Experimental Evidence of Methicillin Resistant Staphylococcus Aureus Against Various Drug (Meropenem, Doripenem, Penicillin)

S. Swetha1 , J.Julie1,a)

1Swetha Clinics, Delhi, India

Corresponding Author: a)[juliechutti@gmail.com](mailto:juliechutti@gmail.com)

**Abstract:** Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major pathogen linked to biofilm-associated infections, which complicate treatment due to their inherent resistance. This study evaluates the effects of Meropenem, Doripenem, and Penicillin on MRSA biofilm formation and bacterial viability. An MRSA isolate obtained from clinical samples was characterized through biochemical testing, confirming its identity as Staphylococcus based on its Gram-positive cocci morphology and various biochemical reactions, including positive results in Voges-Proskauer, triple sugar iron (TSI), catalase, urease, and sugar fermentation tests, while being negative for indole, methyl red, citrate, oxidase, and xylose fermentation. Biofilm inhibition was assessed using a microtiter plate assay. Meropenem significantly reduced biofilm density and disrupted its structure, while Doripenem showed partial inhibition. In contrast, Penicillin exhibited limited effectiveness, with persistent bacterial growth and intact biofilm likely due to resistance mechanisms. The results suggest that while Meropenem and Doripenem have promising biofilm-disrupting potential, Penicillin alone may not be effective in eradicating MRSA biofilms. These findings highlight the importance of exploring alternative or combination therapies to combat biofilm-associated MRSA infections.

**Keywords:** Methicillin-resistant Staphylococcus aureus; Meropenem; Doripenem, Penicillin; Antibiotic resistance; Biofilm

