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Systematic review

Effect of emergency department antibiotic delivery time and protocol compliance on infection after open fractures: a systematic review and meta-analysis

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Abstract

Background: Antibiotic prophylaxis is established in open fracture management, the infection benefit associated with specific emergency department delivery thresholds. This review evaluated delivery time, compliance, and infection outcomes. **Methods:** Original comparative studies published through May 2026 were examined. All comparisons were observational. Comparisons involved heterogeneous populations. Injury to antibiotic and arrival to antibiotic intervals were distinguished. Timing findings were synthesized narratively. An exploratory random-effects meta-analysis combined two studies reporting infection in patients receiving guideline-compliant versus noncompliant prophylaxis. **Results:** Ten primary studies addressed timing, compliance, or protocol implementation. Delays exceeding 66 minutes after injury and 120 minutes after emergency department presentation were associated with infection in individual cohorts. Other studies, including a May 2026 cohort, found no significant association at the one-hour arrival threshold. In two compliance cohorts comprising 416 patients, infection occurred in 19 of 128 compliant patients and 51 of 288 noncompliant patients. The pooled risk ratio was 0.84 (95% confidence interval 0.52–1.37; $I^2=0\%$). This outcome represented surgical and nonsurgical infections rather than exclusively deep fracture infection. Protocol implementation studies show reduced broad-spectrum antibiotic use without significant infection reductions. **Conclusion:** Observational data supports avoiding preventable antibiotic delays without establishing a universal infection threshold. The exploratory compliance estimate still inconclusive. Standardized exposure clocks, fracture-specific outcomes, and adjustment for injury severity are essential for interpreting emergency department antibiotic performance.

Keywords: Open fractures; antibiotic prophylaxis; emergency department; antibiotic timing; compliance; fracture-related infection.

Introduction

Open long-bone fractures vary in anatomical distribution and injury severity, with tibial shaft fractures representing the most frequent location in an established epidemiological cohort (1). Lower-limb injuries displayed more severe soft-tissue damage and associated musculoskeletal trauma than upper-limb fractures (1). These differences establish the clinical context for examining antibiotic delivery: patients presenting with an open fracture do not enter emergency care with equivalent injury burdens or comparable infection susceptibility (1,2).

Systemic antibiotic prophylaxis forms an established component of open-fracture treatment, supported by randomized and quasi-randomized comparisons against placebo or no antibiotic (2). This evidence addresses whether antibiotics are beneficial; it does not establish the magnitude of benefit associated with a particular emergency department administration deadline (2,3). The Surgical Infection Society consequently emphasized short-course prophylaxis and identified substantial limitations in

the evidence supporting broader antimicrobial regimens (3).

The Eastern Association for the Surgery of Trauma recommended prompt gram-positive coverage, additional gram-negative coverage for type III injuries, and contamination-specific treatment when indicated. Its recommendations defined prophylaxis duration according to fracture severity and soft-tissue coverage, making compliance a multidimensional exposure encompassing antibiotic selection and treatment length (4). Updated Surgical Infection Society guidance in 2022 recommended against extended-spectrum coverage for types I and II and against coverage beyond gram-positive organisms for type III fractures without active infection (5). These differences show that adherence to one historical protocol does not represent adherence to every contemporary recommendation (4,5).

Data defining an optimal first-dose deadline still less secure than data supporting prophylaxis itself (6). A Cochrane review identified no randomized comparisons of antibiotic initiation timing, despite evaluating antibiotic duration and surgical

management (6). A subsequent systematic review of fourteen timing studies identified heterogeneous results and important methodological limitations (7). The present review evaluated emergency department antibiotic delivery time and protocol compliance as distinct exposures, examining reported infection outcomes without treating arrival-based and injury-based measurements as interchangeable.

Methods

Study design and eligibility

This review used PRISMA reporting principles to examine antibiotic delivery and protocol compliance in open extremity fractures (Fig 1). Eligible original studies evaluated first-dose timing, adherence to prophylactic antibiotic recommendations, or implementation of an antibiotic protocol and reported infection outcomes. Randomized trials, prospective cohorts, retrospective cohorts, and comparative implementation studies were eligible. Studies restricted to established infection treatment, closed fractures, laboratory models, isolated dental injuries, or local antibiotics without a systemic prophylaxis comparison were excluded.

Information sources and search strategy

The review period extended from database inception through 31 May 2026. The specified information sources were PubMed, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials, supplemented by PubMed Central and reference checking. The search combined open-fracture terms with antibiotics, prophylaxis, emergency department, time, timing, delay, compliance, adherence, protocol, infection, and osteomyelitis. Relevant controlled vocabulary and database-specific syntax were incorporated.

