ICM ON OPEN INJURIES – CONSENSUS RECOMMENDATION DOCUMENT

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RQ 2: Should intravenous cefuroxime be adopted as the standard prophylactic antibiotic for open fractures, or should antibiotic selection be guided by local hospital protocol?

Section 1: Background (<300 words)

Managing open fractures demands early, effective antibiotic prophylaxis – not as an afterthought, but as one of the few time-critical interventions that meaningfully alters the risk of fracture-related infection (FRI). The question of which antibiotic to use has, however, remained unsettled for decades. Cefuroxime, a second-generation cephalosporin, has been adopted as a convenient single-agent standard in several international protocols on the basis of its broader Gram-negative cover compared to first generation ones and twice-daily dosing. The counterargument – retaining

locally-guided selection, stratified by Gustilo-Anderson (GA) grade, local antibiogram data, MRSA prevalence, and available resources – reflects the reality that no single regimen suits every institution or every wound.

Before engaging with the evidence, an important caveat must be stated plainly: not a single study in the reviewed corpus directly evaluates intravenous cefuroxime as a prophylactic agent in open fractures. Every inference we draw about cefuroxime is therefore indirect – drawn by analogy from comparisons of first-generation cephalosporins against locally-tailored or broad-spectrum alternatives, and from one large prospective cohort that, for the first time, stratifies surgical site infection (SSI) risk by the generation class to which cefuroxime belongs. That study is the closest the literature currently comes to answering this question, and its findings are consequential.

Known facts: Gram-positive organisms – principally Staphylococcus aureus, including MRSA – account for the majority of early open fracture colonisations and between 37.8% and 62.5% of established FRI isolates. A standardised, narrow-spectrum cephalosporin, given promptly and within an organised protocol, has consistently matched or outperformed broader alternatives in infection prevention. Critically, how quickly we give the antibiotic and how quickly we achieve definitive wound coverage matters more, in the available data, than which antibiotic we choose.

Unknown/gaps: Whether cefuroxime, evaluated directly against first-generation agents, would perform equivalently, better, or worse in infection prevention remains unknown – no trial has tested it. Whether the generation-class signal identified by Yang et al. applies outside the Chinese hospital setting in which it was observed is unclear. And whether the practical benefits of standardising on any single agent – faster delivery, fewer prescribing errors, simpler pharmacy stocking – would, in a real-world setting, outweigh any agent-specific pharmacological shortcoming for cefuroxime is a question the current literature simply cannot answer.

Section 2: Data extraction table

Twenty studies are included . All data are drawn exclusively from the evidence corpus. No study directly evaluates cefuroxime. Abbreviations: GA = Gustilo-Anderson; FRI = fracture-related infection; SSI = surgical site infection; PIP-TAZ = piperacillin-tazobactam; CTX = ceftriaxone; AKI = acute kidney injury; GCT = guideline-concordant therapy; OR = odds ratio; aOR = adjusted odds ratio; CI = confidence interval; MRSA = methicillin-resistant Staphylococcus aureus; MDR = multidrug-resistant.

S.no	Author, Year, Country	Study Design	Sample Size	Population (Inclusion/Exclusion)	Groups Compared	Key Results
1	Via et al., 2023, USA	Retrospective cohort	n=159	GA III open fractures; single Level I trauma centre	Standardised cefotetan monotherapy vs heterogeneous locally-selected regimens	No significant difference in SSI or deep infection. Fewer re-operations with cefotetan. Supports single-agent standardised protocol for GA III.

2	Prebianchi et al., 2023, Brazil	Retrospective cohort	n=1,041	Open fractures all GA grades; single institution	Narrow vs broad-spectrum antibiotic; varying durations of prophylaxis	Type of antibiotic (not duration) correlated with FRI rates. Broader-spectrum agents not consistently superior. Duration beyond guideline-recommended period conferred no additional benefit.
3	Sheibani et al., 2025, Iran	Prospective cohort	n=600 (GA III)	GA III; high local MRSA prevalence setting	Vancomycin + amikacin vs	Vancomycin + amikacin significantly outperformed

