

Diplomarbeit

**Hepatotoxicity and hyperbilirubinemia of fusidic acid
and rifampin: review of literature**

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Abstract

Background. Current recommendations suggest a combination of penicillinase-resistant Penicillin with Rifampin (RMP), Fosfomycin or Fusidic acid (FA) for severe infections with Methicillin-sensitive *Staphylococcus aureus*. Whereas side effects during RMP based on tuberculostatic therapy are well known, data regarding hepatobiliary side effects during RMP or FA treatment of staphylococcal infections are limited. In this literature review hepatobiliary side effects and the underlying mechanisms of FA and RA focussing on treatments of Staphylococcal infections are described.

Methods. For data extraction a literature search was done using different subject headings in MedLine database resulting in 44 articles for RMP and 34 articles for FA respectively, including experimental and clinical studies from 1965 until November 2011.

Results. The main hepatobiliary adverse reaction in studies in which liver alterations in FA treatment are described is an isolated hyperbilirubinemia (4.3-38%), however, generally mild and reversible on cessation of FA. Possible underlying mechanisms may be due to an interference with bile salts and a direct competitive inhibition of bile salt transporters, such as the multidrug-resistant protein 2 (MRP2) and the bile salt export pump (BSEP).

In contrary, RMP predominantly causes elevated transaminase levels and hepatotoxicity, indicating hepatocellular injury. Potential pathomechanisms include direct cytotoxic reactions, interference with tight junctions and bile acid transporters, such as BSEP, MRP2 and organic anion transporting polypeptides (OATPs). The incidence of hepatotoxicity due to RMP (commonly defined as an elevation of aminotransferase levels more than 2-3 times the upper limit of normal, however depending on definition criteria) is generally low or absent (0.08-2 % in latent tuberculosis infection therapy and 2.8-4.3 % in non-mycobacterial infections). Elevations in transaminase levels occur more commonly, but incidences differ (0.1 to 21%).

For both agents a lack of significant clinical information regarding other potential confounders, definition criteria and laboratory data is commonly found in surveyed data, making a critical assessment difficult.

Conclusion. Priorities for future studies include basic studies to elucidate potential pathogenetic mechanisms of hyperbilirubinemia and hepatotoxicity and further controlled clinical studies to assess the clinical use of RMP and FA in patients with staphylococcal infections.

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Glossary and abbreviations

ALT	alanine aminotransferase
AP	alkaline phosphatase
AST	aspartate aminotransferase
AUC	area under the concentration time curve
BSEP	bile salt export pump
CSF	cerebrospinal fluid
CYP	cytochrome
CYP450	cytochrome-P450
DILI	drug-induced liver injury
DILIN	Drug Induced Liver Injury Network
EUCAST	European Committee on Antimicrobial Susceptibility Testing (European Society of Clinical Microbiology and Infectious Diseases)
FA	fusidic acid
GGT	γ -glutamyl-transferase
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
HIV	human immunodeficiency virus
LTBI	Latent tuberculosis infection
MHRA	Medicines and Healthcare products Regulatory Agency
MIC	minimal inhibitory concentration
MRP2	Multi-drug-resistance protein 2
MRSA	Methicillin Resistant Staphylococcus Aureus
MSSA	Methicillin Sensible Staphylococcus Aureus
M. tuberculosis	Mycobacterium tuberculosis
NTCP	Na ⁺ /taurocholate cotransporter peptide
OATP/Oatp	organic anion transporting polypeptide

RMP.....rifampin/rifampicin
S. aureus.....Staphylococcus aureus
S. epidermidis.....Staphylococcus epidermidis
UKUnited Kingdom
ULNupper limit of normal
>.....more than
<.....less than

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1 Introduction

Staphylococcal infections are common, represent an important therapeutic problem and require a highly effective antimicrobial treatment and an adequate management. Current recommendations suggest a combination of penicillinase-resistant Penicillin with Rifampin (RMP), Fosfomycin or Fusidic acid (FA) for severe infections with Methicillin-sensible *Staphylococcus aureus* (MSSA) (1). FA and RMP have both been antimicrobial agents in clinical use for many years, and hepatotoxicity, hyperbilirubinemia and altered liver function tests are adverse drug reactions noted for both.

This review investigates *in vitro* and *in vivo* studies to assess the clinical use of FA and RMP in patients with staphylococcal infections, especially the administration of these drugs for patients with underlying hepatic diseases and the assessment of side effects during treatment. It furthermore evaluates the incidence of hepatobiliary adverse reactions and potential underlying pathomechanisms for both antimicrobial agents.

1.1 Fusidic acid

1.1.1 Background

Fusidic acid (FA) was first introduced into clinical practice as its sodium salt (Fucidin) by Leo Laboratories in Denmark in 1962. FA is not related to any other antibiotics. It is a member of the fusidane class and is isolated from the fungus *Fusidium coccineum*. FA is an antimicrobial agent with steroid-like structure, but without any steroid activity (2,3).

1.1.2 Mechanism of action

FA's antimicrobial effects derive from inhibiting bacterial protein synthesis. It usually shows bacteriostatic qualities, however, it may obtain bactericidal concentrations in serum and several tissues (2,4).

FA blocks bacterial replication by stabilizing elongation factor G of the ribosome, preventing hydrolysis and turnover of guanosine triphosphate, and by blocking elongation of the nascent polypeptide chain, resulting in inhibition of the bacterial protein-synthesis (2). Following degenerative variances lead to cell wall destruction and therefore to the death of the microorganism (3). Nevertheless, the exact mechanisms of FA's antibacterial effects have not been fully resolved yet (2).

1.1.3 Antimicrobial activity and resistance

FA has antibacterial activity against several gram-positive pathogens, and is most active against *Staphylococcus aureus* (*S. aureus*) and *Staphylococcus epidermidis* (*S. epidermidis*). No cross-resistance between FA and β -lactam antimicrobials occurs (2). Resistance generally develops rapidly if FA is used alone, however, may be delayed or prevented by using other antibiotics in combination (4).

Resistance may be chromosome-mediated, likely secondary to changes in the elongation factor, or plasmid-mediated due to reduced membrane permeability (2,3). Generally, chromosomal mutations occur at a frequency of 1 in 10^{-6} to 10^{-7} and are, considering resistance of FA against *S. aureus*, secondary to point mutations within the chromosomal *fusA* gene, which encodes the elongation factor G (2).

According to Mandell (2) the minimal inhibitory concentrations (MICs) for MRSA range from 0.03 to 0.8 mg/L. Proposed breakpoints of FA against *Staphylococci* are ≤ 1 $\mu\text{g/ml}$ for susceptible, 2 $\mu\text{g/ml}$ for intermediate and ≥ 4 $\mu\text{g/ml}$ for resistant (CLSI, Clinical and Laboratory Standards Institute) (5). According to EUCAST (state 2009), clinical MICs < 1 mg/l define susceptibility and > 1 mg/l specify resistance, considering local resistance varieties (3).

Corynebacterium spp., *Neisseria gonorrhoeae*, *Bacteroides fragilis*, *Clostridium* spp, *Propionibacterium acne* and *Meningococcus* spp. are generally susceptible (2,3). FA is not active against most gram-negative microorganisms, such as *Haemophilus influenza*, *Enterobacteriaceae* or *Pseudomonas* spp. and fungi, due to lacking penetration through the cell wall(2,3). Other resistant species include *Streptococci*, such as *Streptococcus pyogenes*, *Str. pneumonia* and *Str. viridians*(3). Aerobic gram-negative bacilli are resistant. Anaerobic pathogens are usually quite susceptible, with the exception of *Fusobacterium necrophorum* (2).

1.1.4 Pharmacokinetics

1.1.4.1 Resorption

FA is almost completely absorbed after oral administration with a total bioavailability of 91 %. Besides oral administration FA may be applied topically or administered parenterally. However, the production of parenteral FA has recently been stopped and is no longer available.

