### A Review Article on the Effectiveness of Rifampin in the Treatment of Staphylococcal Meningitis

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### Abstract

**Introduction:** Staphylococcus aureus is a gram positive bacteria which causes severe infections such as meningitis. Rifampin is widely used as an adjuvant therapy in the treatment of S. aureus infections. Thus, this systematic review is conducted to assess the effect of rifampin in meningitis treatment is similar studies. **Materials and methods:** Current study is a systematic review aimed to assess the effect of S. aureus meningitis. This study was performed by searching Science direct, Medline, Pubmed, Google scholar, SID, Springer, and Scopus databases using rifampin, meningitis, and S. aureus during 2000 to 2018. **Results:** Systematic review of several studies prove the effectiveness of rifampin in the treatment of staphylococcal meningitis. Of the 32 relevant studies, 10 studies which showed the highest effectiveness of rifampin in the treatment of staphylococcal infections were qualitatively analyzed among which 7 studies evaluated the effectiveness of rifampin in the treatment of staphylococcal meningitis and the rest 3 studies evaluated the effectiveness of rifampin and other antibiotics in the treatment of staphylococcal infections. Most studies insisted on the effectiveness of rifampin in the treatment of staphylococcal meningitis. **Discussion:** Results of this study suggested that rifampin reduces the staphylococcal meningitis episodes and to some extent its mortality. As a result, rifampin may be used as an adjutant therapy in staphylococcal meningitis.

Keywords: Meningitis, Staphylococcus Aureus, Rifampin

### INTRODUCTION

Bacterial meningitis is associated with high mortality and morbidity rates, especially in critically ill patients. Initial appropriate antibiotic therapy is the cornerstone in the treatment of bacterial meningitis <sup>[1-5]</sup>. Combination therapy with corticosteroids have greatly improved in the last decade. De gans and Van de beek concluded in 2002 that initial administration of dexamethasone in patients with bacterial meningitis reduced mortality and improved symptom recovery and complication prevention <sup>[6]</sup>. However, using corticosteroids in this setting is associated with many questions and obscurity [7]. Thus, evaluation of the pharmacokinetic and pharmacodynamics properties of antibiotics such as fosfomycin and rifampin showed that these medications are appropriate alternatives for management of bacterial meningitis<sup>[8]</sup>.

S. aureus meningitis is an uncommon disease which accounts for 1-9% of bacterial meningitis<sup>[9]</sup>. The two clinical forms of S. aureus meningitis include: 1) postoperative meningitis which is a nosocomial infection secondary to neurosurgeries and trauma; 2) spontaneous infection secondary to extra-CNS staphylococcal infection <sup>[10-12]</sup>. Most studies on S. aureus report it to be sensitive to methicillin; yet, recent studies indicate increased prevalence of methicillin resistant staphylococcus aureus (MRSA) <sup>[13]</sup>. Most MRSA cases are nosocomial infections manifested after neurosurgeries which is directly associated with mortality of these patients (10-45%) <sup>[14, 15]</sup>. The relationship between higher mortality and MRSA meningitis are reported in different studies <sup>[13]</sup>. Combination therapy is recommended in patients with CSF infection <sup>[16, 17]</sup>.

S. aureus accounts for 1-3% of meningitis cases in the United States, which is associated with a mortality of more than 50% in adults <sup>[18, 19]</sup>. S. aureus meningitis accounts for 0.3-8.8% of all bacterial meningitis cases worldwide <sup>[20-22]</sup>. In the recent years, increasing numbers of S. aureus meningitis are being reported which requires the implementation of a new and different approach in the treatment of these patients <sup>[23-28]</sup>. The

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most common antibiotic for the treatment of is nafcillin in S. aureus meningitis sensitive to methicillin and vancomycin with or without rifampin or trimethoprim/sulfamethoxazole [23, 29-31].

