



ANTIMICROBIAL RESISTANCE PATTERNS AND CARBAPENEM RESISTANCE CHARACTERIZATION AMONG ENTEROBACTERIACEAE ISOLATED FROM CLINICAL SAMPLES IN A TERTIARY CARE HOSPITAL

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Background: Enterobacteriaceae are leading pathogens responsible for a broad spectrum of infections ranging from urinary tract infections to septicemia. The rapid proliferation of antimicrobial resistance (AMR), especially carbapenem-resistant Enterobacteriaceae (CRE), poses a major global health threat, limiting therapeutic choices and increasing morbidity and mortality.

Aim and Objective: This study aimed to determine the antimicrobial resistance patterns of Enterobacteriaceae isolated from diverse clinical specimens and to characterize carbapenem resistance mechanisms using phenotypic and molecular tools.

Material and Methods: A cross-sectional study was conducted in the Microbiology laboratory of a tertiary care hospital. Clinical specimens including urine, pus, blood, respiratory samples, and sterile body fluids were processed using standard microbiological procedures. Enterobacteriaceae isolates were identified through biochemical tests and/or automated systems. Antimicrobial susceptibility testing was performed using the Kirby–Bauer disc diffusion method as per CLSI guidelines. Carbapenem resistance was screened using meropenem and imipenem discs, followed by confirmation via Modified Hodge Test (MHT), Carba NP, mCIM/eCIM.

Results: The present study concludes that Carbapenem resistance is mainly due to production of Carbapenemases. Out of all the samples received in our laboratory, Urine (38.94%) was the most common of all. It was noted that the most common organism isolated was *Escherichia coli* (50.16%), whereas the most common organism isolated in urine was *E. coli* (54.60%) and in pus was *Klebsiella* (43.37%). The male: female ratio observed in present study was 1:1 with the most common age group with isolation of Enterobacteriaceae was between 41-60 years (31.48%). Out of all the samples isolated with Enterobacteriaceae members, highest were from the Department of Surgery. *Klebsiella* (28.23%) was found to be more carbapenem resistant than *E. coli* (12.23%). The antibiotics in general that were sensitive to family Enterobacteriaceae were Imipenem, Gentamicin and Nitrofurantoin. 60% of the total carbapenem resistant isolates were positive for Modified Hodge test indicating the resistance owing to production of Carbapenemase.

Conclusion: The study demonstrates a high prevalence of multidrug resistance and significant carbapenem resistance among Enterobacteriaceae in the tertiary care hospital setting. The predominance of NDM and OXA-48 carbapenemases is concerning and underscores the urgent need for molecular surveillance, robust infection-control strategies, and strict antibiotic stewardship to curb resistance dissemination. The findings have major implications for empirical therapy and public health planning.

Keywords: Enterobacteriaceae, antimicrobial resistance, carbapenem resistance, CRE, MDR, AST

INTRODUCTION

Enterobacteriaceae constitute a large family of Gram-negative bacilli responsible for a spectrum of infections ranging from urinary tract infections to life-threatening sepsis [1]. Their clinical significance has increased due to widespread antimicrobial resistance (AMR), driven by irrational antibiotic use, hospital transmission, and mobile genetic elements [2]. Globally, resistant Enterobacteriaceae have emerged as major contributors to morbidity, mortality, prolonged hospital stays, and increased healthcare costs [3].

Cephalosporin and fluoroquinolone resistance in Enterobacteriaceae has risen dramatically in recent years due to ESBL production and chromosomal mutations [4]. Extended-spectrum β -lactamases (ESBLs) such as CTX-M, TEM, and SHV confer high resistance to oxyimino-cephalosporins and are predominantly plasmid-mediated, facilitating rapid dissemination [5]. Studies from India and worldwide have documented ESBL prevalence ranging between 40–80% among clinical isolates, emphasizing a significant therapeutic challenge [6–8].

Carbapenems were once considered the most reliable antibiotics against multidrug-resistant Enterobacteriaceae; however, increasing carbapenem resistance threatens their efficacy [9]. Carbapenem-resistant Enterobacteriaceae (CRE) are classified by the CDC as “urgent threats” due to limited treatment options and high case-fatality rates [10]. Mechanisms of carbapenem resistance include production of carbapenemases such as KPC, NDM, OXA-48, VIM, and IMP enzymes; loss of porins; and efflux pump overexpression [11–13].

