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Detection of Carbapenemase Production in Clinical Isolates of *Escherichia coli* and *Klebsiella* Species

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A B S T R A C T

The increasingly frequent application of carbapenemases induces a selective pressure on bacteria to acquire resistance against carbapenems. A large variety of carbapenemases have been identified in Enterobacteriaceae. The emergence of carbapenemases in *E. coli* and *Klebsiella species* possess a serious therapeutic problem in hospitals because carbapenems are often antibiotics of last resort for the treatment of serious infections caused by multidrug-resistant bacteria. The main aim of this study to determine the carbapenem-resistant strains of *Escherichia coli* and *Klebsiella species*. Detection of carbapenemase enzyme in the carbapenem-resistant *Escherichia coli* and *Klebsiella species*. This is a cross-sectional study, performed in the bacteriological laboratory. A total of 204 strains of *Escherichia coli* and 122 strains of *Klebsiella species* were isolated from patients admitted & attending the OPD at Sharda Hospital during the study period. The identification of the clinical isolates was based on morphological and biochemicals characterization. Result: Among the total number of bacterial growth received during the study period, the *E. coli* (204) was more in number as compared to other bacterial strains followed by *Klebsiella species* (122), *Pseudomonas species* (117), *Staphylococcus aureus* (100) and *Enterococcus species* (80). Among the following specimen i.e, urine (58.8%), was highly received during the study period followed by pus (15.3%) and sputum (7.5%). Colistin (100%) and Polymyxin B (100%) is found to be the most sensitive drug. Gentamicin (19.6%) and Cefuroxime (12.2%) are the least sensitive drugs. In the present study, we found that the *Klebsiella species* (75%) and *Escherichia coli* (64%) was the major reason of carbapenemase production but the organisms incidentally were susceptible to colistin and polymyxins (100%) followed by other antibiotics. This is a welcome finding in times of increasing carbapenem resistance & is reason enough to suggest the use of Polymyxins in the health care settings where the carbapenems to be used for the treatment of infections caused by Enterobacteriaceae.

Introduction

The genus *Escherichia* and *Klebsiella* belong to the family of Enterobacteriaceae. *Escherichia coli* are one of the most common members of the family Enterobacteriaceae and often exist as commensal in the gastrointestinal tract of humans and animals.

Klebsiella pneumoniae is the most clinically relevant *Klebsiella species* and is responsible for over 70% of human infections due to this genus [(1)]. In humans, *K. pneumoniae* most often colonizes the gastrointestinal tract, skin, and nasopharynx and is an important cause of serious community-onset infections such as necrotizing pneumonia, pyogenic liver abscesses, and endogenous endophthalmitis [(2)].

Various types of infections are caused by *E. coli* and *Klebsiella species* including urinary tract infections, neonatal meningitis, skin infections, sepsis, and intestinal infections more frequently than other members of the Enterobacteriaceae.

The increasingly frequent application of carbapenemases induces a selective pressure on bacteria to acquire resistance against carbapenems. A large variety of carbapenemases have been identified in Enterobacteriaceae belonging to three classes of beta-lactamases: classes A, B, and D [(4)]. These classes are of the greatest clinical importance among nosocomial pathogens.

The emergence of carbapenemases in *E. coli* and *Klebsiella species* possess a serious therapeutic problem in hospitals because carbapenems are often antibiotics of last resort for the treatment of serious infections caused by multidrug-resistant bacteria. These bacteria have the potential to spread rapidly within the hospital environment and also across the continent[(6)]. Detection of carbapenemases thus plays a crucial role as an infection control issue because they are often associated with extensive antibiotic-resistant, treatment failures and infections [(7).]

The present study is conducted to identify the carbapenemase resistance in *E. coli* and *Klebsiella species* from both in and outpatient samples in our tertiary care hospital.

The main aim of this study includes to determine the carbapenem-resistant strains of *Escherichia coli* and *Klebsiella species.* Detection of carbapenemase enzyme in the carbapenem-resistant *Escherichia coli* and *Klebsiella species*.

