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MINIREVIEW

Role of Rifampin against Staphylococcal Biofilm Infections *In Vitro*, in Animal Models, and in Orthopedic-Device-Related Infections

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ABSTRACT Rifampin has been used as an agent in combination therapy in orthopedic device-related infections (ODRI) for almost three decades. The aim of this review is to provide data regarding the role of rifampin against biofilm infection *in vitro*, in animal models, and in clinical ODRI. Available data are gathered in order to present the rational use of rifampin combinations in patients with periprosthetic joint infection (PJI). The role of rifampin is well defined in patients with PJI and is indicated in those who fulfill the Infectious Diseases Society of America criteria for debridement and implant retention or one-stage exchange. It should be used with care because of the danger of rapid emergence of resistance. Potential drug interactions should be considered.

KEYWORDS prosthetic joint infection, *Staphylococcus*, rifampin

The role of rifampin in nonmycobacterial infection has been analyzed since the 1970s. Mandell and Vest (1) showed that rifampin kills intracellular staphylococci and has a high efficacy against systemic and local staphylococcal infection in a mouse model. A decade later, Tshefu et al. (2) showed that rifampin could prevent and eliminate experimental staphylococcal implant-associated infections. As first evidence for the clinical role of rifampin combinations against orthopedic implant-related infections (ODRIs), Widmer et al. (3) demonstrated an 82% success rate in 11 patients treated with debridement and implant retention (DAIR) in 1992. However, the clinical role of these rifampin-containing regimens remains controversial even today. One reason for this may lie in the fact that rifampin combination therapy works only reliably in a selected patient group (4, 5).

The efficacy of different antibiotics against device-associated biofilms has been repeatedly tested *in vitro*. The correlation between *in vitro* drug efficacy against biofilm staphylococci and its efficacy *in vivo* is far from perfect. For example, whereas daptomycin was highly effective against a staphylococcal biofilm *in vitro* (6), it failed in an animal model (7). Biofilm tolerance is time dependent and manifests over a few days (8). This may explain part of the discrepancy between *in vitro* and *in vivo* studies where the experimental conditions are not comparable.

SEARCH STRATEGY AND SELECTION CRITERIA

We identified references for this narrative review through searches of PubMed and Embase electronic databases using the following combinations of terms (alternative terms grouped in parentheses): ("prosthetic joint infection" or "periprosthetic joint infection" or "prosthetic knee" or "prosthetic hip" or "prosthetic shoulder") and staphyloc*; ("orthopedic device" or "orthopedic implant") and staphyloc*, using the filter

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"humans"; ("prosthetic joint infection" or "periprosthetic joint infection" or "prosthetic knee" or "prosthetic hip" or "prosthetic shoulder") and staphyloc* and rifamp*; Rifamp* and biofilm and staphylococ*; ("implant" or "device") and rifamp* and staphyloc*, using the filter "other animals". The time frame of the search included publications from 1966 to July 2018. We also consulted book chapters dealing with staphylococcal biofilms and periprosthetic joint infection (PJI).

RIFAMPIN AGAINST BIOFILM STAPHYLOCOCCI *IN VITRO*

Implant-associated infections are difficult to eradicate even with the use of antibiotics which are highly bactericidal *in vitro* against planktonic microorganisms (9, 10). Lacking or slow penetration of an antimicrobial agent in the biofilm cannot be the major reason for tolerance since even vancomycin, a large molecule, has a fair biofilm penetration (10–12). Furthermore, in clinical medicine, prolonged treatment can lead to an accumulation in the extravascular compartment (13). Tolerance of biofilm microorganisms to most antibiotics is not caused by classic resistance mechanisms but depends on multicellular strategies (14). Microorganisms in a biofilm have an anaerobic or microaerobic metabolism, and they downregulate DNA, protein, and cell wall synthesis. This is very different from the behavior of planktonic microorganisms. Bactericidal activity against stationary-phase bacteria *in vitro* has been shown to correlate with the cure rate of implant-associated infection in a tissue-cage animal model. This correlation was shown for *Staphylococcus epidermidis*, *Staphylococcus aureus*, and *Escherichia coli* (15–18). Rifampin performed better than other antibiotics against staphylococcal biofilms *in vitro* when tested under favorable conditions (i.e., tested in combination with another antistaphylococcal agent and an inoculum of $<5 \times 10^6$ CFU) (19–24). However, under unfavorable conditions (i.e., tested as a single agent), biofilm killing by rifampin does not correlate with its good *in vivo* efficacy because of the emergence of resistance (19).

