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REVIEW ARTICLE

Pharmacology, Dosing, and Side Effects of Rifabutin as a Possible Therapy for Antibiotic-Resistant *Acinetobacter* Infections

Matthew C. Phillips,[1] Noah Wald-Dickler,[1,2] Katherine Loomis,[1] Brian M. Luna,[3] and Brad Spellberg[1]

[1]Los Angeles County + University of Southern California Medical Center, Los Angeles, California, USA, [2]Division of Infectious Diseases, Keck School of Medicine, University of Southern California, Los Angeles, California, USA, and [3]Department of Molecular Microbiology and Immunology, Keck School of Medicine, University of Southern California, Los Angeles, California, USA

Acinetobacter baumannii has among the highest rates of antibiotic resistance encountered in hospitals. New therapies are critically needed. We found that rifabutin has previously unrecognized hyperactivity against most strains of *A. baumannii*. Here we review the pharmacology and adverse effects of rifabutin to inform potential oral dosing strategies in patients with *A. baumannii* infections. Rifabutin demonstrates dose-dependent increases in blood levels up to 900 mg per day, but plateaus thereafter. Furthermore, rifabutin induces its own metabolism after prolonged dosing, lowering its blood levels. Pending future development of an intravenous formulation, a rifabutin oral dose of 900–1200 mg per day for 1 week is a rational choice for adjunctive therapy of *A. baumannii* infections. This dosage maximizes AUC_{24} to drive efficacy while simultaneously minimizing toxicity. Randomized controlled trials will be needed to definitively establish the safety and efficacy of rifabutin to treat *A. baumannii* infections.

Keywords. *Acinetobacter*; pharmacology; optimal dosing; rifabutin.

Antibiotic resistance is one of the greatest challenges confronting 21st century clinical medicine. *Acinetobacter baumannii* is among the most antibiotic-resistant organisms encountered in hospitals and is one of the few bacteria strains that has acquired resistance to all known antibiotics [1, 2]. Extremely drug-resistant (XDR) *A. baumannii*, defined as resistant to all available antibiotics except for those that are inferior in efficacy or more toxic than alternatives, make up >50% of isolates from US intensive care units [3]. Such infections account for >23 000 infections and >10 000 deaths per year in the United States alone [3]. Globally, ~75 000 XDR *A. baumannii* infections occur annually, resulting in 30 000 deaths [3]. There is a critical need for new options to treat these infections.

We recently found that rifabutin possesses hitherto unknown hyperactivity against most strains of *A. baumannii* [4]. Rifabutin, which has been approved for use in humans for >30 years, has minimal inhibitory concentrations (MICs) against *A. baumannii* strains that are >50-fold below those of rifampin. However, this hyperactivity was only detectable in vitro in mammalian culture media, and not in rich broth media, which is traditionally used for MIC testing and new antibiotic screens. This lack of hyperactivity in rich media explains why this phenomenon remained undetected for so many decades. Furthermore, rifabutin's hyperactivity in nutrient-depleted, mammalian cell culture media was predictive of hyperactivity in vivo as well. Rifabutin was far more effective at protecting mice from lethal bloodstream and lung infection caused by *A. baumannii* than rifampin, and at doses >10-fold below those of rifampin.

Rifabutin is a spiropiperidyl rifamycin analog with a larger volume of distribution and longer terminal half-life than rifampin. Food and Drug Administration (FDA)–approved in 1992 for the treatment of tuberculosis, rifabutin is typically used to treat mycobacterial infections in patients with advanced HIV, where complex drug–drug interactions often complicate therapy with rifampin. Compared with rifampin, rifabutin's fewer drug interactions permit its safe co-administration with protease inhibitors; it was widely used in the second and third decades of the HIV pandemic, which led to numerous studies of its clinical and pharmacologic properties [5]. In more recent years, renewed interest has surfaced in rifabutin as salvage therapy in combination with other agents in the treatment of refractory, multidrug-resistant *Helicobacter pylori* gastritis.

To date, experience is limited in dosing rifabutin to treat critically ill patients with acute pyogenic bacterial infections. To help guide clinicians in treating XDR *A. baumannii* infections with the currently available oral formulations of rifabutin, we reviewed and amalgamated the published literature on rifabutin pharmacology, clinical efficacy, and toxicity.

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Correspondence: Brad Spellberg, MD, 30140 Avenida Celestial, Rancho Palos Verdes, CA 90275 (bspellberg@dhs.lacounty.gov).

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METHODS

The PubMed database was searched using the following terms: "rifabutin" in combination with "clinical pharmacokinetics" OR "toxicity." The terms were used in combination with publication type: "clinical trial" OR "review." Smaller observational and pilot studies looking at pharmacokinetics were also included. We reviewed references in identified articles, including review articles. Exceedingly rare toxicities reported only in case reports were excluded. Our search revealed 48 clinical trials and studies and 4 review articles [6–9], from which we abstracted data on rifabutin pharmacokinetics and toxicities in the treatment of human infections.

