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Original Research Article

Study of Carbapenem Resistant Klebsiella Pneumoniae in a Tertiary Care Hospital in Ahmedabad

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Abstract

Introduction: Enterobacteriaceae that produce resistant to carbapenem are becoming an increasing problem worldwide. Carbapenems were the choice for the therapeutic management of multidrug resistant gram negative bacterial infections. Due to a shortage of alternative medicines, multidrug-resistant (MDR) and carbapenem-resistant Klebsiella pneumoniae have become major therapeutic challenges in various countries.

Material &Method: The retrospective study was conducted in the department of Microbiology, Narendra Modi medical college, Ahmedabad, Gujarat over a period of one year i.e. from January 2022 to February 2023. A total of 1790 Klebsiella pneumoniae isolated from various clinical samples were subjected for antimicrobial susceptibility patterns and further tested for carbapenemase production by phenotypic method, Modified Hodge test based on CLSI guidelines 2019.

Results: Total 23,516 various clinical samples were received, of that 1790 (7.6%) Klebsiella pneumoniae isolated from various clinical samples like sputum and endotracheal secretions, wound swabs, urine, pus etc. From 1790 Klebsiella pneumoniae isolates, 760 (42.5%) were imipenem resistant. Modified Hodge test were performed of 760 imipenem resistance isolates, 267(35.1%) were positive. The predominant source of carbapenemase producer Klebsiella pneumoniae isolates were found in respiratory specimens (48.8%) and wound swab (20%). Antibiogram showing maximum sensitivity to minocycline, tigecycline.

Conclusion: Early detection of carbapenemase producing Klebsiella spp. may avoid future spread of these isolates and ensure better patient care and timely introduction of appropriate infection control measures.

Keywords: Klebsiella pneumoniae, Carbapenemase resistance, Ertapenem, KPC.

Introduction

Enterobacteriaceae that produce carbapenemases are becoming an increasing problem worldwide [1]. Carbapenems were the choice for the therapeutic management of multidrug resistant gram negative bacterial infections. Currently, the spread of carbapenem-resistant bacteria has caused grave concerned due to the limited choice in antibiotics for treating infections caused by them [2].

Resistance in bacteria is due to the production of carbapenem hydrolyzing enzymes called carbapenemases. These bacteria have the potential to spread rapidly within the hospital environment and across the country [3,4]. Mechanism of carbapenem resistance is mainly due to production of carbapenemases; these belong to class A of β-lactamases. Specific β-lactamases enzymes in molecular classes A, B & D have carbapenemases activity1. β-lactamase class A which includes K. pneumonia and Enterobacteriaceae having enzymes KPC, SME, NMC- A,IMI, GES [1]. Klebsiella pneumoniae carbapenemase (KPC) was first identified in year 2000 among isolates of K. pneumoniae in the United States of America; this mechanism has been identified in many countries and has spread across the globe [5]. Early detection of carbapenem-resistant Klebsiella pneumoniae infections can lower morbidity and death rates. Due to a shortage of alternative medicines, multidrug-resistant (MDR) and carbapenem-resistant Klebsiella pneumoniae have become major therapeutic challenges in various countries [6].

In India, rapid evolution of bacterial resistance may be due to a complex interaction of several factors such as higher burden of infectious disease, treatment uncertainty, lack of treatment guidelines, inadequate access to standard laboratory facilities,

self-medication, prescription based on availability, antibiotics prescribed by unqualified health professionals, poor population-wide insurance coverage, inadequate adherence to universal hygiene and infection control measures and an education level [7,8].

Material and Methods

A laboratory record based retrospective study. The present study was conducted in the department of Microbiology, Narendra Modi medical college, L.G. General Hospital, Ahmedabad, Gujarat over a period of one year i.e. from January 2022 to February 2023. A total of 1790 Klebsiella pneumoniae isolates were collected from various clinical samples like blood, sputum, urine, wound swabs; catheter tips, pus, body fluids etc. were processed for isolation and identification of bacterial pathogens according to the standard microbiological techniques. Direct gram stain was done from all specimens except blood. The specimens were inoculated into Nutrient agar, Mac-Conkey agar and Blood agar medium and incubated at 37 °C for overnight.

All received samples were proceeding according to standard microbiological technique (three days' procedure) for bacterial isolation and identification.

