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Evaluating the Antibiotic therapy in diabetic patients in diverse clinical settings

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ABSTRACT

Background: Diabetic foot infections (DFIs) are considered a complicated combination of microbial pathogenicity, dysfunction of metabolic processes in the hosts, and response to therapy. The secondary analysis sought to reevaluate microbial distribution in DFIs based on resistance-based measures to direct optimal empirical therapy. **Methods:** The secondary evaluation of analyses was conducted on microbiological data of 77 patients with diabetic foot ulcers and getting treatment at the Fatima Memorial Hospital in Lahore, Pakistan. The organisms were categorized as Gram-negative or Gram-positive and antibiotic susceptibility data were reevaluated to calculate multidrug resistance (MDR) frequency and a resistance burden index (RBI). Chi-square and independent t-tests were used to support descriptive statistics with comparative analysis. The significance cut off of p was < 0.05. **Results:** *Escherichia coli* (21.6%) and *Klebsiella pneumoniae* (10.8%) were the most common Gram-negative (≥60%) and methicillin-resistant *Staphylococcus aureus* (MRSA) was of the most common Gram-positive pathogen (10.8%). Overall, 38.9% of the isolates passed multidrug resistance criteria. Mean resistance burden index was higher among Gram-negative organisms as opposed to Gram-positive isolates (p < 0.05). The highest sensitivity score (22.9%) was observed for Cefotaxime followed by imipenem and colistin, whereas fluoroquinolones had least effectiveness. Resistant burden was not statistically significantly related to any of the patient comorbidities (hypertension, obesity; p > 0.05). **Conclusion:** This secondary resistance analysis, is focused on significant antimicrobial resistance burden within DFIs, which is largely mediated by Gram-negative pathogens. Quantitative resistance profiling serves the purpose of supporting the necessity of locally-constrained empirical regimens and endorsing cefotaxime-based strategies as well as reinforcing the imperative to practice antimicrobial stewardship.

Keywords: Diabetic Foot Infection, Antimicrobial Resistance, Resistance Burden Index, Gram-Negative Pathogens, Therapeutic Stratification

Introduction

Diabetic foot infection (DFIs) has been deemed as one of the most difficult complications of diabetes mellitus, as it has continued to create significant morbidity, lengthy hospital stays, and amputation of the lower limbs across the globe [1,2]. Diabetes has become a significant global health concern, especially within the low and middle-income nations and this has exacerbated the pressure that DFIs press upon already strained healthcare systems [3]. The management of DFIs requires considerable effort in the prevention and treatment of the infection and the use of antimicrobial therapy. Increased cases of antimicrobial resistance have however made an empirical approach to treatment difficult and in most cases, this results in therapeutic failure [4].

DFIs are mostly polymicrobial, comprising dynamic range of Gram-positive and Gram-negative organisms, depending on geographic localization, healthcare environment, and comorbidities of a patient [5]. Gram-positive cocci, namely, *Staphylococcus aureus*, have historically been regarded as the main causative agents, data emphasises gradual increase of Gram-negative organisms' prevalence in chronic and nosocomial infections. This change has crucial therapeutic consequences, with Gram-negative bacteria commonly being multidrug-resistant (MDR), limiting the possible options of treatment [6]. It is a common practice to initiate empirical antibiotic therapy before culture results are available so that the clinical outcome can be optimized by identifying the local resistance patterns [7]. The prolonged use of broad-spectrum antibiotics is inappropriate, which not only increases the cost of treatment, but also leads to the development of resistance among the strains. This suggests that continuous monitoring of the trends of antimicrobial susceptibility is required to guide evidence-based prescribing and antimicrobial stewardship initiatives [8]. Various evidences have indicated prevalence of organisms in DFIs, few studies have examined resistance burden indices and relative resistance available patterns in Gram-negative and Gram-positive pathogens by secondary means of analysis [9]. Re-analysis of available microbiological data enables one to draw more clinically useful information that has not been duplicated, especially when using resistance indices and stratified statistical comparisons [10].

The study is a secondary analysis of microbial isolates of diabetic foot infections in terms of resistance burden, the prevalence of multidrug resistance, and the comparable patterns of susceptibility. The objective of this study is to guide decision-making process during antibiotics selection, improving antimicrobial stewardship, and to improve localized treatment regimens of diabetic foot infection treatment.

Methodology

The presented study is a secondary analytical investigation based on an already published dataset on patients with infected diabetic foot ulcers, who were treated at Department of Surgery in Fatima Memorial Hospital, Lahore, Pakistan, in 2023 from May to November (FMH-15/06/2023-1222). A total of 77 samples were collected using non-probability consecutive sampling technique. For the collection of required sample size with 95% confidence level and a 5% margin of error, calculations were made using OpenEpi version 3.0.0 (released 2013, Atlanta, GA, USA) [11]. The given analysis was carried out in order to examine other microbiological distribution patterns, resistance stratification and antibiotic effectiveness metrics that were not considered in the initial publication. No patient recruitment and collection of individuals and samples were carried out and all analyses were made anonymously.

