Clin. Lab. 2026;72:XXX-XXX


ORIGINAL ARTICLE

# A Novel Approach Targeting Coagulase-Negative Staphylococcal Infections: Rifabutin's Antibacterial Potential

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## SUMMARY

*Background:* **Coagulase-negative staphylococci (CoNS) are opportunistic pathogens that pose a significant challenge in healthcare settings, particularly among patients with indwelling medical devices. Their ability to form biofilms and exhibit resistance to β-lactam antibiotics, including methicillin, limits treatment options. The increasing prevalence of multidrug-resistant CoNS necessitates alternative therapeutic strategies. This study aimed to evaluate the *in vitro* antimicrobial activity of rifabutin against clinical isolates of CoNS, including *Staphylococcus epidermidis, Staphylococcus saprophyticus, Staphylococcus haemolyticus, Staphylococcus hominis,* and *Staphylococcus lugdunensis*.**
*Methods:* **A total of 70 clinical CoNS isolates were collected from patients at King Abdulaziz University Hospital in Jeddah, Saudi Arabia. Identification and susceptibility profiling were performed using the Vitek 2 system. The antimicrobial activity of rifabutin was assessed using the broth microdilution method to determine the minimum inhibitory concentration (MIC). Rifabutin was prepared in 5% dimethyl sulfoxide (DMSO) and tested in serial two-fold dilutions, with MIC values recorded as the lowest concentration that inhibited bacterial growth. Each experiment was conducted in triplicate to ensure reproducibility.**
*Results:* **The MIC values of rifabutin ranged from 0.016 to 0.063 µg/mL across the tested strains, with the majority of isolates showing an MIC of 0.0312 µg/mL (41.4%) and 0.063 µg/mL (37.1%), while a smaller proportion exhibited an MIC of 0.016 µg/mL (21.4%). The MIC distribution demonstrated consistent inhibitory effects of rifabutin across different CoNS species, with only a 1- to 2-fold variation in susceptibility. These findings suggest that rifabutin is effective against CoNS with a relatively uniform susceptibility profile, making it a promising candidate for the treatment of infections caused by these bacteria.**
*Conclusions:* **Rifabutin demonstrates promising antimicrobial potential against CoNS, highlighting its potential as an alternative therapeutic agent for CoNS-related infections. Given its ability to overcome β-lactam resistance mechanisms, further studies, including *in vivo* assessments, are warranted to explore its clinical applicability.**
**(Clin. Lab. 2026;72:xx-xx. DOI: 10.7754/Clin.Lab.2025.250458)**