Rifampin is a bactericidal antibiotic which belongs to rifamycin group and form the first line choice treatment for pulmonary tuberculosis combined with isoniazid, ethambutol, and pyrazinamide <sup>[32]</sup>. Results of some studies indicate the positive significant effect of rifampin in the treatment of CNS infections caused by different streptococcal and staphylococcal species <sup>[33, 34]</sup>. Despite effective antibiotic therapy, bacterial meningitis is associated with high mortality and morbidity in both children and adults. Bacterial cell walls compounds of gram positive and grime negative bacteria (endotoxin, peptidoglycan, lipoteichoic acid and teichoic acid) stimulate the release of proinflammatory cytokines leading to meningeal inflammation, increased intracranial pressure, and cerebral edema [35-37]. Release of this compounds to CSF in the bacterial lysis process caused by betalactam antibiotics leads to meningeal inflammation following antibiotic therapy [38, 39]. Rifampin and other bactericidal antibiotics releases less proinflammatory lipoteichoic acid and teichoic acid compared with betalactam antibiotics <sup>[40]</sup>. Moreover, rifampin activates glucocorticoid receptors and thus act as an immunodepresor <sup>[41]</sup>. Current systematic review was conducted to assess the effectiveness of rifampin in the treatment of staphylococcal meningitis.

This systematic review is conducted to assess the effectiveness of rifampin in the treatment of staphylococcal meningitis. This study was performed by searching. The primary search was conducted with Science direct, Medline, Pubmed, Google scholar, SID, Springer, and Scopus databases using rifampin, meningitis, and S. aureus during 2000 to 2018 were identified. In the qualitative assessment of studies, 32 studies were found by searching English electronic sources, 8 of which were excluded for being repetitive.

Two subsets of search terms were used, one describing the rifampin (rifampin alone, rifampin + other antibiotic) and the other describing S. aureus meningitis and rifampin (rifampin alone, rifampin + other antibiotic), which were combined in the search using the 'OR' operator). The two subsets of terms were then combined using the 'AND' operator. Only those publications written in English were included. All pertinent articles were retrieved, and the relative reference lists were systematically reviewed in order to identify further reports that could be included in the systematic review. The full search strategy may be found in (Figure 1). Then, the study abstracts were reviewed by two independent researches; in case of disagreement, a third researcher was consulted. Finally, 18 of the 24 studies were relevant and their full-text was obtained. Reviewing the full-text of articles revealed that 8 articles were irrelevant and thus excluded (Figure 1). Lastly, the rest 10 studies were qualitatively evaluated using checklists.

### METHODS



Figure 1: The flow diagram of resource search and study selection

### RESULTS

In this systematic review, 10 studies were selected using main key words including rifampin, meningitis, and staphylococcus during 2000 to 2018.

### **Table 1.** The results of this systematic review of different articles are summarized in the following table:

Reference Number	First Author	Year	Title	Sample Size	Study Design	Dose	Administration route	Final result
[42]	Bretonnière et al	2015	Rifampin use in acute community-acquired meningitis in intensive care units: the French retrospective cohort ACAM- ICU study	50 patients	RCT	10 mg/kg rifampin BID for 3 months	Intravenous administration – oral	Study population includes a group of adult ICU-admitted patients under rifampin treatment for bacterial meningitis. It was concluded that the mortality rate was lower in patients treated with rifampin.
[43]	Bliziotis et al	2007	Rifampin as adjuvant treatment of Gram-positive bacterial infections	8 articles	Systemati c review	-	-	Results of this study showed that rifampin is beneficial in patients with staphylococcal infections. Though, there are limited evidences on the impact of rifampin on gram positive infections.
[44]	Joshua Perlroth et al	2008	Adjunctive Use of Rifampin for the Treatment of Staphylococcus aureus Infections	101 articles	Systemati c review	-	-	Based on the analysis of others' studies, rifampin can be effective as an adjuvant therapy in staphylococcal infections.
[45]	Kelesidis et al	2011	Combination therapy with daptomycin, linezolid, and rifampin as treatment option for MRSA meningitis and bacteremia	Case report	RCT	- 300 mg linezolid BID - also, 30 mg Rifampin BID	Intravenous administration - oral	Results of this study the effectiveness of daptomycin, linezolid, and rifampin in the treatment of S. aureus meningitis.
[46]	Carmen et al	2008	Efficacy of linezolid (LZD), vancomycin (VAN) and its combinations with rifampin (RIF) in the treatment of experimental meningitis due to methicillin-resistant Staphylococcus aureus	25 patients	RCT	15 mg/kg rifampin single dose (daily)	Oral	The effectiveness of linezolid, vancomycin, and their combinations with rifampin was evaluated in the treatment of MRSA meningitis which showed the impact of rifampin in reducing CSF inflammation and bacteria count.
[47]	Riedel et al	2008	Addition of Rifampin to Standard Therapy for Treatment of Native Valve Infective Endocarditis Caused by Staphylococcus aureus	42 patients	RCT	Rifampin for 20 days	Oral	Results of this study provide evidences to used rifampin as an adjuvant therapy in the treatment f MRSA infections.
[48]	Ju et al	2006	Emergence and spread of rifampicin-resistant, methicillin-resistant Staphylococcus aureus during vancomycin-rifampicin combination therapy in an intensive care unit	44 patients	RCT	Vancomycin- rifampin combination therapy	Oral	Results of this study showed that the effectiveness of adding rifampin to vancomycin is unclear in the treatment of S. aureus infection in ICU-admitted patients.