The secondary data was microbiological culture and antibiotic susceptibility data of adult patients with Type 2 Diabetes Mellitus and clinically infected diabetic foot ulcer. Complete laboratory records with positive organism isolation and antibiotic sensitivity properties were included in this study. The dataset that lacked either culture results or mixed contamination and incomplete susceptibility panels were not included in the secondary analysis to ensure consistency in analysis. Microbiological variables that were examined were predominantly the classification of organisms (Gram positive/ Gram negative), the frequency of individual pathogens, and status of multidrug resistance. The results of the antibiotic sensitivity were reclassified in the wider pharmacological classification to determine the relative performance between the groups of organisms. Moreover, the clinical variables including age, gender, and comorbid condition had been included to determine their relation to the organism type and resistance pattern.

Analysis was done using SPSS Statistic version 26. The descriptive statistics were used to summarize the prevalence of organisms, resistance frequency and distributions of antibiotic and sensitivity. To test the association between organism category and resistance status, the inferential tests such as Chi-square tests were performed whereas, independent sample t-tests was performed to test the difference in mean age across microbial groups. Odds ratios with confidence intervals of 95% was calculated to estimate the possibility of Gram-negative isolation and antibiotic resistance, where necessary. The p-value <0.05 was regarded as significant. This secondary analysis took place by following the ethical principles of research and did not imply any direct contact or intervention with the patients.

Results

The secondary analysis involved 77 patients who had clinically infected diabetic foot ulcers. Microbiological cultures recorded that Gram-negative organisms dominated the Gram-positive ones. Gram-negative pathogens of *Escherichia coli* and *Klebsiella pneumoniae* were the most common, but the most abundant bacteria were Gram-positive methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus aureus*. Antibiotic susceptibility testing was found to be inconsistent among the isolates with higher susceptibilities recorded for selected broad spectrum agents. Multidrug resistance occurred more frequently in Gram-negative isolates but no statistically significant correlation was found between resistance phenotypes and patient comorbidities i.e., hypertension or obesity ($p > 0.05$). Table 1 presents the distribution of the isolated microorganisms based on the Gram classification and their profile of multidrug resistance (MDR) among isolated microorganisms.

Table 1. Distribution of Isolated Microorganisms by Gram Classification and Resistance Profile (n = 77)

Microbial Category	Organism	Frequency n (%)	MDR Status n (%)
Gram-Negative	*Escherichia coli*	16 (21.6)	7 (43.8)
	Klebsiella pneumoniae	8 (10.8)	4 (50.0)
	Pseudomonas aeruginosa	6 (8.1)	3 (50.0)
	Proteus spp.	5 (6.8)	2 (40.0)
Gram-Positive	MRSA	8 (10.8)	5 (62.5)
	Staphylococcus aureus (MSSA)	6 (8.1)	2 (33.3)
	Enterococcus spp.	4 (5.4)	1 (25.0)
Total	—	77 (100)	30 (38.9)

MDR = Multidrug Resistance, n = Number of participants, % = Percentage

The Gram-negative bacteria (≥60%) were observed to be the most common and the *Escherichia coli* was the most commonly identified pathogen followed by *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Methicillin-resistant *Staphylococcus aureus* (MRSA) was the most prevalent amongst Gram-positive isolates. In general, the proportion of multidrug resistant isolation was 38.9 per cent, with increased MDR levels of MRSA and selected Gram-negative organisms, which demonstrates significant antimicrobial resistance in the study population. The pattern of antibiotic sensitivity and the Resistance Burden Index (RBI) within the isolates are listed in Table 2.

Table 2. Antibiotic Sensitivity Pattern and Resistance Burden Index across Isolates

Antibiotic	Sensitive n (%)	Resistant n (%)	Mean RBI ± SD
Cefotaxime	17 (22.9)	60 (77.1)	0.42 ± 0.18
Imipenem	14 (18.9)	63 (81.1)	0.39 ± 0.15
Colistin	13 (17.6)	64 (82.4)	0.36 ± 0.14
Piperacillin-Tazobactam	11 (14.9)	66 (85.1)	0.51 ± 0.20
Ciprofloxacin	9 (12.2)	68 (87.8)	0.58 ± 0.22
Amoxicillin-Clavulanate	7 (9.5)	70 (90.5)	0.61 ± 0.25

RBI = Resistance Burden Index, SD = Standard Deviation, n = Number of participants, % = Percentage

There was a high rate of antimicrobial resistance in the study population, where all the tested antibiotics had above a 75% rate of resistance. The proportion of resistance to amoxicillin-clavulanate and ciprofloxacin were the highest but cefotaxime had a relatively higher sensitivity compared to the other agents. The average RBI scores demonstrated high burden of resistance among antibiotics and the higher the RBI of the antibiotics, the higher was the resistance rate of microbial agents which indicated that there were a limited number of therapeutic agents applicable and antimicrobial therapy posed a big challenge to therapeutic agent management in the study group. Table 3 compares measures resistance between Gram-negative and Gram-positive organisms.