					cefazolin + amikacin	cefazolin + amikacin across ESR, CRP, colonisation, clinical infection, deep infection, and abscess formation. Attributed to superior MRSA coverage.
4	Bates et al., 2024, USA	Prospective pharmacokinetic	n=8	Open lower extremity fractures	Standard IV cefazolin; wound-bed concentrations vs S. aureus MIC	Standard IV cefazolin achieved wound-bed concentrations above the S. aureus MIC for ~100% of the dosing interval. Confirms

						adequate tissue penetration.
5	Shifko et al., 2024, USA	Retrospective cohort	N not specified per group	GA III; Level I trauma centre	Ceftriaxone + vancomycin (post-2019) vs cefazolin + gentamicin (pre-2019)	Non-significant trend: lower 1-year treatment failure with ceftriaxone + vancomycin (32% vs 45%, p=0.16). Underpowered.
6	Patanwala et al., 2019, USA	Retrospective cohort	GA III subset	GA III open fractures	Cefazolin monotherapy vs cefazolin + aminoglycoside	Equivalent infection rates (15% vs 16%). No dose-response relationship with aminoglycoside.

					(clinician discretion)	Supports cefazolin monotherapy as adequate for GA III.
7	Alpar, 1988, UK	Randomised controlled trial	n=60	Open fractures all grades; single centre	Cephradine (broad-spectrum cephalosporin) vs flucloxacillin (narrow anti-staphylococcal)	0% wound infection with cephradine vs 1 osteomyelitis + 1 gas gangrene with flucloxacillin. Only RCT in corpus. Dated; allocation concealment not described.

8	de la Garza-Paez et al., 1992, Mexico	Before-after cohort	Not specified	Open fractures all grades; single institution	Pre- vs post-adoption of standardised grade-stratified single-agent protocol (cefotaxime)	Infection rate fell from 8.5% to 3.7% following protocol adoption. Supports benefit of standardisation per se.
9	Weant et al., 2015, USA	Narrative guideline review	N/A	Open fractures all grades	EAST vs SIS guideline synthesis	EAST adds aminoglycoside for GA III; SIS finds insufficient evidence for gram-negative extension. Both endorse early 1st-gen

						cephalosporin and limited duration.
10	Mody/Ponna et al., 2026, USA	Retrospective propensity-matched cohort	47,692 pre-match; 1,527 matched pairs	Open lower extremity fractures; TriNetX database; all GA grades	Cefazolin monotherapy vs piperacillin-tazobactam	Cefazolin significantly outperformed PIP-TAZ across SSI, osteomyelitis, sepsis, reoperation, readmission, thromboembolism, AKI and mortality at 90 days and 1 year. Exception: higher nonunion/malunion with cefazolin in GA

						III (likely confounding by indication; injury severity not captured in TriNetX).
11	Lloyd et al., 2017, USA	Retrospective cohort	n=1,044 (combat trauma)	Combat-related open fracture injuries	Expanded gram-negative (EGN) coverage vs narrow prophylaxis alone	EGN modestly reduced extremity SSTI (22% vs 28%) but no benefit for osteomyelitis. Significantly more antibiotic-resistant Gram-negative organism recovery (49% vs 40%).

						Resistance cost identified.
12	Redfern et al., 2016, USA	Retrospective cohort	n=71 (GA III)	GA III; single Level I trauma centre	Cefazolin + gentamicin vs piperacillin-tazobactam	Equivalent 1-year SSI rates (32.4% vs 31.4%, p=NS). Underpowered. Supports equivalence between narrow+aminoglycoside and PIP-TAZ for GA III.
13	Lack et al., 2015, USA	Prospective cohort	n=195	GA III open tibia fractures; 93.4% received cefazolin	Timing: antibiotics <66 min vs >66 min; wound	Delay >66 min to antibiotics (OR 3.78) and >5 days to

					coverage <5 days vs >5 days	wound coverage (OR 7.39) independently predicted infection. FRI ranged 2.8% (both early) to 40.5% (both delayed). Timing is dominant predictor, independent of agent.
14	Sisson et al., 2026, USA J Orthop Trauma	Retrospective cohort; sequential pre/post	n=136 (67 CTX, 69 PIP-TAZ)	Adults; GA II/IIIa; Level I centre 2020-2023. Exclusions: <6 months follow-	CTX 2g IV monotherapy (post-May 2022) vs PIP-	No significant difference in FRI (25.4% vs 29.0%, p=0.501) or AKI

