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REVIEW

Rifampin as adjuvant treatment of Gram-positive bacterial infections: a systematic review of comparative clinical trials

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Abstract We reviewed the bibliographic evidence from comparative trials regarding the role of rifampin as adjuvant treatment in the treatment of Gram-positive infections [PubMed (1/1950–7/2006)]. Only studies reporting comparative outcome data in patients treated with an antibiotic regimen with the addition or not of rifampin were included. Eight comparative studies were identified [all were randomized controlled trials (RCTs)], five reporting on infections caused by staphylococci (*S. aureus* in 97% of patients) and three by streptococci. There was no statistically significant difference in mortality between the treatment arms (with and without rifampin) in any of the included studies. Clinical cure was achieved more commonly ($p<0.05$) in the rifampin treatment arm in 3/8 studies; in staphylococcal infections of orthopedic stable implants and in beta-hemolytic streptococcal pharyngitis in children (one RCT each), and in one RCT that reported on patients with various staphylococcal infections. However, no statistically significant difference in cure of the infection between the two groups was found after pooling data from two RCTs (121 patients) that reported on patients with various staphylococcal infections (odds ratio=0.57; 95% confidence interval 0.27–1.17). No differences were noted between the two groups regarding relapse of infection or adverse events. There is only limited evidence from comparative trials regarding the role of rifampin as adjuvant therapeutic agent for infections caused by Gram-positive bacteria, not allowing for definitive conclusions on this important management question. More controlled trials are necessary for better evaluation of this practice.

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Introduction

Rifampin has been commonly used in combination with other drugs for the treatment of tuberculosis. There is evidence derived from various laboratory and clinical studies that this therapeutic agent may also be successfully used in combination with other regimens for the treatment of other infections such as urinary tract infections (UTIs), bone infections, endocarditis, foreign body-related infections, respiratory tract infections, bacterial meningitis, as well as skin and soft-tissue infections [1–4]. Moreover, similarly favorable results have been reported with the use of rifampin as monotherapy or in combination with other agents for the eradication of chronic carriage of Gram-positive bacteria [5, 6].

Guidelines from the Infectious Disease Society of America (IDSA), American Heart Association (AHA), and the British Society for Antimicrobial Chemotherapy (BSAC) have commented on the use of rifampin in combination with other antibacterial agents for the treatment of endocarditis caused by Gram-positive bacteria [7, 8]. More specifically, both the AHA and BSAC guidelines for treatment of infective endocarditis recommend rifampin

as adjunctive therapy for patients with prosthetic valve endocarditis caused by oxacillin-susceptible and resistant coagulase-negative staphylococci and *S. aureus*. The BSAC guidelines also recommend the use of rifampin for native valve endocarditis in combination with vancomycin for patients with endocarditis caused by methicillin-resistant *S. aureus* (MRSA) or for patients who have a penicillin allergy. In addition, the BSAC and Hospital Infection Society and Infection Control Nurses Association recommend the use of rifampin with vancomycin for treatment of prosthetic joint and bone infections caused by MRSA [9].

Although laboratory and non-comparative clinical studies provide some evidence regarding the efficacy and safety of the use of rifampin as an additional antibacterial therapy in infections caused by Gram-positive bacteria [10–13], definitive conclusions for the usefulness of this treatment strategy may be drawn only by comparative (controlled) studies. Thus, we sought to review the available clinical evidence from studies comparing an antibiotic therapy (regimen) with the same therapy combined with rifampin (regimen plus rifampin).

Methods

Data sources

We searched PubMed (1/1950–7/2006) for comparative (randomized or non-randomized) trials. Search terms included "rifampin", "rifampicin", "Gram-positive", "endocarditis", "osteomyelitis", "foreign body infection", "graft infection", "*Staphylococcus*", "*Streptococcus*", "*Enterococcus*", "monotherapy", and "combination", as well as combinations of these terms. In addition, references from the full papers that were reviewed were further examined for relevance.

