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Research Article

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Colistin Sparing Strategies to Overcome Resistance: Can We Save Future!

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ABSTRACT

Background: Colistin is the last resort drug to treat multidrug-resistant organisms. The most common isolate obtained in the healthcare is *Klebsiella* sp., which is usually resistant to carbapenems owing to carbapenem-resistant genes. This study was undertaken to analyze the resistance trend of *Klebsiella* sp. and its sensitivity to beta-lactams, beta-lactams inhibitor combinations, carbapenems, and aminoglycoside. Emphasis was laid on finding the possibilities of colistin salvage strategies and placement of ceftazidime-avibactam in the antibiotic policy.

Methods: Data from India and clinical samples isolating *Klebsiella* species were included. Genes included in the study were AMP C, TEM, CTXM1, KPC, OXA, NDM, and SHV. Antibiotics included in the study were amikacin, gentamicin, ceftriaxone, cefepime, ceftazidime, ciprofloxacin, amoxiclavulanic acid, ampicillin-sulbactam, pipercillin tazobactam, ceftazidime avibactam, Imipenem, meropenem, tigecycline, colistin, minocycline, aztreonam.

Results: Among 10524 isolates from India (2004-2021), 7910 were Gram negatives. 1996 (25.23%) isolates of *Klebsiella* species were identified. 65.76% were males. Antibiotic Sensitivity pattern was analyzed. Carbapenem resistance was found in 49.04%. Among Carbapenem-resistant isolates, the NDM gene was detected in 51.14%, and 93.67% were sensitive to ceftazidime avibactum in the remaining 48.86% isolates. Genes were analyzed. A 2x2 chi-squire test revealed that the OXA gene was connected with carbapenem resistance towards *Klebsiella* isolates (OR: 103 (44.8-236.8), p=0.001). Moreover, the effect of the OXA gene on ceftazidime avibactam resistance was found to be null (p>0.05).

Conclusion: This study concludes that ceftazidime-avibactam is a good alternative among NDM-negative carbapenem-resistant isolates and can be a treatment option. Routine testing of ceftazidime avibactam with aztreonam in ICU isolates is to be done. This study emphasizes detecting resistant genes in all critical cases to avoid accidental use of antibiotics, which is one of the leading causes of antibiotic resistance. Colistin antibiotics should be reserved for isolates where all the drug combinations fail.

Key-words: Colistin, Carbapenems, Klebsiella isolates, Sparing Strategies, Overcome Resistance, Multidrug-resistant

INTRODUCTION

Colistin was introduced in 1959, but it was withdrawn due to its side effects. [1] Since it has broad spectrum activity on all Multidrug-resistant (MDR) Gram-negative organisms, it is now widely used. [2,3]. It is a fact that there are no new antibiotics in the pipeline, and the armamentatrium is limited with the advent of resistance and no new research by pharma industries. We need to save the last resort drugs and thus use alternative options for treatment. The most deadly pathogen is Klebsiella sp. with the highest mortality [4,5]. Carbapenems are often used as the last resort antibiotics

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for treating serious infections caused by multidrug-resistant organisms. The resistance to carbapenem antibiotics due to carbapenem hydrolyzing enzymes is now a worldwide issue. Klebsiella sp. harbors many carbapenem resistance genes, including MBL, NDM, OXA48, KPC, Amp C. [6] Colistin resistance has also been reported. [7] Making policy at institute, state, and national levels is important to strategize colistin-sparing methodologies. [8] Carbapenem resistance is 66-79% [9], MBL is 46 % [10], NDM is 56 % [11]. Colistin resistance in *Klebsiella* sp. is 19% [12]. This study was undertaken to analyze the resistance trend of *Klebsiella* sp. and its sensitivity to beta-lactams, beta-lactams (inhibitor combinations), especially ceftazidime avibactam, carbapenems, aminoglycoside over the years of study. In this study, emphasis was laid on finding the possibilities of colistin salvage strategies and placement of ceftazidime-avibactam in the policy.