	[Publish Ahead of Print]	protocol change		up; transfers; primary amputation; vancomycin within 48h.	TAZ monotherapy (pre-May 2022)	(11.9% vs 15.9%, p=0.636). Gram-negative FRI comparable (16.4% vs 15.9%, p=0.549). Multivariate: diabetes independently predicted FRI (OR 6.62, 95% CI 1.87-23.46, p=0.003). Note: sequential cohorts; soil contamination higher

						in CTX group (11.9% vs 1.4%, p=0.015).
15	Salomon et al., 2022, USA Surg Infect	Retrospective cohort	n=619 (355 cefazolin, 264 ceftriaxone)	Open extremity long-bone fractures; all GA grades; Level I centre 2015-2019. Exclusions: cephalosporin allergy; both agents given; no antibiotic.	Cefazolin (1st-gen) vs ceftriaxone (3rd-gen) monotherapy; all GA grades incl. GA III subgroup	No significant differences in non-union (p=0.801), superficial SSI (p=0.649), deep SSI (p=0.837), osteomyelitis (p=0.653), re-operation (p=0.746), re-admission (p=0.857), limb loss (p=0.266), or

						mortality (p=0.787). Multivariable: only GA grade 3 predicted infection (OR 2.99, p<0.001). Ceftriaxone associated with lower costs per patient (all grades: $20,542 vs $25,490).
16	O'Connell et al., 2022, USA Surg Infect	Retrospective cohort	n=120 (97 PIP-TAZ, 23 GCT)	Adult GA III open long-bone fractures; Level I academic centre (Mayo Clinic);	PIP-TAZ vs guideline-concordant therapy (GCT: 1st-gen	Univariable: PIP-TAZ more infections at 6 weeks (23.7% vs 4.3%, p=0.042).

				Jan 2008-Aug 2018. Exclusions: >24h at outside facility; immunosuppression; drug allergies.	cephalosporin +/- aminoglycoside)	Multivariable (adjusted for ISS): antibiotic choice OR 5.81 (95% CI 0.73-46.25, p=0.096) - underpowered (120/251 required). PIP-TAZ group: longer median LOS (16 vs 9 days, p=0.001).
17	Yang et al., 2025, China Int J Surg	Prospective cohort (SSIOS database); 1-year follow-up	n=3,582 (1st-gen: 1,957; 2nd-gen:	Adult open fracture patients; tertiary university hospital; Oct 2014-Dec	1st-gen vs 2nd-gen vs 3rd-gen cephalosporins as perioperative	Overall SSI 8.07%. 2nd-gen significantly higher SSI vs 1st-gen (ARD 3.70%, 95% CI

			1,219; 3rd-gen: 406)	2020. Exclusions: therapeutic antibiotics pre-admission; >=2 generations; immunocompromised; antibiotics >72h post-admission; lost to follow-up.	prophylaxis. Primary outcome: SSI at 1 year (CDC NHSN criteria).	1.90-5.51%; aOR 1.604, 95% CI 1.212-2.124, p=0.001); higher Gram-positive infection (aOR 1.915); higher MDR infection (aOR 2.004). 3rd-gen not significantly different from 1st-gen (aOR 1.234, p=0.341). Generation ranked 9th of 28 risk factors.

						No interaction with GA grade (p>0.05 for all subgroups).
18	Lin et al. (PREP-IT Investigators), 2025, Multinational J Bone Joint Surg Am	Secondary analysis of prospective multicentre RCT cohort (34 sites; North America/Europe)	n=3,331	Adults with surgically fixed open extremity fractures; 34 centres. Exclusions: managed at non-participating hospital; active infection; incomplete follow-up.	Cefazolin monotherapy (58%) vs ceftriaxone monotherapy (10%) vs cefazolin + gentamicin (6%). Instrumental variable analysis for SSI within 90 days and reoperation within 1 year.	Overall SSI 6.9%; no overall significant differences between regimens. GA I/II subgroup: ceftriaxone trended to near 3-fold higher SSI vs cefazolin (OR 2.73, 95% CI 0.96-7.79, p=0.06). GA III: cefazolin+gentamicin

						showed 75% reduction vs cefazolin (OR 0.25, 95% CI 0.03-2.02, p=0.19), NS. No benefit with antibiotics >2 days.
19	Collopy et al., 2022, USA Air Med J	Retrospective cohort; descriptive feasibility; no comparator arm	n=278	Adult trauma patients; air/ground critical care transport; Level 2 centre; Jan 2014-Jun 2017.	Prehospital cefazolin (2g IV, 1st-gen); infection rate and safety as primary outcomes	Overall infection rate 6%. No anaphylactic/allergic reactions. 31.3% received redundant 2nd dose in ED (handover failure).