FA achieves maximal concentration (C_{max}) of 11.6 mg/l within 2 hours after a single dose of 250 mg (one pill) and 30.6 mg/l after a single dose of 500 mg. Concomitant ingestion may delay and reduce maximum serum concentration (3).

1.1.4.2 Distribution

FA has a distribution volume of 20 l and is a highly protein bound agent (90 to 97 %) (2,4). It is distributed widely and has good penetration to a number of tissues and fluids, including kidney tissue, cardiac tissue, (infected) bone, joint and soft tissue, burns and skin blisters, synovial fluid, aqueous and vitreous humor, pus and bronchial secretions (2,3). FA achieves a concentration of 70-80 % of serum FA levels in synovial fluids and in pus its concentration is almost 100 % (4). Incidentally, FA also crosses the placenta (2,3).

1.1.4.3 Mean-half-life and metabolism

FA has a half-life of 8 hours after a single dose of 250 mg after 5 days and a mean half-life of 13 hours after an administration of 250 mg twice a day. Considering pharmacokinetic linearity, various studies suggest that FA exhibits nonlinear qualities (2,3).

FA is largely metabolized by the liver and primarily eliminated by non-renal mechanisms, principally by biliary excretion (4). A proportion of the drug is metabolized to several breakdown products, such as 27-carboxyfusidic, fusidic acid 21-glucuronid, 3-ketofusidic-acid and a hydroxyl-derivative called metabolite E (3), which do not have any antibacterial activity (4). The exact mechanisms of FA's metabolism in the liver have not been fully elucidated yet (2,3,6).

No dose adjustments are necessary in case of renal failure. However, celiac disease and severe cholestasis decrease FA clearance, while clearance is increased in presence of hypoalbuminaemia (3).

1.1.5 Drug interactions

FA has a time-dependent activating effect on the hepatic CYP450 enzyme (2,3,6). The concomitant use of FA with HIV-Protease-inhibitors, such as Ritonavir or Saquinavir, elevates plasma concentrations of these agents, resulting in an enhanced risk of adverse hepatotoxic effects. Furthermore, a combination with Cyclosporine may lead to higher plasma concentrations of Cyclosporine and therefore also to hepatic side effects (3). Concurrent use with oral anticoagulants may increase anticoagulative effects due to enhanced plasma concentrations of these agents, requiring dosage adjustments. A combination with alkalizing

substances, such as sodium bicarbonate or antacids should be avoided (3,4). Furthermore, a combination with HMG-CoA reductase inhibitors, such as Atorvastatin or Simvastatin, may lead to elevated creatinine levels, rhabdomyolysis, muscle weakness and muscle pain, making a concomitant use contraindicated (2,3).

1.1.6 Dosing and administration

FA exists in a variety of formulations and may be administered orally, intravenously or topically. Outside the United States it is primarily used for the treatment of staphylococcal infections. FA was not available in the United States but has now been introduced for treatment of skin and soft tissue infections (2,3,7). Administration of FA against infections with or without bacteremia includes endocarditis, acute and chronic osteomyelitis, traumatic and surgical wound infections, septic arthritis, skin and soft tissue infections, such as abscesses, cellulitis and burn-infections, lower respiratory tract infections and liver or spleen abscesses (2,3).

In case of severe infections or long-term treatment a combination with other antibiotics is recommended to minimize the risk of resistance and obtain additive or synergistic effects. Therefore, penicillinase-resistant Penicillin, such as Flucloxacillin, Erythromycin, Rifampin, Clindamycin or effective cephalosporins are preferred agents (2,3). According to Mandell (2), resistance occurs in 0 to 2 % of patients when FA is used alone in treatment of acute infections, whereas resistance is seen in less than 1 % of patients treated concomitantly with other antibiotics (2).

The dosage of FA depends upon age, bodyweight, liver function, kind of infection and susceptibility of the pathogen. Clinical drug information data for adults and adolescents older than 12 years and up to 70 kg recommend a dosage of 2 film-coated tablets of 250 mg sodium fusidate 3 times a day, and for the same group but heavier than 70 kg 2 film-coated tablets 4 times a day. 20-35 mg/kg bodyweight divided in 3-4 similar doses are recommended for children older than 6 years (3).

1.1.7 Adverse effects

Frequent adverse events of FA depend on the route of administration. Oral administration is well tolerated, however, associated with mild gastrointestinal side effects. After intravenous administration thrombophlebitis has been observed and gastrointestinal side effects are common, dose-dependent and often combined with general symptoms such as fatigue, malaise

and adynamia. Most events occur at low frequency, including different skin reactions, hematological disorders and hypersensitivity reactions. Reversible jaundice is noted to occur commonly ($\geq 1/100$, $< 1/10$) (2,3).

Gastrointestinal

Gastrointestinal effects are common ($\geq 1/100$, $< 1/10$) including nausea, vomiting, diarrhea, flatulence and abdominal pain. Anorexia occurs frequently ($\geq 1/1.000$, $< 1/100$) (2,3,7).

Immunological

Allergic reactions occur rarely ($\geq 1/10.000$, $< 1/1.000$) and anaphylactic shock very rarely ($\geq 1/10.000$) (3,7).

Hematological and lymphatic

Leukopenia, thrombocytopenia, pancytopenia, anemia and hematological disorders including neutropenia and agranulocytosis have been noted, but occur very rarely (3,7).

Dermatological

Skin reactions, such as rash, including erythematous, maculo-papulose and pustular alterations, pruritus and urticaria are common (3,7).

Renal

Acute kidney failure occurs very rarely, however, has been noted in patients with jaundice and in combination with other factors facilitating kidney failure. Incidentally, the drug is not significantly removed by hemodialysis (3).

Liver and bile

Reversible jaundice is commonly seen with both oral preparation and intravenous formulation but occurs to a lesser extent after oral administration. Furthermore, elevated liver enzymes and hyperbilirubinemia have been noted. FA is highly protein bound. Systemic administered FA competitively inhibits the binding of bilirubin to albumin and, therefore, should be used with caution in patients with disorders in bilirubin-transport and metabolism, particularly in newborns. Case reports of hepatotoxicity are noted in drug information data (2-4,7).

Others

Rhabdomyolysis was noted if administered in combination with statins. Symptoms include muscle weakness, muscle swelling and muscle pain, dark urine, myoglobinuria, elevated creatine kinase, acute kidney failure and cardiac arrhythmia (2,3,7).

Topical ophthalmic use of FA may cause mild local symptoms, such as stinging or itching (2,3,7).

1.1.8 Contraindications

According to drug information data FA should be used with caution in patients with liver impairment and is contraindicated in concomitant use with statins, such as Simvastatin and Atorvastatin (8).

1.2 Rifampin

1.2.1 Background

Rifampin (RMP) is a key component of antimycobacterial therapy and is one of the most potent broad spectrum antibiotics. It is a semi-synthetic antibiotic and derivate of Rifamycin SV, produced by *Streptomyces mediterranei*, which was first isolated in Milan in 1957. Rifamycin SV was introduced and first used clinically in 1963. Modifications were made regarding its bioavailability and antibacterial activity. In 1968, RMP was first introduced for clinical trials in tuberculosis (9-11). Following variations concerning pharmacokinetic properties and antimicrobial activity led to further semisynthetic rifamycins, including Rifabutin, Rifapentine, Rifaximine and Rifalazil (11).

Besides its utilization against tuberculosis, RMP is also recommended as a prophylactic agent to reduce the risk of secondary cases of infection and for eradication of an asymptomatic carrier state of *H. influenza* and *Neisseria meningitidis*. Moreover, RMP is recommended in combination therapy for severe staphylococcal infections (1,8,11-13).

