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Current Susceptibility Trend of Antibiotics in a Tertiary Care Hospital - Need to Emphasize on Alternate Therapeutic Agents

Manisha Khandait[1], Tapesh Bansal[2] and Pankaj Mandale[3*]

[1]Department of Microbiology, Aakash Healthcare Super Specialty Hospital, Dwarka, Sector 3, New Delhi, India.
[2]Department of Medicine, Paras Hospital, Gurgaon, India.
[3]Venus Medicine Research Centre, India.

Authors' contributions

This work was carried out in collaboration among all authors. Author MK designed the study, performed the statistical analysis and wrote the protocol. Author TB and PM managed the analyses of the study. Author PM managed the literature searches and wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: In the light of changing anti-microbial resistance pattern, the understanding of the local antibiogram is essential in the antibiotic selection procedures and preparation of hospital antibiotic policy.
Aim: This retrospective study was aimed to analyze the antibacterial susceptibility pattern of major isolates from ICU and IPD.
Materials and Methods: Antimicrobial susceptibility testing was done for a total of 565 Gram-negative isolates including *E. coli, K. pnuemoniae, A. baumannnii* and *P. aeruginosa* from ICU and IPD patients enrolled between July 2016 to December 2016.
Results: The majority of the isolates were reported from urine samples (52%) in IPD and sputum (59%) in ICU. The susceptibility to BL/BLI was 50-75% in IPD patients and Carbapenem

**Corresponding author: E-mail: Dr.mandalepankaj@gmail.com;*

susceptibility was reported in more than 75% except *P. aeruginosa*. In ICU patients, the beta-lactam/beta-lactam inhibitor (BL/BLI) susceptibility ranged between 20-60% and the carbapenem susceptibility was around 40%-75%. The susceptibility of CSE-1034 (Ceftriaxone + Sulbactam + EDTA) was almost similar to minocycline and amikacin ranging from 50-90% against different species. Compared to carbapenems, the CSE-1034 performed overall better than carbapenems against *P. aeruginosa* and *A. baumannii* and was comparable to carbapenems against Enterobacteriaceae. The susceptibility of colistin ranged from 92-97% in both IPD and ICU isolates.

Conclusion: Considering the value of carbapenems and colistin as the last option for multi-drug resistant (MDR) bacterial infections, irrational prescription of these drugs should be stopped. The use of ampicillin-sulbactam, cefepime and gentamicin from 1st line antibiotics in ICU patients can help to reduce the load on 2nd line antibiotics. Among 2nd line drugs, CSE-1034 along with amikacin should be an empirical choice of treatment for bacterial infections where the 1st line drugs are suspected to fail and the need of carbapenems arises.

Keywords: CSE-1034; antibiotics; multi-drug resistance; carbapenems; BL/BLIs.

1. INTRODUCTION

Antimicrobial resistance (AMR) is an increasingly recognized concern across the globe [1,2]. It has been estimated that by 2050, 10 million lives a year will be at risk due to emergence of infections by multi-drug resistant (MDR) pathogens [3]. The US Center for Disease Control and Prevention (CDC) estimates that antibiotic resistance is responsible for more than 2 million infections and 23,000 deaths each year in the United States at a direct cost of $20 billion and additional productivity loss of $35 billion [4]. Overuse of antibiotics is considered as the prime reason for the rise in antimicrobial resistance. Various countries like BRICS (Brazil, Russia, India, China and South Africa) account for 3/4th of total usage of antibiotics in the world [5]. Mechanisms behind antimicrobial resistance in these microorganisms include production of extended spectrum ß lactamases (ESBL) and metallo ß lactamase (MBL), changes in membrane permeability, over-expression of efflux pump and production of biofilms [6].

Infections due to MDR pathogens is not limited to particular organ system and includes wide range of infections including urinary tract infection, blood stream infection, intra-abdominal infection, lower respiratory tract infection, skin and soft tissue infection, etc [7,8]. Considering the rise in the incidence of multi-drug resistant pathogens globally, there is a need to study the prevalence and susceptibility profile of various pathogens on a regular basis [9,10]. A routine surveillance helps to establish, modify the treatment guidelines and guide the clinicians for the prescription of appropriate empirical antimicrobial therapy. In light of this, we aimed to conduct a microbial surveillance study in Paras hospital, India to study the susceptibility profile of the major pathogens including *E. coli, K. pnuemoniae, A. baumannii* and *P. aeruginosa* culture isolates from ICU and IPD patients against first and second line of antibiotics.