MATERIALS AND METHODS

The ATLAS data from Pfizer was included in our study as it has the parameters needed for this study. Data from India and clinical samples isolating Klebsiella species from 2004 to 2021 were included in this study.

Demographic details, which included age, gender, and location of the samples, were analyzed. The age group provided in the table was used for analysis. To make data sorting easy, samples were broadly categorized into urine, blood, respiratory samples, skin and soft tissue infection (SSTI), and sterile body fluids. The stomach, liver, and gall bladder samples were categorized into others.

Data, where variables like age, sex, and location were missing, were excluded from the study location provided in the data was classified into ICU, Ward, OPD, Emergency. Genes presented in this data include–ESBL, AMP C, TEM, CTXM, KPC, OXA, NDM, and SHV.

MBL was excluded from the study as it was absent in this data.

Antibiotics included in the study are aztreonam, amikacin, gentamicin, ceftrioxone, cefepime, ceftazidime, levofloxacin, ciprofloxacin, amoxiclavulanic acid, ampicillin sulbactam, pipercillin tazobactam, ceftazidime avibactam, Imipenem, meropenem, minocycline, tigecycline, colistin.

Klebsiella species resistant to carbapenem (imipenem or meropenem) were taken as carbapenem-resistant. Species resistant to either ceftrioxone or ceftazidime were taken as cephalosporin-resistant isolates.

Statistical Analysis- For continuous data, normality was tested using the Kolmogorov-Smirov test. For non-normal continuous data, NPR was used to compare the groups as appropriate. Categorical data were presented in frequency (N) and percentage (%). One-way analysis of variance (ANOVA) followed by the least significant difference (LSD) test was applied to multiple antibiotic comparisons and their sensitivity pattern. The Oxa gene compared with antibiotics using 2×2 contingency table calculators available online at (http://faculty.vassar.edu/187lowry/VassarStats.html). Statistical analysis was carried out using the statistical package for social science, version 22 (SPSS-22, IBM, Chicago, USA), and graphs were prepared using Prizm software. Two-tailed p-value<0.05 has been considered as significant. All statistical calculations were carried out using the statistical package for the social science, version 16.0 (SPSS Inc. Chicago, IL, USA).

Ethical approval- The above study was approved by the Human Ethical Committee of the Department of Microbiology, Integral Institute of Medical Sciences and Research, IU, Lucknow, India.

RESULTS

In this study, 7910 of the 10524 bacterial isolates (Gram Positive and Gram Negative organisms) from India collected over 18-year period (2004–2021) were Gram-negative. A total of 1996 (25.23%) isolates of *Klebsiella* species were identified. This was a retrospective analysis of the data provided (ATLAS). Clinical samples in the table were categorized into five main groups, as shown in Fig. 1a. Respiratory samples account for 33.6% of the total samples. Location was specified in 1908 samples, categorized into four groups, as shown in Fig. 1b. Most samples were from the ICU. Gender was specified in 1989 samples: 1308(65.76%) were males, and the rest were females. Age group was mentioned in 1957 samples. The age group is shown in Fig. 1c. Most of the subjects belonged to 19–64-year age group.

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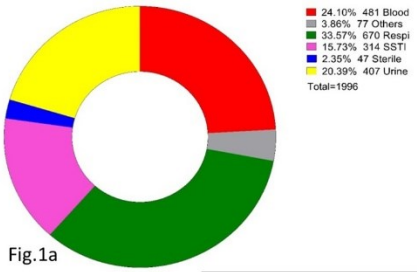

