Advanced Material Strategies to Combat Beta-Lactam Resistance in Multidrug-Resistant Pseudomonas Sp.

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**Abstract:** *Paeruginosa* is a Gram-negative, opportunistic pathogen causing severe infections in immunocompromised individuals & is highly resistant to multiple antibiotics, including beta-lactams. Biochemical tests confirmed the bacterium identification as *Pseudomonas sp.,* by its rod shape, motility, and various metabolic properties. The combination of doripenem and meropenem demonstrated a dose-dependent increase in histamine release, indicating a significant impact on bacterial cells and a potential inflammatory response. Cell viability assays indicated a reduction in bacterial viability with increasing concentrations of the combined antibiotics, demonstrating their synergistic efficacy. The antibiofilm activity of these antibiotics, both individually and in combination, was evaluated against *Pseudomonas sp.* Biofilm studies indicated that while each antibiotic alone moderately reduced biofilm density, their combination significantly disrupted biofilm formation, highlighting a synergistic effect. This study underscores the potent effects of combined beta-lactam antibiotics on *Pseudomonas sp.,* providing insights into their potential clinical applications in treating resistant infections.

**Keywords:** *Pseudomonas aeruginosa;* Beta-lactams; Antibiotics; Cell viability

# Introduction

Multidrug-resistant *Pseudomonas aeruginosa* is a prevalent and difficult nosocomial infection, with incidence rates ranging from 11.5% to 24.7%, according to the INFORM database [(Kunz Coyne et al., 2022)](https://paperpile.com/c/l2blsR/URNF). The definition of MDR *Pseudomonas aeruginosa* has evolved over the years. In 2008, the CDC classified it as resistance to at least one antibiotic in at least three separate classes to which *P. aeruginosa* is typically susceptible. These classes include antipseudomonal penicillins, cephalosporins, carbapenems, aminoglycosides & fluoroquinolones  [(Magiorakos et al., 2012)](https://paperpile.com/c/l2blsR/uc0p). *Pseudomonas aeruginosa* is a ubiquitous Gram-negative bacterium responsible for nosocomial infections and can cause fatal infections in immunocompromised individuals, such as cancer patients, post-surgery patients, those with severe burns, or individuals infected with HIV [(Gomila et al., 2018; Madhumitha & Muralidharan, 2021)](https://paperpile.com/c/l2blsR/zszA+pIzu). *P. aeruginosa* has developed significant resistance to traditional disinfectants and antibiotics, making it challenging to eradicate from hospital environments & to treat infected patients [(Langendonk et al., 2021)](https://paperpile.com/c/l2blsR/Hknp). Due to its "plastic" genome, which can vary in size from 5.5 to 7 Mb, *Pseudomonas aeruginosa* genome is significantly larger than that of other bacteria, including *E. coli*, which is only about 4.6 Mb. The variation in genome size reflects the variety of the accessory genome, which may constitute for up to 20% of the overall genome. The accessory genome encodes a diverse set of genes, including transcriptional regulators, transporters, metabolic pathways and two-component regulatory systems [(Muthukumarasamy et al., 2020)](https://paperpile.com/c/l2blsR/OeWH). This leads into an extremely adaptable metabolic capacity and the ability to create secondary metabolites and polymers from various carbon sources. This metabolic adaptability enables *Pseudomonas aeruginosa* to adapt to a wide range of environments and infect individuals with weakened immunity, physiological abnormalities and trauma [(Mielko et al., 2019)](https://paperpile.com/c/l2blsR/mLmh). The bacterium's antibiotic resistance is considerably more obvious in infections with biofilms, which the pathogen rapidly develops [(Ciofu & Tolker-Nielsen, 2019)](https://paperpile.com/c/l2blsR/r6rK). Most *Pseudomonas aeruginosa* infections are associated with biofilm development and the generation of different virulence factors [(Gajdács et al., 2021)](https://paperpile.com/c/l2blsR/qpfd). Biofilms are complex bacterial aggregations that form their own extracellular polymeric matrix. This structure is an important survival strategy for bacteria, allowing them to tolerate unexpected environmental changes such as temperature fluctuations and nutrition availability [(Moradali & Rehm, 2020)](https://paperpile.com/c/l2blsR/dMgb). Biofilms contribute to antibiotic resistance by making drug penetration harder, changing bacterial metabolism, and containing antibiotic-insensitive persister cells [(Povolotsky et al., 2021)](https://paperpile.com/c/l2blsR/1AKe). Antibiotics may be administered orally or intravenously to treat a number of *Pseudomonas aeruginosa* infections, such as lung infections, bone infection and septicemia. Inhalation of particular antibiotics