CE 1.0 ANCC Contact Hours

Update in Therapeutics: Prophylactic Antibiotics in Open Fractures

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ABSTRACT

Acute management of open fractures is associated with high morbidity and mortality. Recommended antibiotic regimens for all Gustilo–Anderson fracture grades include first-, second-, and third-generation cephalosporins. Expanded gram-negative coverage is recommended for Grade II and III fractures if a first- or second-generation cephalosporin is selected, and additional anaerobic coverage is required if the open fracture is contaminated with organic or farm-related material. Open fractures endure a high rate of bacterial contamination, and antibiotics have demonstrated effectiveness at reducing infection rates when initiated early. Provided that the expected microbial spectrum is covered, antibiotics should be selected on the basis of patient-specific factors and hospital protocols.

Key Words

Gustilo, Injury, Open fracture, Prophylactic antibiotic, Trauma

Acute management of open fractures has historically been a priority and it continues to draw attention due to the high morbidity and mortality from associated complications. An open fracture is any bone fracture (primarily long bone, historically excluding digits) that involves soft tissue injury and communicates with the external environment. The overall amount of energy transferred via the mechanism of injury is related to the extent of trauma; open fractures are, therefore, more common in high-energy versus low-energy trauma. A wide variety of complications can occur secondary to the fracture such as compartment syndrome, nonunion, loss of function, neurovascular injury, infection, osteomyelitis, and amputation. High infection rates notoriously occur with open fractures, and wounds accompanying the fracture are presumed to become infected (Gustilo & Anderson, 1976). Subsequent research confirms the high rate of bacterial contamination in open fractures and demonstrates reduced infection rates when effective antibiotics are initiated early (Patzakis & Wilkins, 1989). Severity of open fractures is frequently categorized using the modified Gustilo–Anderson classification system and/or the abridged version (Table 1), though other classification systems have been explored. Prognostic value of the modified Gustilo–Anderson classification system assists with determination of treatment course; however, the high interobserver variability rate is a major limitation (Brumback & Jones, 1994). Overview of treatment for open fractures includes tetanus immunization, copious wound irrigation, operative debridement, definitive fixation, and prophylactic antibiotics. Appropriate prophylactic antibiotic selection and duration of therapy for open fractures continue to be a subject of discussion.

The most common bacteria associated with infections after open fracture include *Staphylococcus epidermidis, S. aureus*, β-hemolytic streptococci (e.g., *Streptococcus pyogenes*), and gram-negative bacilli (e.g., *Pseudomonas aeruginosa*, *Enterobacter cloacae*) (Bratzler et al., 2013; Robinson et al., 1989). Increased presence of methicillin-resistant *S. aureus* (MRSA) occurs in patients with any of the following: prior MRSA infection, prior MRSA nasal carriage, wound(s) present on admission, residents of nursing homes, recent prolonged health care exposure, and prior medical history consisting of diabetes mellitus or heart failure (McKinnell, Miller, Eells, Cui, & Huang, 2013). A prospective, randomized, nonblinded trial explored the safety and possible need for MRSA coverage in open fractures. Rates of MRSA colonization in the study population were similar to the general population (Saveli et al., 2013).

Recommended antibiotic regimens for all fracture grades include first-, second-, and third-generation cephalosporins (Table 2). Expanded gram-negative (EGN) coverage is recommended for Grade II and III fractures if a first- or second-generation cephalosporin is selected, and additional anaerobic coverage (e.g., penicillin G) is required if the open fracture is contaminated with organic or farm-related material. In the event of a true cross-sensitivity or allergy to cephalosporins, clindamycin and aztreonam may be considered for gram-positive and gram-negative coverage, respectively. [See Clinical Pearl section for updated information on penicillin cross-sensitivity.] Fluoroquinolones have been discouraged because of the proposed negative impact on fracture healing,

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The authors declare no conflicts of interest.

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DOI: 10.1097/JTN.0000000000000348

TABLE 1 Abridged Gustilo–Anderson Grading System[a]

Grade	Description
I	Wound <1 cm, clean, simple fracture pattern
II	Wound >1 cm, no extensive tissue damage, simple fracture pattern
IIIa	High-energy mechanism, extensive soft tissue damage with adequate coverage
IIIb	High-energy mechanism, extensive soft tissue damage with inadequate tissue coverage, wound contamination
IIIc	High-energy mechanism, extensive soft tissue damage with inadequate tissue coverage, wound contamination, plus arterial injury requiring repair, concerns for limb preservation

[a]*Adapted from Gustilo and Anderson (1976) and Gustilo, Mendoza, and Williams (1984).*

increasing bacterial resistance, and the lack of clear advantage over regimens containing a combination of a cephalosporin and gentamicin (Hoff, Bonadies, Cachecho, & Dorlac, 2011). Recommendations for a specific antibiotic and dose combination are not provided in open-fracture guidelines, but cefazolin and gentamicin are suggested (American College of Surgeons Trauma Quality Improvement Program [ACS TQIP], 2016; Hoff et al., 2011). Addition of vancomycin to the prophylactic antibiotic regimen is not necessary for routine coverage, but it would be reasonable to consider for patients who have elevated risk for developing MRSA infection (McKinnell et al., 2013). Provided that the expected microbial spectrum is covered, antibiotics should be selected on the basis of patient-specific factors and hospital protocols.