Study selection

Two reviewers (FN and IB) independently searched the literature and examined the identified relevant studies for further inclusion in the review. A study was considered eligible if it reported comparative data regarding the clinical effects of rifampin when administered as an adjuvant antibacterial therapy for the treatment of infections caused by Gram-positive cocci. The included study should report comparative data regarding the mortality, effectiveness, or toxicity of the two regimens (a regimen without and the same regimen with rifampin added to it). Case reports, case series, and experimental studies were excluded from the analysis. Only studies written in English, German, French, Italian, Spanish, or the Greek language were further reviewed and analysed.

Data extraction

Two reviewers (FN and IAB) independently extracted data from the reviewed studies. Any disagreement between the two reviewers was resolved by consensus in meetings with another author (MEF). The following data were extracted from each study: year of publication, clinical setting, patient population, number of patients receiving each regimen, antimicrobial agents and doses used, and outcomes of treatment, namely mortality, cure and relapse of infection, and toxicity.

Outcomes

All-cause and infection-related mortality, clinical cure, microbiological cure, and relapse of infection, as well as any toxicity observed during treatment, were the outcomes of interest. Cure was defined as the complete resolution of the signs and symptoms of the different infections. Clinical improvement was defined as a significant improvement in patient's clinical condition, without the resolution of all symptom(s) or sign(s) indicative of infection. Clinical failure was defined as a lack of change or deterioration of clinical condition. Relapse was defined as reappearance of symptoms and signs indicative of recessive infection with the same pathogen, after the end of a treatment that was considered to be clinically successful.

Statistical analysis

Dichotomous and continuous variables were compared by chi-square and *t*-test respectively. P value<0.05 denoted statistical significance. Whenever appropriate, pooled odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by the fixed effect model (Mantel-Haenszel) or, in case of heterogeneity, by the random effects model (Der Simonian and Laird). Heterogeneity between trials was assessed by the chi-square test, in which a value<0.1 was considered to denote statistically significant heterogeneity.

Results

Selected studies

We initially retrieved 1,684 studies by our search strategy. After reviewing abstracts and full papers of possibly relevant studies, only eight comparative studies fulfilling our inclusion criteria were identified, all of which were randomized controlled trials (RCTs) [14–21]. The main characteristics of the analyzed studies are summarized in Table 1. As shown, in five studies the effect of the addition of rifampin to antibacterial regimens was evaluated in

Table 1 Characteristics of the reviewed studies

Study (1st author, year of publication)	Type of study	Study population (number of patients)		Type of infection-patient population	Causative pathogen	Regimen	Regimen + rifampin	Mean treatment duration (days)	
		Regimen	Regimen + rifampin					Regimen	Regimen + rifampin
Staphylococcal infections									
Zimmerli 1998	Double blind, placebo-controlled RCT	15	18	Staphylococcal infection associated with stable orthopedic implants	*S. aureus* (26/33) *S. epidermidis* (7/33)	Flucloxacillin 2 g q6h IV or vancomycin 1 g q12h IV for 2 weeks, then ciprofloxacin 750 mg q12h p.o.	Flucloxacillin or vancomycin + rifampin 450 mg q12h p.o. for 2 weeks, then ciprofloxacin + rifampin 450 mg q12h p.o.	90–180*	90–180*
Levine 1991	RCT	22	20	Endocarditis	MRSA	Vancomycin 1 g q12h IV	Vancomycin + rifampin 600 mg q24h p.o.	28	28
Norden 1986	RCT	8	10	Chronic osteomyelitis	*Staphylococcus aureus*	Nafcillin (or cephalothin or cephapirin) 20 mg/kg q4h IV (maximum 12 g/day)	Nafcillin (or cephalothin or cephapirin) + rifampin 300 mg q12h (35–50 kg), 300 mg q8h (51–74 kg), 600 mg q12h (75–100 kg) p.o. (maximum 1,200 mg/day)	42	42
Van der Auwera 1985	Double-blind, placebo-controlled RCT	32	33	Staphylococcal infections**	*Staphylococcus aureus*	Oxacillin 3 g q6h or vancomycin 1 g q12h IV	Oxacillin (or vancomycin) IV + rifampin 600 mg q12h p.o.	21.7	20.2
Van der Auwera 1983	RCT	29	27	Staphylococcal infections**	*Staphylococcus aureus*	Oxacillin 3 g q6h or vancomycin 1 g q12h IV	Oxacillin (or vancomycin) + rifampin 300 mg q12h IV	9 (range 3–28)	15 (range 3–43)
Streptococcal infections									
Klugman 1995	RCT	11	10	Bacterial meningitis in children	Cephalosporin-resistant *Streptococcus pneumoniae*	Ceftriaxone 80 or 100 mg/kg q24h or 50 mg/kg q12h IV	Ceftriaxone + rifampin 10 mg/kg q12h p.o. or via nasogastric tube, during the last 4 days of therapy	NR	NR
Vincent 1993	RCT	11	9	Psoriasis associated with streptococcal infection	Streptococcus beta-hemolytic	Penicillin V or erythromycin 250 mg q6h p.o.	Penicillin V or erythromycin + rifampin 300 mg q12h p.o. during the last 5 days of therapy	14	14
Chaudhary 1985	RCT	39	40	Streptococcal pharyngitis in children	Group A *Streptococci*	Penicillin V potassium 80,000 U/kg/day (max 3,200,000 U/day) q6h p.o.	Penicillin V potassium + rifampin 20 mg/kg/day (max 600 mg/day) q6h. p.o., during the last 4 days of therapy	10	10