Manuscript accepted July 7, 2025

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## KEYWORDS

coagulase-negative staphylococci, Rifabutin, MIC, AMR, Repurposing

## INTRODUCTION

Coagulase-negative staphylococci (CoNS) are a diverse group of staphylococcal species that are naturally present as part of the human skin and mucosal microbiota [1]. Historically regarded as less pathogenic than coagulase-positive *Staphylococcus aureus*, CoNS have increasingly been recognized as significant opportunistic pathogens, particularly in hospital settings [2]. They are a leading cause of healthcare-associated infections, especially in patients with indwelling medical devices such as catheters, prosthetic joints, and heart valves [3]. CoNS-related infections, including bloodstream infections, endocarditis, and surgical site infections, pose significant treatment challenges due to their ability to form biofilms on medical devices [4]. These biofilms act as a barrier, protecting the bacteria from both the host immune system and antimicrobial agents [5].
The epidemiology of CoNS infections has evolved with the growing use of invasive medical devices and the increasing prevalence of immunocompromised patients [6]. Common species implicated in clinical infections include *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, and *Staphylococcus haemolyticus, Staphylococcus hominis, Staphylococcus lugdunensis* [7,8], with S. epidermidis being the most frequently isolated [9]. These infections are associated with high morbidity, prolonged hospital stays, and increased healthcare costs [10].
Coagulase-negative *Staphylococci* exhibit resistance to β-lactam antibiotics through several mechanisms, with the most notable being the production of altered penicillin-binding proteins (PBPs) and β-lactamase enzymes [11,12]. The primary mechanism of β-lactam resistance in CoNS, particularly in *S. epidermidis*, involves the production of PBP2a, an altered penicillin-binding protein encoded by the *mecA* gene located on the mobile genetic element SCCmec. PBP2a has a low affinity for β-lactam antibiotics, enabling the bacteria to maintain cell wall synthesis even in the presence of these drugs, thereby conferring resistance to methicillin and other β-lactams [13,14]. Additionally, some CoNS strains produce β-lactamase enzymes, such as penicillinase, which hydrolyze the β-lactam ring in antibiotics like penicillin, rendering them ineffective [15]. While this mechanism alone does not confer methicillin resistance, it can contribute to resistance when combined with PBP alterations.
Biofilm formation further complicates the treatment of CoNS infections [16]. Biofilms create a protective matrix that limits antibiotic penetration and shields bacteria from the host immune response [16]. This makes infections involving medical devices particularly difficult to treat with standard β-lactam therapies [17]. Other mechanisms, such as efflux pumps and mutations in regulatory genes, may also contribute to reduced antibiotic susceptibility by lowering intracellular antibiotic concentrations or altering bacterial cell wall properties [18].
A growing concern in the management of CoNS infections is their increasing resistance to multiple antibiotics, including methicillin and vancomycin [11,19]. Methicillin-resistant CoNS are now prevalent in healthcare settings, significantly reducing treatment options and complicating infection control efforts [20]. The combination of resistance mechanisms and biofilm-associated persistence underscores the urgent need for alternative therapeutic agents capable of overcoming these challenges.
Drug repurposing, also known as drug repositioning, is a strategy that involves identifying new therapeutic uses for existing drugs that have already been approved for other conditions [21,22]. This approach offers several advantages, including reduced development time, lower costs, and well-established safety profiles [23,24]. Given the rising threat of antimicrobial resistance (AMR), repurposing existing antibiotics has gained attention as a promising alternative to developing novel antibiotics from scratch.
Rifabutin, a rifamycin-class antibiotic, is primarily used for the treatment of Mycobacterium avium complex (MAC) infections and tuberculosis (TB), particularly in HIV-positive patients. It functions by inhibiting bacterial RNA polymerase, thereby blocking transcription and preventing bacterial replication [25,26]. Rifabutin has been investigated for its efficacy against a range of bacterial pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococci*, and group A *Streptococci*. Additionally, it has demonstrated activity against several Gram-negative bacteria, such as *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Haemophilus influenzae*, *Campylobacter jejuni, Helicobacter pylori*, and *Chlamydia trachomatis* [27,28]. Notably, its antimicrobial potential extends to coagulase-negative staphylococci (CoNS), including *S. epidermidis, S. saprophyticus, S. haemolyticus, S. hominis,* and *S. lugdunensis*. This study represents the first *in vitro* assessment of rifabutin's activity against CoNS, providing new insights into its potential applications.

## MATERIALS AND METHODS

### Bacterial Collection

Coagulase-negative *Staphylococcal* isolates (*Staphylococcus epidermidis, Staphylococcus saprophyticus, Staphylococcus haemolyticus, Staphylococcus hominis,* and *Staphylococcus lugdunensis*) were obtained from patients treated at King Abdulaziz University Hospital in Jeddah, Saudi Arabia. The collection process complied with the ethical standards of the King Abdulaziz University Ethics and Research Committee, with approval granted under Reference No. 301-24, in alignment with the Declaration of Helsinki.

### Storage and Culture Preparation

The collected isolates were stored in glycerol at -80°C to preserve their viability. Prior to analysis, the samples were thawed and cultured on blood agar plates (HiMedia, India) to confirm purity. The cultures were incubated aerobically at 37°C overnight to ensure sufficient bacterial growth.

