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Research Article

Antimicrobial Resistance, Pathogen Transmission and Cross-Infections across Regions and Borders

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Abstract: Antimicrobial resistance is now considered a global dilemma and threat to many antibiotics running in clinical practices. In Pakistan, its worst consequences appear and rise day by day, especially in hospital and community-acquired healthcare settings. In Khyber Pakhtunkhwa (KP) especially in Peshawar, most of the Tertiary Care Hospitals, have a big flow of in and outpatients throughout the country as well across the border from Afghanistan, Iran, and Middle Eastern countries. So, the opportunities for cross infections, and transmission of Multidrug resistance/superbug strains are higher up, which needs to be assisted and evaluated. The current study was a combined prospective and retrospective nature study carried out in the endocrinology ward, in a tertiary care hospital in, Peshawar, KP, Pakistan. To ensure a thorough evaluation of treatment outcomes and the validity of the findings, the study attempted a combination of prospective monitoring and retrospective analysis to assess AMR, CSTs, and hospital stay longevity among 97 DFU inpatients. DFU was most prominent in the age range of 51-60 years, followed by 41-50 and patients above 60 years of age, respectively. Various antibiotics were prescribed to DFU patients. Among antibiotics, cefoperazone-Salbactam combination was highly prescribed (31.8%) followed by Linezolid (18.8%), and Ciprofloxacin and Meropenem (13.6% each). Patients having an age limit of 10-40 years were mostly resistant to antibiotic regimens including Ampicillin-clavulanic acid, cefipime, and cefoperazone-sulbactam. Similarly, patients in the age limit 41-50 were resistant to cefotaxime-sodium and ceftazidime. Furthermore, patients in the ages ranging 51-60 were resistant to co-trimaxazole, levofloxacin and moxifloxacin. In contrast, patients above the range of 61 years were found to be resistant to Ampicillin-clavulanic acid, cefipime, cefotaxime, ceftriaxone, co-trimaxazole, and levofloxacin. In conclusion, there is a strong need for comprehensive studies considering pathogen transmission, and cross-border infections in Pakistan to prevent the growing issue of AMR.

Keywords: Antimicrobial Resistance, Beyond Borders, Cross-Infections, Multidrug resistance, Superbugs.

1. INTRODUCTION

Pakistan has shared international borders with Afghanistan, Iran, China, Tajikistan and India. Diversities in regional, socio-cultural, and religious attributes and shared various norms, traditions, relations, business exchanges, health concerns, sports, education, import and exports across borders and gate-passes. Afghanistan shares a 2670 Km, shared border with Pakistan, they have the highest exchanges of human across-boarders (Chaman border, Baluchistan and Torkham border, Khyber Pakhtunkhwa (KP), as compared to other neighbouring countries. Most of the Afghan

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people come to Pakistan for business, jobs, sports, and health-treatment concerns. They are seeking treatment, especially in the public and private sector hospitals like Hayatabad Medical Complex (HMC), Khyber Teaching Hospital (KTH), Lady Reading Hospital (LRH), North-West General Hospital and Research Center (NWGH-RC), Rahman Medical Institute (RMI) and many more in private sectors. Each day thousands of Afghan people come to Peshawar for various ailments treatment. So, there may be chances that they may bring or go back with MDR pathogens. (Figure 1), depicts the human traffic and mobility across borders for various purposes, but the most associated are health concerns. The spread of MDR has increased due to human traffic and mobility in cross-border regions throughout the globe, which may be considered to increase AMR, especially in underdeveloped countries, where there are no strategies to overcome excessive misuse of antibiotics. So, regional infection prevalences are one of the key factors in AMR/MDR prevalences, which are mostly ignored in Asian countries like Afghanistan, Iran, Pakistan, India, Nepal, Sri Lanka and most of the Arabic countries.

Diabetes mellitus (DM) is a global dilemma, which are highly prevailed in Asian countries. The complications associated with DM are life-threatening and lead to permanent organ damage and disabilities [1]. Uncontrolled Diabetes mellitus may extend into various complications, among which one of the common complications is diabetic foot or diabetic foot ulcer (DFU) [2]. It may be due to poor glycemic control, vascular diseases, neuropathies and poor foot care by diabetic patients. In 15% of diabetic patients, a sore or wound at the bottom of the foot may commonly occur [3].

