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ANTIMICROBIAL DRUG SUSCEPTIBILITY OF S. EPIDERMIDIS IN INFECTIVE ENDOCARDITIS

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Abstract

Background: Staphylococcus epidermidis strains are considered to be one of the major causes of bacterial infective endocarditis. The present investigation was done to study the demographic prevalence and pattern of antibiotic resistance of S. epidermidis strains isolated from bacterial infective endocarditis patient blood.

Methods: Among admitted patients from 2022-2024 of Public hospitals, a cross-sectional investigation was done. The strains were cultured on various selective media and identified by biochemical tests and subjected to PCR. Antibiotic susceptibility of the isolates was done by Kirby-Bauer disk diffusion method as per guidelines of CLSI.

Results:

Out of 606 bacterial infective endocarditis patients were screened, 9% (54/606) were found positive for S. epidermidis in which 6.4% (39/606) were males and 2.4% (15/606) were female patients. However, 61-70 years old age group was highly affected with (5%). Baloch ethnic group was predominantly affected with (4.6%). Lower socioeconomic class was extremely affected with (5.2%). The main risk factor was dental procedures (3%) and intravascular catheters implantation (3%). S. epidermidis was highly resistant against Erythromycin (96%) and Amoxicillin (94%) while, susceptible against Meropenem (94%). PCR amplification was performed on positive isolates of S. epidermidis harbour 16Sr RNA gene of 478bps.

Conclusion: This study concluded that S. epidermidis emerged as a primary causative agent of bloodstream infections. Emerging antibiotic resistance emphasize the importance of ongoing surveillance and the development of novel therapeutic strategies. Early identification of resistance profiles through laboratory testing and adherence to evidence-based treatment protocols are essential for improving outcomes in infective endocarditis patients.

Keywords: Antibiotics, Infective, Endocarditis, PCR, Staphylococcus, Epidermidis.

Introduction

Staphylococcus epidermidis is a catalase-positive, coagulase-negative gram-positive coccus, the most common commensal organism in the human skin flora. Prosthetic devices such as heart valves, joints, indwelling catheters, and immune compromise are risk factors for S. epidermidis infection (1). Coagulase-negative staphylococci are a varied group of organisms that can cause bloodstream infection (BSI) and other types of infections. The source of CoNS BSI is commonly but not always associated with infection of an indwelling medical device. With an increasing number of prosthetic devices being implanted and an aging population globally, the role of CoNS needs re-evaluation, and an appreciation of CoNS species identification in infective endocarditis (IE) is warranted. Recent advances in microbiologic screening have identified new species and dissected apart the larger group of CoNS and allowed for new insights about species and subtypes that wasn't previously feasible such as recognizing the role of different species of CoNS in causing both native tissue and prosthesis-related infections (2).

Infective endocarditis (IE) is a disease that affects multiple systems and results from infection, usually bacterial, of the endocardial surface of the heart. It has been recognized as a pathological entity for hundreds of years and as an infectious process since the nineteenth century (3).IE is a relatively rare but life-threatening disease. In a systematic review of the global burden of IE, crude incidence ranged from 1.5 to 11.6 cases per 100,000 person-years, with high-quality data available from only ten mostly high-income countries (4). Untreated, mortality from IE is uniform. Even with the best-available therapy, contemporary mortality rates from IE are approximately 25% (5).

Almost any type of structural heart disease can predispose to IE. Rheumatic heart disease was the most frequent underlying lesion in the past, and the mitral valve was the most commonly involved site (6). In developed countries, the proportion of causes related to rheumatic heart disease has declined to ≤5% in the past two decades. However, in developing countries, rheumatic heart disease remains the most common predisposing cardiac condition for IE (7).

Prosthetic valves and cardiac devices (such as permanent pacemakers and cardioverter defibrillators) are significant risk factors for IE. Rates of implantation of these devices have increased dramatically in the past several decades. Consequently, prosthetic valves and cardiac devices are involved in a growing proportion of IE cases (8). For example, in a recent cohort of 2,781 adults in 25 countries with definite IE, one-fifth had a prosthetic valve and 7% had a cardiac device (5).

