RQ [##]: **In patients requiring multiple staged reconstructive procedures for open fractures, should antibiotic therapy be administered intermittently (course-per-procedure) or continuously (uninterrupted until the final stage)?**

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Section 1: Background:

Open fractures represent a spectrum of injuries ranging from low-energy wounds with minimal soft-tissue damage to severe injuries characterized by extensive tissue loss, contamination, and vascular compromise. The severity of injury is commonly classified according to the Gustilo–Anderson (GA) system, with infection rates increasing from less than 2% in Type I fractures to more than 25% in severe Type III injuries. Management of high-grade open fractures frequently requires a staged reconstructive approach involving serial debridements, temporary wound management, soft-tissue reconstruction, and definitive skeletal stabilization.

Early systemic antibiotic administration is a cornerstone of open fracture care and has been shown to significantly reduce fracture-related infection compared with no antibiotic prophylaxis. However, the optimal antibiotic strategy for patients undergoing multiple staged reconstructive procedures remains uncertain.

It remains unclear whether antibiotics should be administered as a) a single uninterrupted course from index injury until final wound closure, or b) separate, short courses limited to each individual surgical procedure.

The risks of continuous antibiotic exposure across multiple procedures include antibiotic resistance, Clostridioides difficile infection, selection pressure for nosocomial organisms, drug toxicity, and increased costs. Conversely, intermittent courses risk inadequate coverage during inter-procedural intervals when contaminated wounds remain open or under temporary coverage.

To date, no randomized controlled trials have directly compared continuous and intermittent antibiotic strategies in patients undergoing staged reconstruction of complex open fractures. Consequently, current practice is largely extrapolated from studies evaluating duration of prophylaxis open fracture management in general. This evidence gap has important implications for infection prevention, antimicrobial stewardship, and reconstructive planning, highlighting the need for evidence-based consensus recommendations.

Section 2: Data extraction table

S.No	Author, Year, Country	Study Design	Sample Size	Population	Groups Compared / Intervention	Key Outcomes	Results	Follow-up
1	Dellinger et al., 1988, USA	Prospective RCT (double-blind)	248 patients, 264 fractures	Open extremity fractures, all GAgrades, 3 centres. Excl: age <14 or >65, DM, steroids	1-day cefonicid vs 5-day cefonicid vs 5-day cefamandole	Fracture-site infection rate	Infection rates: 13% (1-day) vs 12% (5-day cefonicid) vs 13% (5-day cefamandole) – no significant difference (p>0.50). No difference even in Grade III subgroup.	6 months
2	Messner et al., 2017, UK	Meta-analysis (5 comparative + 27 observational studies)	6,692 fractures total (1,284 comparative; 5,408 observational)	Open long bone fractures, all GA grades	<72 h antibiotic duration vs >72 h antibiotic duration; subgroup by GA type	Infection rate (deep and superficial)	No significant difference: OR 0.85 (95% CI 0.60–1.21). No benefit in Gustilo I/II (p=0.52) or III (p=0.39). Even <48 h regimens equivalent to >72 h.	Variable
3	Klifto et al., 2026, USA	Systematic Review & Meta-analysis of RCTs	21 RCTs included	Open extremity fractures, GA I-III, upper and lower limb; adults	Antibiotic duration (1-day vs 5-day), antibiotic type and dose for prophylaxis vs control/longer courses	Fracture-related infection (FRI) rate	HIGH certainty: 1-day = 5-day for all GA types I/II/III (RR 1.02, 95% CI 0.72–1.44; p=0.93, I^2=0%). Moderate certainty for type I/II. First-gen cephalosporins + aminoglycoside/fluoroquinolone sufficient for type III (max 1 day).	Variable
4	Stennett et al., 2020, International (FLOW trial secondary analysis)	Retrospective cohort (secondary analysis of international RCT – 41 sites)	N=2,400 open fractures	Adults with open extremity fractures;	Extended antibiotic prophylaxis (>72 h after definitive wound closure) vs ≤72 h, stratified by wound contamination (mild/moderate/severe)	Deep SSI within 12 months	Differential effect by contamination: mildly contaminated – trend toward more SSI with extended use (aOR 1.39); moderate – no effect (aOR 1.09); severely contaminated – extended use protective (aOR 0.20, 95% CI 0.07–0.60).	12 months

