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A prospective surveillance of ESKAPE pathogens in the ICU of a tertiary care hospital

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Abstract

Objective: "ESKAPE" pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa,* and *Enterobacter* species) constitute two thirds load of all health care-associated infections (HAIs). Patients admitted to ICUs are more susceptible to infections due to the presence of various favourable factors. Therefore present study was undertaken in ICUs of a tertiary care hospital to reveal infectious disease burden due to "ESKAPE" pathogens and their antimicrobial resistance patterns.

Methods: This study included all patients admitted to ICUs under study. Each patient underwent initial standard bacterial culture on admission, followed by twice weekly prospective surveillance cultures for ESKAPE pathogens until discharge. The information regarding demographic profile, cause of admission, surgical procedure performed, results of surveillance cultures for ESKAPE pathogens and antibiogram profile of the ESKAPE pathogen isolates was collected.

Results: Out of these 490 patients, bacterial cultures were positive in 88 (18%) cases. Majority of cases were from Obstetrics & Gynaecology.133 clinical specimens were positive for bacterial pathogens on culture. Overall ESKAPE pathogens were isolated in 69.2% of positive bacterial cultures from various clinical specimens. *Staphylococcus aureus* was isolated from 28.6% clinical specimens, followed by 24.1% *Acinetobacter baumannii*, 10.5% *Klebsiella pneumonia*, 2.3% each of *Pseudomonas aeruginosa* and *Enterobacter* species. Overall 86.7% of blood stream infections were caused by ESKAPE pathogens. ESKAPE pathogens were isolated from the 83% tracheal tip, 60% pus, 19.2% urine specimens.

Conclusions: Thus, continuous monitoring and surveillance of ESKAPE pathogens in high risk settings like ICUs may prove to be a useful tool.

Keywords: ESKAPE; antimicrobial resistance; Enterococcus faecium; Staphylococcus aureus; Klebsiella pneumonia; Acinetobacter baumannii; Pseudomonas aeruginosa

Introduction

"The world is on the brink of losing these miracle cures," Dr Margaret Chan, WHO Director-General, said in reference to the antibiotic agents that are considered as miracles of modern medicine.[1] A consistent surge in the infections caused by antibiotic resistant bacteria is imposing therapeutic dilemmas to the clinicians. Both the gram-positive and gram-negative bacteria have been showing increasing resistance for various presently available antibiotics in the hospital and community settings.[2-4]

WHO has pointed out that antimicrobial resistance is of particular concern for developing countries like India due to their high burden of infectious diseases. India is among the countries with highest load of bacterial diseases which makes her critically dependent on antibiotics for limiting the morbidity and mortality rates.[1] The non-existent antibiotic policy in majority of the hospitals leading to antibiotics overuse and misuse, over the counter availability of antibiotics including the last resort carbapenem antibiotics worsens the scenario. Furthermore, rampant and unregulated use of antimicrobials for veterinary, agricultural practices make the present situation alarming.[5,6]

Rice has reported that the "ESKAPE" pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* species) are responsible for the majority of infections in the US hospitals.[3] This report further emphasizedthat these "ESKAPE" pathogens are efficient in "escaping" the effects of available antibacterialagents.[3,7]

"ESKAPE" pathogens constitute two thirds load of all the health care-associated infections (HAIs).[4]Centers for Disease Control and Prevention (CDC) has reported an increase in infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium*(VRE), and fluoroquinolone-resistant *Pseudomonas aeruginosa*.[8] The number of deaths due to MRSA infections are more than HIV/AIDS and tuberculosis combined in US hospitals.[9,10] Patients admitted to intensive care units (ICUs) are more susceptible to infections due to the presence of various comorbid conditions impairing host immunity, invasive monitoring and use of broad-spectrum antimicrobials as a routine.[11]

Emergence and establishment of ESKAPE pathogens pose a serious threat of having no effective antibiotics available in near future. With meagre hope for availability of newer antibiotics anytime soon, it is of utmost importance to utilise the available resources judiciously. The continuous monitoring and surveillance of ESKAPE pathogens in high risk settings like ICUs may prove to be crucial in the better understanding of infections by these multidrug resistant ESKAPE pathogens.Therefore this present surveillance study was undertaken in the intensive care units of a tertiary care hospital to reveal the infectious disease burden due to "ESKAPE" pathogens and their antimicrobial resistance patterns.

Materials and methods

A prospective surveillance study was carried out in the eight bedded Main and seven bedded Neurosurgical ICUs of a 1000-beddded medical centre in north India. The Main ICU is an Adult Medical Surgical ICU. The period of surveillance extended from December 2016 to May

2017. Data was recorded on a predesigned performa by the infection control team of the hospital constituted by a microbiologist and an infection control nurse during the routine surveillance rounds. This study included all the patients admitted to the intensive care units under study. Each patient underwent initial standard bacterial culture on admission, followed by twice weekly prospective surveillance cultures for ESKAPE pathogens until discharge. Pus specimens were collected from the surgical sites in cases with formation of surgical wound abscess. The information regarding the demographic profile, cause of admission, surgical procedure performed, results of surveillance cultures for ESKAPE pathogens and antibiogram profile of the ESKAPE pathogen isolates was collected.

