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ORIGINAL ARTICLE

# Activity of cefiderocol on extensively drug-resistant *Pseudomonas aeruginosa* from burn wound infections in Mansoura, Egypt

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## ABSTRACT

**Background and Objectives:** Increased *Pseudomonas aeruginosa* antibiotic resistance limits treatment options and is associated with a higher level of mortality and mordacity. The purpose of this research was to identify class 1 and 2 integrons, carbapenemase, *SHV*, and *TEM* genes in extensively drug-resistant (XDR) *P. aeruginosa* isolated from infected burns and evaluate their in vitro cefiderocol activity.

**Materials and Methods:** By using the disc diffusion method, the antimicrobial susceptibility of 110 *P. aeruginosa* isolates collected from infected burns were evaluated. XDR *P. aeruginosa* were screened phenotypically for carbapenemase and extended spectrum β-lactamases (ESBLs) production. Both MIC Test Strip and disc diffusion were employed to test the cefiderocol susceptibility. PCR was used to assess carbapenemase, *SHV* and *TEM* genes and integrons class 1 and 2.

**Results:** From the 110 *P. aeruginosa*, 54 isolates (49%) were XDR. TEM gene was detected in 35 isolates. Among XDR isolates, carbapenemase genes were detected in 31.5%, with *NDM* being predominant Thirty XDR isolates had class1 integrons. All isolates were sensitive to cefiderocol and its $MIC_{50}$/$MIC_{90}$ was 0.5/1.5mg/L (range 0.064-1.5mg/L).

**Conclusion:** Nearly half the *P. aeruginosa* isolates from burn infections were extensively drug-resistant. Cefiderocol's in vitro activity demonstrated that it is a promising therapy alternative for treating extensively drug-resistant *P. aeruginosa* in burn patients.

**Keywords:** *Pseudomonas aeruginosa*; Extended detection and response; NDM; Carbapenemase; Burn

## INTRODUCTION

*Pseudomonas aeruginosa* is an ubiquitous opportunistic bacteria causing many infections with high rates of mortality and morbidity both globally and in patients suffering from burns due to its high capacity to acquire antimicrobial resistance causing over 300,000 annual deaths (1, 2).

Burn disturbs the skin natural innate immunity and burn patients are more vulnerable to nosocomial infections by opportunistic pathogens such as *P. aeruginosa*. *P. aeruginosa* possesses several virulence factors in addition to its high antibiotics resistance resulting in difficult burn healing and bad

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prognosis (1, 3).

*P. aeruginosa* has several antibiotic resistance mechanisms such as β-lactamases production, extended spectrum β-lactamases (ESBLs) and metallo-β-Lactamases (MBLs) causing resistance to β-lactams, efflux pumps and mutations and each isolate may have several resistance strategies (3-5).

Multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug-resistant (PDR) *P. aeruginosa* are the most common bacteria responsible for burn infections (1). The genes that encode class B carbapenemases (MBLs),Verona integron-encoded β-lactamase (VIM) and imipenemase (IMP) and extended-spectrum lactamases (ESBLs) like *SHV, TEM* and *CTX-M,* which hydrolyze broad-spectrum β-lactams like cephalosporins, meropenem, monobactams, and imipenem are frequently linked to antibiotic resistance in *Pseudomonas aeruginosa* (6).

Given the growing antibiotic resistance and lack of alternatives to therapy, especially for patients with impaired immune systems, the growing incidence of high-risk MDR and XDR *P. aeruginosa* clones is evolving as a concern of public health. WHO (2017) states that carbapenem resistant *P. aeruginosa* has been classified in the "critical" category, requiring immediate use of innovative therapeutic modalities (4).

Polymyxins like polymyxin B and colistin are alternative options to manage infections with MDR/XDR *P. aeruginosa* despite their limited therapeutic potential, there is increasing incidence of colistin resistance (4, 6).