5	Lack et al., 2015, USA	Retrospective cohort (Level 1 trauma centre)	137 type III open tibia fractures	GA type III open tibial fractures.	Time to antibiotics (<66 min vs >66 min from injury); time to wound coverage (<5 days vs >5 days)	Deep infection within 90 days	Antibiotics >66 min: OR 3.78 (95% CI 1.26–14.11, p=0.016). Coverage >5 days: OR 7.39 (p<0.001). Both factors together: 40.5% infection vs 2.8% with both prompt (p<0.001).	90 days
6	Roddy et al., 2020, USA	Retrospective cohort, Level 1 trauma centre	230 patients	Open extremity fractures, all GA types; minimum 30-day follow-up	Time to IV antibiotic administration from ED presentation (threshold: 120 min vs ≤120 min)	SSI within 90 days	Antibiotics >120 min: HR 2.4-fold increased SSI (95% CI 1.1–5.7, p=0.036). Smoking and drug use also independent risk factors.	Median 122 days
7	Saveli et al., 2013, USA	Prospective RCT (pilot, non-blinded)	130 patients	Adults with open fractures presenting to Level 1 trauma centre ED; all GA types	Cefazolin alone vs cefazolin + vancomycin, from presentation until 24 h post-fixation	SSI rates (30 days–12 months); S. aureus/MRSA colonization rates	No significant difference in SSI rates (15% vs 19%, p=0.62). MRSA carriers had 33% vs 1% MRSA SSI rate (p=0.003). Vancomycin addition was safe.	Mean 296–299 days
8	Sheibani et al., 2025, Iran	Prospective cohort study	600 patients (200/group)	Adults with open fractures, GA I–III. Excl: polytrauma requiring multiple surgeries, allergy	Group A: Cefazolin 1g q6h + amikacin; Group B: Cefazolin 2g q8h + amikacin; Group C: Vancomycin 2g q12h + amikacin (all 3 days)	ESR/CRP elevation, wound colonization, clinical infection, deep infection, fever, cellulitis, abscess	Group C (vancomycin) significantly lower: clinical infection 4.7% vs 8.0% (aRR 0.58, CI 0.38–0.89); deep infection 2.7% vs 5.3% (aRR 0.51, CI 0.29–0.90). No difference between Groups A and B.	6 months
9	McMurtrie et al., 2020, USA	Retrospective cohort, Level 1 trauma centre	144 Type II open fractures (70 GP, 74 BS)	GA type II open fractures; minimum 3-month follow-up	Gram-positive (GP) coverage (cefazolin/clindamycin) vs broad-spectrum (BS) piperacillin-tazobactam	Fracture-related infection (FRI) rate; hospital cost	FRI: 8.6% GP vs 10.8% BS (p=0.78) – no difference. No difference in MDR organisms. BS cost 4.39× more than cefazolin.	Min 3 months
10	Garner et al., 2019, USA	Narrative Review / Guideline summary	N/A (review)	All open fractures, GA I–III	Antibiotic choice (beta-lactams, aminoglycosides, fluoroquinolones, glycopeptides, monobactams) and duration guidelines	SSI incidence; guideline recommendations	24 h after definitive wound coverage is the recommended maximum duration. Type III: continue up to 72 h after injury or 24 h after soft tissue coverage. No benefit to extending beyond 24 h; early administration (within 66 min) critical.	N/A