is also used to treat lung infections in people with cystic fibrosis or other lung diseases [(Garcia-Clemente et al., 2020)](https://paperpile.com/c/l2blsR/7COY). β-lactam antibiotics (BLAs) are commonly used as antibacterial drugs to treat various infectious diseases [(Tooke et al., 2019)](https://paperpile.com/c/l2blsR/QtGX). BLAs have either a bicyclic or monocyclic structure with a four-membered β-lactam ring, which is the drug's susceptible site [(Bush, 2018)](https://paperpile.com/c/l2blsR/knSL). Enzymes called β-lactamases break down the β-lactam ring of antibiotics, making them ineffective. *Pseudomonas aeruginosa* contains a chromosomally encoded Class C β-lactamase called AmpC [(Noufal et al., 2021; Tooke et al., 2019)](https://paperpile.com/c/l2blsR/QtGX+SFvU). Class C β-lactamases are very active against penicillins and cephalosporins [(Poole, 2011)](https://paperpile.com/c/l2blsR/rDfI). AmpC is involved in the inherent resistance to several penicillins, including ritipenem, faropenem & sulopenem [(Okamoto et al., 2001)](https://paperpile.com/c/l2blsR/g9Aj). The primary classes of β-lactams used clinically encompass molecules with a bicyclic nucleus, including penicillin-like β-lactam antibiotics, cephalosporins, and carbapenems. Additionally, they include monocyclic systems such as monobactams [(Tooke et al., 2019)](https://paperpile.com/c/l2blsR/QtGX). Meropenem is a carbapenem-type beta-lactam antibiotic noted for its broad-spectrum efficiency and minimal toxicity. Meropenem, like other classic antibacterial drugs, has a time-dependent bactericidal effect by blocking bacterial cell wall synthesis [(Streit et al., 2016)](https://paperpile.com/c/l2blsR/pBx2). Doripenem, a carbapenem antibiotic having a wide range of antibacterial properties. It functions similarly to imipenem against gram-positive pathogens and has a meropenem-like antibacterial spectrum against gram-negative organisms. Doripenem's activity against P. aeruginosa has been found to be equivalent to meropenem [(Girija et al., 2019; Huang et al., 2022)](https://paperpile.com/c/l2blsR/CSQ3+ebcc).The aim of this study is to investigate the mechanisms of resistance in multidrug-resistant Pseudomonas sp., particularly against beta-lactam antibiotics such as meropenem and doripenem, and to explore the effectiveness of various strategies, including antiallergic and antibiofilm activities, to combat these resistant strains.

# Materials and methods

*P. aeruginosa*, an oral pathogen, has been collected from hospitals and S. On cetrimide agar, the culture was grown for 24 hours at 37°C. *Pseudomonas aeruginosa* colonical morphology was examined under a microscope after incubation.A biochemical analysis was performed on *Pseudomonas aeruginosa* samples that were collected from For identification, the pathogens were streaked on cetrimide agar medium, and several biochemical characteristics were evaluated according to [(S. et al., 1975)](https://paperpile.com/c/l2blsR/LYZK). Tests were specifically conducted to evaluate the following: Lactose fermentation, indole production, the methyl red test, the Voges-Proskauer test, citrate utilization, catalase activity, urease activity, inositol fermentation, triple sugar iron agar utilization, as well as starch, sucrose, xylose, and maltose fermentation. To measure histamine release from *Pseudomonas sp.,* treated with various concentrations of a meropenem and doripenem combination, the method developed by [(Dib et al., 2023)](https://paperpile.com/c/l2blsR/gsx9) was used. Overnight bacterial suspensions were transferred to conical flasks containing 10 mL of LB medium with different concentrations of meropenem and doripenem. The suspensions were then transferred to 250 mL conical flasks and incubated on an orbital shaker at 37°C for 24 hours. Following incubation, 1 ml aliquots were extracted from each flask, centrifuged at 2500 rpm for 15 minutes, and the supernatants were collected. To assess the effect of antibiotic treatments on histamine release, histamine concentrations in the supernatants were quantified using an ELISA kit following the manufacturer's instructions.Meropenem and Doripenem ability to inhibit biofilm formation by *Pseudomonas sp.,* was tested using the approach outlined by [(Alenazy, 2023)](https://paperpile.com/c/l2blsR/mBXW). Bacterial cultures were incubated in a microtiter plate at room temperature for 24 hrs to achieve a concentration of up to 109 cells/ml, allowing biofilm to form. The biofilms were then treated with various meropenem and doripenem concentrations (250 - 1000 µg/ml) at room temperature for an additional 48 hours. Biofilm quantification was carried out using crystal violet staining, with OD measurements taken at 570 nm. Untreated cultures acted as controls, and a sterile medium was used as the blank. The biofilm inhibition percentage was determined using the formula:

% of Inhibition = 100 - (sample / control) × 100

*Pseudomonas aeruginosa* (103 cells/ml) was inoculated into a 6-well plate and allowed to form a biofilm for 24 hours. The biofilm was then treated with a combination of meropenem and doripenem for 12 to 48 hours. After 48 hours of incubation, the biofilm was stained with acridine orange and propidium iodide to differentiate between live and dead cells [(Shinde et al., 2021)](https://paperpile.com/c/l2blsR/X2PQ).

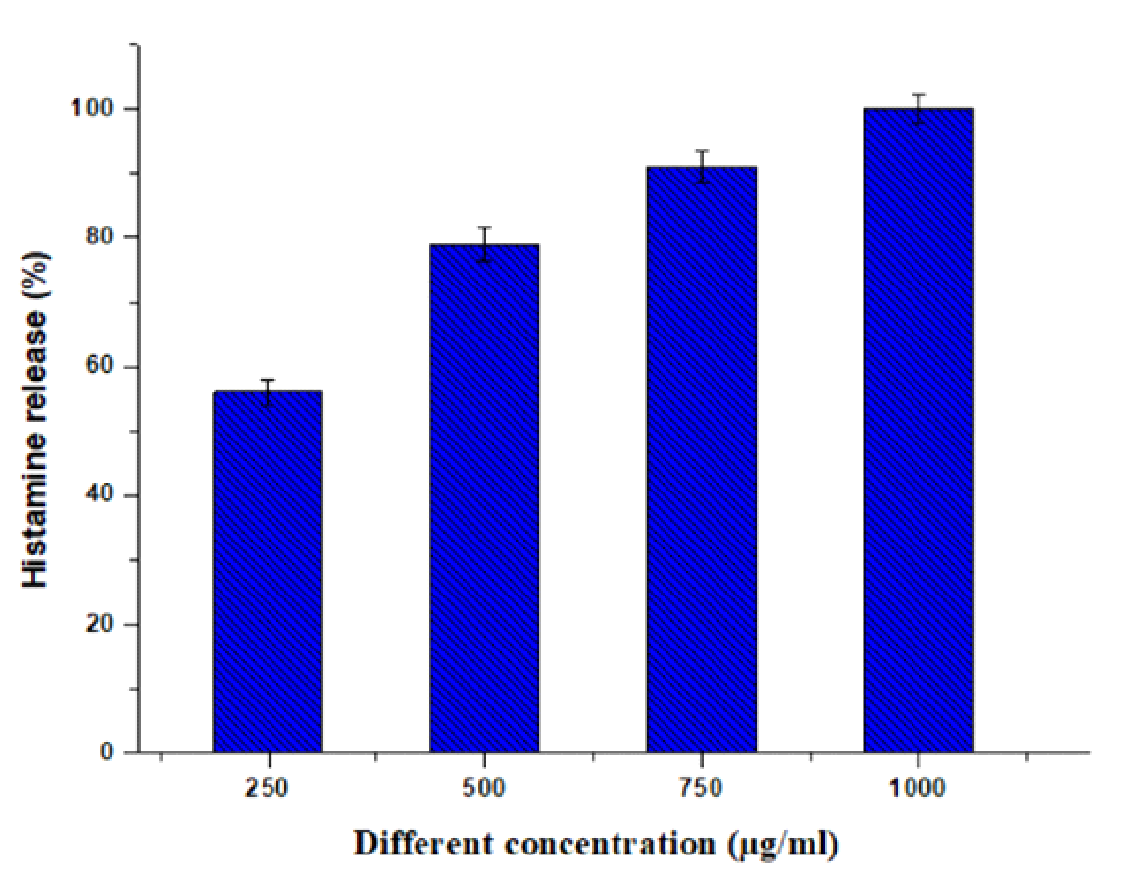
# Results

*Pseudomonas aeruginosa* is a Gram-negative opportunistic bacterium that leads to serious infections immunocompromised individuals and is highly resistant to multiple antibiotics, including beta-lactams. Based on the biochemical test (Table 1), it has a rod shape and is motile, which is consistent with the presence of flagella that allow movement. The indole test was negative, aligning with the fact that Pseudomonas species do not produce indole from tryptophan. Both the Methyl Red & Voges-Proskauer tests were negative, which is expected as *Pseudomonas species* do not produce stable acid end products or acetoin from glucose fermentation. The bacterium tested positive for citrate utilization, demonstrating its ability to use citrate as a sole carbon source. Triple Sugar Iron test was negative, indicating the absence of acid or gas production from glucose, lactose, and sucrose fermentation. The oxidase test was positive, consistent with the production of cytochrome c oxidase by *Pseudomonas species.