Materials and Methods

The study was conducted in a bacteriology laboratory in Sharda Hospital, Greater Noida. It was a cross-sectional study. The study was conducted from December-2019 to November 2020. All the clinical isolates of *Escherichia coli* (*E. coli*) & *Klebsiella* species are processed during the study period.

All the carbapenem-resistant *E. coli* and *Klebsiella* species isolates were included in the study. Whereas exclusion criteria were not applicable in the study.

Methodology including all the specific specimens, tests for species identification such as direct microscopy (gram stain), hanging drop, biochemical reactions (catalase, oxidase, ICUT, MR test, VP test, nitrate reduction test, oxidation-fermentation test, decarboxylase test, sugar fermentation test, and AST.

Incubation of culture media

For incubation Bacteriological incubator was used which helps to grow and maintain the bacteriological culture at 37ºC. [(8)]

Sample Processing

All the isolates of clinical samples were processed for *E. coli* & *Klebsiella species* as per the standard guidelines (9).

Antimicrobial Susceptibility Testing was performed on Mueller-Hinton Agar (MHA) by Kirby-Bauer Disk-Diffusion method as the screening was done by this method as per the CLSI guidelines 2019 (9).

Carbapenem resistance was detected by interpreting the zone diameters of imipenem, meropenem, and ertapenem as per the CLSI 2019 guidelines (9).

Detection of carbapenemase in carbapebem resistant *E. coli* and *Klebsiella species*.

Screening Test

Screening tests in the laboratory, acarbapenem-intermediateor- the resistant result should always raise the suspicion of possible carbapenemase production, as they should reduce carbapenem susceptibility within the susceptible range in isolates of members of the family Enterobacteriaceae. The best carbapenem for screening is unknown. In the present study, the screening was done by the Kirby Bauer Disk-Diffusion method.

Disk diffusion method (Kirby Bauer)

The Kirby-Bauer test, also known as the disk diffusion method, is the most widely used antibiotic susceptibility test in determining what choice of antibiotics should be used when treating an infection. [15]

Confirmatory test

A confirmatory test in the laboratory was done to confirm the resistance of the carbapenems which was screened during the screening method.

Ethylenediaminetetraacetic acid (EDTA) impregnated disc test

An enhancement in the zone of inhibition in the area between the Imipenem alone and the EDTA-Imipenem combined discs in comparison with the zone of inhibition on the far side of the drug was interpreted.

Observations and Results

A total no. of 204 strains of *Escherichia coli* and 122 strains of *Klebsiella species* were isolated from patients admitted & attending the OPD at Sharda Hospital during the study period (1st December 2019 – 30th November 2020).

The table given below depicts the number of patient samples received in the bacteriology laboratory for culture & sensitivity during the study period.

Among the total number of bacterial growth received during the study period, the *E. coli* (204) was more in number as compared to other bacterial strains followed by *Klebsiella species* (122), *Pseudomonas species* (117), *Staphylococcus aureus* (100), and *Enterococcus species* (80).

Demographic Distribution of Various Samples Collected

Out of 204 isolated organisms, 48% were from male patients and 51.9% were from female patients indicating higher rates of samples collected from females during a study period.

Out of 122 isolated organisms, 38.8% were from female patients and 61.4% from male patients indicating higher rates of samples collected from males during a study period

Age-Wise Distribution of Organisms

The maximum number of isolates were obtained from the age group (21-30) i.e, (25.4%) in *Escherichia coli* and (22.1%) in *Klebsiella species* followed by the age group (41-50 years) of age i.e, (14.7%) and (15.5%) and followed by (61-70years) i.e, (9.8%) and (20.4%) in *Escherichia coli* and *Klebsiella* species respectively.

Among the following specimen i.e, urine (58.8%), was highly received during the study period followed by pus (15.3%) and sputum (7.5%) as shown in the previous table 4.

