ORIGINAL ARTICLE

ANTIMICROBIAL SUSCEPTIBILITY PATTERN OF AEROBIC BACTERIAL ISOLATES FROM DIABETIC FOOT ULCERS OF SUDANEASE PATIENTS

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ABSTRACT

Background Foot ulcers are one of the most common complications of poorly controlled diabetes and it causes great morbidity and mortality among diabetic patients. **Objectives:** This study was aimed to assess the antimicrobial susceptibility pattern of diabetic foot infection isolates from different Wagner's grades of Sudanese patients. **Methods**: This study was conducted in the period from December 2017 - March 2018 in a Diabetes Center in Sudan. A total of 152 diabetic patients who admitted with different grades of foot ulcers were randomly enrolled in the study. The patients were grouped using Wagner's classification. Tissue biopsies and deep swabs were collected from the ulcers for aerobic cultures. The isolates were identified using phenotypic and biochemical properties. Antibiotic susceptibility test was performed using the Kirby Bauer disk diffusion method according to the guidelines of the Clinical and Laboratory Standards Institute guidelines (CLSI). **Results**: The mean age of the patients was 54.31 (SD ± 12.1) years. The mean duration of diabetes was 14 (SD ± 8) years. Of 152 samples 181 aerobic bacteria were isolated. The isolates were mostly Gram-negative bacteria. The most frequent bacteria was *proteus* spp. (35.3%), Methicillin Resistant *Staphylococcus aureus* MRSA 14.4% and Coliform 12.2%, respectively. The results of antibiotic sensitivity tests revealed the most sensitive antibiotics for Gram negative rods were Aikacin, Imipenem and Meropenem and for Gram positive was Vancomycin. The most resisted antibiotic by Gram negative bacteria was Cotrimoxazole. The best antibiotic for Gram negative isolates were as follow: For Coliform as Augmentin, for E. coli and *K. oxytoca* as Meropenum, for *K. pneumoniae* as Amikacin + Ciprofloxacin, for *P. mirables* as Meropenum + Amikacin + Imipenem, for *P. vulgaris*, Amikacin + Meropenem and for *P. aeruginosa*, Amikacin + Imepenem. The best antibiotics for Gram positive isolates were as follow: For *Acinobacter* as Aikasin, for *S. aureas*, Erythromycin, for *S. aureas* (MRSA), Vancomycin, for *S. aureas* (VRSA), Ceftriaxone, for *Saph. Coagulase –ve* Vancomycin. The most sensitive antibiotic for most of the isolates was Meropenem. **Conclusion**: Gram-negative bacteria were more prevalent and the most common bacteria isolated in this study was Proteus spp. For Gram positive was *methicillin-resistant Staphylococcus aureusn* (MRSA). The most sensitive antibiotics for *Proteus* were Meropenem, Amikacin and Imepenum respectively. The most sensitive antibiotic for both Gram positive and Gram negative pathogens was meropenem. Further studies for isolation of organisms from infected diabetic foot ulcers in different epidemiological circumstances is essential to understand the variation of isolates and antibiotic sensitivity in different studies.

Keywords: *diabetic foot ulcer, aerobic bacteria, Wagner's classification*

1. INTRODUCTION

Diabetic foot infection –DFI, the most frequent diabetes complication represent a major cause of morbidity and mortality among patients [1]. Approximately 25% of diabetic patients develop an ulcer during their lifetime, and about half of these ulcers become infected [2, 3]. It is estimated that every 30 seconds, a lower limb is lost as a consequence of diabetes worldwide [4]. Most common site of diabetic ulcers is the foot. Many reasons are known to cause diabetic foot ulcers, neuropathy, neglecting this part of the body, the shape of the arch and toes and the colonization of bacteria and fungi between the toes [5, 6]. These ulcers carry a big psychological and financial load on the patients' family and the community health system. Early infections are generally monomicrobial, whereas advanced infections are mainly polymicrobial and low grades are usually infected with gram-positive organisms [7]. Inappropriate antibiotic treatment and frequent hospital admission, can predispose to infection with drug resistnt bacteria [8]. In recent years, the number of the incidents and complications-related to diabetic foot infections (DFIs) has drastically increased due to increased incidence of multidrug-resistant organisms [9].

