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ORIGINAL ARTICLE

# Antibiotics and open fractures of the lower extremity: less is more

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## Abstract

**Purpose** Infectious complications in open lower extremity fractures contribute to significant morbidity. Historically, orthopedic guidelines have recommended Grade III fractures receive a first generation cephalosporin and an aminoglycoside. Despite these guidelines, few studies have evaluated the utility of adding an aminoglycoside in this patient population. At our trauma center, we have a unique trauma service where half of our surgeons treat Grade III open fractures with a cephalosporin alone and half use a cephalosporin + aminoglycoside. We hypothesized that our outcomes were the same between the two groups.

**Methods** We identified all Grade III fractures of the lower extremity admitted to our urban Level I Trauma Center over the 5-year study period. Charts were retrospectively reviewed to identify demographic information, injury severity score (ISS), fracture location, grade of fracture, type of antibiotic administered, incidence of acute kidney injury (AKI), surgical site infection (SSI), hardware removal, hospital length of stay (HLOS), and disposition. Patients were classified into two groups: those treated with a cephalosporin alone (CEPH) or cephalosporin + an aminoglycoside (CEPH + AG).

**Results** A total of 126 grade III fractures of the lower extremity were admitted our Trauma Center during the 5-year study period. There were 65 (52%) patients in the CEPH group and 61 (48%) in the CEPH + AG group. Demographics, ISS, fracture location, grade of fracture, rate of SSI, need for hardware removal, and disposition were not different between the two groups. In contrast, patients in the CEPH group had a 4% incidence of AKI, while the incidence was 10% of patients in the CEPH + AG group ($p < 0.05$).

**Conclusion** The addition of an AG to antibiotic prophylaxis in open lower extremity fractures was associated with a significant increase in AKI with no change in the incidence of wound infection or hardware removal. Cephalosporins alone may be sufficient for prophylaxis in Grade III open fractures of the lower extremity. A large-scale prospective randomized trial is needed to confirm these findings and inform clinical practice.

**Keywords** Trauma · Open fracture · Extremity fracture · Antibiotics · Prophylaxis

**Abbreviations**

| | |
|---|---|
| ISS | Injury severity score |
| ICU | Intensive care unit |
| LOS | Length of stay |
| SSI | Surgical site infection |
| DSI | Deep space infection |
| OSI | Organ space infection |
| AKI | Acute kidney injury |
| IM nail | Intramedullary nail |
| ORIF | Open reduction internal fixation |

## Introduction

In the United States, there are approximately 6 million fractures each year and 200,000 are classified as open fractures [1, 2]. Open fractures usually result from high-energy mechanisms when bone or bone fragments penetrate the skin and are exposed to the external environment [3]. Consequently, these types of fractures are at significantly increased risk for infectious complications and morbidity. Further, compared to closed fractures, open fractures are associated with higher

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rates of long-term dysfunction, and malunion [4]. Given the potential for severe disability, these injuries are typically treated very aggressively. Historically, an open fracture would result in early amputation, due to the concern for the development of overwhelming sepsis. However, with the development of aseptic technique, and later the introduction of antibiotic usage, the successful management of open fractures has become commonplace [4].

Today's standard of care includes the usage of antibiotics for the treatment of all open fractures [4]. Antibiotics should be administered as soon as possible following the injury. The class and duration of antibiotic therapy are highly variable but generally determined by the Gustilo and Anderson classification of open fractures [5, 6]. Currently, a first generation cephalosporin is recommended within 3 h of injury for all open fractures. In Grade III fractures, Gram-negative coverage is also recommended by orthopedic, trauma, and infectious society guidelines [7–9]. In clinical practice, this Gram-negative coverage is usually administered in the form of an aminoglycoside [4]. The data in support of this practice is scant. In addition, concerns over antibiotic overutilization, C. diff associated colitis, and the risk of nephrotoxicity has brought the usage of aminoglycosides into question. The trauma patient is particularly susceptible to renal injury due to factors such as renal hypoperfusion, intraoperative hypotension, and the concomitant administration of intravenous contrast agents for diagnostic and therapeutic interventions [4]. Trauma also affects our population without bias; as such, it is not uncommon to manage a trauma patient with pre-existing renal disease. Therefore, it is important to recognize the potential for renal injury and be cognizant of this during the management of complex trauma patients. The primary aim of this study is to investigate the necessity of aminoglycoside usage for patients with open Grade III lower extremity fractures.

