

## ORIGINAL ARTICLE

**Sensitivity of Amoxicillin-Clavulanic Acid in Diabetic Foot Ulcers: A Cross-Sectional Study from Khyber Teaching Hospital, Peshawar**

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**ABSTRACT**

**Objective:** This study aimed to determine the sensitivity of amoxicillin-clavulanic acid in Diabetic Foot Ulcer patients admitted to the Department of Medicine, Khyber Teaching Hospital, Peshawar.

**Study Design:** Cross-sectional study.

**Place and Duration of Study:** This study was conducted at the Department of Medicine, Khyber Teaching Hospital, Peshawar, Pakistan from November 27, 2021, to May 26, 2022.

**Methods:** A total of 141 patients (aged 35–80 years) with type 2 diabetes and Diabetic Foot Ulcer of at least 2 weeks' duration were enrolled using a non-probability consecutive sampling technique. After obtaining ethical committee approval and informed consent, culture specimens were collected from the ulcers and processed in the hospital laboratory for culture and sensitivity testing. Data were analyzed using Statistical Package for Social Sciences (SPSS) version 22.

**Results:** The study population had a mean age of  $56.56 \pm 15$  years, with 59.6% males and 40.4% females. The mean ulcer duration was  $3.71 \pm 2.8$  weeks, and the mean HbA1c was  $7.91 \pm 1.9\%$ . A majority (72.3%) of the patients were classified as having long-standing diabetes. The most isolated organisms were *Pseudomonas* spp. 40 (28.4%), *Staphylococcus aureus* 38 (27%), *Escherichia coli* 30 (21.35%), *Klebsiella* spp. 15 (12.8%), and mixed growth 8 (10.6%). Overall, sensitivity to amoxicillin-clavulanic acid was observed in 63.8% of the isolates.

**Conclusion:** Amoxicillin-clavulanic acid demonstrated moderate sensitivity against the microbial isolates from DFUs in our cohort. These findings may assist clinicians in selecting appropriate empirical antibiotic therapy for DFU management. Further studies are warranted to monitor changing microbial patterns and to assess the clinical outcomes associated with antibiotic therapy.

**Keywords:** *Amoxicillin-Clavulanic Acid, Antibiotic Resistance, Diabetic Foot, Foot Ulcer, Pseudomonas, Staphylococcus Aureus.*

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**Introduction**

Diabetic foot ulcers (DFUs) are among the most serious and disabling complications associated with type 2 diabetes mellitus, frequently resulting in extended hospital stays, limb amputations, and higher mortality rates.<sup>1,2</sup> DFUs have increasingly

become a growing concern in Pakistan, where diabetes and its associated complications are on the rise.<sup>3</sup> Diabetic Foot Ulcers (DFUs) stem from multiple reasons, generally including peripheral neuropathy, peripheral artery disease, and also foot deformities that change the pressure distribution.<sup>4</sup> Moreover, constant hyperglycemia and nonenzymatic glycation deactivate normal wound healing processes, increasing the chances of infection and complications.<sup>5</sup>

Managing DFUs is challenging and typically involves a multidisciplinary team. A key aspect of treatment is the prompt administration of appropriate antibiotics to control infections. DFUs are challenging to

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manage, especially given that caring for them requires a multi-faceted approach. Controlling infections through immediate antibiotic administration, known as the empirical approach, is effective in theory, but it poses a challenge in practice due to the presence of numerous bacteria.<sup>6,7</sup> There's a growing body of evidence highlighting shifts in DFUs towards more resistant bacteria without control, signifying local resistance patterns that need to be properly monitored.<sup>8,9</sup>

Amoxicillin-clavulanic acid is routinely used as an empiric treatment for infected DFUs due to its broad-spectrum activity. However, its efficacy has been reported to vary in recent research, thus the value of region-specific evidence in making therapeutic choices.<sup>10</sup> To address such a necessity, our research tested the in vitro susceptibilities of pathogens from DFUs seen at our center to amoxicillin-clavulanic acid. The results are designed to inform more evidence-based antibiotic therapy and assist in reducing the increasing issue of antimicrobial resistance in diabetic foot infections.