patients with infections caused by staphylococci (*S. aureus* in 207/214 patients) [16–19, 21] and in three studies by streptococci [14, 15, 20]. A variety of infections was examined in the analyzed studies. Of note, in the study by Vincent et al. [20] cultural or serologic evidence of beta-hemolytic streptococcal colonization was considered to play a role in the clinical course of specific forms of psoriasis. However, the pathophysiologic mechanism behind this phenomenon was not acknowledged (i.e., it was not known whether true infection by streptococci co-existed with psoriasis). The hypothesis that streptococcal suppression by antibacterial agents could lead to improvement of psoriasis was examined in that study.

Administration of study drugs - duration of treatment

The dose and route of administration of the study drugs, as well as the mean duration of treatment are presented in Table 1. Rifampin was given orally in all but one of the studies [19]. The mean duration of treatment was similar for the two treatment groups (groups with and without rifampin in the treatment regimen) in each of the included studies, with the exception of two studies [15, 19]. However, due to the variety of infections examined in the studies, there were also variations in the duration of treatment from one study to the other. The daily dose of rifampin ranged from 600 mg to 1200 mg.

Mortality

Staphylococcal infections

The outcomes of interest of the included studies are shown in Table 2. All five studies provided data regarding mortality. No deaths occurred in the two studies that reported on patients with osteomyelitis [17, 21]. Both mortality due to infection and all-cause mortality were reported in the two studies by Van der Auwera et al. [18, 19]. There was no statistically significant difference in mortality between the two treatment arms in any of the five included studies. Pooling of the data from the two studies by Van der Auwera et al., which evaluated similar patient populations, showed no statistical significance in all-cause and infection-related mortality between the two treatment groups: OR 1.18; 95% CI 0.34–4.13 (fixed effect model), and OR 3.13; 95% CI 0.60–16.21 (fixed effect model) respectively.

Streptococcal infections

Mortality was reported in two of the three analyzed studies [14, 20]. No deaths occurred in these two studies, a fact explained by the mild infections examined in them (psoriasis and pharyngitis caused by streptococci). However, no data on mortality was reported in the third study, in which the focus was bacterial meningitis in a pediatric population.

Cure of infection

Staphylococcal infections

Eighty-two and 100 patients were evaluated for clinical outcome of infection in the treatment arms without and with rifampin respectively (Table 2). Cure was achieved more commonly ($p<0.05$) in the rifampin treatment arm in two of the included studies [19, 21]. However, statistical significance in favor of the group that received a combination with rifampin, in one of these two studies, was reached only after pooling improved and cured patients (Table 2) [19]. On the other hand, the study by Zimmerli et al. was prematurely discontinued due to the fact that all failures occurred in the same treatment group (the one without adjuvant rifampin) [21]. No statistically significant difference in cure of the infection between the two treatment groups was found after pooling of the data from the two studies by Van der Auwera et al.: OR 0.57; 95% CI 0.27–1.17 (fixed effect model).