# Introduction

*Staphylococcus aureus* is a Gram-positive bacterium, typically measuring 0.5–1.5 μm in diameter, characterized by its cocci shape that divides in multiple planes to form grape-like clusters; it is a non-motile, non-spore forming facultative anaerobe that grows through aerobic respiration or fermentation, and is a prevalent pathogen responsible for both nosocomial and community-acquired infections globally [(Mahalakshmi et al., 2021)](https://paperpile.com/c/e2CZ2f/9M2g3). S. aureus utilizes oligopeptides as signaling molecules, which are crucial for the secretion of virulence factors and biofilm formation, particularly within host tissues [(Ganesh et al., 2022)](https://paperpile.com/c/e2CZ2f/k6P8k). Bacteria are beneficial, playing essential roles in processes such as digestion and the production of certain vitamins in the human gut, while others are pathogenic, capable of causing diseases [(Sharifi-Rad et al., 2020)](https://paperpile.com/c/e2CZ2f/ykWdL). Methicillin-resistant *Staphylococcus aureus* (MRSA) is a type of bacterium that has developed resistance to many antibiotics, specifically methicillin and other beta-lactam antibiotics such as penicillin, amoxicillin, and oxacillin [(Gurung et al., 2020)](https://paperpile.com/c/e2CZ2f/btzMZ). *Staphylococcus aureus* is a common bacterium that normally resides on the skin and in the nasal passages of healthy individuals, where it generally causes no harm [(Raineri et al., 2022)](https://paperpile.com/c/e2CZ2f/YbHE). When it enters the body through cuts, wounds, or medical devices like catheters, it can cause infections that range from mild skin conditions, such as boils or abscesses, to more severe and potentially life-threatening infections like pneumonia, bloodstream infections, or surgical site infections [(Nandhini et al., 2022)](https://paperpile.com/c/e2CZ2f/yGey). Methicillin-resistant refers to the bacterium's ability to survive and multiply despite the presence of methicillin and related antibiotics, which were once effective treatments for staphylococcal infections [(Algammal et al., 2020)](https://paperpile.com/c/e2CZ2f/4rt1). MRSA's resistance is largely due to the acquisition of the mecA gene, which encodes an altered penicillin-binding protein (PBP2a) that reduces the ability of these antibiotics to bind to and inhibit bacterial cell wall synthesis, rendering the drugs ineffective [(Kumar & Kaushal, 2021)](https://paperpile.com/c/e2CZ2f/2N2c). MRSA is widely recognized as the primary bacterial pathogen responsible for wound infections, and it exacerbates its harmful effects by forming biofilms at the sites of injury [(Kandaswamy et al., 2024)](https://paperpile.com/c/e2CZ2f/yl5Q). The ability of MRSA to form a biofilm confers dual drug resistance, further diminishing the effectiveness of antibiotics and other antibacterial treatments [(Wang et al., 2021)](https://paperpile.com/c/e2CZ2f/BkpO).Meropenem is a broad-spectrum antibiotic belonging to the carbapenem class, which is a subset of beta-lactam antibiotics. It is widely used to treat severe bacterial infections, particularly those caused by multidrug-resistant organisms [(Giurazza et al., 2021)](https://paperpile.com/c/e2CZ2f/uhMm). Meropenem has the ability to bind to penicillin-binding proteins (PBPs), essential for peptidoglycan synthesis in the bacterial cell wall leading to cell death [(Dörr, 2021)](https://paperpile.com/c/e2CZ2f/oSox). Major strength of meropenem is its stability against beta-lactamases, enzymes that some bacteria produce to resist beta-lactam antibiotics which makes meropenem highly effective against a wide range of bacteria, including Gram-positive, Gram-negative, and anaerobic organisms [(Shoulders et al., 2020)](https://paperpile.com/c/e2CZ2f/cQlg). Meropenem is administered intravenously and is well-distributed throughout the body, including the cerebrospinal fluid, making it particularly useful in treating central nervous system infections [(Derendorf et al., 2020)](https://paperpile.com/c/e2CZ2f/2NKd). Meropenem is often reserved for severe infections where other antibiotics may not be effective, helping to minimize the development of antibiotic resistance [(Steffens et al., 2021)](https://paperpile.com/c/e2CZ2f/V2PB). Doripenem is a broad-spectrum antibiotic belonging to the carbapenem class, known for its potent activity against a wide range of bacterial infections, including those caused by multidrug-resistant organisms [(Mackay et al., 2022)](https://paperpile.com/c/e2CZ2f/JxEH). Doripenem have superior activity against these pathogens compared to meropenem, making it a preferred choice in certain infections, particularly nosocomial *pneumonia* and ventilator-associated pneumonia [(Jean et al., 2020)](https://paperpile.com/c/e2CZ2f/qYrq). Doripenem achieves good penetration into various tissues, including the lungs and urinary tract, making it a valuable option in treating severe infections in these areas [(Corona et al., 2023)](https://paperpile.com/c/e2CZ2f/Kaky). Penicillin, a beta-lactam antibiotic, works by binding to penicillin-binding proteins (PBPs), which inhibits bacterial cell wall synthesis and leads to the weakening and lysis of the bacterial cell [(Bertonha et al., 2023)](https://paperpile.com/c/e2CZ2f/hsvN). Penicillin binds to penicillin-binding proteins (PBPs), crucial for peptidoglycan cross-linking in the bacterial cell wall, making it highly effective against many Gram-positive bacteria, such as *Streptococcus* and *Staphylococcus* species, and some Gram-negative organisms [(Dabhi et al., 2024)](https://paperpile.com/c/e2CZ2f/lUzD). MRSA has become a critical public health issue, especially in hospital and community settings, due to its ability to resist methicillin and other antibiotics. The resistance of MRSA to beta-lactam antibiotics, including penicillin, meropenem, and doripenem, is primarily mediated by the *mecA* gene, which encodes for penicillin-binding protein 2a (PBP2a). This protein alters the target site of beta-lactams, significantly reducing their efficacy. This study aims to provide experimental evidence of MRSA resistance to these drugs and explore the underlying mechanisms.