2. MATERIALS AND METHODS

2.1 Sample Collection

A retrospective analysis study on antibiotic susceptibility data obtained during July 2016 to December 2016 was conducted at Dept. of Microbiology, Paras hospital, Gurgaon, Haryana. The study was approved by the ethical committee of the hospital. Various clinical samples (N=565) used for pathogen isolation were obtained from patients with urinary tract infections, respiratory tract infections, blood stream infections and gastro-intestinal infections. The different clinical samples used for pathogen isolation were urine, blood, sputum, endo-tracheal secretions, BAL, sputum, TT secretions, ascitic fluids, bile and samples from drains.

The collection and processing of the samples were done as per common Standard Operating Procedures.

2.2 Isolation and Processing of Samples

All the samples were collected aseptically in sterile containers and inoculated on the different selective and non-selective culture media as per the standard microbiological techniques. Details of the culture media used for the isolation of pathogens from various clinical samples are given in Table 1. Blood samples collected in brain heart infusion (BHI) broth and incubated overnight at 37°C. These samples were further

sub-cultured on the selective or non-selective media and incubated aerobically overnight at 37°C. Organisms were identified on the basis of colony morphology, gram staining, motility and biochemical reactions. Biochemical reactions were performed by inoculating the bacterial colony in a nutrient broth at 37°C for 2– 3 hours [11].

2.3 Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing was done by Broth micro-dilution method using Vitek 2 as recommended by the CLSI guidelines (2016) [12]. The disc diffusion method [13] was used to determine the susceptibility of CSE-1034. The statistical analysis was done using graph-pad.

3. RESULTS

3.1 Sample Collection and Identification of Pathogens

A total of 6175 clinical samples [ICU (n=1485) and IPD (n=4690)] were collected from the suspected patients at Paras Hospital, Haryana and processed for pathogen isolation. Out of 6175 clinical samples processed, Gram negative pathogens were isolated from 565 (9.15%) [ICU (n=166) and IPD (n=399)] patients (Table 1). Among these 565 patients, 48% (n=271) of the patients were males and 52% (n=294) represented female population. The age of the patients included in the study ranged between 35 to 76 years, with a mean age of 51. The most common co-morbidities associated with the patients were diabetes mellitus (n=65), hypertension (n=54) and chronic kidney diseases (n=21).

On the basis of morphological and biochemical screening, four most prevalent pathogens (91.1%) were *K. pneumoniae., E. coli, A. baumannii* and *P. aeruginosa,,* whereas other pathogens including *Salmonella spp., Proteus spp.* and *Citrobacter spp.* contributed least to the pool (8.5%). In the present study, we further perused only predominant pathogens including *K. pneumoniae, E. coli, A. baumannii* and *P. aeruginosa.*

Of the 399 Gram negative isolates from IPD clinical specimens, the majority of the isolates were reported from urine samples (52.13%; 208/399) followed by blood (38.09%; 152/399) whereas the majority of the clinical samples processed from ICU patients were respiratory tract specimens (59.04%; 98/166) followed by blood (28.9%; 48/166).

K. pneumoniae and *E. coli* were the most prevalent (31% each) pathogens reported from IPD whereas *K. pneumoniae* (39.76%) followed by *P. aeruginosa.* (28.92%) were predominantly reported from ICU (Table 2).

3.2 Antibiotic Susceptibility Profile of Clinical Isolates from IPD Patients

Antibiogram profile of all the pathogens obtained from IPD clinical specimens is presented in Tables 3 & 4. Data suggested that the susceptibility observed to all first line antibiotics were less than 50% in IPD patients except ampicillin-sulbactam, cefepime and gentamicin. The *Enterobacteriaceae* family exhibited 20-46% susceptibility to aztreonam and amoxycillin-clavulanate whereas the susceptibility of other Gram negative bacilli was negligible.

