

Comparing the Efficacy and Safety of Linezolid versus Amoxicillin-Clavulanic Acid in the Management of Moderate to Severe Diabetic Foot Infections

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Abstract:

Background: Diabetic foot infections (DFIs) represent a major global health challenge, frequently leading to hospitalization, lower extremity amputation, and significant mortality. The choice of empirical antibiotic therapy is complicated by the polymicrobial nature of DFIs and the rising prevalence of multidrug-resistant organisms, particularly methicillin-resistant *Staphylococcus aureus* (MRSA). This study aimed to compare the clinical and microbiological efficacy of Linezolid, a potent anti-Gram-positive agent, with Amoxicillin-Clavulanic Acid, a broad-spectrum antibiotic, in treating moderate to severe DFIs.

Methods: In a prospective, open-label, randomized controlled trial conducted from 2021 to 2023, 300 patients with moderate to severe DFIs were enrolled. Participants were randomized in trial, to receive either Linezolid (600 mg IV/PO q12h) or Amoxicillin-Clavulanic Acid (1.2 g IV q8h or 625 mg PO q8h) for 7-14 days. The primary outcome was clinical cure rate at the test-of-cure visit (14 days after treatment completion). Secondary outcomes included microbiological eradication, incidence of adverse events, and duration of hospital stay.

Results: Linezolid demonstrated a significantly higher clinical cure rate compared to Amoxicillin-Clavulanic Acid (85.3% vs. 73.3%, $p=0.01$). Microbiological eradication was also superior in the Linezolid group (80.0% vs. 66.7%, $p=0.02$). Subgroup analysis revealed Linezolid's pronounced efficacy against MRSA (90% vs. 25%, $p<0.001$), whereas Amoxicillin-Clavulanic Acid was more effective against Gram-negative pathogens (82% vs. 48%, $p=0.003$). The overall incidence of adverse events was comparable between groups (22% for Linezolid vs. 18% for Amoxicillin-Clavulanic Acid, $p=0.40$).

Conclusion: Linezolid is a superior therapeutic option for DFIs where Gram-positive bacteria, especially MRSA, are suspected or confirmed. Amoxicillin-Clavulanic Acid remains a valuable agent for polymicrobial infections with significant Gram-negative involvement. Tailoring empirical antibiotic therapy based on local antimicrobial resistance patterns and individual patient risk factors is crucial for optimizing outcomes in DFI management.

Introduction:

Diabetes mellitus has reached epidemic proportions globally, with its complications posing a severe burden on healthcare systems, particularly in developing nations like Bangladesh. Among the most

debilitating and costly of these complications are diabetic foot ulcers (DFUs), which affect 15–25% of diabetic individuals during their lifetime¹. A critical progression of DFUs is diabetic foot infection (DFI), which significantly increases the risk of

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hospitalization, lower extremity amputation, and mortality².

The pathophysiology of DFI is multi factorial, arising from a triad of peripheral neuropathy, peripheral arterial disease, and an impaired immune response. This environment facilitates microbial invasion and colonization, often leading to complex, polymicrobial infections³. The microbiological landscape of DFIs is diverse, commonly involving Gram-positive cocci (e.g., *Staphylococcus aureus*, including MRSA, and streptococci), Gram-negative bacilli (e.g., *Escherichia coli*, *Pseudomonas aeruginosa*), and anaerobic bacteria⁴.

The selection of optimal empirical antibiotic therapy is paramount. Delays or inappropriate choices can lead to treatment failure, limb loss, and sepsis. International guidelines, such as those from the Infectious Diseases Society of America (IDSA), recommend regimens based on infection severity and local resistance patterns⁵. However, the optimal empirical regimen remains a subject of debate, especially in regions with high MRSA prevalence.

Amoxicillin-Clavulanic Acid, a broad-spectrum β -lactam/ β -lactamase inhibitor combination, is widely used for its coverage against many Gram-positive, Gram-negative, and anaerobic organisms⁶. Conversely, Linezolid, an oxazolidinone antibiotic, offers excellent bioavailability and potent activity against resistant Gram-positive bacteria, including MRSA and Vancomycin-resistant enterococci⁷. While both are recommended in various guidelines, direct comparative data from robust randomized trials in Bangladeshi populations are scarce.

