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PROPHYLACTIC ANTIBIOTICS FOR OPEN & CONTAMINATED EXTREMITY FRACTURES

Evidence Based Medicine Guideline

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SUMMARY
The administration of antibiotic prophylaxis in patients with open fractures is based on the classification of open fracture (e.g. Type I, II, III). Additionally, the choice of antibiotic agent(s) and duration of prophylaxis differs based on the type of open fracture and if contamination is present (e.g. freshwater, saltwater, soil, etc.).

RECOMMENDATIONS

- **Level 1**
  - None
- **Level 2**
  - Gram positive organism coverage is recommended in Type I and Type II open fractures.
  - Both Gram-positive and Gram-negative organism coverage is recommended in Type III open fractures.
- **Level 3**
  - Antibiotic prophylaxis should be administered as soon as possible and continued for 24 hours in Type I and II open fractures.
  - Cefazolin is recommended in non-contaminated Type I and II open fractures (use clindamycin if cephalosporin allergy present).
  - Antibiotic prophylaxis should be administered as soon as possible and continued for up to 72 hours, but no more than 24 hours after wound closure, in patients with Type III open fractures.
  - Piperacillin-tazobactam is recommended in patients with Type III open fractures (clindamycin +/- gentamicin may be used if penicillin allergy present).
  - For open fractures with saltwater contamination, add doxycycline for *Vibrio vulnificus* coverage.
  - For open fractures with freshwater contamination, ceftriaxone should be used for Type I and Type II fractures to cover *Aeromonas hydrophilia* and cefepime should be used for Type III fractures (use ciprofloxacin if cephalosporin allergy present).
  - For open fractures with soil contamination, antibiotics targeting *Clostridium* spp. are recommended (add metronidazole or switch to piperacillin-tazobactam if broader coverage needed).

INTRODUCTION

Open extremity fractures are common injuries that occur in the trauma population with a reported incidence of 31 per 100,000 patients (1). In conjunction with surgical intervention, these patients often receive prophylactic antibiotics to prevent complications including skin and soft tissue infections and osteomyelitis. Risk factors for infection following open fractures include severity of soft tissue injury, extent and type of contamination, timing of treatment, antibiotic prophylaxis, surgical intervention, and patient factors (1). Antibiotics should be administered within 1 hour of injury and continued for at least 24 hours to decrease the risk of infection. Antimicrobial therapy should be selected based on the type of open fracture (2).

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Supported by multiple, prospective randomized clinical trials or strong prospective, non-randomized evidence if randomized testing is inappropriate.
- **Level 2:** Supported by prospective data or a preponderance of strong retrospective evidence.
- **Level 3:** Supported by retrospective data or expert opinion.

Open extremity fractures are classified using the Gustilo-Anderson Classification System:

Table 1: Gustilo-Anderson Classification System (3)

Classification	Description
Type I	Open fracture with wound < 1 cm in length and clean
Type II	Open fracture with wound 1-10 cm without extensive soft-tissue damage, flaps, or avulsions
Type III	Open fracture with wound > 10 cm, with extensive soft tissue injury or amputation
Type IIIA	Adequate soft-tissue coverage of a fractured bone despite extensive soft-tissue laceration or flaps, or high-energy trauma irrespective of the size of the wound
Type IIIB	Extensive soft-tissue injury loss with periosteal stripping and bone exposure
Type IIIC	Open fracture associated with vascular injury requiring repair

Common bacteria that infect open fractures include skin flora (*Staphylococcus* spp., *Streptococcus* spp.). Expanded gram negative coverage is warranted in Type III open fractures to cover *Enterobacterales* spp. In contaminated open fractures, additional bacteria are introduced depending on the type of contamination (Table 1); thus, antibiotic prophylaxis should be modified to cover these organisms (4,5).

Table 2: Contaminants and Common Organisms (2,6,7)

Contamination	Common Bacteria
Saltwater	*Vibrio* spp.
Freshwater	*Pseudomonas* spp., *Aeromonas* spp.
Soil*	*Clostridium* spp.

*Soil contamination that does not respond to recommended therapy may warrant the addition of antifungal coverage, as fungi and molds can thrive in tropical climates (such as the Southeastern United States).

Additionally, the duration of antibiotic prophylaxis is also dependent on surgical intervention, contamination, and classification of open fracture.