Impaired diabetic wound healing constitutes a major health problem in patients with diabetes which is estimated to occur in 15% of diabetic patients and often requires prolonged hospitalization for its management. The effective antibiotic treatment is essential to control the infection [10]. Chronic diabetic wounds need 3-6 months for dressing and follow up and sometime exceed 6 months J.D.C. [11]. Amputees need restoration and physical therapy to return them to their normal social life [12]. The costs of chronic ulcer care represent a major portion of the health care

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budget and continue to grow at exponential rates, and this is an important issue in developing countries [13]. These wounds can lead to organ damage or even fatal and dangerous infections for patients. Therefore, the need for antibiotic treatment to minimize these complications is extremely important [14, 15]. The current study was aimed to assess the antimicrobial susceptibility pattern of diabetic foot infection in different Wagner's grades of Sudanese patients. A few studies identified the bacterial isolates and their susceptability to common used anitbiotics in Sudan but to our knowledge this study on bacterial isolates from different grades of wounds considering the depth of the wounds was not done in Sudan.

2. MATERIALS AND METHODS

2.1. Study design and setting

This cross-sectional study was conducted from December 2017 to March 2018. The study was conducted in Jaber Abu Eliz diabetes Center (J.D.C) in the capital Khartoum. The center is the largest diabetes clinic specialized in treatment and care of diabetic foot and it receives patients referred from Khartoum state and different region of the country.

2.2. Patients

One hundred fifty two diabetes patients with foot ulcers were enrolled in the study. The patients were attending the outpatient clinic in the Surgery Unit at J. D. C.The patients were grouped according to Wagner diabetic foot ulcer classification into 5 groups [grade 1 , grade 2, grade 3, grade 4 and long standing ulcers (maturation stage)]. The number of patients in each group was as following: 8 patients were grade 1, 19 patients were grade 2, 70 patients were grade 3, 12 patients were grade 4, and 43 patients were long standing ulcer (maturation phase). Specimens were obtained from every patient group. The demographic data including age, sex, duration of diabetes, duration of the ulcer, was collected by face to face interview using a predesigned questionnaire. All the questionnaires were checked for accuracy and completeness. The ulcer duration was determined verbally based on the patient response.

2.3. Collection of microbiological samples

The ulcers were cleaned vigorously with saline and extensively debrided first to avoid the isolation of colonizing flora. Specimens were collected by 2 methods, tissue biopsy (soft tissue and bone) from the central region of the ulcer bed using a 6-mm disposable sterile punch biopsy (Stiefel Laboratories, Ltd., Sligo, Ireland) and placed immediately into a sterile vial containing 2 ml of sterile normal saline. Some samples were collected by deep swab technique from patients with new wound (grade 1) and long-standing wound (maturation phase). All specimens were taken from patients on dressing table. The specimens were transferred within 1 hour to Bacteriology Department at the National Public Health Laboratory, where optimal microbiological culture techniques were used.

2.4. Bacterial isolation and identification

The specimens were inoculated on blood agar and MacConkey agar plates for the isolation of aerobic bacteria. Inoculated blood agar was put into candle jar with carbon dioxide which was needed to enhance bacterial growth [16], and it was incubated for 18-24 h at 35 °C -37°C. Inoculated mac agar was incubated for 18-24 h at 35 °C - 37°C. Gram stain was done from bacterial colonies. Selected isolates from Mac and blood agar were sub-cultured into nutrient agar and incubated to refresh the sample. Additionally, mannitol salt agar was inoculated and incubated at 37°C for 24 hours. The isolates were identified based on colony morphology, colour change, gram-staining results, Urea and indole motility (SIM), and biochemical reactions for catalase, oxidase, coagulase, and other biochemical tests [17-18-19]. In this study, anaerobic bacteria were not investigated due to the limited laboratory facilities.