Cefiderocol looks promising to manage carbapenem resistant infections with XDR and MDR *P. aeruginosa*. It is a siderophore cephalosporin binds ferric iron to penetrate the bacterial membrane inhibiting cell wall synthesis and is highly stable to serine-dependent β-lactamases and MBLs (7-10).

The goal of this study was to detect class one and two integrons, carbapenemase, *SHV* and *TEM* resistance genes among XDR *P. aeruginosa* isolated from infected burn from Burn and Plastic Centre, Mansoura University, Egypt investigating cefiderocol in vitro activity against these isolates.

## MATERIALS AND METHODS

**Bacterial strains.** This study included 110 *P. aeruginosa* non-duplicate isolates previously isolated from burn biopsies received from Burn and Plastic Centre, Mansoura University at Microbiology Diagnostic and Infection Control Unit, Medical Microbiology and Immunology Department, Mansoura University, Egypt between September 2021 to December 2023.

This study accords to Helsinki Declaration and the ethical approval was gained from the Institutional review board of the Mansoura Faculty of Medicine (R24.09.2771).

*P. aeruginosa* isolates were identified by colony morphology, growth on cetrimide agar plates, Gram staining, the growth at 42°C, oxidase test, triple sugar iron (TSI) test, and other laboratory biochemical standards (11).

**Testing for antimicrobial susceptibility.** Antimicrobial susceptibility of *P. aeruginosa* isolates was evaluated utilizing disc diffusion method in compliance with the Clinical Laboratory Standard Institute guidelines (3). These antibiotics were tested: piperacillin (100 µg), aztreonam (30 µg), ceftazidime-avibactam (30/20 µg), ceftazidime (30 µg), cefepime (30 µg), ceftolozane-tazobactam (30/10 µg), imipenem (10 µg), meropenem (10 µg), amikacin (30 µg), tobramycin (10 µg), gentamicin (10 µg), levofloxacin (10 µg), piperacillin/tazobactam (100/10 µg) and ciprofloxacin (5 µg) (Liofilchem, Roseto Degli Abruzzi, Italy) (3). Colistin broth dilution was used to test colistin susceptibility (12).

Classification of *P. aeruginosa* phenotypes as MDR, XDR and PDR were performed as described previously (13). Cefiderocol disc (30 µg) (Liofilchem) via the disc diffusion method and the MIC Test Strip (MTS™ Cefiderocol, Liofilchem) were used to test the cefiderocol susceptibility. The EUCAST guidelines were used to interpret the susceptibility for *P. aeruginosa*. Using the disc diffusion method, ≥ 22 mm is considered as susceptible and <22 mm is resistant and by the MIC Test Strip method, susceptibility is considered as ≤ 2 mg/L while resistant is >2 mg/L (14).

**Phenotypic detection of carbapenemase production.** CARBA PAcE (Mast Diagnostics, company) was used for Rapid Identification of Carbapenemase Producing *P. aeruginosa*. As instructed by the manufacturer, 1-5 µl loopful from *P. aeruginosa* pure fresh culture were added to the tube containing test solution then the tube was mixed well by vortexing for 20 seconds and incubated at 35 ± 1°C for 10 minutes. If the organism's color changed from yellow to orange/

red immediately or within 20 minutes, it was considered as carbapenemase positive.

**Detection of ESBLs by combination disc test (CDT).** The *P. aeruginosa* isolate after overnight culture was tested on a Muller-Hinton agar plate. Discs that entail ceftazidime (30 µg) alone or combined with (10 µg) of clavulanic acid (Liofilchem) were then put 30 mm from one another (center to center). The plate underwent incubation for twenty-four hours at 37°C. When compared to the ceftazidime disc alone, an increase of at least 5 mm in the diameter of the inhibition zone surrounding the ceftazidime-clavulanate disc indicated ESBLs production (15).

**Molecular analysis of XDR *P. aeruginosa* resistance.** By a boiling method, XDR *P. aeruginosa* isolates' DNA were extracted by employing two colonies of the overnight bacterial growth. In a test tube, the colonies were mixed with one milliliter of distilled water, put into a water bath to boil for ten minutes, and then centrifuged at 1000 rpm for five minutes (16).