There are no significant differences in rifabutin pharmacokinetics (PK) between healthy subjects and HIV-infected subjects [8]. However, patients with HIV may require treatment with medications that alter PK parameters, including protease inhibitor antiretrovirals, azole antifungals, and certain macrolide antibacterials. For the purpose of this review, the study arms that included drugs with significant effects on PK parameters were excluded, and all other relevant concomitant drugs were listed.

Patient Consent

This is a literature review; no human subjects research was conducted, so there were no factors necessitating consent.

Pharmacology Overview

At the time of this review, rifabutin is only available in oral capsules with no current intravenous (IV) formulation (Tables 1 and 2). Rifabutin is stable at a broad pH of 2–8 and is highly lipophilic with a pKa of 6.9 [6, 35]. It is rapidly absorbed following oral administration and reaches peak plasma concentrations 2–3 hours after ingestion [9, 23]. However, its overall bioavailability is low, at ~20% after a single oral dose [6, 8, 23]. Furthermore, studies show significant interperson variability of bioavailability with standard 300-mg daily oral dosing [23]. When taken with food, particularly high–fat content food, the rate of absorption is significantly prolonged, with a time to maximum plasma concentration (Tmax) of 5.4 hours (fed) vs 3.0 hours (fasting) and a lag time of 1.6 hours (fed) vs 0.4 hours (fasting) [8, 17].

Although food appears to affect the rate of absorption, it does not impact the extent or fraction of rifabutin absorbed, and the area under the curve for drug concentrations in blood over 24 hours (AUC_{24}) and maximum plasma concentration (Cmax) remains unaffected by food. As a result, rifabutin can be taken with or without food [8].

Rifabutin has a long elimination half-life, with a mean ranging from 31.4 to 58 hours, allowing for ease of once-daily dosing [23]. It is metabolized in the liver, making it safe for use in patients with renal failure without necessitating dose reduction. Owing to its highly lipophilic nature, rifabutin has a very large volume of distribution (8–9 L/kg) and a relatively low Cmax [6, 8]. Its Cmax is dose-dependent, ranging from 0.16 μg/mL after administration of a single 150-mg capsule to 0.9 μg/mL after a single 900-mg administration. Doses >900 mg/d were not associated with further increases in Cmax, ranging from 0.4 μg/mL to 1 μg/mL [23, 24]. Although its Cmax is low, the rifabutin MICs of most *A. baumannii* strains tested in nutrient-depleted media were <0.1 μg/mL [4], readily exceedable by standard rifabutin dosing.

Like its Cmax, rifabutin's AUC_{24} increases in a dose-dependent, approximately proportionate manner up to 900 mg per day (Table 2). At 1200 mg, the AUC_{24} rises slightly and less than proportionately further. The drug's AUC_{24} decreases with chronic use, with a 45% decrease observed in AUC after 21–28 days of daily oral administration [8, 17]. This decline in AUC_{24} was observed across all doses (300–1200 mg per day) studied [23]. This phenomenon is thought to be due to autoinduction of its own hepatic metabolism, as rifabutin is an inducer of cytochrome P450 [23].

The primary PK/pharmacodynamic (PK/PD) driver of rifampin-mediated antibacterial effect is the ratio of AUC_{24} to MIC (AUC_{24}:MIC) [36]. Although less well characterized, rifabutin's PK/PD driver is likely to also be the AUC_{24}/MIC ratio, and indeed in a trial of 169 HIV-positive patients with tuberculous, lower rifabutin AUC_{24}s were associated with a higher rate of treatment failure and development of rifamycin resistance [37]. Thus, chronic dosing may be disadvantageous to its antimicrobial PK/PD driver of AUC_{24}:MIC ratio. High dosing over a short period of time to maximize the AUC/MIC ratio, thus decreasing auto-induction of metabolism that would reduce AUC, may be preferable clinically for acute *A. baumannii* infections.

Tissue Penetration

The lipophilicity of rifabutin allows it to readily cross cell membranes, resulting in a high degree of tissue and intracellular penetration, including in leukocytes, with an intracellular/plasma concentration ratio of 9 in neutrophils and 15 in monocytes [9, 35, 38]. Rifabutin maintains high tissue-to-plasma drug concentration ratios, highlighting its suitability for the treatment of nonbloodstream tissue bacterial infections.

