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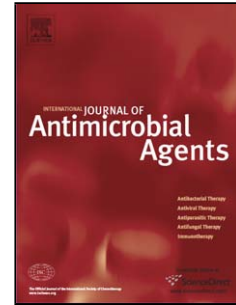
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Rifampicin combined regimens for Gram-negative infections: data from the literature

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ABSTRACT

Multidrug-resistant (MDR) Gram-negative bacterial infections are associated with high morbidity and mortality. Given the lack of availability of new highly effective antimicrobial drugs against multiresistant strains, combination regimens are administered that include rifampicin for its demonstrated in vitro synergism with multiple drugs. A literature review was performed of clinical studies reporting the use of rifampicin in the treatment of MDR Gram-negative bacterial infections. Nineteen studies were found, including only one randomised controlled study. Data in the literature on combined therapeutic regimens with rifampicin are limited and refer mostly to uncontrolled studies. Therefore, the real clinical benefit of using rifampicin-containing therapies for the treatment of Gram-negative multiresistant bacteria in terms of clinical outcome and survival rates still needs to be assessed.

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1. Introduction

Multidrug-resistant (MDR) Gram-negative bacterial infections are associated with high morbidity and mortality [1,2], are more frequently healthcare-associated [1–3] and involve patients in critical settings such as intensive care [4]. Among them, non-fermentative Gram-negative organisms, i.e. *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, are often susceptible only to colistin and occasionally they present pan-resistance [5].

The need to prevent the spread of Gram-negative bacterial infections is actually contrasted by the lack of availability of new antimicrobial drugs that are highly effective against multiresistant strains. Therefore, the use 'old' and disused antimicrobials, such as polymyxins, has been resumed [6,7] and combination therapies including antimicrobials that are synergistic in vitro could be considered [8–15]. Moreover, rifampicin, which is currently used in combination therapies for the treatment of Gram-positive infections, has recently been adopted for the treatment of MDR Gram-negative infections [6,7]. Rifampicin acts by inhibiting DNA-dependent RNA polymerase in bacterial cells, thus preventing transcription to RNA and subsequent translation to proteins.

In vitro studies have already demonstrated the synergistic activity of rifampicin with other antimicrobials, particularly colistin, for the treatment of Gram-negative MDR bacteria, even in those strains with documented resistance to rifampicin alone [15]. Nevertheless, it still remains to be established which are the optimal combinations of rifampicin with other antimicrobials. To assess better the clinical relevance and efficacy of rifampicin against MDR Gram-negative infections, we reviewed the available literature on clinical studies documenting the use of rifampicin in combination with other antimicrobial drugs for the treatment of Gram-negative multiresistant bacterial infections.

2. Methods and results

A review of the literature of clinical studies reporting the use of rifampicin in the treatment of Gram-negative multiresistant bacterial infections was performed. The search was performed through the PubMed database using the following keywords: rifampicin; rifampin; *Acinetobacter*; *Pseudomonas*; *Stenotrophomonas*; *Klebsiella*; *Enterobacter*; and combination treatment. Literature regarding rifampicin combination regimens for other organisms (e.g. *Brucella* spp.) was excluded. Clinical studies reporting the use of rifampicin combination regimens are listed in Table 1.

Overall 19 studies were found published between the years 1992 and 2008, comprising eight observational studies (including five prospective [18,19,22,23,31] and three retrospective studies [25,28,32]), one randomised controlled study [16], eight case reports [12, 17,20,21,24,27,29,33] and two case series [26,30].

The studies referred to the following Gram-negative bacteria: *A. baumannii* (10 studies; 52.6%), of which eight studies included MDR strains and two studies referred to *A. baumannii* strains that were susceptible to imipenem, ticarcillin/clavulanic acid and ampicillin/sulbactam and to gentamicin, ciprofloxacin and ceftriaxone, respectively; *P. aeruginosa* (6 studies; 31.6%), of which five studies included MDR strains; *Acinetobacter ursingii* (1 study; 5.3%); metallo- β -lactamase-producing *Enterobacter cloacae* with intermediate susceptibility to imipenem and full susceptibility to colistin and amikacin (1 study; 5.3%); and *Klebsiella pneumoniae* (1 study; 5.3%).

