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Original Research Article

Carbapenemase detection amongst *Acinetobacter baumannii* and *Klebsiella pnuemoniae*

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Abstract

Introduction: Multidrug and carbapenem resistance is an increasing problem worldwide, which are most commonly seen in *Klebsiella* and *Acinetobacter* in the health care setting. Due to this reason, the interest in older antimicrobial agent, like fosfomycin has increased. Acinetobacter species generally exhibit intrinsic resistance to fosfomycin, combining it with other antibiotics can often make it effective against these bacteria, particularly with multidrug-resistant strains, as fosfomycin can act synergistically with other agents to enhance its antibacterial activity.

Aim and Objective: To detect the production of carbapenemases among carbapenem resistant (CR) *Klebsiella* and *Acinetobacter* spp. and also to know the susceptibility of CR *A. baumannii* and *K. pnuemoniae* to Fosfomycin.

Materials and Methods: Prospective study conducted over a period of 1 year (Jan-Dec 2019) included 120 Clinical isolates of CR *Acinetobacter baumanii* and *Klebsiella pneumoniae* were collected from the patients admitted to a tertiary care hospital, Mysuru, Karnataka, South India. These isolates were subjected to a phenotypic method, the CARBA NP and CARB-ACINETO NP method for *K. pnuemoniae* and *A. baumannii* respectively to detect the carbapenemase production and also subjected to Fosfomycin susceptibility testing.

Result: of the 57 CR *A. baumannii*, about 48(84.21%) were positive and 9(15.7%) were negative for CarbAcineto NP test method. And about 48(84.22%) were sensitive and 9(15.78%) were resistant to fosfomycin. Of the 63 CR *K.pnuemoniae*, about 50(79.63%) were positive and 13(20.63%) were negative for CARBA NP test method. And about 56(88.89%) were sensitive and 7(11.11%) were resistant to fosfomycin.

Conclusion: Our study demonstrated high activity of Fosfomycin against CR *A. baumannii* and *K. pnuemoniae* representing that fosfomycin can be used as an important alternative to carbapenems and also to Colistin (i.e. in colistin resistant isolates).

Keywords: Carbepenem resistance, Carba NP, CarbAcineto, Fosfomycin, Resistance, Multidrug resistance.

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1. Introduction

Carbapenem resistant gram-negative bacterial infections represent a major clinical concern. Carbapenem resistance is defined as resistance to either one or all the carbapenems (ertapenem, imipenem, meropenem and doripenem). Increasing occurrence of infections is seen recently due to CR organism especially in *K. pnuemoniae* and *A. baumanii*.[1]

K. pneumoniae a gram-negative rod-shaped bacterium causing health care associated infections in humans including urinary tract infections, pneumonia, meningitis and sepsis.[3] *Acinetobacter baumanii* is a gram-negative bacterium often associated with nosocomial infections, including bacteremia, pneumonia, meningitis and urinary tract infections and is listed as one of the six top-priority dangerous microorganisms by the Infectious Diseases Society of America (IDSA).[2]

Although *Acinetobacter spp.* shows intrinsic resistance to fosfomycin, it can become much effective against these bacteria when administered in combination with the other drugs.

Multi-drug and carbapenem resistance in an increasing problem worldwide. Of particular concern is the spread of carbapenemases, because these beta-lactamases mediate resistance to all or almost all beta-lactam antibiotics. In

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addition, strains carrying carbapenemases very often harbor resistance mechanisms against several unrelated antibiotics.[4,5,6,7] Only a few antimicrobial agents with clinically significant activities against resistant strains of Gram-negative bacteria are currently at or beyond phase III of development. This might lead to serious therapeutic limitations in treatment of many severe hospital-acquired infections. Due to the increase in multidrug-resistance, the interest in older antimicrobial agents, like fosfomycin, has increased. Fosfomycin is used for the treatment of uncomplicated urinary tract infections as a single-dose oral form.[7,12] Of note, in its intravenous form, the drug is also considered for the treatment of severe infections, like bacteremia and pneumonia, due to multidrug-resistant Gram-negative bacteria. Fosfomycin inhibits the N-acetylglucosamine-3-O-enolpyruvyl transferase, which catalyzes the conversion of UDP-N-acetyl glucosamine to UDP-N-acetyl muramic acid. This enol pyruvyl transferase is essential for any bacterium possessing muramic acid in its cell wall structure. Fosfomycin can enter the bacterial cell only by active transport.[5,6,7] Two transport systems are known to exist, the L-glycerol phosphate system and the hexose monophosphate route. The hexose monophosphate route system is more important and has to be induced, especially by glucose-6-phosphate. Though fosfomycin is intrinsically resistant to CR *A. baumannii* and *K. pnuemoniae*, it is effective against them when administered in combination with the other drugs.[6,7]

