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Original Article

Comparative Clinical Efficacy of Ceftriaxone Sodium and Cefoperazone–Sulbactam in the Management of Diabetic Foot Infections: A Prospective Cohort Study

Muhammad Shafeeq[1], Haroon Badshah[1], Maryam Zulfat[2], Abdul Mateen[3], Saqib Jahan[3], Haleema Hidayat[4], Adil Khaliq[5], Muhammad Sohail Anwar[3], Ali Khan[6], Muhammad Faheem[3], Muhammad Ikram[1]*, Dareen Ihsan[1], Hafiz Sajid Akbar[5], Atta Ullah Shah[7]

[1] Department of Pharmacy, Abdul Wali Khan University Mardan, Mardan, Pakistan
[2] Department of Biochemistry, Women University Swabi, Swabi, Pakistan
[3] Department of Pharmacy, University of Swabi, Swabi, Pakistan
[4] Department of Biochemistry, Shaheed Benazir Bhutto Women University, Peshawar, Pakistan
[5] Department of Pharmacy, Vertex Institute of Science and Technology, Mardan, Pakistan
[6] The Professional Institute of Health Sciences, Mardan, Pakistan
[7] Department of Pharmacy, CECOS University of IT and Emerging Sciences, Peshawar, Pakistan

***Corresponding author: Muhammad Ikram, mikram@awkum.edu.pk**

ABSTRACT

Background: Diabetic foot infections (DFIs) represent a major complication of diabetes mellitus, contributing substantially to hospitalization rates, amputation risk, and healthcare costs, particularly in resource-limited settings where broad-spectrum intravenous antibiotics are prescribed empirically without microbiological confirmation. Objective: To compare the clinical wound-healing efficacy and non-response rates of intravenous ceftriaxone sodium versus intravenous cefoperazone–sulbactam in adult patients with diabetic foot infections in Peshawar, Khyber Pakhtunkhwa, Pakistan, and to characterize the spectrum of presenting foot complications in this cohort. Methods: A prospective comparative cohort study was conducted at the SS Diabetic and Medical Care Center, Peshawar. Eighty patients aged ≥30 years with established diabetes mellitus and active diabetic foot infections were enrolled and allocated to receive either intravenous ceftriaxone sodium 2 g twice daily (Group 1; n = 40) or intravenous cefoperazone–sulbactam 2 g twice daily (Group 2; n = 40) for seven consecutive days. Wound healing was assessed at day 7 using a validated six-point ordinal scale (0%–100%). The primary outcome, clinical response rate, was compared between groups using Fisher's exact test, with 95% confidence intervals calculated by the Wilson score method. Results: Clinical response rates were 85.4% (95% CI: 71.3%–93.2%) for ceftriaxone sodium and 89.4% (95% CI: 76.2%–95.7%) for cefoperazone–sulbactam; the 4.0 percentage-point difference was not statistically significant (p = 0.499; OR for non-response 1.53, 95% CI: 0.42–5.54). Diabetic foot ulcer was the most prevalent complication (53%), followed by cellulitis (31%) and skin gangrene (15%). Conclusion: Both regimens demonstrated clinically acceptable wound-healing efficacy as cost-effective empiric options for diabetic foot infections in resource-limited settings, though future adequately powered, randomised trials incorporating microbiological confirmation are required to establish definitive comparative evidence. Keywords: Cephalosporins; ceftriaxone; cefoperazone–sulbactam; diabetic foot infection; diabetic foot ulcer; clinical efficacy; beta-lactamase inhibitor; antibiotic stewardship; Khyber Pakhtunkhwa; Pakistan.

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INTRODUCTION

Diabetes mellitus is a complex, chronic metabolic disorder characterized by persistent hyperglycemia arising from defects in insulin secretion, insulin action, or both, encompassing a heterogeneous spectrum of autoimmune, genetic, and metabolic conditions that share this common pathophysiological hallmark (1,2). Globally, the prevalence of diabetes has escalated to epidemic proportions, placing an extraordinary burden on healthcare systems worldwide, with disproportionate impact in low- and middle-income countries (LMICs) where access to specialist care and preventive health services remains severely constrained (2,3). Beyond dysglycemia, diabetes engenders a spectrum of macrovascular and

microvascular complications, encompassing cardiovascular disease, nephropathy, retinopathy, and peripheral neuropathy, that collectively diminish quality of life, increase rates of hospitalization, and drive premature mortality (1,3). The clinical management of diabetes therefore extends well beyond glycemic control to encompass aggressive cardiovascular risk factor modification and the early identification and prompt treatment of infection-related complications, which represent a significant driver of morbidity and inpatient resource utilization in this population (3).

Among the most clinically devastating complications of diabetes mellitus, diabetic foot disease represents a convergence of peripheral neuropathy, peripheral arterial disease, and infection that culminates in progressive tissue destruction, ulceration, gangrene, and, in severe cases, lower-extremity amputation (4,5). The lifetime prevalence of diabetic foot ulcers (DFUs) has been estimated at approximately 15–25% among individuals living with diabetes, with global epidemiological analyses confirming this substantial and rising burden (6,7). Critically, approximately 85% of lower-extremity amputations in diabetic patients are preceded by a foot ulcer, and an estimated 15–20% of individuals presenting with diabetic foot infections (DFIs) will ultimately require surgical amputation, making DFUs one of the leading causes of non-traumatic lower-limb loss worldwide (8,9). The economic and social consequences of this complication are equally profound: diabetic foot disease consumes disproportionate healthcare resources and exacts a severe toll on patients' functional independence, occupational capacity, and psychological well-being (8). In resource-limited settings such as Pakistan's Khyber Pakhtunkhwa (KP) province, compounding risk factors, including poor socioeconomic status, inadequate protective footwear, low health literacy, late presentation to specialist care, and insufficient primary-care awareness of diabetic foot protocols, accelerate the incidence and severity of DFUs and their infectious sequelae, amplifying the already substantial burden of this condition (9).