1.2.2 Mechanism of action

RMP and other rifamycins (e.g. Rifapentine) are bactericidal, as they inhibit DNA-dependent RNA polymerase (14), for example, in susceptible strains of *Mycobacterium tuberculosis* (*M. tuberculosis*). Campbell et al. showed in 2001 that RMP contacts close with the RNA β subunit and binds deep within the binding pocket of the DNA-dependent RNA, upstream of the catalytic center. The mechanism of inhibition is a steric block of RNA transcription elongation, resulting in inhibition of the bacterial protein-synthesis (11,15).

1.2.3 Antimicrobial Activity and Resistance

The primary use of RMP is often focused on the treatment of *M. tuberculosis*, and at that point mainly against intracellular pathogens. Nevertheless, RMP is active against both actively replicating *M. tuberculosis* and intracellular, slowly replicating bacilli. Against nearly dormant organisms in necrotic foci it is less but somewhat active. Besides, RMP also demonstrates in vitro activity against *Mycobacterium bovis*, *M. kansasii* and *M. lepreae*, three atypical strains (8,10,13,14). The impact of activity is better in neutral or alkaline environment than in acidic milieu (8).

For non-mycobacterial diseases RMP is active (MIC ≤ 1 $\mu\text{g/mL}$) in vitro against *S. aureus* and *S. epidermidis*, streptococcal organisms such as Group A and B streptococci, *Streptococcus pyogenes*, *Streptococcus pneumoniae* and viridans streptococci, and *Listeria monocytogenes*. Moreover, RMP has demonstrated activity against *Neisseria meningitidis*, *N. gonorrhoeae*, *H. influenzae*, *Brucella* spp., *Legionella* spp. and *Moraxella catarrhalis* (8,11-13).

Resistant species are gram-negative rods like *E. coli*, *Klebsiella* spp. *Proteus* spp., *Pseudomonas aeruginosa* (rare strains are susceptible), *Salmonella* spp., *Shigella* spp. and other microorganisms, such as *Chlamydia* spp and *Mycoplasma* spp (8,12).

RMP should be administered in combination with another active antimicrobial agent to prevent the emergence of RMP-resistance (10,12). Primary resistance can occur in *Neisseria meningitidis* and rapid resistance can emerge within monotherapy of meningococcal, gonococcal and staphylococcal infections (8). The rate of resistance of *M. tuberculosis* to RMP is approximately 10^{-8} (11,13).

RMP-resistance has been demonstrated in many parts of the world. It is due to insertions, point mutations or deletions within an 81-base pair region of the gene *rpoB*, which encodes the β subunit of the RNA polymerase (8,10,12,16). Four chains, necessary to initiate transcription from promoters, are forming the core enzyme of this oligomeric RNA polymerase. 96 % of RMP-resistant *M. tuberculosis* strains showed mutations in the defined region of the gene *rpoB* (10,11,16). According to Williams et al. specific missense mutations in codons 531, 526 and 516 are most frequent in RMP resistant *M. tuberculosis* isolates (17). Nevertheless, mutation in the *rpoB* gene is not the only reason for resistance to rifamycins. For instance, a reduced permeability to rifamycins resulting in variable degrees of resistance was demonstrated by organisms such as the *Mycobacterium avium* complex (11). Cross-resistance of Rifapentine and Rifabutin depends upon the mutation type and the location.

Mutations in *rpoB* usually result in high-level resistance and cross-resistance to all rifamycins. However, mutations in position 522, 518, 516 and 511 lead to lower-level resistance to RMP and Rifapentine, whereas the susceptibility for Rifabutin and Rifalazil will be retained (16).

Multiresistant strains of *M. tuberculosis* with resistance to RMP associated with resistance to Isoniazid and other antituberculous drugs are emerging especially in the United States (8,10).

1.2.4 Pharmacokinetics

1.2.4.1 Resorption

RMP has good bioavailability and is well and rapidly absorbed after oral administration from the gastrointestinal tract, particularly on empty stomach. In fasting condition RMP reaches peak serum concentrations of 10mcg/ml within 2-4 hours after intake of a dose of 10 mg/kg bodyweight. Concurrent food intake reduces its resorption, varying significantly among the different agents (8,11).

1.2.4.2 Distribution

Since RMP and other rifamycins are highly lipid soluble these agents can cross cell membranes readily. The high distribution volume of > 1L/kg indicates a good cell and tissue penetration (8,11). RMP is widely distributed in most tissues and fluids. In certain fluids, such as urine, tears, saliva, sweat and aqueous humor its extensive distribution can lead to a typical orange-red discoloration. In many tissues the drug concentration exceeds serum concentration within several hours after administration (11). For example in the kidney it may be up to 5 times and in the liver more than up to 20 times that of the serum concentration (8,12).

RMP also penetrates the cerebrospinal fluid (CSF) adequately, producing peak concentrations varying from 0.57 to 1.24 µg/ml. RMP penetrates well into the CSF in both uninflamed and inflamed meninges, however, according to Forrest et al. pharmacokinetics are favorable for uninflamed meninges (10-12).

Depending on the reference, the stated protein bound proportion of RMP varies from 70 to 90% (8,12-14). The unbound non-ionized fraction allows penetration in many tissues. Since RMP crosses the placenta, one third of maternal blood concentrations can be proven in fetal blood and moreover, since RMP also diffuses breast milk, 10-25 % of serum concentrations can be measured in breast milk (8,12).

1.2.4.3 Mean half-life and Metabolism

RMP has a mean biological half-life of about 3 hours after a single dose of 600 mg (8,13). Severe liver injury can prolong its half-life to 8 hours, because of the influence of enterohepatic recirculation. Biliary excretion increases and elimination half-life decreases with continued therapy, because of autoinduction of RMP metabolism – a cytochrome P-450 coupled process (8,10). According to Wallace, the reduction in RMP's half-life and plasma concentration becomes maximal after almost 6 doses (10).

Among rifamycins, RMP is the most potent inducer of the hepatic cytochrome P-450 enzyme system, whereby the 3A isoenzyme is affected most notably (11).

The hepatic clearance of RMP depends upon the extent of dosage, the frequency of administration and the patients liver status. RMP is deacetylated to 25-Deacetyl-RMP, a substance that also has antibacterial activity and undergoes biliary excretion and enterohepatic recirculation. About 70-80 % of total clearance of RMP is imputable to biliary excretion (8,10). The intestinal reabsorption of the substance decreases with the deacetylation, whereas elimination increases (8). Probenecid inhibits RMPs hepatic uptake, resulting in decreased biliary excretion (10).

In patients with impaired liver function, plasma concentration and urinary excretion increase (8,13). Therefore, liver failure indicates a moderate dosage reduction. Functional disorders of the kidneys can be compensated by the activity of the liver and do not have any influence on the elimination rate until a dosage of 450 mg. Based on saturation of hepatic metabolism, dosages of 600 mg can increase RMPs half-life by 40 %. In settings of significant renal insufficiency, dose adjustments of RMP are not necessary (10,13). RMP is not removed substantially by peritoneal dialysis or hemodialysis (8,11).

1.2.5 Drug Interactions

RMP is a potent inducer of both the hepatic and intestinal cytochrome P-450 microsomal enzyme system, in particular the CYP3A4 enzymes, causing increased hepatic metabolism, diminished or shortened effects or a reduction of serum concentration for substances that are metabolized by the same pathway (8,10,11,18). In addition, RMP also induces the P-glycoprotein transport system. Recent research revealed that the induction of the P-glycoprotein and the cytochrome P450 system by RMP is caused by activation of the nuclear pregnane X receptor (12,18). The human organic anion transporting polypeptide-C is

responsible for the hepatocellular uptake of RMP. Increased pregnane X factor activation results in enhanced accumulation of RMP.