Given its large volume of distribution, rifabutin has favorable tissue penetration into nearly all organ systems. In lung tissue taken from surgical patients, rifabutin reached concentrations up to 8.6 times that of serum [8]. While penetration of rifabutin into the epithelial lining fluid (ELF) has not been studied, other rifamycins have ELF:plasma ratios between 0.2 and 0.32 [39].

Concentrations of rifabutin in urine and bile have been reported to exceed 100 times that of serum, and levels from tissue in the gastrointestinal (GI) tract exceed that of serum as well [8]. Rifabutin also penetrates muscle tissue, albeit at lower concentrations than in serum [9]. Additionally, rifabutin crosses

Table 1. Pharmacokinetics of Rifabutin in Individuals Without HIV

Reference	Study Population	No.	Therapy Duration	Dose, mg, and Frequency	Cmax, μg/mL	AUC_{0-24}, μg-h/mL	Half-life, h
Allen 1998 [10]	Healthy volunteers	11	14 d 24 d	150 QD	0.16 ± 0.03 0.21 ± 0.04	1.61 ± 0.43 1.94 ± 0.48	N/A
Benedetti 1990 [11]	Healthy volunteers	7	1 d 10 d	450 QD 450 QD	0.62 0.61	9.29 5.80	45 ± 6 58 ± 7
Ford 2008 [12]	Healthy volunteers	15	13 d	300 QD	0.31 (0.27–0.37)	6.11 (5.33–7.01)[a]	N/A
Ghannad 2019 [13]	Healthy volunteers	14	10 d	300 QD	0.54	4.22	N/A
Hamzeh 2003 [14]	Healthy volunteers	17	14 d	300 QD	0.40 ± 0.14	3.37 ± 0.86	N/A
Kraft 2004 [15]	Healthy volunteers	10 14	10 d 10 d	300 QD 300 QD	0.29 0.29	2.56 2.87	N/A
La Porte 2009 [16]	Healthy volunteers	20	Single dose	150 once	0.16 (0.06–0.44)	2.22 (0.90–6.03)	41.3 (11.7–84.8)
Narang 1992 [17]	Healthy volunteers	15	Single dose	150 once, fasted (solution) 150 once, with food (capsule) 150 once, fasted (capsule)	0.24 0.16 0.19	2.71[b] 2.41[b] 2.27[b]	N/A
Polk 2001 [18]	Healthy male volunteers	11	14 d	300 QD	0.38 (0.30–0.48)	3.39 (2.84–4.03)	N/A
Sekar 2010 [19]	Healthy volunteers	15	12 d	300 QD	0.57 ± 0.13	4.66 ± 0.97	N/A
van Ingen 2012 [20]	Pulmonary MAC	51	N/A	4.80 ± 1.46 mg/kg	0.52 ± 0.29	2.28 ± 1.31[c]	N/A
Zhang 2011 [21]	Healthy volunteers	11 9	20 d 20 d	150 QD 150 QD	0.19 ± 0.05 0.18 ± 0.06	1.80 ± 0.40 1.80 ± 0.40	N/A
Zhang 2011 [22]	Healthy volunteers	14	10 d	150 QD	0.19 (30)	1.85 (32)	N/A

Abbreviations: AUC, area under the curve; Cmax, maximal concentration; QD, once daily; N/A, not reported in study.

[a]AUC_{0-48}, area under drug-concentration time curve from time of dosing to 48 hours after dosing.

[b]AUC_{0-168}, area under drug-concentration time curve from time of dosing to 168 hours after dosing.

[c]$AUC_{0-6/7}$, area under drug-concentration time curve from time of dosing to 6 or 7 hours after dosing.

the blood–brain barrier, with 1 study finding cerebrospinal fluid (CSF) drug concentrations to be 50% of plasma after a 450-mg daily dose (mean CSF concentration, 0.047 μg/mL) [34]. Taken together, these tissue PK data indicate biologic plausibility for rifabutin in the treatment of a variety of life-threatening clinical infections, including pneumonia, meningitis, and hepatobiliary diseases, such as cholangitis and cholecystitis.

Rifabutin Clinical Toxicities

Historical therapeutic uses for rifamycins, including rifabutin, have primarily involved prolonged (eg, many weeks to months) therapy for chronic infections (Table 3). Such infections include mycobacterial infections and staphylococcal prosthetic endovascular device or orthopedic hardware infections. Furthermore, use of rifabutin in the treatment or prevention of mycobacterial diseases has historically involved treatment courses lasting many months to even years. Such prolonged exposure increases the likelihood of developing drug toxicity. However, the majority of published data suggest that many rifabutin-associated toxicities do not develop until very high doses are used and/or until patients are exposed to the drug for many weeks (Table 3). Although serious hematologic and ocular side effects have been reported after prolonged dosing, in many cases adverse events are reversible with discontinuation of therapy and/or supportive care.

