Original Article

Role of ceftazidime-avibactam on multi-drug resistant and extensively drug resistant gram-negative bacterial isolates

Saha MR[a], Rahman T[b], Barman AC[c], Hasan MR[d], Barai L[e]

ABSTRACT

Background: *Infections caused by multi-drug resistant (MDR) gram-negative bacteria are becoming very common and now pose a serious public health threat worldwide, as they are difficult to treat due to few treatment options and are associated with high morbidity and mortality. The combination of ceftazidime with the β-lactamase inhibitor avibactam seems to be the right choice in this situation. The aim of the study was to evaluate the in vitro activity of ceftazidime-avibactam and other commonly used antibiotics on MDR and extensively drug resistant (XDR) Enterobacterales and Pseudomonas aeruginosa (P. aeruginosa).*

Methods: *This observational study was conducted in the Department of Microbiology, BIRDEM General Hospital, Dhaka, Bangladesh during January to June, 2022. To report in vitro data for ceftazidime-avibactam on gram-negative isolates a total of 130 (3rd generation cephalosporin resistant) MDR major gram-negative isolates from 65 urine and 65 pus/wound swab samples were taken. Besides, a total of 150 XDR (only colistin sensitive) major gram-negative bacterial isolates from urine and pus/wound swab samples were also taken for this study. Only Esch. coli, Klebsiella sp., P. aeruginosa were included for this study.*

Results: *Esch. coli (79.4%) was most prevailing in urine and P. aeruginosa (97.3%) in pus/wound swab sample. Esch. coli and Klebsiella sp. showed 100% resistance to amoxicillin-clavulunate in urine and pus/wound swab sample. MDR Esch. coli and Klebsiella sp. showed 73.5% and 68% resistance to piperacillin–tazobactum whereas 2.9% and 0.0% to meropenem. A total 9.2% resistance were seen in ceftazidime-avibactum among all MDR major gram-negative isolates and 82.7% ceftazidime-avibactum were resistance to XDR major gram-negative isolates.*

Conclusion: *This analysis presented high susceptibility rates to ceftazidime-avibactam against Enterobacterales strains as well as for MDR phenotype and ESBL phenotype. Ceftazidime- avibactam also achieved the second highest activity result against P. aeruginosa strains including MDR and carbapenem-resistant (CR) phenotypes. These data highlight the need for continued surveillance of antimicrobial activity to treat infections caused by CR phenotypes and for which the options are extremely limited as well as the need for novel antimicrobials.*

Keywords: β-*lactamase inhibitor, ceftazidime-avibactam, gram-negative isolates, multi-drug resistant, extensively drug resistant.*

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Author information

a. Mili Rani Saha, Associate Professor, Dept. of Microbiology, BIRDEM General Hospital, Dhaka, Bangladesh.
b. Tanjila Rahman, Assistant Professor, Dept. of Microbiology, BIRDEM General Hospital, Dhaka, Bangladesh
c. Arjun Chandra Barman, Medical Technologist, Dept. of Microbiology, BIRDEM General Hospital, Dhaka, Bangladesh.
d. Md. Rokibul Hasan, Junior experimental officer, Dept. of Microbiology, BIRDEM General Hospital, Dhaka, Bangladesh.
e. Lovely Barai, Professor & Head, Dept. of Microbiology, BIRDEM General Hospital, Dhaka, Bangladesh.

Address of correspondence: Dr. Mili Rani Saha, Associate Professor, Dept. of Microbiology, BIRDEM General Hospital, Dhaka, Bangladesh. E-mail: milisaha77@yahoo.com