Global prevalence of DFU among diabetic patients is about 6.3%, whereas only in Asia, where its prevalence is about 5.5%. The highest number of DFU patients was reported in Belgium at 16.6%, where the least accounted for in Australia which is about 1.5%. The highest number of DFU patients was reported in Belgium at 16.6%, where the least accounted for in Australia is about 1.5%. Though, DFU may be associated with the global burden of diabetes, which estimated in 2019, that 9.3%, almost 463 million people have diabetes mellitus. It will be raised to 10.2% (578 million) in 2030, while in 2045, it may reach 10.9% (700 million) [4, 5].

As in Pakistan, we do not have that much prospective research, that's why we don't have exact prevalences, especially in each province. Though very few and limited publications were founded on DFU patients in Pakistan. It has been found that the prevalence of DFU patients in Pakistan ranges from 2.1 to 50.9%, which may be considered an alarming situation [6]. If the infections in DFU are uncontrolled it may lead to limb loss [7]. The uncontrolled infections may be associated with antibiotic non-responsiveness, which is considered as an AMR/MDR or extended drug resistance (XDR). A limb is lost every 3 h in Australia as a result of uncontrolled infections in DFU. It is estimated that approximately 50%-70% of all lower limb amputations are due to DFU [8]. In addition, it is reported that every 30 s one leg is amputated due to DFU worldwide [9]. Most of the diabetes related-deaths are associated with DFU, which attributes up to 8% among other complications [10].

Antibiotics are effective against pathogenic bacteria, but excessive consumption and misuse may lead to the development of genetic mutations extended to resistance [11]. Overcrowded inpatient hospital wards and hospital-acquired cross infections may enhance the global burden of AMR/MDR infections. Overconsumption, decreased responsiveness, and long hospital stays may indicate AMR. As we know, mostly in Pakistan and many other Asian countries, antibiotics are prescribed without CSTs and rely on empirical therapy which may be due to high burdens of infections, limited hospital and healthcare facilities, and longer hospital stay which increase the healthcare costs.

The current study is an approach, to determine the cross-border infection demographics, antibiotic consumption, responsiveness and hospital stay longevity specifically in DFU inpatients in a tertiary care hospital in Peshawar. It is an attempt that evaluate the antibiotic excessive use, switching over from one class to another class of antibiotics, and the hospital stay prolongation in DFU inpatients.

2. MATERIALS AND METHODS

2.1. Study Universe

The current study was a combined prospective and retrospective nature study carried out in the endocrinology ward, in a tertiary care hospital of,

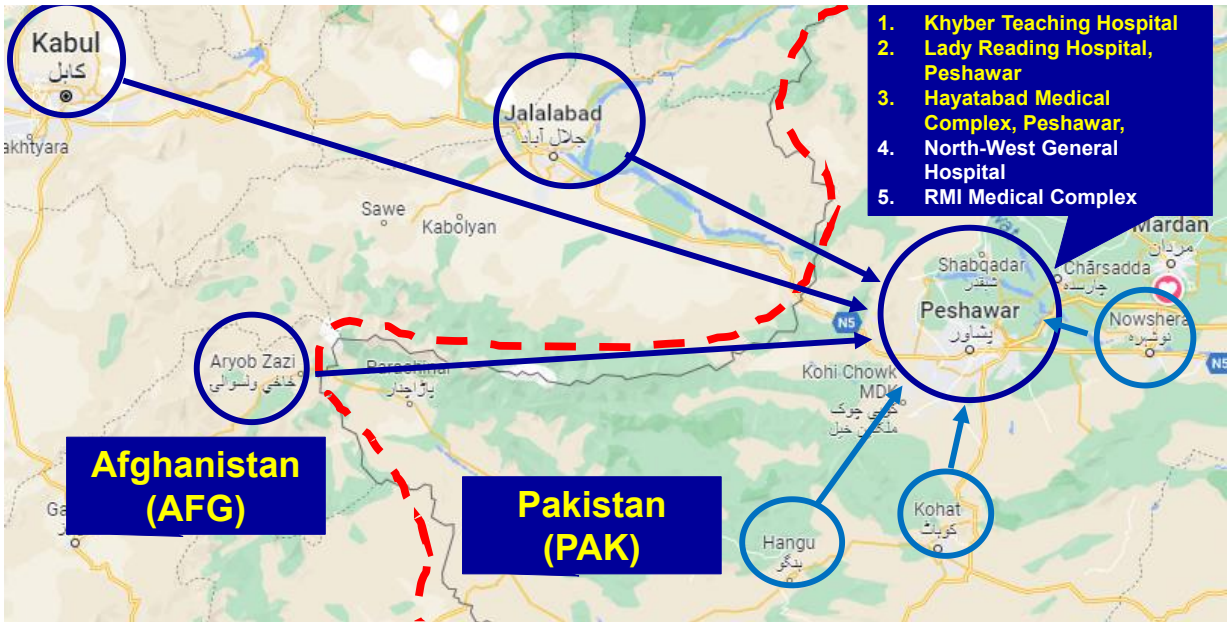

Fig. 1. Pakistan-Afghanistan border, periphery cities and hospitals (Source Google map with modification).

