

## ORIGINAL ARTICLE

# Evaluation of In vitro Activity of Cefiderocol and Ceftolozane-Tazobactam against Extended-Spectrum $\beta$ -Lactamase-Producing Coliform and Multidrug Resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*

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## ABSTRACT

### Key words:

Ceftolozane-tazobactam;  
Cefiderocol; ESBL  
Enterobacteriales; *P. aeruginosa*

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**Background:** A worrisome escalation in multidrug-resistant (MDR) Gram-negative bacterial infections which are accompanied with worse outcomes due to inadequate treatment options. There is an imperative requirement to explore new antimicrobials to oppose these resistant strains. **Objectives:** Assessment of antibacterial activity of Cefiderocol and Ceftolozane-Tazobactam against ESBL-Producing coliform and MDR *A. baumannii* and *P. aeruginosa*. **Methodology:** A total of 332 clinical samples were obtained from surgical ICU cases. Pathogenic microorganisms were identified. Antibiotic susceptibility was done for gram negative isolates. Third-generation cephalosporins resistant coliforms were screened for ESBL detection. Ceftolozane-Tazobactam and Cefiderocol activity on ESBL coliform and MDR *P. aeruginosa* and *A. baumannii* isolates was investigated. **Results:** The susceptibility of both ESBL *E. coli*, *K. pneumoniae*, MDR *P. aeruginosa*, and *A. baumannii* to ceftolozane/tazobactam was 77%, 70%, 63% and 58% respectively. ESBL *E. coli* and *K. pneumoniae* exhibited MIC<sub>50/90</sub> value of (0.19/0.25 $\mu$ g/mL) and (0.25/0.5 $\mu$ g/mL) for ceftolozane/tazobactam respectively. MDR *P. aeruginosa* showed MIC<sub>50/90</sub> value (2/4 $\mu$ g/mL). MDR *A. baumannii* exhibited high MIC<sub>50/90</sub> value (16/24 $\mu$ g/mL). Cefiderocol was 100% effective against most isolates with different MIC<sub>50/90</sub> values. For ESBL-*E. coli* and *K. pneumoniae*, the MIC<sub>50/90</sub> value was (0.5/1.5 $\mu$ g/mL). For MDR *P. aeruginosa* and *A. baumannii*, the MIC<sub>50/90</sub> value was (0.75/2 $\mu$ g/mL) and (0.25/2 $\mu$ g/mL) respectively. **Conclusion:** Cefiderocol exhibits superior activity against ESBL coliform and MDR *A. baumannii*, *P. aeruginosa* compared to ceftolozane-Tazobactam.

## INTRODUCTION

Globally, antimicrobial resistance (AMR) in Gram-negative bacteria, particularly Enterobacteriales, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* is on rise and alarmingly to global health security. This is primarily due to the spread of ESBLs, ampC-lactamases, as well as carbapenemases strains, which are significant causes of community and nosocomial infections.<sup>1,2,3</sup>

Infections caused by Enterobacteriaceae that produce ESBLs or multidrug-resistant Gram-negative bacteria (MDR) commonly treated with carbapenems therapy, a broad-spectrum antibacterial agent.<sup>4</sup>

Unfortunately, overuse of carbapenems has resulted in the evolution of carbapenem resistance among gram-negative bacilli, which have the ability to spread throughout the hospital and community causing a worldwide public health crisis.<sup>5,6</sup> As a result of spread

of carbapenem resistance, carbapenem-sparing substitutes including  $\beta$ -lactam/  $\beta$ -lactamase inhibitors must be utilized to decrease carbapenem use and carbapenem resistance.<sup>7</sup>

Ceftolozane-tazobactam (CFT), has been approved by Food and Drug Administration having antibacterial effect on MDR *P. aeruginosa*.<sup>8</sup> Additionally, CFT persists a preferred antimicrobial agent for the treatment of MDR *P. aeruginosa* accused infections.<sup>9</sup> Ceftolozane is a new wide spectrum cephalosporin byproduct of ceftazidime, that is not affected by ESBLs and AmpCs  $\beta$ -lactamases.<sup>10</sup>

