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ORIGINAL ARTICLE

Prevalence of ESKAPE pathogens and Antibiotic Susceptibility Status in Skin and Soft Tissue Infections from a tertiary care teaching hospital in South India

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Abstract

Background: ESKAPE "(*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* sp.)" pathogens are commonly found in infections affecting the skin and underlying tissues. ESKAPE pathogens often exhibit widespread multidrug resistance in hospitals, contributing significantly to Hospital-acquired infections. ESKAPE pathogen prevalence can combat the vast challenge of Antibiotic Resistance (ABR). **Materials and Methods:** "The microbiological statistics of ESKAPE infections and sensitivity between January 2020 and October 2022 were extracted from the laboratory records and analysed for the bacterial profile and antibiotic sensitivity pattern". **Results:** Out of the 2037 pathogens isolated from Skin and soft tissue infection, 1308 were ESKAPE pathogens accounting for a prevalence of 64.2%. *Staphylococcus aureus* (n=340/1308; 25.99%) was the predominant pathogen followed by *Pseudomonas aeruginosa* (n=332/1308; 25.38%). Among Gram-negative isolates, 29.43% exhibited multidrug resistance (MDR). Carbapenemase was found to be a frequent mechanism of resistance, highest among *Acinetobacter* species (n=99; 64.7%), followed by *Klebsiella pneumoniae* (n=109; 37.07%). Amp C production was seen most commonly in *Enterobacter* species (n=93; 61.2%), followed by *Klebsiella pneumoniae* (n=172; 58.5%) whereas ESBL production was seen in *Enterobacter* species (n=46; 30.03%). **Conclusion:** ESKAPE pathogens are critical etiologic agents of Skin and soft infections. Regular studies are vital for evaluating bacterial susceptibility and highlighting the importance of policies to reduce hospital infections and enhance antibiotic prescription oversight. Understanding virulence and resistance markers is critical for tailoring treatment strategies based on local antibiograms and managing related infections.

Keywords: ESKAPE, MDR, Antimicrobial resistance, soft tissue infections, Ulcer

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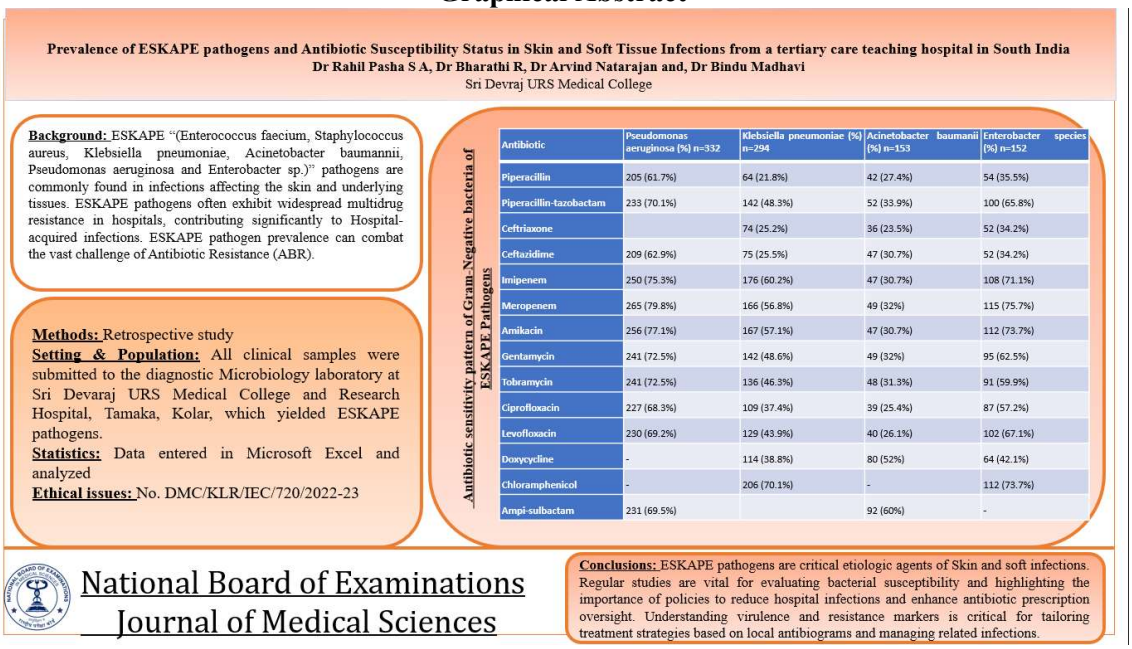
Graphical Abstract



