C.V.R.B.), Dell Medical School at the University of Texas at Austin, Austin, Texas.

Address for reprints: Teri L. Hopkins, PharmD, Department of Pharmaceutical Services, University of Maryland Medical Center, 22 S Greene St, Baltimore, MD 21201; email: terihopkins2@gmail.com.

DOI: 10.1097/TA.0000000000001164

Infection and sepsis are common sequelae of traumatic injuries secondary to bacterial contamination at the site of injury. In addition, trauma patients are predisposed to infection because of impaired host defenses, compromised sterile compartments, and invasive surgical procedures required to repair injuries.[1,2] Therefore, antibiotics are frequently administered to patients with various types of traumatic injuries in order to prevent infection and sepsis-related morbidity and mortality.

Unlike antibiotic prophylaxis for surgery, antibiotics given to prevent infection after traumatic injuries are never truly prophylactic because bacterial contamination has already occurred. Because adequate antibiotic concentrations are not present in the tissue at the time of inoculation, the term *presumptive* therapy is more applicable to trauma infections.[3]

Although there is a clear benefit to presumptive antibiotic therapy for many traumatic injuries, exposure to antibiotics is also associated with the risk of emergence of resistant bacteria. Third-generation cephalosporins have been shown to select for vancomycin-resistant *Enterococcus* and extended-spectrum β-lactamases, and fluoroquinolones have been associated with methicillin-resistant *Staphylococcus aureus* and fluoroquinolone-resistant gram-negative organisms. Another untoward complication of antibiotic use is superinfection with *Clostridium difficile* after elimination of normal bacterial flora,[4] which has been associated with third-generation cephalosporins, fluoroquinolones, and clindamycin. While these agents have been most often associated with resistance and *C. difficile*, there is risk of resistance with any antibiotic use due to selective pressure on bacteria.[5]

It is important to consider these risks and the associated cost of complications for presumptive antibiotic therapy for traumatic injuries.[3] Therefore, the purpose of this review is to evaluate specific traumatic injuries where presumptive antibiotics are indicated, incorporate guidelines and evidence when available, and give recommendations that balance the risks and benefits of presumptive antibiotic therapy in a concise review. Indications for presumptive antibiotics addressed in this review include penetrating abdominal trauma; open extremity fractures; penetrating brain injury (PBI); facial, sinus, and skull fractures; saltwater and freshwater injuries; and human and animal bites.

METHODS AND SEARCH CRITERIA

An electronic search of PubMed database was performed to identify publications relevant to the material of interest. The following search terms were used: "trauma infections," "presumptive antibiotics," "penetrating abdominal injury," "open extremity fracture," "penetrating brain injury," "facial fracture," "sinus fracture," "skull fracture," "aquatic injuries" "human and animal bites." Randomized trials, reviews, meta-analyses, and observational studies published in the English language were included in the literature review. References of studies and review articles were reviewed for additional publications to be included. No date restriction was used for the literature search, which concluded in February 2016.

PRESUMPTIVE TREATMENT OF TRAUMA INJURIES

Penetrating Abdominal Injury

The incidence of infection after penetrating abdominal injury ranges from 7% to 11% with preoperative antibiotics and upward of 30% to 70% with only postoperative antibiotics.[6,7] Risk factors for infection include mechanism of injury, number of intra-abdominal organs injured, presence of shock, and the choice of antibiotic treatment.[8] Penetrating abdominal injury can lead to various infectious complications when the peritoneal cavity is breached, including postoperative wound infections and intra-abdominal abscess.[6,8] Enterobacteriaceae are the organisms most frequently isolated from aerobic cultures after penetrating abdominal injury, with *Escherichia coli* as the predominant pathogen, followed by *Enterobacter cloacae* and *Klebsiella* species.[9] Gram-positive pathogens such as *Enterococcus faecalis* and *S. aureus* are also common.[10] Although anaerobic cultures are not routinely done in many practice settings, *Bacteroides* species are also common pathogens in penetrating abdominal injury.[8,10] Notably, *E. coli* and *Bacteroides* species are more often isolated from patients with colonic injuries, and *E. cloacae* and *Klebsiella* species are more common with stomach or small bowel injuries.[9]

Presumptive antibiotics have been used prior to surgery in patients with penetrating abdominal trauma for several decades, and there have been no randomized controlled trials to date that contest this practice.[6] A retrospective study demonstrated reduced infection rates when antibiotics were given presumptively prior to surgery versus those given only intraoperatively or postoperatively (7% vs. 30% and 33%).[2] A randomized controlled trial comparing kanamycin and cephalothin with kanamycin and clindamycin showed that the inclusion of anaerobic coverage reduced infection rates from 27% to 10%.[11] Prospective, randomized controlled trials have compared various broad-spectrum single and combination regimens, including cefoxitin, cefotetan, clindamycin plus an aminoglycoside, clindamycin plus aztreonam, ceftriaxone plus metronidazole, ampicillin plus gentamicin plus metronidazole, and penicillin G plus doxycycline. All regimens included in these studies are thought to offer similar efficacy in reducing penetrating abdominal trauma-related infections.[12–21] A randomized study comparing a 24-hour versus a 5-day course of presumptive antibiotics after surgery reported infection rates of 8% in the 24-hour group and 10% in the 5-day group, suggesting no benefit in continuing antibiotics beyond 24 hours.[22] These findings are supported by several other studies comparing 24 hours to longer durations of presumptive antibiotics for penetrating abdominal trauma.[13,18,23–25]

Presumptive antibiotic therapy for penetrating abdominal trauma should include coverage of commonly isolated pathogens, specifically Enterobacteriaceae, *S. aureus*, and anaerobic bacteria.[6] Coverage of *Enterococcus* species is controversial[8] and should not be specifically included in presumptive antibiotic regimens for abdominal trauma injuries. Although ampicillin-sulbactam offers single-agent coverage of the target pathogens, it should be avoided if *E. coli* resistance is greater than 10% to 20% based on local antibiograms.[6] Similarly, cefoxitin should generally be avoided in the setting of poor local *Bacteroides fragilis* group susceptibility.[26,27] The combination of cefazolin and metronidazole provides adequate coverage for the most common intra-abdominal pathogens. For patients with a true cephalosporin allergy, an aminoglycoside plus clindamycin is a reasonable alternative,[6] although *B. fragilis* group resistance to clindamycin may also be of concern.[27] Therapeutic options are limited in this setting for patients with a severe cephalosporin

allergy, and antibiotic selection should be tailored to local susceptibilities whenever possible.[6]

The 2012 Eastern Association for the Surgery of Trauma practice management guideline for antibiotic use in penetrating abdominal trauma provides a Level 1 recommendation for a single preoperative dose of broad-spectrum antibiotics with aerobic and anaerobic coverage in all patients with penetrating abdominal wounds. A single dose is adequate in the absence of a hollow viscous injury, and antibiotics should be continued for no more than 24 hours in patients with a hollow viscous injury.[28] A summary of recommendations is provided in Table 1.

