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Early Infectious Outcomes Following Addition of Fluoroquinolone or Aminoglycoside to Post-Trauma Antibiotic Prophylaxis in Combat-Related Open Fracture Injuries

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Abstract

Background—We examined combat-related open extremity fracture infections as a function of whether post-trauma antimicrobial prophylaxis included expanded Gram-negative (EGN) coverage.

Methods—Military personnel with open extremity fractures sustained in Iraq and Afghanistan (2009–2014) who transferred to participating hospitals in the United States were assessed. The analysis was restricted to patients with a U.S. hospitalization period of ≥ 7 days. Prophylaxis was classified as narrow (e.g., IV cefazolin, clindamycin, or amoxicillin-clavulanate) or EGN, if the prophylactic regimen included fluoroquinolones and/or aminoglycosides.

Results—The study population included 1044 patients, of which 585 (56%) and 459 (44%) received narrow and EGN coverage, respectively ($p<0.001$). Skin and soft-tissue infections (SSTIs) were more common among patients who received narrow prophylaxis compared to EGN coverage (28% versus 22%; $p=0.029$), while osteomyelitis rates were comparable between regimens (8%). Similar findings were noted when endpoints were measured at two and four weeks post-injury. There was no significant difference related to length of hospitalization between narrow and EGN regimens (median: 34 and 32 days, respectively) or operation room visits (median: 5 and 4). A higher proportion of EGN coverage patients had Gram-negative organisms isolated that were not susceptible to fluoroquinolones and/or aminoglycosides (49% versus 40%; $p<0.001$). In a Cox proportional model, narrow prophylaxis was independently associated with an increased risk of extremity SSTIs (Hazard Ratio: 1.41; 95% confidence interval: 1.09–1.83).

Discussion—Despite seeing a small benefit with EGN coverage related to a reduction of SSTIs, it does not decrease the risk of osteomyelitis and there appears to be a cost of increased antibiotic resistance associated with use. Overall, our findings support the current post-combat trauma antibiotic prophylaxis guidelines, which recommend use of cefazolin or clindamycin with open fractures.

Level of Evidence—Prognostic/Epidemiological Level I

Keywords

clinical practice guidelines; antimicrobial prophylaxis; combat-related infections; extremity infections; open fractures

BACKGROUND

Antimicrobial prophylaxis and thorough debridement are important interventions in the prevention of infectious complications following combat-related traumatic injury. While the use of prophylactic antibiotics active against Gram-positive organisms is uniformly recommended in all relevant post-trauma antimicrobial prophylaxis guidance,^{1–5} the value of expanded Gram-negative (EGN) coverage (e.g., addition of fluoroquinolones and/or aminoglycosides) is uncertain. In particular, two prominent guidelines have divergent recommendations about the role of EGN coverage in Type III open fractures for the prevention of skin and soft-tissue infections (SSTIs) and osteomyelitis.^{1,5} Due to these conflicting recommendations, the development of clear guidance for combat-related trauma proved to be challenging.

Clinical practice guidelines (CPGs) for the prevention and management of post-trauma infections are based on civilian trauma data^{1,2,5–10} where trauma commonly presents with different injury mechanisms (e.g., lower rate of blast injuries), reduced injury severity, and shorter route to tertiary care hospital (as opposed to combat trauma care, which begins in

combat zone and is followed by medical evacuation from theater to a regional hospital before transport to the United States). As a result, the Department of Defense (DoD) Joint Trauma System convened an expert consensus panel to develop guidelines for use in the military setting. The first CPG for the prevention of infections following combat-related trauma was published in 2008 and recommended using cefazolin or clindamycin for post-traumatic antibiotic prophylaxis with all open fractures.¹¹ In 2010, contrasting recommendations were included in a guidance document published by the Joint Trauma System (based on civilian guidelines),^{5,9} which advocated use of EGN coverage along with a Gram-positive regimen when there were Type III open fractures and maxillofacial injuries. These contradictory recommendations were reconciled when a revised CPG (published in 2011)¹² and a corresponding Joint Trauma System guidance document (released in 2012)¹³ both recommended against the addition of EGN coverage to post-trauma antibiotic prophylaxis for open fractures.

Following circulation and publication of the revised CPG in 2011, antibiotic stewardship efforts focused on reducing the use of broad-spectrum antibiotic prophylaxis, along with decreasing the duration of prophylaxis. Specifically, the proportion of wounded military personnel with open fractures who received EGN coverage as part of post-traumatic antibiotic prophylaxis decreased from above 50% to less than 10% in 2013–2014.¹⁴ This marked change in practice patterns allowed us to retrospectively evaluate infectious outcomes in patients with comparable injury severity who sustained open extremity fractures based on whether they did or did not receive EGN coverage (i.e., fluoroquinolones or aminoglycosides).