All the isolates were tested for anti-microbial susceptibility (Hi-Media) by Kirby-Bauer disk diffusion method on Muller-Hinton agar [1]. Imipenem resistant isolates were further proceeding for Modified-Hodge test.

Antimicrobial Sensitivity Testing:

Antimicrobial sensitivity of Klebsiella pneumoniae isolates was performed on Mueller Hinton Agar plates by Kirby-Bauer disk diffusion method according to CLSI guidelines [9]. The following antibiotic discs were used; amikacin-30µg, ciprofloxacin-5µg, levofloxacin-5µg, cefuroxime - 30 µg ceftazidime-30µg, piperacillin/tazobactum--100µg /10µg, cotrimoxazole 25µg, imipenem-10µg, aztreonam – 30 µg, cefoperazone/ sulbactam 75/30 µg, minocycline- 30 µg, tigecycline-15µg. In addition, nitrofurantoin-300µg and fosfomycin-200µg discs were used for isolates recovered from urine. The sizes of the zones of inhibition were interpreted as per CLSI guidelines [9]. All imipenem resistant Klebsiella pneumoniae isolates having zone diameter of ≤ 19 mm as per CLSI 2022 guidelines were further proceed for phenotypic method i.e. Modified Hodge test. These Modified hodge test may be used to confirm the presence of class A carbapenemases i.e. KPCs as described by CLSI in M 100-S26th ed 2019 [10].

Phenotypic confirmation of carbapenemase:

Modified Hodge Test:

Carbapenemase production was further confirmed by Modified Hodge test. The test isolate produces the enzyme and allows growth of a carbapenem susceptible strain (E. coli ATCC 25922) towards a carbapenem disk.

Procedure:

0.5 McFarland dilution of E. coli ATCC 25922 was prepared in 5 ml of broth or saline. 1: 10 dilutions were prepared by adding 0.5 ml of the 0.5 McFarland to 4.5 ml of MHB or saline. A lawn of 1: 10 dilution of E. coli ATCC 25922 was made on a Mueller Hinton agar plate. 10 µg ertapenem susceptibility disks were placed in the center of the test area. Test organism was streaked in a straight line from the edge of the disk to the edge of the plate. Plate was incubated overnight at $35^0C \pm 2^0C$ [10].

Test interpretation:

MHT Positive test has a clover leaf-like indentation of the E. coli 25922 growing along the test organism growth streak within the disk diffusion zone.

MHT Negative test has no growth of the E. coli 25922 along the test organism growth streak within the disc diffusion.

Quality Control:

Positive Control of carbapenemase producing Klebsiella pneumoniae strain 1705 BAA.

Negative Control: an in house known carbapenemase negative Klebsiella strain.

Statistical analysis:

Data has been analysed by using appropriate stastical software tool and Microsoft excel. Data is represented in the form of tables. Categorical variables were compared employing non-parametric tests (chi-square, fisher exact test) whereas continuous variables were compared by using student's t-test. Values have been expressed as mean ± SD and p value <0.05 was considered significant.

Results

Out of 23,516 clinical samples, 1790 Klebsiella pneumoniae were isolated. Among the total 1790 isolates,

760 (42.5%) were resistant and 1030(57.5%) were sensitive to Imipenem. Among the imipenem resistance isolates, 61.4% were males and 38.5% were females whereas among imipenem sensitive isolates 59.8% were males and 40.1% were females, respectively (Table 1).

Table1: Overall distribution of carbapenem resistant and sensitive Klebsiella pneumoniae isolates

Total sample	No. (%)	Sex	
		Male	Female
		No. (%)	No. (%)
Carbapenem resistant	760(42.5%)	466 (61.4)	294 (38.5)
Carbapenem sensitive	1030 (57.5%)	673 (59.8)	357 (40.1)
Total	1790	1139	651

Most of the patients from whom carbapenem resistant Klebsiella pneumoniae were isolated in the age group 50-59 years (26.9%) followed by ≥ 60years (22.1 %.). While carbapenem sensitive were highest isolated in age group of 20-29 years (30.3 %) followed by 30-39years (28.7%). There was no statistical significant difference in age between patients with carbapenem resistant and those with carbapenem sensitive Klebsiella infection ($p>0.05$) (Table-2).