Results

This surveillance study was carried out in the Adult Medical Surgical and Neurosurgical ICUs of a tertiary care hospital. During the study period 268 and 222 patients were admitted to the Adult Medical Surgical and Neurosurgical intensive care units respectively. Out of these 490 patients, cultures were positive for bacterial agents in 88 (18%) cases which included 72 (26.9%) patients in Adult Medical Surgical ICU and 16 (7.2%) in Neurosurgical ICU.

The demographic profile of the patients with positive bacterial culture is depicted in Figure 1. Out of these 88 patients, 59 (67%) were females and 29 (33%) were males.The male to female ratio was 0.49. A female preponderance was seen across all the age groups except 61-80 years age group. The age of the patients ranged from 10 years to 85 years with the majority 54 (61.4%) belonging to 19-40 years of age group followed by 22 (23.9%) in 41-60 years age group.

The frequency distribution of cases with positive bacterial culture on the basis of clinical specialty and surgical procedure performedis shown in Table 1. Majority 28 (31.8%) of the cases were from Obstetrics & Gynaecology, followed by 25 (28.4%) from Surgery, 16 (18.2%) each from Medicine and Neurosurgery, 3 (3.4%) Orthopaedics respectively. Lower segment caesarean section constituted the most common surgical procedure among the patients with positive bacterial isolates on culture, followed by laparotomy, craniotomy and hysterectomy. However, in majority 29 (33%), no surgical procedure was performed (Table 1 and Figure 2).

Frequency distribution of ESKAPE pathogens

Figure 3 shows the overall percentage distribution of ESKAPE pathogens among positive bacterial cultures in ICUs under study. A total of 133 clinical specimens were positive for bacterial pathogens on culture.Overall ESKAPE pathogens were isolated in 92 (69.2%) of positive bacterial cultures from various clinical specimens. *Staphylococcus aureus* was isolated from 38 (28.6%) clinical specimens, followed by 32 (24.1%) *Acinetobacter baumannii,* 14 (10.5%) *Klebsiella pneumonia,* 3 (2.3%) each of *Pseudomonas aeruginosa* and *Enterobacter* species. Overall 86.7% of the blood stream infections were caused by ESKAPE pathogens. *Staphylococcus aureus* was the causative agent in the majority 32 (71.1%) of bacterial culture positive blood specimens, next followed by 5 (11.1%) *Klebsiella pneumoniae* and 2 (4.4%) *Acinetobacter baumannii.* ESKAPE pathogens were isolated from 9 (60%) pus specimens. 4 (26.7%) of these isolates were of *Acinetobacter baumannii,* followed by 3 (20%) *Staphylococcus aureus,* 2 (13.3%) of *Klebsiella pneumoniae.* ESKAPE pathogens were isolated from the 39 (83%) tracheal tip specimens. *Acinetobacter*

*baumannii*was isolated in 26 (55.3%), *Klebsiella pneumoniae* in 6 (12.8%), *Staphylococcus aureus* in 3 (6.4%), 2(4.3%) each of *Pseudomonas aeruginosa* and *Enterobacter* species. In 5 (19.2%) urine specimens, ESKAPE pathogens were the causative agent. *Enterococcus faecium* was isolated in 2 (7.7%), next followed by 1 (3.8%) isolate of *Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Enterobacter* species each (Figure 4).

Antibiogram profile of the ESKAPE pathogen isolates of the Adult Medical Surgical and Neurosurgical intensive care units

Enterococcus faecium was isolated from the two urine specimens. Both the isolates were resistant to ampicillin, ciprofloxacin, Gentamicin-high and sensitive to nitrofurantoin. Only one of the isolates was sensitive to teicoplanin. Linezolid, norfloxacin and vancomycin were assessed in only one of the isolates as per the availability. One of the Isolate was resistant to both teicoplanin and vancomycin. Isolate tested for linezolid, was sensitive to the agent. Antibiogram patterns of *Staphylococcus aureus, Klebsiella pneumonia*e and *Acinetobacter baumannii*are shown in Figures 5, 6 and 7 respectively. Overall *Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii* were isolated from 38, 14 and 32 clinical samples respectively during the study period from the intensive care units under study. *Pseudomonas aeruginosa* was isolated from 3 clinical specimens. These isolates were resistant to amikacin in 66.7% cases. Ceftazidime, piperacillin/tazobactum antibiotic discs were assessed in two and aztreonam, colistin, gentamicin, imipenem, tobramycin were assessed in only one of the three isolates as per the disc availability. Aztreonam, ceftazidime, imipenem, tobramycin were resistant and colistin, gentamicin, piperacillin/tazobactum were sensitive in all the isolates tested. Overall *Enterobacter* species were isolated from the 3 clinical specimens. Amikacin and piperacillin/tazobactum were resistant in 66.7% isolates. Ceftazidime, gentamicin, meropenem were tested in two whereas ampicillin, aztreonam, imipenem, polymixin B, tetracycline, tigecycline, tobramycin were tested in one of the isolates as per the availability of disc. Ampicillin, aztreonam, cefotaxime, ceftazidime, ciprofloxacin, imipenem, meropenem, tetracycline, tigecycline were resistant and colistin, polymixin B, tobramycin were sensitive in 100% of the isolates tested. Gentamicin was resistant in 50% of the isolates.