METHODS

Study Population and Data Collection

Trauma patients were eligible for inclusion in the analysis if they were DoD beneficiaries, 18 years of age or older, and sustained at least one deployment-related open extremity fracture in either Iraq or Afghanistan (June 1, 2009 – May 31, 2014) requiring medical evacuation to Landstuhl Regional Medical Center (Germany) before transitioning to a participating military hospital in the United States. The study population was restricted to patients who were hospitalized for at least seven days in the United States. Data were collected from the time of injury until the patient was discharged from their initial trauma U.S. hospitalization as part of an observational cohort study, the Trauma Infectious Disease Outcomes Study (TIDOS), which was designed to assess the short- and long-term infectious complications related to deployment-related traumatic injuries.¹⁵ This study was approved by the Infectious Disease Institutional Review Board of the Uniformed Services University of the Health Sciences (Bethesda, MD).

Patient data (e.g., age, sex, and military status) and injury characteristics (e.g., injury mechanism, specific traumatic injury pattern, and date/location of injury) were obtained from the DoD Trauma Registry,¹⁶ while infection-related information was retrieved from the supplemental TIDOS infectious disease module.¹⁵ Infections (SSTIs and osteomyelitis) were identified using clinical findings and laboratory test results by reviewing medical records and were classified based upon National Healthcare Safety Network (NHSN)

standardized definitions (Table 1).^{15,17} Infectious disease events were included if there was a clinical diagnosis associated with directed antimicrobial treatment (duration: 5 days for SSTIs and 21 days for osteomyelitis) even if the *a priori* definitions were not met. An infection was excluded from the analysis if an alternate diagnosis was recorded along with discontinuation of antimicrobial therapy. Multidrug-resistant organisms (MDROs) were identified based on NHSN definitions¹⁸ and were collected as part of admission infection control-based surveillance swabs, as well as clinical infection work-ups.

Injury Characterization and Classification

Information related to injury characteristics were obtained from the DoD Trauma Registry and standardized into Abbreviated Injury Scale-defined codes¹⁹ using Tri-Code, an injury coding software system (Digital Innovations, Inc., Forest Hill, MD). Using these anatomically-based injury codes allowed for the categorization of distinct injury types by specific body regions.

Antimicrobial Prophylaxis Classification

As previously described,^{14,20} antibiotic usage was determined through prospective medical record review. Antibiotic prophylaxis regimens were classified as narrow or EGN for the analysis. Narrow antibiotic prophylaxis was defined as any use of cefazolin or clindamycin. Since many patients transited coalition treatment facilities where IV amoxicillin-clavulanate was used as a substitute for cefazolin, this antibiotic (and ampicillin-sulbactam) was also classified as narrow. Coverage was defined as EGN if the patient received a fluoroquinolone (e.g., levofloxacin) and/or aminoglycoside (e.g., gentamicin) in addition to narrow coverage. Patients who received macrolides, antifungals (prescribed due to concern for invasive fungal infections), oral antibiotics (with the exception of oral levofloxacin), and/or antibiotics traditionally used to target MDROs (e.g., carbapenems, piperacillin-tazobactam, and vancomycin) were excluded from the analysis. Patients were also excluded if they did not receive any antibiotics. Patients who received doxycycline for antimalarial prophylaxis (per DoD regulations)²¹ were not excluded from the analysis. Antimicrobial prophylaxis was assessed in the period immediately following injury up to 48 hours (i.e., day of injury and day after the injury) to account for the potential of documentation omissions and multiple transitions of care associated with combat trauma care/medical evacuation.^{20,22} Antibiotics provided immediately after injury prior to admission to combat support hospitals were not included in the analysis.

Statistical Analysis

Primary endpoints were defined prospectively, including SSTI, osteomyelitis, isolation of MDROs, and *Clostridium difficile* infections. Resistance of Gram-negative organisms to fluoroquinolones and aminoglycosides was also assessed. Secondary endpoints included mortality, length of hospitalization, and trips to the operating room.

Categorical variables were compared using Fisher's exact and Chi square tests. Kruskal-Wallis test was used to compare overall continuous variable distributions. Cox proportional hazard univariate and multivariate analyses were used to examine risk factors in time-to-infection models. Kaplan-Meier plots were used to examine time to first infection. Statistical

analysis was performed with SAS® version 9.3 (SAS, Cary, NC). Significance was defined as $p < 0.05$.