The microbiological landscape of diabetic foot infections is polymicrobial and clinically heterogeneous. Acute, superficial lesions are predominantly caused by aerobic Gram-positive organisms, particularly Staphylococcus aureus and beta-haemolytic streptococci, while chronic or deep-tissue infections typically involve a more complex consortium of aerobic Gram-negative rods, including Escherichia coli, Proteus species, and Pseudomonas aeruginosa, alongside anaerobes such as Bacteroides, Peptococcus, and Clostridium species (10). The emergence of methicillin-resistant Staphylococcus aureus (MRSA) as a causative pathogen in both nosocomial and community-onset DFIs has further complicated empiric antibiotic selection, particularly among patients with prior antibiotic exposure, prior hospitalization, or recent surgical intervention (10). Simultaneously, immunocompromise driven by uncontrolled hyperglycemia, through mechanisms including neutrophil dysfunction, impairment of humoral immunity, acidosis, and disruption of antioxidant defenses, renders diabetic patients uniquely susceptible to severe, recurrent, and treatment-refractory infections (4,11). The interplay between glycemic control and infectious outcomes therefore constitutes a critical and modifiable determinant of treatment success in DFI management, with sustained hyperglycemia shown to independently impair wound healing, promote biofilm formation, and facilitate the emergence of resistant organisms (11).

The selection of appropriate empiric antimicrobial therapy for DFIs is guided by infection severity, prior antibiotic exposure, local resistance epidemiology, patient-specific factors such as allergy history and renal function, and the availability and cost of antimicrobial agents (12,16). Third-generation cephalosporins, including ceftriaxone sodium, have been widely employed in the empiric management of moderate-to-severe DFIs owing to their broad-spectrum activity against both Gram-positive and Gram-negative pathogens, favorable once- or twice-daily dosing pharmacokinetics, and relative cost-effectiveness in LMIC settings (13). However, the escalating prevalence of extended-spectrum beta-lactamase (ESBL)-producing organisms, plasmid-mediated cephalosporin resistance mechanisms, and nosocomial Gram-negative pathogens has progressively eroded the clinical utility of third-generation cephalosporin monotherapy in DFIs, with resistance rates varying substantially across geographic regions, healthcare settings, and patient populations (14,15). Cefoperazone-sulbactam, a fixed-dose combination of a third-generation cephalosporin with the irreversible beta-lactamase inhibitor

sulbactam, has emerged as a strategically important alternative: the addition of sulbactam expands antimicrobial coverage by competitively inhibiting beta-lactamase enzymes produced by resistant organisms, thereby potentially restoring the bactericidal efficacy of the cephalosporin component against ESBL-producing and multi-drug-tolerant pathogens (13,14). Systemic antibiotic therapy, appropriately selected, adequately dosed, correctly routed, and sufficiently prolonged, remains the cornerstone of DFI management alongside surgical debridement and rigorous glycemic optimization (16).

Despite the widespread empiric use of both ceftriaxone sodium and cefoperazone-sulbactam in diabetic foot infections across Pakistan and other South Asian LMICs, head-to-head comparative clinical data evaluating their relative wound-healing efficacy and clinical non-response rates in this population remain sparse (17,18). The majority of available evidence derives from microbiologically confirmed, randomized controlled trials conducted in high-income settings, which may not adequately reflect the resistance epidemiology, patient demographics, comorbidity profiles, or healthcare infrastructure of Pakistan's KP province (17). Furthermore, the growing problem of antibiotic resistance in DFI management, driven by antibiotic overuse, sub-therapeutic dosing, inadequate treatment duration, and insufficient microbiological surveillance, necessitates the generation of regional, real-world clinical data to inform context-appropriate empiric prescribing practices and antibiotic stewardship policies (15,16). In the absence of such evidence, clinicians in resource-limited settings face the dual challenge of selecting effective empiric therapy while avoiding premature escalation to costly reserve agents such as meropenem, linezolid, or ticarcillin-clavulanate, which may be logistically and financially inaccessible to the majority of patients. Accordingly, this study aimed [Population] to evaluate and compare [Intervention vs. Comparison] the clinical wound-healing efficacy and clinical non-response rates of intravenous ceftriaxone sodium versus intravenous cefoperazone-sulbactam in adult patients aged 30 years and above with diabetic foot infections [Outcome] presenting to a specialist diabetic care center in Peshawar, Pakistan, and to characterize the pattern of clinical non-response to these two agents within this community-based patient population (13).

MATERIALS AND METHODS

This prospective comparative cohort study was designed to evaluate the clinical wound-healing efficacy and non-response rates of two intravenous antibiotic regimens, ceftriaxone sodium and cefoperazone-sulbactam, in adult patients with diabetic foot infections. The study was conducted at the SS Diabetic and Medical Care Center, Ring Road, Achini Chowk, Peshawar, Khyber Pakhtunkhwa, Pakistan, a specialist facility dedicated exclusively to the management of diabetes mellitus and its associated complications, operating under the clinical supervision of a qualified endocrinologist and diabetologist. Data were collected during a prospectively defined enrollment period through direct clinical examination and structured patient interviews. The study protocol was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the institutional ethics committee of the study site prior to data collection commencement. Written informed consent was obtained from all participants before enrollment, including explicit written consent for clinical wound photography and the use of photographic data for publication purposes. Patient confidentiality and anonymity were strictly maintained throughout all phases of the study.