Table 2: Age wise distribution of Carbapenem sensitive and resistant Klebsiella pneumoniae isolates

Age in years	Imipenem Sensitive	Imipenem Resistant	P value
0 -9	35 (3.4)	54(7.1)	Chi-square = 353.814
10 19	67 (6.5)	64 (8.4)	
20 - 29	313 (30.3)	88 (11.6)	P = 0 (NS)
30 - 39	296 (28.7)	79 (10.4)	
40 - 49	174 (16.9)	102 (13.4)	
50 - 59	53 (5.14)	205 (26.9 %)	
≥60	92 (8.9)	168 (22.1%)	
Total	1030	760	

In our study, it was found that maximum number of Klebsiella pneumoniae strains were recovered from sputum & endotracheal secretions; (40.6%), followed by wound swabs; (18.1%) and urine; (15.4%).

In imipenem resistant isolates (n=760), most of the Klebsiella pneumoniae strains were found in Sputum & endotracheal secretions (53.8%), followed by wound swabs (15.9 %), Urine (11.5 %) and pus (6.9%), respectively (Table-3).

The isolation of Klebsiella pneumoniae from wound swabs, blood and other specimens (catheter tip, drain, fluid, bile, BAL) and body fluids was found to be statistically significant ($p<0.05$).

Table 3: Sample wise distribution of Carbapenem sensitive and resistant Klebsiella pneumoniae isolates

Specimen	Isolates (1790)	Imipenem Sensitive (1030)	Imipenem Resistant (760)	P value
	No. (%)	No. (%)	No. (%)	
Blood	114 (6.3)	86 (8.3)	28 (3.6)	*0.00006
Pus	112 (6.2)	59 (7.7)	53 (6.9)	0.282(NS)
Wound swab	325 (18.1)	204 (26.8)	121(15.9)	*0.035
Sputum & endotracheal secretions	728 (40.6)	319 (41.9)	409(53.8)	0
Fluid (CSF, pleural, ascetic, peritoneal,)	32 (1.7)	20(1.9)	12 (1.6)	0.566
Tissue	108 (6)	86 (8.3)	22(2.9)	0
Urine	276 (15.4)	192 (18.6)	84 (11.5)	0
Others (catheter tip, drain fluid, bile, BAL,)	95 (5.3)	64(6.2)	31(4.0)	*0.046

The antimicrobial sensitivity patterns of the various isolates are depicted in (Table-4). 42.5% (n=760) of the isolates were resistant to imipenem and there was a variable sensitivity to other antimicrobials tested. The isolates exhibited a high degree of resistance to beta-lactam antibiotics including cephalosporins and piperacillin-tazobactam. There was a variable sensitivity to quinolones. Maximum isolates (49.4%) were resistant to ciprofloxacin followed by levofloxacin (35.4%). Gentamicin resistance was seen in (65.2%) isolates and (52.3%) isolates were resistant to amikacin. Nitrofurantion and fosfomycin were tested against 276 isolates recovered from urine, out of which (33.7%) were resistant to nitrofurontoin and 23.2 % were resistant to fosfomycin, respectively. Amongst the other class of antibiotics, (58.8%) were resistant to co-trimoxazole. Maximum numbers of Klebisella isolates were sensitive minocycline (87.1%) and tigecycline (94.5%).

Table 4: Antibiotic susceptibility pattern in Klebsiella pneumoniae isolates

Antibiotic	No. of Isolates : 1790	
	Sensitive No. (%)	Resistant No. (%)
cefuroxime	415(23.1)	1375(76.8)
ceftazidime	642(35.9)	1148(64.1)
piperacillin/tazobactum	960(53.6)	830(46.4)
cefoperazone/ sulbactam	1016(56.7)	774(43.3)
Gentamicin	854(47.7)	936(52.3)
Amikacin	1064(59.4)	726(40.6)
Ciprofloxacin	906(50.6)	884(49.4)
Levofloxacin	1157(64.6)	633(35.4)
Aztreonam	626(35)	1164(65)
Imipenem	1030(57.5)	760(42.5)
Minocycline	1560(87.2)	230(12.8)
Tigecycline	1693(94.5)	97(5.5)
Cotrimoxazole	738(41.2)	1052(58.8)
Chloramphenicol	922(51.5)	868(48.5)
#Nitrofurantoin	183(66.3)	93(33.7)
#Fosfomycin	212(76.8)	64(23.2)

(#Nitrofurantion and Fosfomycin were tested for urine samples only, n=276) The present study revealed that out of the total imipenem resistant isolates, 267(35.1%) was Modified hodge test positive and remaining 493(64.8%) was Modified hodge test negative. In Modified hodge test positives, maximum number of isolates were found in the age group of 50-59 yrs (40.8%), followed by ≥ 60 yrs (32.6%) and 40-49 yrs (11.6%), respectively. Therefore, there was a statistically significant association between a particular age group and Modified hodge test ($p<0.05$) (Table-5).