Open Extremity Fractures

Open extremity fractures are associated with serious risk of infectious complications secondary to exposure of fracture fragments to the outside environment.[31] The most common type of open fracture is the tibial shaft, which is more likely to develop infection due to poor vasculature and limited soft tissue coverage.[32] Infection following open extremity fractures can lead to nonunion and bony instability.[33] Open fractures are graded based on wound size, amount of contamination, degree of soft tissue injury, and vascular compromise (Table 2).[31,33] Because this grading system, termed the Gustilo Classification, has been used to determine the risk of infection and subsequent limb loss, antibiotic recommendations are also made based on this system.[31]

Gram-positive skin flora such as *S. aureus* and *Streptococcus* species are the most common pathogens causing infection after open extremity fractures. Gram-negative bacteria including Enterobacteriaceae and *Pseudomonas* species are more likely to be isolated in Type III fractures because of a higher degree of contamination, as well as the greater degree of tissue injury.[34] The importance of gram-negative coverage in Grade III fractures was demonstrated in a prospective study comparing clindamycin and cloxacillin, which showed exceptionally high infection rates for both clindamycin (29.0%) and cloxacillin (51.8%). In Type III fractures, gram-negative pathogens accounted for 43% of isolates, whereas no gram-negatives were isolated from Type I or II fractures. In addition, this study found that 76% of pathogens cultured during infection were not present in cultures on admission, indicating that these pathogens come from the hospital rather than initial wound contamination.[35] A recent retrospective case-control study demonstrated that 1 day of antibiotics showed no greater infection risk than 2 to 3 days, 4 to 5 days, or more than 5 days, even when Type III fractures were assessed in a multivariate analysis. The median time between trauma and surgery in this study was 0 days, and no difference in infection rates occurred in the setting of delayed closure (median, 2.5 days), which occurred most commonly in Type III fractures. These data suggest 1 day of presumptive antibiotics may be sufficient for all grades of open fracture.[36] Furthermore, a randomized, prospective trial by Dellinger and colleagues[37] found no significant difference in incidence of infection in patients treated for one day compared with 5 days.

Studies evaluating the time interval between injury and antibiotic administration have not been able to establish a significant correlation with improved outcomes. In the absence of specific data regarding timing of administration, presumptive antibiotics should be administered as soon as possible after open fracture injury.[31]

The 2011 East Practice Management Guidelines for prophylactic antibiotic use in open fractures recommend presumptive antibiotics with gram-positive coverage for Types I and II fractures, with the addition of gram-negative coverage for Type III fractures. The preferred antibiotic for gram-positive organisms is cefazolin (Table 1), which can be used in combination with once-daily aminoglycoside administration for Type III fractures. As an alternative regimen for patients with a cephalosporin allergy, clindamycin may be substituted for cefazolin for gram-positive coverage. Although the guidelines recommend the addition of high-dose penicillin for fractures exposed to fecal contamination or farm-related injuries to cover for *Clostridium* species,[31] it is reasonable to use ampicillin-sulbactam plus gentamicin to avoid double β-lactam therapy with cefazolin and penicillin.

The EAST (Eastern Association for the Surgery of Trauma) guidelines recommend continuing antibiotics for 24 hours after wound closure for Types I and II fractures. For Type III fractures, they recommend antibiotics for 72 hours after injury or not more than 24 hours after soft tissue coverage.[31] Based on data showing no benefit beyond 24 hours of antibiotics, our recommendation is to continue antibiotics for no more than 24 hours after wound closure for all fracture types. Treatment of open fractures with water exposure varies slightly and is discussed in a later section.

Penetrating Brain Injury

Penetrating brain injuries in the civilian population may be caused by high-velocity objects, as well as nonmissile, low-velocity objects.[38,39] These are typically the result of accidents, violence, or suicide attempts. Infections resulting from PBIs are more common in military injuries than in the civilian population, with an incidence of 4% to 11% and 1% to 5% respectively, when treated with presumptive antibiotics. Consequently, much of the data on treatment of PBI involve combat injuries, and it is unclear whether this can be extrapolated to the civilian population because of the inconsistent nature of these injuries.[39] In addition, most studies involving PBIs have been focused on neurological issues, and data on microbiology and antibiotic treatment have been largely neglected.[38]

At the time of PBI, skin, hair, and bone fragments contaminated with bacteria are driven into the brain along with the object causing the injury. In the absence of presumptive antibiotics, this can lead to intracranial infection, particularly if these fragments are not removed.[38] Incidence of infection without antibiotics has been reported to be as high as 58% in combat-related injuries and up to 25% in civilian PBIs.[40–42]

In a study of combat-related PBI, gram-positive bacteria were isolated in 70% of cases, and the predominant organisms were *S. aureus* and coagulase-negative staphylococci.[38] *Acinetobacter* species were also common in this population; although this organism is highly associated with combat-related injuries, it has not been shown to be a frequent pathogen in civilian injuries. A small percentage of cultures in this study yielded gram-negative bacteria other than *Acinetobacter*. Based on reports from combat-related injuries, *S. aureus*, coagulase-negative staphylococci, and non-*Acinetobacter* gram-negative bacteria should be suspected.[38] Only one study, conducted in

TABLE 1. Antibiotic Selection and Duration Based Upon Injury Pattern

Injury	Preferred Agent(s)	Alternate Agent(s) (Severe Penicillin and Cephalosporin Allergy)*	Duration
Penetrating abdominal injury	Cefazolin 1–3 g** IV every 8 h + metronidazole 500 mg IV/PO every 8 h	Clindamycin 600–900 mg IV every 8 h† + IV gentamicin every 24h‡	No HVI: single preoperative dose HVI: ≤24 h
Open extremity fractures			
Type I	Cefazolin 1–3 g** IV every 8 h	Clindamycin 600–900 mg IV every 8 h‡	24 h after wound closure
Type II	Cefazolin 1–3 g** IV every 8 h	Clindamycin 600–900 mg IV every 8 h‡	24 h after wound closure
Type III	Cefazolin 1–3 g** IV every 8h + IV gentamicin every 24 h‡	Clindamycin 600–900 mg IV every 8 h‡ + IV gentamicin every 24 h‡	24 h after wound closure
Penetrating brain injury	Ampicillin-sulbactam 3–4.5 g IV every 6 h§ *OR* Ceftriaxone 2 g IV every 12 h ± metronidazole 500 mg IV/PO every 6–8 h¶	Moxifloxacin 400 mg IV/PO every 24 h	If retained fragment(s): immediately following injury and for 5 d postoperatively If no retained fragment(s): at least one dose preoperatively
Facial, sinus, and skull fractures			
Facial fractures			
Open	Cefazolin 1–3 g** IV every 8 h + metronidazole 500 mg IV every 8 h *OR* Ampicillin-sulbactam 3–4.5 g IV every 6h§	Clindamycin 600–900 mg IV every 8h‡	All open fracture types: time of injury to ≤24 h after surgery
Closed	See above	See above	Mandibular fractures/multiple fractures: time of injury to ≤24 h after surgery All other facial fracture types: single preoperative dose
Sinus fractures			
Open/closed	See recommendations for facial fractures	See recommendations for facial fractures	All sinus fracture types: single preoperative dose
Skull fractures			
Open	See recommendations for facial fractures	See recommendations for facial fractures	Single preoperative dose
Closed	Not routinely recommended	Not routinely recommended	N/A
Freshwater and saltwater injuries			
Freshwater	Cefepime 1 g IV every 6 h	Ciprofloxacin 400 mg IV every 8h	Based on injury type, source control, and patient condition
Salt/brackish water	Cefepime 1 g IV every 6 h + doxycycline 100 mg IV/PO BID	Ciprofloxacin 400 mg IV every 8h + doxycycline 100 mg IV/PO BID	
Human and animal bites	Ampicillin/sulbactam 3–4.5 g IV every 6 h§ *OR* Amoxicillin/clavulanate 875 mg PO BID	Doxycycline 100 mg IV/PO BID	3–5 d