Fig.1a

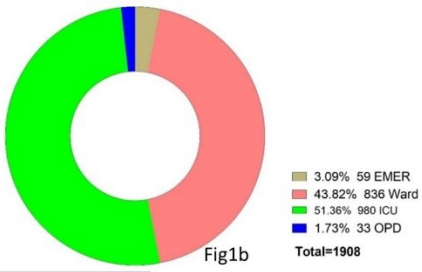

Fig1b

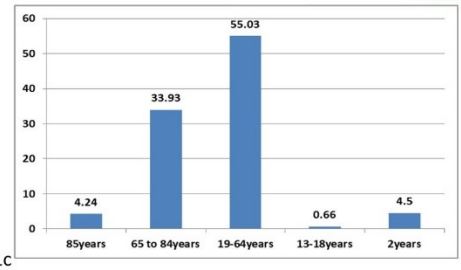

Fig.1c

Fig. 1a: Depicts the distribution of clinical samples into five main types; **Fig. 1b:** Depicts location location-wise distribution of samples; **Fig. 1c**: depicts the age-wise distribution.

All the isolates and their sensitivity are shown in Table 1. Sample-wise antibiotic sensitivity pattern is shown in Table 2. ESBL's were detected in 1022 isolates resistant to one of the third-generation cephalosporins, ceftriaxone or ceftazidime. Among these isolates, only 228 were tested for Amp C and 5(2%) were detected to have both ESBL & Amp C. A 2x2 chi-squire test revealed that OXA gene was connected with carbapenem resistance towards *Klebsiella* isolates (OR: 103 (44.8-236.8), p=0.001). Moreover, the effect of OXA gene on Ceftazidime Avibactam resistance was found to be null (p>0.05) (Table 3).

Table 1: Antibiotic susceptibility of *Klebsiella* sp. N-number samples, S-susceptible strain, R- resistant strain, I-intermediate strains

Antibiotic	Total N	I (%)	R (%)	S(%)
Amikacin	1996	54^{a}_{a} (2.7)	967^{b}_{a} (48.4)	975^{b}_{a} (48.8)
Amoxycillin clavulanate	1996	216^{a}_{b} (10.8)	1118^{b}_{b} (56.0)	662^{c}_{b} (33.2)
Cefepime	1996	129^{a}_{d} (6.5)	1262^{b}_{d} (63.2)	605^{c}_{b} (30.3)
Ceftazidime	1757	47^{a}_{a} (2.7)	1206^{b}_{d} (68.6)	$504^{c}_{d,q}$ (28.7)
Ceftriaxone	369	3^{a}_{e} (0.8)	282^{b}_{e} (76.4)	84^{c}_{e} (22.8)
Imipenem	1678	$37^{a}_{a,f}$ (2.2)	855^{b}_{f} (51.0)	786^{c}_{f} (46.8)
Meropenem	1945	36^{a}_{f} (1.9)	926^{b}_{a} (47.6)	983^{b}_{a} (50.5)
Minocycline	369	54^{a}_{a} (14.6)	103^{b}_{g} (27.9)	212^{c}_{i} (57.5)
Piperacillin tazobactam	1996	95^{a}_{a} (4.8)	1146^{b}_{b} (57.4)	755^{c}_{f} (37.8)
Tigecycline	1996	64^{a}_{c} (3.2)	4^{b}_{h} (0.2)	1928^{c}_{p} (96.6)
Ampicillin sulbactam	1627	$112^{a}_{d,i}$ (6.9)	1066^{b}_{i} (65.5)	449^{c}_{d} (27.6)
Aztreonam	1627	9^{a}_{g} (0.6)	1083^{b}_{i} (66.6)	535^{c}_{q} (32.9)
Ceftazidime avibactam	1627	0 (0)	482_{j} (29.6)	1145_{a} (70.4)
Ciprofloxacin	1627	110^{a}_{i} (6.8)	1096^{b}_{i} (67.4)	421^{c}_{r} (25.9)
Gentamicin	1627	11^{a}_{g} (0.7)	899^{b}_{a} (55.3)	$717^{c}_{b,f}$ (44.1)
Colistin	1627	1524_{J} (93.6)	103_{g} (6.3)	0 (0)

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Different alphabets in superscript and subscript show the difference between I, R and S of individual antibiotics and between antibiotics, respectively. ANOVA, LSD test $p<0.05$.

