ORIGINAL ARTICLE

Assessment of In vitro Activities of Ceftaroline, Ceftazidime/ avibactam and Colistin against different Gram Negative and Gram Positive Isolates

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Key words:
Multidrug resistance, Carbapenem resistant Enterobacteriaceae, methicillin resistant Staph aureus

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ABSTRACT

Background: *Multidrug resistance organisms (MDRO) emergence is recognized as a serious threat to worldwide health and welfare. Infections with MDRO are associated with longer hospitalization periods, relatively high infection-related death, and greater health expenditures. The appearance of carbapenems resistant Enterobacteriaceae (CRE) and vancomycin resistant Staph aureus (VRS) makes the condition worse, since carbapenems and vancomycin were the drug of choice in treatment of MDR Enterobacteriaceae and methicillin resistant Staph aureus (MRSA). Accordingly the evaluation of new drugs used as substitution to other resistant antibiotics became an urgent need worldwide.* ***Objective:*** *The objective of this research is to assess the in vitro activity of ceftaroline, ceftazidime-avibactam and colistin activity against various complicated infections with resistant bacteria.* ***Methodology****: Antibiotic susceptibility of all clinical isolates was performed by the disk diffusion method, and results in interpretation were performed according to CLSI guidelines (2019)* ***Results:*** *concerning Gram-negative bacteria, ceftazidime-avibactam and colistin showed high susceptibility (>85%) and (100%) respectively against Pseudomonas aeruginosa and Enterobacteriaceae, with enhanced antibacterial activity due to the inclusion of avibactam to ceftazidime drug. Ceftaroline demonstrated susceptibility ranged from (53% - 75.8%) against Gram-negative bacteria and (> 75%) against Gram-positive bacteria including MRSA.* ***Conclusion:*** *results showed acceptable susceptibility of both Gram negative and Gram positive isolates against tested antibiotics, however further investigations on increased number of isolates are required.*

INTRODUCTION

Resistance to various antibacterial drugs has emerged in bacterial pathogens, posing a severe public health risk since there are few, if not no, effective antibacterial drugs available for diseases caused by such pathogens[1]. Multidrug-resistant organisms (MDROs) includes both Gram-negative and Gram-positive bacteria. Infection caused by MDRO can cause antibiotic therapy to be delayed, resulting in high mortality and morbidity, longer hospitalization periods, and significant financial losses for both the patient and the country. In 2011, WHO declared "combat drug resistance: no action today, no cure tomorrow"[2].

With the emergence of MDR Enterobacteriaceae, especially those which develop resistance to carbapenems, carbapenem-resistant Enterobacteriaceae (CRE), infections get more challenging to control and treat when they grow resistance to frequently used antibiotics and, in some cases, all available antibiotics, making CRE a public health risk [3]. Besides, increased infection caused by Methicillin-resistant *Staphylococcus aureus (*MRSA), which usually carry resistance genes to other antimicrobial agents, increase the need for novel therapeutic approaches that are both safe and effective [4]. Vancomycin remains the first line of treatment for patients with invasive infections, although a narrow spectrum, renal toxicity, low tissue concentrations, and increased resistance have necessitated the development of other therapeutic options [5].

Ceftaroline, ceftazidime-avibactam and colistin are three relatively new drugs that show promising effects against antibiotic-resistant bacteria. They are widely accessible all around the world. Resistance patterns to ceftazidime-avibactam, Colistin and Ceftaroline throughout the world are still to be characterized since they are essential data for tracking and assessing public health risks [6].

Ceftazidime–avibactam is a novel antibiotic combination that includes avibactam, a novel non-β-lactam β-lactamase inhibitor; and ceftazidime, a third-generation antipseudomonal cephalosporin. When ceftazidime is combined with avibactam, its antimicrobial effect against several β-lactamase-producing bacteria, such as carbapenemase-producing Enterobacterales, is restored [7]. It is also used for treating complicated infections, mainly urinary tract and intra-abdominal infections, in patients with limited or no alternative treatment options and for treating hospital-acquired pneumonia such as ventilator-associated pneumonia (VAP) [8]. Avibactam blocks class A and D carbapenemases in vitro, however, it does not inhibit metallo-β-lactamases[9]. After showing significant efficacy in Phase III trials compared to carbapenems, the FDA authorized Ceftazidime–avibactam [5].