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INTRODUCTION

Multi-drug resistant (MDR) *Enterobacterales, Acinetobacter baumannii*, and *Pseudomonas aeruginosa* (*P. aeruginosa*) are global public health concern due to increasing their prevalence and highest priority to develop newer antimicrobials.[1] In India, high carbapenem-resistant (CR) among *Enterobacterales* has been reported up to 30% for *Esch. coli* and 50% for *Klebsiella pneumonia*.[2] The high rate of imipenem resistant gram-negative bacteria (70.3%) was also reported in Bangladesh.[3] The management of CR gram-negative isolates infections are more challenging owing to limited antimicrobial options. CR isolates exhibit resistance against conventional first-line antimicrobials including cephalosporins, β-lactam/β-lactamase inhibitors, and fluoroquinolones.[4] Colistin and tigecycline have been used at this moment as first-line therapy for managing such infections.[5] However, tigecycline does not attain the required plasma concentrations, and may not be used for treating blood stream infections.[5] Additionally, colistin has been associated with prominent toxicity (both nephrotoxicity and neurotoxicity) may limit its clinical use.[5] Hence, these two regimens can be avoided and the challenges have led to the development of newer antimicrobials.[5] Classical β-lactamase inhibitors (i.e.clavulanic acid, tazobactam and sulbactam) lack activity against many important groups or classes of β-lactamases and thus first-generation β-lactam/β-lactamase inhibitor combinations are frequently ineffective against MDR pathogens yet.[6] Avibactam is a novel, non-*β*-lactam, *β*-lactamase inhibitor.[7] It has a broader spectrum of activity than classical β-lactamase inhibitors, with activity against Ambler class A, class C and some class D enzymes.[7] An important advantage of ceftazidime-avi-bactam is that avibactam can expand the antibacterial activity of ceftazidime against *Enterobacterales* and *P. aeruginosa* by inhibiting AmpC, extended-spectrum *β*-lactamase and carbapenemase producing strains.[8]

Ceftazidime-avibactam is approved for complicated urinary tract infections (including pyelonephritis), complicated intra-abdominal infections (CIAIs), hospital-acquired pneumonia (including ventilator-associated pneumonia), infections caused by aerobic gram-negative bacterial isolates.[8] Ceftazidime-avibactam has been proven to be clinically efficacious in pivotal phase III non-inferiority trials in comparison with carbapenems .[9]

The in vitro activity of ceftazidime-avibactam has been established against extended-spectrum β-lactamase(ESBLs), AmpC β-lactamase, *Klebsiella pneumoniae* carbapenemase (KPC) and OXA-48 producing *Enterobacterales* and *P. aeruginosa* isolates.[10] Similarly, a few real-world evidence studies have published data supporting the use ofceftazidime-avibactam to treat MDR gram-negative infections.[9] So, it is urgent need to investigate sensitivity test of ceftazidime-avibactam to choice antibiotic selection in case of CR gram-negative isolates infections. However, no study has been conducted to assess the in vitro activity of ceftazidime-avibactam on MDR and XDR against gram-negative isolates from Bangladesh.

So this study was undertaken to evaluate in vitro activity of ceftazidime-avibactam on MDR and XDR gram-negative isolates. This type of study update the knowledge of susceptibility profile of ceftazidime-avibactam and guide the clinicians standard treatment for patients with established CR gram-negative infections.

METHODS

This observational study was conducted in the Department of Microbiology, BIRDEM General Hospital, Dhaka, Bangladesh during January to June 2022. A total 130 (3rd generation cephalosporin resistant) MDR major gram-negative isolates from 65 urine and 65 pus/wound swab samples were taken . Beside those isolates total 150 XDR (only colistin sensitive) major gram-negative isolates from urine and pus/wound swab samples were also taken for this study. Only *Esch. coli, Klebsiella sp., P. aeruginosa* were included for this study. Culture was done by standard method[11] and antimicrobial sensitivity test of isolated bacteria by Kirby Bauer disc diffusion technique and zone of inhibition were interpreted according to CLSI guideline (CLSI, 2021).[12] Data were analyzed by WHONET-5 software.

RESULTS

Total 130 (3rd generation cephalosporin resistant) MDR major gram-negative isolates were taken from 65 urine and 65 pus/wound swab sample. Moreover, Total 150 XDR (only colistin sensitive) gram-negative isolates were taken from urine and pus/wound swab sample.

Among total 130 isolates *Esch. coli* (79.4%) was the most prevailing isolates followed by *Klebsiella sp.* (40%), *P.aeruginosa* (2.7%) in urine sample and *P. aeruginosa* (97.3%) was the most prevailing isolates followed by *Klebsiella sp.* (60%), *Esch. coli* (20.6%) in pus/wound swab sample (Table-I).

In urine sample *Esch. coli* showed 100% resistance to amoxicillin-clavulunate, lowest 2% resistance to meropenem. *Klebsiella sp.* showed 100% resistance to amoxicillin-clavulunate, ciprofloxacin and all isolates were sensitive to meropenem., ceftazidime-avibactum and colistin. *P. aeruginosa* showed 100% resistance to ciprofloxacin, meropenem., ceftazidime-avibactum (Table II).