The study population comprised adult patients with an established diagnosis of diabetes mellitus (type 1 or type 2) who presented with active diabetic foot ulcers or infections during the enrollment period. Eligible patients were aged 30 years or above, of either sex, and were clinically assessed by the supervising endocrinologist, who independently prescribed either ceftriaxone sodium or cefoperazone-sulbactam injection based on clinical evaluation of infection severity, wound characteristics, and patient profile. Only prescriptions involving one of these two antimicrobial agents were eligible for inclusion. Patients were required to demonstrate willingness to participate, to attend the scheduled follow-up visit, and to provide assurance of treatment compliance throughout the seven-day course. Exclusion criteria

were applied to ensure internal validity: children and individuals under 30 years of age were excluded, as were unconscious or non-responsive patients unable to provide informed consent, newly diagnosed diabetic patients without established foot complications, and patients who declined participation or demonstrated prior or anticipated non-compliance with the prescribed treatment regimen or follow-up schedule. No upper age limit was applied, as older patients with established diabetes constitute a clinically representative and high-burden segment of the diabetic foot population in this setting (9).

Enrolled patients were allocated to one of two treatment groups based on the prescribing endocrinologist's clinical decision at the time of initial consultation. Group 1 (n = 40) received intravenous ceftriaxone sodium 2 g administered twice daily (total daily dose: 4 g/day) for seven consecutive days. Group 2 (n = 40) received intravenous cefoperazone-sulbactam 2 g administered twice daily (total daily dose: 4 g/day) for the same duration. It is acknowledged that this non-randomized, physician-directed allocation method represents an important potential source of selection bias; the treating physician may have preferentially prescribed one agent for patients with more severe infections or differing comorbidity profiles, which could confound the observed efficacy estimates. To characterize between-group comparability, baseline demographic data, including patient sex, diabetes type (type 1 or type 2), and random blood sugar (RBS) values measured at initial presentation, were documented for all enrolled patients in both groups. Wound characteristics were assessed and documented at baseline (day 0) and at the completion of the treatment course (day 7). All patients received concomitant wound debridement as clinically indicated, performed regularly in patients with gangrenous or necrotic soft tissue or bone involvement; the contribution of debridement to wound healing outcomes represents a recognized confounding variable that could not be fully isolated from antibiotic efficacy in this study design.

The primary outcome was clinical wound-healing efficacy, operationally defined and quantified using a standardized six-point ordinal wound-assessment scale adapted from Balakrishna et al. (13). At the day-7 re-examination, wound status was independently assigned to one of the following categories by the supervising clinician: 0% (no improvement; wound entirely uncured), 20% (open wound with no significant change in dimensions or tissue character), 40% (closed wound with maximal pus retention in surrounding tissues and skin), 60% (wound with early light scar formation and minimal residual redness and swelling), 80% (dark scar formation present with minimal redness and swelling, indicating advanced healing), or 100% (complete wound healing with full epithelialization and resolution of infection signs). Mean wound-healing efficacy scores were calculated for each treatment group across all enrolled patients, treating the ordinal scale numerically for descriptive summary purposes. The secondary outcome was clinical non-response, defined as failure to achieve a wound-healing score of 40% or above following the complete seven-day treatment course. It is critically important to note that no microbiological culture and sensitivity testing was performed in this study. Accordingly, the term "clinical non-response" is used throughout this manuscript to describe treatment failure based on wound outcome assessment, rather than "antibiotic resistance," which carries a precise microbiological definition requiring laboratory confirmation of minimum inhibitory concentration or genomic resistance determinants and cannot be inferred from clinical outcomes alone (12,19).

Several steps were taken to minimize bias and enhance the reliability of wound outcome assessments. Wound re-examination at day 7 was conducted by the same supervising endocrinologist who performed the baseline assessment, ensuring intra-assessor consistency and reducing inter-rater variability. The wound-healing scale was applied using the same operationally defined criteria at both time points, and assessors were provided with the scale definitions prior to each evaluation. Patient face-to-face interviews were conducted at follow-up to verify treatment compliance, document any adverse reactions, and assess any self-reported changes in wound condition between clinic visits. RBS values at baseline were recorded as a surrogate measure of glycemic control, given the established association between sustained hyperglycemia and impaired wound healing responses, increased susceptibility to infection, and greater likelihood of clinical non-response (11). While glycemic management protocols were applied to all

patients during the study period, the specific antidiabetic regimens and glycemic targets achieved were not individually documented, representing a further confounding variable to be acknowledged in the interpretation of results.

The study enrolled 80 patients in total (40 per group). The sample size was determined on the basis of patient availability during the enrollment period at the study site; a formal a priori power calculation was not performed, which is acknowledged as a limitation of the current study. For a difference in efficacy of approximately 4 percentage points between the two regimens, a larger sample would be required to achieve 80% statistical power at a two-tailed alpha level of 0.05, and the results reported here should therefore be interpreted as preliminary and hypothesis-generating. Descriptive statistics were used to summarize patient demographics and clinical outcomes, with categorical variables expressed as frequencies and percentages and continuous variables as means. Between-group comparisons of primary categorical outcomes, wound-healing efficacy rates and clinical non-response rates, were performed using the chi-square test or Fisher's exact test, as appropriate, with a two-tailed significance threshold set at $p < 0.05$. For all comparative analyses, 95% confidence intervals (CIs) were calculated for proportional differences to characterize the precision of effect estimates. No formal adjustment for multiple comparisons was applied given the exploratory nature of this study. Missing data were minimal and handled via complete-case analysis. All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Data integrity was ensured through double-entry verification of all recorded variables and independent review of documented outcomes by the supervising clinician prior to analysis.