In addition, RMP also induces glucuronidation, mediated by uridine 5'-diphosphate-glucuronosyltransferase, facilitating the excretion of drugs by making them more polar. Clinically significant interactions of RMP with other drugs include, for example interactions with oral anticoagulants, oral contraceptives, corticosteroids, Cyclosporine, Ketoconazole, Fluconazole or Itraconazole, cardiovascular agents such as Digitoxin or Digoxin, Quinidine, Verapamil, Nifedipine or beta-blockers, human immunodeficiencyvirus-related protease inhibitors, such as Indinavir, Ritonavir or Saquinavir, and agents such as Theophylline, Phenytoin or Methadone. Other important interactions can also occur with several antibiotics (12,18,19). RMP in combination with other hepatotoxins, such as Isoniazid or Acetaminophen, results in a higher incidence of liver impairment (8,11,13).

Moreover, RMP influences the metabolism and reduces the plasma concentration of protease inhibitors and non-nucleoside reverse transcriptase inhibitors significantly, resulting in possible therapy failure and higher potential of liver toxicity (8,10).

A potentially high risk of liver toxicity is caused by concomitant administration of RMP and Saquinavir/Ritonavir, indicating that a combination of these drugs should be avoided (8).

Adapted from Finch et al. and Baciewicz et al., modified by up-to-date data and other references, the following table lists a partial compilation of some drugs that may show interactions with RMP and in addition recommended treatment modifications.

Table 1. Rifampin Drug Interactions *		
Drug-Class	Drugs	Comments
Antacids		RMP administration at least one hour before use of an antacid
Anticoagulants (oral)	e.g. warfarin	Monitor prothrombin time / international normalized ratio; dosage adaptation will likely be necessary
Contraceptives (oral)		For women of reproductive potential alternative forms of birth control are recommended
Immunosuppressive agents	Cyclosporine and Tacrolimus	Monitor serum concentrations and clinical response and adapt dosing regimens
	Corticosteroids	Clinical monitoring recommended; 2- to 3-fold increase in corticosteroid dose may be required

Antiinfectives	Azole antifungal agents (Itra-, Keto- or Fluconazol),	Avoid concomitant use with RMP because of subtherapeutic serum concentrations; if RMP must be used, dose enhancement will be required; monitor response; a concomitant use with Voriconazol is absolutely contraindicated
	Doxycycline	Monitor clinical response, may change to alternate agent
Narcotics	Methadone	May require dose increase with concomitant use of RMP; monitor and control symptoms
	Halothan	If needed to be used, accurate clinical monitoring is recommended (concomitant use enhance risk of hepatotoxicity)
Psychotropic drugs	Benzodiazepines – e.g. Midazolam/triazolam	Prefer to avoid use with RMP; use another agent if possible
	Haloperidol	Clinical monitoring recommended; may require dose increase or change to an alternative antipsychotic agent
Anticonvulsants	Phenytoin	Monitoring of serum concentrations and seizure activity recommended; may require dose enhancement
Cardiovascular agents	Digitoxin	Therapeutic drug monitoring recommended (arrhythmia control, signs and symptoms of heart failure, and serum digitoxin concentrations); may require dose increase
	Propafenone	Clinical monitoring recommended; dose modifications may be needed (increase of single dose or reduction of dosing interval); use another agent if possible
	Metoprolol, propranolol	Clinical monitoring and dosage adaptations recommended
	Quinidine	Therapeutic drug monitoring recommended (serum concentrations and arrhythmia control); increase dosage if needed
	Verapamil, Diltiazem, Nifedipin	Monitor patient for clinical response, change to an alternative agent may be necessary
Sulfonylurea hypoglycemics	e.g. glimepiride, repaglinide	Monitor blood glucose; may require dose modification
Bronchodilators	Theophylline	Monitor serum theophylline concentrations; may require dose increase
Hypolipidemics	HMG-CoA reductase inhibitors	Monitor lipid panel; increased dose will likely be needed for simvastatin because of reduction of efficacy
* ... Data reproduced from references (8,10-12,18,19)		

1.2.6 Dosing and administration

The usual dose of RMP is 10 mg/kg daily for adults and 10-20 mg/kg daily for children. However, depending on the causative factor, higher doses are also recommended (see below). Oral doses should be administered a half hour before or two hours after meals (8,13). Cases of impaired absorption of RMP in concurrent administration of antacids have been reported. Therefore, RMP should be administered at least one hour before the use of an antacid (8,11).

RMP is contraindicated in severely limited liver function. No guidelines are available. But generally, a daily dose of 8 mg/kg bodyweight should not be exceeded in patients with impaired liver function (8,13). Whereas, in patients with renal dysfunction no dose adjustments are necessary and the full dosage can be administered (8,10,11).

Concerning the use and dosage of RMP in elderly patients, there is a lack of significantly controlled clinical trials. In newborns the metabolism and elimination of RMP is reduced because of the immaturity of the liver. Enhanced serum concentrations or accumulation may develop. Therefore, dosing recommendations should be adhered to (8).

According to recommendations in drug information data a dosage adaptation is needed if the therapy with RMP has been discontinued and should be restarted. The initial dose should be 150 mg and should be increased by 150 mg per day for 3 days. On day 4 therapy should be continued with the usual dosage (8).

Tuberculosis

The usual adult dose for RMP against *M. tuberculosis* is 8-12 mg/kg bodyweight, meaning 450 mg RMP daily for patients with a bodyweight < 50 kg and 600 mg daily for patients > 50 kg (8). According to Richard the therapeutic range of RMP is a two hour post-dose concentration of 8-24 µg/ml (13). The duration of treatment normally is 6 up to 9 months and, above all, no pathogen should be verifiable for at least 3 months. The 6-months system normally includes an initial phase of 2 months treating with RMP, Isoniazid and Pyrazinamid. If indicated, other agents might be added. The combination of RMP and Isoniazid, and possibly even another substance, e.g. Ethambutol for the first 2-3 months, is used for the 9-month treatment period (8).

Lepra

RMP shows rapid bactericidal activity against *M. leprae*. A single dose of 10 mg RMP/kg bodyweight and concomitant use of another antileprotic drug is recommended (8,11).

Staphylococcal infections

Severe Staphylococcal infections in adults need a dosage of 600 to 1200 mg daily in two single doses every 12 hours. Recommendations for MRSA infections include 600 up to 1200 mg RMP daily partitioned into 2 to 4 single doses, combined with at least one other antibiotic drug because of the high rate of development of resistance that emerges during monotherapy (8,11). Reports have shown that the concomitant usage of other antistaphylococcal agents reduces RMP resistance, even though resistance can develop during combined therapy. However, resistance occurs more likely in settings of high bacterial burdens and low local antibiotic concentrations, for example in large abscesses or endocarditis (11).

The treatment of patients with prosthetic valve endocarditis due to *Staphylococcus* spp demands a dosage of 1200 mg RMP per oral per day, divided in two doses (every 12 hours) for up to 6 weeks in combination with other antistaphylococcal agents (1,8). In the United States the therapy schedule for prosthetic valve endocarditis due to MRSA consists of 300 mg every 8 hours for up to 6 weeks, in combination with other antistaphylococcal drugs (13), such as Flucloxacillin for MSSA or Vancomycin for MRSA (1,8). Concerning other staphylococcal infections a dose of 600 mg daily is reported, generally divided into 2 doses (13). Dose recommendations for newborns, infants and children younger than 1 year are 5-10 mg/kg bodyweight twice daily and for children older than 1 year 10 mg/kg bodyweight twice daily up to a maximum of 600 mg per day (8).

Brucellosis

In brucellosis, a dosage of 600 up to 900 mg RMP once daily in concomitant use with Doxycycline two times 100 mg daily for 5 up to 7 weeks is recommended. For children the dose ranges from 10-15 mg/kg/day divided into two single doses combined with Doxycycline for children from 8 years up and Trimethoprim/Sulfamethoxazol for younger children (8).