Discussion

In the present surveillance studyof the ICUs, a female preponderance was seen. It was probably because,a large number of the cases admitted to the Main ICU were from Obstetrics & Gynaecology Department and lower segment caesarean section constituted the most commonly performed surgical procedure in the bacterial culture positive patients collectively among the two ICUs under study. The majority of the cases with positive bacterial culture belonged to economically productive age group i.e. 19-60 years, further contributing to the financial hardships of the affected households.

The distribution of antimicrobial resistance is not uniform across various bacterial species. This resistance problem seems to be more concentrated in ESKAPE pathogens.[3] Concerned with the emergence of the antibiotic-resistant ESKAPE pathogens, IDSA issued a ‘‘Call to Action for the Medical Community’’.[7]In February 2017, WHO released its first ever catalogue of antibiotic-resistant "priority pathogens". The bacteria listed in this catalogue are perceived as the greatest threat to mankind due to their high incumbent antimicrobial resistance and for which the

research and development of newer antibiotics is urgently needed. Drug resistant ESKAPE pathogens were among the priority 1(critical) and 2 (high) pathogens.[12]Our study revealed the isolation of ESKAPE pathogens in 69.2% of positive bacterial cultures from various clinical specimens in the ICUs of a tertiary care hospital.Our findings are in line with the previous study involving the one year surveillance of ESKAPE pathogens in an ICU of Monterrey, Mexico by Llaca-Diaz JM *et al*which have also identified ESKAPE pathogens in 64.5% of clinical isolates in their.[13]Similarly, available data from National Healthcare Safety Network also reported the involvement of ESKAPE pathogens in over 40% of infectionsin ICU patients.[14]

In the present study, overall *Staphylococcus aureus* (28.6%) was most commonly isolated pathogen from clinical specimens positive for bacterial culture, followed by 24.1% *Acinetobacter baumannii*, 10.5% *Klebsiella pneumoniae*, 2.3% each of *Pseudomonas aeruginosa*&*Enterobacter* species and 1.5% *Enterococcus faecium*. Our findings were in concordance with the Extended Prevalence of Infection in Intensive Care (EPIC) II study that showed *Staphylococcus aureus* (20.5 %) as the most frequently isolated organism.[15]Ghanshani R *et al* have also reported 20.9% *Acinetobacter baumannii*isolates on bacteriological culture in their study of the medical ICU at a tertiary care hospital in North India. However the same study demonstrated, the frequency isolation of other pathogens as 19.7% *Klebsiella pneumoniae*,14.0% *Pseudomonasaeruginosa*, 8.2% *Staphylococcus aureus* and 5.0% *Enterococcus* species.[16]In their study, Llaca-Diaz JM *et al* identified the more frequently isolated organisms as*Acinetobacter baumannii*(15.8%), *Pseudomonas aeruginosa* (14.3%), *Staphylococcus aureus* (14.2%) and *Klebsiella pneumoniae*(11.3%).[13]

ESKAPE pathogens were isolated from 86.7% blood, 60% pus, 83% tracheal tip, 19.2% urine specimens in our study. *Staphylococcus aureus* was the predominant pathogen in blood stream infections, next followed by *Klebsiella pneumoniae* and *Acinetobacter baumannii*.Most frequently isolated pathogens from pus specimens were *Acinetobacter baumannii* and *Staphylococcus aureus*. A preponderance of *Acinetobacter baumannii*and *Klebsiella pneumoniae* was observed in tracheal tip specimens whereas *Enterococcus faecium*was most frequently isolated pathogens from urine specimens. Llaca-Diaz JM *et al* in their study reported an isolation of ESKAPE pathogens from 51.6% blood, 71.1% respiratory, 57.5% urine specimens. Furthermore, they also documented *Acinetobacter baumannii*and *Staphylococcus aureus* as the most commonly isolated pathogens from blood and respiratory specimens. Same study reported *Pseudomonas aeruginosa* as the most dominant isolate in urine specimens.[13]

Antibiogram profile of the ESKAPE pathogen

Past decade has witnessed an emergence of multi or pan-drug resistant pathogens, consequently leaving the presently available antibacterial drugs less effective or even ineffective. IDSA has raised concerns regarding the lean existing pipeline of new antimicrobial agents with possible activity against these resistant organisms.[7] The dominant factor behind the emergence of multidrug resistant ESKAPE pathogens is unwarranted use of broad spectrum antimicrobial agents. The study by Borg MA reported that over 60% of patients admitted to ICU receive antimicrobial agents.[17]ESKAPE pathogens are reported to be responsible for over 80 % of infections occurring in the ICU.[18]