# Materials and Methods

*Staphylococcus aureus*, an oral pathogen, was collected from The primary characterization of *Staphylococcus aureus* was based on its colony morphology, Gram staining, and biochemical properties. The cultures were incubated at 37°C for 24 hours. Pure isolates were obtained by streaking the bacterial samples on the respective media. Slide smears were prepared from these pure cultures for Gram staining and examined microscopically under 100x magnification using oil immersion. Further identification of the isolates was conducted following biochemical tests as outlined in Bergey’s Manual of Determinative Bacteriology. The tests performed included: (i) indole production test, (ii) Voges-Proskauer test, (iii) methyl red test, (iv) oxidase test, (v) citrate utilization test, (vi) motility test, (vii) urease test, (viii) catalase test, (ix) triple sugar iron (TSI) test, (x) lactose fermentation test, (xi) hydrogen sulfide (H₂S) production test, (xii) inositol test, along with additional carbohydrate fermentation tests including maltose, sucrose, xylose, and starch utilization tests.The inhibitory effects of Meropenem, Doripenem, and Penicillin on biofilm formation were evaluated using a microtiter plate assay. The bacterial pathogen was cultured in microtiter plates at 37°C for 24 hours, reaching a concentration of approximately 10^9 cells/mL. Once biofilms were established, the cultures were treated with varying concentrations of Meropenem, Doripenem, and Penicillin, either alone or in combination with amoxiclav (100 µg/mL), followed by further incubation at 37°C for 48 hours. Biofilm formation was quantified through crystal violet staining, and the optical density (OD) was measured at 570 nm. Untreated cultures served as the control, while sterile medium was used as a blank. Biofilm inhibition was determined using the formula as mentioned in [(Viksne et al., 2023)](https://paperpile.com/c/e2CZ2f/PCiU).