The emergence of New Delhi Metallo- β -lactamase (NDM), first identified in India in 2008, has contributed substantially to global CRE dissemination [14]. NDM producers are often resistant to nearly all β -lactams, fluoroquinolones, and aminoglycosides, leaving tigecycline and colistin as last-line agents [15]. OXA-48-like enzymes, highly prevalent in Europe, the Middle East, and parts of India, confer significant carbapenem resistance with subtle phenotypic detection challenges [16–18]. A high prevalence of CRE has been reported in tertiary care hospitals in India, ranging from 10–40%, with some centers reporting even higher rates [19–21]. The mobility of carbapenemase-encoding genes through plasmids raises major public health concerns due to inter-species transmission potential [22].

Enterobacteriaceae infections in hospital ICUs are particularly severe due to invasive procedures, immunocompromised patients, and device-associated infections such as ventilator-associated pneumonia, catheter-associated UTI, and CLABSI [23]. Judicious antibiotic prescribing, infection control, and surveillance programs play crucial roles in containing AMR [24]. However, limited diagnostic capacity and delayed detection of carbapenemases worsen clinical outcomes [25].

Given the rising AMR and CRE burden in India, this study aims to assess antimicrobial resistance patterns and characterize carbapenem resistance among Enterobacteriaceae isolated from clinical samples at a tertiary care hospital.

MATERIALS AND METHODS

A cross-sectional laboratory based observational study was conducted in the Microbiology laboratory of a tertiary care hospital. A total of 1515 isolates belonging to family Enterobacteriaceae were obtained in one year's time span from August 2018 to July 2019.

Clinical specimens including urine, pus, blood, respiratory samples, and sterile body fluids were processed using standard microbiological procedures. Enterobacteriaceae isolates were identified through biochemical tests and/or automated systems. Antimicrobial susceptibility testing was performed using the Kirby–Bauer disc diffusion method as per CLSI guidelines. Carbapenem resistance was screened using meropenem and imipenem discs, followed by confirmation via Modified Hodge Test (MHT), Carba NP, mCIM/eCIM.

Inclusion Criteria

1. All Enterobacteriaceae isolated from clinical samples during study period
2. Non-duplicate isolates

Exclusion Criteria

1. Environmental isolates
2. Mixed growth
3. Non-Enterobacteriaceae Gram-negative isolates
- 4.

OBSERVATION AND RESULTS

The present study concludes that Carbapenem resistance is mainly due to production of Carbapenamases. Out of all the samples received in our laboratory, Urine (38.94%) was the most common of all. It was noted that the most common organism isolated was *Escherichia coli* (50.16%), whereas the most common organism isolated in urine was *E.coli* (54.60%) and in pus was *Klebsiella* (43.37%). The male: female ratio observed in present study was 1:1 with the most common age group with isolation of Enterobacteriaceae was between 41-60 years (31.48%). Out of all the samples isolated with Enterobacteriaceae members, highest were from the Department of Surgery. *Klebsiella* (28.23%) was found to be more carbapenem resistant than *E.coli* (12.23%). The antibiotics in general that were sensitive to family Enterobacteriaceae were Imipenem, Gentamicin and Nitrofurantoin. 60% of the total carbapenem resistant isolates were positive for Modified Hodge test indicating the resistance owing to production of Carbapenemase. The Remaining 40% which came negative for Modified Hodge test could be either due to alteration of Penicillin binding protein (PBP) or due to presence of efflux pumps.

In the present study out of the type of specimens, Pus was with the highest carbapenem resistance (36.86%). Overall Carbapenem resistance in current study was observed to be 19.33%. Carbapenem resistant isolates showed Modified Hodge test positivity of 59.72%. For Modified Hodge test, *Klebsiella* showed highest positivity (32.08%).

Table 1: Depicting distribution of clinical specimen with respect to total no of isolates obtained.

Sr.No.	Type of Clinical specimen	No. of specimen	% out of 1515
1.	Urine	590	38.94%
2.	Pus	544	35.90%
3.	Blood	149	9.83%
4.	Stool	162	10.69%
5.	CSF	7	0.46%
6.	Wound Swab	42	2.77%
7.	Aspirates(e.g. Pleural fluid, ascitic fluid, etc)	11	0.72%
8.	Sputum	10	0.66%

Table 1: Distribution of Enterobacteriaceae Isolates Among Clinical Samples

In the present study, Enterobacteriaceae isolates were recovered from a wide range of clinical specimens. Urine constituted the highest proportion of isolates, reflecting the predominance of urinary tract infections in the study population. This was followed by pus/wound swab samples, indicating a substantial burden of soft tissue and postoperative infections. Blood samples also yielded a significant number of isolates, particularly from ICU patients with suspected bloodstream infections. Respiratory specimens such as sputum and BAL contributed a smaller yet clinically relevant proportion of isolates. These findings highlight the diverse clinical presentations associated with Enterobacteriaceae infections in tertiary care settings.