The aim of this study was to determine the Carbapenemases production in CR *A. baumannii* and *K. pnuemoniae* by using a phenotypic method, the CarbAcineto and CARBA NP method respectively. And this study was also aimed to detect the susceptibility of fosfomycin in CR *A. baumannii* and *K. pnuemoniae*.

2. Materials and Methods

The present study was carried out in the Department of Microbiology, JSS Hospital, Mysuru, Karnataka, India for a period of 1 year i.e., from January 2019-December 2019. Clinical isolates of *Acinetobacter baumanii* and *Klebsiella pnuemoniae* that are carbapenem (resistant to at least any one of the Carbapenems or to all) resistant were included and carbapenem sensitive *Acinetobacter baumanii* and *Klebsiella pnuemoniae* were excluded from the study.

2.1. Procedure

The clinical samples like, Pus, Sputum, ET secretions, BAL, Blood and other Body fluids received were processed on standard culture media (i.e., streaked on NA, BA and MA), which enables for the phenotypic identification of the organism. The isolated organisms of *A. baumannii* and *K. pnuemoniae* were subjected to Antimicrobial Susceptibility testing by VITEK-2 method following manufactures instructions. *A. baumannii* was subjected with N281 panel of drugs and *K. pnuemoniae* was subjected with N280 panel of drugs. CR *A. baumannii* and *K. pneumonia* were collected (carbapenem resistance is defined as resistance of the organism to one or all of the carbapenems like imipenem, meropenem, ertapenem and doripenem) and subjected to CarbAcineto NP and CarbaNP test respectively.

2.2. Detection of carbapenemases by CARBA NP method: CarbaNP Test was performed following the protocol recommended by CLSI 2019.[13]

1. Bacteria which were grown overnight on Mueller-Hinton agar (MHA) were scraped off with a loop and suspended in a 1.5-ml Eppendorf tube containing 100µl of 20 mM Tris-HCl lysis buffer and mixed using a vortex device for 5seconds.
2. This lysate was mixed with 100 µl of an aqueous indicator solution consisting of 0.05% phenol red with 0.1 mmol/liter ZnSO4, previously adjusted to pH 7.8 and 6 mg/ml imipenem or 12 mg/ml imipenem-cilastatin injectable form (equivalent to 6 mg of imipenem standard powder) (reaction tube) and, as a control tube, the phenol red solution without antibiotic
3. These tubes was incubated at 35°C and monitored throughout 2 hours for colour change from red to orange/yellow in the antibiotic-containing tube, which was interpreted as a positive result.[13] The positive control was ATCC BAA-1705 *K. pnuemoniae* and negative control was ATCC 25922 *E. coli*.

2.3. CarbAcineto NP test

The CarbAcineto NP test was adapted from the updated version of the CarbaNP test in order to use the test for *Acinetobacter spp*.[14]

In this updated version, the lysis buffer was replaced by a 5 M NaCl solution, avoiding any buffer effect, and the bacterial inoculum was doubled from one-third to one-half of a calibrated loop (10µl) to a full calibrated loop in order to increase the enzyme quantity. Briefly, a full calibrated loop (10µl) of the tested strain was recovered and resuspended in two 1.5-ml Eppendorf tubes (A and B) containing 100µl of 5 M NaCl.[14]

In tube A (internal control), 100µl of the revealing solution containing a pH indicator (phenol red) was added. 100µl of an extemporaneously prepared revelation solution supplemented with 6 mg/ml imipenem was added to tube B (test tube). Both the tubes A and B were incubated at 37°C for a maximum of 2 h. Optical reading of each tube by observing color change was performed.[14]

