

Review

Pseudomonas aeruginosa Resistance – A Challenge in the Treatment of Healthcare-Associated Infections

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Abstract

Infections caused by *Pseudomonas aeruginosa* pose a significant threat to human health and are the main contributors to mortality in the United States, Japan, and Europe. These pathogens are the leading causes of nosocomial infections, particularly in immunosuppressed patients. *P. aeruginosa* develops resistance to a wide range of antibiotics through various mechanisms, including efflux pumps, chromosomal mutations, and the production of beta-lactamases. The high heterogeneity among different strains and the ability to code for a diverse range of proteins make *P. aeruginosa* exceptionally difficult to treat. These characteristics complicate the development of effective therapeutic agents. New therapies are being explored to combat resistance, including antibiotic combinations and bacteriophages, which show promising results. Despite advances in research, infections caused by *P. aeruginosa* remain a significant social and health problem, requiring urgent measures to effectively manage antibiotic resistance effectively.

Keywords: *Pseudomonas aeruginosa*, antibiotic resistance, hospital-acquired infections (HAI), novel approaches, ceftolozane-tazobactam, ceftazidime-avibactam, phage therapy

Резюме

Инфекциите, причинени от *Pseudomonas aeruginosa*, представляват сериозна заплаха за здравето на хората и са основни фактори за смъртност в САЩ, Япония и Европа. Тези патогени са основни причинители на нозокомиални инфекции, особено при имунокомпрометирани пациенти. *P. aeruginosa* развива резистентност към множество антибиотици чрез различни механизми, включително ефлуксни помпи, хромозомни мутации и производството на бета-лактамази. Наличието на висока хетерогенност сред различните щамове и способността на генома да кодира разнообразие от протеини правят *P. aeruginosa* изключително труден за лечение. Тези особености усложняват разработването на ефективни терапевтични агенти. За борба с резистентността се изследват нови терапии, включително антибиотични комбинации и бактериофаги, които показват обещаващи резултати. Въпреки напредъка в изследванията, инфекциите, причинени от *P. aeruginosa*, остават значителен здравословен и социален проблем, изискващ спешни мерки за ефективно управление на антибиотичната резистентност.

Introduction

According to the WHO, antimicrobial resistance is one of the top ten global health threats, with projections of up to 10 million deaths by 2050. It requires coordinated actions and research to uncover resistance mechanisms and support health programs based on the principles of “One Health.” Alongside understanding resistance mechanisms and searching for new antimicrobial agents, antimicrobial stewardship (AMS) is another crucial direction

in the fight against superbugs. Implementing AMS in the hospital sector improves clinical outcomes, reduces antimicrobial use without increasing mortality or infection-related readmissions, enhances the number of cured patients, and limits the occurrence of surgical infections.

P. aeruginosa is a Gram-negative bacterium belonging to the family *Pseudomonadaceae*. The genome of *P. aeruginosa* (5.5–7 Mbp) is more sig-

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nificant compared to other sequenced bacteria such as *B. subtilis* (4.2 Mbp), *E. coli* (4.6 Mbp) (Pang *et al.*, 2019), and *M. tuberculosis* (4.4 Mbp), and encodes a large number of regulatory enzymes involved in metabolism, transport, and efflux of organic compounds. The increased coding capacity of the *P. aeruginosa* genome enables significant metabolic flexibility, high adaptability, and resilience to environmental changes (Klockgether *et al.*, 2011; Stover *et al.*, 2000), including during antibiotic treatment courses.

P. aeruginosa is an opportunistic bacterium associated mainly with hospital-acquired infections (HAIs), especially in intensive care units (ICUs). These infections can lead to ventilator-associated pneumonia (VAP), bloodstream infection (BSI), catheter-associated urinary tract infection (cUTI), and surgical infection (Baudet *et al.*, 2024). This pathogen rarely affects healthy individuals but causes high morbidity and mortality in immunosuppressed patients (Sadikot *et al.*, 2005). *P. aeruginosa* is part of the group of “ESKAPE” pathogens, which are the most common causes of life-threatening healthcare-associated infections due to their ability to evade the effects of numerous antibiotics and their multidrug resistance profile.