2.5. Antibiotic susceptability test

Antibiotic susceptibility test was performed using the Kirby Bauer disk diffusion method according to the guidelines of the Clinical and Laboratory Standards Institute guidelines (CLSI) [20]. The antibiotics tested for Gram-positive bacteria were, Amikacin, Ciprofloxacin, Augmentin, Ceftazideme, Gentamicin, Clindamycin, Ceftriaxone, Meropenem, Erythomycin, Oxacillin, Vancomycin. Cotrimoxazole, For Gram negative bacteria the antibiotic tested were Augmentin, Amikacin, Cotrimoxazole, Ceftazidime, Ceftriaxone, Ciprofloxacin, Imepenem, Meropenem, piperacillin and Gentamicin. Multidrug-resistant organisms (MDROs) were defined as bacteria that were resistant to more than one or all classes of antibiotics [21-22]

2. 8. Data quality control

Aseptic technique was used throughout sampling and handling procedures by using sterile materials, flaming and icebox. For remarkable studies of microorganism, pure culture was used. Solutions and equipment containing water were autoclaved at 121°C for 15 to 20 minutes. The sterility of the media was detected by incubating 5% of the batch at 37°C for 18-24h.

2.9. Statistical methods

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 21 with significance level at 0.05 and CLs 95%, descriptive statistics (mean ±SD) obtained for quantitative variables, while qualitative variables described using frequency and percent difference between frequencies in (table 3) tested by goodness of fit test using chi-square test or Fisher Exact test when needed. The relationships between qualitative variables tested by independence test using chi-square or Fisher Exact test when needed, to obtain the p-value.

2.10. Ethics approval and consent to participate

The ethical approval for this study was obtained from the Ethics Committee of Research Department at the Ministry of Health, Khartoum State, Sudan on 17/8/2017. A written consent was obtained from all participants before their enrolment after explaining the aim of the study. The youngest patient was nineteen years old, so there was no need to obtain informed consent from parent or guardian.

3. RESULTS

A total of 152 diabetic patients were enrolled in this study out of which 135 patients (88.8%) were male and 17 patients (11.2%) were females. The mean age of the patients in the study group was 54.31 with SD ± 12.1years. The mean duration of diabetes was 14 SD ± 8 years. The highest numer of patients 66 (43.7%) were in diabetic duration 12-24 years and 125 (82.2%) were in the age of 40-65 years. The ulcers varied in duration from 1 day to 10 years.

3.1. Microbiological findings:

Bacterial growth was detected in 138 specimens (90.8%) and no growth was seen in 14 specimens (9.2%). Cultures yielded a total of 181 aerobic isolates from different ulcer grades, with a range of 1-3 organisms per sample. In the present work, two types of bacterial infections were detected, monomicrobial 63.82% and poly microbial infections 26.97%. Frequencies of bacteria isolated from the ulcers of the participants are tabulated in Table 1. The number of Gram- negative rods was 120 (66.3 %), higher than Gram-positive 61 (33.7 %), out of 61 Gram- positive bacteria 55 were cocci and 6 were coccobacilli. The most frequent pathogens of all isolates were *Proteus* 35.3%, [*P. mirablis* 26.5%+ *P. vulgaris* 8.8%] followed by *S. aureus* MRSA 14.4% and Coliform 12.2% respectively.The most common isolates in grade 3 ulcers were *P. Mirablis, Staphylococcus* and Coliform where in long standing ulcers they were *P. Mirablis, S. aureus* MRSA and Coagulase negative *staphylococcus*. The most common associated bacteria in polymicrobial infection were *P. Mirablis* with *P. Aerginosa, S. aureos* MRSA and Coliform, respectively. The percentages of Gram negative to Gram-positive bacteria in each ulcer grades are shown in Table 2.

3.2. Antibiotic sensitivity:

The results of antibiotic sensitivity tests revealed the most sensitive antibiotics for Gram negative rods were Aikacin, Imipenem and Meropenum and for Gram positive was Vancomycin. The most resisted antibiotic by Gram negative bacteria was Cotrimoxazole. The best antibiotics for Gram negative isolates were as follow: For Coliform as Augmentin, for *E. coli s,p* as Meropenum, for *K. oxytoca sp*, as Meropenum, for *K. pneumoniae sp* as Amikacin + Ciprofloxacin, for *P. mirables sp* as Meropenum + Amikacin + Imipenem, for *P. vulgaris sp*, as Amikacin + Meropenem and for *P. aeruginosa sp*, as Amikacin + Imepenem. The best antibiotic for Gram positive isolates were as follow: For *Acinobacter sp* as Aikasin, for *S. aureas sp*, as Erythromycin, for *S. aureas* (MRSA) as Vancomycin, for *S. aureas* (VRSA), as Ceftriaxone, for *Saph. Coagulase –ve sp* as Vancomycin. The most sensitive antibiotic among all isolates was Meropenem. The most sensitive antibiotics for each grade are illustrated in table 4. Sensitivity pattern of Gram-negative and gram positive bacteria isolated from diabetic foot ulcers are illustrated in table 2 and 3.