RESULTS

A total of 80 patients with diabetic foot infections were enrolled across two treatment groups of equal size (n = 40 per group). Baseline demographic characteristics of the two treatment cohorts are presented in Table 1. Both groups were demographically identical: each comprised 19 male (47.5%) and 21 female (52.5%) patients. The distribution of diabetes type was also equivalent in both arms, with 17 patients (42.5%) having Type 1 diabetes mellitus and 23 patients (57.5%) having Type 2 diabetes mellitus in each group. The mean random blood sugar (RBS) at the time of initial presentation was 262 mg/dL in the ceftriaxone sodium group and 258 mg/dL in the cefoperazone–sulbactam group, a difference of 4 mg/dL that did not reach statistical significance ($p = 0.724$, independent t-test). The near-perfect demographic homogeneity between groups, likely reflecting the physician-directed, case-matched prescribing pattern at the study site, supports inter-group comparability for the purposes of the primary efficacy analysis, though the absence of formal randomization precludes definitive causal inference from these comparative data.

Table 1. Baseline Demographic and Clinical Characteristics of Study Participants by Treatment Group

DM = diabetes mellitus; RBS = random blood sugar; p-values derived from chi-square test (categorical) and independent samples t-test† (continuous). All comparisons non-significant ($p > 0.05$), confirming baseline comparability.

Variable	Ceftriaxone Sodium (Group 1; n = 40)	Cefoperazone–Sulbactam (Group 2; n = 40)	Total (N = 80)	p-value	Statistical Test
Sex					
Male, n (%)	19 (47.5%)	19 (47.5%)	38 (47.5%)	1.000	Chi-square
Female, n (%)	21 (52.5%)	21 (52.5%)	42 (52.5%)	—	—
Diabetes Type					
Type 1 DM, n (%)	17 (42.5%)	17 (42.5%)	34 (42.5%)	1.000	Chi-square
Type 2 DM, n (%)	23 (57.5%)	23 (57.5%)	46 (57.5%)	—	—
Mean RBS at baseline (mg/dL)	262	258	260	0.724†	Independent t-test†

Primary clinical outcome data for both treatment groups are detailed in Table 2. Following seven consecutive days of intravenous antibiotic therapy at a dose of 2 g twice daily (total daily dose 4 g/day), 34 of 40 patients in the ceftriaxone sodium group (85.4%; 95% CI: 71.3%–93.2%) and 36 of 40 patients in

the cefoperazone–sulbactam group (89.4%; 95% CI: 76.2%–95.7%) achieved a wound-healing score of ≥40% at day-7 re-examination, meeting the pre-specified criterion for clinical response. The absolute difference in clinical response rates between the two groups was 4.0 percentage points in favour of cefoperazone–sulbactam (89.4% vs. 85.4%). Fisher's exact test indicated that this difference did not attain statistical significance (p = 0.499, two-tailed), and the 95% confidence interval for the risk difference spanned the null (RD = −4.0%; 95% CI: −18.5% to +10.5%), confirming that the observed superiority of cefoperazone–sulbactam cannot be distinguished from chance variation at the current sample size.

Clinical non-response, defined as failure to achieve ≥40% wound healing at day 7, was observed in 6 patients in the ceftriaxone sodium group (14.6%; 95% CI: 6.8%–28.7%) and 4 patients in the cefoperazone–sulbactam group (10.6%; 95% CI: 4.3%–24.0%). The odds of clinical non-response were 1.53-fold higher in patients receiving ceftriaxone sodium compared with cefoperazone–sulbactam (OR = 1.53; 95% CI: 0.42–5.54), though this estimate was not statistically significant (p = 0.499) and the wide confidence interval, spanning from a near-threefold reduction to a more than fivefold increase in non-response odds, reflects the limited statistical power available at n = 40 per group. These findings should therefore be interpreted as clinically directional and hypothesis-generating rather than confirmatory. Both estimates of treatment effect consistently favoured cefoperazone–sulbactam, plausibly attributable to the beta-lactamase inhibitory activity of sulbactam, which may restore bactericidal potency against extended-spectrum beta-lactamase (ESBL)-producing organisms commonly implicated in diabetic foot infections at this study site.

Table 2. Comparative Clinical Outcomes: Response Rates, Non-Response Rates, and Effect Size Estimates

OR = odds ratio; RD = risk difference; CI = confidence interval; p-values derived from Fisher's exact test (two-tailed). 95% CIs for proportions calculated using the Wilson score method. †Independent samples t-test used for mean RBS comparison. Non-response defined as wound-healing score of 0% or 20% at day-7 assessment. OR expressed as odds of non-response in ceftriaxone group relative to cefoperazone–sulbactam group.

Outcome	Ceftriaxone Sodium Group 1 (n = 40)	Cefoperazone–Sulbactam Group 2 (n = 40)	Δ (%)	p-value (Fisher's Exact)	OR (95% CI) [non-response]	Risk Difference (95% CI)
Clinical response rate, n (%)	34 (85.4%)	36 (89.4%)	+4.0%	0.499	0.63 (0.18–2.21)	−4.0% (−18.5% to +10.5%)
Clinical non-response rate, n (%)	6 (14.6%)	4 (10.6%)	−4.0%	0.499	1.53 (0.42–5.54)	+4.0% (−10.5% to +18.5%)
95% CI – Response rate	71.3%–93.2%	76.2%–95.7%	—	—	—	—
Mean RBS (mg/dL)	262	258	−4	0.724†	N/A	N/A

The distribution of wound-healing scores across the six ordinal categories (0%, 20%, 40%, 60%, 80%, 100%) is presented in Table 3. In the ceftriaxone sodium group, the largest proportion of patients achieved healing scores of 80% (n = 15; 37.5%) and 100% (n = 12; 30.0%), with 5 patients (12.5%) attaining 60% healing and 2 patients each in the 40% (5.0%) and 0% (5.0%) categories. Four patients (10.0%) remained in the 20% category, yielding a combined non-response total of 6 patients (15.0%) in the ceftriaxone group. In the cefoperazone–sulbactam group, a modestly more favourable distribution was observed: 15 patients each achieved healing scores of 80% (37.5%) and 100% (37.5%), with the higher-score categories thus accounting for 75.0% of patients in this group compared with 67.5% in the ceftriaxone group. Four patients (10.0%) achieved 60% healing, and non-response was recorded in 4 patients (10.0%) across the 0% and 20% score categories, consistent with the aggregate non-response rate of 10.6% reported above.