This randomized controlled trial was designed to bridge this knowledge gap by directly comparing the clinical and microbiological efficacy, safety, and tolerability of Linezolid versus Amoxicillin-Clavulanic Acid in the management of moderate to severe DFIs in a tertiary care setting in Bangladesh.

Materials and Methods:

Study Design and Setting:

A prospective, open-label, randomized controlled trial was conducted at the 250 Bedded General Hospital and Pabna Medical College Hospital, Pabna, Bangladesh, between January 2021 and December 2023. The study protocol was approved by the institutional ethics committee, and written informed consent was obtained from all participants.

Participants

Adult patients (aged 18–80 years) with type 1 or type 2 diabetes mellitus presenting with a moderate or severe DFI, as defined by the IDSA/IWGDF criteria [5], were eligible for inclusion. A confirmed microbial pathogen from deep tissue culture or purulent discharge was required.

Exclusion criteria included: severe renal impairment (creatinine clearance <30 mL/min) or hepatic dysfunction; receipt of systemic antibiotics for >24 hours within the 72 hours prior to enrollment; known hypersensitivity to Linezolid, Amoxicillin-Clavulanic Acid, or any of their components; and pregnancy or lactation.

Randomization and Interventions

Eligible patients were randomized in a 1:1 ratio to one of two treatment groups using a computer-generated randomization sequence with block sizes of four, stratified by infection severity (moderate vs. severe).

- Group A (Linezolid): Received Linezolid 600 mg intravenously or orally every 12 hours.
- Group B (Amoxicillin-Clavulanic Acid): Received Amoxicillin-Clavulanic Acid 1.2 g intravenously every 8 hours or 625 mg orally every 8 hours.

The treatment duration was 7 to 14 days, based on clinical response, with a maximum of 14 days. All patients received standard wound care, including surgical debridement, off-loading, and glycemic control, as per institutional protocols.

Outcome Measures

The primary outcome was the clinical cure rate, assessed at the test-of-cure (TOC) visit 14 days after the end of therapy. Clinical cure was defined as the complete resolution of signs and symptoms of the baseline infection (e.g., erythema, swelling, pain, purulence) such that no further antibiotic therapy was required.

Secondary outcomes included:

1. Microbiological eradication: Documented clearance of the baseline pathogen(s) at the TOC visit.
2. Incidence of adverse events (AEs), monitored throughout the treatment period and graded as mild, moderate, or severe.
3. Duration of hospital stay (in days).

Statistical Analysis

The sample size was calculated as 150 patients in each group to provide 80% power at a 5% significance level ($\alpha=0.05$) to detect a 15% absolute difference in clinical cure rates. Data were analyzed using SPSS Statistics version 28.0. Categorical variables (e.g., cure rates, eradication rates) were compared using the Chi-square test or Fisher's exact test, as appropriate. Continuous variables (e.g., age, hospital stay) were compared using the Student's t-test. A p-value of <0.05 was considered statistically significant.

Results:

Baseline Characteristics:

A total of 300 patients were enrolled and randomized, with 150 patients in each treatment group. The baseline demographic and clinical characteristics were well-balanced between the two groups, indicating successful randomization (Table I).

Primary Outcome: Clinical Cure

At the TOC visit, the Linezolid group demonstrated a statistically significant higher clinical cure rate compared to the Amoxicillin-Clavulanic Acid group

(85.3% vs. 73.3%, $p=0.01$; Odds Ratio: 2.1, 95% CI: 1.2–3.7).

Secondary Outcomes

1. **Microbiological Eradication:** The overall microbiological success rate was significantly higher in the Linezolid group (80.0% vs. 66.7%, $p=0.02$). A subgroup analysis by pathogen type revealed stark contrasts (Table II).
2. **Adverse Events (AEs):** The overall safety profile was similar between the two groups. A total of 33 patients (22%) in the Linezolid group and 27 patients (18%) in the Amoxicillin-Clavulanic Acid group experienced at least one AE ($p=0.40$). Gastrointestinal disturbances (nausea, vomiting, diarrhea) were the most common AEs with Linezolid. In the Amoxicillin-Clavulanic Acid group, diarrhea and transient elevation of liver enzymes were most frequently observed. No serious, life-threatening AEs were attributed to either study drug.
3. **Hospital Stay:** The mean duration of hospital stay shorter in the Linezolid group, though the difference was not statistically significant (7.5 ± 3.1 days vs. 8.2 ± 3.5 days, $p=0.12$).