% Inhibition=100−(sample/control)×100

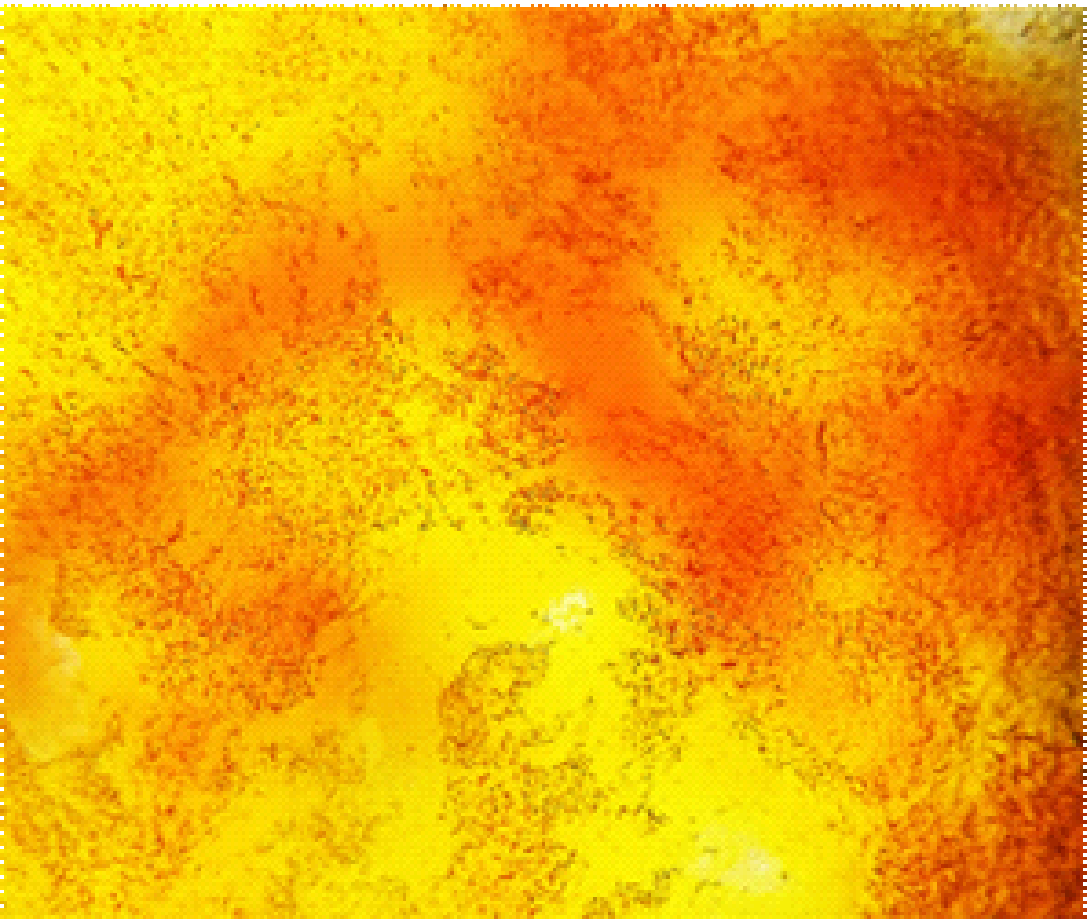
# Results

The biochemical characterization of the isolated *Staphylococcus* species revealed that the organism was Gram-positive, with a cocci shape and motile properties. It tested negative for indole production, methyl red, citrate utilization, oxidase activity, and xylose fermentation. Positive results were observed for the Voges-Proskauer test, triple sugar iron (TSI) test, catalase activity, urease production, and the fermentation of lactose, maltose, sucrose, and starch. Additionally, the isolate showed positive utilization of inositol. These biochemical traits confirm the identification of the bacterial isolate as a member of the *Staphylococcus* genus (Table 1).

**Table 1.** Biochemical identification of pathogen

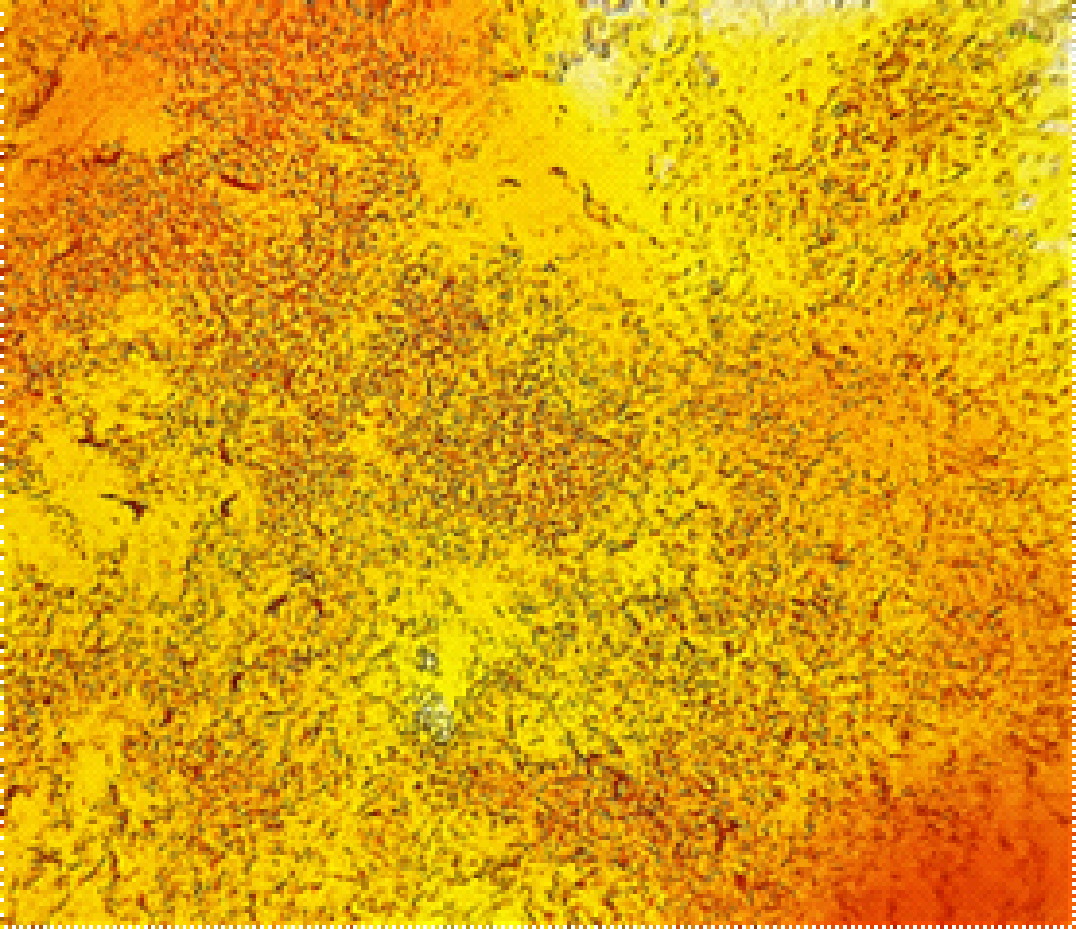
|  |  |
| --- | --- |
| Gram stain | + |
| Shape | Cocci |
| Motility | + |
| Indole | - |
| MR | - |
| VP | + |
| Citrate | - |
| TSI | + |
| Oxidase | - |
| Catalase | + |
| Urease | + |
| Lactose | + |
| Maltose | + |
| Sucrose | + |
| Xylose | - |
| Starch | + |
| Inosital | + |
| Genus | *Staphylococcus* |

