Original Research Article

ESKAPE pathogens: Trends in antibiotic resistance pattern

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Abstract

Background: Trend in resistance pattern of ESKAPE (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter, Pseudomonas aeruginosa,* and *Enterobacter*/E.coli species) pathogens and their prevailing patterns in different types of infections was analyzed in this study. **Methods:** During a Three year study period (01 Jan 2013 to 31 Dec 2015), identification and susceptibility testing of ESKAPE pathogen were performed as per Clinical Laboratory Standards Institute (CLSI) guideline. Chi square for trend was used to analyze Trend in antibiotic resistance. **Results:** A reduction in Vancomycin resistant Enterococci (VRE) over the years from 6.0% in 2013 to 2.6% in 2014 and 1.2% in 2015 (p for trend=0.04) was observed during the reference period. Decline in trend was also noticed for Methicillin Resistant Staphylococcus aureus (MRSA) (i.e.) 41.2%, 25% and 20% respectively from 2013-15 (p for trend >0.05) and for ESBL Klebsiella pneumoniae 89%, 74% and 51% (p for trend is <0.0001).Regardless, a high prevalence of Multi drug resistant (MDR) Acinetobacter resistance was noted at baseline, but a less significant declining trend (52%, 71%, 25%) was followed over the years (p for trend >0.05). Klebsiella and Pseudomonas showed least proportion of resistance (≈2%) with a very good susceptibility profile among the ESKAPE pathogens. VRE, MRSA and MDR Acinetobacter were most commonly isolated from UTI (43%), wound swabs (50%) and Respiratory tract infections (76%) respectively. **Conclusion:** A declining trend in resistance pattern of ESKAPE organisms from the recent past was observed in this study. To facilitate better clinical decisions these findings should be emphasized in infection control training for health care providers.

Key Words: ESKAPE, Resistance, Trends.

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INTRODUCTION

In the past decade, several antibiotic-resistant pathogens have been identified as causes of serious infections among hospitalised patients.[1-4] WHO and CDDEP (Centre for Disease Dynamics, Economics and Policy) has warned about raising levels of drug resistant bacteria in India.[2,3] This worrisome problem in India is due to over the counter availability of antibiotics which has led to misuse and abuse of antibiotics in humans, cattle, poultries and food industry. Also inadequate knowledge, awareness and compliance with regards to basic infection control practices among health care professionals had added to the problem within the hospitals[2, 3]. All the above mentioned factors has led to the emergence and escalation of resistance among ESKAPE pathogens (*Enterococcus spp, Staphylococcus aureus, Klebsiella pneumonia, Acinetobacterbaumanii, Pseudomonas aeruginosa*, and *Enterobacter species*)[5-11] The increased prevalence rates of the Multi Drug resistant (MDR) strains of above mentioned pathogens is a major public health concern, particularly in hospitals and other health care settings. The ESKAPE pathogens, as identified by the IDSA[5-7] in 2004 and specific drug resistant strains described by Rice, pose a threat to the immunocompromised and healthcare institutions. According to the latest data from the Centres for Disease Control and Prevention, these ESKAPE bacteria are

responsible for two-thirds of all healthcare-associated infections[9-10] and continue to play a significant role in overall global mortality[4] and morbidity especially in Intensive Care Units. Infections caused by the resistant strains of the ESKAPE bacteria are significantly and universally associated with poor clinical outcomes, compared with their susceptible counterparts. The poorer outcomes are such as longer hospital stays, increased mortality, and higher hospitalization cost. The incidence and adverse consequences of infections caused by the above mentioned antimicrobial-resistant organisms continue to increase[1,6,9,15] In the current situation of escalating antibiotic resistance it is essential to report sensitivity pattern of these MDR ESKAPE in order to inform the health care providers to choose appropriate empirical therapy and infection control measures[15,16,17]. Many studies have reported about the prevalence rates and antimicrobial resistance (AMR) caused by ESKAPE in hospital settings and how to combat the resistance[9-20]. The aim of the present surveillance study is to assess the trend in antibiotic resistance pattern for ESKAPE organisms and profile of ESKAPE from different clinical specimens at our tertiary care centre. There is dearth of literature on this aspect of antibiotic resistance pattern especially among low and middle income countries where there is greater access to over the antibiotics. The objective of this study is to monitor the profile of ESKAPE pathogens from different clinical specimens, to report the dynamic antibiotic susceptibility trending of the same and to highlight the trends in specific Drug resistance of ESKAPE. This will be of valuable information to clinicians and infection control committee.