Table-I:
Baseline Demographic and Clinical Characteristics

Characteristic	Linezolid Group (n=150)	Amoxicillin-Clavulanic Acid Group (n=150)	p-value
Mean Age (years $\pm$ SD)	58.2 $\pm$ 11.8	59.8 $\pm$ 10.9	0.25
Male Sex, n (%)	92 (61.3%)	88 (58.7%)	0.65
Type 2 Diabetes, n (%)	142 (94.7%)	140 (93.3%)	0.81
Infection Severity, n (%)			0.75
- Moderate	90 (60.0%)	87 (58.0%)	
- Severe	60 (40.0%)	63 (42.0%)	
Baseline Pathogens, n (%)			
- Gram-positive	98 (65.3%)	95 (63.3%)	0.78
- of which MRSA	38 (25.3%)	33 (22.0%)	0.55
- Gram-negative	45 (30.0%)	53 (35.3%)	0.38

Table-II:
Microbiological Eradication Rates by Pathogen Type

Pathogen	Linezolid Group	Amoxicillin-Clavulanic Acid Group	p-value
All Gram-positive	85/98 (86.7%)	65/95 (68.4%)	0.002
MRSA	34/38 (89.5%)	8/33 (24.2%)	<0.001
Gram-negative	22/45 (48.9%)	44/53 (83.0%)	0.003

Discussion:

This randomized controlled trial provides robust evidence supporting the differential efficacy of Linezolid and Amoxicillin-Clavulanic Acid in the management of DFIs, largely dictated by the underlying microbiological etiology.

The superior clinical and microbiological efficacy of Linezolid is primarily attributable to its potent activity against Gram-positive bacteria, particularly MRSA. The 90% eradication rate of MRSA in the Linezolid group underscores its critical role as a first-line therapeutic option in settings with a high prevalence of this multidrug-resistant pathogen⁸. This finding is consistent with previous studies, such as those by Lipsky et al., which established Linezolid as a highly effective agent for complex skin and soft tissue infections, including those with MRSA⁹.

Conversely, Amoxicillin-Clavulanic Acid demonstrated excellent activity against Gram-negative organisms, with an 82% eradication rate, reaffirming its position as a broad-spectrum workhorse for polymicrobial infections where Enterobacteriaceae are prominent^{6,10}. However, its profound lack of efficacy against MRSA (25% eradication) is a significant limitation, highlighting the danger of its empirical use in MRSA-endemic areas without adequate MRSA coverage.

The comparable safety profiles of both drugs are reassuring for clinical practice. The higher incidence of gastrointestinal events with Linezolid is well-documented and is often manageable¹¹. The potential for myelosuppression (e.g., thrombocytopenia) with Linezolid, though observed in a small percentage of our patients, necessitates periodic monitoring of blood counts, especially during extended therapy (>2 weeks)¹². The hepatotoxicity associated with Amoxicillin-Clavulanic Acid was mild and reversible in our cohort, consistent with its known safety profile¹³.

Our findings have direct clinical implications. They advocate for a pathogen-directed approach to DFI management. In regions or patients with a high risk for MRSA (e.g., prior colonization, recent hospitalization, recurrent infections), Linezolid represents a superior empirical choice. For infections where clinical signs suggest a strong Gram-negative component, or in settings with low MRSA prevalence, Amoxicillin-Clavulanic Acid remains a viable and cost-effective option.

Limitations:

This study has several limitations. The open-label design may introduce potential for bias, though objective endpoints were used to mitigate this. The follow-up period was limited to 30 days, preventing assessment of long-term outcomes like ulcer recurrence or re-infection. Furthermore, we excluded critically ill and renal impaired patients, limiting the generalizability of our findings to these subgroups.

Conclusion:

This study demonstrates that Linezolid is significantly more effective than Amoxicillin-Clavulanic Acid for achieving clinical and microbiological cure in moderate to severe DFIs, particularly those caused by Gram-positive bacteria, including MRSA. Amoxicillin-Clavulanic Acid retains its utility for infections with documented or suspected Gram-negative involvement. The cornerstone of successful DFI management lies in tailoring empirical antibiotic therapy based on local antimicrobial resistance data, individual patient risk factors for resistant organisms, and the clinical presentation of the infection.

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