Streptococcal infections

In the study by Vincent et al. it was reported that antibiotic treatment (with or without rifampin) had no effect on the course of specific forms of psoriasis, and the study was terminated prematurely [20]. Klugman et al. reported that similar clinical effects were achieved by both regimens (with and without rifampin) in the two groups of children with bacterial meningitis [15]. In addition, in that study it was noted that the addition of rifampin significantly enhanced patients' cerebrospinal fluid bactericidal activity against ceftriaxone-resistant strains that were used for laboratory testing. Finally, Chaudhary et al. reported that the addition of rifampin to penicillin V was accompanied by a statistically significant higher proportion of cure in children with streptococcal pharyngitis, 4–7 days after the end of treatment ($p<0.01$, Table 2) [14].

Relapse

Staphylococcal infections

Relapse was reported in the study that included only patients with chronic osteomyelitis, who were followed up

Table 2 Outcomes of interest in the reviewed studies

Study-1st author & year of publication	Follow-up period		Cure		Mortality		Relapse		Adverse effects	
	Regimen	Regimen + rifampin	Regimen	Regimen + rifampin	Regimen	Regimen + rifampin	Regimen	Regimen + rifampin	Regimen	Regimen + rifampin
Staphylococcal infections										
			Number of patients (%)							
Zimmerli 1998	33 months (range 15–41)	35 months (range 24–26)	7/12 (58%)	12/12 (100%)	0/12 (0%)	0/12 (0%)	NR	NR	1/15 (7%)	2/18 (11%)
Levine 1991	28 days (long-term follow-up was not possible)		15/19 (79%)	16/18 (89%)	2/22 (9%)	1/20 (5%)	NR	NR	NR	NR
Norden 1986	2–4 years (every 6 months for 2 years and then yearly)		4/8 (50%)	8/10 (80%)	0/8 (0%)	0/10 (0%)	3/8 (38%)	1/10 (10%)	3/8 (38%)	1/10 (10%)
Van der Auwera 1985	NR		18/32 (56.2%)*	20/33 (60.6%)*	Due to infection 2/32 (6.25%) All-cause 2/32 (6.25%)	Due to infection 1/33 (3%) All-cause 2/33 (6%)	NR	NR	14/32 (44%)	13/33 (40%)
Van der Auwera 1983	NR		12/29 (41%)**	18/27 (67%)**	Due to infection 4/29 (14%) All-cause 4/29 (14%)	Due to infection 1/27 (4%) All-cause 3/27 (11%)	NR	NR	NR	NR
Streptococcal infections										
			Number of patients (%)							
Klugman 1995	NR		The authors of the study mentioned that both regimens had similar clinical outcomes. Also, the addition of rifampin significantly enhanced cerebrospinal fluid bactericidal activity (against ceftriaxone-resistant strains used for laboratory testing).							
Vincent 1993	42 days		0/11 (0%)	0/9 (0%)	0/11 (0%)	0/9 (0%)	NA	NA	NR	NR
Chaudhary 1985	1st follow-up: 4–7 days after the end of therapy 2nd follow-up: 18–30 days after the end of therapy		28/39 (72%) †	40/40 (100%)	0/39 (0%)	0/40 (0%)	2/39 (5%) ††	6/40 (15%) ††	NA	NA

Abbreviations: NA: non-applicable, NR: not reported

* Clinical improvement was noted in 8/32 (25%) in patients receiving monotherapy and in 9/33 (27.2%) of patients receiving combination with rifampin. If improved and cured patients are combined, then an overall favorable outcome has occurred in 26/32 (81%) patients receiving monotherapy and in 29/33 (88%) patients receiving combination with rifampin ($p=0.06$)

** Clinical improvement was noted in 5/29 (17%) patients receiving monotherapy and in 7/27 (26%) of patients receiving combination with rifampin. If improved and cured patients are combined, then an overall favorable outcome has occurred in 17/29 (59%) patients receiving monotherapy and in 25/27 (93%) patients receiving combination with rifampin ($p<0.001$)

† 8/11 patients that failed had both microbiologic and clinical failure, whereas the other three only had microbiologic failure

†† Refers to 2nd follow-up

for 2–4 years (Table 2). No difference in relapse was found between the two treatment groups in that small study [17].