Introduction

Skin and soft tissue infections (SSTIs) affect the skin, subcutaneous tissues, and associated structures [1]. SSTIs include a wide variety of infections, ranging from localized and superficial to deep and invasive infections, including "impetigo or ecthyma, to severe, life-threatening infections, such as necrotising fasciitis" [2,3].

ESKAPE pathogens are among the most prevalent bacteria causing skin and soft tissue infections [4]. ESKAPE pathogens are linked to higher mortality rates and financial expenses [5]. ESKAPE pathogens employ various mechanisms, such as "changing the target (by altering topoisomerase enzymes or ribosomal subunits), reducing drug absorption (by altering outer membrane (OM) proteins), forming biofilms or a protective exo-polysaccharide matrix, producing degrading enzymes (by producing beta(β)-lactamases), overexpressing efflux pumps, or adopting alternative metabolic pathways (by adapting folic acid metabolism) for its pathogenesis and virulence" [6].

Inappropriate antibiotic usage results in increasing antibiotic resistance among the ESKAPE pathogens. The multidrug-resistant ESKAPE pathogens result in delayed healing, increasing mortality rates [7]. Resistance mechanisms have been developed by ESKAPE pathogens against a variety of antibiotics, including "Carbapenems, Glycopeptides, Macrolides, Fluoroquinolones, Tetracyclines, β-lactams, and combinations of β-lactam and β-lactamase inhibitors" [8]. The rise in antimicrobial resistance has reduced skin and soft tissue infection treatment options.

In the current scenario, monitoring resistance patterns among ESKAPE pathogens worldwide is the need of the hour. The local data regarding the antimicrobial susceptibility pattern is limited.

The purpose of the study is to determine the frequency of skin and soft

tissue infections among the Kolar population, as well as the pattern of antibiotic resistance displayed by ESKAPE bacteria.

Materials and Methods

A retrospective study was carried out from 2020 to 2022 at Sri Devaraj Urs Medical College in Kolar in the Department of Microbiology. Regardless of age or gender, patients from critical areas and OPD who had been diagnosed with SSTIs were included. This study excluded patients with infected burns, those on previous antibiotic therapy, and those hospitalised for longer than three days. The bacterial isolates from clinical samples (pus, wound swab, tissue) collected from SSTIs were processed per standard operating procedures in Bacteriology. Colony characteristics, gram stain, and standard biochemical tests identified the bacterial isolates [9].

Antibiotic Susceptibility Testing

"The Kirby Bauer disk diffusion technique was used to identify the antibiotic susceptibility pattern of bacterial isolates". The Broth culture of the test organism matching 0.5 Mc Farland Standard was streaked on the Muller Hinton agar (MHA) plate. Antibiotic disc panels were used based on CLSI guidelines [10]. The MHA plates were incubated for 18 hours at 37^0C, and the antibiotic susceptibility was recorded as sensitive and resistant per CLSI guidelines [10].

Detection of Resistance Mechanisms

"Multi-drug resistance (MDR), Extended Spectrum β-Lactamase (ESBL) was detected by Phenotypic disc confirmatory test, The AmpC Disk test detected AmpC β-Lactamase."

Multi-drug resistance (MDR)

"MDR (multidrug-resistant) refers to the acquired resistance of a microorganism to at least one drug in three or more antimicrobial groups. In this study, a Gram-negative bacterium was classified as MDR if it exhibited resistance to antibiotics from the β-lactam, aminoglycoside, and quinolone families" [11,12].