Peshawar, Khyber Pakhtunkhwa (KP), Pakistan. To ensure a thorough evaluation of treatment outcomes and the validity of the findings, the study attempted a combination of prospective monitoring and retrospective analysis to assess AMR, CSTs, and hospital stay longevity among DFU inpatients. By combining previous information from patient records with real-time observations of antibiotic usage, our method ensured a thorough evaluation of treatment outcomes in DFU patients.

The hospital comprised more than 33 Departments, 1797 beds, above than 1350 physicians and surgeons, with 450 other technical staff. The hospital provides both medical and surgical services to both inpatients, n= 139693 and outpatients (OPD), n= 535912, emergency patients n= 1061690, in the last year, 2022 (https://www.lrh.edu.pk/, retrieved on 26-Septmeber-2023).

2.2. Including/Excluding Criteria

Only those DFU patients (included across borders) were included in the study who were hospitalized (in-patients) for their severe sepsis, ulcers and infections. Outpatients and all DFU patients were excluded from this study who visited the hospital for their routine checkups, and dressings or had incomplete medical records.

2.3. Patient Data Collection Procedure

Both prospective and retrospective procedures and methodology used by Haleema et al., 2023 were adopted with a little modification for data collection [12]. The regional vicinity and cross-border DFU inpatients were specifically sorted out and were noted down for AMR, identified through CSTs. The Patient antibiotic consumption records were properly checked for DM and DFU diagnosis. Patient ID, name, age, sex, locality, date of Admission (DOA), and date of discharge (DOD) for hospital longevity/stay were specifically noted. Antimicrobial therapy and antibiotic consumption charts, dose and regimen schedules were properly evaluated for responsiveness and sensitivity. Empirical therapy and culture sensitivity tests (CSTs) were properly followed and noted down. An Excel sheet was properly maintained for the said parameters.

2.4. DFU Inpatient Demographics

DFU inpatient demographics were identified through age group ranges (including across borders). We classify the patient demographics into various age ranges, which start from 10 years and extend up to 60 and above years. The patient's demographic (regional vicinity and across borders) were further sorted for male and female DFU inpatients' which were separately tabulated, according to the following age groups (**Table 1**).

2.5. Culture Sensitivity Tests (CSTs)

As we know in Pakistan, mostly we have empirical therapies for antibiotic prescriptions, which means,

Table 1. DFU in patients' demographics (age ranges).

Age ranges (years)	DFU inpatients from Pakistan (n=x)	DFU inpatients Across borders (n=y)
10-29 Years		
30-40		
41-50		
51-60		
61-above		

that the physicians/clinicians prescribe antibiotics without CSTs. So, we also collected information for empirical and CST therapies, especially in DFU inpatients. CSTs were also noted down from the patient medication history profile.

2.6. Hospital Stay and Longevity

The hospital stays and longevity (H-S/L) were calculated from the date of admission and date of discharge in all DFU inpatients including across. The date of admission and discharge were all mentioned on the patient medication chart history.

2.7. Antibiotic Consumption and Responsiveness

During the hospital stay, antibiotic consumptions were properly monitored and evaluated in DFU inpatients in both regional and across-border inpatients. The sensitivity and responsiveness were properly monitored and followed for antimicrobial resistance and sensitivity. During the hospital longevity, switching over from the initial antibiotic therapy to another antibiotic treatment was also noted down. Age range-wise antibiotic consumption and responsiveness were also evaluated for AMR. Empirical therapy and CSTs were also properly observed for each patient [12].

2.8. Statistical Analysis

The co-relation of hospital stay and antibiotic was evaluated through regression correlation and t-test multiple while using GraphPad Prism. Another mode, the mean median and percentages were calculated through MS Word Excel.