Antibiotic Susceptibility Pattern of Enterobacteriaceae in *Escherichia Coli* and *Klebsiella* Species

Escherichia Coli

There are 4 classes of antibiotics tested for antibiotics susceptibility in Enterobacteriaceae. These included -lactams (penicillins, cephalosporins, and carbapenems), aminoglycosides (gentamicin), fosfomycin, fluoroquinolones (levofloxacin, ciprofloxacin), tetracyclines, and polymyxins (colistin and Polymyxin B).

Amongst all the classes, polymyxins emerged as the most effective class of drugs against *E. coli* followed by Fosfomycin and penicillins.

Klebsiella Species

Amongst all the antibiotics, polymyxins (colistin and polymyxin B) were found to be most effective against *Klebsiella species*. They were followed by Fosfomycin, Tetracycline, Meropenem, Imipenem, and Ertapenem. Whereas, Gentamicin and Amoxyclav were found to be the most resistant drugs. Also, Cefuroxime was found to show resistance.

Screening Test

Out of 326 clinical isolates of GNB, 139(42%) isolates were resistant to carbapenems (imipenem, ertapenem, meropenem).

A total number of 64 isolates of *Escherichia coli* were carbapenem-resistant from 204 isolates. Whereas, a total number of 75 isolates of *Klebsiella species* were carbapenem-resistant from 122isolates.

A total number of 139 isolates were carbapenem-resistant in *Escherichia coli* and *Klebsiella species* out of 326 isolates.

Prevalence of MBL production was highest in *Klebsiella species* (51.8%), followed by *Escherichia coli* (48.1%), as shown in table 8.

All the isolates were identified based on culture characteristics, gram staining, and biochemical reactions. The isolates were subjected to antimicrobial susceptibility testing.

Out of 326 clinical isolates of GNB, 133(42%) isolates were resistant to carbapenems (imipenem, ertapenem, meropenem).

Prevalence of MBL production was highest in *Klebsiella species* (51.8%), followed by *Escherichia coli* (48.1%), as shown in the previous table.9.

Results and Discussion

The present study was conducted to know the prevalence of carbapenemase production in clinical isolates of *Escherichia coli* and *Klebsiella species* in our hospital and to know their antibiotic susceptibility profiles and resistance patterns. In our study 868 bacterial isolates were cultured from various (13,639) clinical specimens over 12 months, 204(23.5%) isolates were identified as *Escherichia coli* and 122(14%) as *Klebsiella species*.

Higher prevalence was observed in a study conducted by André Birgy *et al.,* in 2012 where *E. coli* was 57.7%. in another study conducted by Wonkeun Song, *et al.,* in 2015, 23.8% *Klebsiella species* were isolated(20).

In this study, the maximum number of isolates were obtained from the age group (21- 30 years) i.e, (25.4%) in *Escherichia coli* and (22.1%) in *Klebsiella species* followed by the age group (41-50 years) of age i.e, (14.7%) and (15.5%) and followed by (61- 70years) i.e, (9.8%) and (20.4%) in *Escherichia coli* and *Klebsiella species* respectively. The high prevalence was observed in *E. coli* (33%) and low prevalence was observed in *Klebsiella species* (13%) in a study done by Kathleen Chiotos *et al.,* in 2016.(19) Bacteriological profile in our study revealed the maximum number of strains of *Escherichia coli* and *Klebsiella species* in this study were isolated from urine (58.8%), followed by pus (15.3%) and sputum (7.5%) to be the most common carbapenem-resistant pathogens. This result was comparable with the study done by Setegn Eshetie *et al.,* in 2015, maximum isolated Enterobacteriaceae were from urine (87.6%%).