Detection of ESBL by Disk diffusion test (DDT)

"Cefotaxime (30µg) or Ceftazidime disks (30µg) with and without clavulanate (10µg) were used. A difference of ≥5mm between the zone diameters of either cephalosporin disks and their respective cephalosporin/clavulanate disk was considered phenotypic confirmation of ESBL production." [11, 12]

Modified Amp C Disc method

"A lawn of ATCC 25922 E. coli was made on an MHA plate, a 30-µg of cefoxitin disk and a sterile filter paper disk (called an Amp C disk) were placed adjacent, and 10 µl of enzyme extract was added to Amp C disk and plate was incubated aerobically for 18 to 24 hours at 37^0C. Indentation of the cefoxitin-sensitive zone near the Amp C disk was considered as Amp C production, and no distortion was considered Amp C nonproducer" [11,12].

Results

A total No of 2037 Organisms grown from skin and soft tissue infection during the study period - January 2020 to October 2022 of these ESKAPE pathogens were 1308 **(**64.2%) (Figure 1 and Table 1).

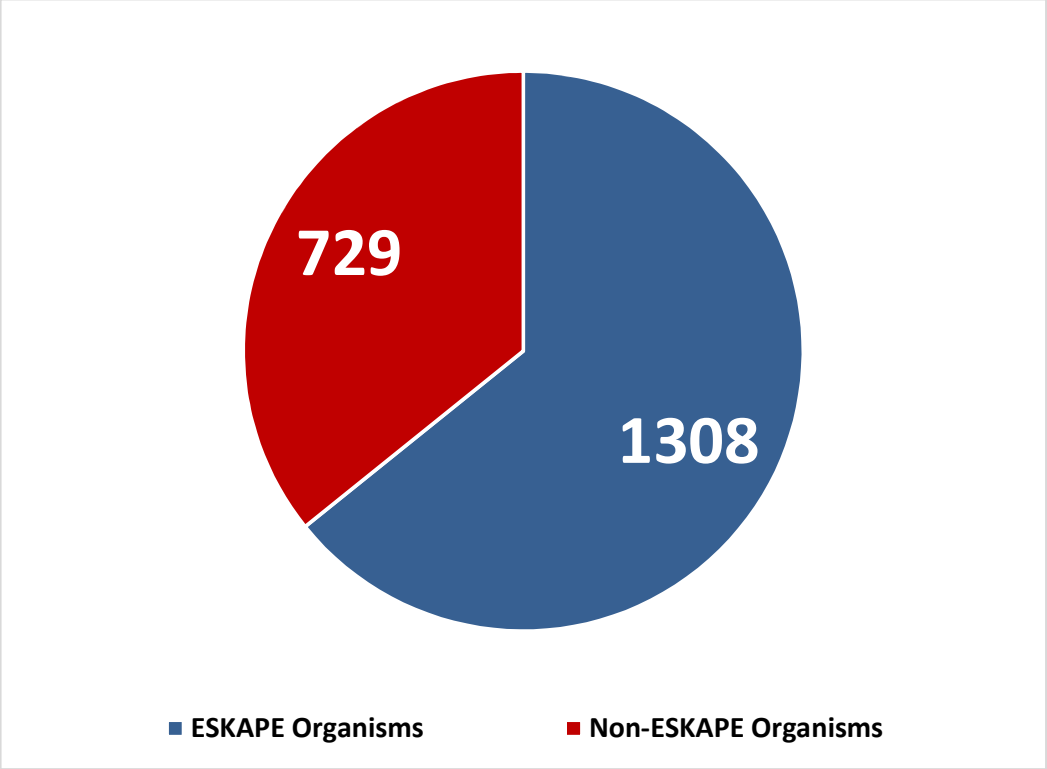


Figure 1. Prevalence of ESKAPE Organisms

Table 1. Distribution of ESKAPE pathogens (n=1308)

Organism	**Percentage (%)**
Staphylococcus aureus	340 (25.99%)
Pseudomonas aeruginosa	332 (25.38%)
Klebsiella pneumoniae	294 (22.48%)
Acinetobacter baumannii	153 (11.7%)
Enterobacter species	152 (11.62%)
Enterococcus faecium	37 (2.83%)

The most common organism among ESKAPE pathogens was *Staphylococcus aureus* 340 (25.99%), followed by *Pseudomonas aeruginosa* 332 (25.38%), *Klebsiella pneumoniae* 294 (22.48%), *Acinetobacter baumannii* 153(11.70), *Enterobacter species* 152 (11.62%) and *Enterococcus faecium* 37(2.83) (Table 2).