Mechanisms of resistance in *P. aeruginosa*

P. aeruginosa is intrinsically resistant to many antimicrobial agents, which can be mediated by restricted uptake of antimicrobials through the outer membrane (reduction in permeability due to porin channel mutations), efflux pumps that expel antibiotics from bacterial cells, and/or by the action of drug-degrading enzymes (carbapenemases) (Pesingi *et al.*, 2019). The main resistance mechanisms observed in *P. aeruginosa* can be categorized into three types:

- Intrinsic resistance is characterized by low permeability of the outer membrane, expression of multidrug efflux pumps, and the synthesis of enzymes that inactivate antibiotics. Intrinsic resistance is a type of resistance that organisms possess naturally, without prior exposure to specific antimicrobial agents. It is an innate characteristic of the species and results from genetic and physiological factors. The efflux pumps MexAB-OprM and MexXY-OprM are well-recognized in *P. aeruginosa*. The MexAB-OprM system is responsible for resistance to macrolides, lincomycin, quinolones, chloramphenicol, β -lactams, and tetracyclines (Pesingi *et al.*, 2019).
- Acquired resistance is achieved through hor-

izontal transfer of resistance genes or mutational changes (Breidenstein *et al.*, 2011). Bacteria can acquire antibiotic resistance through mutational changes or the acquisition of resistance genes through horizontal gene transfer (Munita and Arias, 2016). Acquired drug resistance can be attained by mutations in chromosomal genes that encode regulatory proteins. In addition to the high intrinsic resistance in *P. aeruginosa*, acquired resistance significantly contributes to developing multidrug-resistant strains (Henrichfreise *et al.*, 2007).

- Adaptive resistance enables bacteria to withstand antibiotic exposure by temporarily altering gene and protein expression in response to environmental changes. This form of resistance is reversible when the environmental stimulus is removed (Sandoval-Motta and Aldana, 2016). In *P. aeruginosa*, biofilm formation and the development of persister cells are well-studied adaptive resistance strategies that contribute to chronic infections. (Taylor *et al.*, 2014).

In hospitals, *P. aeruginosa* can be found in various sources such as respiratory therapy devices, antiseptics, soaps, sinks, mops, medications, as well as physiotherapy and hydrotherapy pools (Lister *et al.*, 2009). A study published in 2021 shows that *P. aeruginosa* is responsible for 7.1%–7.3% of all healthcare-associated infections. The most common manifestations of this pathogen are associated with the development of surgical wound infections, urinary tract infections, blood infections, bacteremia, and pneumonia. *P. aeruginosa* is the most frequently encountered Gram-negative pathogen in hospital-acquired pneumonia. *P. aeruginosa* accounts for 10%–20% of the isolated microorganisms in cases of ventilator-associated pneumonia (VAP), ranking second after *Staphylococcus aureus*. Mortality from VAP caused by *P. aeruginosa* ranges between 32%–42.8% (Reynolds and Kollef, 2021).

In 2024, a report from the European Centre for Disease Prevention and Control (ECDC) was published, stating that in 2020, 12.7% of patients hospitalized in intensive care units (ICUs) for more than two days developed at least one ICU-acquired healthcare-associated infection (HAI) under surveillance (pneumonia, bloodstream infection, or urinary tract infection). The report indicates that with stays in the ICU longer than two days, 8% of patients develop pneumonia, with 71% of pneumonia cases associated with intubation. In these cases,

the most frequently isolated pathogen is *P. aeruginosa*, with 25.8% of the isolates exhibiting resistance to carbapenems (European Centre for Disease Prevention and Control. Healthcare-associated infections acquired in intensive care units. In: ECDC. Annual Epidemiological Report for 2020. Stockholm: ECDC; 2024, 2024).

Figure 1 presents data from the Annual Epidemiological Report for 2023 (European Centre for Disease Prevention and Control. Antimicrobial resistance in the EU/EEA (EARS-Net) - Annual Epidemiological Report 2022. Stockholm: ECDC; 2023., 2023), covering a six-year period (2018–2023). The provided information includes the countries for which data is available in ECDC. Significant differences are observed in the prevalence of isolated *P. aeruginosa* strains in intensive care units (ICUs) in European countries. Among the countries with the highest percentages of isolated *P. aeruginosa* strains are Bulgaria, Romania, and Hungary.

In 2018, Bulgaria reported 36%, with this percentage increasing to 54% in 2023, indicating a significant upward trend. Similarly, Romania started at 40% in 2018, and peaked at (56%) in 2023. Hungary also showed substantial growth, rising from 40% in 2018 to 57% in 2021, before slightly decreasing to 37% in 2023.