All carbapenemase *P. aeruginosa* phenotypically positive isolates were investigated for carbapenemase genes; $bla_{IMP}$, $bla_{OXA-48}$, $bla_{NDM}$, $bla_{VIM}$, and $bla_{KPC}$ using multiplex PCR employing previously described primers as shown in Table 1 (17). PCR for ESBLs genes; *SHV* and *TEM* were screened among CDT positive isolates (18). Duplex PCR was used to screen Class 1 and 2 integrons in all isolate of XDR *P. aeruginosa* (19).

## RESULTS

This study included 110 *P. aeruginosa* isolates from patients having clinical signs of burn infections attending Burn and Plastic Centre and laboratory diagnosed at MDICU, Mansoura University, Egypt over 28 months. Female comprised the majority of cases; 68 (62%). The patients' age ranged from 15-62 years.

The antimicrobial susceptibility testing of the 110 *P. aeruginosa* isolates revealed that 49% (54/110) of the tested isolates were XDR, none of the tested isolates were PDR, while 39% (43/110) were MDR.

**XDR *P. aeruginosa* antimicrobial susceptibility testing.** *P. aeruginosa* isolates displayed a high susceptibility to colistin (66.7%). About half of the *P. aeruginosa* tested isolates were susceptible to ceftolozane-tazobactam, imipenem, ceftazidime/avibactam and meropenem. Resistance to gentamicin, amikacin, tobramycin, and aztreonam was shown to

**Table 1.** Genes, primers and products size of multiplex PCR employed to detect carbapenemase, ESBLs and Class 1 and 2 integrons

| Gene | Sequence (5′–3′) | Product Size (bp) | Reference |
|---|---|---|---|
| $bla_{IMP}$ | GGAATAGAGTGGCTTAAYTCTC | 232 | 17 |
| | GGTTTAAYAAAACAACCACC | | |
| $bla_{VIM}$ | GATGGTGTTTGGTCGCATA | 390 | 17 |
| | CGAATGCGCAGCACCAG | | |
| $bla_{OXA-48}$ | GCGTGGTTAAGGATGAACAC | 438 | 17 |
| | CATCAAGTTCAACCCAACCG | | |
| $bla_{NDM}$ | GGTTTGGCGATCTGGTTTTC | 621 | 17 |
| | CGGAATGGCTCATCACGATC | | |
| $bla_{KPC}$ | CGTCTAGTTCTGCTGTCTTG | 798 | 17 |
| | CTTGTCATCCTTGTTAGGCG | | |
| *SHV* | GAGTATTCAACATTTCCGTGTC | 471 | 18 |
| | TAATCAGTGAGGCACCTATCTC | | |
| *TEM* | TCAGCGAAAAACACCTTG | 861 | 18 |
| | CCCGCAGATAAATCACCA | | |
| Integron class 1 | CAGTGGACATAAGCCTGTTC | 160 | 19 |
| | CCCGAGGCATAGACTGTA | | |
| Integron class 2 | CACGGATATGCGACAAAAAGGT | 789 | 19 |
| | GTAGCAAACGAGTGACGAAATG | | |

be high. The isolates showed no sensitivity to ceftazidime or cefepime (Table 2).

Overall, 41/54 (76%) were positive CDT for ESBLs production. Seventeen out of 26 carbapenems resistant *P. aeruginosa* (65%) were positive by CARBA PAcE test. All isolates were sensitive to cefiderocol. Cefiderocol $MIC_{50}$/$MIC_{90}$ values for XDR *P. aeruginosa* isolates were 0.5/1.5mg/L (range 0.064-1.5mg/L) (Fig. 1).

**Prevalence of β-Lactamase genes and Class1 and 2 integrons.** PCR results revealed that two isolates of *P. aeruginosa* (3.7%) carried *TEM* and *SHV* genes.