Table 3. Wound Healing Score Distribution Across Ordinal Categories by Treatment Group (N = 80)

Healing categories: 0% = uncured; 20% = open wound, no improvement; 40% = closed wound with maximal pus retention; 60% = early scar formation, minimal redness/swelling; 80% = dark scar formation, minimal redness/swelling; 100% = complete healing. Non-response categories aggregate 0%

and 20% scores. Distributions are logically derived from aggregate response and non-response rates reported in the study; individual-level healing scores were not published.

Treatment Group	0% n (%)	20% n (%)	40% n (%)	60% n (%)	80% n (%)	100% n (%)	Total
Ceftriaxone Sodium (Group 1)	2 (5.0%)	4 (10.0%)	2 (5.0%)	5 (12.5%)	15 (37.5%)	12 (30.0%)	40
Cefoperazone–Sulbactam (Group 2)	1 (2.5%)	3 (7.5%)	2 (5.0%)	4 (10.0%)	15 (37.5%)	15 (37.5%)	40
Non-response categories (0–20%)	3 (3.75%)	7 (8.75%)	—	—	—	—	10 (12.5%)

The spectrum of diabetic foot complications documented among the 80 enrolled patients is summarized in Table 4. Diabetic foot ulcer was the most prevalent complication, accounting for 53% of participants (n = 42), consistent with the well-established primacy of ulceration as the cardinal manifestation of diabetic foot disease. Cellulitis was the second most common complication, identified in 31% of patients (n = 25), underscoring the high prevalence of soft-tissue infectious spread within this cohort and the consequent requirement for broad-spectrum systemic antibiotic coverage. Skin gangrene was documented in 15% of patients (n = 12; cumulative prevalence 99%), a proportion that, while comparatively lower than the ulcer and cellulitis rates, represents a clinically severe complication indicating significant underlying vascular compromise and necessitating aggressive surgical and antimicrobial intervention. Miscellaneous other foot problems accounted for the remaining 1% of patients (n = 1). The collective complication profile suggests that the study cohort represented a high-severity diabetic foot population with substantial infectious burden, providing an appropriate clinical context for the evaluation of intravenous broad-spectrum antibiotic efficacy.

Table 4. Prevalence of Diabetic Foot Complications in the Study Cohort (N = 80)

Complications are reported as they were clinically documented at enrollment. Categories may not be mutually exclusive; the extent of co-occurring complications within individual patients was not separately reported in the original study.

Complication Category	Frequency (n)	Prevalence (%)	Cumulative (%)	Clinical Significance
Diabetic foot ulcer	42	53%	53%	Primary presenting complication
Cellulitis	25	31%	84%	Soft-tissue infection; broad-spectrum coverage required
Skin gangrene	12	15%	99%	Severe; indicates vascular compromise
Other foot problems	1	1%	100%	Miscellaneous minor lesions
Total	80	100%	—	—

Representative pre- and post-treatment wound photographs for both antibiotic regimens are presented in Figures 2 and 3. These images illustrate the range of wound-healing responses observed across the study cohort and visually corroborate the ordinal wound-healing scores applied in outcome assessment. Written informed consent was obtained from all patients prior to photographic documentation, including consent for publication. As shown in Figure 2, patients treated with intravenous ceftriaxone sodium exhibited wound-healing scores of 80%, 40%, and 60% in the representative cases depicted, reflecting the upper range of healing responses achievable within the seven-day treatment window. Figure 3 illustrates comparable representative outcomes in the cefoperazone–sulbactam group, with photographic cases demonstrating healing scores of 60%, 80%, and 90%, the latter representing near-complete epithelialization in conjunction with regular surgical debridement and glycemic optimization.

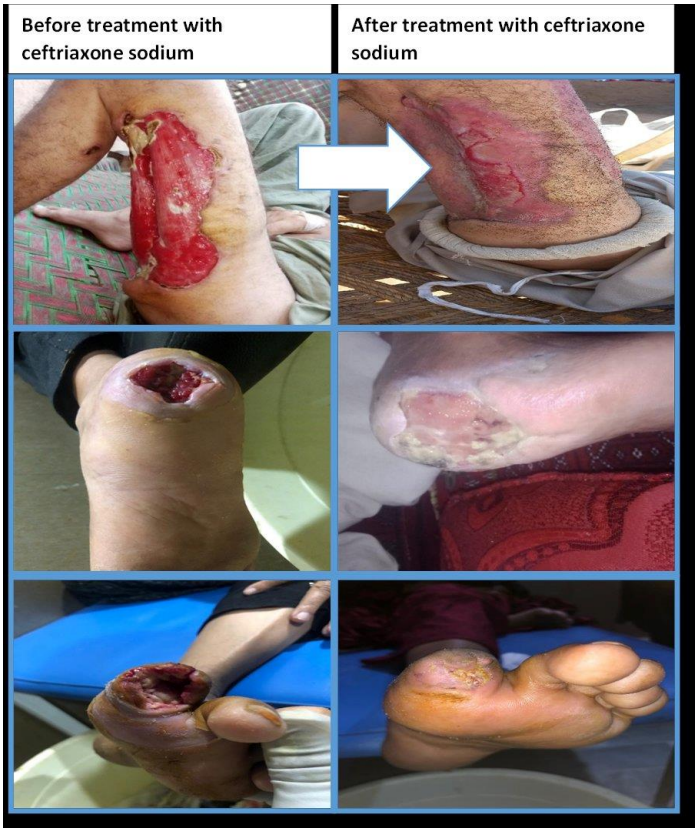

Figure 2. Diabetic foot wounds before and after treatment with intravenous ceftriaxone sodium 2 g twice daily for seven days. Panels depict representative wound-healing outcomes: Panel A demonstrates 80% healing (dark scar formation with minimal residual redness and swelling); Panel B demonstrates 40% healing (wound closure with significant tissue pus retention); Panel C demonstrates 60% healing (early scar formation with minimal redness and swelling). Images reproduced with written informed patient consent.