On the other hand, countries such as Germany and France maintained relatively stable percentages in the range of 25–30%. Germany recorded its highest percentage in 2021 (29%), while France maintained values around 20–26% throughout the period. Countries like Denmark and Norway stood out with some of the lowest percentages of

P. aeruginosa isolates in ICUs. Denmark showed values between 4% and 9% throughout the analyzed period, while Norway reported values between 3% and 6%. Other countries with low percentages included Portugal and Iceland, where values remained below 15%.

Some countries exhibited fluctuating percentages of isolates over the years. For example, Latvia showed significant variation, increasing from 31% in 2018 to 51% in 2021, followed by a drastic decrease to 12% in 2023. Similarly, Lithuania showed variability, with values ranging from 26% to 35% during the analyzed period.

P. aeruginosa is one of the most antibiotic-resistant pathogens, making it a significant challenge in the treatment of hospital-acquired infections. This microorganism demonstrates the ability to develop resistance to multiple classes of antibiotics, including beta-lactams, carbapenems, and fluoroquinolones, through key chromosomally encoded resistance mechanisms such as membrane porins (OprD), enzymes, and the expression of multidrug efflux pumps.

Beta-lactam antibiotics, fluoroquinolones, and aminoglycosides are the most commonly used antibiotics for treating infections caused by *P. aeruginosa*. Table 1 presents data on the antibiotic resistance of *P. aeruginosa* in Bulgaria and the EU/EEA countries for the period 2018–2023. For all antibiotic groups analyzed, a clear disparity is observed between the values in Bulgaria and those in the EU/EEA, with Bulgarian values significantly exceeding those in other countries.

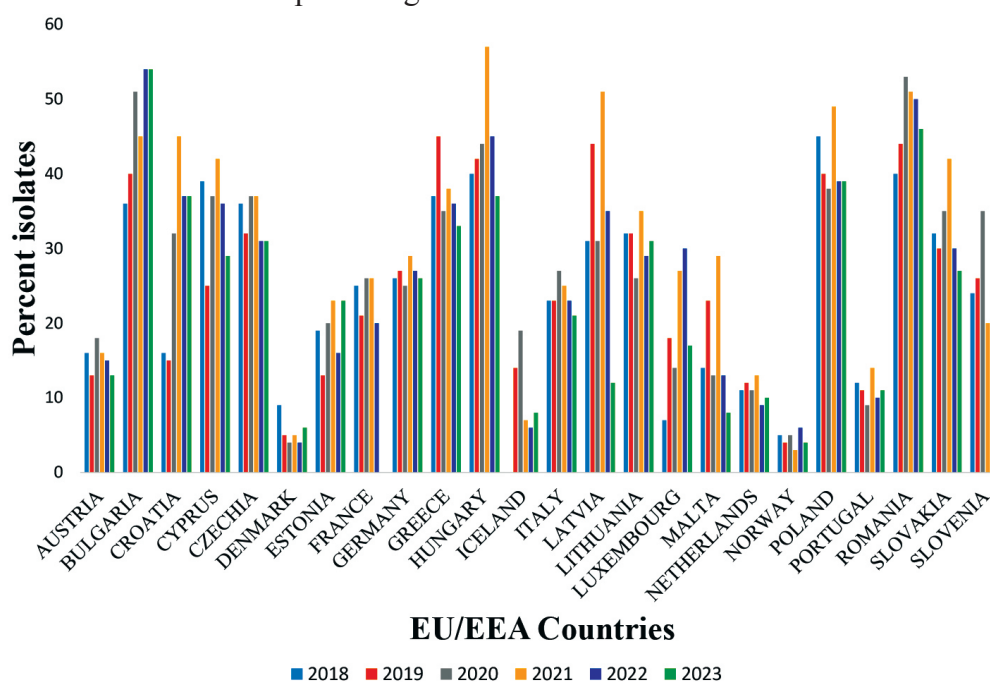


Fig. 1. Annual percentage of *P. aeruginosa* isolates reported from patients in ICUs 2018-2023

Table 1. Percentage of isolates with resistance phenotype (%) by *P. aeruginosa* and antimicrobial group/agent, 2023 EU/EEA range, Bulgaria, 2018–2023