Table 5: Age wise distribution of Modified hodge test positive and Modified hodge test negative isolates

Age (yrs)	Hodge test +ve No. (%)	Hodge test –ve No. (%)	Total	P-value
0 to 9	2 (0.7)	10 (2.0)	12	
10 to 19	6 (2.2)	23 (4.7)	29	
20 to 29	13 (4.9)	38 (7.7)	51	Chi-square = 19.88
30 to 39	19 (7.1)	46 (9.3)	65	
40 to 49	31 (11.6)	39 (7.9)	70	P = *0.00290
50 to 59	109 (40.8)	231 (46.8)	340	
≥60	87 (32.6)	106 (21.5)	193	
Total	267	493	760	

The predominant source of carbapenemase producing isolates were found in sputum & endotracheal secretions (25.2 %) followed by wound swabs (19.1%), urine (10.1%) and pus (8.2%) respectively. Less number of carbapenemase producing isolates were recovered from samples like blood, drain fluid, tissue, catheter tip and BAL. However, the isolation of Klebsiella pneumoniae producing carbapenemase by using Modified hodge test from various samples was found to be statistically non-significant ($p>0.05$) (Table-6).

Table 6: Sample wise distribution of Modified hodge test positive and Modified hodge test negative isolates.

Specimens	Hodge test +ve No. (%)	Hodge test –ve No. (%)	Total	P-value
Blood	11(4.1)	17 (3.4)	28	
Pus	22 (8.2)	31 (6.3)	53	Fischer exact test = 52.149
Wound swab	51 (19.1)	70 (14.2)	121	
Sputum & endotracheal secretions	192 (25.2)	217 (44.0)	409	
Fluid (CSF, pleural, ascitic, peritoneal)	3 (1.1)	9 (1.8)	12	
Tissue	8 (2.9)	14 (2.8)	22	P = 1.00 (NS)
Urine	27 (10.1)	57 (11.6)	84	
Others (catheter tip, drain fluid, bile, BAL,)	11 (4.1)	20 (4.0)	31	

The antibiogram of carbapenem resistant isolates with Modified hodge test positive and modified hodge test negative isolates was shown in (Table-7). It was observed that among carbapenemase producing isolates,

maximum resistance was seen for cephalosporins like cefuroxime (71.3 %), ceftazidime (65.9%) and piperacillin plus tazobactum (55.4%) and cefoperazone/ sulbactam (51.6 %), whereas least resistance was seen against tigecycline (17.2%) and Minocycline (19.9%).

Table 7: Antimicrobial susceptibility profile of Modified hodge test positive and Modified hodge test negative isolates

Antibiotic	Hodge test +ve (267)		Hodge test –ve (493)		P value
	Sensitive No. (%)	Resistant No. (%)	Sensitive No. (%)	Resistant No. (%)	
Cefuroxime	76 (28.4)	191 (71.3)	96 (19.5)	397 (80.5)	*0.038
Ceftazidime	91 (34)	176 (65.9)	117 (23.7)	376 (76.3)	*0.031
Piperacillin/tazobactum	119 (44.5)	148 (55.4)	142 (28.8)	351 (71.2)	*0.002
Cefoperazone/ sulbactam	129 (48.3)	138 (51.6)	153 (31)	340 (69)	*0.001
Gentamicin	96 (35.9)	171 (64)	212 (43)	281 (57)	*0.035
Amikacin	118 (44.2)	149 (55.8)	231 (46.9)	262 (53.1)	0.23(NS)
Ciprofloxacin	114 (42.7)	153 (57.3)	219 (44.4)	274 (55.6)	0.32(NS)
Levofloxacin	144 (53.9)	123 (46)	257 (52.1)	236 (47.9)	0.71(NS)
Aztreonam	154 (57.7)	113 (42.3)	267 (54.2)	226 (45.8)	0.91(NS)
Minocycline	214 (80.1)	53 (19.9)	358 (72.6)	135 (27.4)	0.72(NS)
Tigecycline	221 (82.8)	46 (17.2)	389 (79)	104 (21)	0.77(NS)
Cotrimoxazole	104 (39)	163 (61)	217 (44)	276 (56)	*0.094
Chloramphenicol	94 (35.2)	173 (64.8)	198 (40.2)	295 (59.8)	*0.095
#Nitrofurantoin	12 (44.4)	15 (55.6)	36 (63.2)	21 (36.8)	*0.08
#Fosfomycin	18 (66.7)	9 (33.3)	42 (73.7)	15 (26.3)	0.27(NS)