*Of penicillin skin test positive patients, only ~2% have cross-reactivity with cephalosporins[29]; incidence of cross-reactivity is dependent on cephalosporin side chain.[30]
**Weight-based dosing for cefazolin—single preoperative dose: <80 kg = 1 g, 80–120 kg = 2 g, >120 kg = 3 g; scheduled dosing: ≤120 kg = 1 g, > 120 kg = 2 g.
†Weight-based dosing for clindamycin: ≤120 kg = 600 mg, >120 kg = 900 mg.
‡Once-daily extended-interval dosing.
§Weight-based dosing for ampicillin/sulbactam: ≤120 kg = 3 g, >120 kg = 4.5 g.
¶Weight-based dosing for metronidazole: ≤120 kg = every 8 h, > 120 kg = every 6 h.
BID, twice daily; HVI, hollow viscous injury; IV, intravenous; PO, orally.

TABLE 2. Grading of Open Extremity Fractures[28,34]

Type I	Open fracture with a skin wound <1 cm in length and clean
Type II	Open fracture with a laceration >1 cm in length and without extensive soft tissue damage, flaps, or avulsions
Type III	Open segmental fracture with >10 cm wound with extensive soft tissue injury or a traumatic amputation (special categories in Type III include gunshot fractures and open fractures caused by farm injuries)

Colombia, has reported on the microbiology of PBIs in civilian trauma patients. In this report, methicillin-susceptible *S. aureus* was isolated from 54% of cultures, followed by *Streptococcus pneumoniae* (15%), *Klebsiella pneumoniae* (15%), methicillin-resistant *S. aureus* (8%), *and E. coli* (8%).[40] The role of anaerobes in PBI-associated infections is unclear, as most studies either did not culture for anaerobes or did not isolate any anaerobic bacteria.[38] Theoretically, the involvement of anaerobic organisms would be based on the trajectory of the bullet or other penetrating object. Therefore, anaerobic bacteria may become pathogens of concern if the penetrating injury reaches the sinuses or oropharynx as they are local flora at these sites.

The benefit of presumptive antibiotics after PBI in civilians has not been assessed in randomized trials. In an observational cohort study, 33.8% of the 59 patients who received presumptive antibiotics developed an infection, compared with 19.8% of the 101 patients without antibiotics. However, this finding was significant only in the univariate analysis and did not persist when a multivariate analysis was conducted.[40] Published data from clean neurological procedures show a benefit to at least a single dose of antibiotics prior to surgery and the current Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery support this practice.[43] Because a benefit to presumptive antibiotics has been demonstrated in clean neurosurgical procedures, this evidence provides support for the use of presumptive antibiotics for PBI with a grossly contaminated wound. In addition, because of a suspected causal relationship between retained fragments and infection, the retention of potentially contaminated debris may require a longer treatment duration.[42] Preferred antibiotics for presumptive treatment after PBI have not been established by randomized trials.[38,39] The "Infection in Neurosurgery" Working Party of British Society for Antimicrobial Chemotherapy recommends intravenous amoxicillin-clavulanate or intravenous cefuroxime with metronidazole based on data from case studies using various broad-spectrum antibiotic regimens, including penicillin and chloramphenicol, clindamycin and ceftriaxone, and flucloxacillin, cefuroxime, and metronidazole.[38]

Because there is no evidence from randomized trials to guide antibiotic selection, treatment should be based on common pathogens, central nervous system (CNS) penetration, and local susceptibilities. Ampicillin-sulbactam provides adequate coverage of most common pathogens and reaches sufficient concentrations in the CNS. If local resistance to gram-negative bacteria such as *E. coli* and *K. pneumoniae* is greater than 10% to 20% for ampicillin-sulbactam, ceftriaxone with or without metronidazole is an acceptable alternative (Table 1). For patients with a severe β-lactam allergy, moxifloxacin can be considered as an alternative treatment option. The optimal duration for continuing antibiotics after PBI is also unclear, with current recommendations ranging from 5 days[38] to 7 to 14 days.[39] In the absence of data demonstrating improved outcomes with a longer duration of treatment, we recommend limiting presumptive antibiotics to a 5-day course in cases involving retained fragments.[38] For cases where all fragments are removed, it may be reasonable to limit antibiotics to one preoperative dose. Randomized trial data are needed to determine an optimal duration of antibiotics for PBI.

Facial, Sinus, and Skull Fractures

Facial, sinus, and skull fractures are characterized by multiple different injury patterns and may be exposed to varying degrees of bacterial contamination depending on the proximity of the fracture to the oral cavity and nasal passages.[44] The incidence of infection after maxillary and mandibular surgery is 10% to 15% when presumptive antibiotics are used prior to surgery,[4] compared with approximately 50% without antibiotics.[45] Mandibular fractures are at the highest risk of developing infection, particularly if the fractures occur in tooth-bearing sections of the mandible.[46] Skull fractures also carry significant risk of infection, depending on the type and severity of the fracture. Basilar skull fractures are often associated with cerebrospinal fluid leak, and patients are at risk of developing meningitis.[47] Open fractures are more often associated with wound infections.[48–50]

Facial and sinus fractures are exposed to bacteria colonizing the head and neck, oral cavity, and mucous membranes of the sinus and nasal passages. These include gram-positive organisms such as *S. aureus*, *Streptococcus* species, *Micrococcus* species, *Corynebacterium* species, and *Propionibacterium* species, and gram-negative anaerobic organisms, including *Bacteroides* species, *Porphyromonas* species, *Prevotella* species, and *Fusobacterium* species.[44] Skull fractures can contaminate the CNS with bacterial flora of the nose and throat, so similar organisms are involved in these infections.[47]

