Review Article

Antibiotic Prophylaxis in Open Fractures: Evidence, Evolving Issues, and Recommendations

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Abstract

Open fractures are often associated with high-energy trauma and have an increased risk of infection because of surrounding soft-tissue damage and the introduction of environmental contaminants that may communicate with the fracture site. The Gustilo-Anderson classification of open fractures has been used to guide prophylactic antibiotic therapy because different types of open fracture have been shown to have varying rates of surgical site infections with different combinations of pathogens. Prophylactic treatment with various classes of antibiotics, including penicillins and cephalosporins, aminoglycosides, and fluoroquinolones, has evolved over the past half century. More recently, broader spectrum agents including monobactams and glycopeptides have been used for additional coverage. Duration of antibiotic therapy remains variable between institutions, and antibiotic choice is not standardized. Coverage for nosocomial and multidrug-resistant organisms is an ongoing area of clinical research.

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An open fracture is any fracture accompanied by a break in skin that communicates with the fracture or its associated hematoma. To date, the Gustilo-Anderson classification (Table 1) is the most widely accepted classification system for open fractures and is often used to dictate antibiotic management.[1,2] Limitations have been described with this system, leading to alternatives such as the Orthopaedic Trauma Association Open Fracture Classification systems (OTA-OFC).[3] Concern for infection motivates the use of prophylactic antibiotics because traumatic injuries are responsible for up to 19% of cases of osteomyelitis.[4] However, pathogens demonstrate seasonal and geographic variation, as well as variation with fracture severity.[5] It is not surprising that confusion exists when discussing appropriate antibiotic management of open fracture patients with regard to both type of antibiotic and duration of use. The current review discusses today's antibiotic prophylaxis regimens and describes current research into more effective prophylaxis algorithm.

Classes of Prophylactic Antibiotics

Beta-Lactam Antibiotics

Penicillins and cephalosporins are beta-lactam antibiotics that work in a bactericidal fashion. They attach to penicillin-binding proteins and prevent cell wall synthesis, leading to cell lysis and death. Microbes can be resistant to beta-lactams, but penicillin continues to be the preferred antibiotic against *Clostridium* species

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Table 1

Gustilo-Anderson Classification of Open Fractures[1,2]

Type	Details
I	Open fracture with a wound less than 1 cm long, low energy, without gross contamination
II	Open fracture with a wound 1–10 cm long, low energy, without gross contamination or extensive soft-tissue damage, flaps, or avulsions
III	A: Open fracture with a wound greater than 10 cm with adequate soft-tissue coverage, or any open fracture due to high-energy trauma or with gross contamination, regardless of the size of the wound B: Open fracture with extensive soft-tissue injury or loss, with periosteal stripping and bone exposure that requires soft-tissue coverage in the form of muscle rotation or transfer C: Open fracture associated with arterial injury requiring repair

associated with barnyard injuries contaminated with soil or feces.[6] In a study of wound cultures from 352 consecutive open long bone fractures done in 1976, 60% grew gram-positive cocci susceptible to cephalothin.[1] Since then, first-generation cephalosporins have been the most common and most effective prophylactic agent given after open fractures. The infection rate after cefazolin prophylaxis is markedly lower when compared with the use of penicillin or streptomycin.[7] The early administration of first-generation cephalosporins in patients with open fractures is broadly supported as is evident in systematic reviews by both Isaac et al and Chang et al.[8,9] Because gram-positive cocci are the most common infectious agent in open fractures, the Surgical Infection Society, a consortium of surgeons and infectious disease specialists, suggests coverage with clindamycin in penicillin-allergic patients,[10] and the Eastern Association for the Surgery of Trauma updated its recommendations in 2011 to suggest usage of vancomycin in penicillin-allergic patients presenting to hospitals with a high rate of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infections.[6]

Piperacillin-Tazobactam

It is a bactericidal combination of a β-lactam and a beta-lactamase inhibitor that provides broad-spectrum gram-positive, gram-negative, and anaerobic coverage. Data on use in the setting of open fractures are limited, but Redfern et al[11] have demonstrated noninferiority in type III open injuries as monotherapy when compared with dual therapy with cefazolin and gentamicin. Use of piperacillin-tazobactam in this setting may serve to limit variability and confusion with regard to dosing, as well as limit potential adverse reactions to aminoglycosides in the setting of severe open injuries.