(#Nitrofurantion and Fosfomycin were tested for urine samples only, n=276). *stastically significant.

Further the antimicrobial susceptibility pattern of carbapenemase producers and non-carbapenemase producers showed statically significant in cefuroxime. Ceftazidime, piperacillin-tazobactam, cefoperazone- sulbactam, gentamycin, cotrimoxazole, chloramphenicol and nitrofurantoin in urine isolates ($p<0.05$).

Modified Hodge's Test (MHT) for detection of Carbapenemase production

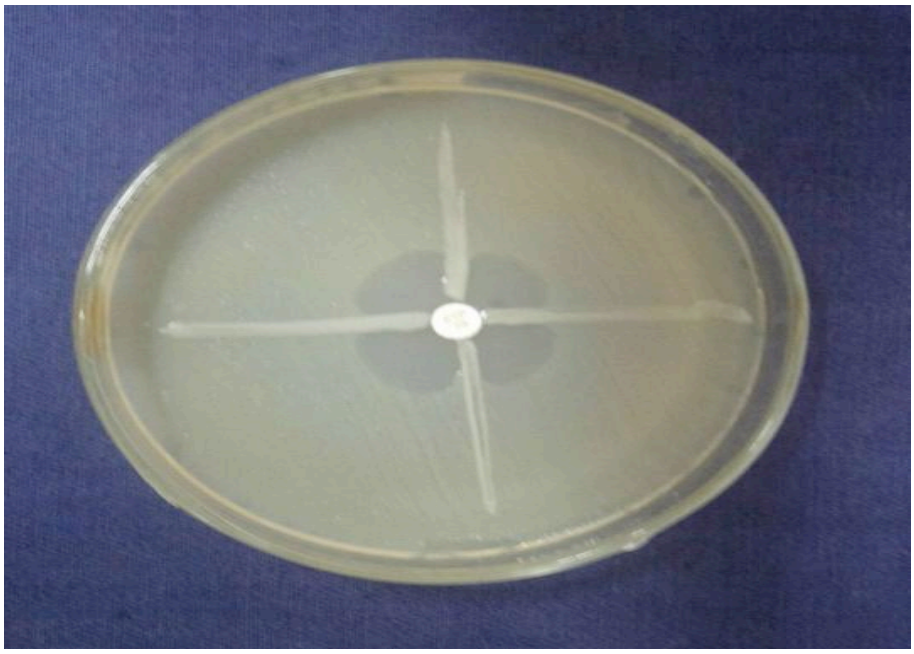

Figure 1: Positive test with clover leaf -like indentation

Discussion

Spread of multidrug-resistant (MDR) gram-negative pathogens is one of the major hazards for patients requiring long-term hospitalization or hospitalization in intensive care units (ICU) [11]. As carbapenems have long been considered the

antibiotic class of last resort in the treatment of infections caused by multidrug-resistant gram-negative organisms, the dissemination of carbapenem resistance among pathogenic bacteria has been declared a "global sentinel event" [12].

In our study, imipenem resistant isolates 267 (35.1 %) were modified hodge test positive while 493 (64.7 %) were modified hodge test negative. Those Modified Hodge Test negative isolates, likely to be mediated by presence of extended spectrum β – lactamases or plasmid borne Amp C in combination with impermeability due to porin loss and efflux pumps.

Modified hodge test positivity for Imipenem resistant isolates of our study was 35.1 %, which was higher reported than study done by Remya P et al [20] that is 24.86 % in south India while study done by Shanmugam P et al [22] showed much higher 82.6% in Chennai.

