

CONSENSUS RECOMMENDATION

RQ: In patients undergoing delayed soft tissue coverage, should antibiotic therapy be continued until definitive closure is achieved?

Background

Open fractures with delayed soft tissue coverage, particularly Gustilo-Anderson type IIIB/IIIC tibial and distal lower-extremity injuries, have a high risk of fracture-related infection because of contamination, devitalized tissue, exposed bone or implants, and compromised vascularity.^{1,2,5,6,11,20,28,32} All included literature agrees that systemic antibiotics are an essential adjunct, but not a substitute for high-quality debridement, irrigation, skeletal stability, and healthy soft tissue coverage.^{1,3,5,11,28,32} Early antibiotic administration is the most consistent protective factor, with multiple reviews and guidelines recommending administration as soon as possible, ideally within 1-3 hours of injury.^{1,7,13,18,19,20,28} The controversial issue is duration: whether prophylactic systemic antibiotics should be continued throughout the period of an open wound until definitive flap/closure, or stopped after a defined short course. The available evidence is indirect and heterogeneous. Randomized evidence and systematic reviews have not shown superiority of prolonged prophylaxis over short-course regimens.^{14,17,26} EAST-derived and contemporary reviews generally recommend 24 hours for Gustilo I-II injuries and 48-72 hours for Gustilo III injuries, with discontinuation no later than 24 hours after definitive soft tissue coverage.^{13,18,19,20,26} A large FLOW secondary analysis suggests that extended post-closure prophylaxis may benefit only severely contaminated wounds, while mild/moderate contamination does not benefit and may trend toward harm.¹² Therefore, the consensus must balance infection prevention with antimicrobial stewardship and should distinguish routine prophylaxis from treatment of established or suspected infection.^{13,18,20,26,27}

Data table:

S.no	Article / author / year	Study design	Sample / population	Comparison or intervention	Key outcomes and relevance to RQ
1	Atwan et al., 2020 - Antibiotic utilization in open fractures	Narrative review	Open fractures, mostly lower extremity literature	Antibiotic timing, duration, local antibiotics	Early antibiotics reduce infection. Dellinger RCT: 24 h as effective as 5 days. Recommends 24 h after closure for GA I-II and 72 h after injury but no longer than 24 h after closure for GA III. Local antibiotics may reduce FRI but evidence limited.
2	Halawi & Morwood, 2015 - Acute	Evidence-based review	Open fractures; many tibial studies	Acute management and antibiotic duration	First-generation cephalosporin as early as possible. Optimal duration not well defined; antibiotics should be continued for 24 h. Inconclusive evidence for

	Management of Open Fractures				extending duration or broadening coverage for type III wounds.
3	Seligson & Henry, 1991 - Treatment of Compound Fractures	Review	Compound/open fractures	Early stabilization, sequential debridement, early cover, systemic and local antibiotics	Early soft tissue coverage is critical. Parenteral antibiotics reduce acute infection/osteomyelitis; PMMA bead local antibiotics may help in high-grade injuries. Historical support for aggressive wound care rather than indefinite systemic antibiotics.
4	Heckmann et al., 2021 - Delayed debridement beyond 24/48h	Retrospective cohort	96 open tibia fractures	Debridement <24 h vs 24-48 h vs >48 h	Infection 13.3%, 17.2%, 9.1% respectively; no significant increase with delayed debridement. Antibiotics generally 24-72 h postoperatively. Does not support using prolonged antibiotics as a substitute for organized surgery.
5	Diwan, Eberlin & Smith, 2018 - Principles and practice of open fracture care	Review / practice principles	Open fractures requiring orthoplastic care	Early antibiotics, debridement, fixation, soft tissue closure	Antibiotics are urgent but adjuvant; early definitive reconstruction within 48-72 h gives best results. Emphasizes debridement and soft tissue envelope, not prolonged systemic prophylaxis.
6	Ryan & Pugliano, 2013 - Controversies in Initial Management	Critical review	40 studies on open fracture management	Debridement, antibiotics, cultures, closure timing	Antibiotics essential. Type IIIB/IIIC higher infection risk and need flap coverage. Recommends urgent debridement and timely closure after necrotic tissue removal; optimal duration remains debated.
7	Gustilo, 1979 - Use of Antimicrobials in Open Fractures	Prospective/retrospective clinical series + microbiology	158 cultures; 520 prospective patients in later cohort	Antibiotics before surgery and 3 days postoperatively	Antibiotics within 3 h help prevent sepsis. Duration used was 3 days post-op in historical series; antibiotic role secondary to debridement, irrigation, and definitive wound care.
8	Millan-Reyes et al., 2025 - Complex wounds systematic review/meta-analysis	Systematic review/meta-analysis	17 wound studies across trauma/surgical/chronic wounds	NPWT, dressings, irrigation, antibiotic regimens	NPWT reduced infections (RR 0.590). Antibiotic therapies reduced infections when administered within 24 h of injury. Supports wound strategy optimization but not prolonged prophylaxis until closure.