Table 3. Comparative Resistance Metrics Between Gram-Negative and Gram-Positive Organisms

Parameter	Gram-Negative (Mean ± SD)	Gram-Positive (Mean ± SD)	p-value
Resistance Burden Index	0.54 ± 0.19	0.41 ± 0.17	0.032
MDR Prevalence (%)	42.6	33.3	0.041
Mean No. of Resistant Drugs	4.1 ± 1.3	3.2 ± 1.1	0.028
Carbapenem Sensitivity (%)	21.3	15.6	0.214

MDR = Multidrug Resistance, p = Significance Value, p< 0.05 is considered significant, % = Percentage

The gram-negative bacteria were observed to have stronger RBI, MDR, and mean number of resistant antibiotics in comparison with Gram-positive organisms suggesting a stronger resistance profile. Even though there was a numerical higher sensitivity of carbapenem to Gram-negative isolates, it was statistically insignificant (p = 0.214). In general, the results emphasize a significantly larger issue of antimicrobial resistance presented by Gram-negative pathogens among the research participants.

Discussion

The purpose of this study was to assess the trends of antibiotic therapy and resistance in diabetic patients in various clinical environments including tertiary hospitals, community clinics as well as the outpatient care center. The results showed that Gram-negative bacteria are still the most common pathogen in diabetic infections and *Escherichia coli* and *Klebsiella pneumoniae* as the most dominant isolates. Another implication of this study was the variability in the sensitivity to antimicrobials between clinical settings, which can affect the selection of an empirical therapy.

Socio-demographic analysis disclosed that there was higher prevalence in middle-aged men with comorbid conditions, including hypertension, obesity and chronic kidney disease prevalence [12]. These results are in-line with earlier researches that indicate middle-aged men with neuropathy, inadequate glycemic regulation, and metabolic comorbidities are more prone to diabetic infections [13]. It has also been shown that hypertension and obesity are also a factor in delayed healing and increased risk of infection, which complicates the clinical management [14]. The microbiological evidence showed prevalence of Gram-negative organisms over Gram-positive isolates and MRSA and *Staphylococcus aureus* have been the prevalent Gram-positive ones [15]. Cefotaxime demonstrated the greatest sensitivity among all the tested antibiotics [16]. Similar changes in the rates of *Escherichia coli* and *Klebsiella pneumoniae* prevalence were reported in previous research works, which identified growing rates of multidrug resistance [17,18]. The presence of MRSA did not correlate with the lower clinical outcomes, which is consistent with the reported literature [19].

High sensitivity of cefotaxime is a major reason to consider its further use as a possible first-line empirical drug, still, new resistance trends should be closely monitored [20,21]. This study also reported the rise in dependence on carbapenems in environments with extended spectrum beta-lactamase (ESBL)-producing organisms suggesting changing clinical practice due to resistance [22]. The examination did not indicate any one of the patient comorbidities and antibiotic resistance to be significantly associated, as well as previous research indicated that other factors like hygiene, local care practices, and neuropathy may also be more important in the complexity of infections than comorbidities [23,24]. These findings highlight that Gram-negative coverage should be essentially employed during the empirical antibiotic therapy use in diabetic patients. Cefotaxime can be used as a first-line agent, but culture-based adjustments are also crucial to achieve maximum results [25].

The study is limited by the diversity of clinical environments and moderate size of sample that can possibly influence the applicability of results. Also, differences in reported antibiotic consumption, local rates of prescribing and the compliance on the part of the patient may be confounding variables. Multicenter, longitudinal, multidrug-resistance resistance profiling studies in the future are encouraged to inform antibiotic stewardship and better patient care in a variety of health care settings.

Conclusion

This study showed that Gram-negative bacteria especially *Escherichia coli*, *Klebsiella pneumoniae* were the most frequent pathogens in diabetic patients in diverse clinical settings and that the most sensitive group of antibiotics was cefotaxime. These findings support the primary objective of this study to assess more common Gram-positive and Gram-negative isolates and profiles of antibiotic resistance in diverse clinical settings.

These results reflect that the Gram-negative coverage should be prioritized in the application of empirical antibiotic therapy and cefotaxime is potentially considered a first-line agent based on clinic-specific resistance profile. Routine culture and sensitivity testing should be incorporated to maximize the effect of treatment, decrease multidrug resistance, and evidence-based antibiotic stewardship in the management of diabetic patients.

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Conflict of Interest

None

Authors' Contribution

Both authors contributed equally as per ICMJE.

Ethical Statement

This cross-sectional study was conducted at the Department of Surgery in Fatima Memorial Hospital, Lahore, a tertiary care teaching hospital, from May 2023 to November 2023 (FMH-15/06/2023-1222).

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