The *rpoB* gene encodes the β subunit of the bacterial RNA polymerase. Mutations in the *rpoB* gene (i.e., a single base pair exchange) results in an amino acid substitution and, consequently, in reduced affinity of the β subunit for rifampin (25). This mechanism has been observed for both *S. aureus* and *S. epidermidis* (25–27). Mutations leading to resistance are associated with a reduction in the level of fitness of the strain *in vitro* (paired competition experiments). However, resistant bacteria generally acquire a compensatory mutation which allow them to persist. Thus, emergence of resistance is clinically relevant and should be prevented by appropriate use of rifampin (28). On the basis of rifampin MIC and population distribution of *S. aureus*, Aubry-Damon et al. (25) proposed a breakpoint of $\leq$0.5 mg/liter in 1998. A decade later, Hellmark et al. (29) demonstrated single nucleotide polymorphisms in the *rpoB* gene of *S. epidermidis* displaying an MIC of 0.25 mg/liter. The current proposed CLSI breakpoint for rifampin is $\leq$1 mg/liter (provided that the compound is not used alone) (30), and the EUCAST breakpoint is $\leq$0.06 mg/liter (31).

A good efficacy against *in vitro* biofilms under favorable conditions, but lack of efficacy in animal models, has been reported (6, 7). These findings are difficult to interpret. The difference may be because microorganisms in so-called young biofilms (i.e., up to 2 to 3 days old) can still be killed by several antibiotics that have no efficacy against implant-associated infections *in vivo* (8).

RIFAMPIN IN IMPLANT-ASSOCIATED INFECTIONS IN ANIMAL MODELS

The ideal animal model for testing antimicrobial efficacy against implant-associated infection should evaluate complete elimination of biofilm bacteria from the device (2, 15, 16, 32). In some experimental models, efficacy is estimated by measuring bacterial counts in the fluid or tissue surrounding the implant. This does not reflect killing of biofilm bacteria since these bacteria are not in biofilm state (33). Therefore, it is important to focus on studies that measure the killing of device-adhering bacteria. The tissue-cage infection animal model simulates human implant-associated infection. This model was introduced to test the pathogenesis of such infections (34, 35). Later, the

TABLE 1 Cure rate in the guinea pig tissue-cage infection model

Microorganism	Antibiotic regime	Cure rate	*P* [a]	Reference
S. epidermidis B3972 (clinical strain)	Ciprofloxacin	0/12 (0 %)	<0.01	Widmer et al. 1990 (15)
	Ciprofloxacin + Rifampin	12/12 (100 %)		
S. aureus ATCC 29213 (MSSA)	Vancomycin	0/12 (0 %)	<0.01	Zimmerli et al. 1994 (16)
	Vancomycin + Rifampin	9/12 (75 %)		
	Ciprofloxacin	2/12 (17 %)	<0.001	
	Ciprofloxacin + Rifampin	11/12 (92 %)		
S. aureus ATCC 29213 (MSSA)	Levofloxacin	0/12 (0 %)	<0.05 for comparisons Levofloxacin alone versus combination therapy	Trampuz et al. 2007 (17)
	Levofloxacin + Rifampin	21/24 (88 %)		
	Levofloxacin + ABI-0043[b]	22/24 (92 %)		
S. aureus ATCC 43300 (MRSA)	Linezolid	0/12 (0 %)	<0.001 for comparisons Linezolid alone versus combination therapy	Baldoni et al. 2009 (36)
	Linezolid + Rifampin	12/20 (60 %)		
	Levofloxacin + Rifampin	20/22 (91 %)		
S. aureus ATCC 43300 (MRSA)	Daptomycin	0/12 (0 %)	<0.001	John et al. 2009 (7)
	Daptomycin + Rifampin	8/12 (67 %)		
S. aureus ATCC 43300 (MRSA)	Dalbavancin	0/12 (0 %)	<0.001	Baldoni et al. 2013 (37)
	Dalbavancin + Rifampin	5/14 (36 %)		
S. aureus ATCC 43300 (MRSA)	Fosfomycin	0/12 (0 %)	<0.001	Mihailescu et al. 2014 (42)
	Fosfomycin + Rifampin	10/12 (83 %)		