9	Patzakis et al., 1978 - Clostridial contaminated open fracture wounds in rats	Animal experimental study	Open tibia/femur fracture rat model	Antibiotics vs none; primary vs open wounds	Antibiotics reduced mortality in clostridial contamination. Supports early appropriate antimicrobials for contamination, especially anaerobic risk, but animal data cannot define human prophylaxis duration.
10	Bates et al., 2024 - IV cefazolin tissue levels in open lower-extremity fractures	Prospective pharmacokinetic study	8 adults, GA II and IIIA open fractures	IV cefazolin microdialysis at injured vs control limb	Cefazolin remained above S. aureus MIC for 24 h in moderately severe injuries. Supports adequacy of standard dosing in GA II/IIIA; not evidence for prolonged courses in IIIB/IIIC.
11	Dheenadhayalan et al., 2023 - Management of open fractures narrative review	Narrative review / practice guideline	Open fractures, orthoplastic approach	Early antibiotics, debridement, fixation, local antibiotics, NPWT	Early systemic antibiotics reduce complications. Gram-negative coverage, local antibiotics, cultures, fix-and-flap, and NPWT remain controversial. Stresses orthoplastic care.
12	Stennett et al., 2020 - FLOW secondary analysis	Retrospective cohort secondary analysis	2400 FLOW trial open extremity fractures	Extended >72 h after definitive closure vs ≤72 h; stratified by contamination	Deep SSI: 5% mild, 8% moderate, 23% severe. Extended prophylaxis protective only in severe contamination (aOR 0.20); no benefit in moderate and trend toward increased SSI in mild wounds.
13	Hoff et al., 2011 - EAST guideline update	Practice management guideline	27 evidence articles reviewed	Antibiotic selection and duration	Level I: start gram-positive coverage ASAP; add gram-negative for type III; add penicillin for fecal/clostridial contamination. Level II: type III antibiotics for 72 h after injury or not >24 h after soft tissue coverage.
14	Ondari et al., 2016 - 24 h vs 5 days in Gustilo II tibia	Unblinded RCT	77 GA II open tibia fractures analyzed	24 h vs 5 days prophylactic antibiotics after debridement	No significant infection difference: 23% vs 19% (p=0.699). Time to antibiotic administration associated with infection (p=0.004). Supports short-course prophylaxis.
15	Breugem & Strackee, 2006 -	Seminar review	Grade IIIB tibia literature	Early vs delayed flap coverage	Early aggressive debridement followed by soft tissue cover within 3-5 days

	Timing of soft tissue coverage of IIIB tibia				appears to reduce osteomyelitis and delayed union; evidence quality limited. Does not recommend prolonged systemic prophylaxis as solution to delay.
16	Tan et al., 2025 - Delayed soft tissue coverage in IIIB/IIIC lower extremity	Retrospective cohort	18 distal tibia/ankle/foot GA IIIB/IIIC free flaps; mean coverage 12.9 d	Early ≤ 7 d vs delayed ≥ 8 d coverage	Only 1 soft tissue infection; no osteomyelitis. They used early IV cefazolin/gentamicin, cefazolin until 24 h after free flap, then oral amoxicillin-clavulanate 7 d; also serial consultant-led debridement/local antibiotics. Small high-bias support for individualized prolonged regimens.
17	Chan et al., 2022 - Cochrane timing review	Cochrane systematic review	3 RCTs; 613 participants, 617 open fractures	Antibiotic duration and timing of wound closure	Very low-certainty evidence. 24 h vs 5 days showed uncertain/no clear benefit. Immediate vs delayed closure effects on deep infection also very uncertain. No trials directly addressed antibiotics continued until delayed closure.
18	Anderson et al., 2011 - Antimicrobial prophylaxis in open lower extremity fractures	Evidence-to-practice review	Systematic reviews, RCTs, guideline statements	Antibiotic choice, timing, duration	GA I-II: first-generation cephalosporin within 3 h, continue 24 h. GA III: add aminoglycoside, continue 48-72 h after injury but no more than 24 h after wound closure. Warns against cultures guiding prophylaxis.
19	Nakamura & Daya, 2007 - Appropriate antimicrobials in wound management	Review	ED wound management, open fractures and joints	Systemic antibiotics for high-risk wounds	Open fracture antibiotics should start within 3 h. Type I-II: 24 h after wound closure; Type III: 72 h or 24 h after wound closure. Special exposures need targeted coverage.
20	Sharr & Buckley, 2014 - Current Concepts Review:	Current concepts review	Open tibial fractures	Antibiotic duration, debridement, cultures, fixation	No evidence that continuing prophylaxis beyond 72 h post-debridement provides benefit; prolonged prophylaxis may increase