LITERATURE REVIEW

Antibiotic Prophylaxis in Type I & II Open Fractures

Eastern Association for the Surgery of Trauma (EAST) guidelines recommend systemic antibiotics that cover Gram-positive organisms (8). Vasenius et al. performed a randomized prospective study evaluating clindamycin vs. cloxacillin for prevention of infection in patients with open fractures (n=227). The overall infection rate for the population was 15% with infection occurring in 9.3% of clindamycin-treated and 20% of cloxacillin-treated fractures ($p < 0.05$). All pathogens causing infection were Gram-positive organisms in Type I and Type II open fractures and in Type III open fractures there were both Gram-positive and Gram-negative organisms. Infection rates were 3.3% and 1.8% for Type I and II fractures, respectively, using clindamycin. Infection rates were 20% and 3.8% in Type I and II fractures, respectively, using cloxacillin. In Type III open fractures, both clindamycin and cloxacillin showed low effectiveness with the highest infection rates being 75% and 67%. This study highlights that compared to Type III open fractures, Type I and II fractures do not need additional Gram-negative organisms (9).

Yang et al. conducted a retrospective review of isolated Type I open fractures (10). All adult patients received cefazolin 1 g every 8 hours for at least 48 hours. None of the patients who underwent surgery for definitive treatment of fractures had evidence of infection and only one patient received operative debridement within 12 hours.

Chang et al. performed a systematic review and meta-analysis of randomized controlled trials to compare the effectiveness of antibiotic prophylaxis in patients with open fractures (Types I-III) (11). The authors found a large reduction in infection risk with antibiotic use (RR=0.37 [95% CI, 0.21 to 0.66], I^2=0%) with a risk difference of 9.6% fewer infections in the antibiotic prophylaxis groups (95% CI, 5.2% to 12.1%). Three trials evaluated the rates of infection after long duration (3-5 days) and shorter-duration (1 day) prophylactic antibiotic use. Two of the three

trials included the type of open fracture (Type I 25%, Type II 47%, Type III 28% and Type I 28%, Type II 29%, Type III 43%, respectively). Patients received first or second-generation cephalosporins given continuously for 3-5 days. Controls were single-dose cephalosporins, double-dose cephalosporins, and one day of second-generation cephalosporins or single-dose fluoroquinolone. Results demonstrated similar rates of infection between groups receiving 3-5 days and 1 day of antibiotics (RR=0.97 [95% CI, 0.69 to 1.27], I^2=0%), although the trials included mainly Type I and Type II fractures.

Antibiotic Prophylaxis in Type III Open Fractures

EAST guidelines recommend Gram-negative coverage in addition to Gram-positive coverage in patients with Type III open fractures (8). As mentioned above, Vasenius et al. performed a randomized prospective study evaluating clindamycin vs. cloxacillin for prevention of infection in patients with open fractures (9). In patients with Type III open fractures, 21 pathogens (57%) were Gram-positive, and 16 pathogens (43%) were Gram-negative. Both clindamycin and cloxacillin showed low effectiveness in the treatment of Type III open fractures with infection rates of 75% and 67% respectively, necessitating the importance of Gram-negative coverage.

Frantz et al. performed a retrospective comparative study of patients with Type II or Type III open fractures treated with either cefazolin (n=65), cefazolin plus an aminoglycoside (n=47), or piperacillin-tazobactam (n=90) in addition to irrigation and debridement and fracture fixation (12). Both cefazolin-based regimens had higher risk of delayed wound healing (OR 2.49; p=0.047) or superficial infection (OR 3.35; p=0.005) compared to piperacillin-tazobactam therapy. Use of cefazolin alone had higher odds of deep infection requiring return to the operating room compared to piperacillin-tazobactam (OR 3.65; p=0.009). A trend toward higher odds of nephrotoxicity with cefazolin plus aminoglycoside was also observed (OR 3.29; p=0.08).

Shawar et al. evaluated the use of piperacillin-tazobactam 4.5 g every 8 hours (n=23) versus tobramycin 7 mg/kg plus cefazolin 2 g every 8 hours or clindamycin (n=62) for antibiotic prophylaxis in Type III open fractures (13). All patients received “standard of care treatment” including early fracture evaluation, irrigation with normal saline and/or betadine, closed reduction, and splinting. Skin and soft tissue infection occurred in 17 patients (27.5%) in the tobramycin group and 1 patient (4.3%) in the piperacillin/tazobactam group at 30 days (p=0.033). Skin and soft tissue infection occurred in 3 additional patients in the tobramycin group at 60 days (p=0.009). There was no significant difference in adverse events, however, 32% of patients in the tobramycin group had 1 or more adverse events than the piperacillin tazobactam group (13%).