**Table 2.** XDR *Pseudomonas aeruginosa* (54) isolates antimicrobial susceptibility testing

| Antibiotics | Sensitive No (%) | Resistant No (%) |
|---|---|---|
| Aztreonam | 7 (13) | 47 (87) |
| Piperacillin | 9 (16.7) | 45 (83.3) |
| Gentamicin | 6 (11.1) | 48 (88.9) |
| Amikacin | 5 (9.3) | 49 (90.7) |
| Tobramycin | 1 (2) | 53 (98) |
| Ceftazidime | 0 (0) | 54 (100) |
| Cefepime | 0 (0) | 54 (100) |
| Imipenem | 28 (52) | 26 (48) |
| Meropenem | 28 (52) | 26 (48) |
| Piperacillin/tazobactam | 8 (14.8) | 46 (85.2) |
| Ceftolozane/tazobactam | 29 (53.7) | 25 (46.3) |
| Ceftazidime/avibactam | 28 (52) | 26 (48) |
| Ciprofloxacin | 8 (14.8) | 46 (85.2) |
| Levofloxacin | 8 (14.8) | 46 (85.2) |
| Colistin | 36 (66.7) | 18 (33.3) |
| Cefiderocol | 54 (100) | 0 (0) |

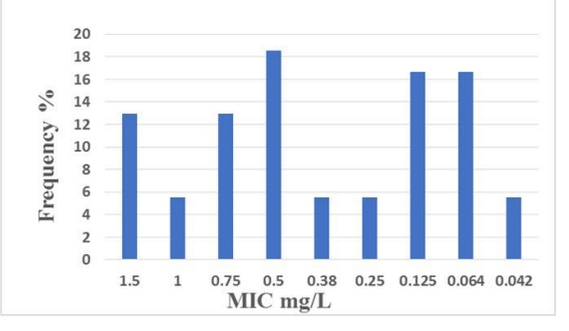


**Fig. 1.** Distribution of cefiderocol MICs for XDR *Pseudomonas aeruginosa* (54) isolates using the MIC Test Strip according to EUCAST breakpoints (14).

*TEM* gene was found in 35 isolates (65%) and *SHV* gene in one isolate (2%).

Carbapenemase genes were found in 17 XDR isolates (31.5%). *NDM* gene was the commonest carbapenemase gene identified among 7 isolates of *P. aeruginosa*. Five isolates carried *VIM* gene, 2 isolates carried *OXA-48* gene and 3 isolates carried mixed genes *NDM* and *OXA-48* genes. Class1 integrons was detected in 55.6% (30/54) of XDR isolates using duplex PCR, while one isolate carried both class I and II integrons.

## DISCUSSION

*P. aeruginosa* is a significant health issue owing to its intrinsic antibiotic resistance and outstanding capacity to acquire resistance (20). XDR *P. aeruginosa* have a limited therapeutic.

This research investigated *P. aeruginosa* strains that were isolated from the infected burn wounds where XDR and MDR *P. aeruginosa* accounted for 49% and 39%, respectively and no PDR isolate was recovered according to previously proposed definitions (13). Given that XDR isolates are a subset of MDR isolates, 88% might be reported as the frequency of MDR (22).

Similarly, in Cairo, XDR *P. aeruginosa* represented 47% of *P. aeruginosa* isolates diagnosed at microbiology laboratory over 5 months (23), while, in Tehran, MDR isolates represented 33% of the isolates obtained from three hospitals' laboratories (24).

XDR and MDR *P. aeruginosa* isolates from female Iranian burn patients accounted for 40% and 50%, of the cases respectively (25).

Prevalence of XDR *P. aeruginosa* varies among different countries. Low prevalence was reported in some countries; 2.8% (1), 15.53% (25), 3.7% (21) and high prevalence (75%) was reported in Iran from burn patients (22).