Amongst all the strains of *Klebsiella species (122)*, the commonest species isolated in human clinical specimens was *Klebsiella pneumoniae* 106 (86.8%) followed by *Klebsiella oxytoca* 16(13.1%). This was similar to the study done by Sakina Yousuf Ali, *et al.,* in 2020.[(23)]

Table.1 Disk diffusion method (Kirby Bauer)

Screening drugs	Dose	Zone Diameter (mm) Sensitive(S)	Resistant (R)
Ertapenem	10µg	≥22	**≤18**
Imipenem	10µg	≥23	**≤19**
Meropenem	**10µg**	**≥23**	**≤19**

Table.2 Total samples received during the Study Period

IPD		
Positives N (%)	**Negatives N (%)**	**Total**
762 (20.6%)	**2930 (79.3%)**	**3692**
OPD		
Positives N (%)	**Negatives N (%)**	**Total**
497 (4.9%)	**9450 (95%)**	**9947**
Total Samples		
1259	**12380**	**13639**

Table.3 Organisms received during the study period.

IPD	**762**
OPD	**497**
Escherichia coli	**204**
Klebsiella species	**122**
Pseudomonas species	**117**
Staphylococcus aureus	**100**
Enterococcus species	**80**

Table.4 Age-Wise Distribution of Organisms

Age Group	*Escherichia coli (%)*	*Klebsiella species (%)*
<1D to 10y	10.7	**9.8**
11 to 20 y	6.3	**3.27**
21 to 30 y	25.4	**22.1**
31 to 40 y	14.7	**9.8**
41 to 50 y	14.7	**15.5**
51 to 60 y	8.8	**8.1**
61 to 70 y	9.8	**20.4**
71 to 80 y	11.27	**09**
81 to 90 y	0.98	**1.6**
90 to 100 y	**-**	**0.8**

Table.5 Specimen Wise Distribution of *Escherichia Coli* and *Klebsiella* Species

Specimen	*Escherichia coli (n=204)*	*Klebsiella species (n=122)*	Total (n=326) / (%)
Urine	153	39	**192 (58.8)**
Pus	27	22	**49 (15.3%)**
Sputum	07	16	**23 (7.5%)**
Blood	04	09	**13 (3.9%)**
Stool	06	0	**06 (1.8%)**
Tip, (catheter, ETT)	-	22	**22 (6.7%)**
Bronchio alveolar lavage (BAL)	02	02	**04 (1.2%)**
Body Fluids	01	01	**02 (0.6%)**
Swabs	-	01	**01 (0.3%)**
Tracheal Secretion	-	07	**07 (2.1%)**
TISSUE	01	02	**03 (0.9%)**
Bronchial Aspirate	01	01	**02 (0.6%)**
Bile	**01**	**-**	**01 (0.3%)**

Table.6 Distribution of carbapenem-resistant isolates

Total number of isolates	**326**	**25.8%**
Carbapenem-resistant in *E. coli*	64	**46%**
Carbapenem-resistant in *Klebsiella species*	75	**53.9%**
Total Carbapenem-Resistant isolates	**139**	**42.6%**

Table.7 Showing Screening Positives for *Escherichia coli* and *Klebsiella species*

	Escherichia coli n= 64	***Klebsiella species n = 75***
Screening Positives	IPM + EDTA	**IPM + EDTA**
n = 139	40	**44**
Percentage (%)	**62.5**	**58.6**

Table.8 Showing Prevalence of MBL Production

	Escherichia coli	***Klebsiella species***	**Total**
ISOLATES	204	122	**326**
MBL (Total) MBL (Positives) MBL (Weakly Positives)	64 08 32	75 27 17	**139** **35** **49**
PERCENTAGE (%)	**31.3%**	**61.6%**	**40.7%**