3. RESULTS

The age range of male and female DFU inpatients' demographics information is mentioned in (Figure 2). DFU was most prominent in the age range of 51-60 years, followed by 41-50 and patients above 60 years of age, respectively. A total of n= 97 DFU inpatients, where the majority of them were male patients of almost all age ranges. Similarly, among these DFU inpatients, in some cases, some patients belonged to Afghanistan, which is a neighbour country to Pakistan. A total of n=8 cases were reported from Afghanistan (male=3, female =5) (Figure 3).

Some of the cases of AMR were reported both from within the regional vicinity of Pakistan as well as from across the border. (Figure 4a) is an

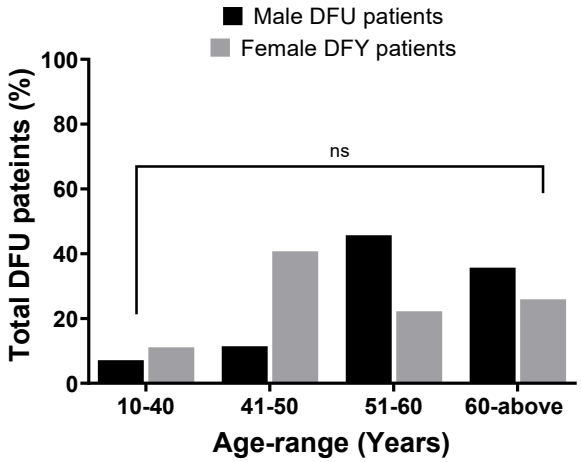

Fig. 2. DFU inpatients age-range demographic information's in tertiary care hospital of Peshawar during (January-March, 2023).

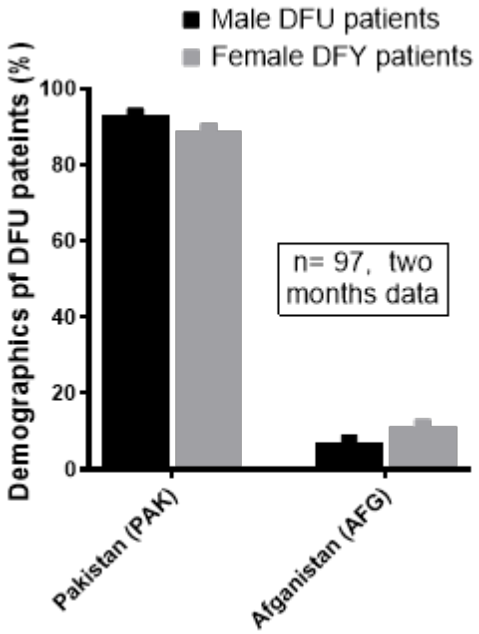

Fig. 3. DFU inpatients demographics including cases reported from Afghanistan (a cross-border), in tertiary care hospital of Peshawar during (January-March, 2023).

across-border AMR case reported of a female (40 Years) from Afghanistan, where Figure 4b is a CST, where the most commonly used antibiotics were highlighted. The CST report of the DFU patient revealed that the strain is MDR showcasing resistance to 12 tested antibiotics including; Penicillin (amoxicillin and amoxicillin+clavulanic acid combination), Cephalosporins (cefixime, cefixime, cefotaxime, ceftazidime, ceftriaxone), Fluoroquinolone (ciprofloxacin, moxifloxacin and levofloxacin), Imipenem, Meropenem and piperacillin+tazobactam combination therapy, respectively (Figure 4). Likewise, (Figures 5a & 5b) show AMR cases and their CSTs reported from the regional vicinity of Pakistan. Moreover, the CST report of the DFU patient from Pakistan (regional vicinity) showed that the strain is MDR showcasing resistance to 08 tested antibiotics including; Penicillin (amoxicillin+clavulanic acid), Cephalosporins (cefipime, cefotaxime, ceftazidime, ceftriaxone), Fluoroquinolone (ciprofloxacin, and levofloxacin), and doxycycline antibiotic therapy, respectively (Figure 5).

Figure. 6 shows the percentage of empirical therapy and CSTs in the current prospective and retrospective study of DFU inpatients.

Various antibiotics were prescribed to DFU patients during the study as shown in (Figure 7). Among antibiotics, cefoperazone-Salbactam combination was highly prescribed (31.8%) followed by Linezolid (18.8%), and Ciprofloxacin and Meropenem (13.6% each). Additionally, clindamycin, cefixime, cefotaxime, moxifloxacin, and clarithromycin were also prescribed to some patients.