Monobactams

Aztreonam is a bactericidal antibiotic that also interferes with cell wall synthesis. It has activity against aerobic gram-negative organisms including *Pseudomonas aeruginosa*, but has no gram-positive or anaerobic coverage. It can be inactivated by extended-spectrum beta-lactamases. Aztreonam is not nephrotoxic but is renally excreted, and dose adjustment is required for patients with renal dysfunction.[12] Aztreonam can be used in place of an aminoglycoside, especially in patients at risk of kidney injury. It also may be used in penicillin-allergic patients with type III fractures in conjunction with gram-positive coverage.[13]

Lincosamides

They represent a small class of antibiotics that function to inhibit protein synthesis by binding to the 50S subunit of bacterial ribosomes. Within this class, clindamycin provides gram-positive coverage and is therefore commonly used and recommended in patients with open fractures who have an allergy to penicillin. Isolated data regarding the nuse of clindamycin in open fractures are limited because patients who are treated with clindamycin are generally pooled with those treated with cefazolin. Patzakis et al conducted a randomized controlled trial looking at clindamycin as a single agent in the prevention of infection in open fractures. Infection rates were comparable with the use of dual-agent therapy (cefamandole/gentamicin) for type I and type II open fractures.[14]

Aminoglycosides

These are concentration-dependent bactericidal antibiotics that work by inhibiting the 30S subunit of the bacterial ribosome. They act against most aerobic gram-negative organisms and were historically widely used for prophylaxis after open fractures[15] but have fallen out of favor because of dose-dependent reversible nephrotoxicity and irreversible ototoxicity. Gram-negative organisms are more likely to be the source of surgical site infections in type III open fractures, which therefore warrant broader coverage than a first-generation cephalosporin.[6] Therefore, aminoglycosides are commonly used in more severe

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open injuries as a way to prevent gram-negative infections.

Bankhead-Kendall et al[16] reported a series of 126 type III fractures treated at their institution over a five-year period. Antibiotic prophylaxis was based on the treating surgeons' preferences, and roughly half of patients (52%) were treated with a first-generation cephalosporin, while the other half (48%) were treated with the addition of an aminoglycoside. No difference in surgical site infection was seen, but a statistically notable increase in acute kidney injury was noted in those treated with aminoglycosides. Tessier et al[17] demonstrated no increased risk of acute kidney injury with prophylactic gentamicin administered at presentation, with an odds ratio of 0.22 (95% CI 0.02 to 2.44). However, they also demonstrated and increasing risk of acute kidney injury with higher injury severity scores and hypotension on presentation.[17] Redfern et al[11] demonstrated no statistical difference in infection rates at 30 days or 1 year after open injury when patients were given cefazolin and gentamicin or only piperacillin-tazobactam (32.4% versus 31.4%, $P = 1$).

Adverse effects attributed to use of aminoglycosides are exposure-dependent, and therefore, once-daily dosing of gentamicin, generally 5 mg/kg/d, is preferred if aminoglycosides are to be used.[18] In a study of 219 patients with type II or III open fractures, daily gentamicin dosing had a lower rate of infection when compared with divided dosing with the equivalent of 5 mg/kg/d given over three doses (6.7% versus 13.6), although this difference did not achieve statistical significance.[19] At the present time, there is insufficient evidence to support routine gram-negative coverage in prophylaxis for all open fractures.[10] Furthermore, given concerns for nephrotoxicity and a lack of evidence supporting its clinical efficacy, we recommend against the use of aminoglycosides in the prophylactic management of open fractures.