Study selection and extraction

Two authors independently screened titles and abstracts, evaluated eligible full reports, and extracted study information using a standardized form. Disagreements were resolved through discussion and agreement between both authors. Extracted variables included design, setting, sample size, fracture location, Gustilo–Anderson grade, antibiotic regimen, exposure definition, infection definition, follow-up, event counts, and adjusted estimates. Patient denominators and fracture-event denominators were distinguished. The synthesis unit was the independent cohort rather than each associated publication.

Appraisal and synthesis

Two authors independently considered confounding, participant selection, exposure measurement, missing data, outcome ascertainment, and selective reporting. Particular attention addressed contamination, injury severity, soft-tissue coverage, transfers, and follow-up completeness. Timing results were synthesized narratively because exposure clocks, thresholds, populations, and effect measures differed. Odds ratios, hazard ratios, and continuous timing coefficients were retained in their reported forms.

An exploratory secondary meta-analysis combined two compliance cohorts using their reported overall infection outcomes. This outcome included surgical and nonsurgical infections and was distinguished from exclusively deep fracture infection. Unadjusted risk ratios compared compliant with noncompliant prophylaxis. Published group sizes and percentages were used to reconstruct event counts when explicit counts were unavailable. Log risk ratios and inverse-variance weights were combined using a DerSimonian–Laird random-effects model, with Wald confidence intervals. Heterogeneity was assessed using Cochran’s Q and I^2 . Individual-study estimates provided sensitivity context. Publication-bias tests and meta-regression were omitted because only two studies contributed.

Protocol implementation contrasts were evaluated separately from individual patient compliance.

Results

The analysis comprised ten original comparative reports addressing antibiotic timing, guideline compliance, or institutional protocol implementation, with study characteristics summarized in Table 1 (8–17). Weber and colleagues followed 686 patients with 737 fractures and observed 46 infections, finding no independent association between antibiotic timing and deep infection. Fracture severity and tibia/fibula location were associated with infection, indicating substantial variation in baseline risk across the cohort (8).

In 137 patients with type III open tibial fractures, Lack and colleagues identified antibiotic administration beyond 66 minutes after injury as an independent infection predictor, alongside delayed wound coverage (9). Roddy et al. evaluated 230 patients and reported a 2.4-fold infection hazard when antibiotics were administered more than 120 minutes after emergency department presentation (10). Zuelzer et al. analyzed 127 primarily closed tibial fractures and reported deep infection in 3 of 86 patients receiving antibiotics within 150 minutes, versus 8 of 41 receiving later treatment (11).

Larger arrival-based analyses did not establish a statistically significant benefit for the one-hour threshold after accounting for their respective analytical limitations (12,13). Grigorian et al. analyzed 3,367 patients with isolated open femoral or tibial fractures and found no significant adjusted association between early antibiotics and inpatient surgical-site infection or osteomyelitis (12). Morgan et al. reported 34 deep infections among 270 patients treated within one hour and 29 among 207 treated later, with no significant difference in their

May 2026 report (13). These results concern different surveillance periods and fracture populations from the earlier tibial studies (9,11–13).

Barton et al. found guideline compliance in 61 of 214 patients, with prolonged prophylaxis accounting for most noncompliance (14). Overall infection occurred in 11.5% of compliant patients and 17.0% of noncompliant patients; corresponding surgical-site infection rates were 4.9% and 9.8% (14). Johnson and colleagues found compliance in 67 of 202 patients, with reported infection affecting 12 compliant and 25 noncompliant patients (15).

The exploratory compliance meta-analysis included 416 patients, with 19 infections among 128 compliant patients and 51 among 288 noncompliant patients (14,15). The calculated pooled risk ratio was 0.84, with a 95% confidence interval of 0.52–1.37, I^2 of 0%, and Cochran's Q of 0.50 (14,15). Individual estimates were imprecise, and the pooled endpoint retained each report's overall infection classification rather than representing a dedicated deep-infection outcome (14,15). The absence of estimated statistical heterogeneity was interpreted cautiously because two small observational comparisons provided limited ability to identify differences between study populations and outcome ascertainment practices across clinical settings (14,15).

Rodriguez et al. compared 101 preprotocol and 73 postprotocol fracture events, documenting reduced aminoglycoside/glycopeptide use without a significant difference in skin and soft-tissue infection (16). Gates et al. compared two 75-patient groups and observed five versus four fracture-site infections within 60 days following a protocol revision (17). Only 31% of postimplementation patients adhered to that revised protocol, limiting interpretation of protocol availability as actual treatment exposure (17).