						82% of prehospital diagnoses confirmed in ED. Overadministration rate 5%. Supports feasibility and safety of early standardised 1st-gen cephalosporin delivery including prehospital.
20	Shawar et al., 2020,	Retrospective cohort; single Level I centre	n=85 (62 tobramycin-based,	Adult GA III open fractures; Jan 2010-Dec 2016.	High-dose tobramycin (7mg/kg) +	Composite AE: no significant difference (32.3% tobramycin vs

	USA Surg Infect		23 PIP-TAZ)	Exclusions: death <24h; primary amputation; both study drugs; traditional-dose tobramycin (<5mg/kg); renal replacement therapy.	cefazolin/clindamycin vs PIP-TAZ (4.5g q8h). Primary: composite AE (nephrotoxicity + SSI + readmission with surgery at 60 days).	13% PIP-TAZ, p=0.10). SSI at 30 days: significantly lower with PIP-TAZ (4.3% vs 27.5%, p=0.033). SSI at 60 days: further cases in tobramycin group only (p=0.009). Nephrotoxicity: 0% tobramycin vs 8.7% PIP-TAZ (NS). Full-regimen delivery: 77 min (PIP-TAZ) vs 179

						min (tobramycin combination), p<0.05.

Section 3: Results summary write-up (up to 500 words)

Twenty studies covering over 56,000 patients were reviewed: one RCT, fourteen cohort studies (including two large registry analyses), one pharmacokinetic study, one before-after cohort, one guideline narrative review, and one prehospital feasibility study. None evaluated cefuroxime directly.

Standardised single-agent protocols versus heterogeneous practice: de la Garza-Paez et al. saw institutional FRI rates fall from 8.5% to 3.7% simply by switching to a standardised grade-stratified protocol using cefotaxime. Via et al. found standardised cefotetan monotherapy equivalent to heterogeneous locally-selected regimens on SSI and deep infection, with fewer re-operations. Alpar's RCT – the only trial in this corpus – recorded 0% wound infection with a

broad-spectrum cephalosporin (cephradine) versus one osteomyelitis and one gas gangrene with flucloxacillin. Collopy et al.'s prehospital cefazolin data (n=278) are telling: a 6% infection rate, no anaphylaxis, and the main safety issue being a 31.3% redundant re-dosing rate caused by handover failures – a systems problem, not an antibiotic problem.

Cephalosporin generation – the most proximate evidence for cefuroxime: Yang et al. (n=3,582; prospective; 1-year follow-up) is the standout study for this question. It is the only dataset in the literature to stratify open fracture SSI risk by cephalosporin generation. The result is clear and uncomfortable for proponents of cefuroxime: second-generation cephalosporins – the class to which cefuroxime belongs – carried a significantly higher SSI risk than first-generation agents (ARD 3.70%, 95% CI 1.90–5.51%; aOR 1.604, 95% CI 1.212–2.124, p=0.001), with higher rates of Gram-positive infection (aOR 1.915) and MDR infection (aOR 2.004). Third-generation agents were not significantly worse than first-generation (aOR 1.234, p=0.341). The generation effect held across all GA grades – it was not confined to high-grade or heavily contaminated injuries.

First- versus third-generation comparisons: Salomon et al. (n=619) found cefazolin and ceftriaxone produced identical outcomes across all grades including GA III – with ceftriaxone costing less per patient. Lin et al.'s PREP-IT analysis (n=3,331, 34 sites) found no overall significant difference, though ceftriaxone showed a worrying near three-fold trend

toward higher SSI in GA I/II fractures (OR 2.73, 95% CI 0.96–7.79, p=0.06) – approaching but not crossing significance. Sisson et al. (n=136, GA II/IIIa) found ceftriaxone and piperacillin-tazobactam interchangeable on FRI and AKI; of note, the strongest predictor of infection in their cohort was not antibiotic choice but diabetes (OR 6.62) – a reminder that the patient matters as much as the drug.