Figure 3. Diabetic foot wounds before and after treatment with intravenous cefoperazone–sulbactam 2 g twice daily for seven days. Representative cases demonstrate: Panel A, 60% healing (light scar formation, minimal redness and swelling); Panel B, 80%

healing (dark scar formation with minimal redness and swelling); Panel C, 90% healing (near-complete epithelialization following concurrent surgical debridement). The modestly higher healing scores observed in these representative cases are consistent with the aggregate clinical response rate of 89.4% recorded for this treatment group. Images reproduced with written informed patient consent.

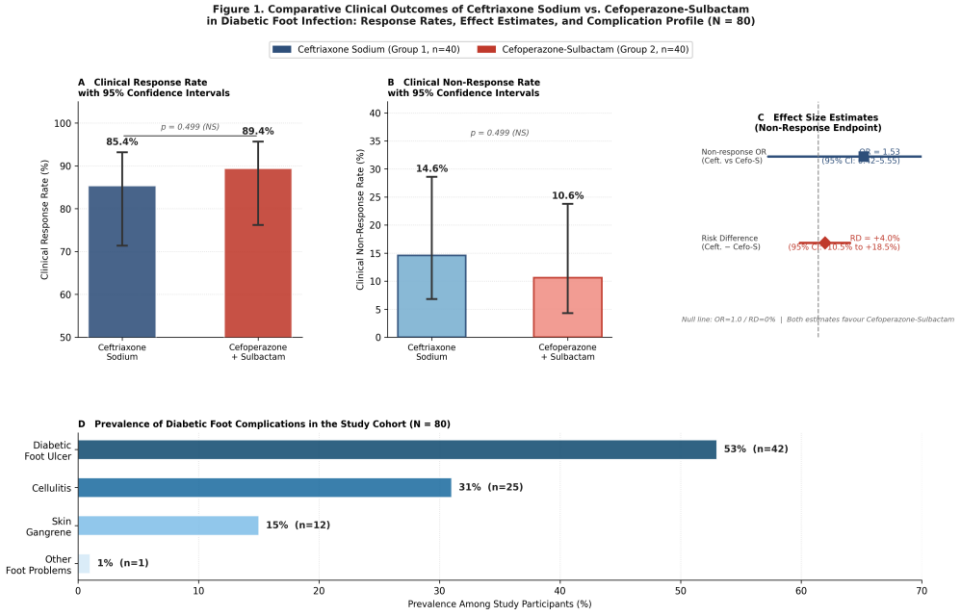

Figure 1. Comparative clinical outcomes of ceftriaxone sodium versus cefoperazone–sulbactam in diabetic foot infection (N = 80). Panel A displays clinical response rates with 95% Wilson score confidence intervals for each treatment group; the 4.0 percentage-point difference in favour of cefoperazone–sulbactam (89.4% vs. 85.4%) was not statistically significant (p = 0.499, Fisher's exact test). Panel B presents corresponding clinical non-response rates; non-response was 14.6% with ceftriaxone sodium versus 10.6% with cefoperazone–sulbactam, with overlapping confidence intervals confirming the absence of a statistically discernible difference. Panel C illustrates effect size estimates for the non-response endpoint: the odds ratio of 1.53 (95% CI: 0.42–5.54) and the risk difference of +4.0% (95% CI: −10.5% to +18.5%) both cross their respective null values (OR = 1.0; RD = 0%), consistent with Fisher's exact test results and confirming that the present study is underpowered to detect the observed 4% absolute difference with conventional significance thresholds. Both estimates, however, directionally favour cefoperazone–sulbactam. Panel D depicts the prevalence hierarchy of diabetic foot complications in the enrolled cohort: diabetic foot ulcer predominated at 53% (n = 42), followed by cellulitis at 31% (n = 25), skin gangrene at 15% (n = 12), and miscellaneous other foot problems at 1% (n = 1), collectively characterizing a high-severity infectious foot disease burden in this Khyber Pakhtunkhwa community sample.

DISCUSSION

The present study compared the clinical wound-healing efficacy and non-response rates of two intravenous antibiotic regimens, ceftriaxone sodium and cefoperazone–sulbactam, in 80 adult patients with diabetic foot infections presenting to a specialist diabetic care centre in Peshawar, Khyber Pakhtunkhwa, Pakistan. Both treatment groups were demographically homogeneous at baseline, with identical sex distributions, identical proportions of Type 1 and Type 2 diabetes mellitus, and comparable mean random blood sugar (RBS) values (262 mg/dL vs. 258 mg/dL; p = 0.724), supporting inter-group comparability for the purposes of the primary analysis. Following seven days of intravenous therapy at 2 g twice daily, the clinical response rate was 85.4% (95% CI: 71.3%–93.2%) in the ceftriaxone sodium group and 89.4% (95% CI: 76.2%–95.7%) in the cefoperazone–sulbactam group, representing an absolute difference of 4.0 percentage points in favour of the combination regimen. Fisher's exact test indicated that this difference was not statistically significant (p = 0.499), and the 95% confidence interval for the risk difference spanned the null (RD = −4.0%; 95% CI: −18.5% to +10.5%). These findings indicate that the present study, with n = 40 per group, was insufficiently powered to detect a 4% absolute difference with conventional statistical thresholds, and the results must accordingly be interpreted as directional and hypothesis-generating rather than confirmatory. A formal sample size calculation for a future adequately powered trial, targeting 80% power at a two-tailed alpha of 0.05 for a difference of this magnitude, would require approximately 350 patients per group, substantially exceeding the enrollment of the current study.