Facial Fractures

Open facial fractures

Presumptive antibiotics have demonstrated benefit in the setting of open extremity fractures, but significant differences exist between open fractures of the extremities and facial fractures. Bacterial flora, blood supply at the fracture site, and surgical management all may impact the risk of infection. Therefore, the benefit of antimicrobial therapy for facial fractures should be evaluated independently of other open fracture types.[51] Presumptive antibiotics are not routinely indicated for fractures of the maxilla, zygoma, or mandibular condyle region because there is low risk of postoperative infection with these fracture types.[52,53] For mandibular fractures, presumptive antibiotics given prior to surgery have demonstrated effectiveness,[54–56] but controversy exists regarding the necessity and optimal duration for antibiotics after surgery.[4] One small prospective study found a lower incidence of postoperative infections in patients with facial fractures receiving 24 hours of cefazolin compared with one preoperative dose.[46] Conversely, other small trials have failed to show a benefit of this practice.[4,54,56] A series of three randomized controlled trials comparing a 5-day antibiotic course to a 1-day course for orbital fractures, mandibular fractures, and

Le Fort and zygomatic fractures after surgery found no difference in infection rates for any of the three fracture types.[57–59]

In the absence of studies comparing specific antibiotics for facial fractures, antibiotic selection should be based on the contaminating microbiologic flora. Cefazolin plus metronidazole or ampicillin/sulbactam provides coverage of common oral flora and is consistent with guidelines for preoperative antibiotics in procedures of the head and neck.[43] An alternative in patients with a severe β-lactam allergy is clindamycin, which provides coverage of gram-positive organisms and anaerobes.[44] Because previous studies evaluating duration of presumptive antibiotics for open facial fractures are of poor quality, our recommendations are based on best practice. Despite weak evidence for some types of facial fractures, it is reasonable to provide a single dose of presumptive antibiotics prior to surgery for all fracture types. The benefit of this practice cannot be refuted based on current literature, but the duration of antibiotics should be limited to no more than 24 hours after surgery, as there is no evidence to support a prolonged duration.

Closed facial fractures

Closed facial fractures are less likely to be exposed to bacteria from the environment, but may still be contaminated with bacteria from the oral cavity and nasal passages. Presumptive antibiotics in closed fractures have been evaluated in studies only in combination with open fractures. A retrospective study of nonmandibular fractures found no difference in infection rates in patients who received additional antibiotics before or after a single preoperative dose.[55] For mandibular fractures, low-level evidence supports continuing antibiotics from time of injury and up to 24 hours after surgery.[46] Antibiotic recommendations are the same as those outlined for open facial fractures.

Sinus Fractures

Evidence for presumptive antibiotics in sinus fractures is limited to two small studies. A randomized trial of 50 patients found no significant difference in sinusitis rates with 3 days of amoxicillin-clavulanate compared with no antibiotics.[60] A retrospective review of frontal sinus fractures with delayed operative intervention found no difference in serious infection rates when antibiotics were given beyond a single preoperative dose.[61] Based on these studies, which do not differentiate between open and closed sinus fractures, we recommend limiting presumptive antibiotics to a single dose prior to surgery for all sinus fractures. Specific recommendations for antibiotics are outlined in the open facial fractures section and summarized in Table 1.

Skull Fractures

Open skull fractures

Evidence supporting presumptive antibiotics for skull fractures is limited by both the small number of studies and shortcomings involving study design.[47] There may be a role for antibiotics in open skull fractures, as these fractures are typically exposed to bacterial contamination.[49,50] However, only one retrospective study in open depressed skull fractures has evaluated this practice. Jennett and Miller[62] reported infection rates of 1.9% with presumptive ampicillin and sulfonamide compared with 10% in the untreated group. Randomized controlled trials are needed to establish a clear benefit of presumptive antibiotic therapy in this setting.[49] Because of limited evidence of benefit, we do not recommend additional therapy beyond a single preoperative dose for open skull fractures (Table 1).[48]

Closed skull fractures

A Cochrane review evaluating both randomized and nonrandomized trial data for basilar skull fractures did not find sufficient evidence to support or refute presumptive antibiotic use regardless of the presence of cerebrospinal fluid leak. In a small study, Ignelzi and VanderArk[63] found that not only were presumptive antibiotics ineffective at preventing CNS infections after basilar skull fractures, but also the isolates in the antibiotic group had a higher incidence of resistance to the antibiotics being prescribed. Only one randomized study has shown a benefit to presumptive antibiotics in basilar skull fractures, but patients with open fractures were also included. Patients who received either ceftriaxone or ampicillin with sulfadiazine for 3 days were compared with untreated patients, and they found a significantly higher incidence of infectious complications in the untreated group (8.7% vs. 0.9%). The incidence of meningitis was no different between groups, and the other infectious complications were related to wound sepsis, suggesting that the benefit seen in this trial may be due to the inclusion of patients with open fractures.[48] Based on the previously mentioned evidence and additional studies showing lack of antibiotic effect on closed fractures,[64,65] we do not recommend routine presumptive antibiotics in closed skull fractures.

Freshwater and Saltwater Injuries

Trauma-related wounds exposed to water have a much higher infection rate than land-based trauma injuries and should therefore be assumed to be contaminated with aquatic pathogens. Bacteria are present in very high concentrations in aquatic environments, and the microbiology of these organisms differs significantly from those encountered in land-based injuries.[66] The bacteriology of trauma-associated wounds also varies based on the water source. The most prevalent bacteria in aquatic environments are facultatively anaerobic gram-negative rods. *Vibrio* species are most common in saltwater, whereas *Aeromonas hydrophila* is the most common bacteria in freshwater lakes, ponds, and streams. Although special consideration is necessary for these unusual aquatic microbes, typical skin flora such as *S. aureus* and *Streptococcus pyogenes* are still the most common pathogens in saltwater and freshwater injuries. Wound infections in aquatic trauma injuries are often polymicrobial, and other typical organisms include *Pseudomonas aeruginosa*, Enterobacteriaceae, *Plesiomonas shigelloides*, *Erysipelothrix rhusiopathiae*, *Legionella pneumophila*, and anaerobes.[66–69]

Mycobacterium marinum is also a pathogen of concern in aquatic injuries; however, this organism is characterized by a more indolent course, and presumptive antibiotics covering *M. marinum* should not be administered routinely.[66,70]