The carbapenemase activity in tube B was detected by a color change of solution to phenol red (red to yellow/orange) resulting from the hydrolysis of imipenem into a carboxylic derivative, leading to a decrease of the pH value.[14]

CarbAcineto NP test results were interpreted as follows: (i) Both tube A red and tube B remaining red indicated a non-carbapenemase-producing isolate, (ii) Both tube A red and tube B turning yellow/orange indicated a carbapenemase-producing strain, and (iii) Both tube A and tube B both turning yellow/orange indicated a non-interpretable result.[14]

Fosfomycin Susceptibility Testing was performed following the Kirby-Bauer disk-diffusion method recommended by CLSI 2019 with the proper controls (ATCC Ps. aeruginosa 27853 and ATCC E. coli 25922).[13]

Test organism (24hr overnight culture) was adjusted to standard 0.5 McFarland and streaked on the Mueller-Hinton agar plate to form a bacterial lawn. The plate is allowed to dry for approximately 5 minutes. The fosfomycin antibiotic is then dispensed onto the plate. Plates are incubated overnight at an incubation temperature of 37 °C (98.6 °F) for 24 hours. After 24 hours the plates are examined and the results are interpretive. Disk diffusion sensitive, intermediate and resistant zone diameter breakpoints (≥16mm=S, 13-15mm=I, ≤12mm=R) is proposed on the basis of the current MIC interpretative criteria recommended by the CLSI 2019.[11,13]

All the reagents, drugs and other requirements for the study were procured from HiMedia Laboratories, Mysuru, Karnataka, India with (LOT No.: 0000375203).

Colistin susceptibility testing was done using Brothmicrodilution method, using the MIKROLATEST kit (LOT: 1710152) with the proper controls (ATCC Ps. aeruginosa 27853 and ATCC E. coli 25922). MIC breakpoints (mg/l) for colistin was interpretated according to CLSI 2019 and EUCAST 2016 guidelines (≤ 2 = sensitive and ≥ 4 = resistant) Since March 2016, the joint CLSI–EUCAST Polymyxin Breakpoints Working Group has recommended the broth microdilution (BMD) method as the reference method to determine susceptibility to colistin (www.eucast.org).[13,16]

3. Result

In the present study, a total of 120 carbapenem resistant isolates were collected over a period of 1 year from Jan-Dec 2019. Of these 120 samples, 57 (47.5%) were CR *A. baumannii* and 63 (52.5%) were CR *K. pneumonia* **Graph 1.**

Of total 120 clinical samples, the male and female ratio was observed as 3:1 i.e., about 90 (75%) were male patients and about 30 (25%) were female patients **Graph 2.**

Of the 120 samples, maximum number of patients were under the age group of 61-70 years accounting for 31(25.8%), followed by the age groups 51-60 years & 21-30 years both accounting for 28 (23.3%) each. Similarly, 41-50 years age group accounts for 11 (9.61%), followed by 11-20 years 12 (10%), 71-80 years accounts for 10 (8.3%), 0-10 years accounts for 5 (4.16%), 31-40 years accounts for 5 (4.16%) & age group ≥80 years accounts for 3 (2.5%) **Graph 3.**

In the present study, maximum number of samples were obtained from medicine ward (25) and neurology ward (25) accounting for 20.83% each. Followed by surgery ward 21 (17.5%), burns ward 20 (16.67%), nephrology ward 8 (6.67%), pulmonary 6 (5%), critical care unit, urology, Orthopedic, pediatric wards all accounting for 3 each i.e. (2.5%), ENT 2 (1.67%) and Plastic surgery 1 (0.83%) **Graph 4.**

Of 120 samples, maximum number of samples received were endotracheal aspirate 42 (35%), pus 33 (27.5%), sputum 20 (16.67%) followed by blood 10 (8.33%), urine 9 (7.5%), aspiration fluid, bile, catheter tip, drain, pleural fluid & throat swab samples all accounting for 1 each i.e. (0.83%) **Graph 5.**