## Methods

After IRB approval, a retrospective review of all patients ≥ 18 years of age, with grade III fractures of the lower extremity was conducted from 2010 to 2015. The Gustilo and Anderson classification was used to classify fractures (Table 1). Patients were divided into two groups: CEPH for patients treated with cephalosporin alone, while CEPH + AG had been with a cephalosporin and an aminoglycoside in combination. Patient demographics, injury specific parameters (ISS, mechanism of injury), grade of fracture, type of antibiotic administered, incidence of acute kidney injury (AKI), surgical site infection (SSI), hardware removal, HLOS, and disposition were recorded. AKI was defined using the RIFLE criteria as either a GFR decrease by 50% or a twofold increase of serum creatinine.

## Statistical analysis

All data were analyzed using SigmaPlot™ 11 software (Systat Software, Inc., San Jose, CA). Statistical difference between CEPH and CEPH + AG groups was determined by either Student's *t* test or Chi square as appropriate. A

**Table 1** Demographics and clinical data

| | Group 1 (CEPH) | Group 2 (CEPH + AG) | *p* value |
|---|---|---|---|
| Demographics | | | |
| Age (year) | 49 ± 22 | 45 ± 17 | 0.4 |
| Sex, male/female | *M* = 37 *F* = 19 | *M* = 22 *F* = 9 | 0.8 |
| Injury severity score (ISS) | 12 ± 10.3 | 11 ± 8.7 | 0.77 |
| Ethnicity | | | |
| Caucasian | 51% | 61% | N/A |
| African American | 32% | 23% | N/A |
| Hispanic | 11% | 10% | N/A |
| Asian | 2% | 0 | N/A |
| Other | 4% | 6% | N/A |
| Mechanism of injury | | | |
| Blunt | 86% | 90% | N/A |
| Penetrating | 14% | 10% | N/A |
| Cause of injury | | | |
| Motor vehicle crash (MVC) | 54% | 61% | N/A |
| Fall | 30% | 19% | N/A |
| Gunshot | 13% | 10% | N/A |
| Other | 3% | 10% | N/A |

$p \leq 0.05$ was considered statistically significant for all analyses.

## Results

Over the 5 year study period, there were 126 grade III fractures of the lower extremity admitted. Overall, patient demographics consisted of age (47 ± 20), sex (68% males vs 32% females) and ethnicity (55% Caucasian, 29% African American, 10% Hispanic, 1% Asian, and 5% other). The mechanism of injury consisted of (88% blunt vs 12% penetrative) and causes of injury (57% MVC, 26% falls, 12% gunshot, and 5% other). The ISS was (12 ± 10), and the hospital length of stay (HLOS) was (10 ± 10). In our patient population, there were 65 (52%) patients in the CEPH group and 61 (48%) in CEPH + AG group. The mean duration of antibiotic administration between the two groups was not different (CEPH 66 h vs CEPH + AG 72 h, $p = 0.4$) The vast majority of our patients received IV contrast during their initial evaluation (CEPH 94% vs CEPH + AG 91%, $p = 0.5$).