MATERIALS AND METHODS

Setting and Clinical Isolates: This retrospective cohort study was conducted at, a tertiary care teaching hospital in South India. Both the outpatient and Inpatient samples submitted for Culture and Sensitivity (C/S) tests were included for the study. This hospital provides tertiary medical care in twenty eight wards, including three ICUs spanning paediatric, medical and surgical units. Reference period for this study is from Jan 2013 to Dec 2015. CLSI guidelines were followed for processing of all clinical samples submitted for culture and sensitivity-C/S (e.g.-Blood, urine, and wound, respiratory and other miscellaneous samples).

Data collection, Antimicrobial Susceptibility and Identification Assays*:* Data related to identification of isolated ESKAPE pathogens and antibiotic sensitivity was extracted from culture and sensitivity (C/S) register. The C/S register is audited for its correctness and completeness on weekly basis by Head of Microbiology department. The species identification and susceptibility testing were performed as per Clinical Laboratory Standards Institute (CLSI) guideline. Antibiotic sensitivity test (AST) were routinely performed using Disk diffusion method and when necessary broth dilution method. Assay control organisms and susceptibility breakpoints were those recommended by the CLSI. Specific resistance of ESKAPE was screened and confirmed by phenotypic methods as per CLSI Guide lines (VRE-Vancomycin resistant Enterococci, MRSA-Methicillin Resistant Staphylococcus aureus, VRSA-Vancomycin Resistant Staphylococcus aureus, Carbapenem resistance-CR and ESBL's for E.coli and Klebsiella)

1. Detection of MRSA and VRSA and VRE Screening for MRSA done by cepoxitin zone size inhibition as per CLSI and confirmation was done by E-test. Vancomycin resistance was confirmed by E-Test method. (E strips from Hi media)
2. ESBL (Extended Spectrum Beta Lactamase) Production: Presumptive ESBL producers were identified by phenotypic screening of cephalosporins. The combination disk method, alone and in combination with inhibitory clavulanic acid, was used to confirm the expression of ESBLs. Both presumptive and confirmatory tests were performed following CLSI guidelines.
3. Carbapenem resistance (CR): Carbapenem resistance for E.coli, Klebsiella, and Pseudomonas and Acinetobacter was screened by disc diffusion method and confirmation was done by E-test. (E strips from Hi media)
4. Multi drug resistance: Multidrug resistance was defined as having a resistance to three or more classes of antimicrobials. The class definitions used in this study was as per Magiorakos *et al.*[21]

Statistical Analysis: Year wise, proportions of clinical specimens tested positive for ESKAPE pathogen were summarized as frequencies and percentages. Predominant type of organism isolated based on different clinical infections were also summarized as percentages. Trends in antibiotic sensitivity pattern of isolated ESKAPE pathogens and resistant trends in last resort Antibiotics of the same were analysed using chi square for trend. Statistical significance was considered at 0.05 levels.

Intervention: We initiated educational Intervention with a five point scale KAP questionnaire Survey on clinicians Knowledge; Attitude and Perception regarding Antimicrobial resistance, Antibiotic stewardship and basic infection control practices during July 2014. Following the survey study an educational intervention was done. It was one day continued Medical Education

encompassing audio Visual Demonstration, didactic lectures, Interactive sessions andPost intervention Questionnaire survey[32]

RESULTS

Bacterial profile of ESKAPE pathogens from different specimen types are shown in TABLE-1. Trends in antibiotic susceptibility of ESKAPE are shown in Figure-1(*Enterococcusand Staphylococcus)*, Figure-3*(E.coli and Klebsiella*) and Figure-5 *(Pseudomonas and Acinetobacter)*.Specific resistance of the ESKAPE pathogens mentioned are shown in Figure-2 (VRE, HCLG, MRSA and VRSA), Figure-4 (ESBL E.coli, ESBLKlebsiella, Carbapenem resistance in E.coliand Klebsiella) and Figure-6 (Carbapenem resistance in Pseudomonas and Acinetobacter and Multidrug resistance in Pseudomonas and Acinetobacter)