3.1. Acinetobacter baumannii: (N=57)

Antimicrobial susceptibility testing pattern in CR *A. baumannii* by vitek-2 method showed that in 57 CR *A. baumannii*, majority of the sensitive pattern to colistin and tigecycline 54 (94.74%) along with minocycline 29 (50.88%). Majority of the resistant pattern was observed in carbapenems (one or more), cephalosporins and quinolones **Table 1.**

Of the 57 CR *A. baumannii*, by CarbAcineto NP method (phenotypic detection of carbapenemase), 48 (84.21%) were positive and only 9 (15.7%) were negative **Graph 6**. Fosfomycin susceptibility testing showed that, about 39 (68.42%) were sensitive, 9 (15.78%) were intermediate and 9 (15.78%) were resistant to fosfomycin by disk diffusion method **Table 2.**

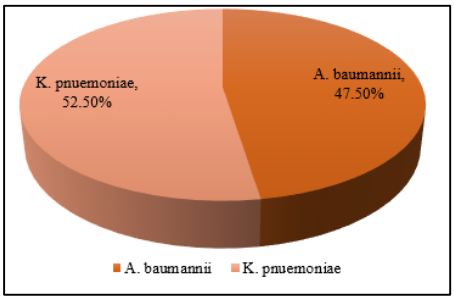
Of the 57 CR *A. baumannii*, fosfomycin showed high activity in the isolates which were received from samples like pus, endotracheal aspirate, and sputum with 66.66%, 65.5%, and 87.5% respectively **Table 3.**

3.2. Klebsiella pnuemoniae: (N=63)

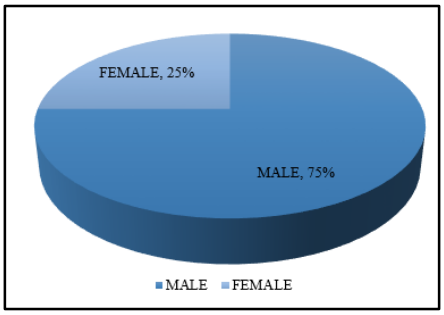
Antimicrobial susceptibility testing in 63 CR *K. pnuemoniae* by Vitek-2 method showed majority of sensitive pattern to colistin 57 (90.48%), tigecycline 55 (81.30%) and gentamycin 25 (39.68%). Intermediate to amikacin and imipenem 15 (23.81%) each. Resistant to carbapenems (one or more) penicillin, cephalosporins and quinolones **Table 4.**

Of the 63 CR *K. pnuemoniae* by CARBA NP Method (phenotypic detection of carbapenemase), 50 (79.36%) were positive and 13 (20.63%) were negative **Graph 7**. Fosfomycin Susceptibility testing by disk diffusion method showed that, about 49 (77.77%) were sensitive, 7 (11.11%) were intermediate and 7 (11.11%) were resistant to fosfomycin **Table 5.**

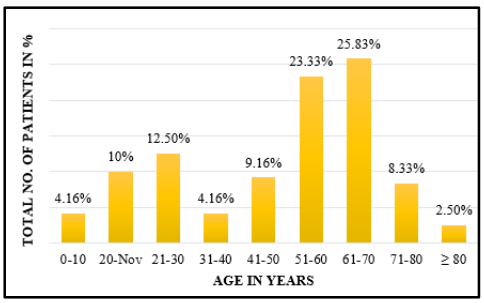
In 63 CR *K. pnuemoniae*, fosfomycin showed high activity in the isolates which were received from samples like endotracheal aspirate, pus, sputum and urine with 92.3%, 71.42%, 83.33% and 66.66% respectively which is shown in **Table 6**.



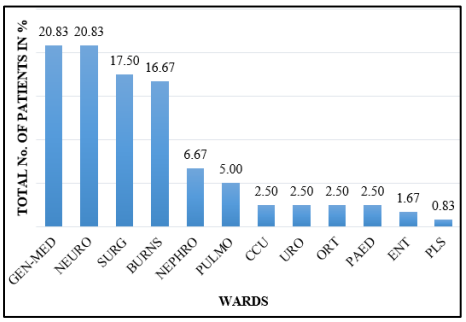
Graph 1: Organism-wise distribution of 57 CR *A. baumannii* and 63 CR *K. pnuemoniae* (N=120)