Table 2. Antibiotic sensitivity pattern of Gram-Positive bacteria of ESKAPE Pathogens

Antibiotic	***Staphylococcus aureus* (%) n=340**	***Enterococcus faecium* (%) n=37**
Penicillin	38 (11.2)	2 (5.4)
Amoxicillin-clavulanic acid	153 (45)	-
Cefoxitin	157 (46.8)	-
Cotrimoxazole	237 (69.7)	-
Gentamycin	216 (63.5)	-
Ciprofloxacin	70 (20.5)	-
Tetracycline	303 (89.1)	6 (16.2)
Doxycycline	282 (82.9)	8 (21.6)
Chloramphenicol	307 (90.2)	20 (54.1)
Clindamycin	216 (63.5)	-
Erythromycin	119 (35)	8 (21.6)
Linezolid	339 (99.7)	30 (81.1)
Vancomycin	340 (100)	30 (81.1)
Levofloxacin	-	8 (21.6)
High-level gentamycin	-	14 (37.8)

The most common gram-positive organism among ESKAPE pathogens was *Staphylococcus aureus* 340(25.99%), followed by *Enterococcus faecium* 37 (2.83). *Staphylococcus aureus* was more sensitive to Vancomycin (n=340; 100%), followed by Linezolid (n=339; 99.70%). 18.9% (n= 7) of Enterococcus species were Vancomycin-resistant (VRE). MRSA was detected at (n=195; 57.35%) and was sensitive to Vancomycin (n=195; 100%) and Linezolid (n=180; 92.30%) (Table 3).

Table 3. Antibiotic sensitivity pattern of Gram-Negative bacteria of ESKAPE Pathogens

Antibiotic	***Pseudomonas aeruginosa* (%) n=332**	***Klebsiella pneumoniae* (%) n=294**	***Acinetobacter baumanii* (%) n=153**	***Enterobacter species* (%) n=152**
Piperacillin	205 (61.7%)	64 (21.8%)	42 (27.4%)	54 (35.5%)
Piperacillin-tazobactam	233 (70.1%)	142 (48.3%)	52 (33.9%)	100 (65.8%)
Ceftriaxone		74 (25.2%)	36 (23.5%)	52 (34.2%)
Ceftazidime	209 (62.9%)	75 (25.5%)	47 (30.7%)	52 (34.2%)
Imipenem	250 (75.3%)	176 (60.2%)	47 (30.7%)	108 (71.1%)
Meropenem	265 (79.8%)	166 (56.8%)	49 (32%)	115 (75.7%)
Amikacin	256 (77.1%)	167 (57.1%)	47 (30.7%)	112 (73.7%)
Gentamycin	241 (72.5%)	142 (48.6%)	49 (32%)	95 (62.5%)
Tobramycin	241 (72.5%)	136 (46.3%)	48 (31.3%)	91 (59.9%)
Ciprofloxacin	227 (68.3%)	109 (37.4%)	39 (25.4%)	87 (57.2%)
Levofloxacin	230 (69.2%)	129 (43.9%)	40 (26.1%)	102 (67.1%)
Doxycycline	-	114 (38.8%)	80 (52%)	64 (42.1%)
Chloramphenicol	-	206 (70.1%)	-	112 (73.7%)
Ampi-sulbactam	231 (69.5%)		92 (60%)	-

The most common gram-negative organism among ESKAPE pathogens was *Pseudomonas aeruginosa* 332 (25.38%), followed by *Klebsiella pneumoniae* 294 (22.48%), *Acinetobacter baumannii* 153 (11.70), *Enterobacter species* 152 (11.62%). *Pseudomonas aeruginosa* was more sensitive to Meropenem (n=265; 79.8%) followed by Amikacin (n=256; 77.10%). *Klebsiella pneumoniae* was more sensitive to Chloramphenicol (n=206; 70.06%) and Imepenem (n=176; 60.20% each). *Acinetobacter baumannii* was more sensitive to Ampi-sulbactam (n=92; 60%), followed by Doxycycline (n=80; 52%) (Tables 4 and 5).