Cefiderocol is a new siderophore cephalosporin with wide antimicrobial effect. Which is composed of a catechol-form siderophore and a cephalosporin base with lateral chains analogous to ceftazidime and cefepime. Cefiderocol can act as a siderophore molecule and chelate extracellular iron because of a catechol moiety. Cefiderocol is transferred to the periplasmic

space over ferric iron transport systems found on the external membrane of Gram-negative bacteria after iron has been chelated. In which cefiderocol disconnects from the iron and attach to Penicillin binding proteins, preventing the amalgamation of cell wall peptidoglycan<sup>11,12</sup>

Cefiderocol has a powerful effect on a variety of MDR gram-negative bacteria, such as enteric and nonfermentive bacteria, and any resistant phenotypes of *P. aeruginosa* as well as CFT resistant strains.<sup>13</sup> Therefore, the aim of the current investigation is to evaluate the efficacy of ceftolozane/tazobactam and cefiderocol against ESBL-producing coliform and MDR *Acinetobacter* strains and *P. aeruginosa*.

## METHODOLOGY

A prospective study was carried out over one year between September 2021 and September 2022 on routine clinical specimens of Tanta University Hospitals, Egypt. A total of 332 specimens from different infection sites including respiratory secretions, urine and wound swab were received from patients admitted to Surgical ICU. Ethical approval for this research was granted by the Ethics and Research Committee, Faculty of Medicine, Tanta university (Approval code 35710/9/22). code number was put in each sample to maintain privacy. All methods were conducted in accordance with the Helsinki Declaration guidelines. Informed consent was taken before carrying out any procedure on study participants.

### Sample processing and pathogen identification

The samples were collected according to laboratory standard and then cultivated on MacConkey, blood, nutrient, and chocolate agar (Oxoid UK) and incubated for 24 hours at 37°C. The bacterial isolates were identified according to accepted standard methods along-with morphology and conventional biochemical tests (urease, citrate, triple sugar iron agar, motility-indole-ornithine decarboxylase, and lysine iron agar)<sup>14</sup>. The isolated species were then confirmed using the VITEK 2TM Compact. (bioMérieux).

### Antimicrobial susceptibility pattern of coliform and non-fermenter Gram negative bacilli

According to the recommendations of the Clinical and Laboratory Standards Institute, gram negative isolates were tested for their antimicrobial susceptibilities using the Kirby-Bauer disc diffusion method on Mueller Hinton agar plates (Oxoid UK) with 0.5 McFarland density suspension.<sup>15</sup> The following antibiotics were used for isolated species: amoxicillin/clavulanate (20/10 µg), piperacillin/tazobactam (100/10 µg), aztreonam (30 µg), ceftazidime (30 µg), cefotaxime (30 µg), ceftriaxone (30 µg), cefoxitin (30 µg), cefepime (30 µg), imipenem (10 µg), meropenem (10 µg), ertapenem (10 µg), amikacin (30

µg), gentamicin (10 µg), levofloxacin (5 µg), tigecycline (15 µg), and colistin (10 µg) (Oxoid, UK).

### ESBL Detection

According to the Clinical and Laboratory Standards Institute's recommendations, all *E. coli* and *Klebsiella* isolates that exhibiting resistance to ceftriaxone ( $\leq 25$  mm), ceftazidime ( $\leq 22$  mm), cefotaxime ( $\leq 27$  mm), or aztreonam ( $\leq 27$  mm) were screened for ESBL detection by Modified Double-Disk Synergy Test and VITEK2 System (bioMérieux) as per specified in the manufactures' instructions.<sup>16,17</sup>

### Modified Double-Disk Synergy Test<sup>16</sup>

Amoxicillin-clavulanate (20/10 µg) disc was placed in the center of inoculated Mueller Hinton agar plates (Oxoid UK) along with four discs of ceftazidime (30 µg), cefotaxime (30 µg), aztreonam (30 µg), and cefepime (30 µg). Which were arranged at a distance ranging between 16 and 20 mm from amoxicillin/clavulanate disc (center to center). A piperacillin tazobactam (100/10 µg) disc was placed at a distance ranging between 22 and 25 mm from the cefepime disc. Any distortion or increase in the zone of inhibition around cefepime or any of the extended-spectrum  $\beta$ -lactamases toward the piperacillin/tazobactam disc or amoxicillin/ clavulanate disc were considered to be ESBL producing organisms.