The AMR percentage among all clinically sensitive antibiotics in DFU patients is depicted in (Figure 8). Patients having an age limit of 10-40 years were mostly resistant to antibiotic regimens including Ampicillin-clavulanic acid, cefipime, and cefoperazone-sulbactam. In addition, patients in the age limit 41-50 were resistant to cefotaxime-sodium and ceftazidime. Furthermore, patients in the age range of 51-60 were resistant to co-trimaxazole, levofloxacin and moxifloxacin. Moreover, patients above the range of 61 years were found to be resistant to Ampicillin-clavulanic acid, cefipime, cefotaxime, ceftriaxone, co-trimaxazole, and levofloxacin.

Lastly, hospital stay and longevity were also assessed for DFU patients as shown in (Figure 9). Mostly, patient stay in the hospital was revealed to be between 6-15 days due to non-responsiveness of antibiotics during antibiotic therapy. This increase in hospital stay can be attributed to AMR as

A

B

Antibiotics	AMR
Amoxicillin	
Amoxicillin-Clavulanic Acid	R
Cefepime	R
Cefixime	R
Cefoperazone-Sulbactam	
Cefotaxime Sodium	R
Ceftazidime	R
Ceftriaxone	R
Ciprofloxacin	R
Clarithromycin	
Clindamycin	
Colistin	
Co-trimoxazole	
Doxycycline	
Erythromycin	
Fusidic acid	
Imipenem	R
Levofaloxacin	R
Linezolid	
Meropenem	R
Moxifloxacin	R
Polymyxin	
Piperacillin-Tazobactam	R
Vancomycin	

Fig. 4. Across border DFU MDR case reported from Afghanistan, Female, age 40 Years, in Peshawar, KP, Pakistan, A) DFU ulceration B) Culture sensitivity tests.

A

B

Antibiotics	AMR
Amoxicillin	
Amoxicillin-Clavulanic Acid	R
Cefepime	R
Cefixime	
Cefoperazone-Sulbactam	
Cefotaxime Sodium	R
Ceftazidime	R
Ceftriaxone	R
Ciprofloxacin	R
Clarithromycin	
Clindamycin	
Colistin	
Co-trimoxazole	
Doxycycline	R
Erythromycin	
Fusidic acid	
Imipenem	
Levofaloxacin	R
Linezolid	
Meropenem	
Moxifloxacin	
Polymyxin	
Piperacillin-Tazobactam	
Vancomycin	

Fig. 5. Regional vicinity (Pakistan) DFU MDR case reported, Male, age 44 Years, in Peshawar, KP, Pakistan, A) DFU ulceration B) Culture sensitivity tests.

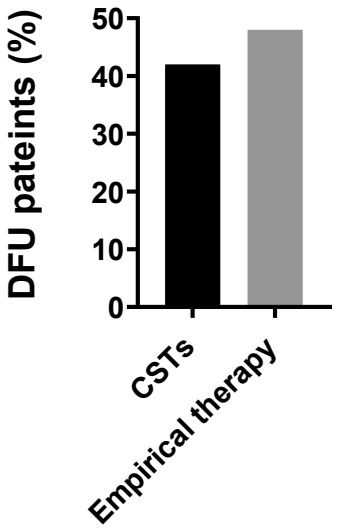

Fig. 6. The percentage of empirical therapies and CSTs performed for DFU inpatients.

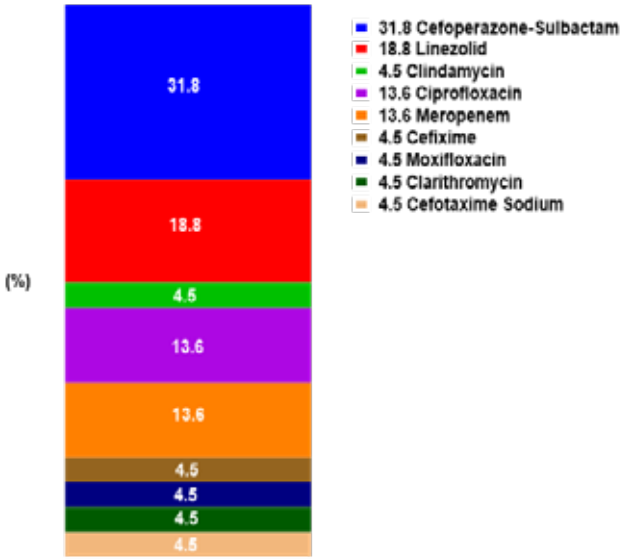

Fig. 7. Antibiotic consumption in DFU.

antibiotics are not working on DFU patients.