The susceptibility to ampicillin-sulbactam was more than 50% for all the species with lowest of 61.54% against *K. Pneumoniae* and highest of 82.9% against *E. coli*. *K. pneumoniae* showed the highest susceptibility to gentamicin whereas the lowest was shown by *A. baumannii* (59.6%). Among cephalosporins, the highest susceptibility was observed towards fourth generation cephalosporin “cefepime”. Among fluoroquinolones, 45-55% of all isolates were susceptible to both ciprofloxacin and levofloxacin except *K. pneumoniae* and *P. aeruginosa*.

Regarding second line drugs, an enhanced susceptibility was observed in IPD patients. Data suggested that the clinical isolates of *E. coli* showed comparatively higher susceptibility (62-94%) to all the antibiotics and the lowest was reported in *P. aeruginosa* (55-83.7%). The susceptibility of *E. coli* was lowest to beta-lactam/beta-lactam inhibitor combinations, and was highest to colistin, polymyxin and tigecycline (95-96%). Among carbapenems, an average of 56% susceptibility was reported against *P. aeruginosa*, 75% against *A. baumannii*, whereas 82-87% of *K. pneumoniae* and *E. coli* were reported susceptible to carbapenems.

The susceptibility rates of CSE-1034 against *K. pneumoniae, E. coli, A. baumannii* and *P. aeruginosa* were 88.9%, 88%, 85% and 75% respectively. The drugs which showed more than 90% susceptibility included minocycline against *K. pneumoniae* and *E. coli* (90% each), colistin against all the isolates (92-97%), *polymyxin B* against *E. coli* (95%).

Table 1. Profile of clinical samples used as a source of the pathogen isolates

Sr. no.	Name of clinical samples	Total no. of samples collected	Number of samples showing growth (%) in IPD	Number of samples showing growth (%) in ICU	Number of samples not showing growth
1	Blood	3056 (IPD=1964; ICU=1092)	152 (7.74)	68 (6.23)	2836
2	Sputum	485	-	98 (20.2)	387
3	Urine	2440	208 (8.52)	-	2232
4	Others*	194	39 (20.10)	-	155
	Total	6175	399 (6.46)	166 (2.69)	5610

Others include pus, wound, tips, fluids, tissue, vaginal swabs, bile*

Table 2. Prevalence of isolates in different clinical specimens

Gram-negative clinical isolates collected from IPD						
Samples	**No. of isolates**	**KP %(n)**	**EC %(n)**	**AP %(n)**	**PA %(n)**	**Other Gram-negative bacilli %(n)**
Blood	152	35.53(54)	22.37(34)	10.53(16)	17.11(26)	14.47(22)
Urine	208	30.77(64)	34.62(72)	-	22.12(46)	12.5(26)
Other clinical samples	39	20.51(8)	48.72(19)	10.26(4)	20.51(8)	-
Total	**399**	**126 (31.58)**	**125 (31.33)**	**20 (5.02)**	**80 (20.06)**	**48 (12.03)**
Gram negative clinical isolates collected from ICU						
Samples	**No. of isolates**	**KP (%) (n)**	**EC (%)**	**AP (%)**	**PA (%)**	**Other Gram-negative bacilli (%)**
Sputum	98	38.78(38)	10.20 (10)	24.49 (24)	26.53 (26)	-
Blood	48	43.75(21)	12.5 (6)	14.58 (7)	29.20 (14)	-
Other clinical samples	20	35 (7)	10 (2)	15 (3)	40 (8)	
Total	166	66 (39.76)	18 (10.84)	34 (20.48)	48 (28.92)	-
Grand Total	565	192 (33.98)	143 (25.31)	54 (9.56)	128 (22.65)	48 (8.50)

KP= K. pneumoniae, EC= E. coli, AB= A. baumannii and PA= P. aeruginosa

Table 3. Susceptibility profile for gram negative bacteria isolated from IPD to first line antibiotics

Antibiotic class	Drugs	KP (126))	KP	AC (20)	AC	EC (125)	EC	PA (80)	PA
		No.	%age	No.	%age	No.	%age	No.	%age
Sulfonamides	Trimethoprim-sulfamethoxazole	12	11.55	6	30	24	18.97		-
	Aztreonam	48	46.15	-	-	50	39.89	-	-
BL-BLI	Amoxicillin-clavulanate	22	21.15	-	-	46	36.79	-	-
	Ampicillin-sulbactam	64	61.54	12.92	64.6	104	82.94	-	-
Aminoglycosides	Gentamicin	92	88.46	11.92	59.6	94	75.03	56	69.62
Cephalosporins	Ceftazidime	22	21.15	6	30	46	36.79	30	37.57
	Cefepime	69	66.35	8.92	44.6	104	83.05	55	68.87
	Ceftriaxone	24	23.08	6	30	55	44.39	-	-
Fluoroquinolones	Ciprofloxacin	19	18.27	8.92	44.6	70	55.26	31	38.57
	Levofloxacin	52	50	8.92	44.6	58	46.26	15	18.65