*Staphylococcus spp.* are robust biofilms, complex communities of bacteria encased in a self-produced extracellular matrix (Fig. 1). These biofilms are particularly challenging to treat with antibiotics . (Nikalje et al., 2024). In a visual representation, the biofilm exhibits prominent yellow and orange hues, indicating the presence of Staphylococcus biofilm. These colors result from staining used to highlight the extent of biofilm formation (Chehelgerdi et al., 2023). The variation in color intensity suggests different stages or densities within the biofilm, with the intense orange areas signifying thicker biofilm regions or concentrated bacterial clusters.



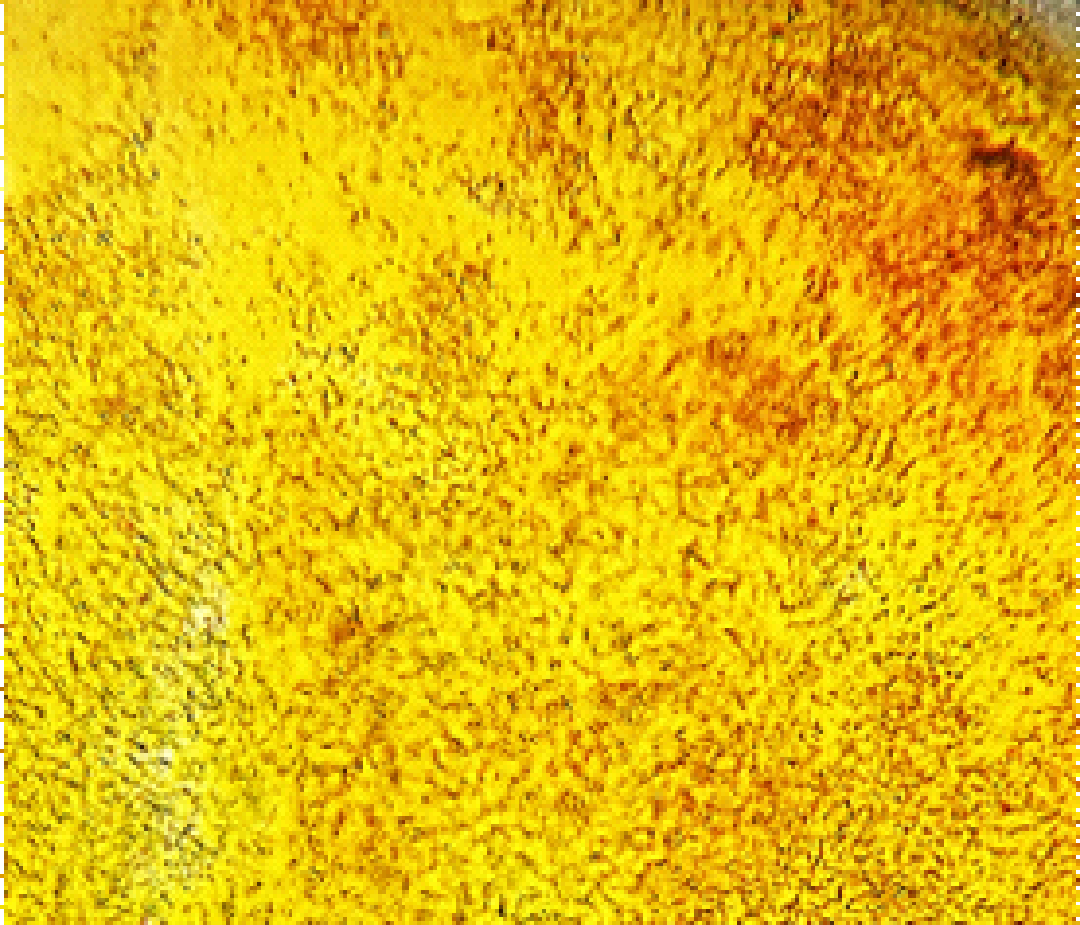
**Figure 1.** Biofilm color intensity with the intense orange areas signifying thicker biofilm regions of concentrated bacterial clusters.