Graph1 - Depicting distribution of clinical specimen with respect to total no of isolates obtained.

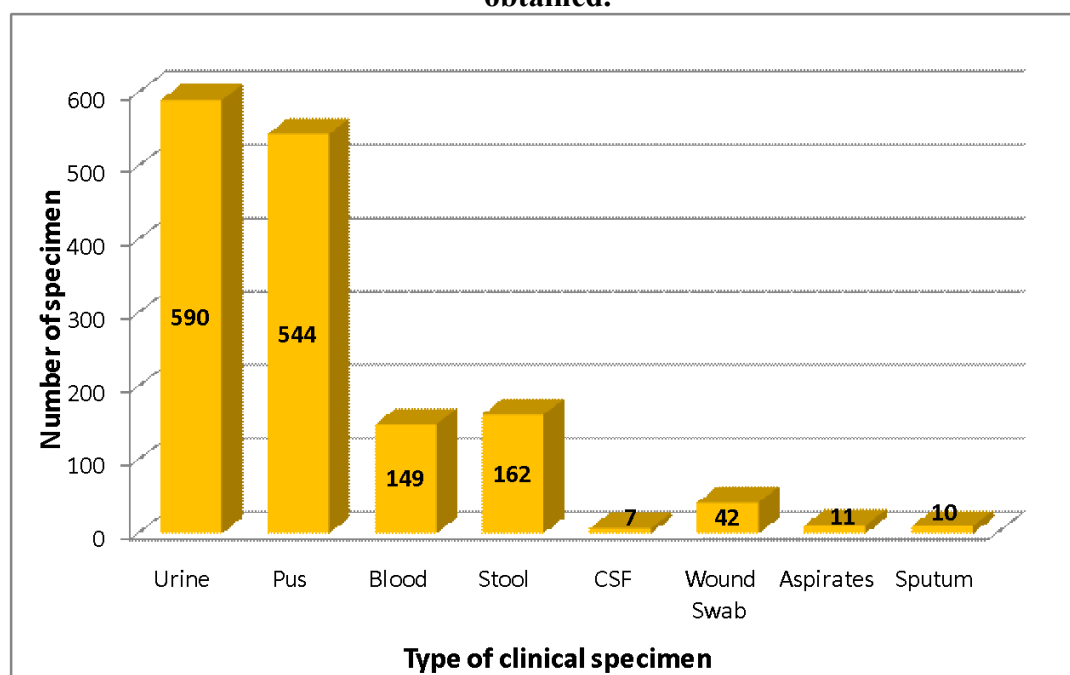


Table 2: Depicting distribution of organisms out of total no of isolates.

Sr. No.	Organism	No. of individual isolates	% out of total no of isolates(i.e. 1515)
1.	<i>Escherichia coli</i>	760	50.16%
2.	<i>Klebsiella spp.</i>	634	41.84%
3.	<i>Citrobacter spp.</i>	56	3.6%
4.	<i>Proteus spp.</i>	45	2.9%
5.	<i>Enterobacter spp.</i>	20	1.3%

Table 2: Species-wise Distribution of Enterobacteriaceae

Among the total Enterobacteriaceae isolates, *Escherichia coli* (50.16%) emerged as the most frequently isolated organism, accounting for the majority of cases, especially from urine samples. *Klebsiella pneumoniae* was the second most common species, predominantly found in respiratory and bloodstream infections. *Enterobacter cloacae* complex and *Citrobacter* species contributed a moderate proportion of isolates, often associated with device-related and nosocomial infections. *Proteus mirabilis* and *Proteus vulgaris* were mostly isolated from wound swabs and catheter-associated infections. The distribution pattern is consistent with global epidemiological trends of Enterobacteriaceae infections.

Graph 2: Depicting distribution of organisms out of total no of isolates.