Antimicrobial group/agent	2018		2019		2020		2021		2022		2023		Average	
	BG	EU/EEA	BG	EU/EEA	BG	EU/EEA	BG	EU/EEA	BG	EU/EEA	BG	EU/EEA	BG	EU/EEA
Piperacillin-tazobactam resistance	32.6	18.5	31.8	19	64.3	19	43.4	19.1	48.7	19.8	38.1	18.5	43.15	18.98
Ceftazidime resistance	20	15.5	30.8	16.5	54.3	15.9	45.8	16.5	56.6	16.9	39.3	15.7	41.13	16.16
Carbapenem (imipenem/meropenem) resistance	25.6	18.8	25.2	19.1	42.9	18.8	32.5	19.2	40.8	20	33.3	18.6	33.38	19.08
Fluoroquinolone (ciprofloxacin/levofloxacin) resistance	30	21.2	29.9	21.6	52.9	20.4	31.3	19.6	39.5	19.4	31	17.9	35.76	20.02
Aminoglycoside (gentamicin/netilmicin/tobramycin) resistance	24.4	12.9	31.8	13.4	32	10.2	25.3	9.7	36.4	9.5	19	9.5	28.15	10.86
Combined resistance to ≥3 antimicrobial groups (among piperacillin-tazobactam, ceftazidime, carbapenems, fluorquinolones and aminoglycoside)	25.8	14.1	30.8	14.4	50	14.6	31.3	13.5	45.5	14.5	31	13.1	35.73	14.03

A. Mechanisms of resistance development to beta-lactam antibiotics

The resistance of *P. aeruginosa* to beta-lactam antibiotics is due to a combination of several key mechanisms that significantly reduce their effectiveness. These mechanisms include the active efflux of antibiotics from the cell via efflux pumps, the enzymatic destruction of beta-lactams by beta-lactamases, and alterations in the cell membrane that limit antibiotic penetration into the intracellular space.

- Efflux pumps: The MexAB-OprM and MexCD-OprJ systems play a role in the extrusion of beta-lactams from the cell, thereby reducing their concentration and effectiveness (Okamoto, 2002).
- Beta-lactamases: *P. aeruginosa* synthesizes beta-lactamases that break down the beta-lactam ring in the antibiotic structure, thereby inactivating it. Examples include AmpC and ESBLs (extended-spectrum beta-lactamases), which degrade penicillins, cephalosporins, and other beta-lactams (Rawat and Nair, 2010).
- Reduced permeability: The absence of OprD

porin reduces carbapenem penetration, leading to resistance to this subclass of beta-lactam antibiotics (Elfadadny *et al.*, 2024).

The data in Table 1 indicate that for piperacillin-tazobactam, the average resistance in Bulgaria is 43.15%, compared to 18.98% in the EU/EEA. The highest value in Bulgaria was recorded in 2020 (64.3%), followed by a decline, but the values remain significantly higher compared to the EU/EEA.

Resistance to ceftazidime in Bulgaria is also high, increasing from 20% in 2018 to 56.6% in 2022. The average resistance in Bulgaria is 41.13%, compared to 16.16% in the EU/EEA. Peaks exceeding 54% were reported in Bulgaria in 2020 and 2022, indicating a serious issue with this antibiotic.

Resistance to carbapenems (imipenem/meropenem) in Bulgaria is similarly high, averaging 33.38% compared to 19.08% in the EU/EEA. A peak of 42.9% was recorded in 2020, but subsequent years showed a decline, albeit not reaching the levels seen in other EU countries. At the beginning of the study period (2018), resistance to carbapenems in Bulgaria was 25.6%, reaching 40.8% in 2022, with a peak of 42.9% in 2020. According to the WHO BPPL (2024 update), carbapenem-re-

sistant *P. aeruginosa* is classified as a “high” priority group (WHO Bacterial Priority Pathogens List, 2024).

B. Mechanisms of resistance development to fluoroquinolones

The mechanisms of resistance to quinolones in *P. aeruginosa* are diverse and include both active efflux systems and mutations affecting antibiotic targets.

- Efflux pumps: MexAB-OprM and MexEF-OprN are associated with the efflux of quinolones from the cell, with MexEF-OprN specifically responsible for quinolone extrusion (Llanes *et al.*, 2011).
- Mutations in DNA gyrase and topoisomerase IV: Mutations in the genes *gyrA*, *gyrB*, *parC*, and *parE* lead to reduced bacterial sensitivity to quinolones by decreasing the binding affinity of antibiotics to their targets (Bruchmann *et al.*, 2013).