Both *Vibrio* species and *A. hydrophila* are capable of causing virulent skin and soft tissue infections that may progress rapidly to necrotizing infections with systemic symptoms in the absence of adequate treatment. Systemic symptoms in sepsis associated with *Vibrio* infection include vomiting, fever, and hypotension, whereas *A. hydrophila* is typically associated with fever,

leukocytosis, malaise, and regional lymphadenopathy. Because of the potential for severe and life-threatening infections, patients with these symptoms or rapidly progressing wounds that have been exposed to saltwater or freshwater should be treated with presumptive antibiotics for *Vibrio* species or *A. hydrophila*, respectively, in conjunction with surgical debridement. Antibiotic selection for aquatic injuries should be based on whether the injury was exposed to saltwater or freshwater.[66,68] Saltwater exposure, of concern for *Vibrio* species, should be treated with a combination of doxycycline and a third- or fourth-generation cephalosporin. Alternatively, fluoroquinolones are effective for presumptive therapy, and some *Vibrio* species, such as *Vibrio parahaemolyticus*, are susceptible to trimethoprim-sulfamethoxazole. If left untreated, case fatality rates for *Vibrio vulnificus* exceed 30% in 24 hours and reach 100% at 72 hours, so antibiotics should be initiated as soon as possible if *Vibrio* is a suspected pathogen. *Aeromonas hydrophila* produces a chromosomally mediated β-lactamase enzyme, making it inherently resistant to penicillins and first-generation cephalosporins.[69] Aminoglycosides, trimethoprim-sulfamethoxazole, aztreonam, tetracycline, ciprofloxacin, and third- and fourth-generation cephalosporins all demonstrate activity against greater than 90% of strains of *Aeromonas* species.[68,69] For freshwater injuries, cefepime provides adequate empiric coverage of *Aeromonas*, as well as other common pathogens, including *S. aureus* and *S. pyogenes*. For injuries exposed to brackish water, a combination of saltwater and freshwater, coverage of *A. hydrophila* and *Vibrio* species is needed. Because there is no clear evidence to guide duration of therapy, antibiotic duration should be based on injury type, source control, and patient condition.[66]

Human and Animal Bites

Human and animal bites are one of the most common types of trauma injuries,[71] accounting for 1% of emergency department visits.[72] The lifetime prevalence of animal bites has been estimated to be greater than 50%, and most of these events occur during childhood. The majority of animal bites reported are dog bites, with cat bites and human bites making up a small minority.[73] Most bite wounds are mild and have little risk of infection with proper wound care.[72,73] However, puncture-type wounds and crush injuries are likely to become infected and can progress to tenosynovitis, septic arthritis, or osteomyelitis in severe cases if not treated.[73,74] Of note, cats' teeth are sharper and are more likely to cause puncture wounds and have a higher risk of becoming infected than dog bites.[75] Organisms isolated from dog and cat bites may include *Pasteurella* species, a facultative anaerobe associated with both purulent and nonpurulent wounds, and *Capnocytophaga canimorsus*, a virulent gram-negative bacteria associated with gangrene, high-grade bacteremia, and fatal septic shock.[74,76] Infections from mammalian bites are often polymicrobial, with both aerobes and anaerobes commonly isolated from these wounds. Polymicrobial wounds are likely to be associated with purulence or abscess, whereas nonpurulent wounds are typically caused by skin flora such as streptococci and staphylococci. Infections from human bites may include streptococci, staphylococci, *Eikenella corrodens*, and anaerobes such as *Fusobacterium* species, *Peptostreptococcus* species, *Prevotella* species, and *Porphyromonas* species.

Literature evaluating the benefit of presumptive antibiotics in human and animal bites is limited by small sample size and heterogeneous study design, which makes selecting patients most likely to benefit from treatment a challenge. No significant benefit of presumptive antibiotics has been seen in low-risk patients who present within 24 hours after dog bites,[77,78] but one randomized trial did show a significant benefit in patients, with cat bites presenting within 24 hours.[79] A randomized study of 48 patients showed a reduction of infection rates from 46% to 0% after human bites with the use of presumptive antibiotics. Conversely, a Cochrane review of eight small randomized trials found no difference with presumptive antibiotics for dog or cat bites, with the exception of hand bites, which were reduced from 28% to 2% with antibiotics.[80] A meta-analysis of randomized controlled trials indicated a benefit of presumptive antibiotics in patients with dog bite wounds, with a number needed to treat of 14.[81] The author concluded that because of the potential risks of presumptive antibiotic therapy, it is reasonable to limit treatment to patients at highest risk of infection.[82] Certain patient populations are particularly vulnerable to infection from bite wounds and are believed to be most likely benefit from presumptive antibiotics. These populations include those who are immunocompromised or asplenic, have advanced liver disease, have edema around the affected area, or have moderate to severe injuries involving the hands and face or who have penetrated the joint capsule.[74]

The most likely pathogens in both animal and human bites can be treated presumptively with ampicillin-sulbactam or, if oral therapy is appropriate, amoxicillin-clavulanate. In patients with a β-lactam allergy, doxycycline may be used as an alternative treatment. The recommended duration for presumptive treatment in high-risk patients is 3 to 5 days (Table 1).[74]

PHARMACOKINETIC CONSIDERATIONS IN TRAUMA PATIENTS

Trauma patients undergo unique physiologic changes that may significantly affect the pharmacokinetic profiles of antibiotics used to treat their injuries. Traumatic injuries lead to tissue damage that may activate a systemic inflammatory response, resulting in an increase in glomerular filtration rate (GFR) by up to 50% to 100%.[83] This supraphysiologic clearance mechanism, termed augmented renal clearance, is caused by increased cardiac output leading to increased organ perfusion. These patients may have a normal serum creatinine that is not reflective of their true renal clearance,[84] and up to 82% of patients with augmented renal clearance will not reach therapeutic concentrations of antibiotics at standard doses.[85] Trauma patients should be screened for augmented renal clearance with an 8- to 24-hour urine creatinine collection and may require empiric dose adjustments to attain pharmacodynamic targets.[84]

Additional evidence suggests that standard dosing of antimicrobials in bleeding patients may be inadequate because of the altered pharmacokinetics of antibiotics in patients with hemorrhagic shock.[86,87] Although more evidence is needed to confirm the benefit of adjusted antibiotic doses, Goldberg and colleagues[28] provide a Level 3 recommendation for a twofold to threefold dose increase in patients with hemorrhagic shock to be repeated after every 10 units of blood is transfused. Goldberg

and colleagues[28] also recommend against the use of aminoglycosides in patients with severe trauma injuries due to suboptimal activity. This is based on limited data from studies showing subtherapeutic aminoglycoside levels in trauma patients because of increased volume of distribution using both traditional and extended-interval dosing.[88,89] While it is crucial to ensure adequate dosing of all antibiotics in trauma patients, avoiding use of aminoglycosides completely eliminates a viable treatment option for many traumatic injuries. By using once-daily extended-interval dosing for aminoglycosides, it is possible to attain adequate serum levels while also limiting nephrotoxicity associated with these agents to 1.2%.[90] Aminoglycosides are included in many of the recommendations provided in this review and are preferred over other agents because of their targeted gram-negative spectrum and the limited collateral damage associated with aminoglycoside use.