[a]Fisher's exact test for categorical variables.
[b]ABI-0043 is a derivative of Rifalazil, which is a rifamycin.

efficacy of different antimicrobial agents against foreign body-associated infection was tested (2, 7, 15–18, 36–42). Table 1 summarizes relevant experiments performed with the tissue-cage infection guinea pig model. In each study, the inoculum was a bacterial suspension containing either $\sim 10^4$ or $\sim 10^6$ CFU of staphylococci. Treatment was started between 24 and 72 h after bacterial inoculation of the tissue cages. All animals were treated for 4 days. Cure was defined as complete absence of the inoculated strain on the explanted device 1 week after stopping antimicrobial therapy. Under these experimental conditions, monotherapy with fluoroquinolones, vancomycin, linezolid, daptomycin, dalbavancin, or fosfomycin fails. In contrast, combination therapy with rifampin is highly efficacious against *S. epidermidis*, methicillin-susceptible *S. aureus* (MSSA), and methicillin-resistant *S. aureus* (MRSA). The excellent bactericidal effect of rifampin against biofilm staphylococci is likely a class effect of rifamycins. Sanchez et al. (43) have shown good effect in four rifamycin derivatives against biofilms *in vitro*. Trampuz et al. (17) demonstrated that, in the tissue-cage infection model, a novel rifamycin derivative (ABI-0043) had the same high cure rate as rifampin. Thus, both antimicrobial susceptibility testing and clinical evaluation of different rifamycins in implant-associated infections should be promoted.

A disadvantage of the described model is the fact that guinea pigs do not support several types of antibiotics (e.g., beta-lactams and clindamycin), and they lose significant weight if antibiotics are given for a prolonged period (i.e., longer than 4 days). Therefore, Lucet et al. (33) tested antimicrobial agents in chronic tissue-cage-associated infections in rats. They started a 6-day treatment course 14 days after infection with MRSA. Under these conditions, no cure was observed. However, rifampin combinations were significantly better at reducing tissue-cage fluid staphylococci than vancomycin or fleroxacin alone. Thus, rifampin short-term treatment was active on planktonic staphylococci but not on the 2-week biofilm of MRSA in this rat model, not even when used as combination therapy. Tshefu et al. (2) could quantify the critical role of the age of the biofilm in the guinea pig tissue-cage infection model. With a treatment delay of up to 12 h, a 2-day therapy could completely eradicate implant-adhering *S. aureus*. When treatment was delayed to 24 and 48 h, the cure rate dropped to 43% and 0%, respectively (2).

In several experimental models, the role of rifampin has been tested in implant-associated osteomyelitis (44–51). Again, the superiority of rifampin combinations could be shown if adequate experimental conditions were chosen. In a wire-associated tibia

osteomyelitis model, combination therapy with vancomycin plus rifampin could completely eradicate MRSA from 7 of 8 (88%) wires (44). In this rat model, a 3-week treatment course was started 4 weeks after infection. Park et al. (48) used the same model and found that wires were sterile in 13 of 13 animals treated with vancomycin plus rifampin but in only 45% of animals treated with tedizolid plus rifampin. Tedizolid could not protect from the emergence of rifampin resistance. Thompson et al. (50) found in a mouse femur implant model that rifampin combination therapy with vancomycin, daptomycin, or linezolid cleared MRSA from a tibia wire in 100% of the mice. Similarly, Niska et al. (46) reported in a mouse model with a Kirschner wire in the femur that *S. aureus* inoculated into a knee joint could be completely eradicated when vancomycin plus rifampin therapy was started 7 days after inoculation and continued for 6 weeks. In contrast to these favorable results, in the study of Jorgensen et al. (45), a 2-week treatment with 11 different antibiotic regimens, including four rifampin combinations, could not eliminate a *S. aureus* biofilm in a tibia implant murine model. In this study, the bacterial inoculum was higher (10^6 CFU versus 10^4 CFU), therapy was started later (11 days versus 7 days), and treatment duration was shorter (14 days versus 6 weeks) than in the Niska study (46). In a rabbit knee prosthesis MRSA infection model, adding rifampin to daptomycin or vancomycin resulted in a higher cure rate than achieved with the regimens without rifampin (100% versus 17% for daptomycin and 75% versus 0% for vancomycin) (47). In this rabbit model, which closely imitates the clinical situation of exogenous PJI, treatment was started at day 7 after infection and continued for 7 days.