Ceftaroline is a cephalosporin antibiotic that has attracted the attention of researchers as a potential therapeutic approach. Nevertheless, comprehensive descriptions of its application are still few. Ceftaroline's antimicrobial effect, like that of other cephalosporins, is due to binding to vital penicillin-binding proteins (PBPs), which inhibits bacterial cell wall production [10]. It has a broad spectrum of bioactivities against Gram-positive infections, including MRSA, and some Gram-negative pathogens. The drug is currently approved by the FDA to treat methicillin-resistant and methicillin-sensitive strains of, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *and Escherichia coli* in adults and children (from 2 months of age) [11].

Colistin (Polymyxin E) was initially utilized intravenously in the 1950s. Due to its antibacterial action for treating different diseases, including infectious diarrhea and urinary tract infections, the FDA authorized colistin as an antibacterial drug against GNB in 1959. Polymyxins have also been used topically for ear and eye infections, as well as selective bowel decontamination, for several decades. Polymyxins were also utilized to treat persistent GNB infections[12]. Colistin is an active antibiotic against Gram-negative organisms that commonly cause life-threatening diseases, such as carbapenem-resistant *E. coli*, *K. pneumoniae*, *P. aeruginosa*, and other Enterobacteriaceae [13].

Unfortunately, colistin abuse and misuse have resulted in the widespread development of colistin-resistant bacteria. Nevertheless, the formation of germs resistant to colistin might occur without any previous exposure to colistin, leaving specialists unable to treat patients [14].

The aim of this study was to evaluate the in vitro activity of Ceftaroline, ceftazidime-avibactam and colistin activity against various complicated infections with resistant bacteria and to assess antimicrobial resistance against these antimicrobial agents.

METHODOLOGY

Patients:

This study comprised 112 isolates presented at the Central Microbiology and Immunology laboratory, Research Institute of Ophthalmology, and Ain Shams University hospitals from January 2021 till June 2021.
All participants provided written informed consent. Approval of the research design was obtained from the ethical committee, Research Institute of Ophthalmology and Ain Shams University hospitals.

Inclusion criteria:

- Age range from 20 to 65
- Both sex (male and female)
- CRE
- MRSA

Exclusion criteria:

- Younger than 20 years' old
- Culture did not meet the criteria of infection

Methods

Confirmation & identification of isolates:

Clinical isolates (Swabs, blood cultures, sputum, Fluids, pus) with some infections types (intra-abdominal infection, skin and skin structure infection, urinary tract infection, blood infections, lower respiratory tract infection, and ocular infection) were cultured on nutrient agar, blood agar, mannitol salt agar, and MacConkey, and all then were incubated at 37°C for 24 hours then isolated colonies were examined as follows:

- Naked eye examination for colonial morphology and characteristic type as of hemolysis on blood agar,
- Microscopic examination of Gram-stained films
- Further identification of the isolates were done by the routine bacteriological method

Antimicrobial susceptibility testing using disk diffusion method:

- Antibiotic susceptibility of all clinical isolates was performed by the disk diffusion method, and results in interpretation were performed according to CLSI guidelines (2019)

  The antibiotics used were:

  - Other antimicrobials were tested in addition to CT, CPT, and CZA, such as carbapenems (meropenem, imipenem, ertapenem), β-lactam/β-lactamase inhibitor complexes (ampicillin-sulbactam, piperacillin-tazobactam, and amoxicillin-clavulanate), ureidopenicillin (piperacillin), cephalosporins (cefotaxime, cefazolin, cefepime, and ceftazidime), monocyclic β-lactams (aztreonam), aminoglycosides (amikacin and gentamicin), fluoroquinolones (levofloxacin, ciprofloxacin,

and moxifloxacin), folate metabolic pathway inhibitors(trimethoprim-sulfamethoxazole), Tetracyclines (Tygacil, Doxycycline), Linezolid, Vancomycin, Teicoplanin, and colistin

- The data were analyzed for *Klebsiella peumoniae*, *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Escherichia coli*, *Staphylococcus aureus* and coagulase-negative *Staphylococcus*, methicillin-resistant *staph aureus*.