CONCLUSIONS

Presumptive treatment in trauma injuries represents a unique role for antibiotic therapy, owing to the occurrence of bacterial contamination prior to the administration of antibiotics. The emergent nature of trauma injuries leads to many challenges with regard to antimicrobial therapy, particularly involving dosing and timing of antibiotics and the limited data indicating optimal duration for presumptive treatment. While evidence from randomized controlled trials is sparse for most types of trauma injury, there is a clear role to presumptive antibiotics in this setting. Balancing the benefits associated with presumptive antibiotic therapy with the risks associated with unnecessary antibiotic use is a challenge best met by limiting the antibiotic use to the minimum duration supported by evidence from well-designed studies.

AUTHORSHIP

All the authors contributed to the design, literature review, and manuscript development.

DISCLOSURE

The authors declare no conflicts of interest.

REFERENCES

1. Schimpff SC, Miller RM, Polkavetz S, Hornick RB. Infection in the severely traumatized patient. *Ann Surg*. 1974;179(3):352–357.
2. Baker CC. Immune mechanisms and host resistance in the trauma patient. *Yale J Biol Med*. 1986;59(4):387–393.
3. Velmahos GC, Toutouzas KG, Sarkisyan G, Chan LS, Jindal A, Karaiskakis M, Katkhouda N, Berne TV, Demetriades D. Severe trauma is not an excuse for prolonged antibiotic prophylaxis. *Arch Surg*. 2002;137(5):537–541.
4. Hindawi YH, Oakley GM, Kinsella CR Jr, Cray JJ, Lindsay K, Scifres AM. Antibiotic duration and postoperative infection rates in mandibular fractures. *J Craniofac Surg*. 2011;22(4):1375–1377.
5. Paterson DL. "Collateral damage" from cephalosporin or quinolone antibiotic therapy. *Clin Infect Dis*. 2004;38(suppl 4):S341–S345.
6. Brand M, Grieve A. Prophylactic antibiotics for penetrating abdominal trauma. *Cochrane Database Syst Rev*. 2009;(4):CD007370.
7. Fullen WD, Hunt J, Altemeier WA. Prophylactic antibiotics in penetrating wounds of the abdomen. *J Trauma*. 1972;12(4):282–289.
8. Luchette FA, Borzotta AP, Croce MA, O'Neill PA, Whittmann DH, Mullins CD, Palumbo F, Pasquale MD. Practice management guidelines for prophylactic antibiotic use in penetrating abdominal trauma: the EAST Practice Management Guidelines Work Group. *J Trauma*. 2000;4:508–518.
9. Schnüriger B, Inaba K, Eberle BM, Wu T, Talving P, Bukur M, Belzberg H, Demetriades D. Microbiological profile and antimicrobial susceptibility in surgical site infections following hollow viscus injury. *J Gastrointest Surg*. 2010;14(8):1304–1310.
10. Morales CH, Villegas MI, Villavicencio R, González G, Pérez LF, Peña AM, Vanegas LE. Intra-abdominal infection in patients with abdominal trauma. *Arch Surg*. 2004;139(12):1278–1285.
11. Thadepalli H, Gorbach SL, Broido PW, Norsen J, Nyhus L. Abdominal trauma, anaerobes, and antibiotics. *Surg Gynecol Obstet*. 1973;137(2):270–276.
12. Fabian TC, Hoefling SJ, Strom PR, Stone HH. Use of antibiotic prophylaxis in penetrating abdominal trauma. *Clin Ther*. 1982;(5 suppl A):38–47.
13. Oreskovich MR, Dellinger EP, Lennard ES, Wertz M, Carrico CJ, Minshew BH. Duration of preventative antibiotic administration for penetrating abdominal trauma. *Arch Surg*. 1982;117(2):200–205.
14. Nichols RL, Smith JW, Klein DB, Trunkey DD, Cooper RH, Adinolfi MF, Mills J. Risk of infection after penetrating abdominal trauma. *N Engl J Med*. 1984;311(17):1065–1070.
15. Jones RC, Thal ER, Johnson NA, Gollihar LN. Evaluation of antibiotic therapy following penetrating abdominal trauma. *Ann Surg*. 1985;201(5):576–585.
16. Heseltine PN, Berne TV, Yellin AE, Gill MA, Appleman MD. The efficacy of cefoxitin vs. clindamycin/gentamicin in surgically treated stab wounds of the bowel. *J Trauma*. 1986;26(3):241–245.
17. Nelson RM, Benitez PR, Newell MA, Wilson RE. Single-antibiotic use for penetrating abdominal trauma. *Arch Surg*. 1986;121(2):153–156.
18. Fabian TC, Croce MA, Payne LW, Minard G, Pritchard FE, Kudsk KA. Duration of antibiotic therapy for penetrating abdominal trauma: a prospective trial. *Surgery*. 1992;112(4):788–794.
19. Griswold JA, Muakkassa FF, Betcher E, Poole GV. Injury severity dictates individualized antibiotic therapy in penetrating abdominal trauma. *Am Surg*. 1993;59(1):34–39.
20. Fabian TC, Hess MM, Croce MA, Wilson RS, Wilson SE, Charland SL, Rodman JH, Boucher BA. Superiority of aztreonam/clindamycin compared with gentamicin/clindamycin in patients with penetrating abdominal trauma. *Am J Surg*. 1994;167(3):291–296.
21. Sims EH, Thadepalli H, Ganesan K, Mandal AK. How many antibiotics are necessary to treat abdominal trauma victims? *Am Surg*. 1997;63(6):525–535.
22. Kirton OC, O'Neill PA, Kestner M, Tortella BJ. Perioperative antibiotic use in high-risk penetrating hollow viscus injury: a prospective randomized, double-blind, placebo-control trial of 24 hours versus 5 days. *J Trauma*. 2000;49(5):822–832.
23. Bozorgzadeh A, Pizzi WF, Barie PS, Khaneja SC, LaMaute HR, Mandava N, Richards N, Noorollah H. The duration of antibiotic administration in penetrating abdominal trauma. *Am J Surg*. 1999;177(2):125–131.
24. Van Rensburg LC, Warren B, Warren V, Muller R. Ceftriaxone (Rocephin) in abdominal trauma. *J Trauma*. 1991;31(11):1490–1494.
25. Dellinger EP, Wertz JJ, Lennard ES, Oreskovich MR. Efficacy of short course antibiotic prophylaxis after penetrating intestinal injury. A prospective randomized trial. *Arch Surg*. 1986;121(1):23–30.
26. Claros M, Citron DM, Goldstein EJ, Merriam CV, Tyrrell KL. Differences in distribution and antimicrobial susceptibility of anaerobes isolated from complicated intra-abdominal infections versus diabetic foot infections. *Diagn Microbiol Infect Dis*. 2013;76(4):546–548.
27. Snydman DR, Jacobus NV, McDermott LA, Golan Y, Goldstein EJ, Harrell L, Jenkins S, Newton D, Pierson C, Rosenblatt J, Venezia R, Gorbach SL, Queenan AM, Hecht DW. Update on resistance of *Bacteroides fragilis* group and related species with special attention to carbapenems 2006–2009. *Anaerobe*. 2011;17(4):147–151.
28. Goldberg SR, Anand RJ, Como JJ, Dechert T, Dente C, Luchette FA, Ivatury RR, Duane TM. Prophylactic antibiotic use in penetrating abdominal trauma: an Eastern Association for the Surgery of Trauma practice management guideline. *J Trauma Acute Care Surg*. 2012;73(5 suppl 4):S321–S325.
29. Solensky R, Khan DA. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol*. 2010;105(4):259–273.