KP= K. pneumoniae, EC= E. coli, AB= A. baumannii and PA= P. aeruginosa

Table 4. Susceptibility profile for gram negative bacteria isolated from IPD to second line antibiotics

Antibiotic class	Drugs	KP (126))	KP	AC (20)	AC	EC (125)	EC	PA (80)	PA
		No.	%age	No.	%age	No.	%age	No.	%age
AAE	CSE-1034	112	88.89	17	85	110	88	60	75
BL-BLI	Piperacillin-tazobactam	75	59.5	11	55	95	76	57	71.25
	Cefoperazone-sulbactam	78	61.90	10	50	95	76	0	0
	Cefepime-tazobactam	79	62.69	11	55	100	80	57	71.25
Aminoglycosides	Amikacin	99	78.57	12	60	108	86.4	60	75
Tetracycline	Minocycline	114	90.48	17	85	113	90.4	61	76.25
Carbapenems	Imipenem	106	84.13	15	75	109	87.5	46	57.5
	Meropenem	104	82.54	15	75	107	85.6	44	55
Peptides	Colistin	115	91.27	16	80	119	95.2	65	81.25
	Polymyxin B	55	43.659	16	80	119	95.2	67	83.75

KP= K. pneumoniae, EC= E. coli, AB= A. baumannii and PA= P. aeruginosa

Table 5. Susceptibility profile for gram negative bacteria isolated from ICU patients to 1st line antibiotics

Antibiotic class	Drugs	KP (66)	KP	AC (34)	AC	EC (18)	EC	PA (48)	PA
		No.	%age	No.	%age	No.	%age	No.	%age
Sulfonamides	Trimethoprim-sulfamethoxazole	8.0	12.1	12.0	35.3	4.0	22.2	-	-
	Aztreonam	2.0	3.0	0.0	0.0	2.0	11.1	-	-
BL-BLI	Amoxicillin-clavulanate	4.0	6.1	-	-	2.0	11.1	-	-
	Ampicillin-sulbactam	40.0	60.6	24.0	70.6	13.0	72.2	-	-
Aminoglycosides	Gentamicin	42.0	63.6	24.0	70.6	12.0	66.7	20.0	41.6
Cephalosporins	Ceftazidime	4.0	6.1	3.0	8.8	2.0	11.1	0.0	-
	Cefepime	46.0	69.7	21.0	61.8	14.0	77.8	16.0	61.5
	Ceftriaxone	4.0	6.1	3.0	8.8	2.0	11.1	-	-
Fluoroquinolones	Ciprofloxacin	4.0	6.1	4.0	11.8	2.0	11.1	2.0	4.2
	Levofloxacin	8.0	12.1	6.0	17.6	4.0	22.2	8.0	16.7

KP= K. pneumoniae, EC= E. coli, AB= A. baumannii and PA= P. aeruginosa

Table 6. Susceptibility profile of Gram negative bacteria isolated from ICU patients to 2nd line antibiotics

Antibiotic class	Drugs	KP (66)	KP	AC (34)	AC	EC (18)	EC	PA (48)	PA
		No.	%age	No.	%age	No.	%age	No.	%age
AAE	CSE-1034	34.0	51.5	24.0	70.6	15.0	83.3	38.0	79.2
BL-BLI	Piperacillin-tazobactam	18.0	27.3	14.0	41.2	10.0	55.6	19.0	39.6
	Cefoperazone-sulbactam	14.0	21.2	14.0	41.2	8.0	44.4	27.0	56.3
	Cefepime-tazobactam	40.0	60.6	16.0	47.1	8.0	44.4	29.0	60.4
Aminoglycosides	Amikacin	28.0	42.4	24.0	70.6	14.0	77.8	35.0	72.9
Tetracycline	Minocycline	34.0	51.5	26.0	76.5	14.0	77.8	37.0	77.1
Carbapenems	Imipenem	28.0	42.4	25.0	73.5	14.0	77.8	20.0	41.7
	Meropenem	26.0	39.4	24.0	70.6	14.0	77.8	20.0	41.7
Peptides	Colistin	62.0	96.8	32	94.1	17	94.4	44.0	91.7
	Polymyxin B	54	81.8	30	88.2	16	88.9	23	47.9
	Tigecycline	24	36.4	30	88.2	18	100	-	-