As the microbial ecosystem of DFUs changes, and in the absence of recent local data, reassessment of the effectiveness of widely prescribed antibiotics is important. The present study fills this void by providing recent information on amoxicillin-clavulanic acid sensitivity of pathogens of DFUs. Such findings will be communicated to clinicians in order to enhance treatment methodologies and patient care. In addition, understanding local microbial patterns is critical to informing institution-specific recommendations and further research aimed at antibiotic stewardship in DFU treatment.

## Methods

This cross-sectional research was carried out in the Department of Medicine, Khyber Teaching Hospital, Peshawar, Pakistan from 27<sup>th</sup> November 2021, to 26<sup>th</sup> May 2022, after taking approval from the Ethical Review Board of the institute vide letter no: IRB-MED-2021-020-14445, held on 07<sup>th</sup> July 2021. A total of 141 patients with a confirmed diagnosis of type 2 diabetes mellitus presenting with diabetic foot ulcers (DFUs) lasting longer than two weeks were included. A non-probability consecutive sampling technique chose participants. The inclusion criteria mentioned male and female patients aged 18 years and above, with a clinically diagnosed type 2

diabetes (As per American Diabetic Association-ADA diagnostic criteria) and apparent DFUs.<sup>11</sup> To preserve the validity of microbial cultures, those who were on antibiotic therapy, had underlying immunosuppressive conditions, or had ulcers of traumatic origin were not included in the study.

Before data collection began, ethical clearance was issued by the hospital's Ethical Review Committee. Informed written consent was signed by all participants. Samples were then taken under sterile conditions from the base of the ulcer using either a sterile swab or tissue samples while taking care to avoid contamination from the adjacent areas of skin. The collected samples were promptly transported to the hospital's microbiology laboratory for culture and sensitivity testing.

Bacterial cultures were performed on standard media, and organisms were identified based on colony morphology, Gram staining, and biochemical characteristics. Antibiotic sensitivity testing was conducted using the Kirby-Bauer disk diffusion method in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines.<sup>12,13</sup> Special emphasis was placed on assessing sensitivity patterns to amoxicillin-clavulanic acid, considering its common use in empirical therapy for diabetic foot infections.

Data were then entered and analyzed using Statistical Package for the Social Sciences (SPSS), version 22. Descriptive statistics such as means and standard deviations were calculated for continuous variables, while categorical variables were presented as frequencies and percentages. Associations between various clinical and microbiological parameters with antibiotic sensitivity were examined using chi-square tests, and a *P*-value of less than 0.05 was considered statistically significant.

## Results

Out of 141 patients, the mean age was  $56.56 \pm 15$  years with a male predominance (59.6% males, 40.4% females). The mean duration of DFU was  $3.71 \pm 2.8$  weeks, and the mean HbA1c was  $7.91 \pm 1.9\%$ . Microbiological analysis revealed that *Pseudomonas* spp were isolated in 28.4% of cases, followed by *Staphylococcus aureus* (27%). Overall, 63.8% of the isolates were sensitive to amoxicillin-clavulanic acid. (Table 1).

**Table 1: Demographic characteristics**

Parameter		Frequency	Percentage
Age	Mean age	56.56 ±15.095	
Sex	Male	84	59.6
	Female	57	40.4
Duration of ulcer	≤ 4 weeks	3.71 ± 2.831	-
	> 4 weeks	7.91 ± 1.95	-
Type of diabetes	Old	102	72.3
	New onset	39	27.7
Microorganism isolated	Staph aureus	38	27.0
	Klebsiella	8	12.8
	Pseudomonas	40	28.4
	E. Coli	30	21.3
	Mix	15	10.6
Sensitivity to amoxicillin clavulanic acid	Yes	90	63.8
	No	51	36.2

