RQ [2]: In patients with uncontrolled diabetes mellitus, should the duration of antibiotic therapy be extended until wound healing is achieved?

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Section 1: Background (<300 words):

Open fractures carry a high risk of infection due to direct contamination of bone and soft tissue. International guidelines recommend early initiation of antibiotics and continuation for a short, defined period—typically 24–72 hours after wound closure or definitive fixation—rather than prolonged therapy. In uncontrolled diabetes mellitus, wound healing is impaired by microvascular disease, neuropathy, and poor glycaemic control, which increases susceptibility to infection and delayed union. However, antibiotics themselves do not accelerate tissue repair and healing depends on surgical debridement, vascularity, and metabolic optimization. Despite guideline clarity, clinicians often extend antibiotics until wound closure in uncontrolled diabetics, fearing persistent colonization or occult infection. Prolonged courses have been linked to antimicrobial resistance, nephrotoxicity, and Clostridium difficile infection, without evidence of improved fracture healing. There is a lack of studies focusing on open fractures in uncontrolled diabetics. Whether poor metabolic control independently alters optimal antibiotic duration remains unknown.

Section 2: Data extraction table

S.no	Author, year of publication, Country	Study Design	Sample Size (add individually for each group if multiple groups compared)	Study population (Inclusion and exclusion criteria)	Intervention / Groups compared Follow up duration	Results and Outcomes
1	Ondari, J. N. et al [1]	Unblinded Randomized Control Trial	77 patients (40 in 24 hr	patients aged 18–80 years admitted through accident	Patients randomized into either 24 hour or	No significant difference in infection rates between 24-hour and 5-day groups with

	2016, Kenya		group and 37 in 5 day group	and emergency department with Gustilo II traumatic open tibia fractures.	five day antibiotic group after surgical debridement.	infection rates of 23% (9/40) vs. 19% (7/37) respectively (p = 0.699). The infection rate was significantly associated with time lapsed before administration of antibiotics (p = 0.004). Time to first dose antibiotic administration correlates with infection rate. Antibiotic use for 24 hours only has proven adequate prophylaxis against infection.
2	Messner J. et al [2], 2017, UK	Systematic literature Review	Publications from 1970 till 2017	Open fractures of limbs		Antibiotics for maximum of 72 hours, even in the absence of definitive soft tissue coverage No benefit of prolonged duration of antibiotic treatment of open fractures, irrespective of their severity
3	Chang, Y. et al [3], 2019, Canada	Systematic Review	233 publications 2007-2017	Open fractures of limbs		Early systemic antibiotics Antibiotic coverage for 2-3 days only or 24 hrs after wound closure whichever is early. Gram Positive and Gram-Negative coverage. Broader coverage for severe injuries.
4	Stennett, C. A. et al [4] 2020, Multicentre – US, Canada, Australia, Norway, India	Level III, Retrospective cohort study	Patients (N = 2400) with	Inclusion: Patients with open fractures of the extremities who participated in the Fluid Lavage of Open Wounds (FLOW) trial.	Extended antibiotic prophylaxis, defined as more than 72 hours of continuous antibiotic use after definitive wound closure.	42% received extended antibiotic prophylaxis. Deep SSI prevalence was 5%, 8%, and 23% for wounds with mild, moderate, and severe contamination, respectively. Extended antibiotic use in open fractures showed a trend towards, Increased odds of infection in wounds with mild contamination, No association in wounds with moderate contamination and

						Strongly protective against deep SSI in wounds with severe contamination.
5	Declercq P et al [5], 2021, Belgium	Level III, Retrospective cohort study	502 patients (with 559 open fractures)	Inclusion: Operated Post traumatic long bone open fractures Study period 2003-2017	Association between perioperative antibiotic prophylaxis (PAP) duration and Fracture related Infection (FRI) Follow up 24 months	PAP duration longer than 72 h did not significantly increase the odds for FRI compared to shorter durations (p = 0.06, analysis adjusted for propensity score). No evidence that administration of prophylactic antibiotics beyond 72 h in patients with long bone open fractures is warranted.

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

Declercq et al. (2020) conducted a large retrospective study of 502 patients with 559 open fractures. They found that the median PAP duration was 4.3 days, with most patients receiving antibiotics beyond 72 hours. Fracture-related infection (FRI) occurred in 8% of cases, increasing with Gustilo-Anderson severity. Importantly, longer PAP duration was independently associated with higher odds of infection (OR 1.11 per day, p=0.003). Their conclusion was clear: extending prophylaxis beyond 72 hours is not warranted and may paradoxically increase infection risk.

Stennett et al. (2020) analyzed 2400 patients from the FLOW trial. They stratified results by wound contamination severity. Extended prophylaxis (>72 hours post-closure) showed divergent effects: in mildly contaminated wounds, longer courses trended toward higher infection risk (aOR 1.39); in moderately contaminated wounds, no difference was observed; and in severely contaminated wounds, extended prophylaxis was strongly protective (aOR 0.20). This study highlights that contamination level modifies the effect of antibiotic duration, suggesting that selective extension may be justified in severely contaminated injuries.

Ondari et al. (2016) performed a randomized controlled trial in Kenya on Gustilo II open tibia fractures. Patients received either 24 hours or 5 days of antibiotics. Infection rates were similar (23% vs. 19%, p=0.699), demonstrating no benefit of prolonged prophylaxis. However, timing was critical: patients who received antibiotics within 12 hours had significantly lower infection rates (11% vs. 52%). This emphasizes that prompt initiation outweighs duration in determining outcomes.