KP= K. pneumoniae, EC= E. coli, AB= A. baumannii and PA= P. aeruginosa

3.3 Antibiotic Susceptibility Profile of Clinical Isolates from ICU Patients

Antibiogram profile of the pathogens obtained from ICU patients is presented in Table 5 and Table 6. The average susceptibility rate of first line of antibiotics against all pathogens was less than 10% except gentamicin, ampicillin-sulbactam and cefepime which was similar to IPD patients. The susceptibility rate to ampicillin-sulbactam was 60-70%, 63-77% to gentamicin and 61-78% to cefepime. Among second line of antibiotics tested, the overall susceptibility of all isolates to 2nd line drugs tested was lower by 10-20% in ICU patients except *K. pneumoniae*. A big drop in the susceptibility rate by 40-50% was observed against *K. pneumoniae* in ICU patients. Among BL/BLIs, *K. pneumoniae* exhibited almost similar susceptibility to cefoperazone-sulbactam and pip-taz (21-27%) and 60% to cefepime-tazobactam. The susceptibility rates of *A. baumannii* and *E. coli* were 41-55% and *P. aeruginosa* was 40-60%. Interestingly, *E. coli* showed highest susceptibility to pip-taz and *P. aeruginosa* showed similar susceptibility to cefoperazone-sulbactam and cefepime-tazobactam. Among carbapenems, 40% susceptibility was observed against *K. pneumoniae* and *P. aeruginosa* and 70-77% against *A. baumannii* and *E. coli.* The susceptibility rates of different pathogens to CSE-1034 were almost similar to amikacin and minocycline. Among all the pathogens tested, *K. pneumoniae* exhibited least susceptibility of 40-50% to all the drugs tested whereas the susceptibility observed against all other pathogens was between 70-83%. Among peptides, the susceptibility rate of 92-97% was reported towards colistin whereas the average susceptibility of 86% was reported towards polymyxin-B by all pathogens except *P. aeruginosa* (47.9%). The susceptibility of tigecycline was lowest against *K. pneumoniae* (36.4%) and highest against *E. coli.*

4. DISCUSSION

WHO in February 2017, has published the list of pathogens for which new antibiotics are urgently needed and the list includes carbapenems resistant *K. pneumoniae, E. coli, Acinetobacter spp.* and *Pseudomonas spp.* among others [13]. These species are declared the most critical MDR pathogens and have become resistant to a number of antibiotic classes, including carbapenems, the best available antibiotics for treating multidrug resistant bacteria [14].

This retrospective study was therefore aimed to find out the antibiogram profile of these particular pathogens against first and second line of antibiotics in our hospital. This study assumes importance in the light of continuously changing anti-microbial resistance trends with time. The comprehensive understanding about the local hospital antibiogram helps to eliminate non-performing drugs and update the hospital based antibiotic policies. Further, these surveillance studies help to reduce the mortality and failures associated with empiric therapy.

The current study revealed that the susceptibility rates observed were less than 50% in IPD patients and less than 10% in ICU patients to all the first line antibiotics tested except ampicillin-sulbactam, cefepime and gentamicin. The high level of resistance towards first line of antibiotics reported in IPD patients clearly indicate about the growing trend of multi-drug pathogens in the community acquired infections as well. Though a minimal amount of 10% susceptibility was reported to first line drugs in ICU patients, however it strongly indicates that all ICU patients don't suffer from MDR infections. A thorough check of medical history should be done before starting any therapy as some patients admitted in ICU could be suffering from community acquired infections and can be prescribed first line antibiotics. Moreover, a good sensitivity reported towards ampicillin-sulbactam, cefepime and gentamicin among first line drugs in both ICU and IPD patients suggests that their prescription can be increased in our hospital however on rotational basis to reduce the load on 2nd line antibiotics. Though susceptibility rates towards 2nd line antibiotics reported among IPD patients was higher than ICU patients but still, a good amount of resistance was observed towards all pathogens in IPD patients which is actually worrisome. The overall susceptibility to BL/BLI was 50-75% in IPD patients and carbapenem susceptibility was reported to be more than 75% except *P. aeruginosa*. In ICU patients, the BL/BLI susceptibility ranged between 20-60% and the carbapenem susceptibility was around 40% for *K. pneumoniae* and *P. aeruginosa* and 75% for *E. coli* and *A. baumannii*. Surprisingly, cefoperazone /sulbactam and cefepime/tazobactam performed comparatively better than carbapenems against *Pseudomonas*. Similar to our observations, Abdul et al. [15] have also reported that BL-BLI combinations performed better than carbapenems against pseudomonas. They have reported a susceptibility rate of 32-77% to imipenem. Datta