* Additionally, the catalase test was positive, showing the bacterium can break down hydrogen peroxide into water and oxygen. The urease test was also positive, suggesting the presence of the enzyme urease that hydrolyzes urea into NH₃, CO₂. The pathogen did not ferment lactose, maltose, sucrose, xylose, or inositol, which is characteristic of *Pseudomonas species*. However, it tested positive for starch hydrolysis, indicating the production of amylase that breaks down starch into simpler sugars. These biochemical test results collectively confirm the identification of the bacterium as *Pseudomonas sp.,*

**Table 1**. Biochemical Identification of *Pseudomonas sp.,*

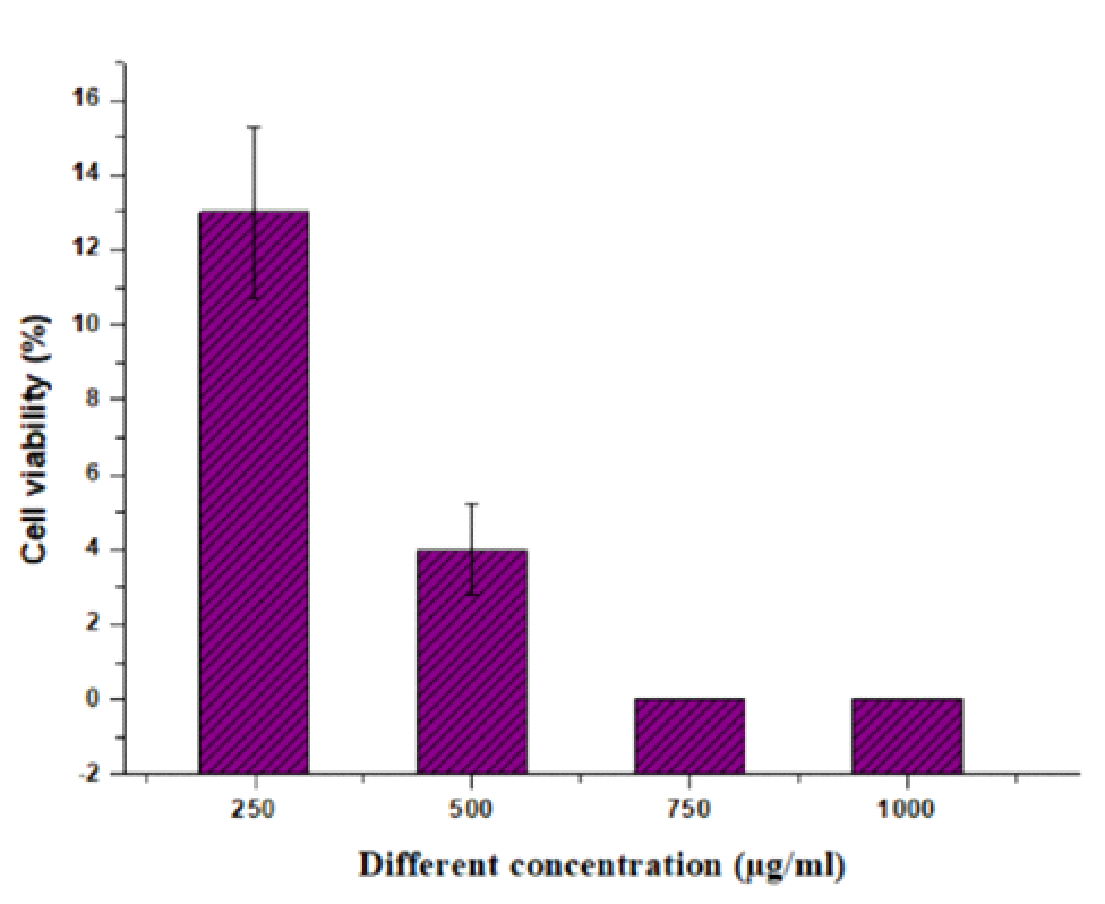
|  |  |
| --- | --- |
| **Biochemical characteristics** | **Results** |
| Gram stain | Positive |
| Shape | Rod |
| Motility | Positive |
| Indole | Negative |
| MR | Negative |
| VP | Negative |
| Citrate | Positive |
| TSI | Negative |
| Oxidase | Positive |
| Catalase | Positive |
| Urease | Positive |
| Lactose | Negative |
| Maltose | Negative |
| Sucrose | Negative |
| Xylose | Negative |
| Starch | Positive |
| Inosital | Negative |