S. epidermidis results in approximately 13% of prosthetic valve endocarditis infections, with a high rate of intracardiac abscess formation (38%) and mortality (24%) (9). S. epidermidis strains usually resist against several types of antibiotic classes such as Tetracyclines, Aminoglycosides, Cephalosporins, Fluoroquinolones, Penicillins, and Macrolides (10). Nowadays, resistant S. epidermidis has become a serious problem in hospitals. Resistant staphylococcal strains are responsible for about 100,000 cases of infections with around 10% mortality rate each year in the USA (11). The presence of certain antibiotic resistance genes is responsible for the occurrence of antibiotic resistance MecA, aacA-D, tetK and tetM, ermA and ermC, msrA and msrB, linA and vatA, and vatB and vatC antibiotic resistance genes are responsible for the occurrence of resistance against methicillin, aminoglycosides, tetracyclines, macrolide-lincosamide-streptogramin B, macrolides, lincosamides, and streptogramin A groups of antibiotics, respectively (12). The aim of this study was to check the prevalence of infective endocarditis caused by Staphylococcus epidermidis in patients of Balochistan and to check the antibiotic resistivity of S. epidermidis in the region.

Materials and Methods

Samples Collection

From June 2022 to March 2024, a total of 606 samples were collected from the patients who were suspected of having Bacterial Infective Endocarditis (BIE) to the Sandmen Provisional Hospital

(SPH) and Bolan Medical Complex Hospital (BMCH) Quetta. From each patient one blood sample (~1–5mL) were taken into the sterile CBC tubes. This research was carried out in compliance with the Helsinki declaration, under approval from the University (CAS/ 45/15-20), and with permission from the hospital's ethical committee (E.C 18–12/2022).Inclusion criteria for bacterial infective endocarditis (BIE) were (a) identification of a specific bacterial agent (from blood) in culture media, clinical history, and inflammation of the endocardium (b) acute BIE clinical signs and symptoms include fever, headache, malaise, dyspnea, anorexia, weight loss, back pain, general weakness, fatigue. The exclusion criteria were as follows (a) cardiac patients who had no specific reason of death (b) patients who got antibiotic treatment within 24 hours as admitted to health centre. The demographic data of the patients such as age, gender, socioeconomic status and ethnic group were recorded. The collected blood samples were identified through gram staining, biochemical tests, antibiotic susceptibility tests and PCR.

Isolation and Identification

The blood samples were inoculated with brain heart infusion (BHI) liquid medium and incubated at 37ºC for 24 hours. The overnight bacterial culture was streaked into specific medium Mannitol salt agar (MSA) for the isolation of Staphylococcus epidermidis, and incubated at 37ºC for 48 hours. After this incubation period, gram staining, biochemical tests, antibiotic susceptibility test and PCR identification were among the common methods used to investigate and identify bacterial colonies.

Antibiotic Susceptibility

Antibiotic susceptibility testing was performed on S. epidermidis isolates. A 0.5 MacFarland standard bacterial culture was prepared and spread on Mueller-Hinton agar plates (Oxoid, United Kingdom) and antibiotic discs were placed at equal distances. Then the plates were incubated at 37ºC for 24 hours. The zones of inhibition were measured and interpreted, according to Clinical and Laboratory Standards Institute (CLSI) guidelines. Susceptibility of S. epidermidis isolates was tested against various antibiotics including Amoxicillin 25µg, Amikacin 25µg, Ciprofloxacin 30µg, Ceftriaxone 30µg, Ceftazidime 5µg, Erythromycin 15µ, Gentamycin 10µg, Levofloxacin 5µg, Meropenem 10µg, Tetracycline 30µg, Rifampicin 5µg, Vancomycin 30µg. S. epidermidis ATCC 12228 was used as a quality control organism in antimicrobial susceptibility determination.

Molecular Identification of S. epidermidis

Molecular identification of isolates was performed by PCR amplification of the S. epidermidis 16Sr ribonucleic acid (RNA) gene. The incubated bacterial culture was used for the DNA extraction using a DNA purification kit (Gene All ®Biotechnology Seoul, South Korea). After DNA extraction, the DNA templates were stored at -20ºC for future use. Primer sequences used for 16SrRNA gene amplification were (91E-F 5'-GGA ATT CAA A(T/G) G AAT TGA CGG GGG C-3') 13E-R -3'-CGG GAT CCC AGG CCC GGG AAC GTA TTC AC-5' (13). PCR reaction mixtures had a total volume of 25µl, containing 11µl of PCR master mix (amaR PCR Gene Direx SIMPLYTM Seoul, South Korea), 10µl of PCR water, 1µl of forward primer, 1µl of reverse primer and 2µl of DNA. PCR thermal cycling included initial denaturation at 94ºC for 2 minutes, denaturation at 94ºC for 1 minute, annealing at 55°C for 1 minute, extension at 72ºC for 2 minute and final extension at 72ºC for 5minute set for 30 cycles. The final PCR products were examined by gel electrophoresis using an ultraviolet (UV) light transilluminator for visualization.