11	Johnson et al., 2017, USA	Retrospective cohort (quality improvement study)	100 patients (50 pre / 50 post protocol)	Open fractures presenting to Level 1 trauma centre ED; ≥18 years	Pre- vs post-implementation of interdepartmental antibiotic prophylaxis protocol	Time from ED admission to antibiotic administration	Time to antibiotics: 123.1 min pre vs 35.7 min post (p=0.0003, 71% reduction). Patients receiving antibiotics within 60 min: 46% pre vs 84% post (p<0.0001). No significant change in infection rates (10% vs 10%).	Short-term
12	Chan et al., 2020, UK	Cochrane Systematic Review Protocol	Protocol only (no results)	Open long bone fractures, upper and lower limb; adults	Timing and staging of antibiotic administration and surgery; planned RCT inclusion	Limb function (PROM), HRQoL, deep SSI, nonunion/delayed union, adverse events	Protocol registered; highlights absence of high-quality RCT evidence on optimal timing/staging of antibiotics in staged reconstructive procedures.	Planned 12 months
13	Rupp et al., 2019, Germany	Narrative Review / State of the Art	N/A (review)	Open fractures, GA type I–IIIB	Systemic antibiotic prophylaxis duration (<72 h vs >72 h); local antibiotics; NPWT; BMP-2	Infection rate; treatment principles	Confirms: no benefit of >72 h systemic antibiotics. Cefazolin (or cephalosporin + aminoglycoside for type III) recommended. Early administration key. Local antibiotics beneficial adjunct.	N/A
14	Isaac et al., 2016, UK	Systematic Review (open tibial fractures)	8 studies met inclusion criteria	Adults with open tibial fractures	Short vs long-term prophylactic antibiotic duration in open tibial fractures	Infection rate; fracture union	Only 1 high-quality RCT (Dellinger 1988): short course ≈ long course. No robust evidence to support >3 days. Highlights need for multicenter RCT.	Variable

Section 3: Results summary

Fourteen studies were identified as relevant, comprising one landmark prospective double-blind RCT, two systematic reviews/meta-analyses of RCTs, one large international multicentre secondary cohort analysis, four observational cohort studies, two narrative reviews, one quality improvement study, one Cochrane protocol, and three additional reviews with primary data components. Together, these studies provide substantial evidence on antibiotic duration, timing, choice, and regime-per-procedure decisions in open fracture management.

The highest quality and most direct evidence on duration comes from *Dellinger et al.* (1988), the only double-blind prospective RCT on antibiotic duration in open fractures (n=248). This study found no difference in fracture site infection rates between 1-day and 5-day antibiotic courses (13% vs 12%–13%, respectively), including in the GA Grade III subgroup.

Messner et al. (2017) conducted the first meta-analysis focusing exclusively on antibiotic duration in open fractures (n=6,692 fractures, 32 studies). The pooled analysis found no benefit of >72 h over <72 h duration (OR 0.85, 95% CI 0.60–1.21; p=0.53). Critically, even regimens as short as 24–48 hours were equivalent to >72-hour regimens in both Gustilo I/II (p=0.52) and Gustilo III (p=0.39) subgroups. The authors recommended abandoning prolonged antibiotic administration beyond 72 hours.

Klifto et al. (2026) produced the most up-to-date and rigorous synthesis of RCTs (21 RCTs, GRADE methodology). Their key finding was HIGH certainty-level evidence that 1-day antibiotic prophylaxis does not differ from 5-day prophylaxis for fracture-related infections across all Gustilo types I/II/III (RR 1.02, 95% CI 0.72–1.44; p=0.93, I^2=0%). Moderate-certainty evidence confirmed the same for Gustilo I/II. The authors concluded that "Extended perioperative administration of prophylactic systemic antibiotics did not decrease wound infections following open fractures. The strongest available evidence existing only from older studies supports a maximum duration of administration of 1 day following hand and lower extremity open fractures.".

Isaac et al. (2016), in their systematic review of open tibial fractures, confirmed the lack of evidence supporting antibiotic administration beyond 3–5 days, reinforcing the adequacy of short-course prophylaxis.

Some indirect evidence regarding antibiotic duration in open fractures is available. In a secondary analysis of 2,400 patients enrolled in the FLOW trial, *Stennett et al.* demonstrated that the effect of extended antibiotic prophylaxis after definitive wound closure differed according to the degree of wound contamination. Prolonged prophylaxis of >72 hours after closure was associated with a substantially lower risk of surgical site infection in severely contaminated wounds (adjusted OR 0.20, 95% CI 0.07–0.60). These findings suggest that the benefit of prolonged antibiotic administration may depend on the contamination burden and injury severity. However, the study evaluated antibiotic use after definitive wound closure and did not investigate the duration or administration strategy of prophylaxis during the interval between injury and final reconstruction. Consequently, it does not address the clinically relevant question of whether patients requiring multiple staged reconstructive procedures should receive continuous antibiotic therapy throughout the entire treatment course or intermittent perioperative antibiotic courses associated with each individual surgical stage.