Redfern et al. conducted a retrospective cohort study to compare rates of surgical site infection in patients with Type III open fractures who received antibiotic prophylaxis with cefazolin plus gentamicin (n=37) vs. piperacillin/tazobactam (n=35) (14). Early antibiotic administration and operative debridement within 6-8 hours was performed in all patients if possible. Of the 72 patients included in the study, 23 patients experienced surgical site infections. A total of 21 patients had deep infections, and 8 patients had superficial infections occurring at 1 year. Rates of surgical site infection at 1-year were 32.4% in the cefazolin plus gentamicin group and 31.4% in the piperacillin/tazobactam group (p=1.0). There were no statistically significant differences in rate of 30-day surgical site infections between groups (21.6% vs 11.4%, p=0.35).

Regarding duration of antimicrobial therapy in Type III open fractures, EAST guidelines recommend antibiotics to be continued for 72 hours after injury or not > 24 hours after soft tissue coverage has been achieved (8).

Antibiotic Prophylaxis in Contaminated Open Fractures

Water Contamination:

Applebaum et al. recommends antibiotic therapy with doxycycline plus ceftazidime or a fluoroquinolone for saltwater contamination (2). For freshwater contamination, the authors recommend a fluoroquinolone or a 3rd or 4th generation cephalosporin.

Noonburg G recommends doxycycline and ceftazidime or a fluoroquinolone in patients with saltwater contamination (15). Freshwater contamination should be treated with ciprofloxacin, levofloxacin, or a 3rd or 4th-generation cephalosporin (e.g. ceftazidime, ceftriaxone).

Zhu et al. performed a descriptive study of open fractures contaminated by seawater (6). All patients received intravenous cephalosporin antibiotics and were taken to the operating room for further wound irrigation and debridement and stabilization of the fracture. Out of the 1397 patients included, 107 patients had seawater contamination. The overall wound infection rate of seawater contaminated wounds was significantly higher than that of wounds without seawater contamination (39% vs 21%, $p<0.001$). The rate of deep infection was significantly higher in the seawater contamination group in patients with Type III fractures (15.2% vs 5%, $p=0.03$). Sensitivity tests showed that levofloxacin, ciprofloxacin, and imipenem were the most effective antibiotics for the treatment of infection in seawater-contaminated wounds.

Soil Contamination/Farmyard Injuries:

Applebaum et al. recommend high-dose penicillin in patients with soil contamination (2). According to Moran et al., wounds with soil contamination are at higher risk for harboring *Clostridium tetani* and other *Clostridium* spp (16). Nakamura et al. recommend the addition of high-dose penicillin to established open fracture regimens to provide anaerobic overage against *Clostridium* spp (17). In order to avoid duplicate beta-lactam coverage, metronidazole can be added for anaerobic coverage instead in Type I and Type II fractures or in patients with penicillin allergies. In patients with Type III fractures and no penicillin allergy, piperacillin-tazobactam can be used as monotherapy.

Table 3: Antibiotic Prophylaxis for Contamination Based on Open Fracture Classification*

	No Contamination	**Freshwater Contamination**	**Saltwater Contamination**	**Soil Contamination**
Type I & II Fractures	Cefazolin 2g IV Q8H Allergy: Clindamycin 600 mg IV mg Q8H or 450 mg PO Q8H	Ceftriaxone 2 g IV Q24H Allergy: Ciprofloxacin 400 mg IV Q12H or 500 mg PO Q12H	Ceftriaxone 2g IV Q24H **PLUS** Doxycycline 100 mg IV/PO Q12H Allergy: Ciprofloxacin 400 mg IV Q12H or 500 mg PO Q12H **PLUS** Doxycycline 100 mg IV/PO Q12H	Cefazolin 2g IV Q8H **PLUS** Metronidazole 500 mg IV/PO Q12H Allergy: Clindamycin 600 mg IV Q8H or 450 mg PO Q8H
Type III Fracture	Piperacillin-tazobactam 4.5 g IV Q8H Allergy: Clindamycin 600 mg IV mg Q8H or 450 mg PO Q8H **+/-** Gentamicin 5-7 mg/kg IV	Cefepime 2g IV Q8H Allergy: Ciprofloxacin 400 mg IV Q12H or 500 mg PO Q12H	Piperacillin-tazobactam 4.5 g IV Q8H **PLUS** Doxycycline 100 mg IV/PO Q12H Allergy: Ciprofloxacin 400 mg IV Q12H or 500 mg PO Q12H **PLUS** Doxycycline 100 mg IV/PO Q12H	Piperacillin-tazobactam 4.5 g IV Q8H Allergy: • Cefepime 2 g IV Q8H **PLUS** Metronidazole 500 mg IV Q12H • Ciprofloxacin 400 mg IV Q12H or 500 mg PO Q12H **PLUS** Metronidazole 500 mg IV Q12H (if cephalosporin allergy)

*Recommended dosing regimens are based on normal renal function

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