et al. [16] have reported carbapenem resistance of 7.87% among *Enterobacteriaceae* strains whereas carbapenem resistance rate ranging from 2% to 80% in various multi drug resistant organisms including *E. coli, Klebsiella spp., Pseudomonas spp.* and *Acinetobacter spp.* has been reported in a tertiary care hospital in Delhi [11].

The antibiotic susceptibility reported by Abdul et al. [15] for different antibiotics tested is also almost similar to our pattern. Increase in carbapenems resistance has been linked with excessive carbapenem consumption. Hence selection pressure on carbapenems need to be reduced either by reducing their consumption by using alternative drugs or developing newer therapeutic options. There are several publications about use of alternative agents for treating ESBL infections rather than carbapenems so as to reduce selection pressure without compromising clinical outcomes [17,18]. Interestingly, the current data reveals a very important picture of comparable susceptibility of CSE-1034 to minocycline and amikacin. When compared to carbapenems, the susceptibility of CSE-1034 was comparable to carbapenems in Enterobacteriaceae, however the CSE-1034 performed better than carbapenems against *P. aeruginosa* and *A. baumannii* in both IPD and ICU patients. In case of amikacin, the performance of CSE-1034 was better than amikacin against *K. pneumoniae* in ICU patients. The rising carbapenem resistance worldwide has been an important concern and pressurizes the need to develop alternate drugs to reduce the selective pressure on this antibiotic class. Emerging evidence on the effectiveness of CSE-1034 could prove a very encouraging trend, helping clinicians to choose CSE-1034 rather than being overly dependent on carbapenems. And one of the best evidences comes in the form of clinical trial and post marketing surveillance studies. Data published from different centers have consistently reported high in vitro susceptibility and good in vivo performance of CSE-1034 against different MDR bacterial infections [19,20,21,22,23]. The sensitivity of colistin reported between 92-97% for different pathogens in this study is a matter of grave concern and needs to be addressed. Various centers located across India have reported a colistin sensitivity of 90-97% [24,14]. The excessive consumption of colistin associated with the rise in MDR infections has probably led to rise in colistin resistance throughout the world [25,26].

A drug that has emerged with the potential of being used as carbapenem sparing options either empirically or as a de-escalation therapy includes CSE-1034. However, the less number of samples examined and a limited study period are the limitations of this study and should not be undermined. This kind of studies should be conducted on larger number of isolates to establish the exact antimicrobial trends. May be once we start using this CSE-1034 option at a larger scale, we can monitor clinical outcomes and come up with more conclusive evidence.

5. CONCLUSION

Overall, the rising carbapenem resistance among gram-negative strains as a consequence of excessive consumption of carbapenems is a matter of big concern. The appropriate use of 1st line antibiotics in ICU patients can help to reduce the load on 2nd line antibiotics. From the present study, it is evident that the use of ampicillin-sulbactam, cefepime and gentamicin from first line drugs can be increased in our hospital however on rotational basis to reduce the load on 2nd line antibiotics. Among 2nd line drugs, CSE-1034 along with amikacin should be an empirical choice of treatment for bacterial infections where the 1st line drugs are suspected to fail and the need of carbapenems arises. Considering the value of carbapenem and colistin as the last option for MDR bacterial infections, irrational prescription of these drugs should be stopped. Moreover, these types of studies should be conducted in regular to monitor the changing local susceptibility patterns.

CONSENT

As per international standard patient's written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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