30. Antunez C, Blanca-Lopez N, Torres MJ, Mayorga C, Perez-Inestrosa E, Montañez MI, Fernandez T, Blanca M. Immediate allergic reactions to cephalosporins: evaluation of cross-reactivity with a panel of penicillins and cephalosporins. *J Allergy Clin Immunol*. 2006;117(2):404–410.
31. Hoff WS, Bonadies JA, Cachecho R, Dorlac WC. East Practice Management Guidelines Work Group: update to practice management guidelines for prophylactic antibiotic use in open fractures. *J Trauma*. 2011;70(3):751–754.
32. Rodriguez L, Jung HS, Goulet JA, Cicalo A, Machado-Aranda DA, Napolitano LM. Evidence-based protocol for prophylactic antibiotics in open fractures: improved antibiotic stewardship with no increase in infection rates. *J Trauma Acute Care Surg*. 2014;77(3):400–407.
33. Dellinger EP. Antibiotic prophylaxis in trauma: penetrating abdominal injuries and open fractures. *Rev Infect Dis*. 1991;13(suppl 10):S847–S857.
34. Hauser CJ, Adams CA Jr, Eachempati SR. Surgical Infection Society guideline: prophylactic antibiotic use in open fractures: an evidence-based guideline. *Surg Infect (Larchmt)*. 2006;7(4):379–405.
35. Vasenius J, Tulikoura I, Vainionpää S, Rokkanen P. Clindamycin versus cloxacillin in the treatment of 240 open fractures: a randomized prospective study. *Ann Chir Gynaecol*. 1998;87(3):224–228.
36. Dunkel N, Pittet D, Tovzaeva L, Suvà D, Bernard L, Lew D, Hoffmeyer P, Uçkay I. Short duration of antibiotic prophylaxis in open fractures does not enhance risk of subsequent infection. *Bone Joint J*. 2013;95-B(6):831–837.
37. Dellinger EP, Caplan ES, Weaver LD, Wertz MJ, Droppert BM, Hoyt N, Brumback R, Burgess A, Poka A, Benirschke SK, et al. *Arch Surg*. 1988; 123(3):333–339.
38. Bayston R, de Louvois J, Brown EM, Johnston RA, Lees P, Pople IK. Use of antibiotics in penetrating craniocerebral injuries. "Infection in Neurosurgery" Working Party of British Society for Antimicrobial Chemotherapy. *Lancet*. 2000;355(9217):1813–1817.
39. Kazim SF, Shamim MS, Tahir MZ, Enam SA, Waheed S. Management of penetrating brain injury. *J Emerg Trauma Shock*. 2011;4(3):395–402.
40. Jiminez CM, Polo J, España JA. Risk factors for intracranial infection secondary to penetrating craniocerebral gunshot wounds in civilian practice. *World Neurosurg*. 2013;79(5–6):749–755.
41. Kaufman HH, Schwab K, Salazar AM. A national survey of neurosurgical care for penetrating head injury. *Surg Neurol*. 1991;36(5):370–377.
42. Antibiotic prophylaxis for penetrating brain injury. *J Trauma*. 2001; 51(2 suppl):S34–S40.
43. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, Fish DN, Napolitano LM, Sawyer RG, Slain D, Steinberg JP, Weinstein RA; American Society of Health-System Pharmacists Infectious Disease Society of America Surgical Infection Society Society for Healthcare Epidemiology of America. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm*. 2013;70(3):195–283.
44. Brooke SM, Goyal N, Michelotti BF, Guedez HM, Fedok FG, Mackay DR, Samson TD. A multidisciplinary evaluation of prescribing practices for prophylactic antibiotics in operative and nonoperative facial fractures. *J Craniofac Surg*. 2015;26(8):2299–2303.
45. Peterson LJ. Antibiotic prophylaxis against wound infections in oral and maxillofacial surgery. *J Oral Maxillofac Surg*. 1990;48(6):617–620.
46. Campos GBP, Lucena EES, da Silva JSP, Gomes PP, Germano AR. Efficacy assessment of two antibiotic prophylaxis regimens in oral and maxillofacial trauma surgery: preliminary results. *Int J Clin Exp Med*. 2015;8(2):2846–2852.
47. Ratilal BO, Costa J, Pappamikail L, Sampaio C. Antibiotic prophylaxis for preventing meningitis in patients with basilar skull fractures. *Cochrane Database Syst Rev.* 2015;4:CD004884.
48. Demetriades D, Charalambides D, Lakhoo M, Pantanowitz D. Role of prophylactic antibiotics in open and basilar fractures of the skull: a randomized study. *Injury*. 1992;23(6):377–380.
49. Dunn LT, Foy PM. Anticonvulsant and antibiotic prophylaxis in head injury. *Ann R Coll Surg Engl*. 1994;76(3):147–149.
50. Borkar SA, Prasad GL, Gupta DK, Sinha S, Mahapatra AK. Compound elevated skull fracture: a clinical series of three patients with a review of the literature. *Turk Neurosurg*. 2013;23(4):514–517.
51. Miles BA, Potter JK, Ellis E III. The efficacy of postoperative antibiotic regimens in the open treatment of mandibular fractures: a prospective randomized trial. *J Oral Maxillofac Surg*. 2006 ;64(4):576–582.
52. Morris LM, Kellman RM. Are prophylactic antibiotics useful in the management of facial fractures? *Laryngoscope*. 2014;124(6):1282–1284.
53. Lauder A, Jalisi S, Spiegel J, Stram J, Devaiah A. Antibiotic prophylaxis in the management of complex midface and frontal sinus trauma. *Laryngoscope*. 2010;120(10):1940–1945.
54. Zallen RD, Curry JT. A study of antibiotic usage in compound mandibular fractures. *J Oral Surg*. 1975;33(6):431–434.
55. Chole RA, Yee J. Antibiotic prophylaxis for facial fractures: a prospective, randomized clinical trial. *Arch Otolaryngol Head Neck Surg*. 1987;113(10): 1055–1057.
56. Baliga SD, Bose A, Jain S. The evaluation of efficacy of post-operative antibiotics in the open reduction of the zygomatic and mandibular fracture: a prospective trial. *J Maxillofac Oral Surg*. 2014;13(2):165–175.
57. Zix J, Schaller B, Iizuka T, Lieger O. The role of postoperative prophylactic antibiotics in the treatment of facial fractures: a randomised, double-blind, placebo-controlled pilot clinical study. Part 1: orbital fractures in 62 patients. *Br J Oral Maxillofac Surg*. 2013;51(4):332–336.
58. Schaller B, Soong PL, Zix J, Iizuka T, Lieger O. The role of postoperative prophylactic antibiotics in the treatment of facial fractures: a randomized, double-blind, placebo-controlled pilot clinical study. Part 2: mandibular fractures in 59 patients. *Br J Oral Maxillofac Surg*. 2013;51(8):803–807.
59. Soong PL, Schaller B, Zix J, Iizuka T, Mottini M, Lieger O. The role of postoperative prophylactic antibiotics in the treatment of facial fractures: a randomised, double-blind, placebo-controlled pilot clinical study. Part 3: Le Fort and zygomatic fractures in 94 patients. *Br J Oral Maxillofac Surg*. 2014;52(4):329–333.
60. Schmidt RS, Dodson KM, Goldman RA. Prophylactic antibiotic therapy for fractures of the maxillary sinus. *Ear Nose Throat J*. 2015;94(4–5):170–177.
61. Bellamy JL, Monedijk J, Reddy SK, Flores JM, Mundinger GS, Manson PN, Rodriguez ED, Dorafshar AH. Severe infectious complications following frontal sinus fracture: the impact of operative delay and perioperative antibiotic use. *Plas Reconstr Surg*. 2013;132(1):154–162.
62. Jennett B, Miller JD. Infections after depressed fracture of skull. Implications for management of non-missile injuries. *J Neurosurg*. 1972;36(3):333–339.
63. Ignelzi RJ, VanderArk GD. Analysis of the treatment of basilar skull fractures with and without antibiotics. *J Neurosurg*. 1975;43(6):721–726.
64. Dagi TF, Meyer FB, Poletti CA. The incidence and prevention of meningitis after basilar skull fracture. *Am J Emerg Med*. 1983;1(3):295–298.
65. Villalobos T, Arango C, Kubilis P, Rathore M. Antibiotic prophylaxis after basilar skull fractures: a meta-analysis. *Clin Infect Dis*. 1998;27(2):364–369.
66. Noonburg GE. Management of extremity trauma and related infections occurring in the aquatic environment. *J Am Acad Orthop Surg*. 2005; 13(4):243–253.
67. Gold WL, Salit IE. *Aeromonas hydrophila* infections of skin and soft tissue: report of 11 cases and review. *Clin Infect Dis*. 1993;16(1):69–74.
68. Diaz JH, Lopez FA. Skin, soft tissue and systemic bacterial infections following aquatic injuries and exposures. *Am J Med Sci*. 2015;349(3):269–275.
69. Weber CA, Wertheimer SJ, Ognjan A. *Aeromonas hydrophila*—its implications in freshwater injuries. *J Foot Ankle Surg*. 1995;34(5):442–446.
70. Jernigan JA, Farr BM. Incubation period and sources of exposure for cutaneous *Mycobacterium marinum* infection: case report and review of the literature. *Clin Infect Dis*. 2000;31(2):439–443.
71. Stefanopoulos PK, Tarantzopoulou AD. Facial bite wounds: management update. *Int J Oral Maxillofac Surg*. 2005;34(5):464–472.
72. Ellis R, Ellis C. Dog and cat bites. *Am Fam Physician*. 2014;90(4):239–243.
73. Kennedy SA, Stoll LE, Lauder AS. Human and other mammalian bite injuries of the hand: evaluation and management. *J Am Acad Orthop Surg*. 2015;23(1):47–57.
74. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan SL, Montoya JG, Wade JC. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59(2):e10–e52.
75. Goldstein EJ. Bite wounds and infection. *Clin Infect Dis*. 1992;14(3):633–638.
76. Butler T. *Capnocytophaga canimorsus*: an emerging cause of sepsis, meningitis, and post-splenectomy. *Eur J Clin Microbiol Infect Dis*. 2015; 34(7):1271–1280.
77. Elenbaas RM, McNabney WK, Robinson WA. Prophylactic oxacillin in dog bite wounds. *Ann Emerg Med*. 1982;11(5):248–251.