4. DISCUSSION

The current study is an attempt to find out the cross-border AMR infections in DFU patients. The study included 97 DFU patients from Pakistan as well as Afghanistan. All the medical records of these patients were evaluated for antibiotic consumption. Additionally, the CST reports were also taken into consideration for figuring out the susceptibility and resistance pattern of bacteria that caused these infections. The ratio of DFU patients was found to be higher in the age ranges 51-60, followed by 41-50 and above 60 years, respectively. It was noticed that patients in the age range of 51-60 years or above presented with comorbidities such as hypertension. Due to its contribution to peripheral vascular disease and delayed wound healing, hypertension is linked to an increased risk of diabetic complications,

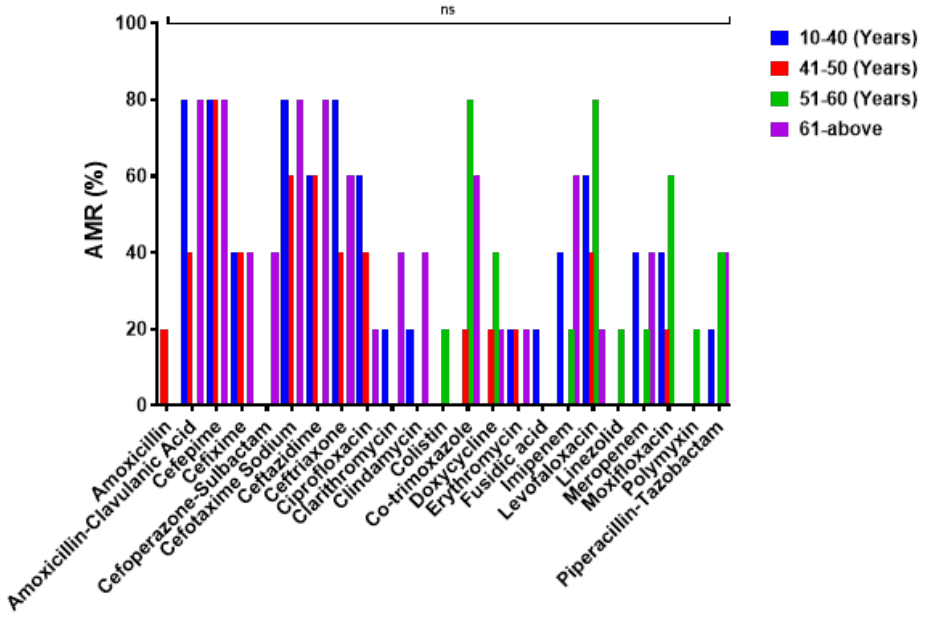

Fig. 8. Antimicrobial resistance percentage among all clinically sensitive antibiotics in DFU in-patients.

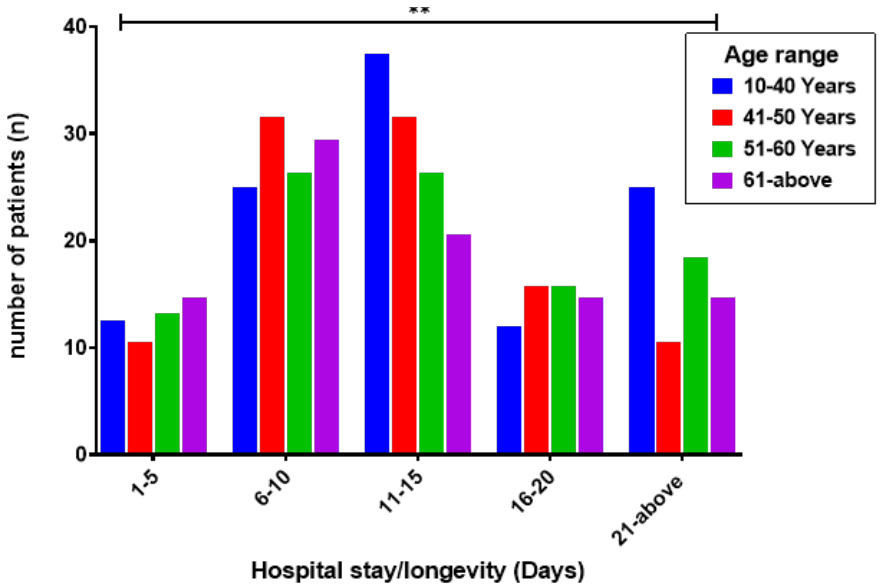

Fig. 9. Hospital longevity of DFU in-patients.

including DFUs [13]. For DFU patients, the existence of hypertension as a comorbidity in this age range emphasizes the significance of proactive measures, including blood pressure control [14], to maximize treatment success and lower the risk of consequences including infection and amputation [8].