RESULTS

Study Population

During the study period (June 2009 - May 2014), there were 2564 patients with combat-related trauma transitioned through the medical evacuation pipeline to a participating U.S. hospital. Of these trauma patients, 419 had a hospitalization period less than seven days and 791 did not have qualifying extremity trauma, so they were excluded. An additional 310 trauma patients were excluded based on their antibiotic prophylaxis regimen. As a result, 1044 military personnel who sustained an open extremity fracture met the inclusion criteria for the analysis.

The 1044 trauma patients were primarily male (99%) and injured in support of operations in Afghanistan (95%) via a blast mechanism (81%), resulting in severe injuries (injury severity score [ISS]²³ median of 22; Table 2). The median duration of hospitalization for the study population was 33 days. Patients with only lower extremity open fractures were the majority (58%), whereas patients with open fractures of either both the upper and lower extremities or only upper extremities represented 24% and 19% of the study population, respectively. Injury codes based on general anatomic site for open fracture varied with 'lower leg' ($n=608$), 'thigh' ($n=364$), and 'forearm' ($n=223$) being predominant. When specific bones were identified, 36% of patients had a fracture of the tibia/fibula only, 13% with a femur fracture only, and 22% with a fracture of both tibia/fibula and femur.

A total of 585 (56%) patients received a narrow post-trauma antibiotic regimen, while 459 (44%) received EGN coverage ($p < 0.001$). Patients who received EGN coverage had a larger proportion of blast injuries (84% versus 79%; $p = 0.025$; Table 2); however, there was no significant difference in injury severity (median ISS: 22 for both groups) or units of blood transfused within 24 hours (median of 9 versus 10). In addition, 427 (93%) and 554 (95%) patients in the EGN coverage and narrow regimen groups ($p = 0.260$), respectively, received doxycycline antimalarial prophylaxis.

Antimicrobial Use Patterns

Narrow prophylaxis was exclusively cefazolin (and/or clindamycin) for 74% of patients, whereas 26% received at least one dose of a beta-lactam beta-lactamase inhibitor (e.g., IV amoxicillin-clavulanate). For patients with EGN coverage, 81% received a fluoroquinolone in addition to a narrow regimen, 10% received an aminoglycoside, and 9% received both a fluoroquinolone and aminoglycoside. Narrow-spectrum antibiotics were received by all but six patients in the EGN group. When a patient's regimen was classified as narrow, they had a significantly shorter duration of antibiotic use (median: 3 days; interquartile range: 2–6 days) compared to use of narrow-spectrum antibiotics among patients in the EGN group (median: 6 days; interquartile range: 3–11 days; $p < 0.001$). Over the study period, use of EGN prophylaxis significantly declined from 73% during 2009–2010 to 6% in 2013–2014 ($p < 0.001$).

Non-Infection Outcomes

Between the patients who received EGN coverage and a narrow regimen, there was no significant difference in number of operating room visits (median of 4 versus 5, respectively) or duration of hospitalization (median of 32 versus 34 days) (Table 3). There was also no difference in mortality between the two groups and the deaths that occurred were in very severely injured soldiers and not due to SSTI or osteomyelitis.

Among patients who received EGN coverage, 49% had Gram-negative organisms isolated (from any site) that were not susceptible to fluoroquinolones and/or aminoglycosides compared to 40% among patients who received a narrow regimen ($p<0.001$; Table 3). When restricted to patients with Gram-negative organism recovery (311 patients with EGN coverage and 433 patient in the narrow regimen group), the proportion of organisms that were resistant to fluoroquinolones and/or aminoglycosides was 73% and 55%, respectively.

Infection Outcomes

A total of 262 patients developed SSTIs, of which 235 had SSTIs that were classified as deep (i.e., involves deep soft tissues, such as fascia and muscle layers of the wound), while 45 were categorized as superficial (i.e., involves only skin and subcutaneous tissue). Eighteen patients had both deep and superficial SSTIs. Among the 262 patients, 28% had a SSTI event involving the lower leg (e.g., tibia/fibula), 42% the thigh (e.g., femur), and 11% had infections with both the lower leg and thigh. The majority of extremity SSTI events fulfilled the NHSN diagnostic criteria (94%), whereas only a few (6%) qualified as an infection event based only on antibiotic use directed at the wound for greater than five days. Extremity SSTIs were more common in patients who received narrow prophylaxis (28% versus 22%; $p=0.029$; Table 3).

Eighty-two patients developed osteomyelitis with the lower leg and thigh being the site of infection for 34% and 29% of patients, respectively. The proportion of osteomyelitis was comparable between regimen groups (8%). In addition, there was no significant difference in the isolation of a MDRO (colonizing and/or infecting isolates), methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococcus* within the first two weeks of injury with narrow prophylaxis and EGN coverage. Furthermore, there was also no significant difference in the proportion of non-extremity infections and *Clostridium difficile* infections between the groups.

