Research Article

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ß-Lactamase and Antibiogram in Some Gram-Negative Bacteria Isolated from Foot Ulcer Patients

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Abstract

The foot infection is the most consequence of diabetes mellitus, which greatly increases the risk of lower limb amputation. Effective antibiotic therapy is crucial in the treatment of these illnesses. The gram-negative bacterial samples from individuals with diabetic foot infections are evaluated in this study for their pattern of antibiotic susceptibility. Eighty-foot ulcer patients in total were collected, and 115-gram negative bacteria were taken, identified, and confirmed for antibiotic sensitivity using several drugs from various families. Finally, the phenotypic detection of extended spectrum beta lactamase, AMPC, and metallo-beta-lactamase MBL was performed. The results found different types of gram-negative bacteria isolated which are *E. coli, Pseudomonas spp*., *Klebsiella spp*., and *Proteus spp*. Also, the results show the different percentages of resistance of these bacterial isolates to different types of antibiotics and also their different percentage in their sensitivity to different antibiotics. This research revealed that 50% of diabetic foot infections were caused by several microbes. The most often found gram-negative-bacteria were *E coli, Pseudomonas spp.*, *Klebsiella spp.,* and *Proteus spp.* These bacteria were recovered from the taken cases. on the other hand, our study found a noted percentage of different isolated gram-negative bacteria for producing three types of beta-lactamase enzymes.

Keyword: beta lactamase, *Escherichia coli,* gram negative bacteria.

Introduction

The development of chronic diabetes complications is associated with a large part of the burden of the disease, as well as the cost of health care as the most common complication is diabetic foot disease that diabetics fear (1). Diabetic foot is characterized by several pathological complications such as neuropathy, peripheral vascular disease, foot ulceration and infection with or without osteomyelitis, leading to the development of gangrene and even necessitation limb amputation (2). Among the most serious and deadly effects of diabetes continues to be foot ulcers, which are also a very upsetting issue for diabetic people (3). Diabetes foot ulcers and infections with bacterial pathogens are a significant medical, social, and economic issue as well as a main cause of morbidity and mortality, mainly in poor countries (3,4). For diabetes patients, infected foot ulcers are a significant source of morbidity and can eventually result in gangrene and amputations (5,6). Several studies have been shown wide range of organisms of multidrug resistant bacteria such as staphylococcus aureus and ESBL producing gram negative bacteria and their associated complications have created a big health concern among the medical practitioners (7). Numerous organisms have the potential to surface colonize chronic wounds. Different bacterial agents have been identified from patients in various Iranian regions, according to several investigations (8). If there is a moderate bacterial infection, it is often mono-bacterial, and if there is a serious illness, it is polymicrobial. The patterns of antibiotic susceptibility also vary across different geographic areas (9).

Diabetes patients are more likely to develop foot infections due to neuropathy, vascular insufficiency, and decreased neutrophil activity. About 30 to 50 % of diabetic patients experience peripheral neuropathy, which is crucial in the emergence of a foot infection (10). Foot abnormalities brought on by motor neuropathy increase the likelihood of skin ulcers locally under the pressure of shoes. Following skin breakdown (usually on the planter surface), harmful organisms get access to the underlying tissues. The ensuing wound infection may start off superficially, but if medical attention is delayed, the body's natural defenses are weakened due to neutrophil malfunction and vascular insufficiency, and the infection can progress to deeper structures (11). Therefore, the goal of the current investigation is to isolate and describe causes of bacterial origin in diabetes patients and assess their antibiotic susceptibility. Moreover, to ascertain if gram-negative bacteria are capable of manufacturing the beta-lactamase enzyme.

Materials and Methods

From November 2021 to April 2022, foot infections in 80 hospitalized diabetic patients of both sexes with untreated foot infections which had not previously received antibiotics from Rizgary Teaching Hospital in Erbil, Iraq, were screened. Pus or discharges from the ulcer's base were taken

as samples, and deep swabbing technique for debrided necrotic tissues taken. Identification. For the purpose of isolating aerobic bacteria, the materials were inoculated onto MacConkey agar and blood agar. Routine biochemical assays by using Gram's staining were used to detect bacterial samples after being incubated for 24 hours at 37°C (12, 13). Vulnerability assessment in agreement with the references of the National Committee for Clinical Laboratory Standards (NCCLS), Kirby and Bauer's disc diffusion method that used for testing antibiotic susceptibility (14). The used antibiotics include: Cephalexin, Cefotaxime, Ciprofloxacin, Ceftazidime, Carbenicillin, Cloxacillin, piperacillin, Meropenem, Augmentin, Gentamicin, Lincomycin, Kanamycin, Metronidazole.