	Open Tibial Fractures				nosocomial and multidrug-resistant organisms. Recommends 24 h for grade I-II and up to 48 h for grade III.
21	Morgenstern et al., 2018 - Local antibiotic prophylaxis meta-analysis	Systematic review/meta-analysis	8 comparative studies; 2738 open fractures	Systemic prophylaxis plus local antibiotics vs systemic alone	Local antibiotics associated with lower infection rate: 4.6% vs 16.5%, OR 0.30; absolute risk reduction 11.9%. Evidence low/heterogeneous; supports local adjuncts in severe wounds, not prolonged systemic prophylaxis.
22	Aneja et al., 2022 - Local tobramycin injection trial protocol	Prospective RCT protocol	Planned 600 open extremity fractures	Local aqueous tobramycin + standard care vs standard care	Rationale: local antibiotics achieve high wound levels with minimal systemic toxicity. No outcome data yet; included as ongoing evidence direction.
23	Konbaz et al., 2019 - Delay in debridement and infection in open tibia	Retrospective cohort	113 open tibia fractures	I&D ≤6 h vs >6 h; closure and fixation factors	No infection difference by 6-h debridement rule. Infection related to Gustilo grade and leaving wound open at first surgery/external fixation. Supports severity/closure factors over arbitrary timing.
24	Gubara et al., 2025 preprint - Gunshot-related open fractures protocol	Retrospective single-center preprint	289 ballistic open fractures	Pre- vs post-protocol; adherence vs non-adherence	No significant infection rate difference after protocol. Protocol included Type III antibiotics until 24 h after closure and special change to broader therapy if soft tissue coverage delayed >5 days. Low certainty because preprint.
25	Gates et al., 2025 - Institutional prophylactic guidelines	Retrospective chart review	150 open fracture patients	Before vs after institutional guideline change	60-day infection 6.7% vs 5.3%; 12-month 9.3% vs 6.7%; not significant. Low documentation/adherence limited impact. Supports protocol adherence and stewardship.
26	Vanvelk et al., 2022 - Duration of PAP in open fractures	Systematic review and critical appraisal	6 studies including RCTs and cohorts	Different prophylaxis durations including 1 vs 5 days, 72 h cutoffs	Prolonged PAP did not appear beneficial for preventing FRI in most open fractures; evidence limited. Contemporary guidance: GA I-II ≤24 h; GA III discontinue after 72 h or 24 h