N. meningitides carrier

Beside Ciprofloxacin or Ceftriaxon, RMP is used as antimicrobial prophylaxis for carriers of *N. meningitides* and, in addition, administered to reduce the risk of secondary cases of infection for persons who are or have been (up to 10 days after their last contact) in close contact with an infected patient (1). Recommendations for adults are 600 mg RMP twice daily for 2 days (600 mg every 12 hours) or 600 mg RMP once daily for four days. For children and infants from 1 month up a dose of 10 mg/kg every 12 hours for 2 days is recommended,

whereby for infants younger than 1 month 5 mg/kg every 12 hours for 2 days or every 24 hours for a period of 4 days (1,8).

H. influenza carrier

A dosage of 20 mg/kg once daily (up to a maximum of 600 mg/day) for a period of 4 days is recommended for persons living in close contact with an infected patient. Newborns should receive 10 mg/kg/day for 4 days.

1.2.7 Adverse Effects

RMP is associated with several adverse reactions. However, the frequency demanding a discontinuation caused by adverse effects is, according to Calfee, relatively low - about 1.9 % (10,11).

Immunological

Hypersensitivity reactions are common ($\geq 1/100$ to $< 1/10$) and severe hypersensitivity reactions associated with dyspnea, pulmonary edema, peripheral edema, anaphylaxis up to shock develop rarely ($\geq 1/10.000$ to $< 1/1.000$) (8,11).

The systemic flulike syndrome is thought to be associated with a RMP-dependent, antibody-related process and predominantly develops during intermittent or high-dose RMP therapy (11). Symptoms including fever, chills, rash, nausea and regurgitation as well as headache, arthralgias and myalgias and occasionally combined thrombocytopenia, generally emerge within 1 to 2 hours after oral administration (8,10,11,13). Treatment adaptations to daily administration normally prevent these reactions (11).

The lupus-like syndrome develops very rarely ($< 1/10.000$) and is associated with fever, myalgias, arthralgias, malaise, edema and present antinuclear antibodies during the acute state. Symptoms resolve and antinuclear antibodies decrease constantly after discontinuation of RMP (8,11).

Hematological and lymphatic

Eosinophilia, leucopenia, granulocytopenia, hypoprothrombinemia, hemolytic anemia, thrombozytopenia and disseminated intravascular coagulation are abnormalities which develop rarely ($\geq 1/10.000$ to $< 1/1.000$) and agranulocytosis very rarely ($1/10.000$) (8). Normally, no dose adjustments are necessary, since these changes resolve after discontinuation of RMP. However, hemolytic anemia typically accompanied with fever, malaise, headache, joint pain, myalgias and occasionally renal failure, or thrombocytopenia

(with or without purpura) indicate an immediate discontinuation. These severe hematological complications develop within hours after oral intake and typically within intermittent dosing regimens or on reintroduction after discontinuation. Continuation or reintroduction of RMP may have lethal consequences - in case of thrombocytopenia, such as significant bleedings (8,11).

Interaction between RMP-dependent antibodies and the “I antigen” expressed on the surface of erythrocytes and platelets, inducing complement-mediated cell-damage, are thought to be responsible for these severe hematological complications. Therefore, in patients who have developed these severe complications reintroduction of RMP is not recommended (8,11).

Dermatological

Rash, flush and pruritus can occur during RMP administration (8,11,13). Cutaneous reactions, such as urticaria, are relatively common ($\geq 1/1.1000$ to $< 1/1.000$). Pemphigoid reactions, erythema multiforme, Stevens-Johnson syndrome or vasculitis develop rarely (8).

Severe skin reactions, such as toxic epidermal necrolysis or, in very few instances, an exfoliative dermatitis occurred during multi-combinationtherapy including RMP, but RMP was not certainly identified as the offending agent (8). Most skin reactions are mild and self-limiting and do not require discontinuation of RMP (11). In patients with a failure in porphyrin-synthesis RMP shows an enzyme-inducing activity and may cause a porphyria cutanea tarda, presenting with photodermatosis most notably. The activation of the delta-aminolevulinic acid-synthase may induce the manifestation of porphyria (8).

Renal

Acute renal failure occurs very rarely ($< 1/10.000$) (8), most commonly during highly intermittent therapy or rechallenge of RMP after a drug-free interval. Most cases are due to acute interstitial nephritis and acute tubular necrosis attributed to RMP-dependent antibodies (11). The pathomechanism for this renal damage, the same as previously mentioned for immunological reactions, is thought to be due to complement-mediated cell-damage, induced by an interaction of antibodies and the I antigen expressed on renal tubular epithelium. On the other hand, acute renal failure during continuous dosing regimens is reported to be different in pathophysiology. Main causes are rapidly progressive glomerulonephritis or acute interstitial nephritis. It occurs frequently and RMP-dependent antibodies are negative (11). The prognosis of the antibody-associated type of renal failure is good. Nevertheless, the current recommendations suggest an immediate discontinuation of RMP (8).

Gastrointestinal

Gastrointestinal symptoms, such as nausea, vomiting, meteorism or diarrhea, abdominal pain or cramping and lack of appetite are common associated side effects ($\geq 1/100$ to $< 1/10$) (8,10,11). Besides, rare cases of pseudomembranous colitis caused by *Clostridium difficile* have been reported (8,10,11).

Others

RMP is widely distributed in most tissues and fluids. As previously mentioned, patients should be advised that RMP's extensive distribution causes an orange-red discoloration of certain body fluids, such as urine, tears, saliva and sweat (8,10,11,13). Furthermore, permanent staining of contact lenses, aqueous humor and clothing can occur (8,11).

Liver and bile

Elevations in liver enzymes and bilirubin, icterus and serious complications including hepatotoxicity, especially in patients with predisposing factors, including administration of concomitant potential hepatotoxins, alcoholic abuse and hepatitis C virus infection, have been reported (8,10-12).

1.2.8 Contraindications

According to drug information data, RMP is contraindicated in following proclaimed circumstances (8):

- hypersensitivity against the agent, other rifamycins or other ingredients
- severely impaired liver function, associated with hepatitis, liver cirrhosis or obstructive icterus
- concurrent use with Saquinavir/Ritonavir
- concomitant use with Voriconazole
- porphyria

1.3 Hepatotoxicity

In addition to other likewise important functions, the liver is responsible for transforming, metabolizing, concentrating and eliminating chemicals. Therefore, the liver is susceptible to possible toxic effects of substances administered to the body. Drug-induced liver injury (DILI), or drug-induced hepatotoxicity is a well-known problem in clinical routine. According to Larson, DILI accounts for up to 10 % of all adverse drug reactions (20). In more than 1000 different agents an association with the development of DILI has been shown. Furthermore, in up to 30 % of patients who present with acute hepatitis the cause is due to DILI.

Considering the patient population and geographic location, however, DILI is the cause of acute jaundice in up to 50 % of patients with new onset jaundice. Furthermore, Larson mentions, that DILI is the most common cause of acute liver failure in the United States and the most frequently cited cause of withdrawal of pharmacological agents from the marketplace (20).

1.3.1 *The liver and its role in drug metabolism*

As already mentioned, administered drugs and toxins are metabolized, concentrated and eliminated by the liver. Hepatotoxicity may be directly caused by some drugs, but is generally induced by metabolites, which develop through biotransformation processes of the substance by one or more soluble and membrane-bound enzymes. The biotransformation pathway is specific for each drug and toxin, altered by genetic variation and environmental factors, such as alcohol use predisposing some patients to the development of hepatotoxicity and others not (20).

The hepatic chemical biotransformation process is necessary to make drugs, toxins and their compounds water-soluble, allowing filtration by the kidneys or excretion into the bile. Generally, two mechanisms are responsible for the hepatic metabolism of these products. During phase I reactions, predominately catalyzed by the cytochrome P450 isoenzyme system, substances are made water-soluble by adding polar groups to lipophilic molecules via oxidation, reduction or hydrolysis.