Most published literature on rifabutin-associated toxicities comes from patients with HIV, for whom rifabutin was studied as prophylaxis or treatment of disseminated disease from *Mycobacterium avium complex* (MAC). Early studies of rifabutin sought to replicate its in vitro antiretroviral effects in clinical trials of HIV patients [24, 40]. While ultimately unsuccessful at treating underlying HIV, these trials elucidated prototypic toxicities of rifabutin, such as leukopenia and arthralgias.

Side effects in those early trials of rifabutin monotherapy appeared after prolonged usage at dosages significantly higher than those commonly used today. For example, in a small dose-finding trial of 16 patients with HIV, rifabutin doses of ≥1200 mg resulted in 90% of patients developing arthralgias after the eighth week of the trial [24]. In a separate dose escalation trial, 90% of patients with HIV receiving doses in excess of 1000 mg per day for over 16 weeks also developed arthralgias, which reversed with discontinuation of the drug. Two patients developed reversable uveitis, both after receiving dosages in excess of 1200 mg for 14–16 weeks. A mild, transient leukopenia was seen in 1 of the 16 patients in this dose escalation trial, and a reversable increase in transaminases occurred in 31% of patients after 12 weeks of receiving >1800 mg per day of rifabutin [34]. Leukopenia was also documented in a separate antiretroviral trial in 7% of patients receiving 600 mg of rifabutin, twice per day for 28 days [40].

Table 2. Pharmacokinetics of Rifabutin in HIV-Infected Individuals

Study	Number of Subjects	Relevant Concurrent Medications	Duration of Therapy	Rifabutin Daily Dose, mg	Cmax, Mean ± SD or Median (Range), μg/mL	AUC_{24}, Mean ± SD or Median (Range), μg-h/mL	Half-life, h
Skinner 1989 [23]	5 6 5 5	None	Single dose	300 QD 600 QD 900 QD 1200 QD	0.37 0.52 0.90 0.90	5.4 ± 0.6 10.2 ± 0.6 11.7 ± 3.6 13.2 ± 1.2	38 ± 12 38 ± 13 32 ± 8 38 ± 19
Skinner 1989 [23]	5 6 5 5	None	28 d	300 QD 600 QD 900 QD 1200 QD	0.37 0.52 0.90 0.90	3.9 ± 0.6 3.0 ± 0.6 7.2 ± 2.7 9.6 ± 1.2	38 ± 12 38 ± 13 32 ± 8 38 ± 19
Weiser 1989 [24]	4	None	4–66 wk	2250 QD	0.574	N/A	N/A
Gatti 1999 [25]	10: wasting syndrome 10: no wasting syndrome	AZT (n = 12) DDI (n = 9) TMP-SMX (n = 12)	Single dose Single dose	300 once 300 once	0.34 ± 0.14 0.55 ± 0.16	7.36[a] 7.95[a]	31.446.0
Benetor 2007 [26]	7 with TB	Isoniazid	21 d	300 twice weekly	0.43 (0.34–0.56)	4.10 (3.18–5.27)	N/A
Boulanger 2009 [27]	10 with TB	Isoniazid Pyrazinamide Ethambutol	14–28 d	300 3 times weekly	0.30 (0.15–0.55)	2.71 (1.39–3.98)	N/A
Nguyen 2014 [28]	25 with TB	Isoniazid Pyrazinamide Ethambutol	14 d	300 QD	0.79 (0.34–1.11)	5.64 (2.72–8.88)	N/A
Moyel 2002 [29]	14	None	14 d	300 QD	0.31 (32.8)	3.01 (28.0)	N/A
Trapnell 1996 [30]	12	Zidovudine Fluconazole	14 d: AZT + fluc 14 d: AZT only	300 QD		5.4 ± 2.4 3.03 ± 1.12	N/A
Naiker 2014 [31]	15 with TB	Isoniazid Pyrazinamide Ethambutol	28 d	300 QD	0.29 (0.25–0.38)	3.05 (2.65–3.43)	N/A
Ramachandran 2013 [32]	16 with TB	Isoniazid Pyrazinamide Ethambutol Atazanavir Ritonavir	Minimum 14 d	150 3 times weekly	0.33 (0.19–0.48)	4.61 (2.07–5.34)	N/A
Ramachandran 2019 [33]	45 with TB	Isoniazid Pyrazinamide Ethambutol Atazanavir Ritonavir		300 3 times weekly (n = 36) 150 QD (n = 9)	0.75 (0.52–1.23) 0.58 (0.26–0.81)	9.27 (7.00–12.34) 6.32 (3.91–10.33)	N/A
Siegal 1990 [34]	16	None	4–66 wk	300 QD to 2400 QD (stepwise increase)	0.1 0.6		N/A

Abbreviations: AUC, area under the curve; AZT, zidovudine; fluc, fluconazole; Cmax, maximal concentration; DDI, didanosine; QD, once daily; TB, tuberculosis; TMP/SMX, trimethoprim/sulfamethoxazole.