					after wound closure, whichever comes first.
27	Cusack et al., 2021 abstract - Risk factors after antibiotic prophylaxis	Conference abstract	Open fracture adults, single center	Risk factors for infection/AKI/MDRO/C. difficile and guideline adherence	Abstract indicates concern for antibiotic-associated complications and guideline adherence; limited extract available. Supports stewardship considerations; not direct evidence for continuing until closure.
28	Cross & Swiontkowski, 2008 - Treatment principles	Review	Open fractures	Antibiotics, timing, local delivery, closure	Early antibiotics are paramount. Authors state they typically maintain antibiotics until wound closure and table suggests longer durations for IIIB/IIIC; this is expert practice and older, less stewardship-focused evidence.
29	Hill et al., 2017 abstract - Modified prophylaxis protocol	Conference abstract	189 open fracture patients	Pre- vs post-protocol	Infection fell 23.3% to 7.1% post-protocol despite low full adherence; median antibiotic duration 48 vs 54.7 h. Does not show need for continuation until closure.
30	Araiza et al., 2016 abstract - Single antibiotic prophylaxis for GA II/IIIA	Conference abstract retrospective	286 patients / 340 GA II/IIIA fractures	Monotherapy vs multidrug; duration >24 h vs ≤24 h	Deep infection 9.7%. Monotherapy 6.5% vs multidrug 15.3%; in regression, antibiotic duration >24 h was not significant. Tobacco was only significant predictor.
31	Bandalovic et al., 2015 - Antibiotic prophylaxis in closed lower limb fracture ORIF	Retrospective study	347 young healthy closed lower limb fractures	Antibiotic prophylaxis vs none	No significant SSI reduction. Not directly about open fractures; illustrates that prophylaxis benefit is context-dependent and overuse should be avoided.
32	Whiting et al., 2024 - Open fractures evidence-based best practices	Meeting proceedings / review	Open fracture best practices	FRI prevention strategies	FRI prevention includes host optimization, antibiotics, debridement, stability, and soft-tissue coverage. Antibiotics within 60 min before surgery and up to 24 h after surgery; Type III may need short gram-negative

					expansion; definitive coverage ideally within 48 h of fixation.
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Results:

Across the included literature, the most consistent finding is that early systemic antibiotic administration reduces infection risk, while extended prophylactic duration has not shown clear additional benefit.^{1,7,13,14,18,19,20,26} Reviews of open fracture care and the EAST guideline support immediate gram-positive coverage, broader coverage for Gustilo type III injuries, and targeted anaerobic coverage for fecal/farm/clostridial contamination.^{5,6,11,13,18,19,28,32} Multiple sources emphasize that antibiotics are adjunctive; high-quality debridement, irrigation, skeletal stability, and timely viable soft tissue coverage remain the decisive interventions.^{2,3,5,11,15,28,32}

Randomized and comparative evidence does not support prolonged systemic prophylaxis as a routine strategy. Dellinger et al. randomized 264 open extremity fractures to 24 hours or 5 days of antibiotics and found no infection difference.^{1,26} Ondari et al. found no significant difference between 24 hours and 5 days in Gustilo II open tibia fractures, while delayed initiation of antibiotics correlated with infection.¹⁴ Vanvelk et al. identified only six eligible studies on prophylaxis duration and concluded that prolonged perioperative antibiotic prophylaxis does not appear beneficial in most open fractures.²⁶ The Cochrane review similarly found very low-certainty evidence and no direct trial addressing continuation until delayed closure.¹⁷

The largest dataset, the FLOW secondary analysis by Stennett et al., suggests nuance: extended prophylaxis after definitive closure may reduce deep SSI in severely contaminated wounds but not in mild/moderate contamination, where prolonged use may be neutral or harmful.¹² Delayed coverage studies support early orthoplastic reconstruction when feasible, but they do not prove that antibiotics should be continued solely because a wound remains open.^{1,5,6,15,16,23,32} Some older expert reviews and small retrospective series maintained antibiotics until closure; these practices are low-certainty and conflict with newer stewardship-focused reviews and guidelines.^{3,16,20,26,28} Local antibiotic adjuncts may reduce infection in severe injuries but should be considered an adjunct to, not a replacement for, systemic prophylaxis and surgery.^{3,11,21,22,28,32}

Discussion:

This research question specifically asks whether prophylactic systemic antibiotics should be continued until definitive soft tissue closure in patients whose coverage is delayed. The answer is not directly tested by a high-quality RCT.^{17,26} Most available trials compare short-course versus longer-course antibiotics, or analyze antibiotic duration after wound closure.^{12,14,17,26} Therefore, the recommendation must be based on indirect evidence, guideline consistency, biological plausibility, infection-risk stratification, and antimicrobial stewardship.^{13,18,20,26,27,32}

There is strong agreement that antibiotics should be administered early. Patzakis, Gustilo, EAST, Anderson, Nakamura, Atwan, and multiple reviews identify early antibiotic administration as a key infection-prevention step.^{1,7,13,18,19,20,28} The protective effect appears most related to early establishment of bactericidal tissue levels, not indefinite continuation.^{7,10,13,18,19} Bates et al. provide pharmacokinetic support that standard

cefazolin dosing can achieve sustained interstitial concentrations above the *S. aureus* MIC in GA II/IIIA injuries, although this cannot be extrapolated with confidence to IIIB/IIIC wounds.¹⁰