Enterococcus faecium isolates were uniformly resistant to ampicillin, ciprofloxacin, gentamicin-high. We encountered strain resistant to both vancomycin and teicoplanin in our study. However this isolate was sensitive to nitrofurantoin. Llaca-Diaz JM *et al* have reported 8.6% vancomycin resistance in *Enterococcus faecium*.[13] A prospective surveillance study of device-associated infections in adult medical surgical ICU of a tertiary care hospital in North India has reported 25% vancomycin resistant *Enterococcus* species. In line with the findings of present study, Enterococcus isolates from device-associated infections were uniformly resistant to Amoxicillin/clavulanic acid and sensitive to linezolid in this study. However in the same study, half of the isolates were resistant to Gentamicin and ciprofloxacin.[19]

In our study, 51.9% of *Staphylococcus aureus* were methicillin resistant(MRSA). Another study by Indian Network for Surveillance of Antimicrobial Resistance (INSAR) groupinvolving 15 Indian tertiary care centres and extending over a period of 2 years has reported an overall 41% MRSA prevalence. Furthermore, MRSA isolation rates were reported to be43% in 2008, that further increased to 47% in 2009.[20] The percentage susceptibility to cotrimoxazole, ciprofloxacin, erythromycin, gentamicin were 76.9%, 25%, 43.3%, 63.6% respectively in present study that was in agreement to susceptibility of 70%, 36%, 52%, 69% respectively in study by INSAR group. All *Staphylococcus aureus* isolates were sensitive to vancomycin and linezolid in both the studies.[20]

Our study revealed 100% resistant to cefotaxime in*Klebsiella pneumoniae* isolates. Another Indian study by Datta S *et al* involving multi-drug resistant *Klebsiella pneumoniae* blood stream infections in a tertiary care hospital has also reported comparable rate of 97% cefotaxime resistance.[21] Piperacillin/tazobactum, ciprofloxacin, amikacin resistance rates were 91.7%, 88.9%, 66.7% in present study and these were in concordance with previous study reporting 84%, 84%, 45% for the same antibiotics respectively.[21] Another recent study has also reported comparable resistance rates for ciprofloxacin, amikacin and gentamicin.[19] However, a very high resistance was documented against carbapenems in our study in comparison to other studies.[19,21] All *Klebsiella pneumoniae* isolates were uniformly sensitive to colistin in present surveillance study similar to another Indian study.[19]

All *Acinetobacter baumannii* isolates were resistant to ceftazidime, imipenem and gentamicin. Rynga D *et al* have reported 0%, 10%, 4% sensitivities to ceftazidime, imipenem and gentamicin respectively.[22] Moreover susceptibilities to cefotaxime, aztreonem, amikacin, ciprofloxacin were 0%, 0%, 3%, 1% in their study and our study demonstrated 6.25%, 15.4%, 6.5%, 6.7% susceptibilities to same antibiotics respectively. In our study we revealed 60.9% sensitivity to tigecycline which was comparable to 58% as reported by their study. All *Acinetobacter baumannii* isolates were sensitive to colistin in our study which was in agreement with the other study that reported 97% susceptibility.[22]Mathai AS *et al* have reported comparable resistance rates to cefotaxime and ceftazidime in their study involving Acinetobacter infections in a tertiary level ICU. However, our study has reported higher resistance to amikacin and meropenem. *Acinetobacter baumannii* isolates were uniformly sensitive to polymyxin B in present study, Mathai AS *et al* have documented 13% resistant Acinetobacter isolates.[23]

Our study has reported comparable colistin, ceftazidime and amikacin susceptibility patterns for *Pseudomonas aeruginosa*to other recent study.[19]*Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter* species were uniformly sensitive to colistin or polymyxin B in our study. However, we observed very high resistance to tested cephalosporin antibiotics among all the gram-negative members of the ESKAPE group of pathogens.

Emergence of ESKAPE pathogens is the result of long term inadvertent use of available antibiotics. ESKAPE pathogens pose a serious threat of having no effective antibiotics available in near future. We have reached end of the rope, with meagre hope for newer antibiotics, it is now crucial to utilise the available resources judiciously. Thus, the continuous monitoring and surveillance of ESKAPE pathogens in high risk settings like ICUs may prove to be a useful tool in the better understanding and utilisation of scarce available resources against infections by multidrug resistant ESKAPE pathogens.