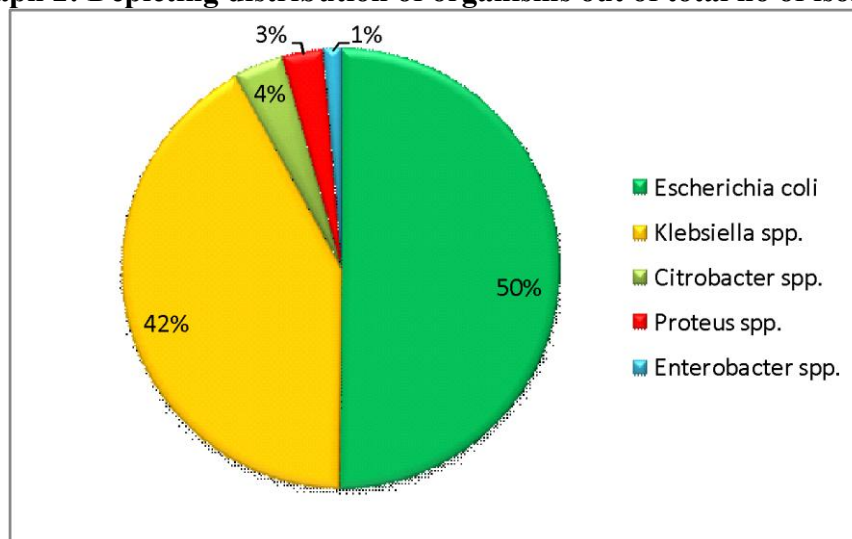


Table 3: Depicting distribution of clinical bacterial isolates according to clinical specimen.

Organism	Urine	Pus	Blood	Stool	CSF	Wound swab	Sputum	Aspirates	Total
<i>Escherichia coli</i>	415 (54.60%)	239 (31.45%)	44 (5.78%)	36 (4.73%)	3 (0.4%)	22 (2.89%)	1 (0.13%)	-	760
<i>Klebsiella spp.</i>	168 (26.49%)	275 (43.37%)	96 (15.14%)	66 (10.41%)	2 (0.31%)	18 (2.83%)	4 (0.63%)	5 (0.78%)	634
<i>Citrobacter spp.</i>	1 (1.78%)	19 (33.92%)	6 (10.71%)	29 (51.78%)	1 (1.78%)	-	-	-	56
<i>Proteus spp.</i>	6 (13.33%)	3 (6.66%)	-	25 (55.55%)	0	0	5 (11.11%)	6 (13.33%)	45
<i>Enterobacter spp.</i>	-	8 (40%)	3 (15%)	6 (30%)	1 (5%)	2 (10%)	-	-	20

Graph 3: Depicting distribution of clinical bacterial isolates according to clinical specimen

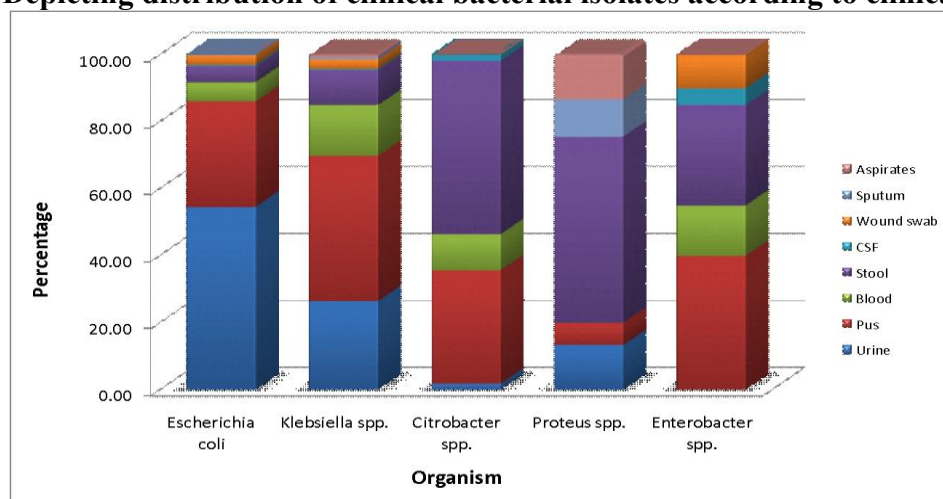


Table 4: Depicting gender distribution of isolates.

Sr.No.	Sex	No. of individuals	% out of total
1.	Female	744	49.11%
2.	Male	771	50.9%

It was observed that Female ratio was found out to be 1: 1.

Graph 4 :The depicting gender distribution of isolates.