RESULTS

Between March and June of 2021, 112 isolates were collected. The majority of isolates were obtained from individuals > 50 (77, 68.75%), followed by patients 40-50 years (20, 17.85%), followed by patients 20-30 (15, 13.39%) CRE. Regarding Sex ratio, the male was 73 (65.17%) to female 39 (34.82%)

The infection were, 33 (29.46%) isolates were collected from lower respiratory tract infections, 42 (37.5%) from urinary tract infections, 12 (10.71%) from intra-abdominal infections, and 25 (22.32%) from the blood. Isolates were obtained from patients in the general medical, pediatric and surgical wards, the intensive care units (ICUs), and the surgical ICUs.

Out of the 112 isolates, 70 (62.5%) isolates proved to be Gram-negative, while 42(37.5%) of the isolates were Gram-positive. The 70 Gram-negative isolates were classified according to the result of the biochemical reactions as 17 *E.coli* (24.3%), 33 *K. pneumoniae* (47.1%) and 20 *P. aeruginosa* (28.6%). On the other hand, the Gram-positive bacteria were classified into 11 methicillin sensitive staph aureus (MSSA) (26.2%), 27 (64.3%) MRSA and four coagulase-negative staph (9.5%). The results are shown in table 1.

Table 1: classification of isolated bacteria

Total isolates (n= 112)					
Gram negative (n=70) 62.5%			**Gram positive (n= 42) 37.5%**		
E.coli	*P. aeruginosa*	*K. pneumoniae*	MSSA	Coagulase –ve staph (CONs)	MRSA
N= 17 24.3%	N=20 28.6%	N=33 47.1%	N=11 26.2%	N=4 9.5%	N= 27 64.3%

P. aeruginosa isolates showed the highest susceptibility to piperacillin-tazobactam, ciprofloxacin and levofloxacin with sensitivity reaching (90%), they also showed high susceptibility to amikacin and gentamicin with sensitivity (85%, 80%) respectively, while the least susceptibility was to tobramycin as it reached (60%). Concerning *K. pneumoniae*, the isolates showed highest susceptibility to Tygacil, Cefoperazone Sulbactam and piperacillin- tazobactam with sensitivity reaching (97%, 94%, 91%) respectively, while they show lowest susceptibility to Cefazolin (33%) and cefotaxime (36%). Finally, the susceptibility of *E.coli* isolates was highest to Imipenem, Piperacillin tazobactam and Tygacil reaching (88%), however, cefazolin and cefepime showed the least susceptibility against *E.coli* strains (29%) (Table2).

Table 2: Antibiogram of the isolated Gram negative bacteria:

Antimicrobial Agent	*P. aeruginosa* 20		*K. pneumoniae* 33		*E.coli* 17	
	S	**R**	**S**	**R**	**S**	**R**
Imipenem	15 (75%)	5 (25%)	26 (79%)	7 (21%)	15 (88%)	2 (12%)
meropenem	15 (75%)	5 (25%)	24 (73%)	9 (27%)	14 (82%)	3 (18%)
Ertapenem	NA		21 (64%)	12 (36%)	13 (76%)	4 (24%)
Piperacillin	15 (75%)	5 (25%)	13 (39%)	20 (61%)	7 (41%)	10 (59%)
Amoxicillin Clavulanate	NA		25 (76%)	8 (24%)	12 (71%)	5 (29%)
Ampicillin Sulbactam	NA		25 (76%)	8 (24%)	10 (59%)	7 (41%)
Piperacillin tazobactam	18 (90%)	2 (10%)	30 (91%)	3 (9%)	15 (88%)	2 (12%)
Cefazolin	NA		10 (33%)	23 (67%)	5 (29%)	12 (71%)
Cefotaxime	NA		12 (36%)	21 (64%)	6 (35%)	11 (65%)
Cefoperazone Sulbactam	15 (75%)	5 (25%)	31 (94%)	2 (6%)	15 (88%)	2 (12%)
Ceftriaxone	14 (70%)	6 (30%)	29 (89%)	4 (11%)	13 (76%)	4 (24%)
Cefepime	16 (80%)	4 (20%)	24 (73%)	9 (27%)	5 (29%)	12 (71%)
Gentamicin	16 (80%)	4 (20%)	28 (85%)	5 (15%)	12 (71%)	5 (29%)
Tobramycin	12 (60%)	8 (40%)	24 (73%)	9 (27%)	10 (59%)	7 (41%)
Clindamycin	NA		21 (64%)	12 (36%)	7 (41%)	10 (59%)
Amikacin	17 (85%)	3 (15%)	29 (89%)	4 (11%)	13 (76%)	4 (24%)
Ciprofloxacin	18 (90%)	2 (20%)	28 (85%)	5 (15%)	14 (82%)	3 (18%)
Levofloxacin	18 (90%)	2 (10%)	27 (82%)	6 (18%)	13 (76%)	4 (24%)
Tygacil	NA		32 (97%)	1 (3%)	15 (88%)	2 (12%)

S: Sensitive, R: Resistant
NA: Not applicable

Table 3: Antibiogram of the isolated Gram positive bacteria

Antimicrobial Agent	MRSA 27		MSSA 11		CoNS 4	
	S	R	S	R	S	R
Imipenem	NA		9 (82%)	2 (18%)	2 (50%)	2 (50%)
meropenem	NA		10 (91%)	1 (9%)	3 (75%)	1 (25%)
Ertapenem	NA		7 (64%)	4 (36%)	2 (50%)	2 (50%)
Piperacillin	NA		8 (73%)	3 (27%)	1 (25%)	3 (75%)
Amoxicillin Clavulanate	NA		9 (82%)	2 (18%)	3 (75%)	1 (25%)
Ampicillin Sulbactam	NA		8 (73%)	3 (27%)	3 (75%)	1 (25%)
Piperacillin tazobactam	NA		9 (82%)	2 (18%)	4 (100%)	0 (0%)
Cefazolin	NA		4 (36%)	7 (64%)	0 (0%)	4 (100%)
Cefotaxime	NA		6 (55%)	5 (45%)	3 (75%)	1 (25%)
Cefoperazone Sulbactam	NA		9 (82%)	2 (18%)	3 (75%)	1 (25%)
Ceftriaxone	NA		7 (64%)	4 (36%)	1 (25%)	3 (75%)
Cefepime	NA		7 (64%)	4 (36%)	2 (50%)	2 (50%)
Gentamicin	NA		NA		NA	
Tobramycin	NA		NA		NA	
Amikacin	NA		NA		NA	
Vancomycin	25 (93%)	2 (7%)	10 (91%)	1 (9%)	3 (75%)	1 (25%)
Ciprofloxacin	23 (85%)	4 (15%)	8 (73%)	3 (27%)	3 (75%)	1 (25%)
Levofloxacin	21 (78%)	6 (22%)	8 (73%)	3 (27%)	3 (75%)	1 (25%)
Tygacil	25 (93%)	2 (7%)	10 (91%)	1 (9%)	4 (100%)	0 (0%)