Fig.1

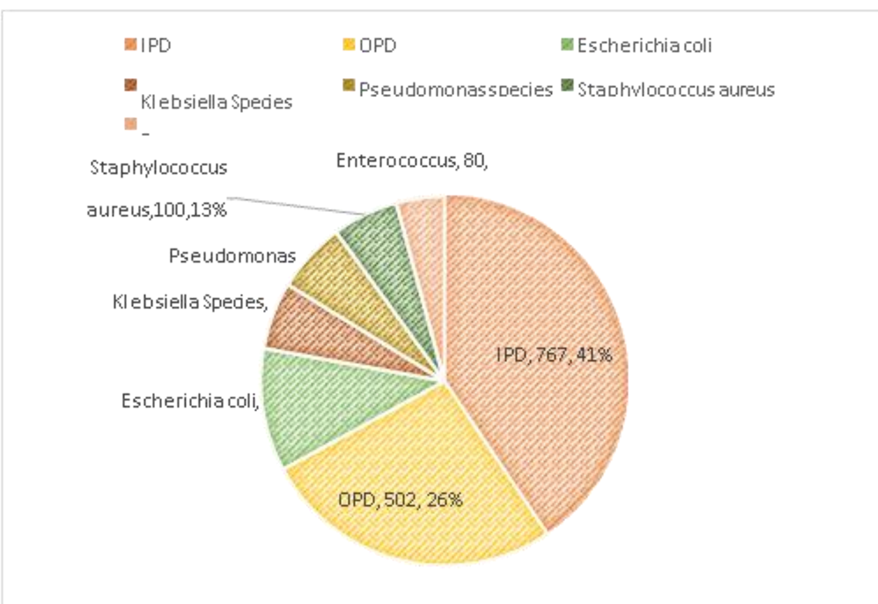


Fig.2 Showing Male: Female Ratio for *Escherichia coli*.

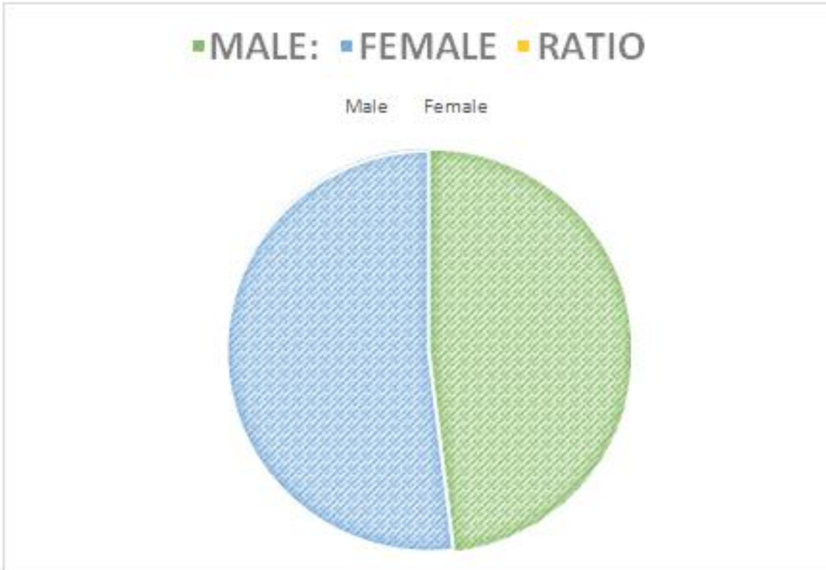


Fig.3 Showing Male: Female Ratio for *Klebsiella species*.