### Antibacterial Agents

The antibacterial activity of rifabutin was evaluated. The compound was procured from Sigma UK and dissolved in 5% dimethyl sulfoxide (DMSO) (Sigma, USA) to ensure proper solubility and stability. The preparation of the antibacterial agent was carried out with precision to guarantee reliable and reproducible results. To ensure accuracy, all working concentrations required for the antimicrobial assays were freshly prepared from the stock (original stock is 10 mg/mL) using the dilution equation $C1V1 = C2V2$ where C1 and V1 represent the concentration and volume of the stock solution, and C2 and V2 represent the desired final concentration and volume. This method ensured precise and consistent dosing across all experimental replicates.

### Identification of Coagulase-Negative *Staphylococci*

Each bacterial isolate was first identified and then subjected to antimicrobial susceptibility testing using the Vitek 2 system (bioMérieux, France). The identification and testing process was conducted following the manufacturer's guidelines to ensure precision and reliability. Specifically, the gram-positive strain GP CARD VITEK panel, designed for use within the VITEK 2 system (BioMérieux, Durham, NC, USA), was employed for the comprehensive analysis of bacterial isolates. To facilitate optimal bacterial growth and accurate identification, all isolates were incubated under aerobic conditions at 37°C for a period of 24 hours. This incubation period allowed the isolates to reach an adequate growth phase, ensuring the accuracy of the subsequent susceptibility testing results.

### Antibacterial Susceptibility Testing

The broth microdilution method was used to assess the antibacterial efficacy of rifabutin. Serial two-fold dilutions of the compound were prepared, starting at a concentration of 1 µg/mL. The MIC was determined as the lowest concentration that inhibited visible bacterial growth. Each test was performed in triplicate, and the average MIC values were calculated for accuracy.

## RESULTS

### Minimum Inhibitory Concentration (MIC) of Rifabutin Against Coagulase-Negative Staphylococci

We evaluated the antimicrobial efficacy of rifabutin against a total of 70 clinical isolates of coagulase-negative *Staphylococci* (CoNS). The tested strains included 46 isolates of *S. epidermidis*, 5 isolates of *S. saprophyticus*, 10 isolates of *S. haemolyticus*, 5 isolates of *S. hominis*, and 4 isolates of *S. lugdunensis*. The MIC values across all tested strains ranged from 0.016 to 0.063 µg/mL, indicating a moderate variation in susceptibility. A breakdown of MIC distribution among the tested isolates revealed that the majority of strains exhibited an MIC of 0.0312 µg/mL (29 isolates, 41.4%) and 0.063 µg/mL (26 isolates, 37.1%), while a smaller proportion showed an MIC of 0.016 µg/mL (15 isolates, 21.4%). These findings suggest that rifabutin demonstrates a consistent inhibitory effect across different CoNS species, with only a 1- to 2-fold MIC variation, indicating relatively uniform susceptibility patterns.

## DISCUSSION

The evaluation of rifabutin's antimicrobial efficacy against coagulase-negative staphylococci (CoNS) clinical isolates provides valuable insights into its potential as an antimicrobial agent for treating infections caused by these bacteria. CoNS, particularly *Staphylococcus epidermidis*, are commonly associated with nosocomial infections, especially in immunocompromised patients or those with indwelling medical devices [29]. This study for the first time assessed the activity of rifabutin against CoNS. The moderate variation in the MIC values of rifabutin observed in this study suggests that it exhibits consistent antibacterial activity across multiple CoNS species.

The MIC range of rifabutin observed in this study (0.016 - 0.063 µg/mL) is within the range of susceptibility seen with other antimicrobial agents, indicating that rifabutin may be a viable option for treating CoNS infections. The finding that the majority of isolates exhibited MIC values of 0.0312 µg/mL (41.4%) and 0.063 µg/mL (37.1%) demonstrates that most of the tested CoNS strains were susceptible to rifabutin, highlighting the potential effectiveness of this antibiotic in clinical settings. This result aligns with previous studies showing that rifabutin has a strong inhibitory effect against a variety of gram-positive organisms, including staphylococci [27].