S: Sensitive, R: Resistant
NA: Not applicable

Regarding Gram positive bacteria, MRSA showed highest susceptibility to vancomycin and Tygacil (93%) and lowest to clindamycin (74%). MSSA showed highest susceptibility to meropenem, vancomycin and Tygacil with sensitivity reaching (91%) while the lowest susceptibility was to Cefazolin and Clindamycin with sensitivity (36%, 55%) respectively. Finally, highest susceptibility of CONs went to Piperacillin tazobactam and Tygacil (100%) and the lowest was to cefazolin (0%) and piperacillin (25%) (Table 3)

When the isolated Gram-negative bacteria were tested against ceftazidime-avibactam, ceftaroline and colistin, *E.coli* proved to be most susceptible to colistin (100%), followed by ceftazidime avibactam as 15 isolates (88.2%) were sensitive to the antibiotic, and the least susceptibility was to ceftaroline with (53.4%) susceptibility. *K. pneumoniae* showed highest susceptibility to colistin (93.9%), ceftazidime-avibactam (87.9%) and ceftaroline (75.8%). Regarding the pseudomonas, all the isolates (100%) were susceptible to colistin, 19 isolates (95%) were sensitive to ceftazidime-avibactam. The addition of avibactam to ceftazidime highly increased the susceptibility of gram-negative bacteria in comparison to ceftazidime alone (Table 4).

Table 4: Susceptibility of Gram-negative isolates (70 isolates) to Tested antibiotic

Antimicrobial agents	*E. coli* n=17		*K. peumoniae* n=33		*P. aeruginosa* n =20	
	S	R	S	R	S	R
Ceftazidime-avibactam (CZA)	15 (88.2%)	2 (11.8%)	29 (87.9%)	4 (12.1%)	19 (95%)	1 (5%)
Ceftaroline (CPT)	9 (53%)	8 (47%)	25 (75.8%)	8 (24.2%)	NA	NA
Colistin (Col)	17 (100%)	0 (0%)	31 (93.9%)	2 (6.1%)	20 (100%)	0 (0%)

S: Sensitive, R: Resistant,
NA: Not applicable

Concerning Gram Positive bacteria, about (63.3%) of isolated *S. aureus*, (75%) of Cons and (77.8%) of MRSA were susceptible to Ceftaroline (Table 5)

Table 5: Susceptibility of Gram-positive isolates (42 isolates) to Tested antibiotic

Antimicrobial Agents	*MSSA* n=11		*CONs* n=4		*MRSA* n =27	
	S	R	S	R	S	R
Ceftazidime-avibactam	NA	NA	NA	NA	NA	NA
Ceftaroline	7 (63.3%)	4 (36.4%)	3 (75 %)	1 (25%)	21 (77.8%)	6 (22.2%)
Colistin	NA	NA	NA	NA	NA	NA

S: Sensitive, R: Resistant,
NA: Not applicable

DISCUSSION

A recent World Health Organization research reported widespread antibiotic resistance throughout the world. Antibiotic resistance is a serious problem worldwide, and there are significant variations in the pattern of resistance. The World Health Organization stated that antibiotic resistance is rising globally, mainly concerning in Africa due to poor health and environmental practices such as poor waste management, poor infection control, antibiotic over-prescription, food security, overuse of antibiotics in farming, and limited access to the most recent antibiotics [15].

Ceftaroline, ceftazidime-avibactam, and colistin are relatively novel antibiotics that are effective against a wide range of bacterial strains, including some that have inherent antibiotic resistance. The underlying patterns of resistance to those drugs must yet be determined, and there is an urgent need for worldwide antibiotic resistance surveillance [16].

In the present study, we evaluated the overall in vitro activities of Ceftaroline, Ceftazidime–avibactam and colistin. Gram-negative bacteria showed the highest susceptibility to colistin ranging from 100% in *E.coli* and *P. aeruginosa* to 93.3% in *K. pneumoniae.* Isolated Enterobacteriaceae also showed high susceptibility exceeding 85% to ceftazidime-avibactam, while pseudomonas isolates showed susceptibility to ceftazidime-avibactam by 95%. The susceptibility of ceftaroline against *E.coli* was about 53%, while for *K. peumoniae* was about 77%.