[a]$AUC_{0\text{-}96}$, area under drug-concentration time curve from time of dosing to 96 hours after dosing.

A multitude of studies investigating rifabutin for MAC prophylaxis and treatment have been conducted in patients with HIV. These trials were conducted with much longer treatment durations, typically 6 months, but with some as long as 2 years. Trials typically utilized dosages of rifabutin between 150 mg and 600 mg per day, with most utilizing the now standard dosage of 300 mg per day. As part of a regimen for prophylaxis against MAC in patients with HIV, rifabutin was used either with or without a macrolide. In trials investigating the use of rifabutin for treatment of pulmonary MAC, rifabutin is typically used as part of a multidrug regimen with ethambutol, macrolides, or aminoglycosides. Side effects in these larger trials most commonly report gastrointestinal intolerance as the most common side effect, occurring in 1 trial in up to 33% of patients receiving rifabutin and azithromycin [51]. Neutropenia was typically seen in dose-dependent frequencies, with up to 31% of patients receiving 600-mg daily doses compared with only 18%–23% of patients receiving dosages between 300 and 450 mg [44–47]. However, it was not seen during the first 1–2 weeks of therapy. Multiple trials also reported arthralgias and elevated transaminases.

As mentioned, uveitis is a well-described, unique, and potentially sight-threatening toxicity associated with rifabutin that is worth special attention. Most reports of rifabutin-associated uveitis occurred only with very high doses over 1200 mg, after many weeks of therapy, and were reversible in most cases with drug discontinuation or topical therapies [34, 50, 57]. In a large trial comparing rifabutin, azithromycin, or the combination of both for MAC prophylaxis, only 5 out of 460 (1.1%) rifabutin recipients developed uveitis [51]. Uveitis was considerably more common when rifabutin was used at a dosage of 450 mg per day. In a trial following nearly 1200 patients over the course of 2 years, 42 patients developed uveitis, primarily those receiving both clarithromycin and rifabutin, between which a significant drug–drug interaction exists. The development of uveitis led to dose reduction of rifabutin from 450 mg to 300 mg. Before