Acinetobacter baumannii was defined as MDR if isolates were found to be resistant to three of six anti-Gram-negative classes of antimicrobial agents (ureidopenicillins, cephalosporins, carbapenems, quinolones, aminoglycosides and monobactams) [281,29]. Pan-resistant *A.*

baumannii strains were defined as being resistant to antipseudomonal penicillins, cephalosporins, carbapenems, quinolones and aminoglycosides [31]. *Pseudomonas aeruginosa* was considered MDR if it was resistant to three or more classes of antipseudomonal agents (antipseudomonal penicillins, cephalosporins, carbapenems, quinolones, aminoglycosides and monobactams) [25].

The clinical studies on *A. baumannii* infections enrolled 89 patients overall, of which 75 (84.3%) were referred to Intensive Care Units (ICUs) and 1 patient was admitted to an infectious diseases ward; the ward of provenience was not specified for the remaining 13 patients (14.6%).

In the *P. aeruginosa* studies 138 patients were enrolled overall (1 patient was likely described in two studies), of which 1 (0.7%) was an ICU patient, 1 patient was admitted to an infectious diseases ward and 1 patient was referred to the outpatients clinic; for the remaining 135 patients (97.8%) the ward of provenience was not specified.

Acinetobacter baumannii infections reported in the clinical studies ($n = 89$) were as follows: 61 (68.5%) ventilator-associated pneumonia (VAP), of which 4 were associated with bloodstream infections (BSIs) and 2 were associated with surgical site infections; 10 (11.2%) BSIs; 9 (10.1%) hip infection and joint infections of knee prosthesis; 3 (3.4%) intra-abdominal abscesses; 2 (2.2%) meningitis; 1 (1.1%) empyema; 1 (1.1%) venous catheter-related bacteraemia; 1 (1.1%) pneumonia in a non-ICU patient that was associated with skin and soft tissue infection of the lower limb; and 1 (1.1%) chronic community-acquired pneumonia in a patient with pulmonary tuberculosis.

Regarding *P. aeruginosa* infections ($n = 138$), the following clinical diagnoses were reported: 121 (87.7%) bacteraemia; 5 (3.6%) osteomyelitis in diabetic patients; 4 (2.9%) diabetic foot infections without osteomyelitis; 1 (0.7%) patient with non-Hodgkin's lymphoma with abscess of the lungs, perineum and gluteus; 2 (1.4%) cellulitis; 1 (0.7%) central venous catheter-related sepsis in a patient with acquired immune deficiency syndrome (AIDS) and cerebral toxoplasmosis; 1 (0.7%) pneumonia in a patient with common variable immunodeficiency; and 1 (0.7%) VAP; for 2 patients (1.4%) the site of infection was not specified.

The in vitro synergistic activity of rifampicin plus colistin was demonstrated in four of six clinical studies on *P. aeruginosa* infections. Regarding *A. baumannii*, only one study reported in vitro synergism between rifampicin and colistin and of rifampicin plus meropenem [29].

The in vitro synergism between rifampicin and colistin was also reported for *E. cloacae* by Tascini et al. [33].

The cure rate for *P. aeruginosa* infections was 77.9% (53 of 68 patients treated with rifampicin-containing regimens), whereas for *A. baumannii* the cure rate was 74.1% (60 of 81 patients).

The synergistic activities of the drug combinations containing rifampicin were evaluated using the checkerboard method with cation-adjusted Mueller–Hinton broth (Oxoid), which calculates the fractional inhibitory concentration index (FICI) [34]. According to this method, the results of the FICI are categorised as follows: synergistic ($FICI \leq 0.5$); partially synergistic ($0.5 < FICI < 1$); additive ($FICI = 1$); indifferent ($1 < FICI \leq 4$); antagonistic ($FICI > 4$).

The antimicrobial combination regimens for *P. aeruginosa* infections were: rifampicin plus colistin in 10 (14.5%) of 69 patients; rifampicin + colistin + amikacin in 1 patient (1.4%); and rifampicin + β -lactam + aminoglycoside in 58 patients (84.1%). For *A. baumannii*, the antimicrobial combination regimens including rifampicin were: rifampicin + colistin + ampicillin/sulbactam in 5 (6.2%) of 81 patients; rifampicin + colistin in 63 patients (77.8%); rifampicin + meropenem + vancomycin in 1 patient (1.2%); rifampicin + colistin + meropenem in 1 patient (1.2%); rifampicin + imipenem in 10 patients (12.3%); and rifampicin + ethambutol + isoniazid + pyrazinamide in 1 patient (1.2%).

Only one randomised controlled clinical trial was found regarding combination regimens containing rifampicin. Specifically, the authors performed a clinical study on 121 patients with *P. aeruginosa* bacteraemia [16], of which 58 were treated with rifampicin + β -lactam + aminoglycoside whilst the remaining 63 patients received only β -lactam + aminoglycoside. In this study, the cure rate was 75.9% vs. 82.5%, respectively (odds ratio = 1.5, 95% confidence interval 0.57–3.99; $P = 0.364$).