Streptococcal infections

In the study by Chaudhary et al., clinical and bacteriologic evaluation of monotherapy with penicillin V or combination therapy with rifampin was performed at two instances [14]. Specifically, children were evaluated at 4–7 days and at 28–42 days after treatment, with the first follow-up representing the point at which clinical cure was evaluated. All cases of relapse encountered during the second follow-up were attributed by the authors of that study to reinfection, and are presented in Table 2.

Adverse effects

Adverse effects, mostly mild and always reversible, were reported in three of the five reviewed trials (only in patients with staphylococcal infections). In one more study, only the fact that both regimens were similarly tolerated was mentioned [19]. Three patients had to withdraw from therapy due to adverse effects in the combination regimen (one in the study by Van der Auwera et al. [18] and two in the study by Zimmerli et al. [21]), whereas in three more patients the dosage was decreased due to nausea [21]. One patient in the treatment arm without rifampin was withdrawn from therapy due to toxicity [21].

Adverse effects included mild neutropenia, vomiting, diarrhea, rash, transient eosinophilia, transient mild elevation of serum bilirubin or glutamic-pyruvic transaminase, urticaria, and pain at the injection site. In the study by Norden et al., neutropenia was the main adverse reaction seen in both groups (Table 2), and in all cases it was attributed to nafcillin rather than rifampin. Levine et al. reported six cases of azotemia in the monotherapy group; however, only one could be attributed to the antimicrobial therapy (Table 2). It should be noted that gentamicin was also administered to that patient.

Discussion

The main aim of our review was to assess the available evidence from comparative trials for the use of rifampin as adjuvant therapeutic agent in the treatment of infections caused by Gram-positive bacteria. To our surprise, even though there was quite a large number of case reports and case series available regarding the outcome of infections after the combination of standard treatment with rifampin [10, 12, 22–24], there were only a few controlled trials available that compared the effectiveness and toxicity of a standard treatment with and without the addition of rifampin.

No definitive conclusions can be drawn regarding the possible benefits from the addition of rifampin in standard regimens for the treatment of Gram-positive infections, based on the data from the available comparative (controlled) studies. The only study that provides data clearly in favor of the use of adjuvant rifampin therapy for staphylococcal infections is the study by Zimmerli et al., which focused on patients with orthopedic stable implant-related (both with artificial prostheses and internal fixation devices) infections [21]. There is evidence that combined treatment of ciprofloxacin and rifampin is clinically more effective than ciprofloxacin monotherapy when used as a salvage therapy (i.e., in an attempt to avoid removal of the implant). It should be emphasized that these results can be extrapolated only for patients with recent infections of stable implants (the study included patients with 0–21 days duration of symptoms).

The biologic rationale of using rifampin for foreign-body infections and especially orthopaedic implant infections is the good activity of this agent against microbial biofilms, which are frequently found on surfaces of prosthetic devices or damaged tissue [25–28]. Bacteria contained within biofilms are resistant to antimicrobial therapy, due to poor penetration within the biofilm or because of the nutrient limitations and slow-growth or non-growing nature of these bacteria. Although the results of in-vitro antimicrobial susceptibility testing are generally considered helpful in selecting antimicrobial therapy for infections caused by free growing or planktonic bacteria, they cannot be considered necessarily valid for biofilm-associated bacteria, which are several times less susceptible than free growing or planktonic bacteria to the same agent. Coagulase-negative staphylococci and *S. aureus* are commonly associated with biofilm production, making medical treatment of prosthetic infection difficult. It should be emphasized that in-vitro studies and animal models of device-related infections caused by coagulase-negative staphylococci and *S. aureus* have demonstrated that antimicrobial combinations that included rifampin are effective in treating prosthetic infections caused by staphylococcal species [26, 27].