### Ceftolozane-tazobactam Susceptibility Detection

Ceftolozane/tazobactam, Minimum inhibitory concentration (MIC) E test strips (Liofilchem, Roseto degli Abruzzi, Italy) were applied with concentration (0.016–256 µg/mL). For isolates of *E. coli*, *Klebsiella* species producing ESBL & MDR *A. baumannii* & *P. aeruginosa*. Ceftolozane-tazobactam MIC was considered susceptible at  $\leq 4$  µg/mL.

The following reference strains were used as the quality control: ESBL-negative *E. coli* ATCC 25922, ESBL-positive *K. pneumoniae* ATCC 700603, and *P. aeruginosa* ATCC 27853.

### Cefiderocol Susceptibility Detection

ESBL producing *E. coli*, *Klebsiella* & MDR *P. aeruginosa*, *A. baumannii* isolates were selected to antimicrobial susceptibility testing to cefiderocol. Cefiderocol MTS™ (MIC Test Strip), E test strips (Liofilchem, Roseto degli Abruzzi, Italy) were used with concentration (0.016–256 µg/mL)

### Statistical Analysis

All data were analyzed using the (SPSS) 26 programs. The results for quantitative variables were expressed as mean  $\pm$  SD, while qualitative variables were expressed as numbers and percentages.

## RESULTS

### Specimens Characteristics and Classification of Gram-negative Isolates

A total of 157 (47.3%) Gram-negative bacteria were isolated from 332 specimens from different infection sites from patients admitted to surgical ICUs. Other

found isolates were gram positive bacteria 84 (25.3%); fungi 32 (9.6%), while 59(17.7%) show no growth. The gram-negative isolates were composed of 100 Enterobacterales (49 *Klebsiella pneumoniae*, 28 *E. coli*, 12 *Enterobacter cloacae*, 7 *Proteus mirabilis* and 4 *Klebsiella oxytoca*), 24 *Acinetobacter baumannii* and 33 *P. aeruginosa* as illustrated in the table (1).

**Table 1: Descriptive data of type of gram-negative isolates from clinical specimens**

Data		Gram negative organisms N = 157
Age	Range (years)	18 -75
	Mean ( $\pm$ SD)	33.46 ( $\pm$ 19.4)
Gender	Male	89 (56.6%)
	Female	68 (43.3%)
Type of gram-negative isolates	<i>E. coli</i>	28 (17.8%)
	<i>K. pneumoniae</i>	49 (31.2%)
	<i>K. oxytoca</i>	4 (2.5%)
	<i>Enterobacter cloacae</i>	12 (7.6%)
	<i>Proteus mirabilis</i>	7(4.5%)
	<i>Acinetobacter baumannii</i>	24(15.2%)
	<i>Pseudomonas aeruginosa</i>	33(21%)

#### Antibacterial effect of Ceftolozane-tazobactam (CFT) & Cefiderocol:

As illustrated in **table (2)** Twenty-eight *E. coli* (21 ESBL & 7 non ESBL) isolates were evaluated, the effect of CFT on ESBL contrasted with non-ESBL isolates. The non- ESBL isolates, shown a low MIC<sub>50/90</sub> value (0.046/0.19  $\mu$ g/mL) with high susceptibility rate (85%) opposed to the ESBL isolates which exhibited high MIC<sub>50/90</sub> value (0.19/0.25 $\mu$ g/mL) and low percentage of susceptibility (77%). The susceptibility of Cefiderocol against ESBL versus non-ESBL isolates was the same (100%), with low MIC<sub>50/90</sub> value (0.38/0.5  $\mu$ g/mL) for non ESBL contrasted to the ESBL isolates which presented high MIC<sub>50/90</sub> value (0.5/1.5 $\mu$ g/mL).