In our study we have studied the distribution of all the components of ESKAPE pathogens as the causative agents of various morbidities and mortalities in the ICU. Despite volume of publications based on ICU settings, most of the studies have concentrated on the prevalence of gram-negative and gram-positive pathogens. The research analysing the specimen wise distribution of ESKAPE pathogens as the causative agent of various infections in the ICUs is very limited.ESKAPE" pathogens have emerged as the major causative agents of all the HAIs which emphasises the urgent need of continuous monitoring and surveillance of ESKAPE pathogens in high risk settings like ICUs. The strength of our study is that it provides an insight to the prevalence and antimicrobial sensitivity patterns of these ESKAPE pathogens.This study can serve as an important tool in the better understanding of the current distribution and the response patterns of ESKAPE pathogens. It may prove to be useful for the clinicians by aiding them in solving the treatment dilemmas presented by these ESKAPE pathogens often encountered in the ICU settings. As this study has been done in the ICUs of a tertiary care hospital of north India with high patient load, this may help in the utilisation of the interpretations drawn in this study for the improvement of process of early diagnosis and adequate treatment of ESKAPE pathogens. It may further help in the reduction of cost involved in the management of ESKAPE pathogens in the ICU settings by limiting the hospital stay by timely treatment with effective antimicrobial agents rather than relying on the cocktail of inefficient drugs. Our study further emphasises the urgent need for the judicious use of limited available antibiotics to ensure their availability in the future.

The limitation of the present study is that it was restricted to the adult medical surgical and neurosurgical ICUs in the hospital. The inclusion of paediatric and neonatal ICUs of the same hospital probably could have given better insight in the analysis of ESKAPE pathogens. More exhaustive studies involving heterogeneous sampling from multiple centres, environmental surfaces in the ICUs, in-patients extending over longer period of time are required to further substantiate our findings. Despite the limitations, present study provides a better understanding of the distribution and prevailing antibiotic resistance patterns in the ICUs.

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Table 1: Distribution of cases with positive bacterial cultures on the basis of clinical specialty and surgical procedure performed (n=88)

Intensive Care Unit	Number of cases	Clinical specialty	Number of cases	Surgical procedure performed	Number of cases
Adult medical Surgical	72	Medicine	16(18.2%)	None	16(18.2%)
		Obstetrics & Gynaecology	28(31.8%)	Lower segment caesarean section	15(17.0%)
				Hysterectomy	5(5.7%)
				Laparotomy for ectopic pregnancy	1(1.1%)
				Suction & Evacuation	1(1.1%)
				None	6(6.8%)
		Orthopaedics	3(3.4%)	Arthrotomy for septic arthritis	1(1.1%)
				Internal fixation for L_5-L_6 dislocation	1(1.1%)
				None	1(1.1%)
		Surgery	25(28.4%)	Limb amputation	2(2.3%)
				Pancreatic cystectomy	1(1.1%)

				Debridement for diabetic foot	1(1.1%)
				Hemicolectomy	1(1.1%)
				Ileostomy	1(1.1%)
				Laparotomy	13(14.8%)
				Buccal ulcer excision & reconstruction	1(1.1%)
				Hernia repair	1(1.1%)
				Vascular repair	1(1.1%)
				None	3(3.4%)
Neurosurgical ICU	16	Neurosurgery	16(18.2%)	Craniotomy	11(12.5%)
				Decompression	1(1.1%)
				Ventriculoperitoneal shunt	1(1.1%)
				None	3(3.4%)

Figure 1: Frequency distribution of the cases with positive bacterial cultures on the basis of age and gender (n=88)