Table 3. Toxicities of Rifabutin

Study	Study Participants Receiving Rifabutin	Incidence	Dose, mg/d	Other Antimicrobials	Time to Toxicity	Reversible?
Leukopenia						
Torseth et al. 1989 [40]	15 AIDS patients	0.45 0.20	600–900 1200	-	28 d	Yes
Nightingale et al. 1993 [41]	566 AIDS patients	0.02	300	-		
Apseloff et al. 1996 [42]	30 healthy adults	.78	300	AZM or CLR	10 d	Yes
Chien et al. 2014 [43]	221 MTB patients	0.06	300	EMB, INH, and PZA		
Gordin et al. 1999 [44]	102 HIV+/MAC+	0.19	300	CLR and EMB		
Benson et al. 2003 [45]	107 HIV+/MAC+	0.23	450	CLR and EMB		
Naiker et al. 2014 [31]	16 HIV+/MTB+	0.44	150	EMB, INH, PZA, and LPV	28–122 d	
Griffith et al. 1995 [46]	26 MAC patients	0.3	600	AZM/CLR, EMB, and STM	Mean: 2.4 ± 2.2 mo	Yes
Griffith et al. 1996 [47]	53 MAC patients	0.31 0.36 0.14 0.09	600 300 600 (MWF) 300 (MWF)	AZM/CLR	3.9 ± 2 mo 3.7 ± 2.6 mo 4 ± 1.7 mo 4.7 ± 3.5 mo	Yes
Siegal et al. 1990 [34]	16 AIDS patients	0.06	1200–1600	-		Yes
Benson et al. 2000 [48]	780 AIDS patients	0.25 0.26	440	- CLR		
Mori et al. 2015 [49]	29 *H. pylori* patients	0.07	300	PPI and AMX		
Ghannad et al. 2019 [13]	14 healthy adults	0.29	300	MVC		
Uveitis						
Siegal et al. 1990 [34]	16 AIDS patients	0.06 0.06	1200 1800	-	16 wk 14 wk	Yes
Shafran et al. 1994 [50]	59 AIDS patients	0.39	600	FCZ and CLR	Mean 65 d	
Chien et al. 2014 [43]	221 MTB patients	0.005	300	EMB, INH, and PZA		
Havlir et al. 1996 [51]	460 AIDS patients	0.01	300	AZM		
May et al. 1997 [52]	72 HIV+/MAC+	.07	450	CLR and EMB		
Gordin et al. 1999 [44]	102 HIV+/MAC+	0.04	300	CLR and EMB		
Benson et al. 2003 [45]	107 HIV+/MAC+	0.07	450	CLR and EMB		
Cohn et al. 1999 [53]	42 HIV+/MAC+	0.02	300	CLR and EMB	8 mo	
Naiker et al. 2014 [31]	16 HIV+/MTB+	0.04	150	EMB, INH, PZA, and LPV	1 mo	
Griffith et al. 1995 [46]	26 MAC patients	0.08	600	AZM/CLR, EMB, and STM	Mean: 2.4 +/- 2.2 mo	Yes
Benson et al. 2000 [48]	780 AIDS patients	0.02 0.09	440	- CLR	18 wk	
Influenza-like illness						
Torseth et al. 1989 [40]	15 AIDS patients	0.53	300–1200	-	24 h	Yes
Chien et al. 2014 [43]	221 MTB patients	0.03	300	EMB, INH, and PZA		
Gastrointestinal symptoms (abdominal pain, nausea, vomiting, diarrhea)						
Nightingale et al. 1993 [41]	566 AIDS patients	0.03	300	-		
Weiser et al. 1989 [24]	16 AIDS patients	0.06	600	-		
Chien et al. 2014 [43]	221 MTB patients	0.04	300	EMB, INH, and PZA		
Havlir et al. 1996 [51]	460 AIDS patients	0.01	300	AZM		
May et al. 1997 [52]	72 HIV+/MAC+	0.07	450	CLR and EMB		
Benson et al. 2003 [45]	107 HIV+/MAC+	0.29	450	CLR and EMB		
Griffith et al. 1995 [46]	26 MAC patients	0.42	600	AZM/CLR, EMB, and STM	Mean: 2.4 +/- 2.2 mo	
Benson et al. 2000 [48]	780 AIDS patients	0.07 0.05	440	- CLR		
Havlir et al. 1996 [51]	460 AIDS patients	0.27	300	AZM		
Fiorini et al. 2018 [54]	256 *H. pylori* patients	0.12	150	PPI and AMX		
Mori et al. 2015 [49]	29 *H. pylori* patients	0.17	300	PPI and AMX		
Sung et al. 2017 [55]	11 *H. pylori* patients	0.01	300	PPI and AMX		
Ribaldone et al. 2019 [56]	302 *H. pylori* patients	0.03	150	PPI and AMX		
Arthralgias						
Weiser et al. 1989 [24]	16 AIDS patients	0.9	>1000	-	8 wk	
Chien et al. 2014 [43]	221 MTB patients	0.02	300	EMB, INH, and PZA		
Griffith et al. 1995 [46]	26 MAC patients	0.19	600	AZM/CLR, EMB, and STM	Mean: 2.4 +/- 2.2 mo	Yes
Siegal et al. 1990 [34]	16 AIDS patients	0.9	>1000	-	16–66 wk	Yes
Havlir et al. 1996 [51]	460 AIDS patients	0.01	300	AZM		
Ghannad et al. 2019 [13]	14 healthy adults	0.14	300	MVC		
Dermatologic events (rash, flushing, hyperpigmentation, etc.)						