Table 1: Frequency of bacteria isolated from the ulcers of the participants.

		Count	N %	P-value
Gram	G (-ve) rods	120	66.3%	.000
	G (+ve) Cocobacilli	6	3.3%	
	G (+ve)Coci	55	30.4%	
Isolates	Acinobacter	6	3.1%	.000
	Coliforms	22	11.3%	
	E. coli	8	4.1%	
	K. oxytoca	3	1.5%	
	K. pneumonia.	5	2.6%	
	P. mirables	48	24.7%	
	P. vulgaris	16	8.2%	
	P.aeruginosa	19	9.8%	
	S.aureas	8	4.1%	
	S.aureas (MRSA)	26	13.4%	
	S.aureas (VRSA)	4	2.1%	
	Saph. Coagulase –ve	16	8.2%	

Table 2: Sensitivity pattern of Gram-negative bacteria isolated from diabetic foot ulcer infection (resistant: sensitive (resistant %: sensitive %).

	Coliform	E. coli	K. oxytoca	K. pneumonia	P. mirables	P. vulgaris	P. aeruginosa	Total
A1	19: 1 (95%:5%)	8: 0 (100%: 0%)	2: 1 (66.3%:33.7%)	5: 0 (100%: 0%)	33: 7 (82.5%:17.5%)	13: 2 (86.7%:13.3%)	4: 0 (100%:0%)	95
A2	7: 8 (46.7%: 53.3%)	2: 2 (50%: 50%)	0: 1 (0%: 100%)	1: 2 (33.3%: 66.7%)	1: 30 (3.2%: 96.8%)	1: 7 (12.5%:87.5%)	2: 8 (20%:80%)	72
C1	7: 4 (63.6%: 36.4%)	3: 0 (100%: 0%)	2: 1 (66.7%: 33.3%)	2: 1 (66.7%: 33.3%)	30: 6 (83.3%: 16.7%)	12: 1 (92.3%: 7.7%)	1: 0 (100%:0%)	67
C2	14: 1 (93.3%: 6.7%)	2: 2 (50%: 50%)	2: 1 (66.7%: 33.3%)	3: 1 (75%: 25%)	21: 8 (72.4%: 27.6%)	7: 1 (87.5%: 12.5%)	9: 6 (60%: 40%)	78
C3	16: 2 (88.9%: 11.1%)	5: 3 (62.5%:37.5%)	1: 1 (50%: 50%)	3: 1 (75%: 25%)	23: 13 (63.9%: 36.1%)	12: 1 (92.3%: 7.7%)	12: 3 (80%: 20%)	96
C4	18: 4 (81.8%: 18.2%)	5: 3 (62.5%:37.5%)	2: 1 (66.7%: 33.3%)	2: 3 (40%: 60%)	32: 14 (69.6%: 30.4%)	12: 2 (85.7%: 14.3%)	11: 8 (57.9%:42.1%)	117
G	19: 3 (86.4%: 13.6%)	4: 3 (57.1%:42.9%)	1: 2 (33.3%: 66.7%)	3: 2 (60%:40%)	30: 17 (63.8%: 36.2%)	10: 4 (71.4%: 28.6%)	9: 10 (47.4%: 52.6%)	117
M	9: 9 (50%:50%)	0: 5 (0%: 100%)	0: 2 (0%: 100%)	2: 1 (66.7%:33.3%)	1: 33 (2.9%: 97.1%)	4: 9 (30.8%: 69.2%)	4: 8 (33.3%:66.7%)	87
P	2: 0 (100%:0%)	0: 0 (0%: 0%)	0: 0 (0%: 0%)	0: 0 (0%: 0%)	0: 0 (0%: 0%)	0: 1 (0%: 100%)	9: 5 (64.3%:35.7%)	17
I	5: 1 (83.3%:16.7%)	0: 2 (0%: 100%)	0: 0 (0%: 0%)	0: 1 (0%: 100%)	0: 7 (0%: 100%)	0: 3 (0%: 100%)	0: 3 (0%: 100%)	22

Table 3: Sensitivity pattern of Gram- positive bacteria isolated from diabetic foot ulcer infection (resistant: sensitive (resistant%: sensitive%)).