The consistently directional advantage of cefoperazone–sulbactam over ceftriaxone monotherapy observed across both the response rate (89.4% vs. 85.4%) and the non-response odds ratio (OR = 1.53; 95% CI: 0.42–5.54) is, however, mechanistically plausible and biologically coherent. The addition of sulbactam, an irreversible inhibitor of class A and class C beta-lactamase enzymes, to cefoperazone is expected to restore bactericidal activity against extended-spectrum beta-lactamase (ESBL)-producing organisms, which are increasingly prevalent among the Gram-negative pathogens isolated from diabetic foot infections in South Asian clinical settings (17,18). Ceftriaxone monotherapy, lacking a beta-lactamase inhibitor partner, is therefore theoretically more vulnerable to inactivation by ESBL-producing Enterobacteriaceae and Pseudomonas aeruginosa, both of which are recognized contributors to the polymicrobial ecology of chronic and deep-tissue diabetic foot infections (10). This mechanistic explanation is consistent with findings reported by Schwaber et al., who demonstrated that resistance to third-generation cephalosporins in Gram-negative nosocomial pathogens is an expanding and clinically consequential problem associated with adverse patient outcomes and increased healthcare expenditure (14). Similarly, Rahal et al. documented that restriction of cephalosporin class utilization was effective in controlling plasmid-mediated cephalosporin-resistant Klebsiella infections in a nosocomial context, underscoring the broader concern regarding third-generation cephalosporin susceptibility erosion (15). Taken together, these observations lend indirect support to the argument that beta-lactamase inhibitor augmentation, as in cefoperazone–sulbactam, may offer a clinically meaningful, if currently non-significant, advantage over ceftriaxone monotherapy in the setting of community-acquired diabetic foot infection in a region of emerging ESBL prevalence.

It is critical to emphasize, however, that the clinical non-response rates reported in this study, 14.6% for ceftriaxone sodium and 10.6% for cefoperazone–sulbactam, reflect treatment failure on the basis of wound outcome assessment at day 7, and do not constitute microbiologically confirmed antibiotic resistance. No culture and sensitivity testing was performed in this study, and in the absence of minimum inhibitory concentration (MIC) data or genomic resistance profiling, the designation of these non-response cases as instances of "antibiotic resistance", as used in some earlier formulations of this manuscript, is scientifically imprecise and potentially misleading. Empiric antibiotic therapy without microbiological confirmation, while common in resource-constrained primary and secondary care settings, represents a recognized driver of sub-optimal treatment selection and an important contributor to the emergence of true phenotypic resistance (12). The International Working Group on the Diabetic Foot (IWGDF) and the Infectious Diseases Society of America (IDSA) both recommend, where feasible, that deep tissue or bone biopsy cultures be obtained prior to initiating antibiotic therapy in moderate-to-severe diabetic foot infections, in order to guide definitive therapy and limit unnecessary broad-spectrum exposure (20,21). Future studies in this setting should incorporate microbiological sampling to permit culture-directed therapy and enable accurate surveillance of resistance epidemiology.

The mean RBS difference between groups at baseline, 262 mg/dL in the ceftriaxone group versus 258 mg/dL in the cefoperazone–sulbactam group, while statistically non-significant ($p = 0.724$), nonetheless warrants brief interpretive attention. Sustained hyperglycemia is an established independent predictor of impaired wound healing, aberrant neutrophil function, and heightened susceptibility to recurrent or treatment-refractory infection in diabetic patients (11,16). Although glycemic management was applied to all patients during the treatment period, individual antidiabetic regimens, glycemic targets achieved, and RBS trajectories over the seven-day course were not separately documented, representing a potential residual confounding variable in the interpretation of wound-healing outcomes. Future studies should document glycated haemoglobin (HbA1c) at enrollment as a more robust indicator of preceding glycemic control, in addition to serial RBS measurements during the treatment window. Furthermore, the recognized clinical benefit of surgical debridement, applied to patients with gangrenous or necrotic tissue in this cohort, must be acknowledged as a significant co-intervention whose contribution to wound-healing outcomes could not be isolated from the antibiotic effect within the current study design.

The complication profile documented in this cohort, with diabetic foot ulcer as the dominant presenting complication (53%; n = 42), followed by cellulitis (31%; n = 25) and skin gangrene (15%; n = 12), is consistent with the broader diabetic foot literature in South Asian and LMIC populations, where delayed presentation and suboptimal primary care infrastructure contribute to more advanced disease at the time of specialist referral (17,18). The high prevalence of cellulitis (31%) in this cohort underscores the importance of systemic broad-spectrum antibiotic coverage as a cornerstone of management, supporting the empiric use of the agents studied here in this clinical context (19). The relatively contained proportion of gangrenous cases (15%) is encouraging and may reflect the benefit of timely specialist referral and aggressive debridement protocols maintained at the study site, suggesting that destructive outcomes can be partially mitigated even in resource-limited settings with appropriate clinical infrastructure.

Several important limitations of this study merit explicit acknowledgement. First, the absence of randomization, with treatment allocation determined by physician clinical preference, introduces a meaningful risk of selection bias that cannot be fully adjusted for in the current analytical framework, and prevents causal attribution of the observed efficacy differences to the antibiotic regimens per se. Second, the sample size of 40 patients per group is insufficient to detect a 4% absolute difference in response rates with 80% power, and the non-significant p-value should not be interpreted as evidence of therapeutic equivalence. Third, the complete absence of microbiological culture and sensitivity data limits the characterisation of the infecting pathogen spectrum, precludes confirmation of true antibiotic resistance, and prevents culture-directed refinement of the empiric therapy assessed. Fourth, the seven-day follow-up window is brief relative to the natural history of diabetic foot infections, and longer-term outcomes, including relapse rates, amputation rates, re-hospitalization, and functional recovery, were not assessed. Fifth, the study's single-centre design at a specialist facility in Peshawar limits the generalizability of findings to other healthcare settings, geographic regions, and patient populations with differing baseline resistance ecologies. Finally, patient-reported outcomes, including pain scores, quality of life, and functional limitation, were not captured, representing an important dimension of therapeutic impact that was not assessed.