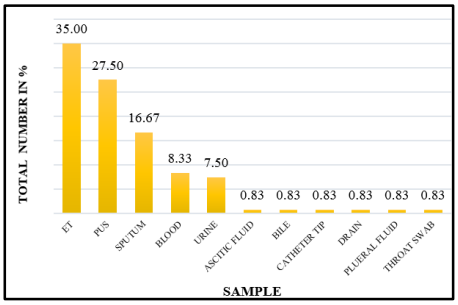
Graph 2: Gender-wise distribution of 57 CR *A. baumannii* and 63 CR *K. pnuemoniae* (N=120)



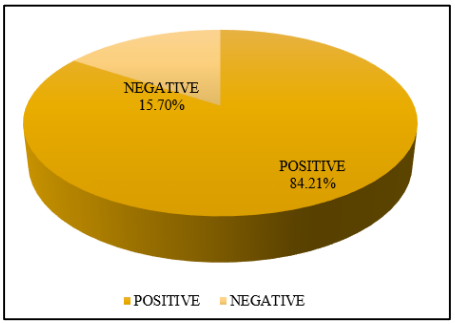
Graph 3: Age- wise distribution of 57 CR *A. baumannii* and 63 CR *K. pnuemoniae* (N=120)



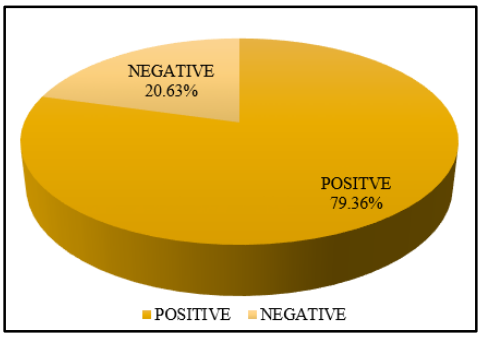
Graph 4: Ward-wise distribution of 57 CR *A. baumannii* and 63 CR *K. pnuemoniae* (N=120)



Graph 5: Sample-wise distribution of 57 CR *A. baumannii* and 63 CR *K. pnuemoniae* (N=120)



Graph 6: Carbapenemase detection in (57)CR *A. baumannii* by CarbAcineto NP method



Graph 7: Carbapenemase detection in (63)CR *K.pnemoniae* by carba NP method

4. Discussion

In our study, the male and female ratio was 3:1 i.e., about 90 (75%) were male individuals and 30 (25%) were female individuals. Whereas in the study conducted by Mehta Pooja B et al. included 52.9% of samples from male individuals and 47.1% of samples from female individuals remarking that more number of male individuals were included in our study.[8]

In our study, majority of the samples were from the patients of age group ranging from 61-70 years 31 (25.83%). Whereas in the study conducted by Mehta Pooja B et al. showed predominant age group ranging from 31-60 years which accounts for 84.3% remarking significant differences in both the study.[8]

Table 1: Antimicrobial Susceptibility Testing of 57 CR *A.baumannii* by Vitek-2 method

Antibiotics in (mcg)	Sensitive no. (%)	Intermediate no. (%)	Resistant no. (%)
Ticaracillin (75)	2 (3.51)	0	55 (96.49)
Cefepime (30)	0	0	57 (100.00)
Ceftriaxone (30)	0	0	57 (100.00)
Cefeperozone/sulbactam (75/30)	7 (12.28)	1 (1.75)	49 (85.96)
Ceftaxidime (30)	0	0	57 (100.00)
Ciprofloxacin (5)	0	0	57 (100.00)
Colistin	54 (94.74)	0	3 (5.26)
Cotrimaxazole (trimethoprim-sulphamethoxazole) (1.25/23.75)	11 (19.30)	0	46 (80.70)
Doripenem (10)	0	0	57 (100.00)
Gentamycin (10)	13 (22.81)	4 (7.02)	40 (70.18)
Imipenem (10)	0	0	57 (100.00)
Levofloxacin (5)	2 (3.51)	7 (12.28)	48 84.21)
Pipperacillin/tazobactam (100/10)	0	0	57 (100.00)
Minocycline (30)	29 (50.88)	3 (5.26)	25 (43.86)
Meropenem (10)	0	0	57 (100.00)
Tigecycline (15)	54 (94.74)	2 (3.51)	1 (1.75)
Note: Colistin susceptibility testing was done using Brothmicro Dilution method and MIC breakpoints (mg/l) for colistin was interpretated according to CLSI 2019[13] and EUCAST guidelines (≤ 2 = sensitive and ≥ 4 = resistant)[16]			