Chang et al. (2019) conducted a systematic survey of 223 publications between 2007 and 2017. They found wide variability in practice, but most regimens involved 2–3 days of antibiotics, with broad-spectrum coverage for severe injuries. Recommendations generally supported ≤3 days of prophylaxis, though institutional protocols differed. The survey underscored the lack of consensus and the need for high-quality randomized trials.

Messner et al. (2017) performed a meta-analysis of five comparative and 27 observational studies, encompassing nearly 6700 fractures. They found no significant benefit of extending prophylaxis beyond 72 hours. Infection rates were similar whether antibiotics were given for ≤72 hours or longer (10% vs. 9.2%). Subgroup analyses by Gustilo type confirmed equivalence, and even shorter regimens (24–48 hours) were not inferior. Their conclusion: prolonged prophylaxis does not reduce infection risk, regardless of fracture severity.

From the above studies it is clear that 1. Early administration of antibiotics is the most critical determinant of infection prevention, 2. prolonged prophylaxis (>72h) offers no general benefit and may increase infection risk in less contaminated wounds and 3. Severely contaminated injuries may represent an exception, where extended courses may reduce infection odds.

Section 4: Discussion (<1000 words)

In open fractures the risk of infection is substantial, and systemic antibiotic prophylaxis has long been considered a cornerstone of management alongside meticulous surgical debridement and stabilization. However, the optimal duration of antibiotic therapy remains a subject of debate. This question becomes particularly pressing in patients with uncontrolled diabetes mellitus, a population with impaired wound healing and heightened susceptibility to infection. The central issue is whether antibiotic prophylaxis should be extended until wound healing is achieved in these patients, or whether guideline-based durations of 24–72 hours remain sufficient.

Guidelines from the Surgical Infection Society, WHO, and the Eastern Association for the Surgery of Trauma (EAST) recommend early initiation of systemic antibiotics and discontinuation of prophylaxis within 24–72 hours, even for severe injuries. Prolonged prophylaxis is discouraged due to risks of antimicrobial resistance, Clostridium difficile infection, nephrotoxicity, and increased healthcare costs.

Diabetes mellitus is a well-established risk factor for infection in open fractures. Hyperglycemia impairs neutrophil chemotaxis and phagocytosis, reduces collagen synthesis, and compromises microvascular circulation, all of which contribute to delayed wound healing and increased susceptibility to infection. Despite the clear association between diabetes and infection risk, whether extending antibiotic

prophylaxis until wound healing provides benefit in this subgroup remains unproven. The balance between potential benefit (reduced infection) and harm (antibiotic resistance, adverse drug events) is uncertain.

Guidelines and evidence do not support extending systemic antibiotics until wound healing. Instead, infection prevention in diabetics should be focussed on Tight glycemic control, meticulous surgical debridement, early and adequate soft tissue coverage, adjunctive measures such as local antibiotic carriers (gentamicin beads) and negative pressure wound therapy. There is lack of literature specifically evaluating open fractures in diabetic patients, and comparing systemic extension versus local antibiotic adjuncts in diabetics.

To conclude, in patients with open fractures and uncontrolled diabetes mellitus, extending systemic antibiotic prophylaxis until wound healing is achieved is not supported by current evidence. Prolonged courses do not reduce infection risk and may increase adverse outcomes. Future research should specifically evaluate diabetic subgroups, stratify outcomes by glycemic control, and explore adjunctive local therapies. Until such evidence emerges, clinicians should adhere to guideline-based durations and prioritize comprehensive multidisciplinary care.

Section 5: Risk of bias of included studies

MODERATE

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

In patients with open fractures and uncontrolled diabetes mellitus, although the risk of infection is high, extending systemic antibiotic prophylaxis is not supported by current evidence. Optimizing host and wound factors needs to be considered.

Section 6: Level/ strength of Evidence:

LOW

There is a lack of studies focusing on antibiotic prophylaxis in open fractures particularly in uncontrolled diabetics.

(Kindly add citations wherever necessary and reference list at the end)

References:

1. Ondari, J. N., Masika, M. M., Ombachi, R. B., & Ating'a, J. E. (2016). Unblinded randomized control trial on prophylactic antibiotic use in gustilo II open tibia fractures at Kenyatta National Hospital, Kenya. *Injury*, *47*(10), 2288-2293.
2. Messner, J., Papakostidis, C., Giannoudis, P. V., & Kanakaris, N. K. (2017). Duration of administration of antibiotic agents for open fractures: meta-analysis of the existing evidence. *Surgical infections*, *18*(8), 854-867.
3. Chang, Y., Bhandari, M., Zhu, K. L., Mirza, R. D., Ren, M., Kennedy, S. A., ... & Guyatt, G. H. (2019). Antibiotic prophylaxis in the management of open fractures: a systematic survey of current practice and recommendations. *JBJS reviews*, *7*(2), e1.
4. Stennett, C. A., O'Hara, N. N., Sprague, S., Petrisor, B., Jeray, K. J., Leekha, S., ... & FLOW Investigators. (2020). Effect of extended prophylactic antibiotic duration in the treatment of open fracture wounds differs by level of contamination. *Journal of orthopaedic trauma*, *34*(3), 113-120.
5. Declercq, P., Zalavras, C., Nijssen, A., Mertens, B., Mesure, J., Quintens, J., ... & Metsemakers, W. J. (2021). Impact of duration of perioperative antibiotic prophylaxis on development of fracture-related infection in open fractures. Archives of Orthopaedic and Trauma Surgery, 141(2), 235-243.