Fluoroquinolones

Fluoroquinolones exert a bactericidal effect by inhibiting DNA gyrase and topoisomerases and preventing bacterial DNA replication. They cover gram-positive microbes and a similar range of gram-negative organisms as aminoglycosides but confer a lower risk of nephrotoxicity and ototoxicity. Deep surgical site infection rates after type IIIA open fractures were 5.4% when covering with cefazolin and gentamicin and 6.5% when covering with cefazolin and ciprofloxacin in a series of 215 patients.[20] Elderly patients and those with independent risk factors for kidney injury due to trauma may benefit from combination prophylaxis with a first-generation cephalosporin and a fluoroquinolone rather than an aminoglycoside antibiotic.[17] Fluoroquinolone-only coverage had a 31% rate of infection in a combined analysis of all type III open fractures compared with 7.7% for a cephalosporin and aminoglycoside combination in a series of 171 open fractures; the infection rates were similar (5.8% and 6.0%, respectively) in type I and II open fractures.[14]

Although exact mechanisms are not clearly defined, some fluoroquinolones inhibit the hepatic metabolism of warfarin, heightening bleeding risk in elderly patients already on therapeutic anticoagulation.[21] Extreme caution should be used in the patient cohort, and fluoroquinolones should be avoided if possible. Fluoroquinolones also have a dose-dependent cytotoxic effect on bone healing in in vivo studies in rats.[22] Ciprofloxacin-treated rat femur fractures showed less bridging bone and diminished torsional strength than those treated with cefazolin 4 weeks after fracture. Cefazolin-treated fractures were not markedly different from the control in torsional strength or stiffness.[22] Histologically, ciprofloxacin treatment showed callus formation incompletely filled with hypocellular cartilage, indicating inhibition of endochondral ossification. Therefore, the use of fluoroquinolones is contraindicated in the pediatric open fracture patient, but effects on adults are less well-delineated.

Glycopeptides

Vancomycin, a glycosylated peptide produced by a soil bacterium, is an alternative choice for coverage against gram-positive organisms in penicillin-allergic patients.[6] Vancomycin inhibits bacterial synthesis by blocking peptidoglycan polymerization. It has time-dependent killing and is slowly bactericidal. Official guidelines state there is insufficient evidence for use of vancomycin alone as open fracture prophylaxis.[10] Vancomycin is now most often used to treat MRSA infections; however, MRSA carriers are more likely to develop MRSA surgical site infections regardless of prophylactic coverage with vancomycin, at a rate of 33% versus 1% in patients negative for MRSA colonization on routine admission surveillance ($P = 0.003$).[23] A review of 1,539 patients showed that the combination of vancomycin and cefepime reduced infection rates in type III open fractures by 3.7% ($P = 0.03$) compared with the combination of cefazolin and gentamicin.[24] In the same study, the rate of vancomycin-resistant MRSA was not markedly increased.

Current Treatment Recommendations

Antibiotic Prophylaxis

The Eastern Association for the Surgery of Trauma (EAST) recommends coverage for gram-positive bacteria with systemic antibiotics at the time of

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presentation for patients with an open fracture.[25] Gram-negative coverage should be added for type III open fractures, and high-dose penicillin should be added for barnyard injuries (ie, those likely to be contaminated with soil or feces).[26] The 2000 EAST guidelines suggest developing specific antibiotic coverage protocols for higher risk injuries such as type IIIB tibia fractures, but specific recommendations are not given.[25] The use of first-generation cephalosporins as soon as possible was also supported in 2011 by the Surgical Infection Society.[10] However, based on the available literature, they were unable to recommend for gram-negative or clostridial coverage.

Intraoperative Wound Cultures

Staphylococcus aureus is the most common cause of surgical site infection after open fracture fixation, while *Enterobacter cloacae* was the most commonly observed infectious species in baseline wound swabs.[27] Although baseline culture swabs taken intraoperatively from a series of 426 open fractures showed *S. aureus* was only seen in 3 patients' baseline swabs, it caused 30% of infections.[27] Patients with positive cultures for any organism during initial wound débridement were more likely to develop an infection, with an odds ratio of 1.92. Only 26.9% of those infections were caused by an organism seen on the initial cultures.[27] Although the clinical significance of these data is unclear, routine cultures at the time of injury are still not recommended.