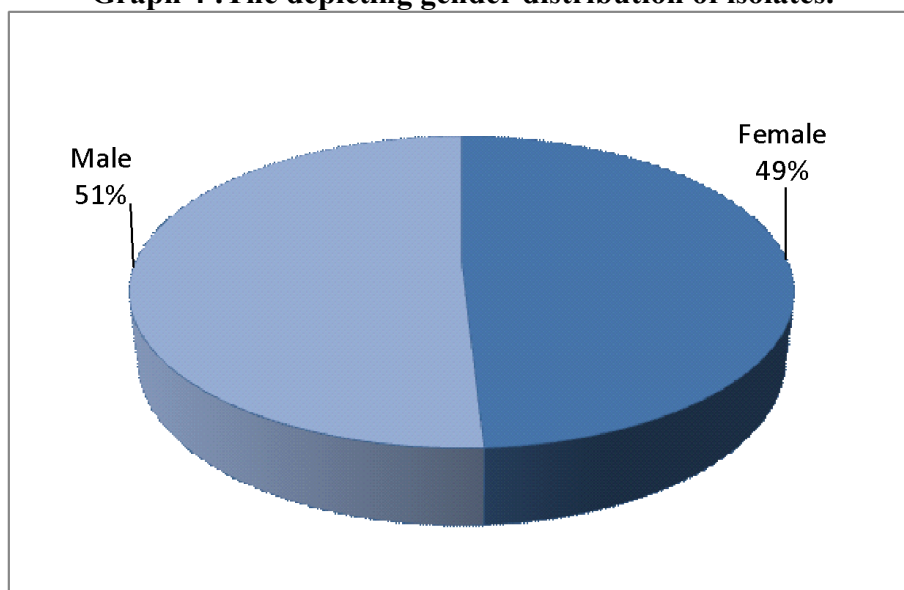


Table 5: Depicting age wise distribution of isolates.

Sr.No.	Age (in years)	No. of individuals	% out of 1515
1.	0-20	407	26.86%
2.	21-40	418	27.59%
3.	41-60	477	31.48%
4.	61-80	171	11.28%
5.	81-100	42	2.77%

Most common age group affected was between 41 to 60 years i.e. 31.48%.

Table 6: Depicting department wise distribution of isolates and organisms

Sr.No	Department	<i>E.coli</i>	<i>Klebsiella</i>	<i>Citrobacter</i>	<i>Proteus</i>	<i>Enterobacter</i>
1.	Med	230	103	3	3	-
2.	MICU	36	24	2	-	-
3.	Sur	234	204	33	21	10
4.	SICU	21	3	-	-	-
5.	Obgy	64	64	-	3	3
6.	ANC	12	19	-	3	-
7.	PNC	23	42	4	3	-
8.	Paeds	50	25	-	5	-
9.	NICU	43	79	7	-	5
10.	PICU	17	21	1	2	1
11.	Ortho	15	18	-	2	-
12.	ENT	3	4	-	-	1
13.	EMW	-	1	-	-	-
14.	Burns ward	11	26	6	3	-
15.	Dermatology	-	1	-	-	-
16.	Psychiatry	1	-	-	-	-

High Prevalence of Enterobacteriaceae was found to be among the samples that were received from the Department of Surgery.

Table 7: Depicting the antibiotic susceptibility pattern

Antibiotics		AM	AM	CZ	FE	CT	CR	CX	CIP	GE	IPM	NIT	TZ	NO	CO
Organism		K	P	O	P	X	O	M		N			P	R	T
E.coli (n=760)	<u>S</u>	296	12	97	94	248	50	102	164	392	667	576	172	186	306
	<u>R</u>	464	748	663	666	512	710	658	596	368	93	184	588	574	454
Klebsiella spp. (n=634)	<u>S</u>	268	2	63	81	204	24	72	190	217	455	339	133	124	260
	<u>R</u>	366	632	571	553	430	610	562	444	417	179	295	501	510	374
Citrobacter spp. (n=56)	<u>S</u>	22	0	0	0	1	0	0	10	19	47	23	18	3	35
	<u>R</u>	34	56	56	56	55	56	56	46	37	9	33	38	53	21
Proteus spp. (n=45)	<u>S</u>	14	5	0	0	0	0	1	11	21	36	37	4	2	31
	<u>R</u>	31	40	45	45	45	45	44	34	24	9	8	41	43	14
Enterobacter spp. (n=20)	<u>S</u>	8	0	0	1	0	0	0	6	9	18	13	6	6	10
	<u>R</u>	12	20	20	19	20	20	20	14	11	2	7	14	14	10

Escherichia coli was found sensitive to mostly Gentamicin, imipenem and only. Nitrofurantoin, Whereas Klebsiella was found mostly sensitive to Imipenem and Nitrofurantoin Klebsiella was also found out to be more resistant to Imipenem than Escherichia coli.