3. Discussion

The two major Gram-negative MDR bacteria for which combination therapy with rifampicin was administered were *A. baumannii* and *P. aeruginosa*. These bacteria are important causes of nosocomial infections, particularly in ICUs, and in the last decade they have represented a considerable burden in terms of increasing incidence, antibiotic resistance and mortality rates [1,2,5,35]. Of note, according to a national microbiological surveillance study, the most common microorganisms isolated among infected patients in the ICU were *P. aeruginosa* (31.8%), methicillin-resistant *Staphylococcus aureus* (14.8%), *A. baumannii*

(12.5%) and *Stenotrophomonas maltophilia* (8.5%) [36]. In the different studies, the rationale for the use of rifampicin was mainly based on the demonstrated synergism of rifampicin with colistin in vitro and in animal studies. Rifampicin is a hydrophobic antibiotic that does not effectively penetrate through the outer membrane of Gram-negative bacteria alone. However, if associated with antibiotics that permeabilise the outer membrane of Gram-negative bacteria (such as colistin), rifampicin may also be effective for Gram-negative bacteria [37,38]. Indeed, it has been observed that the much higher minimum inhibitory concentrations (MICs) of Gram-negative bacteria for rifampicin may not be attributable to a less sensitive target but to reduced penetration of rifampicin through the outer membrane of these organisms [39].

In recent years, rifampicin has been extensively used in association with colistin for MDR Gram-negative infections. Indeed, monotherapy with colistin has been criticised because in some cases it may lead to suboptimal clinical response [18] and to the possible occurrence of resistance [40]. Rifampicin is considered an effective association with colistin for the possible reasons: bactericidal activity; lower toxicity of the association related to the different mechanism of clearance (hepatic, renal); and in vitro synergistic activity. Moreover, the efficacy of rifampicin in association with different antibiotics (colistin, carbapenems) was demonstrated even in the case of documented resistance to rifampicin [8–15,18].

In the study by Korvick et al. [16], the authors evaluated the potential efficacy of rifampicin as an additional antibiotic in combination regimens for the treatment of severe infections associated with high mortality and poor responsive to conventional anti-Gram-negative antibiotics.

From the review of the literature performed here on combination therapies with rifampicin, it was found that almost all the strains of *P. aeruginosa* were MDR (i.e. five of six).

Interestingly, although the antimicrobial susceptibility towards rifampicin was not specified in the different studies, the in vitro synergism test, which was performed in four of the six studies on *P. aeruginosa*, demonstrated synergism between rifampicin and colistin in all cases. Moreover, Tascini et al. [12] also demonstrated the in vitro synergistic activity between colistin, rifampicin and amikacin. The in vitro and also in vivo (animal models) synergistic activity was also demonstrated for *A. baumannii* infections [8,41,42]. In particular, in vitro synergism was demonstrated for MDR carbapenemase-producing *A. baumannii* strains between rifampicin and imipenem, sulbactam/ampicillin and colistin. The association between rifampicin and colistin was also synergistic for isolates that showed higher MICs for rifampicin [8].

In the in vivo animal experimental study conducted by Pantopoulou et al. [42] on neutropenic rats infected with MDR *A. baumannii* strains, the efficacy of colistin was enhanced after co-administration of rifampicin and the results were statistically significant in terms of reduction in mortality rates.

Regarding the clinical advantage in humans of rifampicin-containing regimens over other anti-Gram-negative therapies, we found only one clinical randomised controlled study, specifically on patients with *P. aeruginosa* bacteraemia [16]. As already described in Table 1, the study was a multicentre prospective study and enrolled 121 patients, of which 58 were treated with rifampicin + β -lactam + aminoglycoside whilst the remaining 63 patients were treated only with β -lactam + aminoglycoside. In this study, the difference between the cure rate in the two groups was not statistically significant. Since the findings of this study were based on a single randomised controlled study, which is actually the only one available

in the literature, the real clinical benefit of using rifampicin in the treatment of *P. aeruginosa* infections still needs to be established.

4. Conclusion

Data in the literature on combined therapeutic regimens with rifampicin are limited and refer mostly to uncontrolled studies. Therefore, the real clinical benefit of using rifampicin-containing therapies for the treatment of Gram-negative multiresistant bacteria in terms of clinical outcome and survival rates still needs to be assessed. Randomised controlled clinical studies are needed to confirm the clinical efficacy of rifampicin following its demonstrated in vitro synergism with other anti-Gram-negative drugs such as colistin.