API identification system: It is a multi-test system for media preparation. Each set consists of 20 dehydrated test medium containing micro tubes in plastic strip were rehydrated with a bacterial suspension to be tested (15).

Detection of extend spectrum β-lactamase (ESBL):

Confirmatory double disc diffusion test for ESBL detection: The plasmid-mediated enzymes known as extend spectrum β-lactamases (ESBLs) which consider as many of G-ve bacteria product. The third-generation cephalosporin discs cefotaxime and ceftazidime, amoxicillin-clavulanic acid, and aztreonam, were used in a double disc diffusion test (16).

1- To prepare a bacterial suspension, the turbidity was set to a 0.5 McFarland solution. According to NCCLS recommendations, suspension then streaked on plates of Muller Hinton agar.

2- Muller Hinton agar plates were streaked with the suspension according to NCCLS guidelines.

3- In the middle of the plate, an amoxicillin (20µ g/ml)-calvulanic acid (10 µg/ml) (AMC) disc was positioned.

4- Separate discs containing ceftazidime (30 µg/ml), cefotaxime (30 µg/ml), and aztreonam (30 µg/ml) were put on the plates 1 cm from the edge of disc of amoxicillin-clavulanic acid.

5- Plates were kept for 18–24 hours at 37 °C.

6- Following incubation, a favorable outcome was considered to be an improved zone of inhibition between either one of the β-lactam discs and amoxicillin clavulanic acid.

Detection of AmpC β- lactamase:

Confirmatory disk antagonism test for AmpC enzyme detection: A Muller Hinton agar plate was covered with tested isolates that produced turbidity equal to 0.5 McFarland standards. Cefoxitin (30 µg/ml) and Cefotaxime (30 µg/ml) disks were positioned 20 mm apart from each other center, isolates were considered as positive for AmpC β-lactamase production if they showed inhibiting of one of antibiotics used or both of them or decreased susceptibility to each of them after an overnight incubation (17).

Detection of metallo β- lactamase:

Imipenem (IMP) - EDTA combined disc test: According to the CLSI's recommendations, the bacterial isolates were inoculated into plates with Muller Hinton agar and the IMP-EDTA combined disk test was performed (Institute, 2006). The plate was covered with two (10 µg/ml) imipenem disks, and the required 10 µl of EDTA was then added. The plate was then incubated at 37 °C. The presence of metallo β -lactamase was presumed in the combination disc test if the increase in inhibition zone brought on by the Imipenem and EDTA discs was larger than 7 mm than the Imipenem disc alone. A 0.5 M (Molarity) EDTA solution was made using 186.1 grams of EDTA. NaOH was used to bring the pH of the $2H_2O$ solution to 8.0, and it was then autoclaved to sanitize it. (18).

Results and Discussions

A frequent consequence of untreated diabetes is diabetic foot ulceration. The current study also showed that men are more likely to get infected foot ulcers. These findings are consistent with those of previous research (19- 21) Out of 80 patients with diabetes mellitus, 50 (62.5%) were men and 30 (37.5%) were women. Their age groups were distributed as follows 25---75. The samples of this study showed that 80 of the cases that were taken 75 (93.75%) showed positive culture including different types of gram-negative bacteria pattern against different types of antibodies so we just isolate and detect gram negative bacteria. A total of 115 pathogens were isolated just from gram negative bacterial isolates as showed in table (1). Table (1) shows the number and types of isolates of gram-negative bacteria that were isolated from the patients with diabetic foot ulcer these types of bacteria include *E. coli*, *Klebsiella spp*., *pseudomonas spp*. and *Proteus spp.* (46%, 23.5%, 19.8% and 11.3) respectively. Our results similar to the finding of some studies like (22 ,23 ,24) with different percentage nearby to our finding. The gram-negative colonies were further identified using the API method (Biomeriux., Paris, France). Using the Kirby-Bauer disc diffusion technique and antibiotic discs that are readily accessible in the market, all isolated organisms were tested for antibiotic sensitivity. All patients received the proper antibiotic prescriptions once the data were evaluated in line with clinical and laboratory standards.