The distribution of MIC values among the different CoNS species revealed some variability in susceptibili-

**Table 1. MIC Distribution of Rifabutin Against Coagulase-Negative *Staphylococci.***

| Bacterial species | Number of isolates (n = 70) | MIC range (µg/mL) | MIC distribution (µg/mL) |
|---|---|---|---|
| ***Staphylococcus epidermidis*** | **46** | **0.016 - 0.063** | **0.016 (10), 0.0312 (20), 0.063 (16)** |
| ***Staphylococcus saprophyticus*** | **5** | **0.016 - 0.063** | **0.016 (1), 0.0312 (2), 0.063 (2)** |
| ***Staphylococcus haemolyticus*** | **10** | **0.016 - 0.063** | **0.016 (2), 0.0312 (4), 0.063 (4)** |
| ***Staphylococcus hominis*** | **5** | **0.016 - 0.063** | **0.016 (1), 0.0312 (2), 0.063 (2)** |
| ***Staphylococcus lugdunensis*** | **4** | **0.016 - 0.063** | **0.016 (1), 0.0312 (1), 0.063 (2)** |
| **Total** | **70** | **0.016 - 0.063** | **0.016 (15), 0.0312 (29), 0.063 (26)** |

ty. *Staphylococcus epidermidis* strains, being the most common CoNS isolate, showed a range of MIC values, with a notable proportion of strains exhibiting resistance or reduced susceptibility (MIC 0.063 µg/mL). This variability is likely due to intrinsic factors such as biofilm formation capabilities and genetic diversity within the *S. epidermidis* population.

It has been shown that rifabutin has potent anti-staphylococcal activity [27]. Moreover, they enhance the therapeutic potential of rifabutin by encapsulating it in liposomes to improve accumulation at infection sites. Both free and liposomal RFB exhibited strong antibacterial activity, with MIC values of 0.009 µg/mL for free rifabutin and 0.013 µg/mL for liposomal rifabutin against [27].

Interestingly, *Staphylococcus saprophyticus* and *Staphylococcus haemolyticus* isolates also exhibited a relatively consistent MIC distribution, suggesting a comparable susceptibility to rifabutin. However, the smaller sample size of these species may limit the generalizability of these findings. This study did not observe any significant difference in the MIC values between the different species of CoNS, implying that rifabutin may have a broad-spectrum effect against these pathogens, making it a potential candidate for treating CoNS infections in clinical practice.

The results from this study are consistent with earlier research, which suggests that rifabutin exhibits potent antibacterial activity against a variety of staphylococcal species [25]. Rifabutin's mechanism of action involves inhibition of bacterial RNA synthesis by binding to the bacterial RNA polymerase, which effectively blocks transcription [25]. This mechanism provides an advantage over other antibiotics in treating infections caused by resistant organisms like CoNS, especially those expressing multidrug resistance.

A noteworthy aspect of our findings is the relatively narrow MIC range across all tested isolates. A 1- to 2-fold MIC variation suggests that rifabutin may offer a predictable and reliable efficacy profile, potentially reducing the risk of treatment failure due to microbial resistance. Given the growing problem of multidrug-resistant CoNS, the identification of an antimicrobial agent like rifabutin with relatively uniform efficacy across different strains is encouraging.

Although the demonstrated antimicrobial activity of rifabutin, it is generally not recommended to use rifamycin-class antibiotics as monotherapy. This is primarily due to the rapid development of resistance associated with this group of drugs. When rifamycins are administered alone, bacterial populations can quickly acquire resistance through genetic mutations or adaptive mechanisms, thereby significantly reducing the drug's long-term efficacy [30,31]. Thus  this brings in the future to assess the synergistic activity with other antibiotic against CoNS.