Table 3. Continued

Study	Study Participants Receiving Rifabutin	Incidence	Dose, mg/d	Other Antimicrobials	Time to Toxicity	Reversible?
Nightingale et al. 1993 [41]	566 AIDS patients	0.04	300	-		
Chien et al. 2014 [43]	221 MTB patients	0.1	300	EMB, INH, and PZA		
Gordin et al. 1999 [44]	102 HIV+/MAC+	0.16	300	CLR and EMB		
Griffith et al. 1995 [46]	26 MAC patients	0.15	600	AZM/CLR, EMB, and STM	Mean: 2.4 +/- 2.2 mo	
Havlir et al. 1996 [51]	460 AIDS patients	0.02	300	AZM		
Mori et al. 2015 [49]	29 *H. pylori* patients	0.1	300	PPI and AMX		
Elevated liver function tests						
Chien et al. 2014 [43]	221 MTB patients	0.02	300	EMB, INH, and PZA		
May et al. 1997 [52]	72 HIV+/MAC+	0.03	450	CLR and EMB		
Benson et al. 2003 [45]	107 HIV+/MAC+	0.3	450	CLR and EMB		
Naiker et al. 2014 [31]	16 HIV+/MTB+	0.13	150	EMB, INH, PZA, and LPV	96–106 d	
Griffith et al. 1995 [46]	26 MAC patients	0.12	600	AZM/CLR, EMB, and STM	Mean: 2.4 +/- 2.2 mo	
Siegal et al. 1990 [34]	16 AIDS patients	0.83	>1800	-	12 wk	Yes
Benson et al. 2000 [48]	780 AIDS patients	0.06 0.08	440	- CLR		
Mori et al. 2015 [49]	29 *H. pylori* patients	0.17	300	PPI and AMX		
Thrombocytopenia						
Benson et al. 2003 [45]	107 HIV+/MAC+	0.09	450	CLR and EMB		
Griffith et al. 1995 [46]	26 MAC patients	0.15	600	AZM/CLR, EMB, and STM	Mean: 2.4 +/- 2.2 mo	Yes
Siegal et al. 1990 [34]	16 AIDS patients	0.06	1200–1600	-		Yes
Benson et al. 2000 [48]	780 AIDS patients	0.05 0.05	440	- CLR		
Anemia						
Benson et al. 2003 [45]	107 HIV+/MAC+	0.23	450	CLR and EMB		
Siegal et al. 1990 [34]	16 AIDS patients	0.06	1200–1600	-		Yes
Benson et al. 2000 [48]	780 AIDS patients	0.02 0.02	440	- CLR		
Taste disturbances						
Fiorini et al. 2018 [54]	256 *H. pylori* patients	0.02	150	PPI and AMX		
Mori et al. 2015 [49]	29 *H. pylori* patients	0.03	300	PPI and AMX		
Sung et al. 2017 [55]	11 *H. pylori* patients	0.01	300	PPI and AMX		
Headache						
Fiorini et al. 2018 [54]	256 *H. pylori* patients	0.02	150	PPI and AMX		
Mori et al. 2015 [49]	29 *H. pylori* patients	0.28	300	PPI and AMX		
Ribaldone et al. 2019 [56]	302 *H. pylori* patients	<0.01	150	PPI and AMX		
Ghannad et al. 2019 [13]	14 healthy adults	0.29	300	MVC		
Myalgias						
Fiorini et al. 2018 [54]	256 *H. pylori* patients	<0.01	150	PPI and AMX		
Ghannad et al. 2019 [13]	14 healthy adults	0.07	300	MVC		
Fever						
Mori et al. 2015 [49]	29 *H. pylori* patients	0.28	300	PPI and AMX		
Ghannad et al. 2019 [13]	14 healthy adults	0.14	300	MVC		

Toxicities included in the table were those reported in 2 or more manuscripts.

Abbreviations: AMX, amoxicillin; AZM, azithromycin; CLR, clarithromycin; EMB, ethambutol; FCZ, fluconazole; INH, isoniazid; LPV, lopinavir; MAC, *M. avium* complex; MTB, *M. tuberculous*; MVC, maraviroc; MWF, Monday Wednesday Friday dosing; PPI, proton pump inhibitor; PZA, pyrazinamide; STM, streptomycin.

reduction, the uveitis event rate was 5.68 events per 100 patient-years; after the dose reduction, the event rate dropped to 1.40 per 100 patient-years [48]. Similarly, a case–control study of 229 HIV patients with MAC bacteremia treated with 600 mg of rifabutin daily (along with ethambutol and clarithromycin) reported a cumulative risk of uveitis of 43% at 6 months. Following a dose reduction to 300 mg daily, the 6-month cumulative risk of uveitis was dramatically reduced to 13% [58]. As for neutropenia and arthralgias, uveitis has never been described to occur during the first 7–14 days of rifabutin therapy.

More recently, rifabutin has been used in shorter-course treatment regimens as an adjunct for drug-resistant *Helicobacter pylori* infection. These trials primarily used rifabutin in conjunction with a proton pump inhibitor and amoxicillin for between 5 and 14 days of therapy. Side effects in these trials were minimal and consisted primarily of GI toxicities like diarrhea and abdominal pain [49, 54–56]. Leukopenia was relatively rare, only documented in 1 trial [49], and no cases of uveitis have been documented in trials conducted using rifabutin for the treatment of *H. pylori*.

DISCUSSION

We recently found that rifabutin has hyperactivity against *A. baumannii* when tested in nutrient-depleted, mammalian cell culture media and that this effect accurately predicts in vivo efficacy in mice [4]. Randomized controlled trials are needed to establish clinical benefit against *A. baumannii.* However, adjunctive rifampin therapy was shown to significantly reduce bacterial burden when added to standard therapy in a randomized controlled trial of patients with *A. baumannii* pneumonia, suggesting that adjunctive rifamycin therapy may have some therapeutic benefit [59]. Unfortunately, mortality was not improved in this trial, and hence adjunctive rifampin therapy fell out of favor. But rifabutin is >50-fold more potent than rifampin in vitro when tested in nutrient-depleted media. Furthermore, in vivo rifabutin was far more effective at preventing death during lethal bacteremia and pneumonia in mice, including at doses far below those where rifampin demonstrated some efficacy. Thus, rifabutin has promise to improve outcomes relative to adjunctive rifampin.