Taking these observations together, the efficacy of rifampin combination regimens in subcutaneous- and bone-associated implant infection is well documented in studies that are performed under experimental conditions with (i) low bacterial inoculum, (ii) young biofilm, and (iii) prolonged treatment duration. It is, however, challenging to precisely define these three variables for every implant and host and, moreover, to transfer the findings to humans with ODRI. While the treatment duration can be controlled, the other two variables are difficult to assess at first clinical presentation.

RIFAMPIN IN STAPHYLOCOCCAL PJI IN HUMANS

In a small observational study by Widmer et al. (3) the success rate in 11 patients undergoing DAIR was 82%, indicating a promising activity of rifampin in patients with ODRI. In the following years, mainly retrospective observational studies showed that patients with staphylococcal PJI qualifying for DAIR according to a published algorithm (4) have a success rate between 80% and 95%. In multiple studies in which no rifampin was used, the success rate was only 14% to 68% (52–58). These case series were treated before the publication of an algorithm defining the requirements for the optimal outcome in patients undergoing DAIR (4). Later, multiple studies compared regimens with and without rifampin. However, in these retrospective observational studies, the different treatment regimens were not given in parallel. In a study by Ascione et al. (59), the role of rifampin was tested in 77 patients with hip and knee PJI treated with DAIR, two-stage exchange, or suppressive therapy. The patients who tolerated rifampin throughout the treatment period had the best outcome (91.5% versus 56.7%; $P = 0.0001$). However, in 24% of the patients, rifampin was withdrawn because of adverse events, and not all patients were treated with DAIR. In two other studies, the outcome with rifampin was 81% to 93% and only 41% to 63% without rifampin (60, 61).

DAIR for staphylococcal PJI with a curative approach consists of a rifampin-containing regimen for 3 to 6 months (62). The interpretation of outcome results may be limited in studies with prolonged treatment duration (e.g., mean, 1.5 years in Byren et al. [63]; median, 341 days [interquartile range (IQR), 199 to 398 days] in Peel et al. [64]) or in studies with continued antibiotic suppressive therapy following a defined course of a rifampin-containing regimen. For example, in the study by El Helou et al. (60), three treatment arms were compared in 91 patients with staphylococcal PJI treated with DAIR. The retrospective arms with and without rifampin had similar success rates (68% versus 63%, respectively). Patients in the prospective rifampin arm, who were selected

according to a rational algorithm (4), had a success rate of 93%. Although these results indicate that the rifampin combination therapy in patients improves the outcome provided that Infectious Diseases Society of America (IDSA) criteria for DAIR are fulfilled, the results should be interpreted with caution because of the use of suppressive therapy following the treatment with the rifampin combination.

A randomized controlled study compared the efficacy of a rifampin combination against a placebo combination arm in patients with ODRI (65). In this trial, 33 patients with ODRI (8 hip and 7 knee prostheses and 18 internal fixations) were treated with DAIR. Nine patients dropped out, mainly because of gastrointestinal intolerance. In the per-protocol analysis, the cure rate was 12 of 12 in the rifampin combination group and 7 of 12 (58%) in the control group ($P = 0.02$). After dropout, 7 of 9 cases were treated with a rifampin combination regimen at a lower dose (300 mg twice a day [b.i.d.]), of whom 71.4% were cured. In 8 patients in the rifampin group whose internal fixation device was removed after fracture consolidation, no bacterial growth could be found in the culture of the device. This indicates that suppressive therapy is not needed after rifampin combination therapy as long as the patient has been treated according to a published treatment algorithm (66, 67). In selected cases (e.g., patients with organ damage or end-stage diseases due to multiple comorbidities and at high risk for peri- and postoperative complications), antibiotic suppressive therapy following DAIR may be an option. However, in these cases, rifampin should not be administered. In several observational studies over the following years, the success rate in patients with PJI treated with a defined duration of rifampin combination therapy ranged between 55% and 100% (61, 64, 66, 68–84). This wide range still triggers the discussion on the divergence of outcome results.