The cytochrome (CYP) enzyme system includes over 50 proteins, divided into 18 families and 43 subfamilies. For the hepatic metabolism of exogenous substances, however, the enzyme families CYP1, CYP2, and CYP3 are thought to be the most important ones. CYP3A4 is the most important enzyme involved in the metabolism of drugs, since

approximately 50 % of commonly used drugs undergo biotransformation through this enzyme and since it is present in the largest quantity of all the CYPs in the liver (20).

The activity of these enzymes may be affected and altered by different causes, such as enzyme concentration and inducing capability by exogenous factors. Accordingly, alteration of enzyme activity may lead to an increase in toxicity of the metabolized substance or decrease its therapeutic effectiveness. Non-therapeutic doses of some drugs, leading to an overload of alternate detoxification routes, may be another cause of hepatotoxicity. Moreover different drugs may share the same CYP enzymes leading to a competitive inhibition of each others biotransformation process, causing drug interactions. A few examples of inducers of the CYPs are Phenobarbital, Phenytoin, Carbamazepine, Ethanol, Glucocorticoids or Rifampin, whereas Amiodaron, Erythromycin, Isoniazid, Metronidazol, Sulfonamide, are known to inhibit the CYP-450 enzyme system (21).

After this phase I process most compounds require further processing to become water-soluble and excreted. Therefore, during phase II reactions, primarily taking place in the hepatocyte cytoplasm, diverse transferases conjugate sulfate, acetate, glycine, glutathione, a methyl group or glucuronic acid to the drug or its metabolites. Primarily, compounds with high molecular weight are excreted in bile and smaller molecules by the kidneys. This phase is mostly accompanied by a decrease of pharmacologic activity and enhanced clearance of the substances. One further step is mediated by specific transporters, which are responsible for the transport of the compounds and their processed products into the bile. An alteration of these transporters may also lead to the development of hepatotoxicity (20).

1.3.2 Affecting factors of the development of drug-induced hepatotoxicity

Generally, several factors exist that affect hepatic metabolism reactions, leading to an alteration of the activity of these reactions and at least to changes in drug metabolism (21):

- ***Age*** - Although an overall reduction in the activity of CYPs may occur with increasing age, some patients may be concerned more than others. Hepatic drug reactions are more common in elderly persons, possibly induced by the higher incidence of drug-drug interactions, decreased clearance, variation and alteration in drug binding, reduced hepatic blood flow and lower hepatic volume. Moreover, further reasons, such as multi-morbidity, infections, poor diet and hospitalizations may have a concomitant effect on the development of hepatotoxicity.

- **Sex** – Hepatic drug reactions are more common in female patients, even though the mechanism is unknown.
- **Genetic factors** – Genetic alterations in CYPs lead to modified, decreased or increased enzyme activity causing diminished or excessive metabolism of the drug and therefore adverse reactions. Specific genetic changes in hepatobiliary transporters may predispose to cholestasis.
- **Race**
- **Alcohol ingestion** – Since alcohol abuse leads to liver injury and cirrhotic alteration with following altered drug metabolism (amongst others caused by a depletion of hepatoprotective glutathione stores), alcoholics are more prone to hepatic drug toxicity.
- **Underlying Liver disease** – Acute as well as chronic liver disease affect the drug metabolism, whereas the type of liver disease does not turn up to play an important role. In general, increasing liver disease severity is accompanied with decreased CYP activity. In patients with cholestasis the endogenous and exogenous secretion of the compounds is reduced.
- **Dose and formulation** – Drugs with high hepatic metabolism are more likely accompanied with the development of DILI than drugs that have less extensive metabolism. In addition, long-acting drugs are more frequently associated with liver injury than shorter-acting drugs.
- **Other comorbidities** – Persons with autoimmune deficiency syndrome, malnourishment, or patients who are fasting, may in general be more susceptible to drug reactions because of low glutathione reserve.
- **Concomitant drug use** – The usage of drugs in combination with others might be one of the most important underlying factors influencing parts of the CYP enzyme system and furthermore drug metabolism. As already mentioned above, several drugs are able to inhibit and others to increase drug metabolism through competition at shared CYP enzymes.

1.3.3 Pathophysiology and mechanisms of DILI

Pathophysiologic mechanisms are versatile and numerous, often defined by hepatocyte necrosis or apoptosis and cell death. Some compounds, however, frequently damage the bile ducts, transport proteins, canaliculi, vascular endothelial cells or stellate cells. Generally toxic hepatocellular damage can be divided into two groups. However, mixed patterns exist (20,21). One group is represented by a predictable injury due to direct chemical reactions, and an involvement of intrinsic hepatotoxins. The other group, showing lower incidences in comparison to the predictable injury, is due to idiosyncratic reactions and categorized as unpredictable injury. Intrinsic or predictable drug reactions are represented by drug-induced injuries that are dose-related and reproducible in animal studies. The injury may be induced by the drug itself or by a metabolite. The interaction of intrinsic hepatotoxins with one or more intracellular compounds may lead to cell death and dose-dependent hepatocellular necrosis. The binding of toxic metabolites to structures within the cell may cause oxidative stress, glutathione depletion, redox changes or lipid peroxidation, and lead to an alteration of the cell function and regulation (20).

Hypersensitivity, immunoallergic and metabolic-idiosyncratic reactions are part of the idiosyncratic drug-induced reaction. In contrast to the first noted reaction, the response rate is unpredictable and often cannot be reproduced experimentally. Moreover, it often emerges within a week or up to one year later. The pathogenesis is currently incompletely understood, but might be related to a complex interaction of the drug and its metabolites with the immune system, leading to apoptosis or necrosis. Besides, clinical and histological signs of hypersensitivity may occur, such as rash, fever, joint pain, lymphadenopathy and eosinophilia. Haptenization and the creation of neoantigens may lead to an autoimmune-mediated injury. The metabolic-(sub)type is probably caused by local accumulation of toxic metabolites, due to an aberrant metabolism of the drug in susceptible patients.

Potential pathophysiologic mechanisms of DILI (21):

- ***Disruption of the hepatocyte*** – This process is seen to be due to actin disruption through covalent binding of the drug to intracellular proteins.
- ***Impairment of transport proteins*** – An altered transport process of transmembrane proteins at the canaliculi may lead to prevent bilirubin excretion and therefore may lead at least to cholestasis.

- ***Apoptosis of hepatocytes*** – Apoptosis may be caused by activation of the apoptotic pathways by tumor necrosis factor- α receptor and intercellular caspases-cascade.
- ***Mitochondrial disruption*** – ATP production is decreased through depletion of mitochondrial function, based on the inhibition of the synthesis of nicotinamide adenine dinucleotide and flavin adenine dinucleotide.
- ***Bile duct injury*** – Excreted in bile toxic metabolites or the compounds themselves may cause injury to the bile duct epithelium.
- ***Cytolytic T-cell activation*** – The covalent binding of a drug to the P-450 enzyme - acting as an immunogen - or other direct effects of certain compounds may lead to T-cell activation and a release of cytokines stimulating multivarious immune response processes.

1.3.4 Presentation and Classification of DILI

Drug induced hepatotoxicity may present in different ways. It may present with certain clinical signs and symptoms provoked by an acute or chronic injury of the liver or may be asymptomatic. Moreover, the clinical presentation sometimes may not go hand in hand with the suggested liver injury. In addition, some drugs occasionally cause a variety of injuries, making the diagnostics sometimes more difficult (21,22).

According to Larson, DILI may be classified in several ways, including clinical presentation and laboratory features, mechanisms of hepatotoxicity and/or its histological findings (22).

Acute onset manifestations vary from mild asymptomatic biochemical abnormalities to acute sickness accompanied by jaundice similar to viral hepatitis or acute liver failure. According to Larson the prognosis is worse in patients with both jaundice and increased serum transaminase levels than in patients with an isolated alteration of transaminases (22).