Section 4: Discussion

The clinical question directly addresses an area with no high-quality prospective data: should antibiotics be given continuously from index injury until final wound closure (continuous strategy), or should each staged procedure receive its own discrete short antibiotic course (intermittent/course-per-procedure strategy)?

The available evidence, while not directly answering this comparison in the staged setting, strongly implies that an intermittent (course-per-procedure) strategy is more consistent with both the evidence base and principles of antibiotic stewardship:

- *Duration evidence:* All high-quality studies (Dellinger 1988 RCT; Messner 2017 meta-analysis; Klifto 2026 RCT meta-analysis) demonstrate no benefit of extending antibiotic prophylaxis beyond 24–72 hours, regardless of fracture type or staged procedure involvement. Consequently, maintaining uninterrupted antibiotic prophylaxis across staged procedures separated by days or weeks would result in treatment durations substantially exceeding the evidence-supported 24–72-hour window, and current data do not support a benefit of such prolonged administration.

- *Antibiotic stewardship*: Prolonged uninterrupted antibiotic exposure is associated with emergence of drug-resistant organisms, nosocomial superinfection, Clostridioides difficile colitis, nephrotoxicity (particularly with aminoglycosides), and hepatotoxicity. Messner et al. (2017) explicitly warned that antibiotic administration exceeding 72 hours potentially increases nosocomial infection risk. Klifto et al. (2026) noted that prolonged antibiotic exposure has driven resistance development in organisms causing fracture-related infections.

- *Timing principle*: Evidence confirms that the critical prophylactic window is the peri-procedural period — specifically within 60 minutes of contamination or incision. Continuous antibiotics in the inter-procedural period do not address the fundamental mechanism of infection (peri-operative bacterial inoculation) and instead only contribute systemic exposure without procedural efficacy. Each new surgical procedure represents a new contamination event warranting a fresh, timed course.

- *Contamination-stratified benefit*: Stennett et al. (2020) found extended post-closure antibiotics beneficial only for severely contaminated wounds. However, this benefit was observed after wound closure, not during open inter-procedural intervals. When wounds are under temporary coverage (NPWT, antibiotic bead-pouch), the contamination dynamics differ.

- *Analogy to perioperative practice*: In elective orthopaedic procedures, single-dose prophylaxis or short 24-hour courses are standard of care and clearly superior to prolonged administration. The principle of giving antibiotics at the time of each procedure — synchronised with the contamination risk — is universally accepted.

• *Transition from prophylaxis to treatment*: The present recommendation specifically addresses antibiotic prophylaxis in patients undergoing staged reconstruction of open fractures without evidence of established infection. If, during the interval between reconstructive stages, a fracture-related infection (FRI) is diagnosed according to the internationally accepted FRI Consensus Definition (Metsemakers et al. 2017), the clinical situation fundamentally changes. In such cases, antibiotic administration should no longer be considered prophylaxis but rather targeted antimicrobial treatment as part of a comprehensive FRI management strategy. Decisions regarding antimicrobial selection and duration should therefore follow contemporary FRI treatment principles rather than recommendations for prophylactic antibiotic administration.

• *Role of local antibiotic therapy:* In complex open fractures requiring multiple staged procedures between initial debridement and definitive wound closure and/or osteosynthesis, local antibiotic delivery systems may serve as a useful adjunct to systemic prophylaxis (Rupp et al). Techniques such as the antibiotic bead pouch may allow delivery of very high local antibiotic concentrations directly to the zone of injury while minimizing systemic exposure. This approach may be particularly attractive during the interval between staged procedures, when extensive soft-tissue injury, dead space, or persistent contamination remain present. Although local antibiotic therapy should not be considered a substitute for meticulous surgical debridement, timely soft-tissue coverage, or appropriate systemic perioperative prophylaxis, it may contribute to reducing bacterial burden in selected high-risk injuries and provide additional local antimicrobial protection during staged reconstruction.