A recent case series involving 10 patients at the University of Maryland Medical Center demonstrated the clinical utility of rifabutin as an alternative to rifampin for treating *Staphylococcus aureus* biofilm-associated infections, particularly when rifampin was contraindicated due to drug-drug interactions with chronic medications such as methadone, anticoagulants, antiarrhythmics, antipsychotics, and antiretrovirals. Over a three-year period, rifabutin was used in combination with standard-of-care antibiotics (e.g., cefazolin, ceftaroline, daptomycin) for at least six weeks in patients with prosthetic material infections involving MSSA (n = 6), MRSA (n = 3), or both (n = 1). Rifabutin was well tolerated with no adverse effects, including uveitis, and no infection recurrences were observed during treatment [32]. While the study focused solely on *Staphylococcus aureus* and did not assess CoNS) [32], *in vitro* findings suggest that rifabutin (in this study) may also exhibit effective activity against CoNS. However, clinical evidence supporting its use in such cases remains limited. Due to its more favorable safety profile and lower potential for drug-drug interactions, rifabutin could serve as a valuable adjuvant therapy for CoNS-related staphylococcal biofilm infections when rifampin is contraindicated. Further large-scale clinical studies are needed to better establish its efficacy and safety in this context. Moreover, an *in vitro* study assessing rifampin, rifabutin, rifapentine, and rifaximin against 200 staphylococcal isolates associated with periprosthetic joint infections (PJIs) revealed that rifabutin exhibited a good bactericidal activity among the agents tested. For *S. epidermidis*, the MBBCs were 0.06. These results highlight rifabutin's promising a good antibacterial efficacy, especially against coagulase-negative *Staphylococci* [33] and suggest its potential as an alternative therapy in cases where rifampin is contraindicated. However, further clinical investigations are necessary to validate these findings. While our study was conducted *in vitro*, recent *in vivo* investigations have demonstrated the intracellular activity of rifampin, rifapentine, and rifabutin against *Staphylococcus epidermidis* in osteoblasts -highlighting their potential efficacy in periprosthetic joint infections. Notably, rifabutin showed significant activity against rifampin-susceptible *S. epidermidis*, suggesting its promise in treating intracellular infections [34]. These findings support future *in vivo* studies to evaluate rifabutin's effectiveness against biofilm-associated CoNS infections in animal models. Despite the promising results, there are limitations to this study. The sample size of certain CoNS species, such as *S. saprophyticus* and *S. lugdunensis*, was small, which may limit the robustness of the data for these species. Further studies with larger sample sizes are needed to confirm the findings and evaluate the clinical relevance of rifabutin for CoNS infections, especially those involving multidrug-resistant strains. Additionally, the impact of biofilm formation on rifabutin's efficacy warrants further investigation, as biofilm-related resistance could influence treatment outcomes.

In conclusion, rifabutin demonstrates consistent and effective antimicrobial activity against CoNS isolates, with relatively uniform MIC values across different species. These findings suggest that rifabutin could be a valuable therapeutic option for managing CoNS infections, especially in the context of multidrug resistance. However, additional studies are required to fully understand the factors influencing its efficacy, including biofilm formation and potential resistance mechanisms.

**Financial Statement:**

This research received no specific grant from any funding agency, commercial entity, or not-for-profit organization.

**Declaration of Interest:**

The authors declare no conflicts of interest related to this study.