Rifabutin is approved for use in humans, is inexpensive and generic, is widely available, has excellent tissue penetration, and has a favorable side effect profile. It is safe to use in patients with renal injury, which is present in up to 57% of patients in the critical care setting [60]. Rifabutin reaches therapeutic concentration in tissues relevant to sites of infection caused by *A. baumannii,* including pneumonia, bacteremia, urinary tract infections, and soft tissue infections. Thus, experts may be tempted to add rifabutin to the best-available therapy for these infections given their high mortality and limited alternative therapeutic options [2]. We emphasize the importance of conducting randomized controlled trials to affirm or refute the therapeutic benefit of rifabutin in this context and that having an intravenous formulation available would likely result in superior drug levels. However, until such a formulation and clinical trial results are available, clinicians seeking to use adjunctive rifabutin therapy when confronted by XDR *A. baumannii* infections will need guidance on dosing.

Based on our review of available pharmacokinetic and clinical toxicity data, a high-dose, short-course regimen could achieve the desired balance between maximizing the drug's AUC:MIC ratio to enhance microbial killing, avoiding autoinduction, which diminishes rifabutin blood levels, and minimizing toxicity. Multiple randomized controlled trials have found that 1 week of therapy is adequate to treat nosocomial pneumonia, complicated urinary tract infections, complicated intra-abdominal infections, and severe skin/soft tissue infections [61, 62]. Severe side effects from rifabutin, such as uveitis, arthralgias/arthritis, and leukopenia, have not been described to occur within the first week of therapy, even when very high doses (up to 2400 mg per day) were administered. Thus, dosing for no more than 1 week should enable minimization of side effects, minimizing selection for resistance and still providing adequate potential therapeutic benefit.

The primary question, which dose to administer for that week of therapy, is difficult to define in the absence of controlled clinical trials. Pharmacological studies have found dose-dependent increases in Cmax and AUC_{24} with dose escalation from 150 to 900 mg once per day. With the caveat that only limited published data sets are available, Cmax did not further increase beyond 900 mg, but AUC_{24} slightly increased at a dose of 1200 mg per day. As such, 900–1200 mg once per day for no more than 7 days may be a rational dose to balance the desire to maximize Cmax and AUC_{24} as potential efficacy drivers with the need to minimize toxicity. We emphasize that rifabutin ELF levels are not well established, and this should be a focus of future clinical investigations to help inform pivotal clinical trial conduct. Nevertheless, until such data are available, the plasma:ELF ratios of other rifamycins (0.2–0.32) underscore the need to maximize plasma AUC levels to attempt to achieve adequate ELF levels.

Based on available data, adverse events from such a regimen might reasonably be anticipated to include mild gastrointestinal symptoms and slight increases in hepatic transaminases. Caution would be advised for close laboratory and clinical monitoring for neutropenia and uveitis, particularly in those receiving concurrent CYP3A substrates and in those with underlying liver disease. Many patients studied in the AIDS era with disseminated MAC infections were very seriously ill. However, it is conceivable that acutely ill patients on mechanical ventilators in the intensive care unit may have different propensities for adverse events, as rifabutin and its pharmacokinetics have not been studied in these patients. Thus, as with any off-label drug use, caution should be exercised, with monitoring of hepatic enzymes if adjunctive rifabutin therapy is attempted, particularly in critically ill patients. Furthermore, as an inducer of CYP3A, rifabutin may lower serum concentrations of other medications, including commonly used analgesics in ventilated patients such as fentanyl. Thus careful drug interaction checking should be conducted before using rifabutin in critically ill patients.

Given its relatively poor bioavailability, the development of an intravenous formulation of rifabutin would be ideal given that similar dosages given intravenously (with 100% bioavailability) would result in a 5-fold higher AUC as compared with oral administration. This increased AUC would directly improve the AUC:MIC-dependent killing capacity of rifabutin, thus increasing its efficacy. Despite this limitation, adding rifabutin as an adjunct to current antibiotic therapy in XDR A. *baumannii* infections presents promising potential in addressing the critical need for new therapies to treat infection from this life-threatening pathogen. Rifabutin has already been approved by the FDA, and our review suggests its ideal candidacy for phase III efficacy studies of its role as an adjunctive

therapy for infections caused by *A. baumannii,* particularly those resistant to preferred antimicrobial regimens.

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Potential conflicts of interest. B.L. and B.S. are inventors on a patent for rifabutin therapy for *A. baumannii* infections and own equity in ExBaq, which has licensed the technology for development as an intravenous formulation. The University of Southern California owns intellectual property related to these development efforts. The other authors have no conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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