Table 1: Bacterial profile of ESKAPE pathogens from different specimen types

Bacterial Isolates	Blood	Wound /pus	Respiratory samples**	Urine	Others *	Total Number
	No (%)	No (%)	No (%)	No (%)	No %	
Enterococcus spp	4 (0.6)	25 (2.1)	7 (0.7)	**280** (13.4)	7 (1.6)	**322**
Staphylococcus aureus	66 (10)	310 (26.4)	72 (7.7)	29 (1.4)	85 (19)	**562**
Klebsiella pneumoniae	112 (17.2)	66 (5.6)	339 (36.1)	358 (17)	37 (8.3)	**912**
Acinetobacter spp	37 (6.0)	14 (1.2)	72 (7.7)	15 (0.7)	14 (3.1)	**141**
Pseudomonas aeruginosa	59 (9.0)	292 (25.3)	210 (22.4)	132 (6.3)	135 (30.2)	**828**
Escherichia coli	32 (5.0)	165 (14.1)	28 (2.9)	950 (45)	113 (25.2)	**1288**
Others pathogens	341 (52.4)	301 (25.7)	210 (22.4)	341 (16.2)	56 (12.5)	1249
Total	**651 (100)**	**1172 (100)**	**938 (100)**	**2105 (100)**	**447 (100)**	

*Body fluids, Tissue specimens, Ear& Conjunctival swabs

** Sputum, Throat swabs, Endo tracheal sections

	Year	Enterococci			Staphylococcus		
Total ISOLATES	2013	50	322		170	562	
Total ISOLATES	2014	113			211		
Total ISOLATES	2015	159			181		
		No	%		No	%	
Gentamicin	2013				116	68	↑
	2014				159	75	
	2015				155	86	
HCLG	2013	15	30	↑			
	2014	35	31				
	2015	109	68				
Ampicillin	2013	15	30	↕			
	2014	22	19.4				
	2015	61	38.4				
Cefazolin	2013				90	53	↑
	2014				136	64	
	2015				133	73	
Ciprofloxacin	2013	70	35	↑	80	47	↑
	2014	51	45		105	50	
	2015	85	53.5		132	73	
Nitrofurantoin	2013	9	23	↑			
	2014	28	25				
	2015	65	50				
Erthromycin	2013				85	50	↑
	2014				140	66.6	
	2015				136	75	
Clindamycin	2013				115	67.6	↑
	2014				176	83.3	
	2015				150	85	
Linezolid	2013	50	100	↓	170	100	↕
	2014	113	100		211	100	
	2015	150	94		181	100	
Vancomycin	2013	47	94	↑	50	100	↕
	2014	110	97.3		209	99.1	
	2015	157	98.7		159	100	

↑ = Antibiogram becoming EFFECTIVE

↕ = Antibiogram that is Equivocal

↓ = AntibiogramLosing EFFECTIVENESS

Figure 1: Trends in Antibiotic Susceptibility of *Enterococci and Staphylococci* from 2013-2015