The findings of the present study showed 760(42.5%) were carbapenem resistant while in accordance to a study done by Patel JB et al [14] in New York City and Debby et al [15] in Israel who in their respective studies found isolation rate of carbapenem resistant Klebsiella pneumoniae were to be 26% and 27%, which was lower than our study.

The present study found that out of the 760 imipenem resistant isolates, 61.4% were males and 38.5% were females. There was no statistically significant difference in age between patients with carbapenem resistant and those with carbapenem sensitive Klebsiella pneumoniae infection.

The findings of the above results are in accordance to a study done by Amin A et al [16] in Pakistan who found that majority of the patients were males (60%) than females (40%). Patel G et al [17] in a similar study, revealed that male patients were (59%) and female patients were (41%) and further it was found that there were no significant differences in age ($p=0.70$) or sex ($p=0.51$).

In the present study, it was found that maximum numbers of Klebsiella pneumoniae isolates were recovered from sputum and endotracheal secretions 40.6%, followed by wound swabs 18.1%, which was concordance with study done by Susil Pyakurel et al [18] was observed highest carbapenem resistant Klebsiella pneumoniae in tracheal aspirates (74.4%), followed by catheter tips. Further it was observed that the isolation of Klebsiella from wound swabs, blood and other specimens (catheter tip, drain fluid, bile, BAL) was found to be statistically significant ($p<0.05$). Whereas pus, sputum and endotracheal secretions, tissues, urine and body fluids, it was found to be statistically non-significant. ($p>0.05$)

The present study highlighted, the most alarming situation of highly diverse antibiotics resistance rates against cephalosporins ranging from 45 % to 80 %. About 84.8% were resistant to piperacillin plus tazobactam. There was a variable sensitivity to quinolones. Nitrofurantion and fosomycin were tested against 276 isolates recovered from urine, out of which 93 (33.7%) and 64 (23.2) were resistant respectively. Maximum numbers of Klebsiella pneumoniae isolates were sensitive to minocycline (87.2) and tigecycline (94.5 %). The results of the present study were similar to a study done by Amin A et al [16], who found that the maximum resistance was seen against cephalosporin's ranging from 82.5% to 100%.

The present study observed that among carbapenemase producing isolates, maximum resistance was seen for cephalosporins and piperacillin plus tazobactum, cefoperazone plus sulbactam, monobactams, cotrimoxazole and gentamycin antibiotics whereas least resistance was seen for tigecycline (5.5%) and minocycline (12.8%). Further the antimicrobial susceptibility pattern of carbapenemase producers and carbapenemase non- producers did not vary much except that a significantly higher proportion of carbapenemase producing isolates were resistant to co-trimoxazole ($p<0.05$). The results of our study were in accordance with Parveen M et al [19] who in their study found higher level of resistance to cephalosporins (100%), cotrimaxazole (100%), piperacillin plus tazobactum (100%).

Conclusion

Carbapenem resistant Klebsiella is a major problem in our hospital with isolation rate of 42.5%. As these isolates are resistant to nearly all the available antimicrobial agents, their dissemination may lead to treatment failures with increased morbidity and mortality. The early detection of carbapenemase producing Klebsiella pneumoniae may avoid future spread of these isolates & ensure better patient care and timely introduction of appropriate infection control measures. Options for treating infections with carbapenemase-producing K. pneumoniae are limited; minocycline and tigecycline could be the drug of choice. The escalating prevalence of carbapenem-resistant K. pneumoniae infection and the increasing incidence of this pathogen in United states, India and worldwide mandate further investigation into the epidemiology of and clinical outcomes associated with carbapenem-resistant K. pneumoniae infection.

Limitations of the study

The study was conducted in only one hospital using a small sample size, which may not represent the whole population. Seasonal trend may also affect the result. The study was also limited to a MHT phenotypic confirmatory test only. In such cases, a relatively easy and inexpensive method like the MHT can be one of the best alternatives for the early detection of the carbapenemase producers.[13]although it has several limitations like

low specificity and high false positivity[21]. Others like, Metallo Beta lactamase detection, AmC production detection and genetic detection methods were not possible in our department set up, although many other factors and genes are responsible for carbapenemase activity. Thus, the relationship shown among different factors in this study may not be conclusive. Thus, further studies should be performed in multiple hospitals for a longer period to overcome the present drawbacks.

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