Table 1. Primary data table

Study	Design	sample	Principal finding
Weber (8)	Prospective	686	No adjusted timing association
Lack (9)	Retrospective	137	Increased infection beyond 66 minutes
Roddy (10)	Retrospective	230	Increased infection beyond 120 minutes
Zuelzer (11)	Retrospective	127 timing comparison	Deep infection: 3/86 versus 8/41
Grigorian (12)	Registry	3,367	No adjusted one-hour association
Morgan (13)	Retrospective	477	Deep infection: 34/270 versus 29/207
Barton (14)	Retrospective	214	Compliance: 28.5%
Johnson HC (15)	Retrospective	202	Compliance: 33.2%
Rodriguez (16)	Before–after	174 fracture events	No significant infection change
Gates (17)	Before–after	150	No significant infection change

Table 2. Compliance meta-analysis

Study	Compliant: infections/total	Noncompliant: infections/total	RR (95% CI)
Barton (14)	7/61	26/153	0.68 (0.31–1.47)
Johnson HC (15)	12/67	25/135	0.97 (0.52–1.80)
Exploratory pooled estimate (14,15)	19/128	51/288	0.84 (0.52–1.37)

Discussion

We found that antibiotic timing evidence depends on the exposure clock, fracture population, and infection endpoint, while the exploratory compliance synthesis does not demonstrate a statistically clear association. Positive associations in selected tibial cohorts coexist with null findings in broader arrival-based studies, making a universal biological deadline difficult to infer (9–13). The pooled compliance estimate addresses reported overall infection and therefore provides limited evidence regarding deep infection specifically. Neither compliance cohort isolated the effects of antibiotic selection and duration (14,15).

Variation in outcome definitions is important to this interpretation because superficial infection, osteomyelitis, and fracture-related infection represent different clinical events (10,12,14). The international consensus definition distinguishes confirmatory findings, including communicating sinus tracts, purulence, matching organisms from separate deep specimens, and microorganisms demonstrated histologically. Applying consistent fracture-related infection criteria would strengthen comparisons between studies with different surveillance practices and reduce ambiguity when interpreting antibiotic performance indicators (18). Short inpatient surveillance provides a different outcome window from follow-up extending beyond discharge (11–13).

Protocol compliance need similar precision because deviation encompasses excessive duration, inappropriate spectrum, and delayed initiation rather than a single treatment failure (4,14,15). Stennett and colleagues found that the association between prolonged prophylaxis and deep infection differed by contamination severity, with a protective association in severely contaminated wounds. That observational finding reinforces the importance of injury-specific confounding and prevents a simplistic interpretation that every departure from a standard duration carries an identical infection consequence (19). Historical guideline differences further limit the interpretation of pooled compliance as adherence to a universally accepted antibiotic strategy (4,5).

Antibiotic timing operates within a broader treatment pathway involving debridement, stabilization, and soft-tissue management, which were not standardized across the included cohorts (8,9,11). Morgenstern et al. identified an association between additional local antibiotic prophylaxis and reduced infection in a meta-analysis dominated by observational evidence. Such adjunctive treatment represents another source of clinical heterogeneity when infection outcomes are attributed to emergency department systemic antibiotics (20). Westgeest et al. identified deep infection as strongly associated with nonunion and delayed healing in a prospective cohort (21).

Emergency department implications therefore emphasize rapid recognition, reliable first-dose delivery, and accurate recording of the actual treatment interval within a coordinated trauma pathway (4,9,10). The joint prehospital position statement supports first-generation cephalosporin administration after immediate life threats are addressed, without delaying transport (22). Linking prehospital and hospital timestamps offers a more complete description of exposure than an arrival-based indicator alone, particularly for transferred patients (11,22).

Interpretation still constrained by observational designs, data-derived thresholds, unequal follow-up, and residual confounding from contamination and tissue injury (7–13). The two-study meta-analysis adds numerical transparency without resolving these limitations, and its confidence interval includes clinically important

benefit and harm (14,15). Future comparative research requires consistent infection definitions, separate reporting of compliance components, and adjustment for injury severity and concurrent wound management before attributing infection differences to antibiotic delivery performance.

Conclusion

Emergency department antibiotic delivery time and protocol compliance show inconsistent associations with infection after open fractures. Selected cohorts link longer delays with infection, while larger arrival-based studies do not establish a universal one-hour threshold. The exploratory compliance meta-analysis still inconclusive and concerns reported overall infection rather than exclusively deep fracture infection. Clinical interpretation requires attention to fracture severity, contamination, soft-tissue management, and surveillance duration. Prompt prophylaxis remains part of established open-fracture care.

Abbreviations

CI, confidence interval; RR, risk ratio; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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