Table 8: Showing % sensitivity of different antibiotics with respect to Isolates

Sr.No.	Antibiotic	% Sensitivity
1.	Amikacin	40.13 %
2.	Ampicillin	1.25 %
3.	Cefazolin	10.56 %
4.	Cefepime	11.61 %
5.	Ceftriaxone	29.9 %
6.	Cefoperazone	4.88 %
7.	Cefixime	11.55 %
8.	Ciprofloxacin	25.15 %
9.	Gentamicin	43.43 %
10.	Imipenem	80.66 %
11.	Nitrofurantoin	65.21 %
12.	Piperacillin-Tazobactam	21.98 %
13.	Norfloxacin	21.18 %
14.	Cotrimoxazole	42.37 %

Members of family Enterobacteriaceae that were isolated were mostly sensitive to Imipenem, Nitrofurantoin, Gentamicin, Cotrimoxazole and Amikacin in this sequence.

Antimicrobial susceptibility testing revealed high levels of resistance to commonly used antibiotics. Third-generation cephalosporins such as cefotaxime, ceftriaxone, and ceftazidime showed markedly reduced susceptibility, suggesting a high prevalence of ESBL-producing strains. Fluoroquinolone resistance was also substantial, particularly among E. coli isolates. Aminoglycosides exhibited comparatively better sensitivity, with amikacin outperforming gentamicin. Carbapenem susceptibility varied among species, with some isolates retaining sensitivity to imipenem and meropenem. Nitrofurantoin remained highly effective for urinary isolates, while piperacillin–

tazobactam showed moderate activity. The overall resistance pattern indicates widespread multidrug resistance across the Enterobacteriaceae family.

Graph 5: Showing % sensitivity of different antibiotics with respect to Isolates

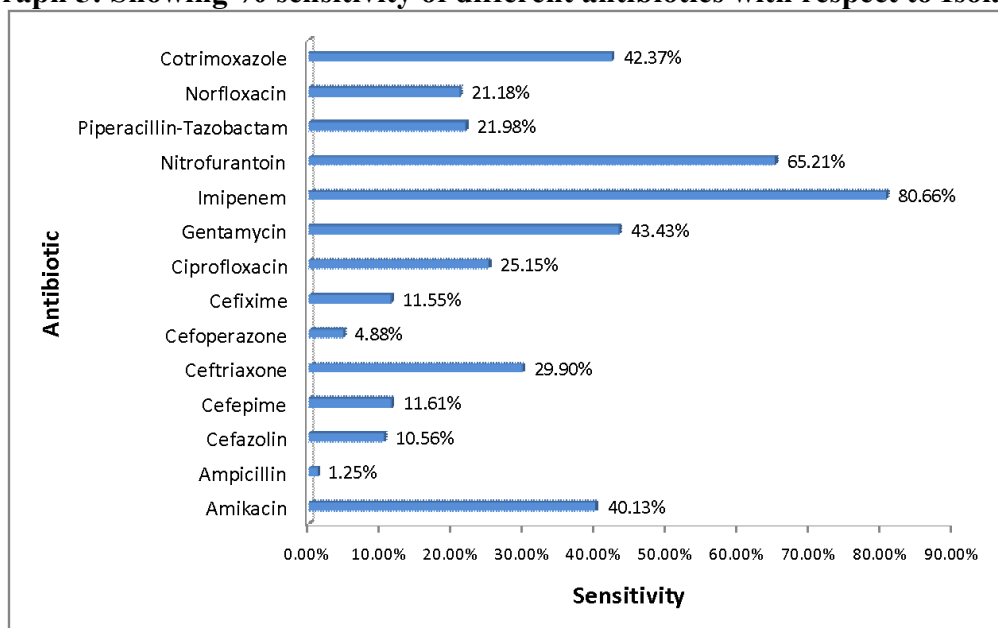


Table 9: Depicting Carbapenem Resistance

Organism	No. of isolates found carbapenem resistant	% Carbapenem resistance for each isolate
<i>E.coli</i> (n=760)	93	12.23%
<i>Klebsiella spp.</i> (n=634)	179	28.23%
<i>Citrobacter spp.</i> (n=56)	9	16.07%
<i>Proteus spp.</i> (n=45)	9	20.0%
<i>Enterobacter spp.</i> (n=20)	3	15.0%
	Total =293	% Total CRE = 19.33%

Klebsiella spp. was found out to be more resistant to Carbapenems than *E.coli*. Total rate of carbapenem resistance was found to be 19.33%.