Time to first SSTI and osteomyelitis diagnosis was a median of 7 (interquartile range: 4–13 days) and 17 days (interquartile range: 8–28 days) post-injury, respectively. Time to infection was also analyzed after the removal of eight SSTI and six osteomyelitis outliers because their infection was diagnosed outside of 45 days from date of injury. Using this subset, patients who received a narrow regimen had a shorter duration following injury to development of SSTIs (Figure 1a). When the SSTIs were restricted to deep SSTIs (data not shown), representing 90% of SSTI events, the results were similar. There was no statistical difference related to timing of osteomyelitis onset between the narrow and EGN treatment groups (Figure 1b).

Gram-negative MDRO infections were common and seen in 79 (30.2%) open fracture patients with SSTIs and 29 (35.4%) patients with osteomyelitis. Notably, of the open fracture patients who developed SSTIs, 34% (34 out of 100) who received EGN coverage had Gram-negative MDRO infections versus 28% (45 out of 162) of those that received narrow coverage ($p=0.286$). Comparable proportions were seen in open fracture patients who developed osteomyelitis where 36% (13 out of 36) and 35% (16 out of 46) of osteomyelitis patients who received EGN and narrow regimens, respectively, had infections involving Gram-negative MDROs ($p=0.901$).

In the unadjusted Cox proportional hazard model used to assess the association of prophylaxis and injury-related factors on the timing of infections following injury, receiving narrow prophylaxis was associated with an increased risk of any extremity wound infection (hazard ratio [HR]: 1.39; 95% confidence interval [CI]: 1.10–1.74) and a SSTI (HR: 1.39; CI: 1.08–1.78). Nevertheless, there was no statistical association with osteomyelitis (HR: 1.00; CI: 0.65–1.55). There was also an increased risk of any extremity wound infection and SSTI with an ISS ≥ 16 (HR: 3.37; CI: 1.55–7.31 and HR: 3.37; CI: 1.46–7.78, respectively). Sustaining a blast-related injury (HR: 3.96 [CI: 2.46–6.38] and HR: 4.30 [CI: 2.51–7.37]), admission to the intensive care unit at LRMC (HR: 1.76 [CI: 1.19–2.60] and HR: 2.16 [CI: 1.39–3.38]) and to a United States based hospital (HR: 3.30 [CI: 2.46–4.41] and HR: 4.30 [CI: 3.07–6.02]), and use of narrow-spectrum antibiotics for 0–3 days (HR: 1.65 [CI: 1.25–2.18] and HR: 1.70 [CI: 1.25–2.31]) and 4–6 days (HR: 1.67 [CI: 1.23–2.27] and HR: 1.69 [CI: 1.21–2.38]) were also significantly associated with risk of any extremity infection and SSTI, respectively. No injury-related or antibiotic duration variables were associated with osteomyelitis risk.

In the adjusted model (Table 4), receipt of narrow prophylaxis remained independently associated with risk of any extremity infection and SSTIs; however, there was no significant association with prophylaxis regimen and osteomyelitis risk. For any extremity infection and SSTIs, sustaining a blast injury and admission to the intensive care unit at a U.S. hospital were also significantly associated with infection risk. Severe injuries (ISS >15) and critical injuries (ISS ≥ 26) were also associated with risk of any extremity infection and SSTIs, respectively. Having a narrow-spectrum antibiotic duration of ≥ 6 and ≥ 3 days was also significantly associated with risk for any extremity wound infection and SSTI, respectively. There were no factors significantly associated with risk of osteomyelitis. Prophylaxis regimen, antibiotic duration, and injury variables were also assessed in a logistic regression model with similar results (data not shown).

Furthermore, a Cox proportional hazard analysis was performed with the same variables after excluding 305 patients (151 and 153 in the narrow regimen and EGN coverage groups, respectively) who received a beta-lactam beta-lactamase inhibitor medication. Similar to the overall study population, use of a narrow regimen in open fractures slightly increased the risk of SSTI (HR: 1.80; CI: 1.28–2.54), but did not increase the risk of osteomyelitis (HR: 1.33; CI: 0.75–2.35). The analysis was also run on a smaller cohort restricted to patients with blast injuries (excluded 198 patients with non-blast injuries [125 and 73 in the narrow regimen and EGN coverage groups respectively]). Similar to the other models, SSTI rates

were lower with EGN coverage (HR: 1.46; CI: 1.12–1.91), and there was no increased risk of osteomyelitis (HR: 0.94; CI: 0.58–1.51).