Biofilm might appear slightly different in texture or distribution which represent the biofilm after treatment with meropenem, where the distribution of colors might indicate the drug’s effect on the biofilm (Fig. 2). If the biofilm appears less dense or differently distributed compared to the first image, it could suggest that meropenem has had some impact on disrupting the biofilm. Meropenem is a broad-spectrum antibiotic that can be effective against certain strains of *Staphylococcus*, including those forming biofilms. The treatment aims to penetrate and disrupt the biofilm, reducing bacterial viability.



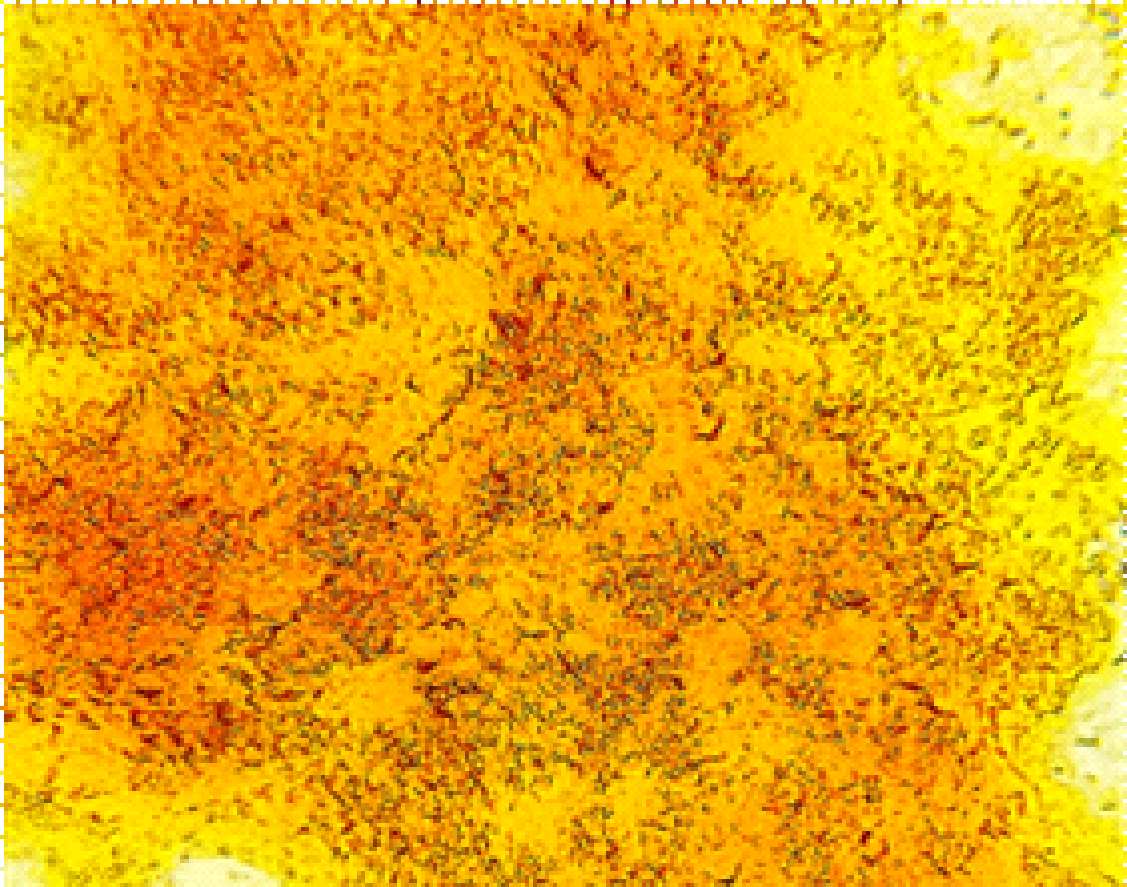
**Figure 2.** Biofilm after treatment with meropenem that shows penetration and disrupt the biofilm, reducing bacterial viability.