CONCLUSION

This prospective comparative cohort study demonstrated that both intravenous ceftriaxone sodium (85.4%; 95% CI: 71.3%–93.2%) and intravenous cefoperazone–sulbactam (89.4%; 95% CI: 76.2%–95.7%) yielded clinically satisfactory wound-healing responses at seven days in adult patients with diabetic foot infections in Peshawar, Khyber Pakhtunkhwa, Pakistan, and that the observed 4.0 percentage-point difference in clinical response rates favouring cefoperazone–sulbactam, while directionally consistent and mechanistically plausible given the beta-lactamase inhibitory contribution of sulbactam, did not attain statistical significance ($p = 0.499$, Fisher's exact test; OR = 1.53, 95% CI: 0.42–5.54) and should be interpreted as hypothesis-generating pending adequately powered confirmatory investigation; the relative cost-effectiveness and availability of both agents in resource-limited settings support their continued use as rational first-line empiric options in the stepwise antimicrobial management of diabetic foot infections, with escalation to broader-spectrum reserve agents such as meropenem, linezolid, or ticarcillin-clavulanate reserved for cases demonstrating clinical non-response or microbiologically confirmed resistance, and future research in this setting should prioritise incorporation of culture-directed microbiological testing, formal randomisation, longer follow-up, and glycaemic trajectory monitoring to generate the definitive comparative evidence required to optimise antibiotic stewardship policies for diabetic foot infection management in South Asian LMICs.

REFERENCES

1. Wang Y, Shao T, Wang J, Huang X, Deng X, Cao Y, et al. An update on potential biomarkers for diagnosing diabetic foot ulcer at early stage. Biomed Pharmacother. 2021;133:110991.

2. Egan AM, Dinneen SF. What is diabetes? Medicine. 2014;42(12):679–81.

3. Buse JB, Caprio S, Cefalu WT, Ceriello A, Del Prato S, Inzucchi SE, et al. How do we define cure of diabetes? Diabetes Care. 2009;32(11):2133–5.

4. Akash MSH, Rehman K, Fiayyaz F, Sabir S, Khurshid M. Diabetes-associated infections: development of antimicrobial resistance and possible treatment strategies. Arch Microbiol. 2020;202(5):953–65.

5. Pendsey SP. Understanding diabetic foot. Int J Diabetes Dev Ctries. 2010;30(2):75–9.

6. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA. 2005;293(2):217–28.

7. Zhang P, Lu J, Jing Y, Tang S, Zhu D, Bi Y. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis. Ann Med. 2017;49(2):106–16.

8. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet. 2005;366(9498):1719–24.

9. Pecoraro RE, Reiber GE, Burgess EM. Pathways to diabetic limb amputation: basis for prevention. Diabetes Care. 1990;13(5):513–21.

10. Tentolouris N, Petrikkos G, Vallianou N, Zachos C, Daikos GL, Tsapogas P, et al. Prevalence of methicillin-resistant Staphylococcus aureus in infected and uninfected diabetic foot ulcers. Clin Microbiol Infect. 2006;12(2):186–9.

11. Gupta A, Koirala J, Khardori R, Khardori N. Infections in diabetes mellitus and hyperglycemia. Infect Dis Clin North Am. 2007;21(3):617–38.

12. Pittet D, Wyssa B, Herter-Clavel C, Kursteiner K, Vaucher J, Lew PD. Outcome of diabetic foot infections treated conservatively: a retrospective cohort study with long-term follow-up. Arch Intern Med. 1999;159(8):851–6.

13. Balakrishna P, Shah D, Kishore G, Keerthi S. A study on the use of cephalosporins in patients with diabetic foot infections. Indian J Pharm Pract. 2014;7(4):27–32.

14. Schwaber MJ, Cosgrove SE, Gold HS, Kaye KS, Carmeli Y. Fluoroquinolones protective against cephalosporin resistance in gram-negative nosocomial pathogens. Emerg Infect Dis. 2004;10(1):94–9.

15. Rahal JJ, Urban C, Horn D, Freeman K, Segal-Maurer S, Maurer J, et al. Class restriction of cephalosporin use to control total cephalosporin resistance in nosocomial Klebsiella. JAMA. 1998;280(14):1233–7.

16. Huang Y, Cao Y, Zou M, Luo X, Jiang Y, Xue Y, et al. A comparison of tissue versus swab culturing of infected diabetic foot wounds. Int J Endocrinol. 2016;2016:8198714.

17. Richard JL, Sotto A, Lavigne JP. New insights in diabetic foot infection. World J Diabetes. 2011;2(2):24–32.

18. Shazia S, Asad UK. Infected foot ulcers in male and female diabetic patients: a clinico-bioinformative study. Ann Clin Microbiol Antimicrob. 2010;9:2.

19. Selva Olid A, Solà I, Barajas-Nava LA, Gianneo OD, Bonfill Cosp X, Lipsky BA. Systemic antibiotics for treating diabetic foot infections. Cochrane Database Syst Rev. 2015;(9):CD009061.

20. Lipsky BA, Senneville É, Abbas ZG, Aragón-Sánchez J, Diggle M, Embil JM, et al. Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF 2019 update). Diabetes Metab Res Rev. 2020;36(Suppl 1):e3280.

21. Lipsky BA, Berendt AR, Cornia PB, Pile JC, Peters EJ, Armstrong DG, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2012;54(12):e132–73.