DISCUSSION

In the years leading up to the publication of the 2011 CPG, DoD combat-related antibiotic prophylaxis recommendations (e.g., 2008 CPG and 2010 Joint Trauma System guidance) were contradictory. This reflected the disagreement on the need for EGN coverage between the Joint Trauma System trauma team members and mirrored the controversy in the civilian trauma literature regarding the use of EGN post-trauma antibiotic prophylaxis in the management of Type III open fractures.^{1,4,5,24–27} The 2011 CPG¹² (and follow-on internal 2012 Joint Trauma System guidance¹³) standardized recommendations for Joint Trauma System trauma providers with the goal of reducing practice variability in the fast-moving and austere environment, which complicates combat trauma care.

Our results demonstrate that the addition of EGN coverage (in the form of a fluoroquinolone or aminoglycoside) to guideline-directed, narrow post-trauma prophylaxis decreased the risk of an extremity SSTI with open fractures. The absolute reduction in risk was approximately 6–7% (number needed to treat = 16.7) with the greatest amount of risk reduction accrued in the first 2–3 weeks following injury. There was no increased risk of osteomyelitis in the patients that received narrow coverage. These findings are consistent with the results of a recent study that examined 90 patients with open fractures of the lower extremities, of which 27 had Grade III fractures according to Gustilo Anderson classification. Among the patients with severe fractures, 59% were prescribed Gram-negative coverage in addition to cefazolin; however, there was no significant difference in rate of osteomyelitis between the groups.²⁸

Based on the reduction of risk of SSTIs, one could argue that this study supports EGN prophylaxis in severe open fractures akin to those encountered in our combat veterans; however, a recommendation must consider the overall benefits and risks placed in the context of the patient setting. Although there was a small effect on SSTIs in our patient population, there was no difference in osteomyelitis rates. This is notable because osteomyelitis tends to affect limb length more than SSTI. Additionally, this cohort represents a high percentage of severely injured combat-trauma patients (particularly severe blast trauma) where SSTI is difficult to accurately diagnose due to the complicated wounds, frequently characterized by extensive soft-tissue and/or muscle loss. Approximately one-fourth to one-third of these patients still developed SSTI regardless of the prophylaxis choice. In our opinion, emphasis is more appropriately placed on thorough and meticulous debridement, timely use of narrow guideline-directed antibiotic prophylaxis, and early recognition and aggressive debridement and empiric broad-spectrum antibiotics when extremity infection is suspected.

Other than slightly decreasing the rate of SSTI, use of EGN conveyed no other benefit and had adverse effects on other outcome measures. Although there was no difference in time of hospitalization, operation room visits, or death outcomes, patients receiving EGN coverage had a higher proportion of recovery of Gram-negative bacteria resistant to EGN antibiotics (49% versus 40%; $p < 0.001$; number needed to harm: 12) and a non-significant increase in

SSTI involving Gram-negative MDROs (34% versus 28%; $p=0.286$), suggesting there is a not surprising antibiotic resistance cost to using EGN prophylaxis. There are also other potential negative impacts of EGN prophylaxis (e.g., effect of aminoglycoside use on renal function and potential toxic effects of fluoroquinolones on bone remodeling); however, these were not examined in our analysis.

While we feel our study supports current recommendations, it is important to emphasize that the guidelines were developed to compliment the clinical judgment of the trauma team. It is also important to note that we excluded patients who received broad-spectrum antibiotics and antifungals, so our findings should not be applied to patients where empiric treatment for sepsis in the early days following trauma is being considered. Due to the high injury severity of our population, our results may also not be applicable to those with minimally injured open fractures.

Our primary limitation is that our analysis was not a randomized control trial, but a retrospective observational study involving a heterogeneous population. However, the clear change in the antibiotic prophylaxis practice patterns that occurred simultaneously with the roll-out period of the new CPG allowed us to study the two management approaches in a period where many of the other factors affecting infection risk (e.g., injury severity and injury mechanism), as well as our clinical definitions of SSTI and osteomyelitis, remained constant. One factor that our retrospective design does not control for is the possibility of varying approach to the diagnosis of osteomyelitis and SSTI by different clinicians, but it is unlikely that clinical criteria changed in a way that would alter our results. Of note, injury severity did decrease towards the end of the study period, with a corresponding reduction in blast injuries. Notwithstanding, the effects seen with SSTI (or lack of effect with osteomyelitis) and prophylaxis regimens did not change after adjusting for injury severity.

Another limitation of our dataset is that duration of antibiotic prophylaxis was longer than what current guidelines recommend. This finding concurs with previously published TIDOS analysis showing prophylaxis durations in excess of guideline recommendations.¹⁴ Duration also varied between treatment groups with the EGN treatment group having a longer duration of use of narrow-spectrum antibiotics. However, while longer prophylaxis duration of narrow-spectrum antibiotics decreased SSTI risk, there was no effect on the risk of developing osteomyelitis with use of longer prophylaxis durations.