Moreover, a total of 49 *K. pneumoniae* (39 ESBL & 10 non ESBL) isolates were evaluated, the non- ESBL isolates, presented a low MIC<sub>50/90</sub> value (0.125/0.25  $\mu$ g/mL) with high susceptibility rate (80 %) contrasted to the ESBL strains which exhibited high MIC<sub>50/90</sub> value (0.25/0.5 $\mu$ g/mL) and low percentage of susceptibility (70%). The susceptibility of cefiderocol against ESBL versus non-ESBL isolates was the same (100%), with low MIC<sub>50/90</sub> value (0.38/0.5

$\mu$ g/mL) for non ESBL in comparison to the ESBL isolates which revealed high MIC<sub>50/90</sub> value (0.5/1.5 $\mu$ g/mL)

Concerning, *P. aeruginosa* strains, the observed effect of CFT on MDR compared to non-MDR, was a lower MIC<sub>50/90</sub> value (1/2  $\mu$ g/mL) and higher susceptibility (87%) for non -MDR than the MDR isolates which presented higher MIC<sub>50/90</sub> value (2/4 $\mu$ g/mL) and lower susceptibility rate (63%). The susceptibility of cefiderocol against MDR versus non-MDR isolates was the same (100%), with low MIC<sub>50/90</sub> value (0.25/0.5  $\mu$ g/mL) for non MDR contrasted to the MDR isolates which exhibited high MIC<sub>50/90</sub> value (0.75/2 $\mu$ g/mL).

The activity of CFT against MDR versus non-MDR *A. baumannii* isolates had shown a low MIC<sub>50/90</sub> value (2/4  $\mu$ g/mL) with higher susceptibility rate (72%) for non -MDR in comparison to the MDR isolates which presented high MIC<sub>50/90</sub> value (16/24 $\mu$ g/mL) and lower susceptibility (58%). The susceptibility of cefiderocol against MDR versus non-MDR isolates was the same (100%), with low MIC<sub>50/90</sub> value (0.19/0.5  $\mu$ g/mL) for non MDR contrasted to the MDR isolates which displayed high MIC<sub>50/90</sub> value (0.25/2 $\mu$ g/mL).

The non- ESBL *Enterobacter cloacae* isolates, revealed a lower MIC<sub>50/90</sub> value (1.5/8  $\mu$ g/mL) and higher susceptibility (88%) than ESBL strains which exhibited higher MIC<sub>50/90</sub> value (2/12 $\mu$ g/mL) and lower susceptibility (79%). The susceptibility of cefiderocol against ESBL versus non-ESBL isolates was the same (100%), with the same MIC<sub>50/90</sub> value (0.125/0.25  $\mu$ g/mL) for both.

*Proteus mirabilis* isolates were 7 (5 MDR & 2 non MDR), the activity of CFT against MDR compared to non-MDR revealed lower MIC<sub>50/90</sub> value (0.5/0.75 $\mu$ g/mL) and higher susceptibility (84%) for non -MDR than the MDR isolates which exhibited higher MIC<sub>50/90</sub> value (0.75/1.5 $\mu$ g/mL) and lower percentage of susceptibility (73%). The susceptibility of cefiderocol against MDR versus non-MDR isolates was the same (100%), with low MIC<sub>50/90</sub> value (0.125/--  $\mu$ g/mL) for non MDR contrasted to the MDR isolates which showed high MIC<sub>50/90</sub> value (0.38/1 $\mu$ g/mL).

For the *K. oxytoca* isolates, the activity of CFT against ESBL versus non-ESBL revealed a low MIC<sub>50/90</sub> value (0.25/0.38  $\mu$ g/mL) with superior susceptibility (90%) for non -MDR contrasted to the MDR strains which showed high MIC<sub>50/90</sub> value (---/0.75 $\mu$ g/mL) and low percentage of susceptibility (85%). The susceptibility of cefiderocol against MDR versus non-MDR isolates was the same (100%), with difficulty in detecting MIC<sub>50/90</sub> value because of small sample size.