**Table 2** Comparison of injury characteristics and interventions

| | Group 1 (CEPH) (%) | Group 2 (CEPH + AG) (%) | *p* value |
|---|---|---|---|
| Fracture characteristics | | | |
| Fracture grade III | 100 | 100 | |
| Multiple orthopedic injuries | 32 | 42 | 0.6 |
| Surgical intervention | | | |
| ORIF | 59 | 48 | 0.47 |
| EX-fixation | 21 | 35 | 0.24 |
| IM nail | 13 | 9 | 0.96 |
| Wound vac | 11 | 13 | 0.95 |

The demographics of each group are similar and listed in Table 1. In addition, our cohorts did not differ in the incidence of other orthopedic injuries in addition to the open fracture (CEPH 48%, CEPH + AG 44% $p = 0.6$) or in the surgical interventions employed in the treatment of their injuries (Table 2).

Clinical parameters demonstrated no difference in the incidence of SSI, infectious-related hardware removal, HLOS, or ultimate disposition. In addition, there was no difference in mean baseline serum creatinine levels between the two groups (CEPH 1.12 mg/dL vs CEPH + AG 0.98 mg/dL). In contrast, patients in CEPH had a 4% incidence of AKI, while the incidence was 10% of patients in CEPH + AG ($p < 0.05$) (Table 3). Two patients from the CEPH + AG group required temporary renal replacement therapy compared to none in the CEPH group. All patients who suffered acute kidney injury did eventually recover and have a return to baseline renal function.

## Discussion

Open fractures result in soft tissue damage and subject the underlying tissues to contamination, which increases the risk of infection [10–12]. Risk factors for developing a fracture-related infection include location of the fracture, fracture severity, time to antibiotic administration, and time to operative management. Empirically, Grade I fractures correlate with a 0–2% rate of infection, Grade II fractures are associated with an infection rate between 2 and 10%, and Grade III fractures become infected 10–50% of the time [10, 11]. The current recommendations regarding the management of open fractures include the early administration of antibiotics. In fact, this has proven to be the most important predictor of subsequent infection. These same guidelines, recommend the addition of Gram-negative coverage for Grade III

**Table 3** Clinical outcomes

| | Group 1 (CEPH) | Group 2 (CEPH + AG) | *p* value |
|---|---|---|---|
| Clinical course events | | | |
| Acute kidney injury (AKI) | 4% | 10% | 0.05* |
| Surgical site infection | 7% | 5% | 0.99 |
| Hardware removal | 4% | 13% | 0.5 |
| Hospital length of stay (HLOS), days | 8 ± 9 | 13 ± 15 | 0.11 |
| Disposition | | | |
| Home | 78% | 90% | N/A |
| Rehabilitation | 9% | 10% | N/A |
| Skilled nursing facility | 2% | 0% | N/A |
| Transfer to another hospital | 2% | 0% | N/A |
| Mortality | 2% | 0% | N/A |

*$p$ value ≤ 0.05 is statistically significant

fractures [12]. A recent study has demonstrated that 76% of surgeons use aminoglycosides for prophylaxis in open fractures. Despite the recommendations and overwhelming clinical implementation, the use of aminoglycosides continues to be a topic of debate due to the scant evidence to support this practice and the potential risks associated with it [9].

When considering the need for empiric Gram-negative coverage for all Grade III open fractures, it is important to review the foundation of this management principle. In the landmark study from 1984, Gustilo reported that 77% of cultures isolated from open fractures were of Gram-negative bacteria. The conclusion was then made to advocate for the usage of aminoglycosides in high-grade injuries [11]. The benefit of Gram-negative coverage was never investigated, but rather arbitrarily made based on the culture isolates. Since that time the practice has remained, despite the lack of any convincing evidence to support it. A commonly referenced prospective, randomized, double-blinded study by Patzakis et al., demonstrated a numerical increase in infection in patients treated with ciprofloxacin alone compared to cefamandole/gentamicin, but the difference did not reach statistical significance. This study suffered from a small sample size (26 in each arm) and each arm technically had Gram-negative coverage. Therefore, the conclusion that aminoglycoside usage is necessary is yet to be validated [13]. Despite this, the current Eastern Association for the Surgery of Trauma (EAST) guidelines support Gram-negative coverage for Grade III fractures [7].