Table 2: Showing antibiotic sensitivity pattern in defined clinical samples

	Urine (%)	Blood (%)	Respiratory (%)	SSTI (%)	Others (%)
Amikacin	45.95	43.45	52.39	50.32	62.34
Amoxycillin clavulanate	35.63	24.12	36.42	31.85	49.35
Cefepime	30.22	24.32	33.13	28.66	48.05
Ceftazidime	28.46	24.30	30.98	25.96	41.27
Ceftriaxone	28.95	12.40	28.15	13.89	52.63
Imipenem	48.80	40.92	48.37	45.04	61.29
Levofloxacin	29.98	25.16	34.93	28.34	48.05
Meropenem	48.38	48.06	52.68	48.39	65.75
Minocycline	57.89	61.24	54.07	41.67	73.68
Piperacillin tazobactam	37.10	31.39	41.79	35.35	55.84
Tigecycline	-	96.05	96.72	96.50	96.10
Ampicillin sulbactam	26.83	25.00	29.72	24.10	39.66
Aztreonam	34.69	31.25	33.08	29.14	46.55
Ceftazidime avibactam	69.65	62.78	75.33	69.42	75.86
Ciprofloxacin	24.39	22.73	27.85	23.74	41.38
Gentamicin	41.73	39.77	46.73	44.96	56.90

Table 3: Comparison between OXA gene and drug sensitiveness

OXA gene	Not detected	Detected	OR (CI) p-value
Carbapenem resistance	174	703	103 (44.8-236.8), 0.001*
Carbapenem sensitive	153	6	-
Ceftazidime Avibactam Resistance	136	338	1.27 (0.98-1.66), 0.07
Ceftazidime Avibactam sensitive	191	371	-

OR: Odds ratio; CI: confidence interval

Among 1996 Klebsiella isolates 49.04% (979) were carbapenem resistant. NDM testing was done in 1055 isolates. Among Carbapenem resistance isolates, ceftazidime avibactam sensitivity, OXA gene and NDM gene detection was done in 874 isolates and NDM gene was detected in 51.14%(447) of the isolates. OXA gene alone was detected in (378) 43.2% of the isolates, OXA and NDM were detected in (324) 37% of carbapenem-resistant Klebsiella isolates. Analysis of NDM-negative isolates with Carbapenem and ceftazidime avibactam sensitivity is shown in Fig. 2. Among this carbapenem isolate with NDM-negative gene (48.8%,427); 400 (93.67 %) isolates were sensitive to ceftazidime avibactam [13]. Isolates where ceftazidime avibactam was resistant along with OXA gene despite the absence of NDM gene (1.48%). Table 4 depicts various genes present in the isolate.

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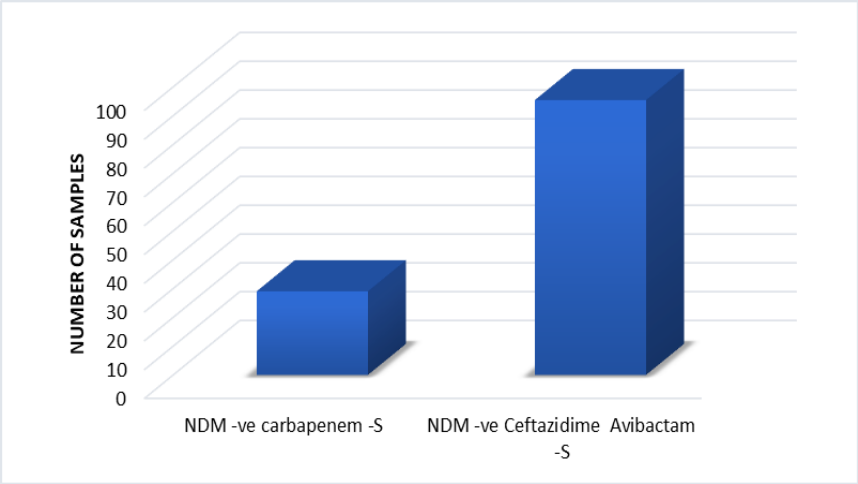