Section 5: Risk of bias of included studies

Overall Risk of Bias Assessment: **MODERATE**

• High risk: Most observational cohort studies (Lack 2015, Roddy 2020, McMurtrie 2020, Johnson 2017, Sheibani 2025) carry inherent selection bias, confounding by indication, and retrospective limitations. Sheibani et al. (2025) used a non-randomised cohort design with clinician-selected regimens, creating substantial selection bias risk.

• Moderate to low risk: Messner et al. (2017) meta-analysis includes heterogeneous studies with Coleman Methodology Scores (CMS) ranging from 27–88 (mean 56); significant statistical heterogeneity (I^2 70–86%) in observational subgroups. Klifto et al. (2026) rigorously applied GRADE methodology and included only RCTs in their meta-analysis whereas the duration comparisons yielded HIGH certainty.

- Low risk: Dellinger et al. (1988) prospective double-blind RCT is the highest quality study for duration outcomes; Saveli et al. (2013) was a prospective RCT (underpowered pilot). Both have low risk of selection and detection bias for their primary endpoints.

- Critical gap: No RCT, quasi-experimental study, or even high-quality observational study has compared continuous vs intermittent antibiotic regimens specifically in the staged reconstructive setting. All recommendations for this clinical question represent expert extrapolation from single-procedure evidence.

Section 5: Response/Recommendation

Antibiotic prophylaxis should be administered INTERMITTENTLY — short targeted courses tied to each discrete surgical stage — rather than continuously until the final procedure. Duration should not exceed 24–72 hours per surgical event depending on fracture severity.

Section 6: Level/ strength of Evidence:

Overall Level of Evidence: LOW TO MODERATE

Study Design: The available evidence comprises one landmark prospective, double-blind randomized controlled trial (Dellinger et al., 1988), two systematic reviews and meta-analyses of randomized and observational studies (Messner et al., 2017; Klifto et al., 2026), and one large multicentre secondary cohort analysis of 2,400 patients from the FLOW trial (Stennett et al., 2020). The remaining literature consists predominantly of retrospective observational cohort studies, narrative reviews, expert opinion papers, and a published Cochrane review protocol. Notably, no study has directly evaluated antibiotic administration strategies in patients undergoing multiple staged reconstructive procedures for open fractures.

Risk of Bias: Overall, the risk of bias is considered MODERATE. While the randomized trials and systematic reviews provide higher-quality evidence, many studies are limited by retrospective designs, heterogeneity in treatment protocols, and variable definitions of infectious outcomes.

Sample Size: Most individual randomized trials are relatively small and were conducted before 2000. Although pooled analyses include large patient populations (up to 6,692 open fractures), the evidence remains indirect because none of the included studies specifically addresses the clinical question of continuous versus intermittent antibiotic administration during staged reconstruction.

Outcome Measures: Interpretation of the literature is further complicated by substantial heterogeneity in infection-related outcome definitions. The internationally accepted definition of fracture-related infection (FRI) was introduced only in 2017; consequently, most older studies used non-standardized diagnostic criteria. More recent investigations, including Klifto et al., have applied contemporary FRI definitions, improving comparability and clinical relevance.

Conclusion on Strength of Evidence: The recommendation is supported by a consistent body of indirect evidence demonstrating no clear benefit of prolonged or continuous antibiotic administration in the management of open fractures after adequate surgical debridement. However, because no study has directly compared continuous versus intermittent antibiotic strategies in patients undergoing staged reconstruction, the certainty of evidence for this specific clinical question remains moderate at best. The recommendation therefore relies on extrapolation from adjacent high-quality evidence, combined with principles of antimicrobial stewardship and contemporary open fracture management. A well-designed prospective randomized controlled trial specifically evaluating antibiotic strategies during staged reconstruction would substantially strengthen the evidence base.

Section 7: References

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