The strongest evidence against routine prolonged prophylaxis comes from randomized duration studies and systematic reviews. Dellinger et al. found no difference between 24 hours and 5 days; Ondari et al. found no difference between 24 hours and 5 days in GA II open tibia fractures; Vanvelk et al. concluded prolonged PAP is not beneficial in most patients; and the Cochrane review found insufficient evidence to support longer regimens.^{14,17,26} EAST and derived summaries recommend limiting systemic prophylaxis: 24 hours for lower-grade injuries and 72 hours after injury or no more than 24 hours after soft tissue coverage for type III injuries.^{13,18,19} Sharr and Buckley explicitly state there is no evidence that prophylaxis beyond 72 hours post-debridement provides benefit and caution that prolonged courses may encourage nosocomial and multidrug-resistant pathogens.²⁰

Delayed soft tissue coverage is an important infection risk factor, especially in IIIB/IIIC tibial injuries.^{1,6,15,16,23} Breugem and Strackee found that early aggressive debridement followed by coverage within 3-5 days appears to reduce osteomyelitis and delayed union.¹⁵ Atwan summarizes evidence that delayed coverage beyond 5 days predicted deep infection in high-grade open tibia fractures.¹ Ryan and Pugliano recommend closure within 7 days once soft tissues are viable and all necrotic tissue is removed.⁶ However, these findings support reducing delay and improving debridement/coverage pathways; they do not prove that continuous systemic prophylaxis throughout the delay prevents infection.^{15,17,26}

The major exception is severe contamination. Stennett et al. showed that extended post-closure prophylaxis was associated with lower deep SSI odds in severely contaminated wounds, but not in mild or moderate contamination.¹² This supports selective extension in grossly contaminated wounds, repeated debridement with residual concern, farm/sewage/marine contamination, vascular compromise, immunosuppression, or when the clinical picture suggests evolving infection.^{12,13,18,19,20} Such treatment should be individualized, preferably with infectious-disease input, and should be considered extended prophylaxis or early treatment rather than routine prophylaxis.^{12,13,26,27}

Local antibiotics may be useful when systemic delivery is compromised by soft tissue stripping and devascularization.^{3,11,21,22,28,32} Morgenstern et al. found significantly lower infection rates with local antibiotic prophylaxis in open limb fractures, although study quality was low.²¹ Henry and Swiontkowski describe PMMA bead pouches in severe open fractures, and modern protocols are testing absorbable or injectable local antibiotics.^{3,21,22,28} Local adjuncts may reduce reliance on prolonged systemic exposure, but evidence remains heterogeneous and safety issues such as nephrotoxicity with high-volume aminoglycoside-loaded carriers require caution.^{21,22,27}

In summary, the balance of evidence favors early appropriate systemic antibiotics for a limited duration, early repeated debridement as needed, local antibiotic consideration in severe wounds, and prompt orthoplastic coverage rather than routine antibiotics until closure.^{1,5,13,18,20,26,32}

Prolonged antibiotics should be reserved for defined high-risk contamination or suspected/confirmed infection, not used automatically because coverage is delayed.^{12,13,18,20,26}

Risk of bias:

Overall risk of bias: Moderate to high for direct evidence; low to moderate for overall direction of evidence because multiple guidelines and reviews converge on limited-duration prophylaxis.

Level / strength of evidence: Low to moderate.

The evidence includes two randomized comparisons of shorter versus longer prophylaxis, multiple systematic reviews, a large 2400-patient FLOW secondary analysis, and guideline statements. However, no RCT directly compares stopping at 48-72 hours versus continuing until delayed flap coverage in GA IIIB/IIIC injuries. Direct evidence is therefore low, but the consistency of systematic reviews and guidelines against routine prolonged prophylaxis raises confidence to a low-to-moderate level.

Final consensus statement:

Routine continuation of systemic prophylactic antibiotics until definitive soft tissue coverage is not recommended in open fractures with delayed wound closure. Antibiotics should be administered as early as possible after injury and discontinued according to evidence-based protocols based on injury severity. For most Gustilo-Anderson type III fractures, prophylaxis should be limited to 48–72 hours after injury and discontinued no later than 24 hours after definitive soft tissue coverage. Prolonged or culture-directed antibiotic therapy should be reserved for patients with severe contamination, persistent devitalized tissue, or suspected or confirmed infection.

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