From the *in vitro* and *in vivo* studies, we have learned that the young age of biofilm and low bacterial load are important for the success of a rifampin-containing regimen. Damaged skin and soft tissue infections (e.g., sinus tract) are clinical signs of high bacterial inoculum and long duration of disease. In patients with fair skin and soft tissue condition (without sinus tract or subcutaneous abscess), the inoculum and the age of biofilm cannot be perfectly assessed.

The duration of symptoms is used as an imprecise parameter for the duration of infection. The maximum duration of symptoms in the aforementioned randomized trial was 21 days (65). Barberan et al. (69) demonstrated that in patients with symptoms for $\leq$1 month, the success rate was 83.4%, and it dropped to 65.2% and 30.8% in patients with 2 to 6 months and $>$6 months of symptoms, respectively.

In a recent study on the role of adjunctive rifampin for patients with *S. aureus* bacteremia, no overall benefit over standard antibiotic therapy could be observed (85). In a retrospective cohort analysis of *S. aureus* native valve infective endocarditis treated with adjunctive rifampin, 9 (21.4%) of 42 cases developed rifampin resistance before clearance of bacteremia (86). Therefore, "early" administration of rifampin is not recommended as a routine treatment in patients with *S. aureus* without symptoms for a hematogenous implant-associated infection. In patients with PJI, the onset of symptoms may reflect the time point of bacteremia and hematogenous seeding to the implant (87) or, alternatively, reactivation of a previously silent implant-associated infection resulting in bacteremia (88). The differentiation between these two manifestations is clinically challenging. In the latter group, typically presenting late after implantation, the biofilm is not young, the duration of symptoms may be misleading, and therefore the failure rate of DAIR may be higher (83, 84).

In patients with reliably short duration of symptoms and intact skin and soft tissue conditions, Giulieri et al. (80) and Laffer et al. (71) showed an improved success rate of 88% in patients with hip PJI (versus 62% in the group treated not according to the algorithm; $P < 0.03$) and of 92.3% in patients with knee PJI (versus 85.7%, respectively). In two other studies, of the patients with hip PJI ($n = 30$) (66) and different ODRIs ($n = 122$) (67) treated according to the criteria for DAIR, 90% had a successful outcome. In the PJI study, the mean time interval from referral to DAIR was 1.1 (range 0 to 3) days (66, 67). This is shorter than that reported in other studies ($>$3 days in 36.6% of patients

in Byren et al. [63]; median, 7 [IQR, 4 to 14] days in Lora-Tamayo et al. [83]). These results highlight the importance of rapid surgical intervention in addition to the variable "duration of symptoms." The earlier the intervention, the better the prognosis for DAIR in staphylococcal ODRI. The difficulty in assessing the duration of infection by the duration of symptoms may partially explain the different outcome results (76, 89, 90).

In addition, there are interclonal differences of biofilm production among staphylococci (91). Hence, whether a biofilm has to be considered as young or old depends also on the bacterial strain (40). Post et al. (92) recently showed that the cure rate of *S. epidermidis* ODRI correlated with the presence of genes responsible for biofilm formation.

Given the antibiofilm activity of rifampin, it should only be given to patients with staphylococcal ODRI treated with DAIR or one-stage exchange. Indeed, most clinical evidence is from patients who underwent DAIR for PJI. With two-stage exchange with a long interval (>6 weeks), rifampin-treated patients do not have an improved outcome (93). In addition, there is a potential risk for superinfection with rifampin-resistant staphylococci, which are selected on the skin microbiome before reimplantation.

The main adverse events caused by rifampin are anorexia, nausea, and vomiting. In addition, the patient may typically but rarely suffer from hepatotoxicity, myelotoxicity, exanthema, or drug fever. A flu-like syndrome may occur in the case of intermittent treatment. Rifampin is a strong inducer of isoenzymes of cytochrome P450. Therefore, potential drug interactions have to be considered before the start and end of therapy (94).

Taking these observations together, rifampin combination therapy should be reserved for patients managed with DAIR and the following conditions: (i) short duration of staphylococcal infection, (ii) fair skin and soft tissue condition, (iii) stable implant, and (iv) documented susceptibility to rifampin. The biggest challenge in clinical practice is the assessment of the duration of infection.