Evolving Frontiers in Antibiotic Prophylaxis

Systemic Versus Local Therapy

There are no aggregate data in humans on the efficacy of topical antibiotic therapy without adjunct systemic prophylaxis.[25] A rat femur model of open femur fractures with 25-mg/kg vancomycin powder applied over the fracture site achieved average concentrations of 1.5 mg/g in surrounding muscle, 199 mcg/g in fractured bone, and 1.8 mcg/mL in plasma.[28] The fracture site concentration of vancomycin with topical application exceeded the typical concentration of vancomycin after intravenous (IV) dosing for 48 hours after application and was undetectable after 96 hours. A similar model of open femur fractures showed topical vancomycin is effective in reducing rates of surgical site infection as long as it is applied within 24 hours after injury and that it was present in detectable serum levels in 20% of specimens after 14 days.[29]

In a study of pelvic and acetabular fractures, topical vancomycin powder applied intraoperatively at the time of wound closure led to fewer surgical site infections and no increase in rates of renal failure: The risk of infection was 14.5% and 4.2% ($P = 0.04$) for the control and treatment groups, respectively.[30] Of note, the rate of infection after application of topical antibiotics was 71% lower in cases with estimated blood loss less than one liter compared with surgeries with a larger estimated blood loss.[30] Unpublished but presented data would suggest that infection rate was also decreased in high-risk fractures, including calcaneus, pilon, and bicondylar tibial plateau, if topical vancomycin was used at the time of definitive fixation and soft-tissue coverage.[31]

Topical application of glycopeptides may avoid systemic adverse effects, and initial in vivo models suggest that topical vancomycin application without systemic prophylaxis may achieve adequate bactericidal tissue concentrations.[28] The use of topical vancomycin is an evolving concept, and preliminary results are promising, but indications for use and dosing remain poorly defined.

Timing of Antibiotic Therapy

Timing of the first dose of antibiotic administration is a priority. Delayed administration of the first dose of antibiotic prophylaxis increases the risk of infection markedly.[32] With only cefazolin as prophylaxis, no deep surgical site infections were seen 90 days after type III open tibia fractures if antibiotics were given within 66 minutes of injury.[33] Seventeen percent of those receiving their first dose of antibiotics after 66 minutes developed deep surgical site infections.[33] This rate was unaffected by patient's smoking, diabetes, age, or injury severity score. There is no change in infection rate with delayed initial surgical treatment in a study of 736 patients[34]; time to surgical débridement is considered to be independent of infection risk as long as débridement is done within 24 hours of injury and gross contamination is not present.[35] Both EAST guidelines and Surgical Infection Society recommend administration of antibiotics as soon as possible.[6,10]

Duration of Therapy

Prolonged antibiotic therapy past 24 hours has not demonstrated a notable decrease in infection risk of open fractures including type III open fractures.[36] A series of 77 type II tibia fractures showed no difference in infection rate between 24 hours and 5 days of antibiotic treatment.[37] Independent of the severity of open fracture, 24 hours of treatment is noninferior to 5 days of treatment with a second-generation cephalosporin in a prospective randomized trial of 248 patients.[38] These findings were echoed in 2015 and 2017 systematic reviews demonstrating no benefit to extended antibiotic treatment.[9,39] EAST currently recommends discontinuing antibiotics 24 hours after wound closure in type I and

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II injuries regardless of the duration of antibiotic therapy between presentation and definitive surgery.[6] In type III open fractures, EAST recommends antibiotics for 72 hours after injury or 24 hours after soft-tissue coverage is achieved.[6] The Surgical Infection Society also found no evidence for prolonged antibiotic treatment.[10]

Coverage of Resistant Organisms

No additional clinical parameters have been developed to predict whether the microbe causing an infection would have been susceptible to the prophylactic antibiotic given at presentation other than the Gustilo-Anderson injury severity classification.[40] In 2008, a tertiary care institution introduced a new prophylactic regimen that excluded aminoglycosides, vancomycin, and penicillin.[13] In an effort to reduce use of broad-spectrum antibiotics and the resultant selection pressure toward resistant microorganisms, the authors used only cefazolin for type I and II open fractures (clindamycin for penicillin allergy) and ceftriaxone for type III open fractures (clindamycin and aztreonam for penicillin allergy). They saw no statistically notable change in surgical site infection rates compared across fracture sites or open fracture types. The MRSA infection rate stayed stable at 2.7% after the change from 3.0% before (P = 1.0). Multidrug-resistant organisms (MDROs) constituted 76.2% of preprotocol infections and 72.2% postprotocol infections (P = 1.0). Notably, aminoglycoside and glycopeptide use decreased from 53.5% to 16.4% ($P < 0.01$).[13]