Statistical analysis

Statistical analysis was done using the SPSS 22.0 statistical software (SPSS Inc., Chicago, IL, USA). Chi-square test and Fisher's exact two-tailed test were used to assess any significant relationship between the prevalence of S. epidermidis strains, and their antibiotic resistance properties. P value < 0.05 was considered as statistical significant level.

Results

In this study, 606 bacterial infective endocarditis patients were screened, 9% (54/606) were found positive for S. epidermidis while 91% (552/606) were found negative. Most of the positive cases from Bolan Medical Complex Hospital were 6% (36/606) and 3% (18/606) were from Sandmen Provisional Hospital. Among these positive samples 6.4% (39/606) were male patients and 2.4% (15/606) were female patients. The age wise distribution showed that 61-70-year-old patients were highly infected (5%) followed by 51-60-year-old patients (2.6%),41-30-year-old patients (0.6%), >70-year-old patients (0.4%). The Baloch ethnic group was predominantly, affected (4.6%) as compared to other groups. The socioeconomic data described that lower class was extremely affected (5.2%) as followed by middle class (2%) and higher class was least infected (1%). Consequently, the dental procedure was major risk factor of bacterial infective endocarditis (3%) as shown in Table 1.

Table 1. Demographic study of Bacterial Infective Endocarditis patients.

Possible risk factors	Positive n(%)	Negative n(%)	Total n(%)	p-value
Hospital				
BMCH	36 (6%)	373 (61.5%)	409 (67%)	0.001*
SPH	18 (3%)	179 (30%)	197 (32%)	
Gender				
Male	39 (6.4%)	414 (68%)	453 (75%)	0.001*
Female	15 (2.4%)	138 (23%)	153 (25%)	
Age				
30-40	0 (0%)	12 (1.9%)	12 (1.9%)	0.001*
41-50	4 (0.6%)	25 (4%)	29 (4.7%)	
51-60	16 (2.6%)	29 (4.7%)	45 (7.4%)	
61-70	31 (5%)	39 (6.4%)	70 (11%)	
>70	3 (0.4%)	86 (14%)	89 (14.6%)	
Ethnic Groups				
Pashtoon	14 (2.3 %)	263 (43 %)	277 (46 %)	0.003*
Baloch	28 (4.6 %)	251 (41 %)	279 (46 %)	
Panjabi	8 (1.3 %)	29 (4.7%)	37 (6%)	
Hazara	1 (0.1 %)	4 (0.6 %)	5 (0.8 %)	
Afghan refugees	3 (0.4 %)	5 (0.8 %)	8 (1.3 %)	
Socio-economic status				
<25k PKR per month	32 (5 %)	327 (54 %)	359 (59 %)	0.002*
26k–45k PKR per month	13 (2 %)	160 (26%)	173 (28 %)	
>45k PKR per month	9 (1%)	65 (11 %)	74 (12 %)	
Risks				
Dental procedures	20 (3 %)	190 (31 %)	210 (35 %)	0.003*
Intravascular catheter	29 (4 %)	191 (31 %)	220 (36 %)	0.009
Wounds/Injuries	5 (0.8 %)	58 (9 %)	63 (10 %)	0.002*

Note: *p-value significance, BMCH (Bolan Medical College and Hospital, SPH (Sandmen ProvisionalHospital), <lessthan, >greaterthan.

S. epidermidis is gram positive, coagulase negative, catalase positive and motile cocci. In the sugar fermentation test S. epidermidis is lactose, glucose and sucrose fermenter while trehalose non fermenter as shown in Table 2.

Table 2. Biochemical Characterization of Staphylococcus epidermidis.

S.No	Morphological Test	Results
1	Microscopy	Cocci
2	Gram staining	Positive
	Biochemical Tests	
3	Coagulase test	Negative
4	Indol test	Negative
5	Methyl red test	Negative
6	Voges-proskauar test	Positive
7	Simmon citrate test	Negative
8	Catalase test	Positive
9	Oxidase test	Negative
10	Urease test	Positive
	Sugar Fermentation Tests	
11	Sucrose test	Positive
12	Glucose test	Positive
13	Trehalose test	Negative
14	Lactose	Positive

The PCR amplification was performed on the positive 9% (54/606) isolates of the S. epidermidis. The results showed that all isolates harbour 16S rRNA gene of 478bp as shown in Figure 1.