During the current study, we came across two special and highly resistant (MDR/superbug) cases of DFU patients. CST report of the DFU patient from Afghanistan revealed that the strain is MDR showcasing resistance to 12 tested antibiotics including; Penicillin (amoxicillin and amoxicillin+clavulanic acid combination), Cephalosporins (cefipime, cefixime, cefotaxime, ceftazidime, ceftriaxone), Fluoroquinolone (ciprofloxacin, moxifloxacin and levofloxacin), Imipenem, Meropenem and piperacillin+tazobactam combination therapy, respectively (Figure 4a). Similarly, the CST report of the DFU patient from Pakistan (regional vicinity) showed that the strain is MDR showcasing resistance to 08 tested antibiotics including; Penicillin (amoxicillin+clavulanic acid),

Cephalosporins (cefipime, cefotaxime, ceftazidime, ceftriaxone), Fluoroquinolone (ciprofloxacin, and levofloxacin), and doxycycline antibiotic therapy, respectively (Figure 4b). In hospital settings, there are higher chances of hospital-acquired infections and cross-infection incidents [15]. For this purpose, the cross-border pathogens and MDR cases need to be reported scrutinized, and treated in controlled, highly hygienic hospital setups to safeguard public health [16].

Various antibiotics were prescribed to DFU patients, such as a cefoperazone-sulbactam combination (31.8%) followed by linezolid (18.8%), and ciprofloxacin and meropenem (13.6% each). Furthermore, clindamycin, cefixime, cefotaxime, moxifloxacin, and clarithromycin were also prescribed to DFU patients with a percentage of 4.5% each. MDR cases were reported from Pakistan as well and some cases were reported from Afghanistan. Furthermore, MDR cases from Afghanistan were resistant to Ampicillin-clavulanic acid, cefotaxime, ceftazidime, ceftriaxone, Meropenem and piperacillin-tazobactam combination. Hospital longevity of the majority of patients was between 6-15 days which is an ample time for cross infections to occur, which may result in the onset of hospital-acquired infections. Specifically, MDR strains can transmit from one patient to another during a hospital stay [17].

During the study, we noticed a shift of resistance towards broad-spectrum antibiotics with an increase in patients' age. Patients having an age limit of 10-40 years were mostly resistant to narrow-spectrum antibiotic regimens including Penicillin and first and 2nd generation Cephalosporins. In addition, patients in the age limit 41-50 were resistant to 3rd generation Cephalosporins. Furthermore, patients in the age range of 51-60 were resistant to broad-spectrum antibiotics such as co-trimaxazole and Fluoroquinolones including levofloxacin and moxifloxacin, respectively. Moreover, patients above the range of 61 years were found to be resistant to penicillins (Ampicillin-clavulanic acid), Cephalosporins (cefipime, cefotaxime, ceftriaxone) and Fluoroquinolones (moxifloxacin and levofloxacin), and co-trimaxazole. This may be linked to antibiotic overuse/misuse, comorbidities in old age, and a weakened immune system to fight off pathogens [18]. Healthcare-associated antimicrobial resistance places a substantial burden on patients [19]. If these scenarios were not taken into consideration, there may be the issues of cross infections, AMR transmission and chances of acquiring MDR infections.

Access to sanitation, proper utilization and purchasing of effective antibiotics are lower in poor nations and refugees which increases the purchasing of low-grade antibiotics, and empirical therapies, which fuels the onset of AMR [20]. Moreover, AMR cases in DFU are now becoming more frequent due to poor sanitation of infected areas of patients as a result of poverty and lack of patient education. During the study, various patients were presented with severe ulcers on their limbs and feet. Additionally, patients also received empirical therapies for their DFU conditions. Merely depending on empirical therapy compromises effective treatment approaches, leaving patients with extended hospital stays and heightened susceptibility to resistant infections [21]. These empirical therapies may result in the prevalence of AMR and can shape the onset of MDR, XDR and superbugs [22]. These resistant infections are responsible for increasing hospital longevity and overall healthcare costs [23]. As evident from the results of this study, the majority of the patients stayed in the hospital for more than one week. This increase in hospital longevity may be associated with infections caused due to drug-resistant strains [24].