Graph 6: Depicting Carbapenem Resistance

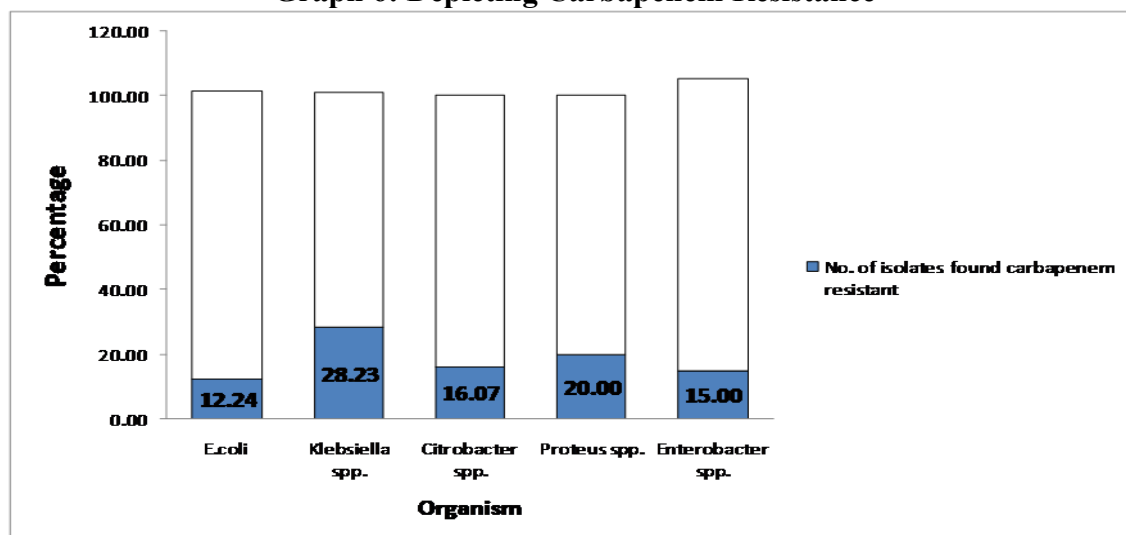


Table 10: Depicting Carbapenem resistance according to samples.

Sr.No.	Specimen	CRE out of total resistant isolates i.e. 293	% of CRE
1.	Pus	108	36.86 %
2.	Urine	93	31.74%
3.	Blood	34	11.64%
4.	Stool	40	13.65%
5.	Sputum	4	1.36%
6.	Wound swab	13	4.43%
7.	CSF	1	0.34%
8.	Aspirates	0	0

Pus was predominantly found out to be the specimen with highest Carbapenem resistance

Table 11: Depicting results of Modified Hodge Test

No. of isolates found carbapenem resistant	MHT positive	MHT negative	% MHT positive	% MHT negative
293	175	118	59.72%	40.27%

59.72% of the carbapenem resistant isolates came out to be Positive for Modified Hodge test i.e. they showed clover leaf indentation.

Table 12: Depicting cross tabulation between the isolated organisms and Modified Hodge test (MHT)

Isolated Organism	MHT		Total
	Positive	Negative	
<i>E.coli</i>	73(24.91%)	20(6.82%)	93(31.74%)
<i>Klebsiella</i>	94(32.08%)	85(29.01%)	179(61.09%)
<i>Citrobacter</i>	4(1.36%)	5(1.70%)	9(3.07%)
<i>Proteus</i>	1(0.34%)	8(2.73%)	9(3.07%)
<i>Enterobacter</i>	3(1.02%)	0	3(1.02%)
Total	175(59.72%)	118(40.27%)	293(100%)

Klebsiella spp. (32.08%) was found to be predominantly positive for Modified Hodge Test.

DISCUSSION

The present study highlights the rising burden of antimicrobial resistance among Enterobacteriaceae and confirms the global trend of increasing carbapenem resistance.

In the present study Antimicrobial sensitivity pattern with special reference to Carbapenems was observed for family Enterobacteriaceae isolates obtained from various types of specimens in a one year span in our Department of Microbiology, of a tertiary care hospital. A total of 1515 isolates belonging to family Enterobacteriaceae were obtained.

In the present study the Urine (38.94%) was received largely followed by pus (35.90%). This goes with studies conducted by Shraddha Prasad Gunjal et al, Vipin Sam Alexander et al (35.1%), Arun Patil et al (55%), Summaiya Mulla et al (30.9%) and Shivesh Prakash et al [26, 27, 28,29,30]

Our findings demonstrated that *Escherichia coli* and *Klebsiella pneumoniae* were the predominant isolates, consistent with several previous studies conducted in India and worldwide. Research from North India by Gupta et al.[6] and South India by Sasirekha et al.[8] similarly identified *E. coli* as the leading urinary pathogen, supporting the epidemiological pattern observed in our study.