The combination of doripenem and meropenem at different concentrations used to treat *Pseudomonas sp.* revealed a dose-dependent increase in histamine release, indicating the antibiotics significant impact on bacterial cells (Fig. 1). At a concentration of 250 µg/ml, histamine release is at 56%, indicating a moderate level of histamine being released. When the concentration is increased to 500 µg/ml, histamine release rises significantly to 79%, showing a substantial increase in response. This trend continues at 750 µg/ml, with histamine release reaching 91%, and at the highest concentration of 1000 µg/ml, histamine release peaks at 100%. This data suggests that as the concentration of the combined antibiotics increases, there is a corresponding increase in histamine release from *Pseudomonas sp.* cells. This could indicate a heightened inflammatory response or cell lysis at higher antibiotic concentrations, highlighting the potent effect of meropenem and doripenem in stimulating histamine release in these bacterial cells.



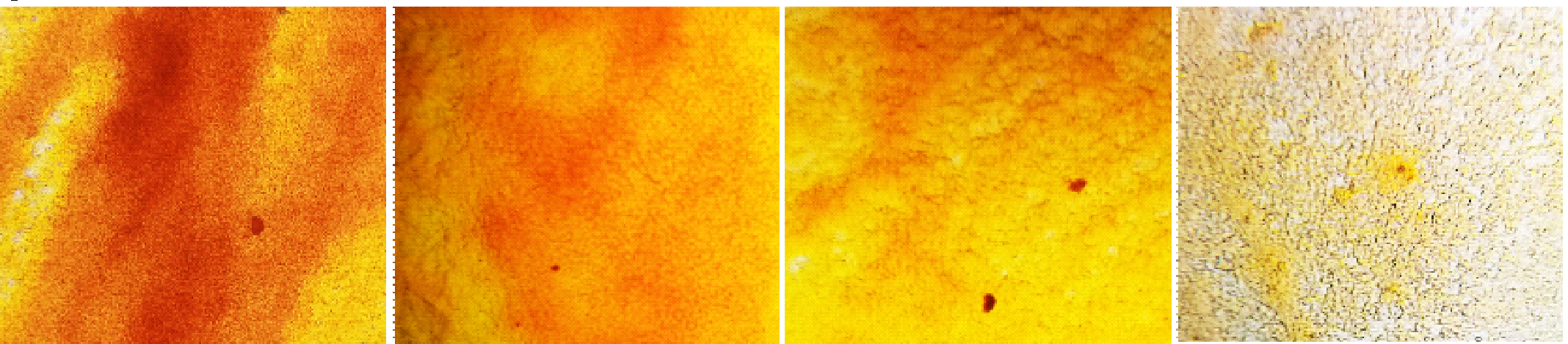
**Figure 1.** Histamine Release from *Pseudomonas* Treated with Antibiotics (Meropenem and Doripenem) at Different Concentrations.