MODE OF ADMINISTRATION AND RIFAMPIN DOSE AND COMBINATION AGENTS GIVEN IN THE MANAGEMENT OF PATIENTS WITH PJI

The systemic bioavailability of rifampin on an empty stomach is 90% to 100%. Hence, there is no scientific rationale for intravenous administration other than inability to swallow or evidence of poor enteral resorption of any intake. Different regimens have been published for daily dosage and frequency of rifampin administration. They range from 300 mg twice daily (95) or 600 mg once daily (96) to 450 mg twice daily (65) or 900 mg once daily (97). The clinical outcome data do not suggest that one regimen is clearly less effective than the other. In our experience, 900 mg once daily is often not well tolerated.

Fluoroquinolones are ideal combination partners for rifampin, as shown in animal models and in human studies (7, 15–17, 36, 49, 65, 68, 74). In the only controlled trial on the use of rifampin combination therapy in patients with ODRI, ciprofloxacin has been used (65). However, since levofloxacin has a low MIC against staphylococci, many observational studies have been performed with levofloxacin as combination partner (72, 79, 96). Recently, Wouthuyzen-Bakker et al. (74) showed that the success rates in patients with early acute PJI caused by MSSA and treated with DAIR were similar with moxifloxacin/rifampin and levofloxacin/rifampin (89% versus 87.5%).

The rate of development of resistant strains is increasing, especially in MRSA. Klein et al. (98) documented a ciprofloxacin resistance rate of 14% in MSSA and 85% in MRSA in patients with bone and joint infection. Thus, other oral combination partners such as trimethoprim-sulfamethoxazole, clindamycin, minocycline, linezolid, and fusidic acid have been proposed. In a retrospective study, 18 patients with PJI treated with DAIR and a clindamycin/rifampin combination had a cure rate of 78% (82). Tornero et al. (73) showed a lower success rate with the addition of an antibiotic whose level is decreased by rifampin interaction (linezolid, trimethoprim-sulfamethoxazole, or clindamycin) compared to that of the fluoroquinolone combination, with remission in 13 of 21 patients (61.9% remission) versus 49 of 54 patients (90.7% remission). Controversial results have

also been reported with the fusidic acid combination (64, 99). In the study by Peel et al. (64), not all patients fulfilled the requirements for DAIR according to IDSA guidelines; some had a sinus tract or a postoperative PJI with a duration of >1 month (62). In a recently prematurely terminated study, after 6 weeks of rifampin plus fusidic acid therapy, fusidic acid exposures were 40% to 45% lower than expected (99). In addition, it has been recently shown that the combination of fusidic acid and rifampin was efficacious only against 2/6 *S. aureus* strains when tested in a static biofilm model (100). Thus, fusidic acid may not be the optimal partner substance for rifampin.

We previously reviewed some special aspects regarding the use of rifampin in ODRI (101). We contend that rifampin should only be started in patients with a dry wound in order to decrease the risk of superinfection with a rifampin-resistant strain from the skin microbiome. Regarding the appropriate rifampin dose, no universally valid recommendation can be given. It has been shown that adverse events are dose dependent, but the efficacy is not when rifampin is given in combination with levofloxacin (72). In that study, the mean daily dose of rifampin was 16.2 ± 4.3 mg/kg body weight. We still propose 450 mg b.i.d., but decreasing the dose to 300 mg b.i.d. in the case of intolerance or, *a priori*, in elderly patients with high risk of intolerance or slow liver metabolism. Other possibilities in clinical practice dealing with nausea and intolerances include switching to 600 mg once per day (o.d.) taken prior to sleep or switching to rifabutin (300 to 450 mg/day), though there are no published studies on this practice.

CONCLUSION

The excellent efficacy of rifampin against biofilm staphylococci has been shown *in vitro*, in animal models, and in patients with ODRI undergoing DAIR. Rifampin should be used in selected patient groups and with care because of the danger of rapid emergence of resistance (28). It is indicated only in patients who fulfill the IDSA criteria for DAIR or one-stage exchange (62). In clinical practice the assessment of the duration of infection is challenging since it may imprecisely correlate with the duration of symptoms. In each patient, adverse events (nausea, vomiting, or liver toxicity) and potential drug interactions should be considered. This is especially relevant in patients taking oral anticoagulants. The best documented combination partners for rifampin are fluoroquinolones. When other companion drugs are used, potential interactions that lead to decreased drug exposure should be considered.

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