Table 2: Fosfomycin susceptibility testing of 57 CR *A. baumannii* by disk diffusion method

Fosfomycin susceptibilty	Total in number	Total in %
Sensitive	39	68.42
Intermediate	9	15.78
Resistant	9	15.78

Table 3: Sample wise distribution of Fosfomycin activity in 57 CR *A. baumannii* with AST by disk diffusion method

Sample	Total No.	Sensitive No. (%)	Intermediate No. (%)	Resistant No. (%)
Ascitic fluid	1	1 (100%)	0	0
Blood	4	2 (50%)	2 (50%)	0
Cathter tip	1	1 (100%)	0	0
ET	29	19 (65.5%)	5 (17.24%)	5 (17.24%)
Sputum	8	7 (87.5%)	0	1 (12.5%)
Plueral fluid	1	1 (100%)	0	0
Pus	12	8 (66.66%)	2 (16.6%)	2 (16.6%)
Throat swab	1	1 (100%)	0	0

Table 4: Antimicrobial Susceptibility Testing in 63 *K. pnuemoniae* by Vitek-2 method

Antibiotics in (MCG)	Sensitive no. (%)	Intermediate no. (%)	Resistant no. (%)
Amikacin (30)	10 (15.87)	15 (23.81)	38 (60.32)
Ampicillin (10)	1 (1.59%)	1 (1.59)	61 (96.83)
Amoxicillin (10)	1 (1.59%)	2 (3.17)	60 (95.24)
Cefuroxime (30)	1 (1.59%)	0	62 (98.41)
Cefuroxime axetil (30)	1 (1.59%)	0	60 (95.24)
Cefepime (30)	6 (9.52)	0	57 (90.48)
Ceftriaxone (30)	2 (3.17)	0	61 (96.83)
Cefeperozone/sulbactam (75/30)	5 (7.94)	0	58 (92.06)
Ceftaxidime (30)	0	0	63 (100.00)

Ciprofloxacin (5)	2 (3.17)	0	61 (96.83)
Colistin	57 (90.48)	0	6 (9.52)
Cotrimaxazole (trimethoprim-sulphamethoxazole) (1.25/23.75)	9 (14.29)	0	54 (85.71)
Gentamycin (10)	25 (39.68)	0	38 (60.32)
Imipenem (10)	7 (11.11)	15 (23.81)	41 (65.08)
Ertapenem (10)	3 (4.76)	0	60 (95.24)
Meropenem (10)	7 (11.11)	0	56 (88.89)
Nalidixic acid (30)	3 (4.76)	0	60 (95.24)
Pipperacillin/tazobactam (100/10)	2 (3.17)	1 (1.59)	60 (95.24)
Tigecycline (15)	55 (87.30)	1 (1.59)	7 (11.11)
Note: Colistin susceptibility testing was done using Brothmicro Dilution method and MIC breakpoints (mg/l) for colistin was interpretated according to EUCAST guidelines (≤ 2 = sensitive and ≥ 4 = resistant) [16]			

Table 5: Fosfomycin susceptibility testing of 63 CR *K. pnuemoniae* by disk diffusion method

Fosfomycin susceptibilty	Total in number	Total in %
Sensitive	49	77.77
Intermediate	7	11.11
Resistant	7	11.11

Table 6: Sample wise distribution of Fosfomycin activity in 63 CR *K. pnuemoniae* with AST pattern by disk diffusion method

Sample	Grand total in No.	Sensitive No. (%)	Intermediate No. (%)	Resistant No. (%)
Bile	1	0	1 (100%)	0
Blood	6	4 (66.6%)	1 (16.6%)	1 (16.6%)
Drain	1	1 (100%)	0	0
ET	13	12(92.3%)	0	1 (7.69%)
PUS	21	15 (71.42%)	3 (14.28%)	3 (14.28%)
Sputum	12	10(83.33%)	1 (8.33%)	1 (8.33%)
Urine	9	6 (66.66%)	2 (22.22%)	1 (1.11%)

In our study, majority of the samples were included from deep endotracheal aspiration 42 (35%). A similar study conducted by by Mehta Pooja B et al. showed alike results i.e. 41.17% samples collected from deep endotracheal aspiration.[8] But in the study conducted by Melda Sinirtas et al.[9] samples from deep endotracheal aspiration included were about 77% remarking that more number of patients in their study were suffering from respiratory diseases.