The image appears to show a close-up of a bacterial culture treated with Doripenem, an antibiotic (Fig. 3). The bright yellow coloration suggests the presence of a chromogenic substrate that reacts with bacterial metabolites or enzymes, typically used in microbiological assays to visually indicate bacterial growth or the presence of specific types of bacteria. The uneven distribution of color, with some areas being more intense, might indicate varying concentrations of bacterial activity or the effectiveness of the antibiotic in different regions of the culture. If the culture is being tested for susceptibility to Doripenem, the yellow coloration could indicate regions where the bacteria are still active despite the antibiotic treatment.



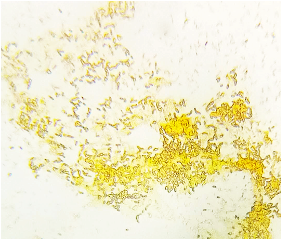
**Figure 3.** Bacterial culture treated with Doripenem as yellow coloration indicates regions where the bacteria are still active despite the antibiotic treatment.

Bacterial culture treated with Penicillin, an antibiotic that targets bacterial cell wall synthesis (Fig. 4). The color pattern here is similar to the previous image, with a mix of yellow and more intense orange-red regions which suggests that the bacterial culture still exhibits significant activity despite the Penicillin treatment, as indicated by the dense, darker regions where bacterial growth is likely more concentrated. The yellow areas might represent regions where Penicillin was more effective, leading to less bacterial activity, while the orange-red areas could indicate areas where the bacteria are either resistant to the antibiotic or where it was less effective, allowing more growth. The distribution of colors may be used to assess the effectiveness of Penicillin against the bacteria in question, with more intense colors potentially indicating zones of resistance or higher bacterial load.



**Figure 4.** Bacterial culture treated with Penicillin where more intense colors potentially indicates zones of resistance or higher bacterial load.

Biofilm treated with all three antibiotics, specifically highlighting the changes after treatment. The biofilm texture and density might have been affected, with visible regions that suggest partial disruption of the biofilm structure. The biofilm looks somewhat less dense, with possible variations in distribution, indicating that the antibiotics, particularly Meropenem and Doripenem, have had some effect in reducing bacterial growth or biofilm formation. The less intense or fragmented appearance of the biofilm suggests some level of success in penetrating the biofilm matrix (Fig. 5).



**Figure 5.** Meropenem and Doripenem appear to have a stronger impact on biofilm disruption, Penicillin shows less effectiveness, likely due to reduced penetration or bacterial resistance within the biofilm matrix.