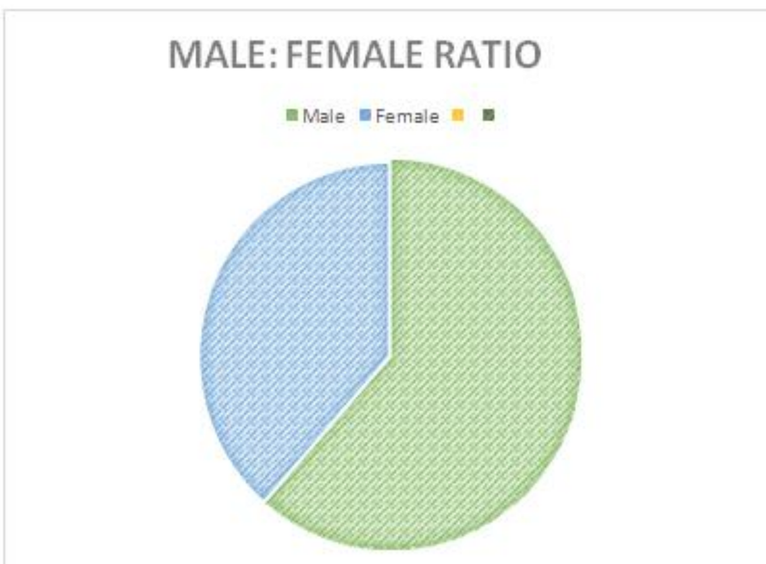
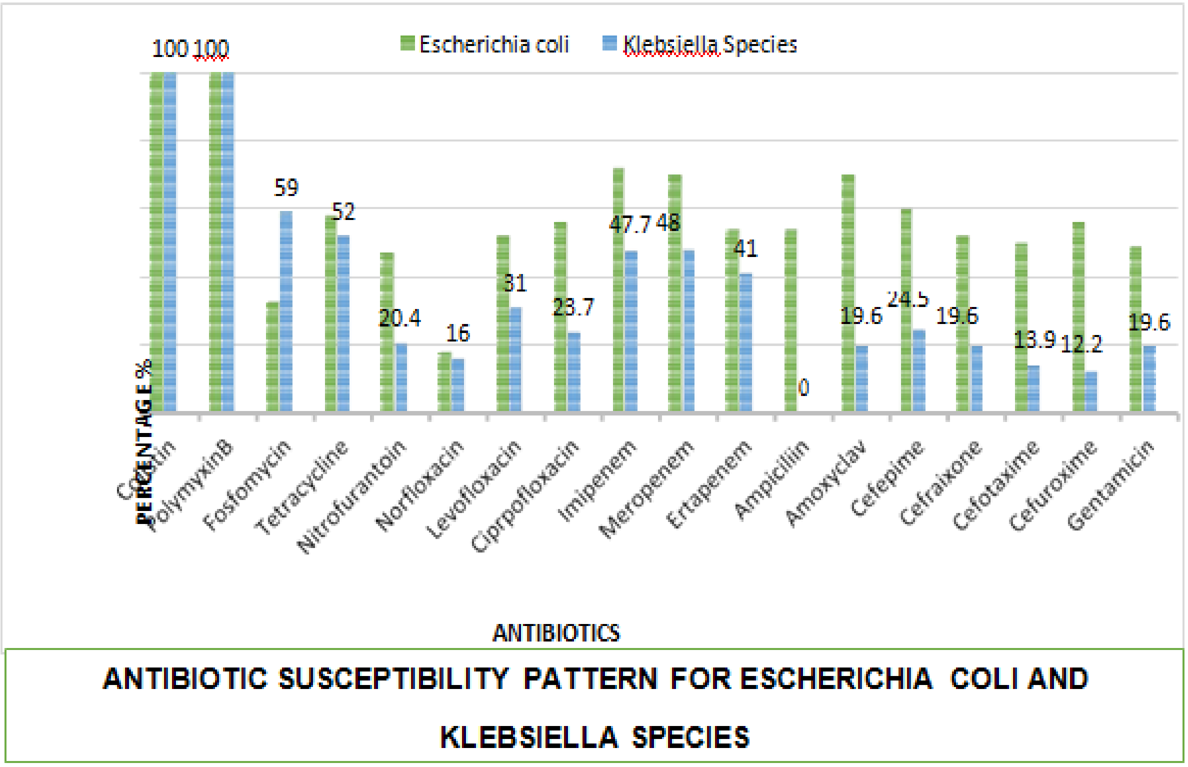


Fig.4



Colistin (100%) and Polymyxin B (100%) is found to be the most sensitive drug. Gentamicin (19.6%) and Cefuroxime (12.2%) are the least sensitive drugs.