First-generation versus broad-spectrum regimens: Mody/Ponna et al. (n=47,692 pre-match) found cefazolin significantly outperformed piperacillin-tazobactam across SSI, osteomyelitis, sepsis, reoperation, readmission, thromboembolism, AKI and mortality. O'Connell et al. found piperacillin-tazobactam associated with more infections than guideline-concordant therapy on univariable analysis (23.7% vs 4.3%, p=0.042), effect not surviving multivariable adjustment in an underpowered model. Where GA III escalation is necessary, Shawar et al. found piperacillin-tazobactam associated with significantly lower 30-day SSI than high-dose tobramycin (4.3% vs 27.5%, p=0.033), without significant nephrotoxicity difference.

Timing as the dominant predictor: Lack et al. frame the whole debate in sharp perspective: within a cohort where 93.4% received the same agent (cefazolin), delaying antibiotics beyond 66 minutes raised the infection odds 3.78-fold, and delaying wound coverage beyond 5 days raised them 7.39-fold – driving FRI rates from 2.8% to 40.5%. Bates

et al. confirm that standard IV cefazolin achieves wound-bed concentrations above the S. aureus MIC throughout the dosing interval. These data suggest that arguing over which cephalosporin to use is secondary to the more fundamental question of how quickly we administer it and how soon we close the wound.

Section 4: Discussion (<1000 words)

This question is, frankly, unanswerable in full: cefuroxime does not appear in a single study across the twenty articles reviewed. What the evidence does permit, however, is a reasoned and evidence-grounded position – and that position has shifted meaningfully with the addition of the seven new studies in this iteration, in particular Yang et al.

The study that changes the conversation most significantly is Yang et al. (n=3,582; prospective; 1-year follow-up). For the first time, SSI risk in open fractures has been stratified by cephalosporin generation class, and the result is something that clinicians recommending cefuroxime should consider carefully: second-generation cephalosporins – cefuroxime's class – carried a significantly higher adjusted risk of SSI than first-generation agents (aOR 1.604, 95% CI 1.212–2.124, p=0.001), along with more Gram-positive infection and more MDR organism recovery. This is not a

subtle or borderline signal; it survived extensive sensitivity analyses and was consistent across all fracture grades. The mechanism is not hard to understand: second-generation agents are relatively weaker against the Gram-positive organisms that dominate early open fracture colonisation, while exerting enough selective pressure to enrich resistant populations.

Lin et al.'s PREP-IT secondary analysis (n=3,331) adds further caution. Although ceftriaxone is a third-generation agent rather than a second-generation one, the near three-fold trend toward higher SSI versus cefazolin in GA I/II fractures (OR 2.73, p=0.06) points in the same direction as Yang et al.: moving away from first-generation cephalosporins in lower-grade fractures appears to carry a risk that outweighs any theoretical benefit from broader Gram-negative cover.

The case for standardising around a first-generation cephalosporin is well-built. de la Garza-Paez et al. showed a near-halving of infection rates after protocol adoption – not because the antibiotic changed, but because the system became consistent. Mody/Ponna et al.'s propensity-matched analysis of nearly 48,000 patients found cefazolin significantly superior to piperacillin-tazobactam across eight major outcomes (surgical site infection , osteomyelitis ,sepsis , reoperation , readmission , thromboembolic events , AKI , and mortality . Salomon et al. and Sisson et al. both confirm that broader-

spectrum cephalosporins and beta-lactam/beta-lactamase inhibitor combinations do not outperform cefazolin – in some cases they may do worse. Patanwala et al. adds that even adding an aminoglycoside to cefazolin in GA III fractures brings no measurable benefit. Collopy et al.'s prehospital cefazolin data – 6% infection rate, no anaphylaxis – reinforce that a standardised first-generation agent is not only pharmacologically sound but operationally deliverable before the patient reaches the operating theatre.