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Competing interests

None declared.

Ethical approval

Not required.

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Table 1

Summary of clinical studies reporting combination regimens including rifampicin (RIF) for Gram-negative bacteria

| Reference; country | Type of study/no. of patients | Pathogen/antibiotic resistance | Site of infection/ward (if specified) | Antimicrobial association | Outcomes |
|--|--|--|---|--|---|
| Korvick et al., 1992 [16]; USA | Multicentre, prospective randomised trial; 121 patients of which 58 treated with RIF- containing regimen | <i>Pseudomonas aeruginosa</i> | Bacteraemia | RIF 600 mg t.i.d. for at least 3 days, then 600 mg b.i.d. for 7 days p.o. + β - lactam + aminoglycoside (58 patients) vs. β - lactam + aminoglycoside (63 patients) | 14 patients died, 44 patients cured vs. 11 patients died, 52 patients cured |
| Tascini et al., 2000 [12]; Italy | Case report | MDR <i>P. aeruginosa</i> (demonstrated in vitro synergism between RIF and COL) | Abscess of the lungs, perineum and gluteus in a patient with non-Hodgkin's lymphoma | RIF 600 mg/24 h i.v. + COL 2 MU/24 h i.v. + AMK 1 g/24 h i.v. | Cured |

| | | | | | |
|-------------------------------------|----------------------------|--|--|--|---|
| Loubinoux et al., 2003 [17]; France | Case report | <i>Acinetobacter ursingii</i> | Bacteraemia in a patient with pulmonary adenocarcinoma undergoing chemotherapy | RIF 1.2 g/24 h + IPM 2 g/24 h i.v. + AMK 900 mg/24 h i.v. | Cured |
| Tascini et al., 2004 [18]; Italy | Prospective, 4 patients | MDR <i>P. aeruginosa</i> (demonstrated in vitro synergism between RIF + COL) | (i) 1 CVC-related sepsis in patient with AIDS and cerebral toxoplasmosis (ii) 1 pneumonia in a patient with common variable immunodeficiency/outpatient clinic (iii) 1 VAP in head trauma/ICU (iv) Multiple abscess of the lungs, perineum and gluteus in patient with non-Hodgkin's lymphoma | (i) RIF 600 mg/24 h i.v. + COL 2 MU b.i.d. i.v. (ii) RIF 600 mg/24 h p.o. + COL 1 MU b.i.d. i.v. + COL 1 MU b.i.d. aerosol (iii) as for (ii) (iv) likely already described (see [12]) | (i) Cured (ii) Cured (iii) Cured (iv) Cured |
| Petrosillo et al., 2005 [19]; Italy | Observational, 14 patients | Carbapenem-resistant <i>Acinetobacter baumannii</i> | 14 VAP/ICU, of which 2 with BSI and 2 SSI | RIF 600 mg/24 h i.v. + COL 2 MU t.i.d. i.v. + A/S (only 5 patients) | 7 died (1 had also <i>Pseudomonas</i> VAP, and 1 had <i>Staphylococcus aureus</i> BSI), 7 cured |

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| Gleeson et al., 2005 [20]; USA | Case report | <i>A. baumannii</i> susceptible to IPM, TIC/CLA and A/S | Meningitis in patient with subarachnoid haemorrhage and ventriculostomy | RIF 600 mg/24 h i.v. + MER i.v. (dose not specified) + VAN (dose not specified) | Cured |
| Sharma et al., 2005 [21]; India | Case report | <i>A. baumannii</i> susceptible to GEN, CIP and CFX | Chronic community-acquired pneumonia in a patient with pulmonary TB under anti-TB treatment containing RIF | RIF 450 mg/24 h p.o. + INH + EMB + PZA | Cured |
| Saballs et al., 2006 [22]; Spain | Prospective clinical study, 14 months, 10 patients | IPM-resistant <i>A. baumannii</i> | (i) 4 VAP/ICU (ii) 3 intra-abdominal abscess/ICU (iii) 1 empyema/ICU (iv) 1 catheter bacteraemia/ICU (v) 1 arthroplasty hip infection/non-ICU | RIF 600 mg/12 h i.v. + IPM 2 g b.i.d. i.v. | (I) 2 cured, 2 died (II) 2 cured, 1 died (III) Cured (IV) Cured (V) Cured |