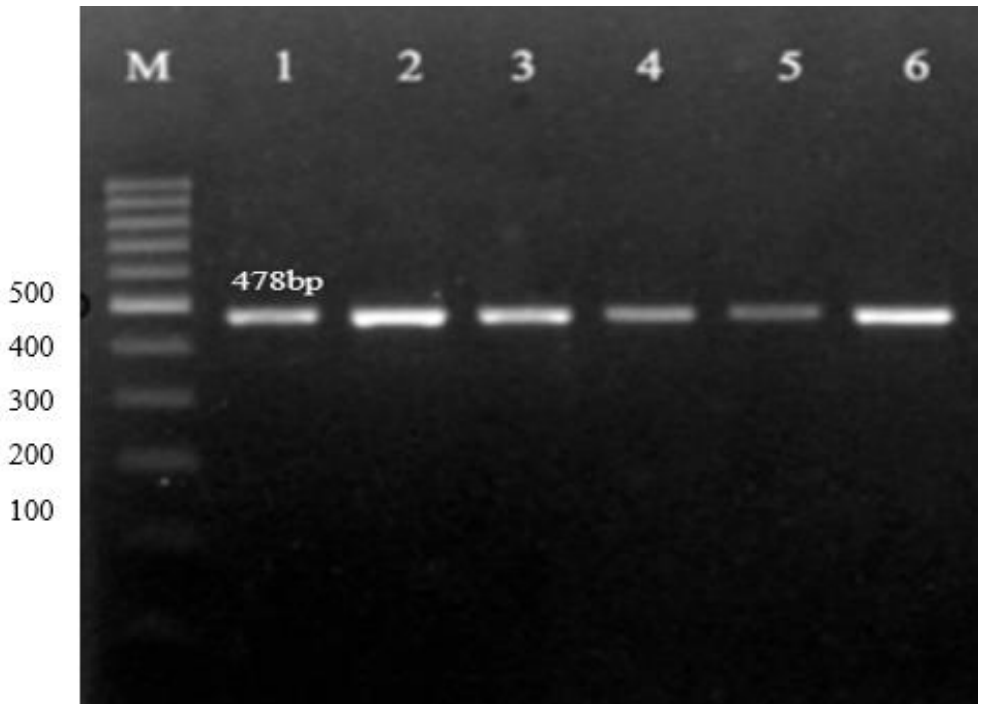

Figure 1. 16S rRNA gene PCR-based identification S. epidermidis from blood of bacterial endocarditis.

Furthermore, the frequently observed clinical features in patients during the course of hospitalization were fever 96% (52/54), followed by headache 91% (49/54), weakness 76% (41/54), and heart murmur 81%(44/54) mentioned in Figure 2.