Our results were similar to (22, 23), indicating that a variety of bacteria can infect those patients. This study revealed that 81.25% Table (2) of diabetic foot infections were polymicrobial in nature. Additionally, more gram-negative pathogens than gram positive bacteria were isolated. Antimicrobial resistance is becoming a bigger problem across the world while treating diabetic feet. Since most bacteria have developed resistance to numerous antibiotics, drug resistance offers a therapeutic challenge not only in hospital environments but also in the general public. In table (3) shows the antibiotics resistance of gram-negative bacteria were isolated and the most *E. coli* isolates (86.8%) showed resistance to AMP. And also *E. coli* isolates showing resistance to (CRO, COT, AIZ and CFM) on the other hand the *E. coli* isolates showed high sensitivity to (IPM, NIT and MEM). While *Klebsiella spp*. showed high

resistance to (AMC and CAZ) and showed high sensitivity to (IPM) on the other hand *Pseudomonas spp*. Showing high resistance to (FM, AMP) while showing high sensitivity to (IPM). And *Proteus spp*. showing high resistance to (AMP) and high sensitivity to (MEM). And with different percentage of resistance and sensitivity to all other types of antibiotics. Some researchers made a similar observation whereas (24-27).

Third-generation cephalosporins and aztreonam can be hydrolyzed, however they are blocked by clavulanic acid. They serve as the first instance where fundamental modifications to the enzymes' substrate spectrum led to ß-lactamase-mediated resistance to ß-lactam antibiotics. (28) Large plasmids, which also include resistance genes to other antimicrobial drugs such aminoglycosides, trimethoprim, sulphonamides, tetracyclines, and chloramphenicol, frequently contain ESBL-encoding genes (29). According to our results in this study we found that a noted percentage of bacterial isolates produce ESBL phenotypically as we do in the study and *E. coli* isolates their isolates produce the higher percentage of ESBL enzymes (73%) as showing in table (4). The improvement of clinical care for patients with infections depends on the capacity to identify AmpC, which would also provide us with accurate epidemiological data. Many Enterobacteriaceae and a few other species have chromosomes that encode ampC β-lactamases, which are clinically relevant cephalosporinases. They contribute to these organisms' resistance to the majority of penicillin, cephalothin, cefazolin, cefoxitin, and combinations of β- lactamase inhibitors and lactams. Gram-negative bacteria's rise in antibiotic resistance is a prominent illustration of how bacteria might pass on resistance to one or more medications. Early discovery of these enzymes is essential given their phenotypic global growth in prevalence, variety, and velocity of spread (30, 31). Additionally, our study found that isolates of *Pseudomonas spp*. were much less likely to produce MBLs than those in this study. This difference in MBL prevalence may be related to the use of different antibiotics in the two countries or it may be linked to a particular mechanism that is common in different regions.

Conclusion: Based on the analysis of the isolates from the sores and testing for antibiotic susceptibility, the study suggest that the suitable management of bacterial infections requires the choice of the right medications. To reduce morbidity, especially amputation, prevention, timely diagnosis, and treatment are required. According to our study, 50% of diabetic foot infections were caused by several microorganisms. The most often isolated gram-negative bacteria from the collected cases were *E coli, Klebsiella spp., Pseudomonas spp.,* and *Proteus spp.* Also, our founding in this study that antibiotic IMP and MEM were the best choice antimicrobial treatment against gram negative bacteria on the other hand our study found a noted percentage of different isolated of gram- negative bacteria for their ability to produce three types of beta-lactamase enzymes including ESBL, AMPC and MBL.

Table (1): Gram negative bacterial species isolated from diabetic foot ulcer:

The isolated bacteria	No. of isolates	%
E. coli	53	46
Klebsiella spp.	27	23.5
Pseudomonas spp.	22	19.2
Proteus spp.	13	11.3
Total	115	100

Table (2): Poly microbial isolation from foot infection:

Isolation type	No. of patients	%
Single bacterial isolates	10	12.5
Two bacterial isolates	40	50
Three bacterial isolates	25	31.25
No bacterial isolates	5	6.25
Total	80	100

Table (3): Antimicrobial resistance of different Gram- negative bacteria isolates from different clinical samples.