Cell viability of *Pseudomonas sp.* treated with a combination of meropenem and doripenem at different concentrations of cell lysate show a significant decrease in cell viability as the concentration increases (Fig. 2). At 250 µg/ml, the cell viability is 13%, indicating that the majority of the bacterial cells are still alive but have been significantly affected by the treatment. As the concentration increases to 500 µg/ml, the cell viability drops sharply to 4%, demonstrating a marked reduction in the number of viable cells. At 750 µg/ml and 1000 µg/ml, the cell viability is completely eradicated, with 0% viability, indicating that the combination of meropenem and doripenem is highly effective at these higher concentrations. Both meropenem and doripenem inhibit cell wall synthesis, leading to bacterial cell lysis. At higher concentrations, their synergistic effects are maximized, overcoming bacterial defenses and enhancing the antibiotics ability to penetrate and disrupt biofilm structures.



**Figure 2.** Cell Viability of *Pseudomonas sp.,*Treated with Antibiotics (Meropenem and Doripenem) at Different Concentrations.

Biofilms are complex bacterial colonies that attach to surfaces and form a self-produced extracellular matrix. They are known for their resilience and resistance to antimicrobial treatments, posing significant challenges in clinical settings. *Pseudomonas* sp. is a notorious biofilm-former, contributing to persistent infections. This study evaluates the antibiofilm activity of two beta-lactam antibiotics, Meropenem and Doripenem, both individually and in combination, against *Pseudomonas* *sp.,* In control, Pseudomonas sp. formed a robust, well-developed biofilm with extensive surface coverage, demonstrating strong biofilm-forming capability under the experimental conditions. This establishes a solid baseline for comparing the effectiveness of the antibiotic-treated samples. Both Meropenem and Doripenem demonstrated moderate antibiofilm activity against *Pseudomonas sp.* at a concentration of 1000 microliters/ml after 48 hours, as evidenced by a noticeable reduction in biofilm density compared to the control. Their mechanisms, which involve inhibiting cell wall synthesis, likely interfere with the bacteria's ability to form and maintain biofilms. However, the persistence of biofilm structures suggests some bacteria may be resistant or that the antibiotics cannot fully penetrate the biofilm. The combination of Meropenem and Doripenem resulted in a significant reduction in biofilm formation, indicating a synergistic effect of the two antibiotics. The biofilm density was markedly reduced, suggesting that the combination therapy disrupts the biofilm more effectively than either antibiotic alone. This enhanced efficacy can be attributed to the complementary mechanisms of action of Meropenem and Doripenem, which together overcome the limitations of individual treatments by improving penetration and disruption of the biofilm matrix.



**Figure 3.** Antibiofilm activity of *pseudomonas sp.,* treated with different antibiotics at different concentrations, a) Control, b) Meropenem, c) Doripenem, d) Meropenem & Doripenem.