**References:**

1. Becker K, Heilmann C, Peters G. Coagulase-negative staphylococci. Clin Microbiol Rev 2014;27;870-926. (PMID: 25278577)

2. Pfaller MA, Herwaldt LA. Laboratory, clinical, and epidemiological aspects of coagulase-negative staphylococci. Clin Microbiol Rev 1988 Jul;1(3):281-99. (PMID: 3058297)

3. Michels R, Last K, Becker SL, Papan C. Update on coagulase-negative staphylococci-what the clinician should know. Microorganisms 2021;9(4):830. (PMID: 33919781)

4. França A. The role of coagulase-negative staphylococci biofilms on late-onset sepsis: current challenges and emerging diagnostics and therapies. Antibiotics (Basel) 2023;12(3):554. (PMID: 36978421)

5. Roy R, Tiwari M, Donelli G, Tiwari V. Strategies for combating bacterial biofilms: a focus on anti-biofilm agents and their mechanisms of action. Virulence 2018;9:522-54. (PMID: 28362216)

6. Von Eiff C, Jansen B, Kohnen W, Becker K. Infection associated with medical devices: pathogenesis, management and prophylaxis. Drugs 2005;65:179-214. (PMID: 15631541)

7. Eltwisy HO, Twisy HO, Hafez MHR, Sayed IM, El-Mokhtar MA. Clinical infections, antibiotic resistance, and pathogenesis of *Staphylococcus haemolyticus*. Microorganisms 2022;10(6):1130. (PMID: 35744647)

8. Natsis NE, Cohen PR. Coagulase-negative *Staphylococcus* skin and soft tissue infections. Am J Clin Dermatol 2018;6:671-7. (PMID: 29882122)

9. Skovdal SM, Jørgensen NP, Meyer RL. JMM Profile: *Staphylococcus epidermidis*. J Med Microbiol 2022;71(10). (PMID: 36306163)

10. Kaye KS, Patel DA, Stephens JM, Khachatryan A, Patel A, Johnson K. Rising United States hospital admissions for acute bacterial skin and skin structure infections: recent trends and economic impact. PLoS One 2015 Nov 24;10(11):e0143276. (PMID: 26599005)

11. Chajecka-Wierzchowska W, Zadernowska A, Nalepa B, Sierpińska M, Laniewska-Trokenheim L. Coagulase-negative staphylococci (CoNS) isolated from ready-to-eat food of animal origin - phenotypic and genotypic antibiotic resistance. Food Microbiol 2015;46:222-6. (PMID: 25475289)

12. Lo TS, Goto M, Hammer KDP. Evaluating the performance of the Alere PBP2a SA Culture Colony Test with the Vitek 2 Antimicrobial Susceptibility Test Card System as reference standard in coagulase-negative Staphylococcus species. Infect Med (Beijing) 2024;3:100126. (PMID: 39291080)

13. Miragaia M. Factors contributing to the evolution of Meca-mediated β-lactam resistance in staphylococci: update and new insights from whole genome sequencing (WGS). Front Microbiol 2018;9:2723. (PMID: 30483235)

14. Lade H, Kim JS. Molecular determinants of β-lactam resistance in methicillin-resistant *Staphylococcus aureus* (MRSA): an updated review. Antibiotics (Basel) 2023;12:1362. (PMID: 37760659)

15. Osman K, Alvarez-Ordóñez A, Ruiz L, et al. Antimicrobial resistance and virulence characterization of *Staphylococcus aureus* and coagulase-negative staphylococci from imported beef meat. Ann Clin Microbiol Antimicrob 2017 May 10;16(1):35. (PMID: 28486995)

16. Ali A, Zahra A, Kamthan M, et al. Microbial biofilms: applications, clinical consequences, and alternative therapies. Microorganisms 2023 Jul 29;11(8):1934. (PMID: 37630494)

17. Dadi NCT, Radochová B, Vargová J, Bujdáková H. Impact of healthcare-associated infections connected to medical devices-an update. Microorganisms 2021 Nov 11;9(11):2332. (PMID: 34835457)

18. Archer GL, Climo MW. Antimicrobial susceptibility of coagulase-negative staphylococci. Antimicrob Agents Chemother 1994; 38:2231-7. (PMID: 7840550)