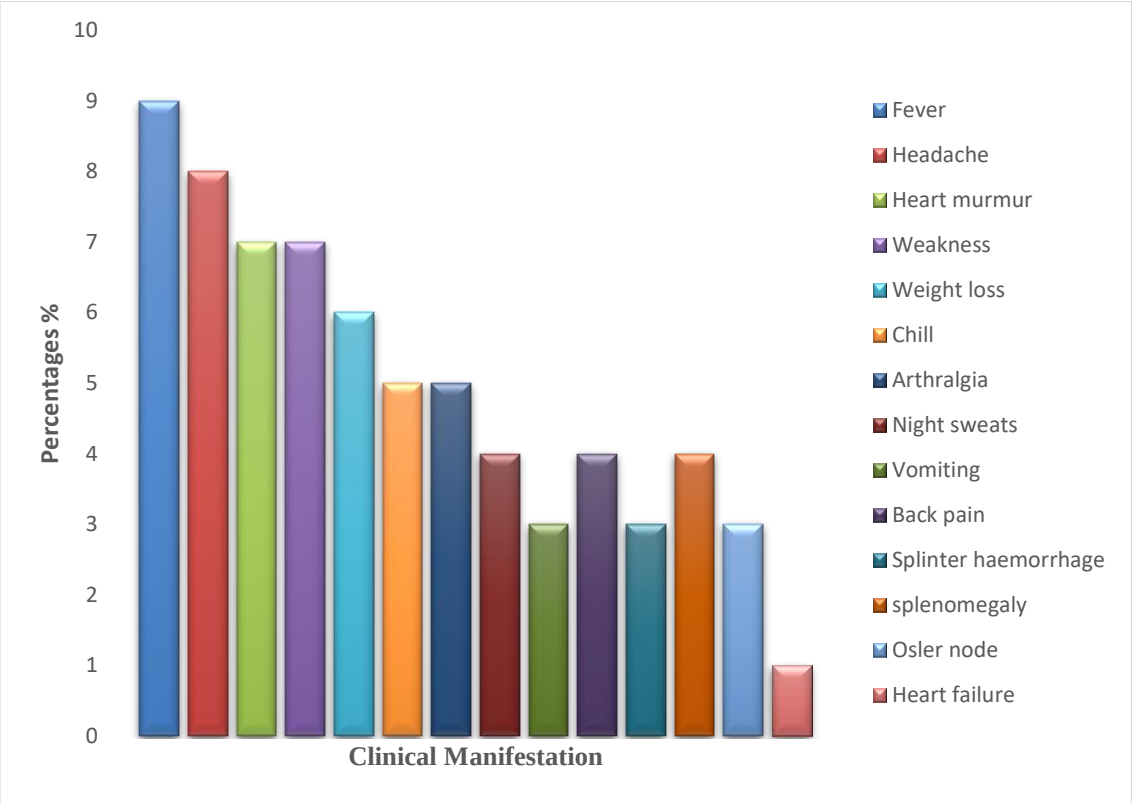

Figure 2. Clinical manifestation of patients suffering from Bacterial Infective Endocarditis.

Table 3 represents the antibiotic resistance pattern of the S. epidermidis strains isolated from infective endocarditis blood samples. S. epidermidis strains embraced the highest prevalence of resistance against Erythromycin (96%), Amoxicillin (94%) antibiotic agents. Reversely, S. epidermidis strains harboured the lowest prevalence of resistance against Meropenem (6%) and Vancomycin (12%) antibiotic agents. The prevalence of resistance against Ciprofloxacin and Rifampicin antibiotic agents were 72%, and 74%, respectively. However, the highest prevalence of susceptibility against Meropenem (94%), Vancomycin (88%) and Ceftazidime (82%).

Table 3. The Antimicrobial Susceptibility Test against S. epidermidis.

Antibiotics	**Abr**	**Conc (µg)**	**S. epidermidis**	
			R	**S**
Amoxicillin	AML	25	47/50 (94%)	3/50 (6%)
Amikacin	AK	25	14/50 (28%)	36/50 (72%)
Ciprofloxacin	CIP	30	36/50 (72%)	14/50 (28%)
Ceftriaxone	CRO	30	10/50 (20%)	40/50 (80%)
Ceftazidime	CAZ	5	9/50 (18%)	41/50 (82%)
Erythromycin	E	15	48/50 (96%)	2/50 (4%)

Gentamycin	GEN	10	13/50 (26%)	37/50 (74%)
Levofloxacin	LEV	5	11/50 (22%)	39/50 (78%)
Meropenem	MEM	10	3/50 (6%)	47/50 (94%)
Tetracycline	OT	30	12/50 (24%)	38/50 (76%)
Rifampicin	RD	5	37/50 (74%)	13/50 (26%)
Vancomycin	VA	30	6/50 (12%)	44/50 (88%)

Note: R (Resistance), S (Susceptible), µg (Microgram).

Discussion

A frequent commensal bacterium of human skin and mucosa is S. epidermidis. Although S. epidermidis was once thought to be nonpathogenic, it is now understood to be a significant opportunistic pathogen. Hospital samples commonly contain S. epidermidis and S. haemolyticus (14,15). However, one of the study in northern India also state that S. haemolyticus (47.8%) as the most common isolate followed by S. epidermidis (33.4%) (16).

To the best of our knowledge endocarditis cause by S. epidermidis in Balochistan is analysed for the first time, it needs to be analysed because bacterial endocarditis significantly increasing gradually. when our data were analysed using Chi-square test and Fisher's exact two-tailed test there were striking and statistically significant gender differences observed. Males are more likely than females to develop IE due various reasons such as biological and social variables contribute to this disparity the biochemical aspects, Hormonal differences, by boosting immune responses, estrogen in females has some protective effects. On the other hand, it has been demonstrated that testosterone in men suppresses some immune system functions, making them more vulnerable to infections like IE. Behavioral and lifestyle Factors Intravenous drug use and exposure to specific environmental hazards are among the behaviors linked to an increased risk of IE that are more common in men. This is a major factor in the increased incidence of IE in men (17).