There are several limitations to relying solely on hospital data when evaluating cross-infections and AMR. These include the possibility of underreporting cases resulting from mild or asymptomatic infections [25], differences in diagnostic procedures between healthcare facilities that could cause differences in reported AMR rates [26], and the impact of previous antibiotic use on resistance patterns. It is essential to apply established processes for data collecting and analysis alongside other monitoring techniques, such as community- and laboratory-based surveillance, to overcome these constraints with hospital data [27]. Furthermore, to effectively combat AMR in healthcare settings, efforts must be made to improve reporting procedures [28], expand diagnostic capabilities, and implement antimicrobial stewardship programs [29].

The results of the study highlight how cross-border healthcare significantly affects antibiotic resistance. AMR and cross-infection patterns found in Khyber Pakhtunkhwa tertiary care hospitals have the potential to significantly affect regional and

global health outcomes, even outside of the local context. AMR strains are becoming more prevalent, which not only puts the local people at risk but also has the potential to spread resistant diseases throughout the entire globe [30]. The spread of AMR strains from KP hospitals to nearby regions and beyond is an urgent concern considering the international movement of individuals and the interconnection of healthcare systems. This might cause multidrug-resistant (MDR) pathogens to spread, which would make common infections more difficult to treat [31]. Concerns over the spread of drug-resistant bacteria are raised by the influx of people seeking medical care in Pakistan from neighbouring countries such as Afghanistan, particularly with regard to DFU. The spread of superbugs and MDR infections is facilitated by these cross-border migrations, which increases the global AMR threat [32].

A multimodal approach is necessary to effectively reduce the spread of cross-infections and antimicrobial resistance (AMR) in the context of the study region. First of all, healthcare facilities may optimize antibiotic use and stop the spread of resistant bacteria by putting antimicrobial stewardship policies into place. For the purpose of reducing transmission within hospital settings, enhanced infection control measures such as isolation protocols and hand hygiene procedures are essential [33]. Enhancing the capacity for antimicrobial susceptibility testing (AST) diagnostics can also direct focused antibiotic treatment and minimize the inappropriate use of broad-spectrum antibiotics [34]. Since pathogens are borderless and rapidly travel across individuals, collaborations with neighbouring countries might encourage cross-border collaboration in the fight against antimicrobial resistance [35]. Working together can help strengthen surveillance systems and track the regional and worldwide spread of resistant infections by facilitating the interchange of information, resources, and credentials [36]. Furthermore, public health education initiatives can increase awareness about safe antibiotic usage and infection prevention, while strong surveillance and monitoring systems are essential for tracking resistance trends and early epidemic detection. Lastly, there is a strong need for global collaboration, one health approach and antibiotic stewardship programs to be implemented [37].

Several factors, such as resource restrictions, infrastructure limitations, and stakeholder participation, affect the feasibility and scalability of proposed interventions to minimize cross-infections and AMR in the context of the current study. In environments with limited resources, antimicrobial stewardship programs may be difficult to establish because they need initial investment in infrastructure, employees, and educational programs [38, 39]. However, by decreasing antibiotic overuse and AMR-related healthcare expenditures, these programs promise long-term cost reductions [40].

5. CONCLUSIONS

The migration of patients seeking medical attention from Afghanistan to Pakistan is a major factor in the spread of drug-resistant infections, which in turn increases the burden of AMR worldwide. Furthermore, considering the high prescription rates of certain antibiotics, the widespread use of empirical antibiotic therapy without culture sensitivity testing in the treatment of DFU patients promotes antibiotic misuse and the development of resistant strains. This highlights the critical need for improved diagnostic techniques and appropriate prescription practices, particularly for the treatment of DFU patients. To address these issues, global collaboration is required. This collaboration includes improving monitoring systems, setting antimicrobial stewardship programs into place, as well as developing antibiotic consumption regulations that consider health disparities and increase access to high-quality healthcare. Lastly, there is a strong need for comprehensive studies considering pathogen transmission, and cross-border infections in Pakistan to prevent the growing issue of AMR.

6. ACKNOWLEDGEMENTS

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7. CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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