19. Fontes CO, Silva VL, de Paiva MR, et al. Prevalence, antimicrobial resistance, and virulence characteristics of mecA-encoding coagulase-negative staphylococci isolated from soft cheese in Brazil. J Food Sci 2013;78:M594-9. (PMID: 23488927)

20. Widerström M, Wiström J, Sjöstedt A, Monsen T. Coagulase-negative staphylococci: update on the molecular epidemiology and clinical presentation, with a focus on *Staphylococcus epidermidis* and *Staphylococcus saprophyticus*. Eur J Clin Microbiol Infect Dis 2012;31:7-20. (PMID: 21533877)

21. Ashburn TT, Thor KB. Drug repositioning: identifying and developing new uses for existing drugs. Nat Rev Drug Discov 2004;3: 673-83. (PMID: 15286734)

22. Farid N, Bux K, Ali K, Bashir A, Tahir R. Repurposing amphotericin B: anti-microbial, molecular docking and molecular dynamics simulation studies suggest inhibition potential of amphotericin B against MRSA. BMC Chem 2023;17:67. (PMID: 37386581)

23. Liu Y, Tong Z, Shi J, Li R, Upton M, Wang Z. Drug repurposing for next-generation combination therapies against multidrug-resistant bacteria. Theranostics 2021;11:4910-28. (PMID: 33754035)

24. Schein CH. Repurposing approved drugs for cancer therapy. Br Med Bull 2021;137:13-27. (PMID: 33517358)

25. Crabol Y, Catherinot E, Veziris N, Jullien V, Lortholary O. Rifabutin: where do we stand in 2016? J Antimicrob Chemother 2016;71:1759-71. (PMID: 27009031)

26. Chien JY, Chien ST, Huang SY, Yu CJ. Safety of rifabutin replacing rifampicin in the treatment of tuberculosis: a single-centre retrospective cohort study. J Antimicrob Chemother 2014;69: 790-6. (PMID: 24243988)

27. Pinho JO, Ferreira M, Coelho M, Pinto SN, Aguiar SI, Gaspar MM. Liposomal rifabutin-A promising antibiotic repurposing strategy against methicillin-resistant *Staphylococcus aureus* infections. Pharmaceuticals 2024;17. (PMID: 38675432)

28. Kunin CM. Antimicrobial activity of rifabutin. Clin Infect Dis 1996;22 Suppl 1:S3-S13; discussion S13-4. (PMID: 8785253)

29. Gomes F, Teixeira P, Oliveira R. Mini-review: *Staphylococcus epidermidis* as the most frequent cause of nosocomial infections: Old and new fighting strategies. Biofouling 2014;30:131-41. (PMID: 24283376)

30. Forrest GN, Tamura K. Rifampin combination therapy for non-mycobacterial infections. Clin Microbiol Rev 2010;23:14-34. (PMID: 20065324)

31. Ganipisetti VM, Dudiki N, Athavale A, Bollimunta P, Maringanti BS. Daptomycin-rifampin-induced rhabdomyolysis, acute renal failure, and hepatic injury: a case report and literature review. Cureus 2023;15(3):e36834. (PMID: 37009360)

32. Doub JB, Heil EL, Ntem-Mensah A, Neeley R, Ching PR. Rifabutin use in staphylococcus biofilm infections: A case series. Antibiotics (Basel) 2020;9(6):326. (PMID: 32545793)

33. Albano M, Karau MJ, Greenwood-Quaintance KE, et al. *In vitro* activity of rifampin, rifabutin, rifapentine, and rifaximin against planktonic and biofilm states of staphylococci isolated from periprosthetic joint infection. Antimicrob Agents Chemother 2019;63 (11):e00959-19. (PMID: 31451499)

34. Fisher C, Patel R. Rifampin, rifapentine, and rifabutin are active against intracellular periprosthetic joint infection-associated Staphylococcus epidermidis. Antimicrob Agents Chemother 2021;65(2):e01275-20. (PMID: 33199387)