Older persons, especially those over 60, are more likely to develop bacterial infective endocarditis (IE). The aging of the world's population and rising survival rates for those with heart disease risk factors have been contributing factors to this trend. The following are the main causes of the increased prevalence in this age group; Increased Comorbidities: Cancer, diabetes, and cardiovascular illnesses are among the underlying medical disorders that older persons are more likely to have. These comorbidities worsen the clinical course of IE in addition to making people more susceptible to infections. Risk factors related to healthcare: Medical procedures, such as pacemaker insertions, prosthetic valve replacements, or repeated hospital stays, are commonly necessary for older adults. As a result, they are more susceptible to infections like Staphylococcus aureus, which is a major cause of IE (17). However, it's also revealed by literature that Rheumatic heart disease, which was historically a major cause of IE, has become less common in wealthier areas, but healthcare-associated IE in elderly persons has become more common. This change is ascribed to improvements in healthcare that increase longevity, frequently through the use of implanted cardiac devices (18).

In this study, we investigated the antimicrobial activities of Twelve antibiotics against S. epidermidis isolated from blood sample of BIE. A great number of these S. epidermidis isolates were susceptible to Meropenum (94%) and, in addition, a majority (88%) was susceptible to Vancomycin despite displaying reduced susceptibility or resistance to Erythromycin (96%) and Amoxicillin (94%). This

might indicate that additional option for the treatment of multidrug resistant S. epidermidis, however, in vivo studies are still lacking.
All S. epidermidis strains had resistance against at least three different types of antibiotics. Unauthorized and illegal prescription of antibiotics is the main reason for the high prevalence of antibiotic resistance (19).

The prevalence of antibiotic resistance of the S. epidermidis strains against Amoxicillin-Clavulanic Acid, Ciprofloxacin, Clindamycin, Erythromycin, Gentamicin, Levofloxacin, Mupirocin, Oxacillin, Rifampin, Tetracycline, and Trimethoprim-Sulfamethoxazole antibiotics was 100%, 100%, 37%, 0%, 33%, 16%, 0%, 80%, 0%, 80%, and 0%, respectively (20). However, literature reported that the prevalence of antibiotic resistance of the coagulase-negative staphylococci strains against Penicillin, Oxacillin, Erythromycin, Tetracycline, Clindamycin, Ciprofloxacin, Trimethoprimsulfamethoxazole, Chloramphenicol, Ceftizoxime, Gentamicin, Rifampin, Teicoplanin, and Vancomycin antibiotics were 94.20%, 79.10%, 89.50%, 59.50%, 53.70%, 52.80%, 58.50%, 39.10%, 26.70%, 29.50%, 18.40%, 2.30, and 0%, respectively (21). High prevalence of multidrug-resistant S. epidermidis was also reported in their investigation. Similar patterns of antibiotic resistance of the S. epidermidis strains were reported from Mexico (22), Spain (23), Iran (24), USA (25), Belgium (26), and Ireland (27).

Conclusions

This study concluded that S. epidermidis emerged as a primary causative agent of bloodstream infections. Staphylococcus epidermidis has emerged as a significant causative agent of BIE, affecting patients across various age groups. Males were found to be more susceptible than females, with individuals in extreme age ranges (61–90 years) facing higher risks due to weakened immunity. The condition was associated with a notable case fatality rate. Increasing antibiotic resistance among pathogens poses a major challenge to effective treatment, emphasizing the need for judicious antibiotic use. Emerging antibiotic resistance emphasize the importance of ongoing surveillance and the development of novel therapeutic strategies. Early identification of resistance profiles through laboratory testing and adherence to evidence-based treatment protocols are essential for improving outcomes in infective endocarditis patients.

Authors Contributions: SK and MK-T conceived the initial idea. All authors participated in conceptualizing and designing the study. SK, MK-T, FA-B, JA-K, LR-S, NR, AH formulated the statistical analyses, managed the datasets, and performed data analysis. SK, ZK and carried out bioinformatics analysis. SK, RA and SA drafted.

Funding: The project was not founded.

Institutional Review Board Statement: The research protocol received approval from the institutional research ethics committee of hospitals and institutions. This study was carried out in accordance with the Helsinki Declaration, as well as with permission from the University (CAS/45/15-20) and the hospital ethical committee (E.C 18-12/2017).

Informed Consent Statement: Written consent was obtained from patients and their parents/guardians to publish this paper. Verbal consent was obtained from illiterate participants.

Data Availability Statement: The data can be acquired from the corresponding author upon submitting an equitable request.

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Conflicts of Interest: All authors have concurred that they harbour no conflicting interests concerning this work.

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