**Table 2: MIC<sub>50</sub> & MIC<sub>90</sub> values distribution of Ceftolozane/ tazobactam (CFT) & Cefiderocol tested against gram-negative isolates**

Bacterial type (No. tested)	CFT MICs(µg/mL)			Cefiderocol MICs (µg/mL)		
	Range	MIC 50	MIC 90	Range	MIC 50	MIC 90
<b><i>E. coli</i></b>						
ESBL (n = 21)	0.064 -1	0.19	0.25	0.19-3	0.5	1.5
NON ESBL (n = 7)	0.046- 0.5	0.046	0.19	0.125-0.75	0.38	0.5
All (n = 28)	0.046 -1	0.125	0.25	0.19-3	0.5	1
<b><i>K. pneumoniae</i></b>						
ESBL(n = 39)	0.049-1.5	0.25	0.5	0.19-3	0.5	1
NON ESBL (n = 10)	0.049-0.38	0.125	0.25	0.19-.075	0.38	0.5
All(n = 49)	0.049-1.5	0.19	0.5	0.19-4	0.5	1
<b><i>P. aeruginosa</i></b>						
Non MDR (n = 2)	0.19-2	1	2	0.25-0.75	0.25	0.5
MDR (n = 31)	0.19-32	2	4	0.38-3	0.75	2
All (n = 33)	0.19-2.5	0.5	1.5	0.25-3	0.5	2
<b><i>Acinetobacter baumannii</i></b>						
Non MDR (n = 2)	0.5-12	2	4	0.19-0.5	0.19	0.5
MDR (n = 22)	1.5-24	16	24	0.38-8	0.25	2
All (n = 24)	0.5-24	12	24	0.19-8	0.25	1
<b><i>Enterobacter cloacae</i></b>						
Non ESBL (n = 8)	0.38-8	1.5	8	0.046-0.38	0.125	0.25
ESBL (n = 4)	1-12	2	12	0.125-1	0.125	0.25
All (n = 12)	0.38-12	2	8	0.064-1	0.125	0.38
<b><i>Proteus mirabilis</i></b>						
Non MDR (n = 2)	0.25- 0.75	0.5	0.75	0.125-0.25	0.125	-----
MDR (n = 5)	0.25-2	0.75	1.5	0.94-1.5	0.38	1
All (n = 7)	0.25-2	0.5	1.5	0.49-1.5	0.25	0.38
<b><i>K. oxytoca</i></b>						
Non ESBL (n = 3)	0.19-0.5	0.25	0.38	0.046-0.125	0.094	-----
ESBL (n = 1)	0.25-0.75	-----	0.75	0.25	-----	-----
All (n = 4)	0.19-0.75	0.25	0.38	0.046-0.25	0.049	0.125

## DISCUSSION

Treatment of nosocomial infections has become more challenging as a result of the evolving and widespread dissemination of MDR Gram-negative pathogens. Novel therapeutic agents are urgently required due to the current therapeutic choices are extremely limited.<sup>18</sup> Therefore, our main objective is to evaluate the in vitro antibacterial activity of Cefiderocol and Ceftolozane-Tazobactam against ESBL coliform and MDR *A. baumannii* and *P. aeruginosa*.

In our study, we found relatively high levels of non-susceptibility to CFT in a clinical collection of ESBL / MDR Gram Negative isolates in comparison with Non ESBL / MDR isolates.

Concerning the ESBL-*E. coli* and ESBL- *K. pneumoniae*, susceptibility rates for both pathogens to

CFT was 77% and 70%, respectively, which were mostly lower than those informed by Amer et al.,<sup>19</sup> who identified high susceptibility rates (100%) among their isolates in both species. also, Araj et al.,<sup>20</sup> reported (100%,96%) susceptibility rates for both pathogens respectively.

Remarkably, the CFT susceptibility rates for *K. pneumoniae* and *E. coli* in the current study were very similar to those published from various nations around the world. Karlowsky et al.,<sup>21</sup> conveyed a susceptibility of 89.7% of Enterobacterales, Kuo et al.,<sup>22</sup> found 81.9% of *K. pneumoniae* and 91.9% of *E. coli* were susceptible, Sader et al.,<sup>23</sup> reported 98.5 % of *E. coli* and 89.6 of *K. pneumoniae*. This difference may be explained by a possibility that ESBL isolates from various countries contain different enzymes.