[49]	Liu et al	2005	Selection of rifampicin- resistant Staphylococcus aureus during tuberculosis therapy: concurrent bacterial eradication and acquisition of resistance	72 patients	RCT	For 2-4 weeks	Oral	Results showed that the desired group had lower resistance and sensitivity to rifampin and tuberculosis infection reduced in the treatment course.
[50]	Legout et al	2014	Factors predictive of treatment failure in staphylococcal prosthetic vascular graft infections: a prospective observational cohort study: impact of rifampin	84 patients	RCT	20 mg/kg rifampin BID	Intravenous administration	In this report, the factors associated with rifampin treatment failure in staphylococcal PVGI was evaluated. Results of this study showed that timely administration of RIF- containing antibiotics are associated with reduced fever, septic shock, and infection.
[51]	Pintado et al	2019	Staphylococcus aureus meningitis in adults: A comparative cohort study of infections caused by meticillin-resistant and meticillin-susceptible strains	350 patients with MRSA staphylococ cal meningitis	RCT	Rifampin for one month	Oral	Evaluation of the clinical and epidemiologic differences between MRSA and MSSA meningitis showed that meningitis severity, underlying disease, and MRSA infection were associated with higher mortality and rifampin was suggested for treatment of these infections.

Table 1 presents 10 articles including 5 articles which assess the effectiveness of rifampin in the treatment of staphylococcal meningitis, 3 articles on the effectiveness of rifampin and other antibiotics in the treatment of staphylococcal infections, and 2 systematic reviews in this regard. All studies insisted on the effectiveness of rifampin administration in the staphylococcal meningitis. According to the results of these studies, rifampin reduced staphylococcal meningitis prevalence and to some extent its mortality.

## The effectiveness of rifampin in the treatment of S. aureus meningitis (42, 51)

Bretonniere et al. study in 2015 and Pintado et al. study in 2018 mainly assess the role of rifampin in the treatment of patients with S. aureus meningitis. Since S. aureus is now resistant to most antibiotics, researchers only assessed the role of rifampin alone. The first study showed the effectiveness of rifampin while the later did not report rifampin effectiveness.

## The effectiveness of rifampin on the staphylococcal infections (43, 44)

Bliziotis et al. systematic review on 8 articles in 2007 and Joshya Perlroth et al. systematic review on 101 articles in 2008 on rifampin administration in patients with staphylococcal infections revealed that rifampin may be a beneficial adjuvant therapy in the treatment of staphylococcal infections. Also, Legout et al. study in 2014 indicated the higher effectiveness of rifampin compared with other antibiotic regimens in the treatment of vascular prosthesis infection caused by S. aureus.

## The effectiveness of rifampin on infectious endocarditis (47)

Riedel evaluated the effect of rifampin in the standard treatment of valvar infectious endocarditis caused by S. aureus which demonstrated the positive effect of rifampin in the treatment of infectious endocarditis caused by S. aureus.

# The effectiveness of combination therapy of rifampin and other antibiotics on staphylococcal infections (45, 46, 48)

Kelesidis et al. (2011) evaluated daptomycin, linezolid, and rifampin combination therapy in the meningitis. Symptom assessment and CSF evaluation of patients revealed the positive effects of combination therapy in the treatment of S. aureus meningitis. Also, Carmen et al. in 2008 evaluated the effect of linezolid, vancomycin, and rifampin in the treatment of S. aureus meningitis and Liu et al. assessed vancomycinrifampin combination therapy. These studies proved the effectiveness of combination therapy in the treatment of S. aureus infection.