78. Callaham M. Prophylactic antibiotics in common dog bite wounds: a controlled study. *Ann Emerg Med*. 1980;9(8):410–414.
79. Elenbaas RM, McNabney WK, Robinson WA. Evaluation of prophylactic oxacillin in cat bite wounds. *Ann Emerg Med*. 1984;13(3):155–157.
80. Zubowicz VN, Gravier M. Management of early human bites of the hand: a prospective randomized study. *Plast Reconstr Surg*. 1991;88(1): 111–114.
81. Henton J, Jain A. Cochrane Corner: antibiotic prophylaxis for mammalian bites (intervention review). *J Hand Surg Eur Vol*. 2012;37(8):804–806.
82. Cummings P. Antibiotics to prevent infection in patients with dog bite wounds: a meta-analysis of randomized trials. *Ann Emerg Med*. 1994; 23(3):535–540.
83. Roberts JA, Roberts MS, Semark A, Udy AA, Kirkpatrick CMJ, Paterson DL, Roberts MJ, Kruger P, Lipman J. Antibiotic dosing in the 'at risk' critically ill patient: linking pathophysiology with pharmacokinetics/ pharmacodynamics in sepsis and trauma patients. *BMC Anesthesiology*. 2011;11:3.
84. Hobbs AL, Shea KM, Roberts KM, Daley MJ. Implications of augmented renal clearance on drug dosing in critically ill patients: a focus on antibiotics. *Pharmacotherapy*. 2015;35(11):1063–1075.
85. Udy AA, Roberts JA, Boots RJ, Paterson DL, Lipman J. Augmented renal clearance: implications for antibacterial dosing in the critically ill. *Clin Pharmacokinet*. 2010;49(1):1–16.
86. Ericsson CD, Fischer RP, Rowlands BJ, Hunt C, Miller-Crotchett P, Reed L 2nd. Prophylactic antibiotics in trauma: the hazards of underdosing. *J Trauma*. 1989;29(10):1356–1461.
87. Reed RL 2nd, Ericsson CD, Wu A, Miller-Crotchett P, Fischer RP. The pharmacokinetics of prophylactic antibiotics in trauma. *J Trauma*. 1992; 32(1):21–27.
88. Townsend PL, Fink MP, Stein KL, Murphy SG. Aminoglycoside pharmacokinetics: dosage requirements and nephrotoxicity in trauma patients. *Crit Care Med*. 1989;17(2):154–157.
89. Toschlog EA, Blount KP, Rotondo MF, Sagraves SG, Bard MR, Schenarts PJ, Swanson M, Goettler CE. Clinical predictors of subtherapeutic aminoglycoside levels in trauma patients undergoing once-daily dosing. *J Trauma*. 2003;55(2): 255–260.
90. Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Quintiliani R. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. *Antimicrob Agents Chemother*. 1995; 39(3):650–655.