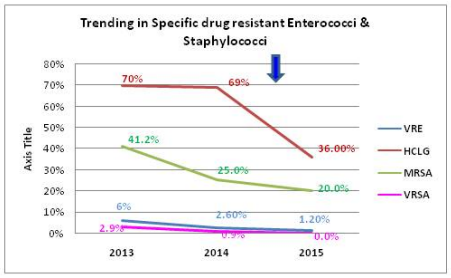

Figure 2

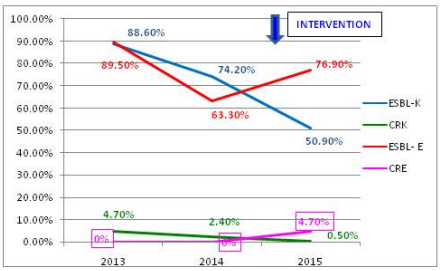

Figure 4

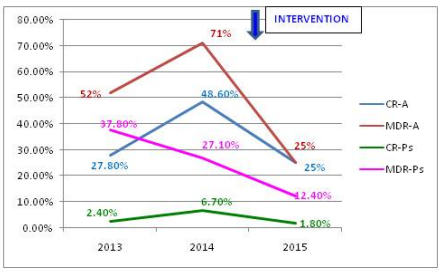

Figure 6

Figure 2: Trending in Specific drug resistant *Enterococci and Staphylococci;* **Figure 4:** Trending in Specific drug resistant *Klebsiella and E.coli;* **Figure: 6:** Trending in Specific drug resistant *Acinetobacter and Pseudomonas*

Legends for Figure-2:

VRE :(p for trend=0.04). Prevalent in UTI-43%, Overall prevalance-2.4% (8/322)
MRSA: (p for trend >0.05). Prevalent in Wound infections-53.2%, Overall prevalance-28.1% (158/562)
VRSA: (p for trend <0.001) Prevalent in wound infection-57.1%, Overall prevalence1.2 % (7/562)
HCLG: High Concentration level Gentamicin. Prevalent in UTI-

	Year	Klebsiella			E.coli		
TotalISOLATES	2013	212			286		
Total ISOLATES	2014	252	912		264	1288	
Total ISOLATES	2015	448			738		
		No	%		No	%	
Amikacin	2013	128	60	↑	220	77	↑
	2014	201	79		230	87	
	2015	412	92		679	92	
Gentamicin	2013	112	53	↓	118	41	↕
	2014	98	40		82	31	
	2015	180	40		281	38	
Ceftazidime	2013	24	11	↑	30	10.5	↕
	2014	65	26		97	36.75	
	2015	220	49		170	23	
Doxycycline	2013	29	22	↑	23	16	↕
	2014	51	22		07	13	
	2015	191	64		28	20	
Ciprofloxacin	2013	64	30	↑	39	14	↕
	2014	100	40		82	31	
	2015	312	70		194	26.2	
Nitrofurantoin	2013	39	48	↑	117	84	↕
	2014	101	78		205	77.6	
	2015	202	95.3		564	94	
Imipenem	2013	202	95.3	↑	286	100	↓
	2014	246	97.6		264	100	
	2015	446	99.5		703	95.2	
Pip-Taz	2013	193	91	↑	233	82	↑
	2014	246	97.6		236	89	
	2015	441	98.4		696	94.3	
Norfloxacin	2013	18	22	↑	22	16	↕
	2014	35	27		51	24	
	2015	59	40		132	22	
Cotrimoxazole	2013	26	32	↑	26	19	↕
	2014	39	30		62	29	
	2015	59	40		162	27.5	

↑ = Antibiogram becoming EFFECTIVE
↕ = Antibiogram that is Equivocal
↓ = AntibiogramLosing EFFECTIVENESS

Figure 3: Trends in Antibiotic Susceptibility of Klebsiella and E.coli from 2013-2015

Legends for Figure-4:

CRK: (Carbapenam Resistant Klebsiella)**:** (p for trend =0.001).Prevalent in UTI-55.6%, Overall prevalance-1.97% (18/912)
ESBL-k: (ESBL klebsiella) **:**(p for trend <0.0001). Prevalent in UTI-45.8%, Overall prevalence-66.1% (603/912)
CRE: (Carbapenem Resistant E.coli**) :**(p for trend >0.05).Prevalent in UTI-68.6%, Overall prevalance-2.7 % (35/1288)
ESBL-E: (ESBL E.coli) **:**(p for trend 0.004).Prevalent in UTI-71.5%, Overall prevalance-76.7% (988/1288)