Another limitation is that the open fracture classification was not fully defined. Nevertheless, fractures in this analysis were primarily the result of blast injuries (81%) and gunshot wounds (16%). Therefore, we feel this study population predominantly represents open Type III fractures that present with environmental contamination and is relevant to both combat and non-combat trauma that occurs under similar conditions.

In addition, antibiotic prophylaxis choice was based on the judgment of trauma providers, so regimens varied. For example, EGN coverage was more common in blast patients who tended to have higher injury severity and more environmental contamination. Yet, when the cohort was limited to only blast trauma patients, the findings were similar. Many patients also received amoxicillin-clavulanate (29% of the study population) with or without EGN

when they were initially treated at a non-U.S. coalition hospital under coalition guidelines.^{26,27} Nonetheless, when these patients were removed from the analysis, the effect of EGN coverage on SSTIs and osteomyelitis did not differ from the total study population.

Information on antibiotics provided by first medical responders prior to admission to combat support hospitals is also lacking. A prior study demonstrated that 28% of combat casualties received one-time point-of-injury antimicrobials (which are not captured in the medical record and may include ertapenem or moxifloxacin),²⁹ so it is possible that a small number of patients who received antibiotics immediately after injury may have been included in the analysis. Our study did not capture who did and did not receive these point-of-injury antimicrobials due to a lack of documentation; however, we feel it is unlikely that the percentage of patients who received these antimicrobials would be different between the treatment groups. It is also unlikely they would have an impact on development of SSTI or osteomyelitis in higher risk individuals where blood product use in the first 24–48 hours often times significantly exceeds 10 units of blood.

In summary, our findings provide evidence to support the current post-combat trauma antibiotic prophylaxis guidelines directing antibiotic choices in open fractures. Importantly, neither the guidelines nor the findings of this study should deter clinicians from using their clinical judgment and individualizing care; however, the results of our retrospective analysis should reassure trauma providers that withholding EGN antibiotics from post-combat trauma antibiotic prophylaxis regimens for extremity injuries will not increase the risk of osteomyelitis. Given the high rates of extremity infections, with or without EGN coverage, clinicians should monitor wound sites closely and initiate treatment as soon as the diagnosis is considered likely.

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Appendix

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Disclaimer

The views expressed are those of the authors do not necessarily reflect the official views of the Uniformed Services University of the Health Sciences, Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., the National Institutes of Health or the Department of Health and Human Services, Brooke Army Medical Center, Walter Reed National Military Medical Center, Landstuhl Regional Medical Center, the U.S. Army Medical Department, the U.S. Army Office of the Surgeon General, the Department of Defense, or the Departments of the Army, Navy or Air Force. Mention of trade names, commercial products, or organization does not imply endorsement by the U.S. Government.

Author Contribution

I/We certify that all individuals who qualify as authors have been listed; each has participated in the conception and design of this work, the analysis of data (when applicable), the writing of the document, and the approval of the submission of this version; that the document represents valid work; that if we used information derived from another source, we obtained all necessary approvals to use it and made appropriate acknowledgements in the document; and that each takes public responsibility for it. Nothing in the presentation implies any Federal/DOD/DON endorsement. Authors acknowledge that research protocol (IDCRP-024) received applicable Uniformed Services University Institutional Review Board review and approval.

Conflict of Interest and Source of Funding Statement

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Figure 1.

Kaplan-Meier survival plots of time to infection diagnosis following injury, stratified by prophylaxis regimen. Plots are censored to infections occurring within 45 days of injury. Eight patients with skin and soft-tissue infections (SSTI) and six with osteomyelitis who fell outside that range were excluded. (A) Time to SSTI: EGN: median of 9 days; (interquartile range [IQR]: 6–13.5 days); narrow: median of 6 days (IQR: 3–12 days). Log-rank chi-square: 4.73 ($p=0.030$); Wilcoxon chi-square: 7.00 ($p=0.008$). (B) Time to osteomyelitis: EGN: median of 14 days (IQR: 5–27); narrow: median of 17.5 days (IQR: 10–26). Log-rank chi-square: 0.025 ($p=0.876$); Wilcoxon chi-square: 0.040 ($p=0.842$).