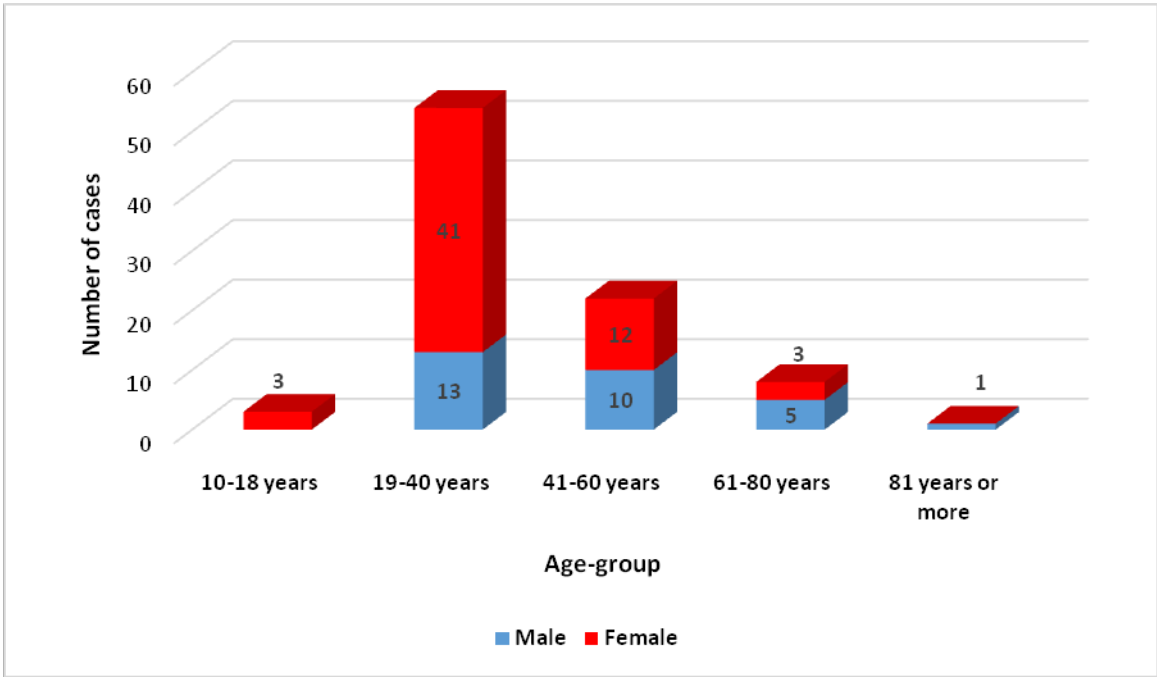

Figure 2: Percentage distribution of various surgical procedures among the patients with positive bacterial cultures (n=88)

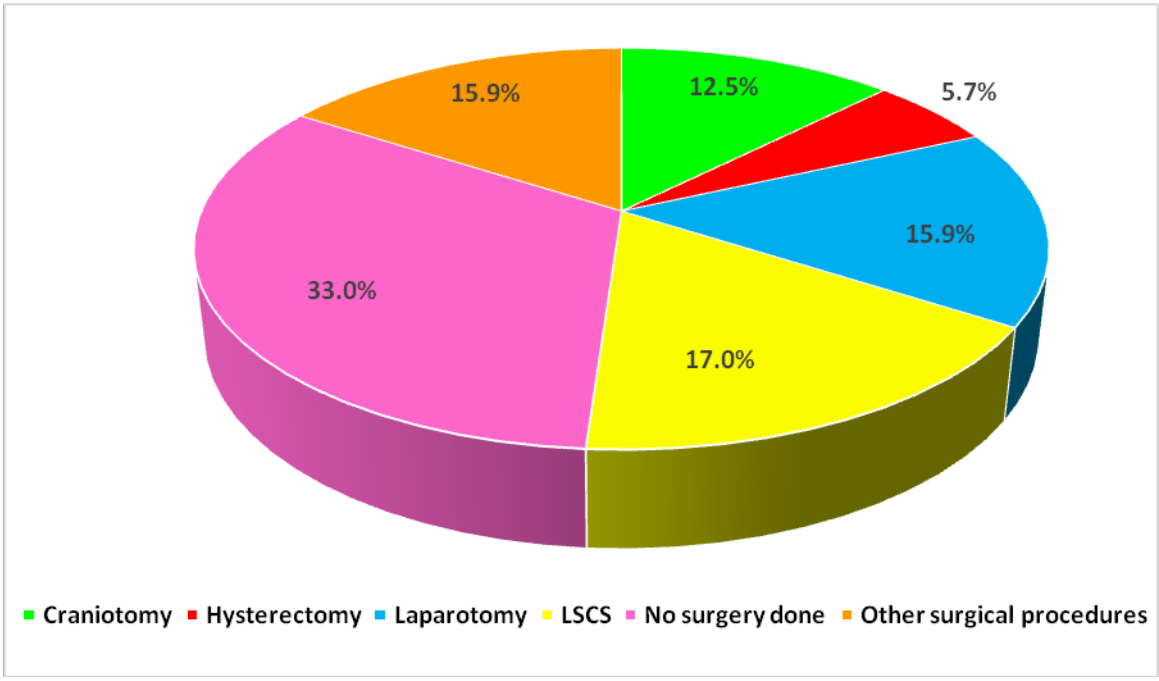

Figure 3: Overall percentage distribution of ESKAPE pathogens among positive bacterial cultures from patients in ICUs under study (n=133)