There are genuine exceptions. Sheibani et al.'s high-MRSA-burden GA III cohort shows clearly that in settings with documented MRSA prevalence, a vancomycin-containing regimen outperforms standard cefazolin-based prophylaxis. We do not interpret this as an argument for cefuroxime; we interpret it as an argument for knowing your local microbiology and having a protocol for it. Lloyd et al.'s combat-trauma data suggest some value in expanded Gram-negative coverage for heavily contaminated, high-energy wounds – but at the cost of significantly increased antimicrobial resistance, and with no benefit demonstrated for osteomyelitis.

When escalation for severe GA III injuries is genuinely warranted, Shawar et al.'s data make a clear case for piperacillin-tazobactam over tobramycin-based combinations: 30-day SSI 4.3% versus 27.5% ($p=0.033$), without meaningful nephrotoxicity difference. It is worth noting that piperacillin-tazobactam was also delivered significantly

faster in that cohort (77 vs 179 minutes for the full regimen), which may have contributed independently to the outcome difference – bringing us back, once again, to the primacy of timing.

Our reading of the twenty studies reviewed leads to the following conclusions. Standardise – it reduces FRI rates. Standardise around a first-generation cephalosporin, not a second-generation one: the available generation-class data counsel against cefuroxime, not for it. Prioritise timing above all else – it is the single most important modifiable variable. When escalation is needed for severe GA III contamination, use piperacillin-tazobactam, not an aminoglycoside. When the local MRSA burden demands it, add vancomycin-based cover within a defined protocol. And do not adopt cefuroxime as the universal standard until it has been directly studied – which, conspicuously, it has not been.

Section 5: Risk of bias of included studies

MODERATE.

The foundational limitation is that no study tests cefuroxime directly, meaning every bias assessment in this corpus applies to an indirect argument. Fifteen of twenty studies are non-randomised cohorts susceptible to confounding by indication – a problem most acute in Mody/Ponna et al. (TriNetX cannot capture injury severity or GA subtype) and in Sisson et al. and Salomon et al. (sequential pre/post protocol designs with meaningful baseline differences, including higher soil contamination in the ceftriaxone group of Sisson et al.: 11.9% vs 1.4%, p=0.015). O'Connell et al., Via et al., Redfern et al., and Shifko et al. were all underpowered for their primary comparisons. Yang et al. is the most important new study but it is single-centre, Chinese, and has an uneven cephalosporin distribution across generations; whether the second-generation signal translates to other epidemiological settings is not yet established. Lin et al./PREP-IT has high-quality prospective data but the antibiotic was not randomised, producing wide confidence intervals for less common regimens. The only RCT (Alpar, 1988) is 60 patients, three decades old, and poorly reported by modern standards. Bates et al. reports a pharmacokinetic surrogate in 8 patients. Sheibani et al. and Lloyd et al. come from settings – high-MRSA Iran and combat trauma respectively – that are difficult to generalise to routine civilian open fracture practice.

Section 5: Response/Recommendation (1-2 lines as a conclusion and recommendation statement for the question)

On the basis of the available evidence, intravenous cefuroxime should not be universally adopted as the standard prophylactic antibiotic for open fractures. Generation-stratified data identify a significantly higher SSI risk with second-generation cephalosporins as a class (aOR 1.604, Yang et al., 2025), cefuroxime has never been directly studied in this indication, and a first-generation cephalosporin – administered promptly, within a standardised protocol – has consistently demonstrated equivalent or superior infection prevention across the available comparative literature. We recommend a standardised first-generation cephalosporin (e.g., cefazolin) as the default prophylactic agent for GA I, II, and most IIIa open fractures, with clearly defined, protocolised escalation pathways for the specific circumstances in which broader cover is justified.

Section 6: Level/ strength of Evidence:

LOW to MODERATE.

Based on 20 studies – predominantly Level III–IV non-randomised cohort designs, with one small dated RCT – covering over 56,000 patients. The evidence grade cannot reach MODERATE for two structural reasons: cefuroxime has never been directly studied in this context, and almost all comparative data come from observational studies with meaningful confounding risk. It reaches LOW–MODERATE rather than remaining at LOW because Yang et al.'s large, well-adjusted, prospective generation-stratified cohort (n=3,582) provides the first class-level pharmacological evidence bearing directly on cefuroxime, and because four independent cohort studies covering over 50,000 patients consistently favour first-generation over broader-spectrum prophylaxis. Conflicting findings in specific subpopulations (Sheibani et al.; Lloyd et al.) prevent an unqualified MODERATE rating.

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