Table 4. "Shows *Staphylococcus* strains to produce iMSLB (inducible macrolide streptogramin b lincosamide resistance) and cMSLB (constitutive macrolide streptogramin b lincosamide resistance)"

	No of Isolates (n=340)	**Percentage (%)**
iMSLB	18	5.29
cMSLB	132	38.82
Total	137	40.29

In our study, 18 (5.29%) *Staphylococcus aureus* isolates were iMSLB, and 132 (38.82%) were cMSLB (Table 5).

Table 5. Distribution of MDR phenotypes

Organism	**No of Isolates**	**Percentage (%)**
***Klebsiella pneumoniae* (n=294)**	105	35.71
***Acinetobacter baumanii* (n=153)**	92	60.13
***Pseudomonas aeruginosa* (n=332)**	45	13.56
***Enterobacter species* (n=152)**	32	21.05
Total (n=931)	274	29.43

Among ESKAPE pathogens obtained from Skin and Soft tissue infections, 29.43% (n=274/931) displayed multidrug resistance. Leading the list was *Acinetobacter baumannii (n=92; 60.13%)*, followed by *Klebsiella pneumoniae* at 35.71% (Table 6).

Table 6. Beta-lactamase production among Gram-negative isolates

	Klebsiella Pneumoniae **(n=294)**	***Acinetobacter baumanii*** **(n=153)**	***Pseudomonas aeruginosa*** **(n=332)**	***Enterobacter species*** **(n=152)**
ESBL	2 (0.68%)	-	-	46 (30.3)
AmpC	172 (58.5%)	-	-	93 (61.2)
Carbapenemase	109 (37.07)	99 (64.7%)	41 (12.3%)	35 (23.0)

Carbapenemase was found to be a frequent mechanism of resistance, highest among *Acinetobacter* species (n=99; 64.7%), followed by *Klebsiella pneumoniae* (n=109; 37.07%). Amp C production was seen most commonly in *Enterobacter* species (n=93; 61.2%), followed by *Klebsiella pneumoniae* (n=172; 58.5%) whereas ESBL production was seen in *Enterobacter* species (n=46; 30.03%).

Discussion

ESKAPE pathogens are exhibiting a rising resistance to numerous antibiotics, primarily due to improper use and excessive consumption of these medications. Inherent factors such as increased efflux pump activity, elevated biofilm formation, and diminished cell wall permeability in resistant bacteria hinder the efficacy of drugs. The pathogens also obtain resistance via horizontal gene transfer and plasmids. The diminishing effectiveness of antibiotics presents a significant threat, underscoring the imperative to prioritise the development of novel drugs, advance therapeutic approaches, and enhance education concerning ESKAPE pathogens.

According to our analysis, as shown in Figure 1, 64.2% (n=1308) of our region's pathogens are ESKAPE. This is in line with research by Masoud SS et al. on the "Extent and Resistance Patterns of ESKAPE Pathogens Isolated in Pus Swabs from Hospitalized Patients", which found that 68.4% of the pathogens were ESKAPE [15].

Staphylococcus aureus remained the most frequent isolated ESKAPE pathogen at 25.99% (n=340), with *Pseudomonas aeruginosa* following at 25.38% (n=332) and *Klebsiella pneumoniae* at 22.48% (294). Dinda V et al. conducted a study at Aga Khan University Hospital and found that among ESKAPE pathogens, *S. aureus* was the most often discovered bacterium. In contrast, *P. aeruginosa* was found to be the most common drug-resistant bacterium at 16.3% (n = 24/147), followed by *S. aureus* at 12.2% (n = 18/147) and *K. pneumoniae* at 10.8% (n = 16/147) in Manyahi et al.'s study on surgical site infections in Tanzania [16,17].