	Acinobacter	**S. aureas**	**S. aureas (MRSA)**	**S. aureas (VRSA)**	**Saph. Coagulase –ve**	**Total**
Augmentin	5: 1 (83.3%: 16.7%)	2: 4 (33.3%: 66.7%)	15: 4 (78.9%: 21.1%)	2: 1 (66.7: 33.3%)	8: 3 (72.7%: 27.3%)	45
Amikacin	2: 2 (50%: 50%)	0: 2 (0%: 100%)	4: 4 (50%: 50%)	0: 0 (0%: 0%)	2: 2 (50%: 50%)	18
C1 Cotrimoxazole	5: 1 (83.3%: 16.7%)	1: 4 (20%: 80%)	8: 6 (57.1%: 42.9%)	0: 1 (0%: 100%)	4: 2 (66.7%: 33.3%)	32
C2 Ceftazidime	3: 0 (100%: 0%)	0: 4 (0%: 100%)	7: 0 (100%: 0%)	0: 0 (0%: 0%)	3: 0 (100%: 0%)	13
C3 Ceftriaxone	5: 1 (83.3%: 16.7%)	1: 4 (20%: 80%)	14: 4 (77.8%: 22.2%)	0: 2 (0%: 100%)	6: 2 (75%: 25%)	39
C4 Ciprofloxacin	5: 0 (100%:0%)	1: 5 (16.7%: 83.3%)	14: 7 (66.7%: 33.3%)	2: 1 (66.7%: 33.3%)	12: 2 (85.7%: 14.3%)	49
E Erythomycin	0: 0 (0%: 0%)	1: 6 (14.3%: 85.7%)	16: 8 (66.7%: 33.3%)	2: 1 (66.7%: 33.3%)	14: 2 (87.5%: 12.5%)	50
G Gentamicin	5: 1 (83.3%: 16.7%)	1: 7 (12.5%: 87.5%)	13: 8 (61.9%: 38.1%)	2: 1 (66.7%: 33.3%)	7: 7 (50%: 50%)	52
M Merpenem	4: 2 (66.7%: 33.3%)	1: 3 (25%: 75%)	7: 7 (50%: 50%)	0: 1 (0%: 100%)	3: 4 (42.9%: 57.1%)	32
O Oxacillin	0: 0 (0%: 0%)	1: 7 (12.5%: 87.5%)	23: 0 (100%: 0%)	3: 0 (100%: 0%)	2: 0 (100%: 0%)	36
V Vancomycin	0: 0 (0%: 0%)	1: 5 (16.7%: 83.3%)	4: 16 (20%: 80%)	3: 0 (100%: 0%)	5: 9 (35.7%: 64.3%)	43
CL Clindamycin	0: 0 (0%: 0%)	1: 5 (16.7%: 83.3%)	7: 4 (63.6%: 36.4%)	2: 1 (66.7%: 33.3%)	11: 0 (100%: 0%)	31

Table 4: Aerobic bacteria and the most sensitive antibiotic for each wound grade.

Wound grade	No of patients	Typical pathogenes	The most sensitive antibiotic for each grade
Zero		Normal skin flora	-
One	8	The percent of Gram-negative to Gram positive 2:1 the most common speicies were *E.coli* and *staph.coagulase –ve.*	Meropenem Vancomycin
Two	19	The percent of Gram-negative to Gram positive 1:1 the most common speicies were *Staphylococcus* and different spp. of Gram negative.	Vancomycin Amikacin
Three	70	The percent of Gram-negative to Gram positive 5:1 the most common speicies were *P. Mirablis, Staphylococcus* and Coliform.	Meropenem Amikacin vancomycin Ceftriaxone
Four	12	No Gram-positive bacteria isolated in this grade, the most common Gram negative were *P. aeruginosa* and *P. Mirablis.*	Amikacin Meropenum Imepenum
Long standing ulcers (maturation phase)	43	The percent of Gram-negative to Gram positive 4:3 the most common speicies were *Proteus, s. sureus* MRSA, *Co agulase negative Staph.* And *P. aeruginosa.*	Amikacin Meropenum Vancomycin