Fig.5 Screening Test

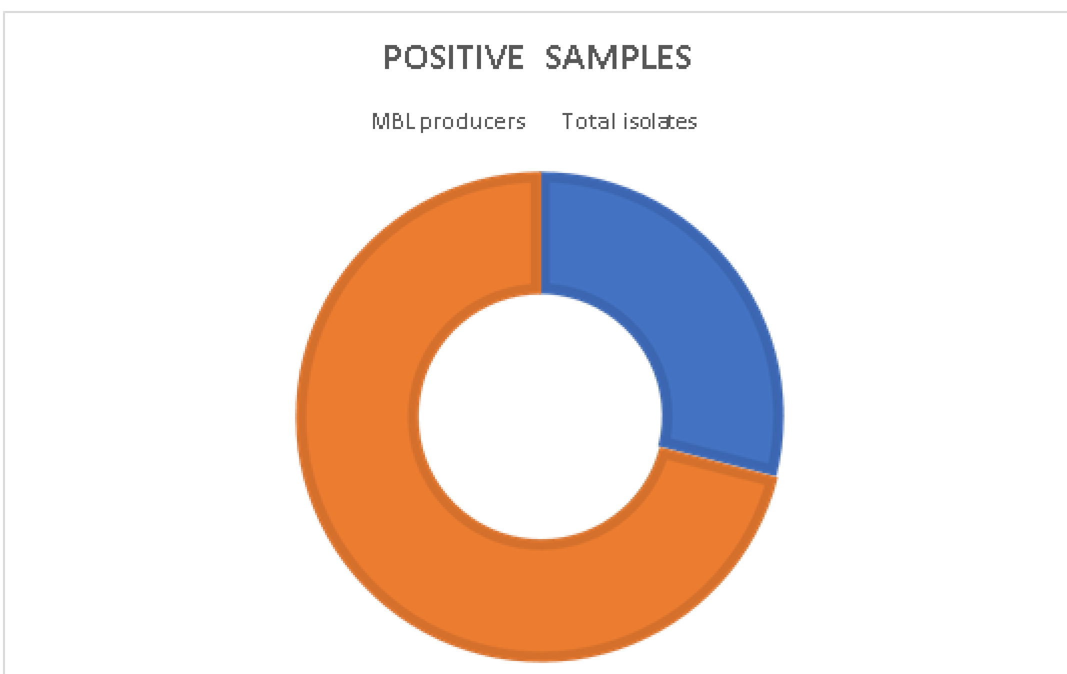
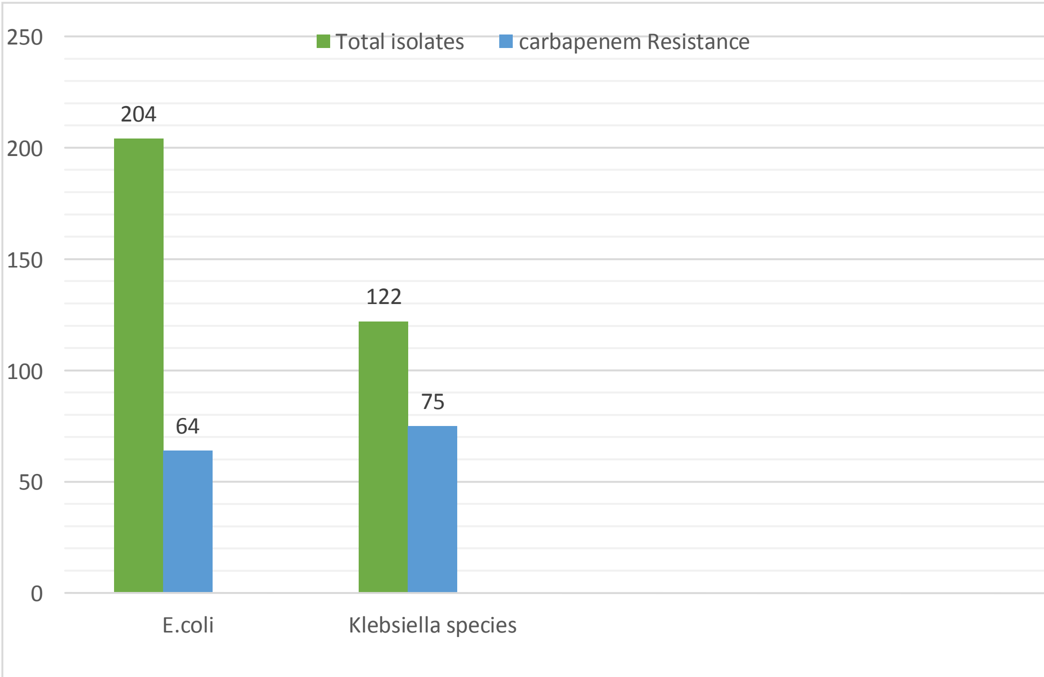