Table 1National Healthcare Safety Network Diagnostic Criteria for Infectious Diseases¹⁷

Infection	Diagnostic criteria
Skin and Soft-Tissue Infection	Patients must meet 1 of criteria
	1 Organism(s) identified from tissue or drainage from affected site by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment (e.g., not Active Surveillance Culture/Testing)
	2 Purulent drainage at affected site
	3 Abscess or other evidence of infection on gross anatomic or histopathological exam
Osteomyelitis	Patients must meet 1 of criteria
	1 Organism(s) identified from bone by culture or non-culture based microbiologic testing method, which is performed for purposes of clinical diagnosis and treatment (e.g., not Active Surveillance Culture/Testing)
	2 Evidence of osteomyelitis on gross anatomic or histopathological exam
	3 Has at least <i>two</i> of the following localized signs or symptoms (* with no other recognized cause): fever (>38.0°C), swelling*, pain or tenderness*, heat*, or drainage*
	And at least <i>one</i> of the following additional criteria:
	a. Organism(s) identified from blood by culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis and treatment (e.g., not Active Surveillance Culture/Testing (ASC/AST) <i>AND</i> imaging test evidence suggestive of infection (e.g., x-ray, CT scan, MRI, radiolabel scan [gallium, technetium, etc.]), which if equivocal is supported by clinical correlation (i.e., physician documentation of antimicrobial treatment for osteomyelitis)
	b. Imaging test evidence suggestive of infection (e.g., x-ray, CT scan, MRI, radiolabel scan [gallium, technetium, etc.]), which if equivocal is supported by clinical correlation (i.e., physician documentation of antimicrobial treatment for osteomyelitis)

Table 2

Characteristics Related to Antibiotic Coverage among Patients with Open Fractures

Characteristics, No. (%)	Total (N=1044)	Narrow (N=585)	EGN ^a (N=459)	P-value
Male	1033 (99.0)	578 (98.8)	455 (99.1)	0.764
Injured in Afghanistan	995 (95.3)	559 (95.6)	436 (95.0)	0.668
<i>Injury Mechanism</i>				
Gunshot	171 (16.4)	106 (18.1)	65 (14.2)	0.086
Blast	846 (81.0)	460 (78.6)	386 (84.1)	0.025
Motor vehicle crash	41 (3.9)	24 (4.1)	17 (3.7)	0.742
<i>Injury Severity Score^b</i>				
median (IQR)	22 (14, 33)	22 (14, 33)	22 (13, 33)	0.847
1–9 (minor)	106 (10.2)	58 (9.9)	48 (10.5)	0.359 ^c
10–15 (moderate)	178 (17.1)	92 (15.7)	86 (18.7)	
16–25 (severe)	301 (28.8)	180 (30.8)	121 (26.4)	
26 (critical)	459 (44.0)	255 (43.6)	204 (44.4)	
<i>Injury Location</i>				0.248
Upper extremity only	196 (18.8)	100 (17.1)	96 (20.9)	
Both upper & lower extremity	247 (23.7)	145 (24.8)	102 (22.2)	
Lower extremity only	601 (57.6)	340 (58.1)	261 (56.9)	
<i>Lower Extremity Sites</i>				0.092
Tibia/fibula only	378 (36.2)	210 (35.9)	168 (36.6)	
Femur only	134 (12.8)	67 (11.5)	67 (14.6)	
Both tibia/fibula & femur	230 (22.0)	144 (24.6)	86 (18.7)	
Other	106 (10.2)	64 (10.9)	42 (9.2)	
<i>ICU admission</i>				0.074
None	415 (39.8)	233 (40.1)	182 (39.6)	
LRMC only	164 (15.7)	104 (17.8)	60 (13.1)	
LRMC ± U.S. hospital	465 (44.5)	248 (42.1)	217 (47.3)	
RBC transfusion requirements 24 hours post-injury, median (IQR)	10 (4, 18)	10 (4, 19)	9 (3, 18)	0.150
<i>Duration of narrow-spectrum antibiotics^d</i>				<0.001
0–3 days	459 (44.0)	306 (52.3)	153 (33.3)	
4–6 days	257 (24.6)	157 (26.8)	100 (21.8)	
>6 days	328 (31.4)	122 (20.9)	206 (44.9)	

EGN - expanded Gram-negative coverage; ICU - intensive care unit; IQR - Interquartile range; LRMC - Landstuhl Regional Medical Center; RBC - red blood cell

^aExpanded Gram-negative (i.e. addition of fluoroquinolone and/or aminoglycoside to narrow coverage)

^bInjury Severity Score is an overall measure calculated for each patient based on the top three maximum Abbreviated Injury Scale anatomical region values²³

^cp-value is for the comparison of the Injury Severity Score profile between the regimen groups

^dDuration is restricted to narrow-spectrum antibiotics: IV cefazolin, clindamycin, amoxicillin-clavulanate, and/or ampicillin-sulbactam