Fig. 2: Analysis of NDM-negative isolates with Carbapenem and ceftazidime avibactam sensitivity. Significance was calculated by Mann Whitney U test at p<0.05**: p=0.001

Table 4: Showing various genes present in the isolates

GENES	%	N
AMPC	8.46	260
TEM	79.24	1055
CTXM1	89.86	1055
KPC	0.47	1055
OXA	68.47	1037
NDM	42.56	1055
SHV	92.70	1055

DISCUSSION

This study shows that carbapenem resistance is 49.04% in Klebsiella isolates. Some studies report the carbapenem resistance similar to our study [14]. A meta-analysis showed that the prevalence of CRKP colonization ranges worldwide from 0.13 to 22%, with a pooled prevalence of 5.43%. In comparison, the incidence of CRKP colonization ranges from 2% to 73%, with a pooled incidence of 22.3% [15]. In India, the prevalence is 22 to 25 % in southern India [16].

Among carbapenem-resistant isolates, 51.14% were detected to have NDM gene. Among carbapenem-resistant NDM gene-negative isolates, 93.6% were sensitive to ceftazidime-avibactam *in vitro*. Some studies showed the prevalence of NDM in carbapenem-resistant isolates at a higher rate than this study.[17]

Therefore, in the absence of NDM gene in carbapenem-resistant isolates ceftazidime avibactum therapy can be a good alternative to colistin in 93.5% of them, as seen in our study. According to Sheilds and Doi, ceftazidime avibactam plus aztreonam can be a good alternative to colistin in cases where NDM was detected.[13]

Therefore, our study shows that at least 93.5% of the carbapenam resistant with NDM negative Klebsiella sp in India can be treated with ceftazidime avibactum alone, and cases where MBL or NDM is detected, can be treated with ceftazidime-avibactam with aztreonam combination thus sparing colistin as a drug of choice. As in this study, only 5.5% of carbapenem-resistant Klebsiella sp were resistant to ceftazidime avibactam, which can be treated with colistin. Colistin resistance is 6.3 % in this study. Colistin resistance is similar to a study from India [18].

Some reports publish colistin resistance of more than 15%. [19] Colistin is a broad-spectrum drug and needs to be saved for the future. The recommendation from this study includes sensitivity testing to Ceftazidime avibactum -aztreonam combination along with resistance gene detection especially in critical care unit

patients to prevent non-judicious use of higher antibiotics like tigecycline and colistin.[20,21]

CONCLUSIONS

The analysis showed that ceftazidime-avibactam is a good alternative among NDM-negative carbapenem-resistant isolates. Ceftazidime avibactum with aztreonam for NDM positive carbapenam resistant *Klebsiella* isolates can be a good alternative. This combination should be tested in areas where resistant isolates are common. Gene detection in all critical cases can avoid inadvertent antibiotic use, as shown in this analysis, which is one of the leading causes of antibiotic resistance today. Colistin antibiotics should be reserved for isolates where all the drug combinations fail.

LIMITATION

The analysis was performed on *Klebsiella* sp isolated from all the locations in various parts of India. Location-wise (OPD/IPD) analysis of carbapenem-resistant isolates could have been performed for better representation. Most of the samples are from ICU and are responsible for skewing data.

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The ATLAS data(Pfizer) obtained through https://amr.vivli.org" was analysed in this study.

CONTRIBUTION OF AUTHORS

Research concept- Areena Hoda Siddiqui, Preetha Rajan
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Supervision- Areena Hoda Siddiqui, Preetha Rajan
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Data collection- Jahangir Ahmad, Shadma Yaqoob
Data analysis and Interpretation- Amar Abhishek
Literature search- Jahangir Ahmad, Shadma Yaqoob
Writing article- Jahangir Ahmad, Shadma Yaqoob
Critical review- Areena Hoda Siddiqui, Preetha Rajan
Article editing- Areena Hoda Siddiqui, Preetha Rajan
Final approval- Areena Hoda Siddiqui, Preetha Rajan

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