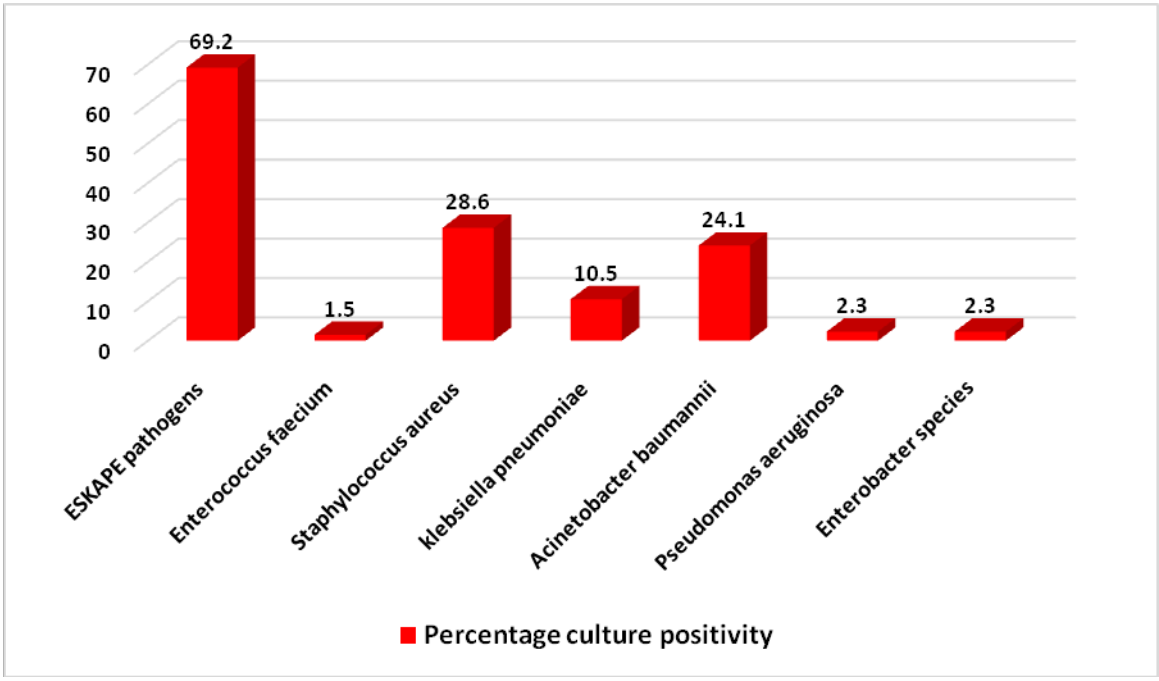

Figure 4: Percentage positivity of ESKAPE pathogens among various clinical specimens

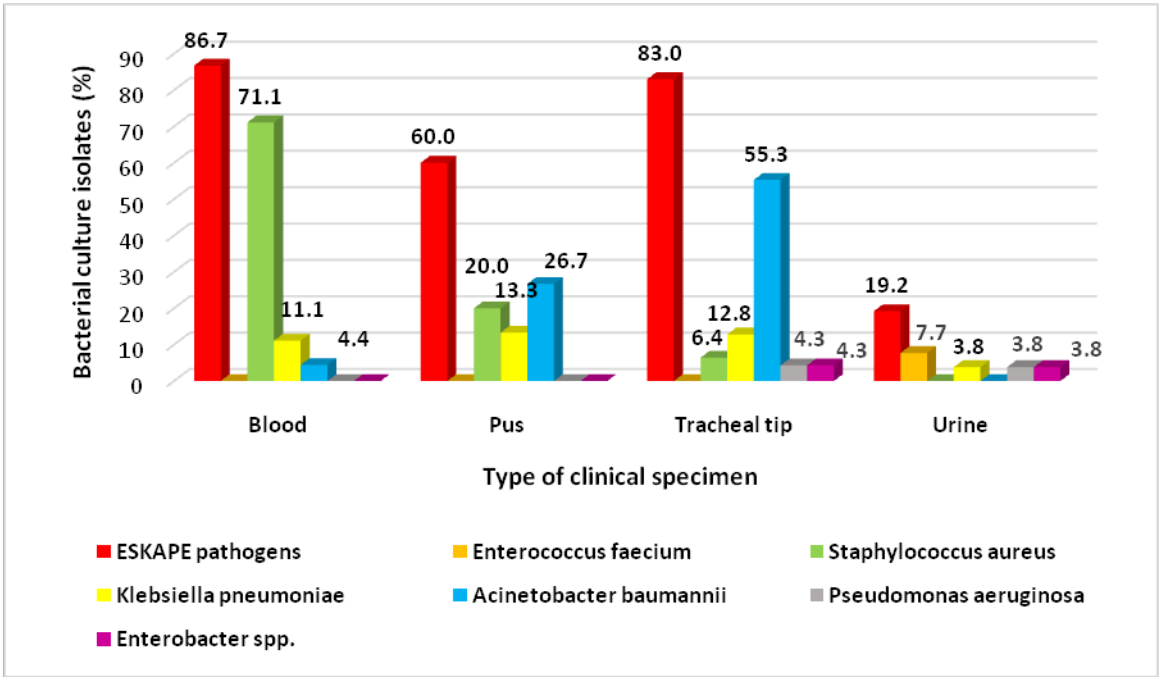

Figure 5: Antibiotic sensitivity profile of *Staphylococcus aureus* isolates in ICUs under study (n=38)