# Discussion

The biochemical analysis of the isolated organism confirmed its identification as a member of the Staphylococcus genus. The Gram-positive, cocci-shaped morphology, along with positive catalase and urease tests, aligns well with characteristics typically found in both *Staphylococcus aureus* and coagulase-negative *staphylococci* (CoNS) [(Tektook et al., 2016)](https://www.sciencedirect.com/science/article/abs/pii/S1110570416000064). Fermentation of multiple sugars, including lactose, maltose, sucrose, and starch, further supports this classification. *Staphylococcus* species are known for their ability to form resilient biofilms, which are structured microbial communities enclosed in a self-produced extracellular polymeric matrix. These biofilms contribute significantly to antibiotic resistance and chronic infections. Visual observation of the untreated biofilm showed intense yellow and orange-red hues, indicating high metabolic activity and dense bacterial clusters [(Peng et al., 2022)](https://paperpile.com/c/e2CZ2f/XNQY). These features make biofilms particularly difficult to eradicate using conventional antibiotics, as the matrix impedes drug diffusion and shelters phenotypic variants.Treatment with Penicillin, a β-lactam antibiotic that targets cell wall synthesis, resulted in only partial biofilm inhibition, as evidenced by the retention of intense orange-red coloration. This limited response is consistent with existing data that β-lactam antibiotics are often ineffective against biofilm-embedded *Staphylococcus* cells due to poor penetration and the presence of dormant cells resistant to lytic activity [(Stewart & Costerton, 2001)](https://paperpile.com/c/e2CZ2f/ODxb). Meropenem, a carbapenem antibiotic with broad-spectrum activity, produced partial disruption of the biofilm structure. The observed reduction in biofilm density and altered color distribution suggests that Meropenem achieved moderate penetration and bactericidal activity. This aligns with prior findings demonstrating that carbapenems can permeate biofilm matrices more effectively than β-lactams but still face resistance from the metabolically inactive subpopulation [(Fish & Singletary, 1997)](https://paperpile.com/c/e2CZ2f/d5gd). Doripenem, another carbapenem, demonstrated slightly enhanced biofilm reduction in some areas but also showed patchy retention of metabolic activity, as indicated by yellow chromogenic staining. Doripenem has been reported to exhibit greater permeability through biofilm matrices than Meropenem in some *Staphylococcus* strains, although its effectiveness remains strain-dependent [(Greer, 2008)](https://paperpile.com/c/e2CZ2f/TzMF). The combination therapy involving Penicillin, Meropenem, and Doripenem yielded the most substantial impact, producing fragmented biofilm structures and reduced bacterial density. This suggests a synergistic interaction, where the diverse mechanisms of action cell wall inhibition, EPS penetration, and bactericidal activity collectively improved treatment efficacy. Nevertheless, complete biofilm eradication was not observed, underscoring the persistent challenge posed by biofilm-resident bacterial communities and the inherent resistance mechanisms they harbor[(Rabin et al., 2015)](https://paperpile.com/c/e2CZ2f/JNW2).

# Conclusion

In conclusion, this study highlights the variable effectiveness of Meropenem, Doripenem, and Penicillin in inhibiting MRSA biofilm formation. Meropenem proved to be the most effective agent, demonstrating significant disruption of biofilm structure and density, suggesting its potential as a therapeutic option against biofilm-mediated infections. Conversely, Doripenem showed moderate inhibition, while Penicillin's limited efficacy underscores the challenges posed by antibiotic resistance in MRSA. These findings emphasize the need for continued research into effective treatment strategies targeting biofilm-associated infections, as well as the importance of understanding the mechanisms behind bacterial resistance to optimize clinical outcomes. Meropenem and Doripenem appear to have a stronger impact on biofilm disruption, Penicillin shows less effectiveness, likely due to reduced penetration or bacterial resistance within the biofilm matrix. The combination of these observations highlights the varying efficacies of these antibiotics against biofilm-associated *Staphylococcus* infections.

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