	Year	Acinetobacter			Pseudomonas		
Total ISOLATES	2013	90	141		201	828	
Total ISOLATES	2014	35			240		
Total ISOLATES	2015	16			387		
		No	%		No	%	
Amikacin	2013	65	72	↑	151	75	↕
	2014	14	40		163	68	
	2015	15	94		374	97	
Ceftazidime	2013	43	48	↕	93	48.3	↑
	2014	10	28.6		146	61	
	2015	13	81.3		302	78	
Amp-Sulbactum	2013	65	72	↕			
	2014	18	45.7				
	2015	15	94				
Gentamicin	2013	35	39	↑	105	52.5	↑
	2014	16	45.1		142	59	
	2015	12	75		312	81	
Ciprofloxacin	2013	46	51	↕	95	47.5	↑
	2014	12	34		164	68.3	
	2015	12	75		312	81.3	
Imipenem	2013	65	72.2	↕	196	97.5	↕
	2014	18	51.4		224	93	
	2015	12	75		380	98.2	
Pip-Taz	2013	75	83	↕	152	75	↕
	2014	18	51.4		224	93	
	2015	13	81.3		352	91	
Pipericillin	2013	34	38	↕	128	64	↑
	2014	25	71		156	65	
	2015	11	69		294	76	

↑ = Antibiogram becoming EFFECTIVE

↕ = Antibiogram that is Equivocal

↓ = AntibiogramLosing EFFECTIVENESS

Figure 5: Trends in Antibiotic Susceptibility of *Acinetobacter and Pseudomonas* from 2013-2015

Legends for Figure-6:

CR-A: (Carbapenem resistant Acinetobacter)**:**(p for trend 0.025). Prevalent in RTI-42.2%, Overall prevalance-32.6% (46/141)

MDR-A: (MDR Acinetobacter) **–** (p for trend >0.05)-Prevalent in RTI-76.3 %, Overall prevalance-53.4% (76/141)

CR: Ps (Carbapenam Resistant Pseudomonas): (p for trend-0.25). Prevalent in miscellaneous infections-89%, Overall prevalance-3.4 %(28/828)

MDR-Ps: (MDR Pseudomonas)**:** (p for trend -0.001). Prevalent in Wound infections-36%, Overall prevalance-22.8% (189/828)

DISCUSSION

Infectious disease aetiology might be due to different bacterial species in a hospital environment and MDR intensifies the possibility of resistance spread leading to decline in efficacy of treatment. Due to increased propensity to become MDR, the ESKAPE pathogens need specific attention and intervention. In the ESKAPE pathogen profile from different specimen types (TABLE-1) Enterococci spp is predominantly isolated from Urine (87%) and Staphylococci from Wound specimens (55%). Among Gram Negatives E.coli and Klebsiella were frequently isolated from Urine, (74% and 39% respectively), Pseudomonas from wound specimens (35%) and Acinetobacter from respiratory specimen (51%). In a study by Anuradhaetal, predominance of Enterococci in Urine and Staphylococci in wound specimens were in concordance with our study, but all the Gram Negatives were frequently isolated from wound specimens[18]. Slavochi etal analysed ESKAPE in Pneumonia and [12] reported Klebsiella (13.8 %) as predominant pathogen followed by Staphylococcus (12.2%). In our study predominant respiratory pathogens were Klebsiella (36%) followed by Pseudomonas (22.6%). A surveillance study of ESKAPE in ICU from Mexico by Jorge martin *et al* reported overall prevalent bug among ESKAPE was Acinetobacter (15.8%), followed by Pseudomonas andKlebsiella (14.3% and 14.2%). Predominant Respiratory tract pathogen was Acinetobacter and Klebsiella (18.8%and18.2%), uropathogen was Pseudomonas (31%). Predominant ESKAPE pathogen at ICU in our study was Klebsiella during the pre-intervention period (2013 and 2014), but E.coli was predominant in 2015.In a study by MeetasharmaetalE.coli was prevalent isolate in all specimens types except Respiratory specimens where Klebsiella was prevalent[25]. In Egyptian study[14] prevalent