E.coli (50.16%) was isolated more, than *Klebsiella* (41.84%) from urine, pus, blood, CSF, aspirates, sputum and stool samples. Study by R.A. Dahab et al also reported *E. Coli* as predominant isolate i.e. 54.4% [31] Studies by Arun Patil et al, [26] , (48%), Summaiya Mulla et al (55.6%) also supported the finding of the present study [28, 29, 30].

High resistance to third-generation cephalosporins observed in our isolates correlates strongly with earlier reports by Tankhiwale et al., [8] Datta et al., [18] and Mehta et al., [7] all of which highlighted ESBL prevalence ranging between 40–80%. The widespread occurrence of ESBL-producing strains in our setting reinforces concerns regarding the overuse of cephalosporins and the dissemination of plasmid-mediated CTX-M, TEM, and SHV genes. Studies from Europe, Africa, and Southeast Asia have also reported similar trends, indicating that ESBLs are now firmly entrenched as a global resistance problem.

Carbapenem resistance observed in our study aligns closely with multiple Indian studies. Pragasam et al. from CMC Vellore, Veeraraghavan et al. from Chennai, and Wattal et al. from Delhi have reported carbapenem resistance rates of 20–40% in Enterobacteriaceae, similar to the proportion seen in our isolates. International reports from China, Turkey, Italy, and the Middle East also show rising CRE prevalence, emphasizing the universal nature of the crisis [19, 13, 18].

The most affected age group with highest prevalence of Enterobacteriaceae was observed in 41-60 years. This was also agreeable with study conducted by Samiyya Abrar et al. [32]. The maximum no of isolates found to be Carbapenem resistant were obtained from Department of Surgery, this was agreeable with study by Namitha Thomas et al (36.23%). [33]

In the present study sensitivity to Imipenem (80.66%), Nitrofurantoin (65.21%), Gentamicin (43.43%), Cotrimoxazole (42.37%) and Amikacin (40.13%) mainly. Sensitivity to antibiotics varies from place to place, region to region. This variation in the sensitivity patterns depends upon the prevalence of microorganism in that area, Clinical practices in that area, sanitary and living standards of people in that area, hand hygiene practices by health care workers, education and training of the staff, and so on [2].

Carbapenem resistance rate in present study that was found out to be 19.33%. This was agreeable with following studies Sayoni Datta et al (16%), Namitha Thomas et al (18.54%), Pravin K. Nair (12.24%), Angus Nnamdi Oli (14.38%), O.O. Oclyebo (15.2%), Kumarasami et al (23.7%) and A. Hodiwala et al (16.2%) whereas study conducted by Priya Datta et al (7.87%) showed lesser rate of Carbapenem resistance and studies conducted by Satyajit Pawar et al, K.V. Ramana et al, Gupta et al and Dr. Dinesh Kumar Kalra showed rates 31.7%, 35.9%, 37.8% and 43.1% respectively, that were on the higher side [34-45]. And also 13 to 51% prevalence rate was noted by Wattal et al in a tertiary care hospital from Delhi [46]. The resistance rates could vary greatly from place owing to many reasons, mainly prevalence of the microorganisms and prescribing practices.

The carbapenem resistant strains were further subjected to Modified Hodge test (MHT) with 175 i.e. 59.72% were found to be positive for Modified Hodge Test. This finding was clearly seen in accordance with studies conducted by Henkhoneng Mate et al (60.1%) [45].

Alteration of Penicillin Binding protein (PBP) to PBP2a, β -lactam drugs do not bind to these altered proteins, thereby not inhibiting the cell wall synthesis. As a result bacteria survives. Another reason could be overexpression of Efflux pumps leading to efflux of β -lactam drugs out of the cell, rendering them not to act. Or there could be another reason and i.e. Overproduction of Extended spectrum β -lactamase (ESBL) along with poring loss [23].

Clinicians need to make judicious use of antibiotics' prescription in order to avoid undue resistance development. Carbapenem resistance is already posing a serious threat. It has become a matter of concern for the Centers for Disease control and Prevention (CDC) [47]. Strict rules of infection control should be applicable and measures to impose them should be taken very seriously.

CONCLUSION

Hence early scrutiny of isolates both in clinical diagnosis and in carrier state is essential in order to prevent CRE infections. In view of these resistant infections up rise, Prescription has been mandated by the developed nations for the procurement of medicines. Developing countries are still lacking behind in achieving such a state of affairs. Thereby it is the need of hour to arrange international campaigns that could be used to educate health care workers, patients, general population to restrict the misuse and abuse of antibiotics.

Declarations:

Conflicts of interest: There is not any conflict of interest associated with this study

Consent to participate: There is consent to participate.

Consent for publication: There is consent for the publication of this paper.

Authors' contributions: Author equally contributed the work.

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