Fluoroquinolones (ciprofloxacin/levofloxacin) also show a high average resistance in Bulgaria—35.76% compared to 20.02% in the EU/EEA. In 2020, the resistance in Bulgaria reached 52.9%, significantly above the average for the period. During the study period, resistance in Bulgaria increased from 30% in 2018 to 39.5% in 2022, reaching a peak of 52.9% in 2020 (Table 1).

C. Mechanisms of resistance development to aminoglycosides

The resistance of *P. aeruginosa* to aminoglycosides is the result of the combined action of several mechanisms that reduce the concentration or effectiveness of these antibiotics within the cell. These mechanisms include the active efflux of antibiotics from the cell through efflux pumps, chemical modification and inactivation of antibiotics by specific enzymes, and structural changes in ribosomes that reduce aminoglycoside binding and action.

- Efflux pumps: MexXY-OprM is an efflux pump that expels aminoglycosides, reducing their intracellular concentration and effectiveness (Masuda *et al.*, 2000; Hocquet *et al.*, 2003).
- Modifying enzymes: Resistance to aminoglycosides is linked to the action of aminoglycoside-modifying enzymes (AME) that inactivate antibiotics. There are three main types of enzymes: aminoglycoside phosphotransferase (APH), aminoglycoside acetyltransferase (AAC), and aminoglycoside

nucleotidyltransferase (ANT). These enzymes alter the antibiotic's structure, rendering it ineffective (Ramirez and Tolmasky, 2010).

- Ribosomal mutations: Mutations in ribosomal genes reduce the effectiveness of aminoglycosides by preventing their binding to ribosomes (El'Garch *et al.*, 2007).

Regarding aminoglycosides (gentamicin/netilmicin/tobramycin), the average resistance in Bulgaria is 28.15%, while in the EU/EEA it is 10.86%. The highest value in Bulgaria was recorded in 2022 (36.4%), while in the EU/EEA the values remained stable at around 10%.

D. Combined resistance to ≥ 3 antimicrobial groups

The average value of combined resistance to three or more groups of antibiotics (piperacillin-tazobactam, ceftazidime, carbapenems, fluoroquinolones, and aminoglycosides) in Bulgaria during the period was 35.73%, compared to only 14.03% in the EU/EEA. In 2020, combined resistance in Bulgaria reached a peak of 50%, which is significantly above the average for the period, while in the EU/EEA, values remained relatively stable below 15%.

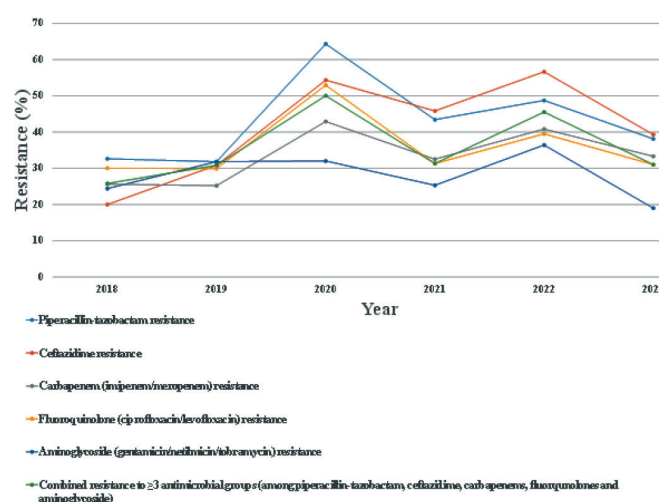


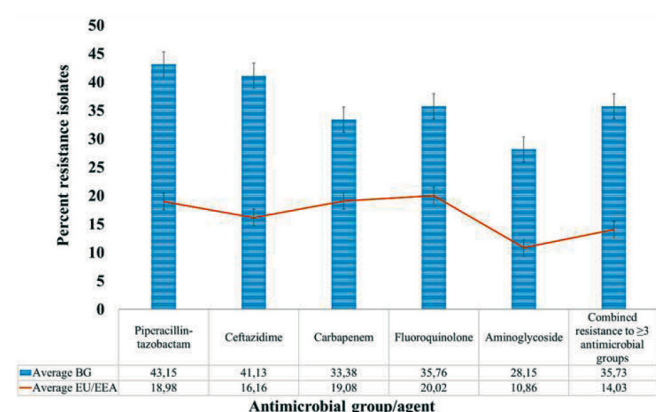
Fig. 2. Trends in antibiotic resistance in Bulgaria (2018–2023)

Figure 2 clearly illustrates the markedly high levels of antibiotic resistance in Bulgaria during the period 2018–2023, with significant peaks in 2020 for almost all antibiotics examined. This is likely linked to increased antibiotic use during the COVID-19 pandemic. Combined resistance to three or more antibiotic groups also reached alarming levels, with a peak of 50% in 2020, highlighting the severity of the issue. Despite a slight decline observed after 2020, resistance levels remain high in all antibiotics, requiring urgent measures to mitigate the problem and manage antibiotic use in the

country.