blood stream pathogen was Klebsiella followed by Staphylococcus aureus which is in concordance with our study. Trending Antibiotic sensitivity of Enterococci and Staphylococcus for three year period was analysed (Fig 1 and Fig 2). There was an improvement in the sensitivity percentage in 2015 for most of the antibiotics tested, when compared to 2013. Enterococci showed an effective sensitivity for all antibiotics except Linezolid which declined in 2015. An equivocal response was seen for Ampicillin. Following educational intervention a continuous down trend in Specific drug resistance for Enterococci and staphylococci (VRE, HLGR, MRSA, and VRSA) was noted as shown in Fig-2.Overall VRE % and MRSA % in our study was 2.4% and 28.1%. This is in concordance with many reported National and international studies where VRE ranges from 1.4-8% and MRSA from 23.6%-59%.[3,12,19,21,23] Two reports from India[18,22] showed higher VRE prevalence rates as 19.9% and 23% respectively and low susceptibility rates for common antibiotics. Trending sensitivity of Klebsiella and E.coli is shown in Fig 3 and Fig-4. Klebsiella shows increase in sensitivity percentage for all the antibiotics following intervention. But for E.coli, effective antibiogram was seen only for Amikacin and Pipericillin-tazobactum. A decline in sensitivity percentage was noted for all other antibiotics tested in spite of educational intervention. In Fig-6 decline in Beta lactamases resistance (ESBL and Carbapenam resistance) was noted for Klebsiella during the post intervention period, while for E.coli there was an increase. Over all ESBLs and Carbapenama resistance for Klebsiella was 66.1% and 1.97% and for E.coli 76.7% and 2.7 % respectively in our study. Carbapenam resistance for both Klebsiella and E.coli was low in our study when compared to our national report. [3]Other studies also show similar prevalence rates for ESBL production in Klebsiella species ranging from 40%-76%.[12,16,20,24] In a study by Ranjani *et al*[27]. ESBL was observed in 39% of E.coli with Imipenem, Amikacinand Nitrofurantoin showing greater than 80% susceptibility rates. Likewise other studies also showed good susceptibility rates for Imipenem, Nitrofurantoin and Amikacin.[24-28] There was a fluctuation in sensitivity percentage as seen in fig-5and Fig-6 for Acinetobacter and Pseudomonas. The sensitivity for most of the commonly used antibiotics was increased in 2015 when compared to 2013, following a decline in 2014. Trending Carbapenem and Multi drug resistance for Acinetobacter and Pseudomonas is shown in Fig-9.Overall Carbapenem and Multidrug resistance percentage for Acinetobacter was 32.6% and 53.4% and for Pseudomonas was 3.4% and 22.8% respectively at our centre. Carbapenam resistance for the above mentioned non fermenters was low in our study when compared to our national report.[3] A higher prevalence rates for Multidrug resistance in Acinetobacter (70%) and Pseudomonas (80%)was reported by Slovachi *et al*[12]and by sudaharansuhanyaetal[30] (MDR Acinetobacter-77%). In a review article[29] Pavani Gandham discussed an increasing MDR Acinetobacter in India. ESKAPE achieved prominent role due to lack of clinical awareness and limited antibiotic development. A national action plan (NAP) identified AMR as a potential threat and strategies were published to combat the same[31]. Our tertiary care center implemented improving awareness and understanding of AMR through effective communication, education and training; *strengthening* knowledge and evidence through surveillance and *reducing* the incidence of infection through effective infection prevention and control. The education intervention [32] which was a multi-centre study (including our tertiary care centre) showed a considerable improvement among clinicians regarding Antimicrobial resistance and Antibiotic policy. Future plans are to *optimize* the use of antimicrobial agents

CONCLUSION

The alarming frequency and increased tendency of extremely drug resistant ESKAPE is world-wide. The awareness of local AMR can support the selection of convenient empirical therapy. Our Observations at our centre shows the current level of high antibiotic resistance pattern and its declining trend from the recent past on the emerging global threat against ESKAPE organisms. Though there was an increase in sensitivity percentage for most of the antibiotics following intervention, a narrow spectrum of sensitivity was observed for commonly used antibiotics. These results should be emphasized in training the health care providers for Basic infection control measures, Antibiotic policy and Antibiotic stewardship. Educational interventions have proved to be only moderately effective in our study. Need for periodic emphasis on Infection control policy and Antibiotic policy to contain the spread of resistance, and select appropriate empirical antibiotic therapy.

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