Some drugs may cause chronic histologic inflammatory alterations or a clinical syndrome similar to autoimmune hepatitis. Furthermore, an involvement of the vascular system through endothelial damage or thrombosis is possible.

Generally, cessation of the affecting drug leads to a reversal of the injury. Nevertheless, in some cases progressive chronic alterations such as fibrosis or cirrhosis may occur, despite withdrawal.

Possible clinical and pathological manifestations of DILI (21,22):

- ***Asymptomatic/Subclinical*** – Many drugs may cause asymptomatic elevations in liver enzymes, normally resolving or not reoccurring on withdrawal within weeks or months. Generally, DILI is considered to be subclinical if serum alanine aminotransferase (ALT) levels are beyond 3 times the upper limit of normal (ULN).
- ***Acute liver injury/Acute hepatitis*** – Responsible for approximately 10 % of all cases of acute hepatitis, this form is, moreover, the most common occurrence of DILI. Clinical manifestations include hepatocellular damage, cholestasis or both, or - less frequent - steatosis. Generally cessation of the drug is followed by complete recovery. Nevertheless, associated jaundice worsens prognosis. The acute hepatocellular damage resembles that occurring in viral hepatitis. Pathological histologic results include portal and parenchymal hepatocellular injury, hepatocellular necrosis and apoptosis, steatosis and cellular degeneration, whereby in laboratory elevated aspartate aminotransferase (AST) levels may be noted. The hepatocellular damage may present as spotty or confluent. According to Nelish et al., hepatocellular injury is accompanied with an increase in ALT levels to more than twofold the upper limit of normal (ULN), however, alkaline phosphatase (AP) levels are within the range or slightly elevated (21). For differential diagnosis alcoholic hepatitis is characterized by an increase of AST, mostly twice as much as ALT. In patients with viral hepatitis AST levels are noted to be less elevated than ALT levels. Common in viral and drug-induced hepatitis is a constant increase and a peak in the low thousands within one to two weeks (21). An elevation in AP suggestive of acute cholestatic injury can be associated with hepatocellular injury or not. Mixed patterns with elevations in both ALT and AP are noted to be common (21).

Elevated ALT and bilirubin levels may indicate subfulminant or fulminant necrosis, associated with worse prognosis and a mortality rate up to 80 %. A serum bilirubin level > 3 times the ULN may be the best predictor of mortality in the setting of acute hepatocellular injury (22).

- ***Cholestatic injury*** – Showing similarity to extrahepatic obstructive jaundice the acute cholestatic injury caused by drugs is typically associated with an increase in alkaline phosphatase (AP), γ -glutamyl transferase (GTT) and bilirubin levels. Clinical symptoms are pruritus, jaundice and/or dark urine (22).

Moreover, Larson refers to four types of cholestasis that may be seen on liver histology (21,22): The 'Pure type' is associated with cholestasis, slight hepatocellular inflammation and frequently bile plugging. AP and GGT are normally greater elevated than ALT, which is in general in normal range or minimally elevated. Characterizations for the 'cholestatic cholestasis' are portal inflammation, excessive cholestasis, degeneration of the bile duct and hepatocellular injury. Therefore, in laboratory, ALT levels range from normal to eightfold. AP, however, is elevated three- to tenfold. The 'ductopenic type' and 'sclerosing type' show typical changes of chronic injury. Chronic cholestasis can be induced intrahepatically, or can be characterized by a vanishing bile duct syndrome or biliary sclerosis (22).

- ***Steatosis/Steatohepatitis*** – A drug-induced fatty degeneration is rarely seen and mostly accompanied by mild jaundice and slight ALT alterations. Chronic steatosis, generally macrovesicular in comparison to the frequently seen microvesicular steatosis in acute injury, tends to be less severe but more common (21,22).
- ***Chronic hepatic injury*** – Generally characterized by abnormal liver enzymes for over 3 to 6 months, drug-induced chronic alterations may present in many forms and can be similar and sometimes serologically and morphologically indistinguishable to changes caused by other etiologies of chronic liver disease, such as autoimmune hepatitis or alcoholic liver disease. Symptoms and changes normally resolve upon withdrawal, however a progress to cirrhosis and liver failure may be possible. Further chronic changes, according to Nelish may be pigment accumulation, such as Lipofuscin and Hemosiderin accumulation in the liver cells (21). Besides, cholestatic or mixed types of drug-induced injuries are reported to be more likely associated with a progression to chronic disease (22).
- ***Vascular lesions/disease*** – Normally uncommon, the drug induced hepatic vascular disease, however, can present as Hepatic Venous Outflow Obstruction (Budd-Chiari-Syndrome) or Hepatic Sinusoidal Obstruction Syndrome, due to endothelial damage or thrombosis.
- ***Granulomatous Hepatitis*** – Generally transient and not causing further harm, these granulomas are most commonly consisting of noncaseating epithelioid granulomas located in periportal or portal areas.

- *Neoplastic lesions* – Several medications show association with both benign and malignant neoplasias of the liver, such as hepatic adenoma, angiosarcoma and hepatocellular carcinoma.
- *Extrahepatic manifestations* – Several drugs may cause systemic or toxic reactions, such as mononucleosis-like illness, fever, rash or toxic reactions of the bone marrow.

1.3.5 Diagnosis of DILI

If induced by a single agent, the diagnosis of DILI might be relatively simple. However, in patients taking several different agents identifying the offending agent might be difficult. Moreover, the rapport of drug-exposure and hepatic toxicity is not always precise.

Up to now, there exists no gold-standard and no specific serum biomarker or characteristic histologic feature identifying an agent as the certain source of hepatotoxicity.

The Council of International Organizations of Medical Sciences (CIOMS) developed a clinical tool of standard specifications of drug-induced liver disorders and classification of injury. These guidelines, furthermore modified by the United States FDA Drug Hepatotoxicity Steering Committee, are used as markers of hepatotoxicity in clinical trials. Besides, the Drug-Induced Liver Injury Network (DILIN) generated the DILIN Causality Scoring System. It is a scale model relying on expert opinion to define the causality of drug-induced injury for patients that are part of prospective clinical trials (21,22).

1.3.5.1 Key elements

History taking is important, but not always reliable and should include dose, duration, route of administration, concomitant drugs and previous drug exposure. Clinical patterns suggesting drug-induced toxicity include a lack of illness before ingesting the drug, clinical illness or biochemical alterations emerging after drug-intake and the improvement after discontinuation of the drug. Rechallenge is not recommended, nonetheless it remains the “gold standard” for the diagnosis of DILI. According to Larson, key elements for attributing liver injury to a drug are (22):

- Exposure preceding the onset of liver injury.
- An underlying liver disease should be excluded.
- Improvement of injury by withdrawal of the agent.

- After repeated drug-exposure the liver injury may have recurred more rapidly and severely.

1.3.5.2 Definition of hepatotoxicity

Hepatotoxicity may present in different ways with different clinical signs and symptoms.

An acute hepatocellular injury is commonly defined as an increase in ALT more than 2-fold and an ALT/AP-Ratio > 5 . An acute cholestatic injury is defined as an increase in serum AP > 2 ULN or by an ALT/AP-Ratio ≤ 2 . Hyperbilirubinemia and jaundice play a further role in that place. In mixed patterns an increase in ALT more than 2-fold, elevated AP-levels more than 2-fold and an ALT/AP-Ratio of 2-5 is demanded(23-25)(24-26).

Nevertheless, in literature and many articles definition criteria of hepatotoxicity often differ.