In pus/wound swab sample *Esch. coli* showed 100% resistance to amoxicillin-clavulunate, piperacillin-tazobactum, aztreonam and lowest 7% resistance to ceftazidime-avibactum, meropenem, amikacin. *Klebsiella sp.* showed 100% resistance to aztreonam, amoxicillin-clavulunate, lowest 7% resistance to ceftazidime-avibactum. *P.aeruginosa* showed 75% resistance to aztreonam, 50% resistance to piperacillin–tazobactum lowest 20% resistance to ceftazidime-avibactum (Table III).

All isolates were sensitive to colistin in all samples (Table II & III).

Among 93 *Enterobacterales* 78(83.9%) were ESBL producing major gram-negative isolates in urine and pus/wound swab (Table IV).

Among 130 MDR major gram-negative isolates 85(65.4%) were resistance to piperacillin-tazobactum, 18(14%) were resistance to meropenem and lowest 12(9.2%) resistance were seen in ceftazidime-avibactum (Table V).

Out of 150 XDR major gram-negative isolates 26(17.3%) were sensitive to ceftazidime-avibactum and 124(82.7%) were resistance to ceftazidime-avibactum (Table VI). Among these XDR *P.aeruginosa* 56(94.9%,) were highly resistance to ceftazidime-avibactum followed by *Esch. coli* 11(78.6%) & *Klebsiella sp.* 57(74%)(Table VI).

Table I. Distribution of three MDR major gram-negative isolates from urine, pus/wound swab (N=130)

Name of isolates	Urine	Pus/wound swab
	No. (%) of resistance	
Esch. coli (n=68)	54 (79.4)	14(20.6)
Klebsiella sp. (n=25)	10(40)	15(60)
P.aeruginosa (n=37)	01(2.7)	36(97.3)
Total isolates (N=130)	65(50)	65(50)

Table II. Resistance pattern of MDR major gram-negative isolates in urine (N=65)

Antimicrobial Drugs	*Esch. coli* (n=54)	*Klebsiella sp.* (n=10)	*P. aeruginosa* (n=1)
		No. (%) of resistance	
β-lactamase inhibitor combinations			
Amoxicillin-clavulunate	54(100)	10(100)	-
Piperacillin–tazobactum	36(67)	7(70)	0(0)
Ceftazidime-avibactum	2(4)	0(0)	1(100)
Carbapenem			
Meropenem	1(2)	0(0)	1(100)
Aminoglycosides			
Amikacin	9(17)	0(0)	0(0)
Gentamicin	16(29)	2(20)	0(0)
Netilmicin	16(29)	2(20)	0(0)
Nitrofurantoin	24(45)	6(60)	-
Amidinopenicillin			
Mecillinam	36(67)	8(80)	
Fluroquinolones			
Ciprofloxacin	48(89)	10(100)	1(100)
Folate pathwayinhibitors			
Cotrimoxazole	35(64)	8(80)	-
Lipopeptides			
Colistin	0(0)	0(0)	0(0)

Table III. Resistance pattern of MDR major gram-negative isolates in pus/wound swab (N=65)

Antimicrobial Drugs	*Esch. coli* (n=14)	*Klebsiella sp.* (n=15)	*P. aeruginosa* (n=36)
		No. (%) of resistance	
Monobactum			
Aztreonam	14(100)	15(100)	27(75)
β-lactamase inhibitor combinations			
Amoxicillin-clavulunate	14(100)	15(100)	-
Piperacillin–tazobactum	14(100)	10(68)	18(50)
Ceftazidime-avibactum	1(7)	1(7)	7(20)
Carbapenem			
Meropenem	1(7)	0(0)	15(42)
Aminoglycosides			
Amikacin	1(7)	6(40)	26(72)
Gentamicin	2(14)	6(40)	29(81)
Netilmicin	3(21)	6(40)	29(81)
Fluroquinolones			
Ciprofloxacin	13(93)	14(93)	33(92)
Folate pathway inhibitors			
Cotrimoxazole	11(79)	13(87)	-
Lipopeptides			
Colistin	0(0)	0(0)	0(0)

Table IV. ESBL producing MDR major gram-negative isolates in urine and pus/wound swab (N=93)

Name of isolates	ESBL producing isolates	Non-ESBL producing isolates
	No. (%) of resistance	
Esch. coli (n=68)	58(85.3)	10(14.7)
Klebsiella sp.(n=25)	20(80)	05(20)
Total (N=93)	78(83.9)	15 (16.1)