### DISCUSSION

#### Individual case studies

Prevalence, complications, and mortality of S. aureus infection is growing in the recent decade. Many clinical evidences show the significant role of rifampin in the

treatment of this infection, especially considering the bactericidal activity and high intracellular concentration of rifampin<sup>[52]</sup>. To evaluate the clinical outcomes of rifampin, authors of this article systematically reviewed the results of studies on the effect of rifampin on the S. aureus meningitis. Results of reviewing these studies revealed that the CSF level of rifampin is higher compared with vancomycin and other antibiotics used in the treatment of S. aureus meningitis. Moreover, rifampin showed desirable effects in the treatment of MSSA and MRSA meningitis and reduced CSF inflammation and bacteria count; this is why the mortality rate was significantly reduced in patients treated with rifampin. The effect of rifampin in the treatment of S. aureus meningitis in ICU-admitted patients was assessed. Patients were treated with 10 mg/kg rifampin twice a day for three months as an adjuvant therapy. In this study mortality of ICUadmitted patients and their GOS was assessed. GOS is widely used to determine the disability caused by severe cerebral injury following CNS disorders including meningeal infections. Findings of this study suggested the positive significant effect of rifampin in reducing the mortality rate of ICU-admitted patients with S. aureus meningitis <sup>[42]</sup>. Kelesidis et al. (2011) conducted a study to evaluate combination therapy with daptomycin, linezolid, and rifampin in methicillin resistant meningitis and bacteremia. In this case report, a 72-year-old man with a history of post traumatic syringolyelia and hydrocephaly was evaluated. This patient was diagnosed with MRSA meningitis. Considering patient's allergy to vancomycin, he was treated with 300 mg IV Linezolid twice a day combined with 300 mg Oral rifampin twice a day. After 6 weeks, evaluation of symptoms and CSF assessment demonstrated the positive and significant effect of rifampin in the treatment of S. aureus meningitis<sup>[45]</sup>. Garrigosc et al. (2008) conducted a study to evaluate the effect of linezolid, vancomycin, and rifampin combination therapy in the treatment of S. aureus meningitis in laboratory rabbits (2-3 kg). A single 15 mg/kg dose of rifampin was administered. Patient CSF was evaluated in 0, 4, 6, and 24 hours in terms of bacterial concentration, WBC number, Lactate and protein concentration. Results of this study suggested that linezolid, vancomycin, and rifampin combination therapy reduces bacterial population and inflammatory parameters of CSF<sup>[46]</sup>. In a similar study aimed to assess the effectiveness of rifampin in the standard treatment of valvar infectious endocarditis caused by S. aureus, 42 patients with valvar infectious endocarditis were evaluated and treated with rifampin for 20 days. The authors concluded that rifampin has positive significant impacts in the treatment of infectious endocarditis caused by S. aureus. Though, rifampin should be added to the standard antibiotic regimen with caution, especially in patients who are infected by HCV since the risk of hepatic complication is significantly increased <sup>[47]</sup>. Another study in 2005 was performed on 44 ICU-admitted patients with MRSA infection to assess the effectiveness of rifampin. Results of this study showed uncertain effect of adding rifampin to vancomycin in the treatment of ICU-admitted patients with S. aureus infections

<sup>[48]</sup>. A study on 72 tuberculosis patients with positive nasal culture for S. aureus was conducted. These patients were treated with anti-tuberculosis regimen (rifampin) for 2-4 weeks. Findings of this study showed reduced number of bacterial count in the nasal culture <sup>[49]</sup>. Legout et al. (2014) studied 84 patients with S. aureus infection caused by implementation of vascular prosthesis under treatment with 20 mg/kg IV rifampin twice a day. Results of their study suggested that this regimen is more effective and reliable compared with most antibiotic regimen in the treatment of S. aureus vascular prosthesis infection <sup>[50]</sup>. Also, Pintado et al. (2018) studied 350 patients with MSSA and MRSA staphylococcal meningitis under rifampin treatment for one month. The results of their study showed that rifampin treatment was not associated with improved survival in these patients <sup>[51]</sup>.

#### Limitations

The present study has several limitations. First, the published experimental studies in the present systematic review, involved only types of RCT studies. Second, we were unable to investigate whether the specific geography zones and dietary types for each study are beneficial in the increase effective of antibiotic therapies. Further studies are required to evaluate this association. Last, we haven't assessed the methodological quality of individual published experimental studies on patients by only using the data shown in each article. Therefore, we might not have assessed the actual performance or biases in individual experimental studies.

### CONCLUSION

This systematic review could show that regardless the microbial resistance against antibiotic therapies (Amoxicillin, Ampicillin, Chloramphenicol, etc.), treatment with rifampin can improved the infection outcome in patients. Results of this study showed that though adding. Consequently, rifampin may be used as an adjuvant therapy in the treatment of S. aureus meningitis. However, further studies in the regard are required.

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