Figure 3 shows the average percentage of isolates with resistant phenotypes of *P. aeruginosa* against various antibiotics and antimicrobial groups from 2018 to 2023. The difference between Bulgaria and the EU/EEA is significant in all categories, likely reflecting issues such as overuse of antibiotics, insufficient control over their prescription, and a lack of effective resistance management programs. This underscores the urgent need for measures to rationalise antibiotic use and improve infection control.

Fig. 3. Average percentage of isolates with resistance phenotype by *P. aeruginosa* and antimicrobial group/agent by 6 years (2018–2023)



New anti-*Pseudomonas* therapies

➤ Ceftazidime-avibactam

This combination is approved for use in Europe and the USA. It is used to treat adult patients with complicated infections such as intra-abdominal infections (in combination with metronidazole), hospital-acquired pneumonia (including ventilator-associated pneumonia), urinary tract infections (including pyelonephritis), and bacteremia. In Europe, it can also be used for infections caused by gram-negative pathogens when no other treatment options are available. Later, the combination was approved for use in pediatric patients over 3 months of age (Daikos *et al.*, 2021).

➤ Imipenem/cilastatin/relebactam

This is another promising therapy to combat resistant *P. aeruginosa* strains. When used alone, imipenem and colistin have a narrower spectrum of action. An *in vitro* study showed that adding relebactam broadens the antimicrobial spectrum. The FDA and EMA have approved this combination, but further studies are required to validate its efficacy and ensure safety in clinical applications (Chen *et al.*, 2020).

➤ Phage therapy

Phage therapy, which uses viruses to treat bacterial infections, has been known for nearly a century. Despite its wide recognition, it is considered an alternative treatment for infections caused by multidrug-resistant strains. A study by Chegini *et al.* indicates that bacteriophages can be used to treat biofilms produced by *P. aeruginosa*. They work by penetrating the biofilms, infecting the bacteria, and destroying the biofilm structure, making the bacteria more susceptible to other therapies. The advantage of phage therapy is that bacteriophages can evolve and adapt alongside the host bacteria, reducing the likelihood of resistance development. However, its main drawbacks include the need for precise selection of phages for specific strains of *P. aeruginosa* and potential immune responses to the phages (Chegini *et al.*, 2020).

➤ Ceftolozane-tazobactam

This combination includes a novel cephalosporin with anti-pseudomonas activity (ceftolozane) and a classical β -lactamase inhibitor (tazobactam). Ceftolozane inhibits PBP3 and also shows an affinity for PBP1b and PBP1c, unlike other β -lactam agents. Additionally, ceftolozane demonstrates stability against ampC-type β -lactamases and is less affected by changes in porin permeability or outer membrane efflux pumps (López Montesinos *et al.*, 2021).

➤ BWC0977

This is a new compound from the oxazolidinone class with a broad spectrum of activity, effective against both gram-positive (e.g., *S. aureus*, *E. faecalis*) and gram-negative (e.g., *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *A. baumannii*, *E. cloacae*, and *P. mirabilis*) pathogens. It is a type II DNA topoisomerase inhibitor with similar activity against DNA gyrase and topoisomerase IV. Currently, in Phase 1 clinical trials, it is one of the promising agents for tackling multidrug-resistant strains (Hameed *et al.*, 2024).

Conclusion

Infections associated with *P. aeruginosa* are among the most severe in the world and are responsible for hundreds of thousands of deaths in the USA, Japan, and Europe. Despite the ongoing battle against multidrug-resistant bacteria, they continue to be one of the significant threats to hu-

man health. *P. aeruginosa* is a pathogen frequently associated with developing nosocomial infections, especially in immunosuppressed patients. The numerous resistance mechanisms identified in this bacterium contribute to the extreme difficulty of treating hospital-acquired infections. A significant challenge in developing effective therapies against *P. aeruginosa* is the increased encoding ability of its genome and the high heterogeneity of proteins among different strains.

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