In 2006, however, the Surgical Infection Society concluded a thorough literature review to evaluate prophylactic antibiotic usage in open fractures [12]. They ultimately concluded, "There is insufficient evidence to support the use of antibiotic coverage extending to Gram-negative bacilli." Additionally in 2011, the United States military performed an evidence-based review on the topic of infection prevention as it relates to extremity injuries [14]. They concluded that the use of aminoglycosides is not supported in the literature. This conflict between the literature and official recommendations has led to significant variability in the care of these patients.

Aminoglycoside antibiotics have been well demonstrated to carry a significant risk of nephrotoxicity. This class of antibiotics has been associated with a 50% increase in baseline creatinine concentration in up to 20% of cases [15]. Recent orthopedic studies have demonstrated an increased incidence in AKI in patients undergoing elective joint replacement who receive prophylactic gentamycin [16]. Given the lack of data regarding the need for Gram-negative coverage in Grade III fractures as well as any specific data that demonstrates superiority of an aminoglycoside over other Gram-negative coverage, avoiding their use as a prophylactic agent seems straightforward. In fact, a recent study at a single institution involved the implementation of a new protocol to strictly enforce the use of ceftriaxone for all Grade III injuries [17]. Their study resulted in a significantly decreased use of aminoglycosides without an associated increase in infection rates. Our study was able to demonstrate that a cephalosporin alone was able to successfully prevent infectious complications, including hardware removal or reoperation, when compared to those patients treated with the addition of an aminoglycoside. Additionally, we established a significantly increased incidence of AKI when an aminoglycoside was used. Therefore, our data would suggest that not only is an aminoglycoside unnecessary for the treatment of Grade III open fractures, but also that it may be detrimental to the patient.

This study was a retrospective, single institution design and therefore has some inherent limitations. The retrospective nature allows for bias by limiting our control over confounding variables and data collection. For example, we were unable to ascertain whether rhabdomyolysis was a significant contributor to any renal dysfunction because patient creatine phosphokinase levels were unavailable. Also, as a single institution we had a relatively small sample size to analyze. Although enough to provide a statistically significant outcome, a larger patient population would allow for results that are more robust. Strengths of our study include our broad inclusion criteria, large sample size compared to contemporary series (60 per arm compared to 20 in other studies) and consistent application of orthopedic principles by being treated in the same trauma center.

Given the overwhelming prevalence of lower extremity injuries and potential for significant morbidity and long-term dysfunction, it is important to have quality evidence-based recommendations for their management. Unfortunately, no such evidence exists to support the current antibiotic recommendations for the management of Grade III fractures. In fact, the contrary is true, and much of the recent literature has been shown to be in direct opposition to the current guidelines. However, there have been some recent studies that demonstrate no association between aminoglycoside usage and AKI. Tessier et al. concluded that hypotension on admission and increased ISS were more closely associated with AKI and demonstrated no increased risk with aminoglycoside usage [18]. Pannell et al. performed a similar retrospective study and concluded that aminoglycosides carried no additional risk of AKI in patients with normal baseline renal function [19]. The current literature does not clearly delineate the best evidence-based practice, and in fact poses more questions. Such as is aminoglycoside coverage warranted at all, which patients are at greatest risk for AKI following antibiotic administration, and is there any role for local antibiotic beads rather than systemic treatment. Ultimately, large prospective trials are needed to determine the best antibiotic regimen and duration. Our study adds to the current literature and demonstrates an association between

aminoglycoside use and AKI; however, further research is required to make more generalized conclusions. We plan to continue our research and this work has provided the foundation for a prospective multi-center trial currently underway.