In the current research, ceftolozane/tazobactam susceptibility was 63% against MDR *P. aeruginosa*, which was low in comparison with result published by Garcia-Fernandez et al.,<sup>24</sup> who reported higher sensitivity rate of 91.3%. also, Karlowsky et al.,<sup>25</sup> found that 96.0% *P. aeruginosa* strains were sensitive to ceftolozane/tazobactam.

As reported by Cabot et al.,<sup>26</sup> the resistance to CFT seems to be high in *P. aeruginosa* mutator family, a possible explanation for this might be due to the presence of several mutations leading to overexpression and structural alterations of AmpC.

Moreover, Farrell et al.,<sup>27</sup> found that CFT had limited activity against *Acinetobacter* spp. with susceptibility rate 34.7% which was near to our result where we reported low percentage of susceptibility (58%).

Interestingly, In the present study, cefiderocol demonstrated strong in vitro antibacterial effect (100%) on most of *Enterobacterales*, *P. aeruginosa* & *A. baumannii* isolates with varying MIC<sub>50/90</sub> values. This may be explained by the catechol group of cefiderocol which permits free iron chelation, allowing its entrance into bacteria over the bacterial iron transport structure. Therefore, cefiderocol may circumvent bacteria's porin-dependent mechanisms of antibiotic resistance.<sup>28</sup>

Concerning the ESBL-*E. coli* and ESBL-*K. pneumoniae* in our research, the MIC<sub>50/90</sub> value was (0.5/1.5µg/mL), Consistent with these reports, Alejandro et al.,<sup>18</sup> who found that among the ceftazidime-resistant *E. coli* & *K. pneumoniae* (n = 141), the MIC<sub>50/90</sub> values were 0.5/2mg/L. similarly Rolston et al.,<sup>29</sup> found that MIC<sub>90</sub> was 2mg/L with susceptibility rates for both pathogens respectively (100,97%). Also, Falagas et al.,<sup>30</sup> published that MIC<sub>50/90</sub> value was (0.5/0.1µg/mL) for ESBL-*K. pneumoniae*

In current study, MDR *Pseudomonas* isolates showed MIC<sub>50/90</sub> value (0.75/2µg/mL), Similarly, Alejandro et al.,<sup>18</sup> notified that MIC<sub>50/90</sub> values of *P. aeruginosa*, involving carbapenem-resistant strains was 0.5–1mg/L. consistent with these findings Jacobs et al.,<sup>31</sup> and Araj et al.,<sup>20</sup> reported MIC<sub>90</sub> values of 0.5–1mg/L. Additionally, Rolston et al.,<sup>29</sup> reported MIC<sub>90</sub> value was (1µg/mL) with 97% susceptibility. In contrast, Falagas et al.,<sup>30</sup> reported lower MIC<sub>50/90</sub> value which was (0.12/0.5µg/mL).

Similarly, for MDR *A. baumannii*, overall, MIC<sub>50/90</sub> value was (0.25/2µg/mL), Araj et al.,<sup>20</sup> reported MIC<sub>50/90</sub> value was (0.12/4µg/mL). Rolston et al.,<sup>29</sup> reported MIC<sub>90</sub> value was (4µg/mL) with 90% susceptibility. Falagas et al.<sup>30</sup> MIC<sub>50/90</sub> value was (0.06/0.5µg/mL)

As reported in previous studies, higher MIC values have been found for isolates of *A. baumannii* (32 mg/L), *P. aeruginosa* (8 mg/L), and *Enterobacteriaceae* (64 mg/L).<sup>28,32</sup>

## CONCLUSION

Cefiderocol has demonstrated superior activity against *Enterobacterales*, *P. aeruginosa*, *A. baumannii* isolates. It is recommended that cefiderocol be considered as an alternative treatment for MDR Gram-negative infections until additional research has been conducted for other MDR Gram-negative infections, especially if there are no other therapeutic choices available.

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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