Staphylococcus aureus displayed the highest sensitivity to Vancomycin (100%) and Linezolid (99.70%). The prevalence of MRSA in our study was at (n=195; 57.35%) and these isolates were

sensitive to Vancomycin (n=195; 100%) and Linezolid (n=180; 92.30%). MRSA prevalence in surgical site infections (SSI) ranged from 15.7% to 63.5% in Indian studies [18]. Our results align with Bhattacharya et al. study on MRSA-related SSI, where *Staphylococcus aureus* exhibited similarly high sensitivity to Vancomycin and Linezolid (100%), with a prevalence of 25.45% [19].

In our study, *Pseudomonas aeruginosa* (25.38%) emerged as the most prevalent gram-negative organism among ESKAPE pathogens causing surgical site infections (SSI), followed by *Klebsiella pneumoniae* (22.48%) and *Acinetobacter* species (11.70%). *Acinetobacter* species exhibited the highest resistance to various antibiotic groups, aligning with Masoud SS et al.'s study titled "Extent and Resistance Patterns of ESKAPE Pathogens Isolated in Pus Swabs from Hospitalized Patients." where *Pseudomonas aeruginosa* was shown to be the most frequent gram-negative bacterium responsible for SSI in their investigation; both *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* showed signs of increased resistance [15].

In our study, 18/340 (5.29%) *Staphylococcus aureus* isolates demonstrated inducible clindamycin resistance (iMSLB), which is in line with the results of Assefa M et al.'s investigation on "Inducible Clindamycin-Resistant *Staphylococcus aureus* Strains in Africa". *S. aureus* had an overall incidence of inducible clindamycin resistance of 19.8%, with a range of 2.9% to 44.0% [20].

According to our study, 29.43% of ESKAPE pathogens were multidrug resistant. *Acinetobacter baumannii (n=92; 60.13%)*, was leading followed by *Klebsiella pneumoniae* at (n=105; 35.71%). In contrast, a study by Foschi D et al. on "Surgical Site Infections caused by multi-drug resistant organisms" reported a higher prevalence of multidrug resistance at 47% [21]. Carbapenemase was found to be a frequent mechanism of resistance, highest among *Acinetobacter* species (n=99; 64.7%), followed by *Klebsiella pneumoniae* (n=109; 37.07%). Amp C production was seen most commonly in *Enterobacter* species (n=93; 61.2%), followed by *Klebsiella pneumoniae* (n=172; 58.5%) whereas ESBL production was seen in *Enterobacter* species (n=46; 30.03%). A study by Mora-Guzmán et al. on Surgical site infection by carbapenemase-producing Enterobacteriaceae reported that carbapenemase-producing bacteria causing SSI accounted for 74.3% [22]. In contrast, a study by Dubinsky-Pertzov et al. on "Extended-spectrum Beta-lactamase-producing Enterobacteriaceae and the Risk of Surgical Site Infection" revealed a lower prevalence, with ESBL-producing bacteria causing SSI at 15.75% [23].

Limitation of Study

Clinical data and outcomes were not taken in our study. Furthermore, antimicrobial susceptibility testing was conducted solely using the Kirby-Bauer method instead of the more sensitive micro-dilution method.

Conclusion

This study underscores the significance of ESKAPE pathogens in skin and soft tissue infections, highlighting challenges from their substantial antimicrobial resistance and heightened virulence. The implications include prolonged illnesses, treatment failures, increased healthcare costs, and elevated mortality risks from MDR/XDR/PDR

strains in human infections. The persistent unnecessary prescription of antimicrobials, especially broad-spectrum ones, despite effective alternatives, is concerning. The research emphasizes the urgent need for regulatory authorities to implement measures limiting over-the-counter sales of antimicrobials and addressing their irrational use to curb the emergence of multi-drug resistant strains.

Ethical Approval

Ethical approval obtained from Sri Devaraj Urs Medical College in Kolar in the Department of Microbiology

Conflicts of interest

The authors declares that they do not have conflict of interest.

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