These results are per those obtained by Zhang et al whose study proved susceptibility exceeding 90% to ceftazidime-avibactam against *p. aeruginosa* and Enterobacteriaceae with elevated antibacterial activity observed from the addition of avibactam (4 mg/L) to ceftazidime. They also proved that susceptibility to Ceftaroline against Enterobacteriaceae ranges from 57% in *K. peumoniae* to 67% in *E.coli*, which are close to the results of Ceftaroline in this study.

The results in this study also agreed with those proved by George and Alfredo as their study reported susceptibility to colistin which exceeds 94% Enterobacteriaceae and 99% in *P. aeruginosa* and susceptibility to ceftazidime-avibactam was more than 90% in both Enterobacteriaceae and *P. aeruginosa.*

Colistin is an antibiotic that can be used to treat gram-negative infections. Toxicity is present at a tolerable level. As a result, the benefits exceed the risks associated with colistin usage. It is recommended that colistin should be used as a last-resort treatment for

infections with carbapenem-resistant gram-negative bacteria. Therefore, it is crucial to monitor colistin use so that this resource is used wisely and only as a last resort in treating severe infections. Therefore, it is critical to make the best use of colistin to guarantee that it remains an effective and safe form of therapy when required[13].

Although the susceptibility of isolated Gram negative bacteria against ceftaroline ranged from 53% to 75% in this study, the susceptibility of isolated Gram positive against the same drug exceeded 77%, especially in MRSA. In Accordance to Zhang et al whose study reported susceptibility to ceftaroline against Gram-positive bacteria that exceeded 89%, including MRSA. Gianluca Morroni et al, also demonstrated in his study that susceptibility of MRSA to ceftaroline exceeded 95%[18].

Shio-Shin et al studied the susceptibility of ceftaroline against Gram positive including MSSA, MRSA and CONs by MIC method, he demonstrated that 96% of MSSA and 93% of MRSA were sensitive to ceftaroline at MIC 1 mg/L and even the resistant strains became susceptible when they increased MIC to 2 mg/L which proved these strains to be dose susceptible strains[19]

Ceftaroline is therefore helpful against gram-positive pathogens and in locations where MRSA infections are common, especially in vancomycin-resistant isolates or to avoid toxicity from vancomycin in susceptible strains[18-19].

Minute differences between one study and the other could be due to the origin of the specimens, area of the study and even tested period since bacterial susceptibility can change over time.

CONCLUSION

In conclusion, the inclusion of avibactam enhanced the efficacy of Ceftazidime against Enterobacteriaceae and *Pseudomonas aeruginosa*. Global antimicrobial susceptibilities to ceftazidime-avibactam, colistin and Ceftaroline were shown to be high in multidrug-resistant patients when resistance to other comparators and antimicrobial agents was reported to be high.

Ceftazidime- avibactam and colistin showed high susceptibility against *E.coli, K. peumoniae* and *P. aeruginosa,* followed by ceftaroline. These in vitro results suggest that these antibiotics may be a valuable option for treating MDR gram-negative bacteria, including CRE.

Ceftaroline proved to have high susceptibility against Gram-positive bacteria, including MRSA, which gives this drug an advantage to be used to treat MRSA infection and as a substitution to vancomycin in vancomycin-resistant strains.

The authors declare that they have no financial or non-financial conflicts of interest related to the work done in the manuscript. Each author listed in the manuscript had seen and approved the submission of this version of the manuscript and takes full responsibility for it. This article had not been published anywhere and is not currently under consideration by another journal or a publisher.

This manuscript has not been previously published and is not under consideration in the same or substantially similar form in any other reviewed media. I have contributed sufficiently to the project to be included as author. To the best of my knowledge, no conflict of interest, financial or others exist. All authors have participated in the concept and design, analysis, and interpretation of data, drafting and revising of the manuscript, and that they have approved the manuscript as submitted.

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