4. DISCUSSION

Foot ulcers are a significant complication of diabetes mellitus and often lead to lower-extremity amputation [23]. Over 20% of the diabetes patients hospitalized are due to diabetic foot ulcers. Effective management of the infection requires isolation and identification of the bacteria and determining their sensitivity to antimicrobial agents [24]. Mistreatment of diabetic foot ulcers can be caused by factors including the use of antibiotics without sensitivity test or incorrect duration of treatment [25]. Diabetes and diabetic foot infections are on the rise worldwide with little data available to guide doctors to achieve effective cure. This study aimed to isolate and identify aerobic bacterial pathogens associated with diabetic foot infections in different grades of wounds and to determine their sensitivity to the commonly used antibiotics. We found that the ulcers varied in duration from 1 day to 10 years which was a long duration range in comparison to a previous study done in the same center [26]. Two patterns of bacterial infections were detected in the present work; monomicrobial infection 63.82% and polymicrobial infections 26.97% with aerobic Gram-negative, especially *proteus* spp as the most common causative agents. In chronic ulcers, especially which have recently been treated with antibiotics, infections are mainly polymicrobial.[27]. The presence of polymicrobial patterns in these ulcers results in the production of virulent factors such as: hemolysin, proteases, and collagenases and these factors cause inflammation, delayed wound healing, and, ultimately, severe chronic ulcers [28]. Those two report was consistent with our results in which ulcers with polymicrobial were delayed healing and severely inflamed. The average numbers of isolates were 1.2 per case which is similar to a study done by . Eithar, et al., (2015) in the same Centre [29]. Charles et al., (2001) reported variation of the bacterial pathogens encountered with the Wagner grades, Low grades are generally infected with gram-positive and these findings were highly consistent with the present work, in which Gram-positive bacteria found in grades 1, 2 and decreased in grade 3 where the ratio of Gram-negative to Gram-positive was 5:1 then it disappeared towards grade 4 and reappeared in long standing ulcers which were in maturation phase [7]. Our study also evaluated the sensitivity of different pathogens to commonly used antibiotics. Meropenem was highly sensitive to *Proteus mirabilis* and this was consistent to Trivedi et al., (2016) who reported that Meropenem inhibited 90% of isolates of Proteus mirabilis [30]. *Staphylococcus aureus* reported a good therapeutic response to all drugs tested against it and the highest resistance was towards Augmentin, this result was consistent with study done by Demetriou (2017) who reported that Clavulanate was one of highly resisted drug by *Staphylococcus aureus* [31]. The most sensitive antibiotics for Gram-negative in our study were Aikacin, Imipenem, Meropenum and this was agreed by Al Benwan et al., (2017) who reported the highest Gram-negative responses were to Piperacillin, Tazobactam, Amikacin, and Imipenem [32]. Also study done by Sekhar et al., (2014) reported the highest therapeutic response of Gram-negative strains was observed towards Amikacin and Meropenem and *Staphylococcus aureus* was 100% resistant to Ciprofloxacin [33] and this was disagree with our results which reported 83.3% sensitivity of *Staphylococcus aureus* to ciprofloxacin. Other studies have shown to some extent the sensitivity of this common strain to Ciprofloxacin [34]. In the present work, the most sensitive antibiotic for both Gram -negative and Gram-positive was Meropenem and this also reported by Perim et al., (2015) [35]. In this study 80% of *Staphylococcus* MRSA responded to Vancomycin and it was also stated by Perim et al., (2015) [35] that

Staphylococcus MRSA responded well to Vancomycin [37]. Further prospective studies are required to evaluate the clinical features along with the response to antibiotic treatment in diabetic foot infection patients.

5. CONCLUSION

Gram-negative bacteria were more prevalent, and the most common bacteria isolated in this study was Proteus spp. For Gram positive was *methicillin-resistant Staphylococcus aureus* (MRSA). The most sensitive antibiotics for *Proteus* were Meropenem, Amikacin and Imepenum respectively. The most sensitive antibiotic for both Gram positive and Gram negative pathogens was meropenem. Further studies for isolation of organisms from infected diabetic foot ulcers in different epidemiological circumstances is essential to understand the variation of isolates and antibiotic sensitivity in different studies.

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