Table 3

Antimicrobial Prophylaxis Regimens and Outcomes

Outcome, No. (%)	Total (N=1044)	Narrow (N=585)	EGN (N=459)	P-value
<i>Any Extremity Infection^a</i>	313 (30.0)	192 (32.8)	121 (26.4)	0.024
SSTI	262 (25.1)	162 (27.7)	100 (21.8)	0.029
Osteomyelitis	82 (7.9)	46 (7.9)	36 (7.8)	0.990
Non-extremity Infections	270 (25.9)	152 (26.0)	118 (25.7)	0.920
<i>Occurrence within 2 weeks of injury</i>				
Any extremity infection	224 (21.5)	141 (24.1)	83 (18.1)	0.019
Extremity SSTI	198 (19.0)	126 (21.5)	72 (15.7)	0.017
Osteomyelitis	34 (3.3)	17 (2.9)	17 (3.7)	0.471
MDRO isolation	317 (30.5)	180 (30.8)	138 (30.1)	0.806
MRSA isolation	50 (4.8)	27 (4.6)	23 (5.0)	0.766
VRE isolation	12 (1.2)	9 (1.5)	3 (0.6)	0.246
<i>Occurrence within 4 weeks of injury</i>				
Any extremity infection	281 (26.9)	177 (30.3)	104 (22.7)	0.006
Extremity SSTI	239 (22.9)	152 (26.0)	87 (19.0)	0.007
Osteomyelitis	63 (6.0)	35 (6.0)	28 (6.1)	0.943
EGN-resistant Gram-negative organism isolation ^b	464 (44.4)	237 (40.5)	227 (49.5)	<0.001
<i>Clostridium difficile</i> during initial hospitalization	15 (1.4)	10 (1.7)	5 (1.1)	0.402
Median visits to OR (IQR)	5 (2, 8)	5 (2, 8)	4 (3, 8)	0.794
Total Hospitalization, median days (IQR) ^c	33 (20, 50)	34 (19, 50)	32 (21, 50)	0.627
Death	5 (0.5)	4 (0.7)	1 (0.2)	0.392

EGN - expanded Gram-negative coverage; MDRO - multidrug-resistant organism; MRSA - methicillin-resistant *Staphylococcus aureus*; OR - operating room; SSTI - skin and soft-tissue infection; VRE - vancomycin-resistant Enterococcus

^aPatients may have both a SSTI and osteomyelitis

^bRecovery of Gram-negative organisms from any site that were resistant to fluoroquinolones and/or aminoglycosides

^cInjury to first discharge from U.S. participating hospital

Table 4

Adjusted Cox Proportional Hazard Analysis of Factors Associated with Time from Injury to Infectious Outcomes

Characteristic	Hazard Ratios (95% Confidence Interval)		
	<i>Any Extremity Wound Infection</i>	<i>Extremity SSTI</i>	<i>Osteomyelitis</i>
<i>Prophylaxis regimen</i>			
EGN ^a	Reference	Reference	Reference
Narrow	1.39 (1.10–1.76)	1.41 (1.09–1.83)	0.99 (0.63–1.56)
<i>Injury Severity Score^b</i>			
1–9 (minor)	Reference	Reference	Reference
10–15 (moderate)	1.74 (0.74–4.08)	1.08 (0.49–3.33)	2.89 (0.64–13.08)
16–25 (severe)	2.33 (1.06–5.13)	2.08 (0.88–4.91)	2.80 (0.64–12.29)
26 (critical)	3.75 (1.70–8.27)	3.31 (1.40–7.79)	4.04 (0.91–18.04)
<i>Injury Mechanism</i>			
Non-Blast	Reference	Reference	Reference
Blast	2.92 (1.80–4.73)	2.98 (1.73–5.15)	1.29 (0.63–2.66)
<i>ICU admission</i>			
None	Reference	Reference	Reference
LRMC only	1.07 (0.71–1.62)	1.29 (0.81–2.07)	0.48 (0.21–1.10)
LRMC ± U.S. hospitals	1.85 (1.32–2.59)	2.39 (1.63–3.52)	0.79 (0.43–1.44)
<i>Duration of narrow-spectrum antibiotics^c</i>			
0–3 days	1.44 (1.08–1.92)	1.50 (1.09–2.05)	1.10 (0.65–1.88)
4–6 days	1.38 (1.01–1.89)	1.38 (0.98–1.96)	1.03 (0.57–1.88)
>6 days	Reference	Reference	Reference

EGN - expanded Gram-negative coverage; ICU - intensive care unit; LRMC - Landstuhl Regional Medical Center; SSTI – skin and soft-tissue infection

^aExpanded Gram-negative (i.e., addition of fluoroquinolone and/or aminoglycoside to narrow coverage)

^bInjury Severity Score is an overall measure calculated for each patient based on the top three maximum Abbreviated Injury Scale anatomical region values²³

^cDuration is restricted to narrow-spectrum antibiotics: IV cefazolin, clindamycin, amoxicillin-clavulanate, and/or ampicillin-sulbactam