Our findings demonstrated that XDR *P. aeruginosa* was highly susceptible to colistin (66.7%) and completely resistant to cefepime and ceftazidime, while about 50% of the isolates were susceptible to ceftazidime/avibactam, imipenem, ceftolozane-tazobactam, and meropenem. The high sensitivity of XDR *P. aeruginosa* to colistin (21, 22, 24, 25), high resistance to carbapenems (21, 22, 24, 25) and the modest activity of β-lactams/β-lactamases inhibitors were reported in the literature previously (21, 23, 25).

Difference in the resistance patterns might be due

to several factors such as the geographical variation of the predominant resistance mechanism (21), different testing methods, demographic data and clinical conditions and improper use of broad-spectrum antibiotics leading to genetic alteration and affecting resistance mechanisms and expression levels. Additionally, the infected populations may have genetic heterogeneity resulting in differences in resistance patterns (26-28).

The present work showed that 48% of XDR *P. aeruginosa* isolates were resistant to carbapenems mainly because of production of carbapenemase genes (65%) mostly *NDM* (41%) followed by *VIM* (29%) which explains the high resistance to ceftazidime-avibactam (29). Similarly, carbapenems high resistance has been reported which might be due to the over usage of carbapenems for management of resistant *P. aeruginosa*, the hygiene measures and long hospital stays for patients with resistant infections. About 80% of carbapenems resistance among XDR isolates was due to carbapenemase genes mainly *NDM* (56%) followed by *OXA-48* (25%) genes (23, 25).

Carbapenems resistance among *P. aeruginosa* is associated with treatment failure and poor outcome. Several carbapenems resistance mechanisms are involved in addition to carbapenemase genes which their prevalence varied by the geographic region (30). The Middle East is considered as a secondary reservoir for *NDM* carbapenemase because of the flow of people from Asian nations (31).

It has been reported that *P. aeruginosa* is the commonest ESBLs-producing bacteria (36%). For this study, ESBLs were observed in 70% of XDR *P. aeruginosa* isolates mainly *TEM* in agreement with the studies of Ghasemian et al. (3) and Rahimi et al. (6) as *TEM* was the common detected gene.

Colistin is an alternative option for managing *P. aeruginosa* antibiotic resistant, yet it is less safe and efficient than β-lactam/β-lactamase inhibitors which are associated with a better prognosis (21). The resistance to colistin among XDR *P. aeruginosa* is increasing worldwide (31) and new antibiotics are considered the last option for the management of antibiotic resistant *P. aeruginosa*.

In our study, cefiderocol was very effective against all XDR isolates with MIC 0.5/1.5mg/L. Similarly, cefiderocol has an excellent potency for treatment of carbapenems resistant *P. aeruginosa* in comparison to β-lactam–β-lactamase inhibitors (12, 32). The most efficient β-lactam medication for resistant *P. aeruginosa* is cefiderocol (97%) compared to ceftolozane-tazobactam (46.6%) and ceftazidime-avibactam (48.4%) and has a favorable clinical outcome (33) and it looks promising against MBLs as no other β-lactams with activity against them (9).

Integrons are DNA elements which enable the bacteria to modulate the antibiotic resistance and are responsible for spread of the resistance especially class1 integron which is widely distributed among MDR bacteria including *P. aeruginosa* (19). In the present study, class1 integrons was detected in 55.6% of XDR isolates in agreement with another study where only class 1 integron was detected among resistant *P. aeruginosa* (19).

The substantial XDR *P. aeruginosa* prevalence in the present study is an alarming issue as it is associated with therapeutic limitation and bad clinical outcomes, yet cefiderocol seems a new promising option to treat infections caused by these resistant isolates. More large-scale studies are mandatory for characterization of these resistant isolates. It is recommended to pay more attention and implement effective controls against these isolates.

## CONCLUSION

The XDR and MDR *P. aeruginosa* prevalence were 49% and 39%, respectively. All XDR *P. aeruginosa* isolates were totally sensitive to cefiderocol and 2/3 of the isolates were susceptible to colistin. Carbapenemase genes were detected in 31.5% of XDR isolates mainly *NDM*. Class1 integrons was detected in 55.6% of XDR isolates.

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