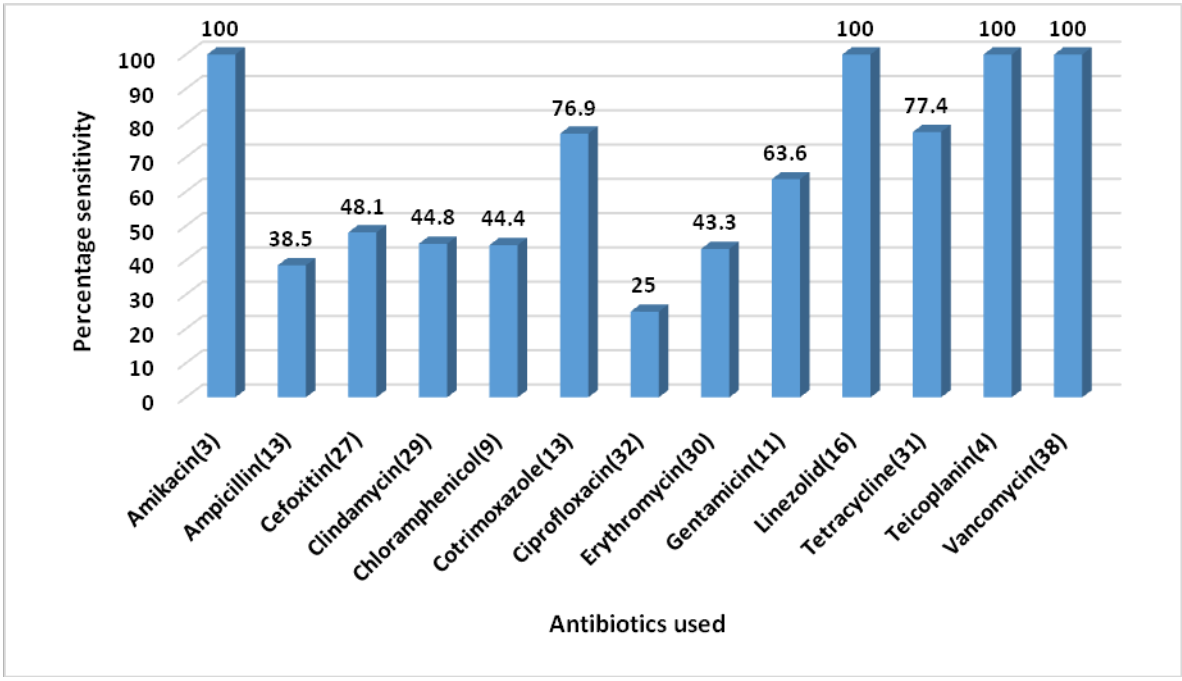

Figure 6: Antibiotic sensitivity profile of *Klebsiella pneumoniae* isolates in ICUs under study (n=14)

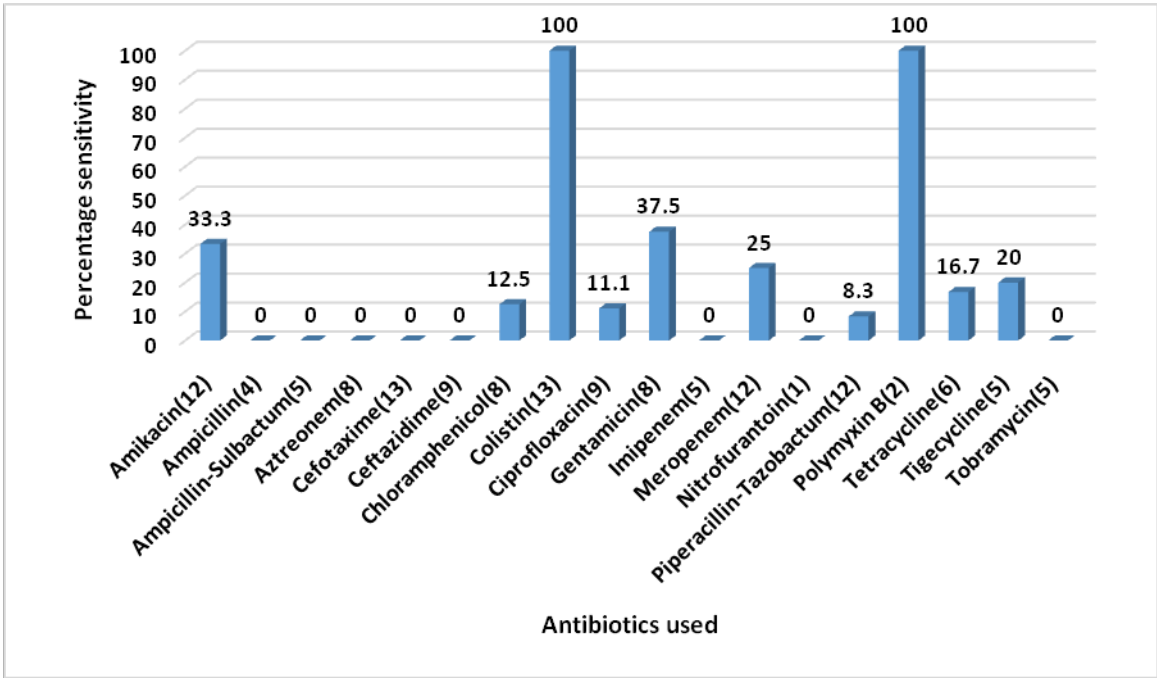

Figure 7: Antibiotic sensitivity profile of *Acinetobacter baumannii* isolates in ICUs under study (n=32)