## Compliance with ethical standards

**Conflict of interest** Brittany Bankhead-Kendall, Tim Gutierrez, Jason Murry, Danny Holland, Vaidehi Agrawal, Khalid Almahmoud, Christopher Pearcy, and Michael S. Truitt declare that they have no conflict of interests.

**Statement of human and animal rights** All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

**Informed consent** After IRB review, this study was deemed exempt from informed consent.

## References


1. Court-Brown CM, Caesar B. Epidemiology of adult fractures: a review. Injury. 2006;37(8):691–7. doi:10.1016/j.injury.2006.04.130.
2. Cross WW 3rd, Swiontkowski MF. Treatment principles in the management of open fractures. Indian J Orthop. 2008;42(4):377–86. doi:10.4103/0019-5413.43373.
3. Zalavras CG, Marcus RE, Levin LS, Patzakis MJ. Management of open fractures and subsequent complications. J Bone Joint Surg Am Vol. 2007;89(4):884–95.
4. Zalavras CG, Patzakis MJ. Open fractures: evaluation and management. J Am Acad Orthop Surg. 2003;11(3):212–9.
5. Buckwalter JA. Advancing the science and art of orthopaedics: lessons from history. J Bone Joint Surg Am Vol. 2000;82-a(12):1782–803.
6. Kim PH, Leopold SS. In brief: Gustilo-Anderson classification. [Corrected]. Clin Orthop Relat Res. 2012;470(11):3270–4. doi:10.1007/s11999-012-2376-6.
7. 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):751–4. doi:10.1097/TA.0b013e31820930e5.
8. Bell S, Davey P, Nathwani D, Marwick C, Vadiveloo T, Sneddon J, et al. Risk of AKI with gentamicin as surgical prophylaxis. J Am Soc Nephrol JASN. 2014;25(11):2625–32. doi:10.1681/asn.2014010035.
9. Obremskey W, Molina C, Collinge C, Tornetta P 3rd, Sagi C, Schmidt A, et al. Current practice in the management of open fractures among orthopaedic trauma surgeons. Part A: management of segmental long bone defects. A survey of orthopaedic trauma association members. J Orthop Trauma. 2014;28(8):e203–7. doi:10.1097/bot.0000000000000033.
10. Hull PD, Johnson SC, Stephen DJ, Kreder HJ, Jenkinson RJ. Delayed debridement of severe open fractures is associated with a higher rate of deep infection. Bone Joint J. 2014;96-b(3):379–84. doi:10.1302/0301-620x.96b3.32380.
11. Patzakis MJ, Wilkins J. Factors influencing infection rate in open fracture wounds. Clin Orthop Relat Res. 1989 243:36–40.
12. 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. doi:10.1089/sur.2006.7.379.
13. Patzakis MJ, Bains RS, Lee J, Shepherd L, Singer G, Ressler R, et al. Prospective, randomized, double-blind study comparing single-agent antibiotic therapy, ciprofloxacin, to combination antibiotic therapy in open fracture wounds. J Orthop Trauma. 2000;14(8):529–33.
14. Murray CK, Obremskey WT, Hsu JR, Andersen RC, Calhoun JH, Clasper JC, et al. Prevention of infections associated with combat-related extremity injuries. J Trauma. 2011;71(2):S235–57. doi:10.1097/TA.0b013e318227ac5f.
15. Humes HD. Aminoglycoside nephrotoxicity. Kidney Int. 1988;33(4):900–11.
16. Bailey O, et al. Antibiotic-related acute kidney injury in patients undergoing elective joint replacement. Bone Joint J. 2014;96(3):395–8.
17. 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):400–7; discussion 7–8; quiz 524. doi:10.1097/ta.0000000000000398.
18. Tessier JM, et al. Prophylactic gentamicin is not associated with acute kidney injury in patients with open fractures. Surg Infect. 2016;17(6):720–3.
19. Pannell WC, et al. Antibiotic related acute kidney injury in patients treated for open fractures. Injury. 2016;47(3):653–7.