# Discussion

[(Krell et al., 2021)](https://paperpile.com/c/l2blsR/RttW)demonstrated Increasing antibiotic concentrations can damage bacterial cells, which can cause histamine to be released and immunological responses to be triggered. This demonstrates how antibiotics can cause bacterial cell leakage or death. [(Herrera-Espejo et al., 2022)](https://paperpile.com/c/l2blsR/WbVP) found that pentamidine exhibits synergistic activity when combined with antibiotics against multidrug-resistant P. aeruginosa clinical strains, indicating its potential as an adjuvant in the treatment of infections caused by MDR P. aeruginosa. Pentamidine effectively synergizes with rifampicin, linezolid, and tetracycline against Gram-negative bacteria by enhancing the activity of hydrophobic, small-molecule antibiotics [(Tang et al., 2023)](https://paperpile.com/c/l2blsR/noyK). However, it does not show synergy with vancomycin. This suggests that the histamine release observed at different concentrations may be influenced by the specific antibiotics used in combination with pentamidine.[(Herrera-Espejo et al., 2022)](https://paperpile.com/c/l2blsR/WbVP) discovered that Meropenem monotherapy had higher in vivo effectiveness with high MIC values, because of sufficient antibiotic exposure at infection sites. In addition, combination of imipenem and meropenem was effective in reducing bacterial spleen concentrations in the ST235 clone and mortality in the ST175 clones. Similarly, [(Lai et al., 2019)](https://paperpile.com/c/l2blsR/YhFe) found doripenem has been shown to possess strong clinical efficacy comparable to other antibiotics in treating acute bacterial infections, including complicated urinary tract infections, with higher success rates and favorable tolerance. For Pseudomonas aeruginosa isolates, meropenem exhibited MIC50 and MIC90 values of ≤1 mg/L and 8 mg/L, respectively, indicating potent activity against this pathogen [(Patel et al., 2019)](https://paperpile.com/c/l2blsR/5N1Y). This is significant given the challenge of treating Pseudomonas aeruginosa due to its propensity for biofilm formation and resistance development. The combined treatment of ciprofloxacin and meropenem showed synergistic effects in a biofilm model, reducing bacterial counts and suppressing resistance, especially with higher epithelial lining fluid penetration of meropenem [(Bilal et al., 2020)](https://paperpile.com/c/l2blsR/1hET). Furthermore, [(Van Gasse et al., 2010)](https://paperpile.com/c/l2blsR/5mj9) compared in vitro activity of doripenem & meropenem against Pseudomonas aeruginosa and multi-drug resistant Enterobacteriaceae revealed similar MIC50 and MIC90 values, with susceptibility rates exceeding 95% for MDR Enterobacteriaceae and approximately 70-75% for Pseudomonas aeruginosa. [(Drzewiecki et al., 2012)](https://paperpile.com/c/l2blsR/Av7E) found doripenem to have the highest in vitro activity against Pseudomonas sp. among the carbapenems tested, with lower MIC values compared to meropenem and imipenem. Sensitivity was similar for Acinetobacter baumannii across all carbapenems, and all Enterobacteriaceae strains were sensitive(Nikalje et al., 2024). Doripenem is thus a viable option for treating multi resistant Gram-negative bacteria, especially in severe infections(Chehelgerdi et al., 2023). [(Bilal et al., 2019)](https://paperpile.com/c/l2blsR/k0JT) found combination of meropenem CI (both 30% and 60% ELF penetration) and tobramycin synergistically suppressed biofilm bacterial regrowth and resistance, with meropenem CI at 60% ELF penetration being particularly effective in significantly reducing biofilm bacteria. [(Wickremasinghe et al., 2021)](https://paperpile.com/c/l2blsR/c8YZ) also found combination of polymyxin B and meropenem significantly reduced biofilm formation in FADDI-PA060 and completely eradicated planktonic and biofilm bacteria in FADDI-PA107. (Haagensen et al., 2017) showed that meropenem reduced PAO1 P. aeruginosa biofilms rapidly, independent of biofilm development.

# Conclusion

This study confirms the identity of *Pseudomonas aeruginosa* through comprehensive biochemical testing and demonstrates the significant impact of combined doripenem and meropenem treatments on this pathogen. The combination therapy exhibited a dose-dependent increase in histamine release, reflecting heightened bacterial cell disruption and potential inflammatory responses at higher concentrations. Cell viability assays revealed the combination's effectiveness in reducing viable bacterial counts, achieving complete eradication at higher doses. Antibiofilm assays showed that while individual antibiotics moderately inhibited biofilm formation, their combination significantly reduced biofilm density, indicating a synergistic effect. These findings highlight the potential of doripenem and meropenem combination therapy in overcoming the challenges of treating Pseudomonas aeruginosa infections, particularly those involving biofilm formation and antibiotic resistance. Future research should focus on clinical trials and exploring the underlying mechanisms of this synergistic interaction to optimize treatment strategies for *multidrug-resistant Pseudomonas aeruginosa* infections.

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