In our study, of the 57 CR *A. baumannii* by phenotypic detection of carbapenemases, about 48 (84.21%) showed positive results and 9 (15.7%) showed negative results by CARB-ACINETO NP method. Whereas in the study conducted by Kim Van Der Zwaluw et al.[10] showed 33.33% positive results and 66.6% negative results for CR *A. baumannii* by Carba NP test remarking that more number of carbapenemase producing *A. baumannii* isolates were included in our study.

Similarly in our study,of the 63 CR *K.pnuemoniae* by phenotypic detection of carbapenemases, about 50 (79.63%) showed positive results and 13 (20.63%) showed negative results by CARBA NP method. Whereas in the study conducted by Kim Van Der Zwaluw et al.[10] showed 94.73% positive results and 5.26% negative results for CR *K. pnuemoniae* by Carba NP test remarking that more number of carbapenemase producing *K.pnuemoniae* isolates were included in their study.

A similar study conducted by Shraddha Sharma et.al[11] received only 2 samples, of which 2 (100%) were sensitive with no resistant pattern for fosfomycin in *A. baumannii* by disc diffusion method remarking that although the sample size in their study was smaller, this result further reinforces the notion that fosfomycin exhibits strong antibacterial activity against *A. baumannii*.

The high percentage of fosfomycin sensitivity observed in our study aligns with previous findings that demonstrate the effectiveness of fosfomycin against *A. baumannii*, even in the carbapenem resistant isolates.

Similarly in our study, of the 63 CR *K. pnuemoniae* by Fosfomycin susceptibility testing method, about 56 (88.89%) showed sensitive pattern and 7 (11.11%) showed resistant pattern to fosmycin. A similar study conducted by Shraddha Sharma et al. showed alike results i.e. n= 29, 26 (89.65%) sensitive pattern and 3 (10.34%) resistant pattern for fosfomycin in *K. pnuemoniae* by fosfomycin disc diffusion method remarking that fosfomycin in both the study has high activity against *K. pnuemoniae*.[11]

5. Conclusion

Multidrug and carbapenem resistance is an increasing problem worldwide, which are most commonly seen in. *K. pneumoniae* and *A. baumanii* in the health care setting. Due to this reason, the interest in older antimicrobial agent, like fosfomycin has increased. Hence the need of evaluating an appropriate test to detect the carbapenemase production in carbapenem resistant isolates is important.

Our study demonstrated high activity of Fosfomycin against CR *A. baumannii* and *K. pnuemoniae* representing that fosfomycin can be used as an important alternative to carbapenems (in carbapenem resistant isolates). Although fosfomycin is intrinsically resistant to carbapenem resistant isolates, it's much effective against them, when administered in combination with the other drugs.

And also high activity for fosfomycin in *A. baumannii* and *K. pnuemoniae* were isolated from the endotracheal aspirate, sputum, pus and urine samples representing that fosfomycin can also be used for the treatment of respiratory tract infections, wound infections along with urinary tract infections.

Although fosfomycin is intrinsically resistant to carbapenem resistant isolates, it's much effective against them, when administered in combination with the other drugs.

6. Abbreviations

CR – Carbapenem Resistant; Cr-Ab – Carbapenem resistant *Acinetobacter baumannii;* AST – Antimicrobial susceptibility testing.

7. Ethical Committee Approval

The authors of this manuscript declare that this scientific work complies with reporting quality, formatting and reproducibility guidelines set forth by the EQUATOR Network. The authors also attest that this study was determined to require the Institutional Ethics Committee review, and the corresponding approval number is JSSMC| PG|227|2018-2019|Dated 02-02-2019.

8. Conflict of Interest

None.

9. Source of funding

None.

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