Fig.6



In our study, *Escherichia coli* was found to be more susceptible to Polymyxins, i.e, Colistin (100%) and Polymyxins B (100%), which correlates with the study done by Beatriz Suay *et al.*, in 2019 where Colistin and Polymyxins were100% sensitive to *E. coli*(18).

Klebsiella species were found to be highly sensitive to antibiotics Colistin (100%) and Polymyxins (100%), followed by Fosfomycin (59%) whereas Cefuroxime (12.2%) was found to be most resistant.

Similar findings were observed by Kathleen Chiotos *et al.*, in their study – the highest sensitivity was observed to Polymyxins followed by Fosfomycin. (25)

The present study highlighted the burden of carbapenem resistance in critical and non-critical areas of our tertiary care hospital. In this study, out of 326 (25.8%) strains of *Escherichia coli* and *Klebsiella species*, 139 (42.6%) were carbapenem-resistant, 64 (46%) isolates are of *Escherichia coli* and 75(53.9%) isolates are of *Klebsiella species*.

Out of 326 strains of *E. coli* and *Klebsiella* isolated during the study period, 139 were resistant to imipenem. Out of these, in *Escherichia coli* 40 (28.7%) and *Klebsiella species* 44 (31.6%) were positive for MBL production by combined disk test (Imipenem + Imipenem EDTA). A similar result was observed in a study conducted by e André Birgy *et al.*, in 2012 where 28.7% were positive for MBL production by combined disk test. [11,18]

The concomitant presence of several different types of β-lactamases in resistant *Enterobacteriaceae* makes it more difficult to detect individual mechanisms, as one mechanism can mask another. Phenotypic detection of combined mechanisms of resistance, such as MBL-expressing isolates, is important for epidemiological purposes and for implementing rapid and specific infection control measures. This is a satisfactory and inexpensive method for characterizing the type of carbapenemase and for detecting associated resistance mechanisms in laboratories when PCR is not readily available.[11] Carbapenem-resistant Enterobacteriaceae (CRE) pose an exponentially increasing threat to public health worldwide. These bacteria possess diverse and versatile mechanisms of drug resistance, which makes control and early detection of infections caused by CRE difficult. However, one striking feature noticed was the carbapenem resistance was more in the urine specimen in the case of both; *Escherichia coli* and *Klebsiella species*.

In the present study, we found that the *Klebsiella species* (75%) and *Escherichia coli (64%)* was the major reason of carbapenemase production but the organisms incidentally were susceptible to colistin and polymyxins (100%) followed by other antibiotics. This is a welcome finding in times of increasing carbapenem resistance & is reason enough to suggest the use of Polymyxins in the health care settings where the carbapenems to be used for the treatment of infections caused by Enterobacteriaceae. Although outbreaks of carbapenemase-producing organisms have been difficult to control, there are data that if systematically implemented, rigorous infection control procedures can halt the spread of these organisms in both hospital and community-acquired infections.

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