The landscape of open fracture antibiotic prophylaxis has been reshaped with the addition of impregnated antimicrobial devices. Several devices are available for use in open fracture management (e.g., beads and antiseptic-coated intermedullary nails); their role as adjunct to systemic antibiotics and possibly in place of systemic antibiotics is still being examined. Current literature has been in favor of their use, including a meta-analysis, which found a decreased infection rate in all grades of the Gustilo–Anderson classification. In addition, severe or Grade III fractures derived the most benefit from adjunct, impregnated implants (Craig et al., 2014).

Substantive literature providing impetus to change current practice has not been published since the most recent updates to the ACS TQIP and the Eastern Association for the Surgery of Trauma (EAST) guidelines. However, results from several studies have been published that support aspects of prophylactic antibiotic care and push to further question current practice. Rodriguez et al. (2014) compared an aminoglycoside-, penicillin-, and glycopeptide- (e.g., vancomycin) free protocol to retrospective data. This pre- and postprotocol implementation study analyzed 174 femur and tibia/fibula open fractures by stratifying both groups according to Gustilo fracture grade, National Healthcare Safety Network risk index, fracture site, and presence of resistant organisms. Implementation of an evidence-based, narrow-spectrum antimicrobial prophylaxis protocol resulted in similar infection rates (Rodriguez et al., 2014). Although there are several limitations to this study, there is validity in challenging the use of broad-spectrum antibiotics and aminoglycosides when potentially less toxic and more streamlined agents could be considered. Most recently, Lloyd et al. (2017) observed infections in respect to administration of EGN coverage in combat-related open fractures. Expanded gram-negative coverage was defined as the addition of a fluoroquinolone and/or aminoglycoside (e.g., gentamicin). Narrow antibiotic prophylaxis incorporated predominantly cefazolin and clindamycin but also included agents with broader coverage (e.g., ampicillin/sulbactam). Despite several flaws and limitations to this study, a small decrease in skin and soft tissue infections was observed with EGN coverage, but a decrease in osteomyelitis was not observed (Lloyd et al., 2017). However, it does generate questions and illustrate a need for further investigation regarding the use of EGN coverage.

Early initiation of prophylactic antibiotics and the duration of treatment are indisputably a crucial aspect in open

CLINICAL PEARL

Antimicrobial stewardship programs and results presented in the recent literature have reexamined the misconceptions surrounding a patient-stated penicillin allergy and the concern for cross-sensitivity with other agents. Original estimates of penicillin allergic patients experiencing cross-sensitivity with cephalosporins were projected using results from studies now older than 40 years, and reactions were reported to occur in as many as 10% of patients. More recent literature suggests that a true cross-sensitivity with cephalosporins occurs in only 2.2% of patients, and anaphylaxis occurs only in less than 0.01% (Macy & Contreras, 2015). The Centers for Disease Control and Prevention (CDC, 2017) states that although 10% of patients report an allergy to penicillin, less than 1% has a Type 1, immunoglobulin E-mediated hypersensitivity (i.e., reaction that occurs immediately or within an hour, hives, angioedema, wheezing/shortness of breath, or anaphylaxis). More than 75% of patients with a distant history of an allergy to penicillin are no longer sensitive after 10 years (CDC, 2017).

TABLE 2 Cephalosporin Generational Chart

First Generation	Second Generation	Third Generation	Fourth Generation	Fifth Generation
Cefazolin	Cefotetan	Cefotaxime	Cefepime	Ceftaroline
Cephalexin	Cefoxitin	Ceftazidime		
	Cefuroxime	Ceftriaxone		
	Cefaclor	Cefdinir		
	Cefprozil	Cefixime		
		Cefpodoxime		

fracture management. Some literature suggests initiating within 3 hr (Patzakis & Wilkins, 1989); ACS TQIP Best Practice Guidelines advocate for the administration of antibiotics in less than 1 hr of presentation to reduce risk of infection (ACS TQIP, 2016). The EAST Practice Management Guideline advocates starting antibiotics as soon as possible (highest-level recommendation) (Hoff et al., 2011). Antibiotics are continued for 24–72 hr depending on the severity of the open fracture and the time soft tissue coverage occurs. For Grade III fractures, the EAST Practice Management Guideline suggests (moderate-level recommendation) continuing antibiotics for 72 hr after injury but not greater than 24 hr from the time soft tissue coverage is achieved (Hoff et al., 2011). Chang et al. (2015) demonstrated through meta-analysis and systematic review that infection rates between longer duration (3–5 days) and shorter duration (one day) of antibiotics were no different. Authors of this review observed significant risk for bias and therefore, results cannot definitively change practice. Nonetheless, it sheds light on an area that requires further research.

The treatment of open fractures require emergent and thorough management. Prophylactic antibiotic therapy is a crucial part of the management to prevent infection and possibly osteomyelitis. Open fractures should be recognized and graded early so that prophylactic antibiotics can be administered as soon as possible and preferably within 1 hr of presentation. Further research may redefine the current recommendations determining the appropriate selection and duration of therapy.

KEY POINTS

- Open fractures endure a high rate of bacterial contamination, and antibiotics have demonstrated effectiveness at reducing infection rates when initiated early.
- Provided that the expected microbial spectrum is covered, antibiotics should be selected on the basis of patient-specific factors and hospital protocols.
- Antibiotic therapy is one component of a complex process for the management of open fractures: tetanus immunization, copious wound irrigation, operative debridement, definitive fixation, and prophylactic antibiotics.
- Discussion continues over the need to provide antibiotics with EGN or MRSA coverage and for the most appropriate duration of therapy; recent literature has yet to provide a substantial shift in practice.

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