**Table 2: Comparison of Amoxicillin-Clavulanic acid sensitivity with demographic characteristics**

Parameter		Sensitivity to amoxicillin clavulanic acid		P-value
		Yes N (%)	No N (%)	
Age	35-50 years	50 (62.5)	30 (37.5)	0.707
	51-80 years	40 (65.6)	21 (34.4)	
Sex	Male	52 (61.9)	32 (38.1)	0.564
	Female	38 (66.7)	19 (33.3)	
Type of diabetes	Old	66 (64.7)	36 (35.3)	0.726
	New onset	24 (61.5)	15 (38.5)	
Duration of ulcer	≤ 4 weeks	48 (90.6)	5 (9.4)	< 0.001
	> 4 weeks	42 (47.7)	46 (52.3)	
Microorganism isolated	Staph aureus	19 (50.0)	19 (50.0)	
	Klebsiella	15 (83.3)	3 (16.7)	
	Pseudomonas	19 (47.5)	21 (52.5)	
	E. Coli	27 (90.0)	3 (10.0)	
	Mix	10 (66.7)	5 (33.3)	

Among patients aged 35–50 years, 62.5% of the bacterial isolates were sensitive, while in the 51–80 age group, sensitivity was observed in 65.6% of cases ( $P=0.707$ ). Similarly, male patients demonstrated a sensitivity rate of 61.9%, whereas female patients had a slightly higher rate at 66.7% ( $P=0.564$ ). The type of diabetes also did not significantly affect the sensitivity pattern. Among those with long-standing diabetes, 64.7% of the isolates were sensitive, while among newly diagnosed cases, the sensitivity was 61.5% ( $P=0.726$ ).

Patients with ulcers of ≤4 weeks' duration showed markedly higher sensitivity (90.6%) compared to those with ulcers of more than four weeks (47.7%), and this association was statistically significant

( $P<0.001$ ). (Table 2).

Regarding microbial isolates, a highly significant variation in sensitivity was noted ( $P<0.001$ ). Isolates of *Escherichia coli* showed the highest sensitivity to amoxicillin-clavulanic acid (90.0%), followed by *Klebsiella* spp. (83.3%) and mixed growth (66.7%). In contrast, only 50.0% of *Staphylococcus aureus* and 47.5% of *Pseudomonas* spp. were sensitive, indicating a lower efficacy of the antibiotic against these organisms. (Table 2).

### Discussion

The results of our study indicate that amoxicillin-clavulanic acid exhibits moderate sensitivity (63.8%) against the bacterial isolates obtained from DFUs. This observation is consistent with previous studies

conducted in similar settings, where amoxicillin-clavulanic acid demonstrated variable efficacy depending on the local microbial spectrum and resistance patterns. The predominance of *Pseudomonas* spp. and *Staphylococcus aureus* in our study reflects a shift toward more resistant and opportunistic pathogens in DFU infections. Notably, isolates such as *E. coli* and *Klebsiella* spp exhibited higher sensitivity, suggesting that amoxicillin-clavulanic acid may still be effective against certain gram-negative organisms in our region. A significant association was observed between ulcer duration and antibiotic sensitivity, with shorter-duration ulcers ( $\leq 4$  weeks) showing markedly higher sensitivity rates. This emphasizes the importance of early diagnosis and timely initiation of appropriate antibiotic therapy in preventing the development of resistant infections. Moreover, the variation in sensitivity across different microbial isolates underscores the need for routine culture and sensitivity testing, rather than relying solely on empirical therapy.