Antimicrobial agents	***E. coli*** **(53)**		***Klebsiella spp.*** **(27)**		***Pseudomonas spp.*** **(22)**		***Proteus spp.*** **(13)**	
	No.	%	No.	%	No.	%	No.	%
AK	18	34	10	37	11	50	4	30.8
AMC	18	34	20	74.1	13	59.1	9	69.2
AMP	46	86.8	11	40.7	6	27.3	13	100
ATZ	35	66	12	44.4	5	22.7	9	69.2
CAZ	32	60.4	20	74.1	15	68.2	8	81.5
CIP	29	54.7	11	40.7	12	54.5	10	76.9
CRO	39	73.6	8	29.6	5	22.7	9	69.2
CEP	31	58.5	7	25.9	5	22.7	10	76.9
CD	41	77.4	8	29.6	6	27.3	11	84.6
COT	36	67.9	16	59.3	11	50	9	69.2
CFM	34	64.2	18	66.7	13	59.1	10	76.9
GEN	17	32.1	15	55.6	12	54.5	8	61.5
IPM	3	5.7	2	7.4	4	18.2	4	30.8
NIT	9	17	5	18.5	6	27.3	6	46.2
MEM	9	17	5	18.5	8	36.4	3	23.1

AK= Amikacin, AMC= Amoxicillin clavunic acid, AMP= Ampicillin, ATZ= Aztreonam, CAZ= Ceftazidime, CIP= Ciprofloxacin, CRO= Ceftriaxone CEP= Cephalothin, CD= Clindamycin, COT= Co-trimethoprim, CFM= Cefepime, GEN= Gentamicin, IPM= Imipenem, MEM= Meropenem, NIT= Nitrofuratin.

Table (4): Percentage of different Beta- lactamase (ESBLs, AmpC and Metallo beta lactamase production in Gram negative bacteria isolates from different clinical samples.

		ESBL beta-lactamase		AmpC beta-lactamase		Metallo beta-lactamase	
		producer	Non-producer	producer	Non-producer	producer	Non-producer
***E. coli* (53)**	**No.**	16	37	0	53	14	39
	%	30.2	69.8	0	100	26.4	73.6
***Klebsiella spp.* (27)**	**No.**	9	18	0	27	6	21
	%	33.3	66.7	0	100	22.2	77.8
***Pseudomonas spp.* (22)**	**No.**	4	18	9	13	0	16
	%	18.2	81.8	40.9	59.1	0	72.7
***Proteus spp.* (13)**	**No.**	2	11	1	12	6	13
	%	15.4	84.6	7.7	92.3	27.3	100
Total (115)	**No.**	31	84	10	105	26	89
	%	27	73	8.7	91.3	22.6	77.4

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البيتا لاكتميز والنتيبايوكرام للبكتريا السالبة المعزولة من تقرحات القدم لدى المرضى المصابين بداء السكري

سيفان حسن بكر

المعهد التقني الطبي في اربيل في جامعة اربيل التقنية

الخلاصة

تعتبر حلات اصابه اقدام مرضى السكري بالتهابات بكتيرية في تزايد دائمي والذي من الممكن ان يؤدي الى بتر الاطراف وان دراسة تأثير استخدام المضادات الحيوية لعلاج هذه الحالات المرضية. وان علاج حالات التقرحات القدمية عند مرضى السكري باستخدام المضادات الحيوية لها تأثير فعال جدا في شفاء الحالة حسب الدراسات السابقة. وفي هذه الدراسة تم عزل ودراسة البكتريا السالبة لصبغة كرام من الحالات المرضية التي تعاني من اصابات القدم بسبب مرض السكري وتم استخدام عدة مضادات حيوية لدراسة مدى مقاومة هذه البكتريا لتلك المضادات ومن أكثر نوع من المضادات لها تأثيرها الفعال على العزلات البكتيرية. وقد تم عزل عدة انواع من البكتريا السالبة واكثرها نسبة عي بكتريا السيدوموناس والكليبسلاو بكتريا بروتيس ومن خلال هذه الدراسة حصلنا على نسب مختلفة ومتفاوتة حسب نوع المضاد الحيوي وقد اطهرت الدراسة التي قمت بأجرائها ايضا على قابلية العزلات البكتيرية على انتاج الانزيمات البيتا لاكتميز بأنواعها المختلفة ومن هذه الدرسة تم الوصول الى نتائج مختلفة من قابلية العزلات البكتريا السالبة لصبغة كرام على مقاومة المضادات الحيوية وقابليتها على زيادة هذه المقاومة لتلك المضادات الحيوية.

الكلمات المفتاحية: البيتالاكتميز الانزيمي،بكتريا ايكولاي' البكتريا السالبة لصبغة كرام.