Table V. Comparison of resistance pattern in ceftazidime-avibactum, piperacillin–tazobactum and meropenem of MDR major gram-negative isolates (N=130)

Name of isolates	Antimicrobial Drugs *No. (%) of resistance*		
	Ceftazidime-avibactum	Piperacillin–tazobactum	Meropenem
Esch. coli(n=68)	03(4.4)	50(73.5)	02(2.9)
Klebsiella sp.(n=25)	01(4)	17(68)	00(00)
P. aeruginosa(n=37)	08(21.6)	18(48.6)	16(43.2)
Total (N=130)	12 (9.2)	85 (65.4)	18 (14)

Table VI. Resistance pattern of ceftazidime-avibactum in XDR gram-negative isolates (N= 150)

Name of isolates	Sensitive	Resistant
	No. (%) of resistance	
Esch. coli(n=14)	03(21.4)	11(78.6)
Klebsiella sp.(n=77)	20(26)	57(74)
P. aeruginosa (n=59)	03(5.1)	56(94.9)
Total isolates (N=150)	26(17.3)	124(82.7)

DISCUSSION

Ceftazidime-avibactam has appeared as a promising therapy for CR gram-negative isolates infections in several clinical studies.[13,14] This study revealed in vitro antimicrobial susceptibility rates for ceftazidime-avibactam and other commonly used antibiotics of clinical isolates of *Esch. coli, Klebsiella sp., P. aeruginosa.*

Highest rate of *Esch. coli* (79.4%) were found in urine and *P. aeruginosa* (97.3 %) in pus/wound swab. This study observed MDR major gram-negative isolates were 9.2% resistant to ceftazidime-avibactam, 65.4% to piperacillin–tazobactum and 14% to meropenem. Ceftazidime-avibactam susceptibility was highest among isolates that were ESBL positive isolates (85.3% *Esch. coli* and 80% *Klebsiella sp.*). This study also noted that Ceftazidime-avibactam achieved the highest susceptibility 95.6% to *Esch.coli* and 96% to *Klebsiella sp.* on MDR major gram-negative isolates. The same trend of high ceftazidime-avibactam susceptibility is observed in several studies.[15,16,17] The above mentioned studies confirms the consistently high activity of ceftazidime-avibactam against this group of bacteria.

This study showed highest 21.6% *P. aeruginosa* were resistance to ceftazidime-avibactam among MDR major gram negative isolates. This is may be due to MBL (metallo-β-lactamases) positivity. A study done by Spiliopoulou et al. showed that ceftazidime-avibactam was not active against MBL-positive isolates. [18]

At the same time, this study provide a important cautionary notes that MDR 4.4% *Esch. coli* and 4% *Klebsiella sp.* were resistance to ceftazidime-avibactam prior to the introduction of these agents to our hospital. This findings suggest that the agents will need to be used judiciously to preserve their activity. Shields et al. reported the emergence of ceftazidime-avibactam resistant strains during treatment among patients with OXA-48 type CRE infections .[19]

This study also showed only 17.3% ceftazidime-avibactam were susceptible in XDR gram negative isolates and highest rate 94.9% XDR *P. aeruginosa* were resistant to ceftazidime-avibactam. This is may be due to MBL-positivity. MBL screening were not done in this study.

Currently, high-dose and combination strategies of this new β-lactam/β-lactamase inhibitors have maximize treatment success in severe CRE infections.[20] A study showed patients treated with ceftazidime-avibactam had a better outcome than those treated with colistin. [21]

Ceftazidime-avibactam should be incorporated in standard antibiogram susceptibility testing as ceftazidime-avibactam treatment initiation are as certain the advantages of its early and appropriate use on a larger scale. This study did not show any clinical data with its efficacy or tolerability. Clinicians must understand susceptibility patterns at their institutions from this study.

Conclusion

Ceftazidime-avibactam demonstrated excellent in vitro activity against important gram-negative isolates. Thus, this drug combination represents a valuable new option for the management of CR gram-negative bacterial infections. Furthermore, the use of sensitivity test can support prompt administration of effective therapy and help in reducing the morbidity and mortality associated with MDR infections. Routine and timely genomic detection of CR genes would help in selection of appropriate antimicrobial therapy as per the local epidemiology. Moreover, the emergence of ceftazidime-avibactam resistant strains during treatment has been reported.

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Conflicts of interest: Nothing to declare.

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