The data from the three studies that included exclusively [16] or some [18, 19] patients with endocarditis caused by *S. aureus* did not provide sufficient evidence in favour of the use of rifampin as an adjuvant therapy for such infections. Nevertheless, we should acknowledge that, generally, randomized controlled trials cannot be easily performed in patients with staphylococcal endocarditis, due both to the prevalence and severity of disease, and to factors relating to the patient populations affected by it (intravenous drug addicts that are commonly lost to follow-

up and patients with prosthetic valves whose therapy frequently includes surgical treatment) [16, 29]. Thus, we believe that we should accept both the AHA and BSAC guidelines, mentioned in the introduction of this paper, although the reviewed studies do not provide sufficient evidence to support them. Until new RCTs that will evaluate the role of rifampin in the treatment of patients with prosthetic valve endocarditis caused by oxacillin-susceptible and resistant coagulase-negative staphylococci and *S. aureus* are available, the treatment of these serious infections should be based on data from non-comparative clinical and/or laboratory studies [3, 11, 12, 22, 30].

The evidence regarding the role of adjuvant rifampin in the antibiotic regimen for the treatment of infections caused by *S. aureus* in general (regardless of the localization of the infection) should be evaluated with caution. Only two studies have reported on this issue, and pooling of their data showed that neither clinical cure nor mortality is affected by the addition of rifampin to a standard anti-staphylococcal regimen [18, 19]. However, the studies included a rather small number of patients, and they are quite old, a fact which may cause difficulty in the extrapolation of their results in various current clinical settings with high prevalence of MRSA. In addition, no subgroup analyses of specific staphylococcal infections (regarding the site of infection) could be performed using data from these two studies.

The three reviewed studies that reported on patients with streptococcal infections included very heterogeneous types of infections and patient populations [14, 15, 20]. In the study by Vincent et al. it was shown that antibiotic therapy with or without the addition of rifampin offers no benefit in the clinical course of specific forms of psoriasis [20]. In the study by Klugman et al., it was reported that similar clinical results were achieved by ceftriaxone monotherapy and combined treatment with rifampin for the treatment of bacterial meningitis due to *S. pneumoniae* in children [15]. However, the authors did not report further details. Thus, no conclusive evidence was provided regarding this type of infection. In addition, meningitis is an infection with unique pathophysiologic characteristics, and thus results from the aforementioned study can not be extrapolated to patients with other types of infection. Finally, the only study that provided sufficient evidence regarding the role of adjuvant rifampin in streptococcal infections was the study by Chaudhary et al. [14]. However, although in that study the combination of rifampin and penicillin V was found to be superior to monotherapy with the latter, regarding both clinical and microbiological outcomes (results with statistical significance), it should be emphasized that this finding has not been widely adopted in clinical practice mainly because of concerns related to adverse effects and possible promotion of rifampin resistance.

The main limitation of our analysis is that we could identify only a small number of studies reporting comparative data regarding the role of adjuvant rifampin in the treatment of Gram-positive bacterial infections. In addition, some of these studies were rather old, and all of them were small and possibly did not have sufficient statistical power to detect differences between the study groups regarding the outcomes of interest. We should emphasize that there are various explanations for the shortage of relevant RCTs, namely the fact that rifampin was launched at a time when RCTs were less common, the diverse types of the infections in which rifampin was added, the fact that rifampin is considered a first-line antimycobacterial drug and thus it is preserved for mycobacterial infections, and finally the traditional reliance on in-vitro findings when choosing appropriate antibiotic therapies.

Another important limitation is the fact that the infections that were evaluated in the reviewed studies were too heterogeneous, not allowing us to pool the results of the studies in a formal meta-analysis. Similarly, we should acknowledge the variations in rifampin doses/durations and the inclusion of comparators that currently are not widely used in clinical practice (e.g. flucloxacillin). Finally, the results from older studies should be extrapolated taking into account current data regarding antimicrobial resistance of Gram-positive bacteria, as well as changes in the available therapeutic options of infections caused by them.

In conclusion, there is only limited available data from comparative trials regarding the role of adjuvant rifampin in infections caused by Gram-positive bacteria. The addition of rifampin to other antimicrobial regimens was found to be beneficial in patients with orthopedic stable implant-related staphylococcal infections. There is no available evidence from comparative trials in favor or against the use of rifampin for all staphylococcal infections, regardless of the site of infection. The only situation in which adjuvant rifampin was found to be useful against streptococcal infections was pharyngitis caused by beta-hemolytic streptococci, in combination with penicillin V. More controlled trials need to be designed in order to provide stronger evidence regarding the addition of rifampin to treatment for infections caused by Gram-positive bacteria.

Transparency declarations None to declare

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