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| Motaouakkil et al., 2006 [23]; Morocco | Prospective, 13 patients | MDR <i>A. baumannii</i> | 13 VAP/ICU | RIF 10 mg/kg/12 h i.v. + COL 1 MU q.i.d. (i.v. route only in patients with <i>A. baumannii</i> BSI) + COL 1 MU t.i.d. aerosol | 13 cured |
| Tascini et al., 2006 [24]; Italy | Case report | MDR <i>P. aeruginosa</i> (demonstrated in vitro synergism between RIF + COL) | Osteomyelitis of right foot in diabetic patient/infectious disease ward | RIF 600 mg/24 h i.v. + COL 2 MU b.i.d. | Cured |
| Tascini et al., 2006 [25]; Italy | Retrospective, 8 patients of which 3 treated with RIF-containing regimens | MDR <i>P. aeruginosa</i> (demonstrated in vitro synergism between RIF + COL) | 3 diabetic foot infections: (i) 1 with osteomyelitis, (ii) 2 without osteomyelitis (iii) 4 diabetic foot infections: 2 with osteomyelitis and 2 without osteomyelitis (iv) 1 diabetic foot infection with osteomyelitis | (i) RIF + COL 1 MU b.i.d. i.v. (ii) RIF + COL 1 MU b.i.d., of which 1 i.v. and 1 i.m. route (iii) COL 1 MU b.i.d., of which 2 i.v. and 2 i.m. route (iv) COL 1 MU b.i.d. i.v. + IPM | (i) Cured (ii) 1 unchanged ^a , 1 dead (iii) 3 cured, 1 dead (iv) Cured |

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| Ostronoff et al., 2006 [26]; Brazil | Case series, 4 patients of which 2 treated with RIF-containing regimens | MDR <i>P. aeruginosa</i> | 1 phlebitis and cellulitis/ICU in a patient with acute lymphoblastic leukaemia submitted to stem cell transplantation 1 cellulitis of the scalp in a patient with acute myeloblastic leukaemia 2 patients with site of infection not specified | RIF 10 mg/kg b.i.d. i.v. + COL 1 mg/kg b.i.d. i.v. | Cured |
| Memikoglu et al., 2007 [27]; Turkey | Case report | MDR <i>A. baumannii</i> | Meningitis in patient with schwannoma | RIF 10 mg/kg/12 h i.v. + COL 2 g t.i.d. i.v. + COL i.t. | Cured |
| Rodriguez Guardado et al., 2007 [28]; Spain | Retrospective, 8 patients of which 1 treated with RIF-containing regimen | MDR <i>A. baumannii</i> | 5 joint infections of knee prosthesis 3 infections of hip prosthesis | 1 patient treated with RIF 600 mg/24 h i.v. + COL 160 mg t.i.d. i.v. 4 patients treated with COL 160 mg t.i.d. i.v. 3 patients treated with COL + VAN | 1 died, 7 cured |

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| Biancofiore et al., 2007 [29]; Italy | Case report | MDR <i>A. baumannii</i> (demonstrated in vitro synergism between RIF + COL and RIF+ MER) | Pneumonia, SSTI of lower limb with purulent secretion/infectious disease ward | RIF 600 mg/24 h i.v. + COL 2 MU t.i.d. i.v. + MER | Cured |
| Totsugawa et al., 2007 [30]; Japan | Case series, 3 patients | <i>Klebsiella pneumoniae</i> | Mycotic aortic aneurysm/cardiovascular surgery ward | RIF-bonded prosthesis + quinolones (one case) or IPM + NET + CAZ (one case) or IPM + FOS+ quinolones (one case) | Cured |

t.i.d., three times daily; b.i.d., twice a day; p.o., oral; MDR, multidrug resistant; COL, colistin; i.v. intravenous; AMK, amikacin; IPM, imipenem; CVC, central venous catheter; AIDS, acquired immune deficiency syndrome; VAP, ventilator-acquired pneumonia; ICU, Intensive Care Unit; BSI, bloodstream infection; SSI, surgical site infection; A/S, ampicillin/sulbactam; TIC/CLA, ticarcillin/clavulanic; MER, meropenem; VAN, vancomycin; GEN, gentamicin; CIP, ciprofloxacin; CFX, ceftriaxone; TB, tuberculosis; INH, isoniazid; EMB, ethambutol; PZA, pyrazinamide; q.i.d., four times a day; i.m., intramuscular; i.t., intrathecal; SSTI, skin and soft tissue infection; NET, netilmicin; CAZ, ceftazidime; FOS, fosfomicin.

^a Clinical findings worsened or persisted without improvement after 7–14 days of treatment.