Authors' Institutional Policy

Based on the available evidence, we have recently revised our institution's policy on antibiotic prophylaxis in the setting of an open fracture. The rational for this change was nonstandardized implementation of a previous policy and concern regarding the use of aminoglycosides in polytrauma patients who are already at elevated risk of acute renal injury due to hypotension and hypovolemia.[16,17] The following policy was developed in conjunction with our General Surgery Trauma division and our Pharmacy department and can be seen in Table 2.

Table 2

Authors' Institutional Policy for Antibiotic Prophylaxis in the Setting of Open Fractures

Type	Details
I and II	Cefazolin 2 g IV immediately and q8 hours × 3 total doses Penicillin allergic: Clindamycin 900 mg IV immediately and q8 hours × 3 total doses
III	Ceftriaxone 2 g IV immediately × 1 total dose Vancomycin 1 g IV immediately and q12 hours × 2 total doses Penicillin allergic: Aztreonam 2 g IV immediately and q8 hours × 3 total doses Vancomycin 1 g IV immediately and q12 hours × 2 total doses

Doses are adjusted based on patient weight when indicated.
IV = intravenous

The authors' institutional policy is to treat type I and II fractures with 2-gram IV cefazolin immediately and then every 8 hours (3 total doses). Type III fractures are given 2-gram IV ceftriaxone immediately (1 total dose) and 1 gram of IV vancomycin every 12 hours for 24 hours (2 total doses). If patients are allergic to penicillin, they are given 900-mg IV clindamycin immediately and then every 8 hours for 24 hours (3 total doses) for type I and II fractures; for type III fractures, they are given 2 grams of aztreonam every 8 hours for 24 hours (3 total doses) as well as 1 gram of vancomycin at the time of presentation and again 12 hours later (2 total doses). Penicillins are added at the discretion of the surgeon if there is fecal or farm contamination. Cultures are not routinely obtained. Doses are based on average body mass and can be adjusted based on weight as indicated. After débridement, antibiotics are continued or discontinued at the discretion of the treating surgeon based on intraoperative findings. Soft-tissue coverage occurs within 1 week of definitive fixation, provided the wound bed is clean and the patient is able to tolerate the planned procedure. All antibiotics are discontinued 24 hours after definitive wound closure unless there is a documented infection.

Summary

Open fractures have a high risk of infection and benefit from both surgical débridement and early antibiotic prophylaxis. There is a clear benefit to the administration of a cephalosporin for gram-positive coverage within 1 hour of presentation after injury. There is no evidence of benefit for the continued administration of antibiotics beyond 24 hours after definitive coverage or débridement and coverage with a sterile dressing.

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Many institutions continue to use aminoglycosides as prophylactic gram-negative coverage in severe open fractures. Prophylactic dosing of aminoglycosides has been shown to be relatively safe in patients without other independent risk factors for kidney injury. There are no current data to support routine prophylaxis with aminoglycosides in all open fractures. Fluoroquinolones should be considered in patients with type III open fractures and pre-existing kidney disease or risk factors for acute kidney injury. Vancomycin is being incorporated into prophylaxis protocols to reduce the incidence of community-acquired and nosocomial MRSA infections. Topical vancomycin powder has evidence for efficacy and avoids the risk of nephrotoxicity with intravenous administration, but should not be used without concomitant systemic antibiotic coverage, and optimal dosing has not yet been defined. Aztreonam can be used for gram-negative aerobic coverage in patients with kidney disease and in patients with a penicillin-allergy to avoid overuse of antibiotics covering MDROs. Although MDROs are becoming more prevalent in the community and in the hospital setting, there is inadequate evidence to suggest prophylactic antibiotic treatment can prevent subsequent MDRO infections.

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