Although the sensitivity rate is acceptable, the observed variability in microbial isolates underscores the need for periodic surveillance of antibiotic resistance patterns in DFUs.<sup>11</sup> Recent local and international studies have reported shifts in the predominant pathogens in DFUs, with increasing rates of multidrug resistance.<sup>12-16</sup>

Our findings are in line with a study by Hamid MH et al., who reported similar sensitivity rates in a comparable patient population. The most common organism was *Proteus* 63 (18.8%), followed by *Staphylococcus aureus* 61 (18.2%), and *Escherichia coli* 52 (15.5%).<sup>14</sup> The resistance to Amoxicillin/Clavulanic acid was observed in 31 (62%), 2 (100%), and 37 (97.4%) of *Proteus*, *Staph aureus*, and *E.coli*, respectively.<sup>14,17</sup> However, other studies have shown that sensitivity may be lower, particularly for gram-negative organisms such as *Pseudomonas aeruginosa*, highlighting the regional differences in microbial ecology.<sup>15,18</sup> In our study, *Pseudomonas* spp. remained the most commonly isolated organism, which is consistent with recent trends in the South Asian region.<sup>16,17,19,20</sup> Abbas G et al. found that *Pseudomonas aeruginosa* is 49 (22.7%) prevalent in Diabetic foot ulcer. Some studies report

*E. Coli* as the most commonly isolated organism, followed by *Pseudomonas* spp.<sup>18,19,21,22</sup> Few antibiotics are sensitive to *Pseudomonas*.

One of the main causes of infection in diabetic foot ulcers is *Staphylococcus aureus*. We found that 50% of all *Staphylococcus aureus* cases were resistant in our study. This rate is in line with a global study conducted by Akhi MT et al. and Dadashi M et al.<sup>20-24</sup>

MRSA is 17% prevalent in diabetic patients globally, according to Zhou S et al. This might be due to the absence of Methicillin-resistant *Staph aureus* in our study.<sup>22,25</sup> Our study shows resistance to few microbial organisms. Another study by per Moya-Salazar J et al. *Staph aureus* was the most common organism in diabetic foot infections among Peruvian patients, 19.9%.<sup>23,26</sup>

The diabetic foot ulcer was associated with patients with prolonged duration of diabetes, poor blood glucose control, no oral hypoglycemic, older age and male gender were more likely to get diabetic foot ulcer patients.<sup>27,28</sup>

Despite the moderate sensitivity observed, the empirical use of amoxicillin-clavulanic acid should be carefully considered, particularly in patients with severe DFUs or those who are at high risk for complications. Clinicians must rely on updated local antibiograms and consider combination therapy or alternative agents in cases where resistance is encountered.<sup>24,25,29,30</sup>

This study has limitations that should be acknowledged. The cross-sectional design hinders any possibility of tracking changes over time in the resistance levels to antibiotics. Because this was a single-center study, it may not apply to other settings or populations. The relatively small sample size was also a potential limitation on the statistical strength of the findings. Furthermore, not studying molecular mechanisms of resistance alongside other possible confounding factors, such as previous exposure to antibiotics and existing medical conditions, adversely affects the microbiological outcomes. Nonetheless, the study adds valuable data concerning local antimicrobial resistance, which can assist in formulating empirical treatment guidelines for diabetic foot infections.

This study offers valuable insights on the patterns of resistance to amoxicillin-clavulanic acid within the

context of diabetic foot ulcers. Such patterns could support the need for more refined antibiotic treatment. For these conclusions, future studies should include more participants from different regions while conducting additional molecular resistance research to enhance the understanding and treatment of DFUs.

### Conclusion

Amoxicillin-clavulanic acid demonstrated moderate sensitivity against the microbial isolates from DFUs in our cohort. The study offers valuable insights into the patterns of resistance to amoxicillin-clavulanic acid within the context of diabetic foot ulcers. These findings may assist clinicians in selecting appropriate empirical antibiotic therapy for DFU management.

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**Conflict of Interest:** The authors declare no conflict of interest

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#### Author Contributions

**IK:** Conception and design of the work

**IA:** Manuscript writing for methodology design and investigation

**ZK:** Writing the original draft, proofreading, and approval for final submission

**ZMW:** Data acquisition, curation, and statistical analysis

**AK:** Validation of data, interpretation, and write-up of results

**IU:** Revising, editing, and supervising for intellectual content