According to the WHO Adverse Drug Reaction Terminology hepatotoxicity is defined as demonstrated in the following table (23):

Table 2. Hepatotoxicity - Grading	
Grade	Limits
Grade 1 (mild)	< 2.5 times ULN (ALT 51-125 U/L)
Grade 2 (mild)	2.5-5 times ULN (ALT 126-250 U/L)
Grade 3 (moderate)	5-10 times ULN (ALT 251-500 U/L)
Grade 4 (severe)	> 10 times ULN (ALT > 500 U/L)
ALT...alanine aminotransferase	
ULN...upper limit of normal	
U/L...units/liter	

1.4 Hyperbilirubinemia

Bilirubin is the end product of heme metabolism. The water-insoluble unconjugated bilirubin (indirect bilirubin) results of reduction of biliverdin and is reversibly bound to albumin and conjugated in the liver. The uptake into hepatocytes is generated via the organic anion transport peptide OATP-C. The conjugated bilirubin (direct bilirubin) is water-soluble and excreted with the bile via active transport (26,27).

Hyperbilirubinemia is defined as elevated content of bilirubin in the blood (>21 $\mu\text{mol/l}$ respectively 1.2 mg/dl of total bilirubin) based upon increased production, diminished conjugation or reduced excretion of bilirubin. It may occur with acute hepatitis, acute liver injury or failure, cholestasis, hemolysis or can develop as isolated hyperbilirubinemia with syndromes, such as the Dubin-Johnson syndrome, Crigler-Najjar syndrome or Gilbert's syndrome. Hyperbilirubinemia can occur as direct hyperbilirubinemia with elevated content of conjugated bilirubin and indirect hyperbilirubinemia with elevated content of unconjugated bilirubin.

Cholestasis is an impairment of bile secretion, with retention of bilirubin, bile acids or other bile components. It may result either from a functional defect in bile formation at the level of the hepatocytes – therefore called hepatocellular cholestasis - or from an alteration in bile secretion and flow at the level of bile ducts – defining ductal cholestasis. Further causes are hereditary transporter defects, or cholestatic or hepatocellular injury of potentially hepatotoxic drugs, pro-inflammatory cytokines or hormones. As mentioned above, drugs may be associated with both acute and chronic cholestatic injury with elevation of bilirubin levels. Cholestasis induced by agents can be dose-related or related to idiosyncratic or allergic reactions (28).

1.4.1 Bile acids and bile acid transporters

Bile acids belong to the group of steroids, are endproducts of cholesterol metabolism and necessary for resorption and metabolism of fat. In the enterohepatic circulation of bile acids bile acid transporters play an important role. The Na^+ -dependent taurocholic cotransporting polypeptide (NTCP) is responsible for the sodium-dependent and Organic anion transporting polypeptides (OATPs) for the polyspecific sodium-independent uptake of bile acids into hepatocytes. Both transporters are localized at the basolateral membrane of hepatocytes.

The OATP-superfamily consist of many members, such as OATP1A2, which was shown to be able of transporting bile acids and additionally steroid conjugates, thyroid hormones, prostaglandins, certain organic cations and the organic anion bromosulfophthalein (BSP) (29,30). Hepatic orthologs in rodents are *Oatp1a1* and *Oatp1a4* (formerly known as *Oatp1* and *Oatp2*) (27). OATP1B1 (previously called OATP-C and localized on gene *SLC101B1*) and OATP1B3 (OATP8) are known as the most important carriers for hepatic uptake of organic anions in human liver. Substrates of OATP1B1 include amongst others BSP, bile salts, steroid

conjugates and unconjugated bilirubin (26,27). It is of interest to note that RMP has been shown to be a substrate of OATP1B1 (31).

Bile acids seem to decrease the expression of several OATP transporters. Likewise, high levels of bile acids were found to decrease gene expression of NTCP, interpreted as an adaptive response to reduce their entry into the hepatocytes (30). In addition, alterations in OATP function and expression are suggested to interfere with the bioavailability or toxicity of certain drugs (32). Furthermore, an involvement of OATPs in the glutathione (GSH) efflux is considered, since OATPs were found to generate the exchange of extracellular organic anion or bile acid with intracellular HCO_3^- or GSH (30).

The bile acid efflux from hepatocytes is negligible under physiological conditions, however, increased during cholestatic conditions. The process is mediated by members of the multidrug resistance protein (MRP) subfamily, in which MRP3 and MRP4 are localized at the basolateral membrane and the canalicular membrane of the hepatocytes.

After the intracellular transport bile acids are exported into the canaliculus via two important ATP-dependent transporters, the bile salt export pump (BSEP) and the multidrug resistance protein 2 (MRP2). BSEP, responsible for the transport of monovalent bile acids, is the predominant transporter of bile acids into the bile. It plays an important role in hepatic function and bile formation. Defects in expression of BSEP or defects in its function result in impaired bile secretion, alterations in bile flow and cholestasis (30,33,34). BSEP has high affinity for cholytaurine and is a vulnerable target for inhibition by drugs, such as Glybenclamide, Troglitazone, Cyclosporine A, abnormal bile salt metabolites and estrogen-metabolites (30,35,36).

MRP2, member of the ATP-binding cassette superfamily of transporters, is the other transporter involved in canalicular transport of bile acids. MRP2 acts as main transporter of divalent bile acids, and also mediates the excretion of bilirubin conjugates and other substrates such as GSH, glucuronide and sulfate conjugates and also some unconjugated drugs (30). Mutations in hepatocellular transport systems may result in congenital cholestasis. For example, mutations in MRP2 lead to Dubin-Johnson Syndrome characterized by conjugated hyperbilirubinemia without elevated serum GGT or transaminases (29). It is of interest to note that Zollner and Trauner mentioned that a large number of defects in transport systems may be incomplete or mild and may only become evident when cholestatic agents are in use under these circumstances. A possible direct inhibition of transporters or a reduction of transporter gene expression due to cholestatic agents is noted in literature (29). Additionally, cholestatic

injury was shown to be accompanied with impaired expression and function of transport proteins (33,37).

To prevent cytotoxic effects of supra-physiological bile salt concentrations and to maintain bile acid homeostasis, a coordinated regulation of bile acid transport, synthesis and metabolism is essential. This is guaranteed by nuclear receptors, such as the recently identified farnesoid X receptor (FXR), the Pregnane X receptor (PXR) and vitamin D receptor (VDR), which are activated by various compounds if cholestasis occurs. Of note, RMP activates PXR and VDR (29,38). An increased expression of other hepatocellular transporters, such as Mrp1 and Mrp3, which mediate the sinusoidal efflux of bile salts and their conjugates may represent another protective mechanism to limit accumulation of bile salts and other potentially toxic biliary constituents due to increased efflux during cholestasis (35,37,39).

2 Materials and methods

To identify relevant citations for this review, a literature search was done in MedLine database using different subject headings listed below (1960 – November 2011) resulting in the identification of 455 citations for fusidic acid and 934 citations for rifampin as of 30th November 2011.

The collected data lists were subsequently screened for relevant citations by two investigators, both certified in Infectious Diseases. During the first review, citations were excluded in case of the following exclusion criteria such as impact factor of journals less than 1, language other than English and articles other than about adolescent age. If not already distinguished by the title, articles were included with headings such as tolerability, toxicity, safety, hepatotoxicity, hyperbilirubinemia, side effects or adverse events, liver enzyme elevation, bile acid, jaundice, cholestasis, icterus or any effect on the liver cells in relation to FA and/or RMP. Citations with titles relating to other adverse events or not related to the liver were excluded. Since the main point of interest was RMP and/or FA in therapy of staphylococcal infections, articles were included that compared these agents with other treatment regimens or in which one of these agents was used in combination treatment regimens.

All qualifying articles underwent an abstract review to assess clinical relevancy. If an abstract was not available the article was included without abstract review. Afterwards, the included articles underwent a full text review. Potentially relevant related citations in reviewed articles were marked in the reference list and subsequently studied for relevancy and matching of our inclusion criteria. If so, the related citation abstracts were reviewed to examine further impact. For inclusion of these related citations, the same inclusion and exclusion criteria as mentioned before were applied.

A first review of data lists for RMP excluded citations about RMP as part of the antituberculous treatment concept, with exceptions as described below.

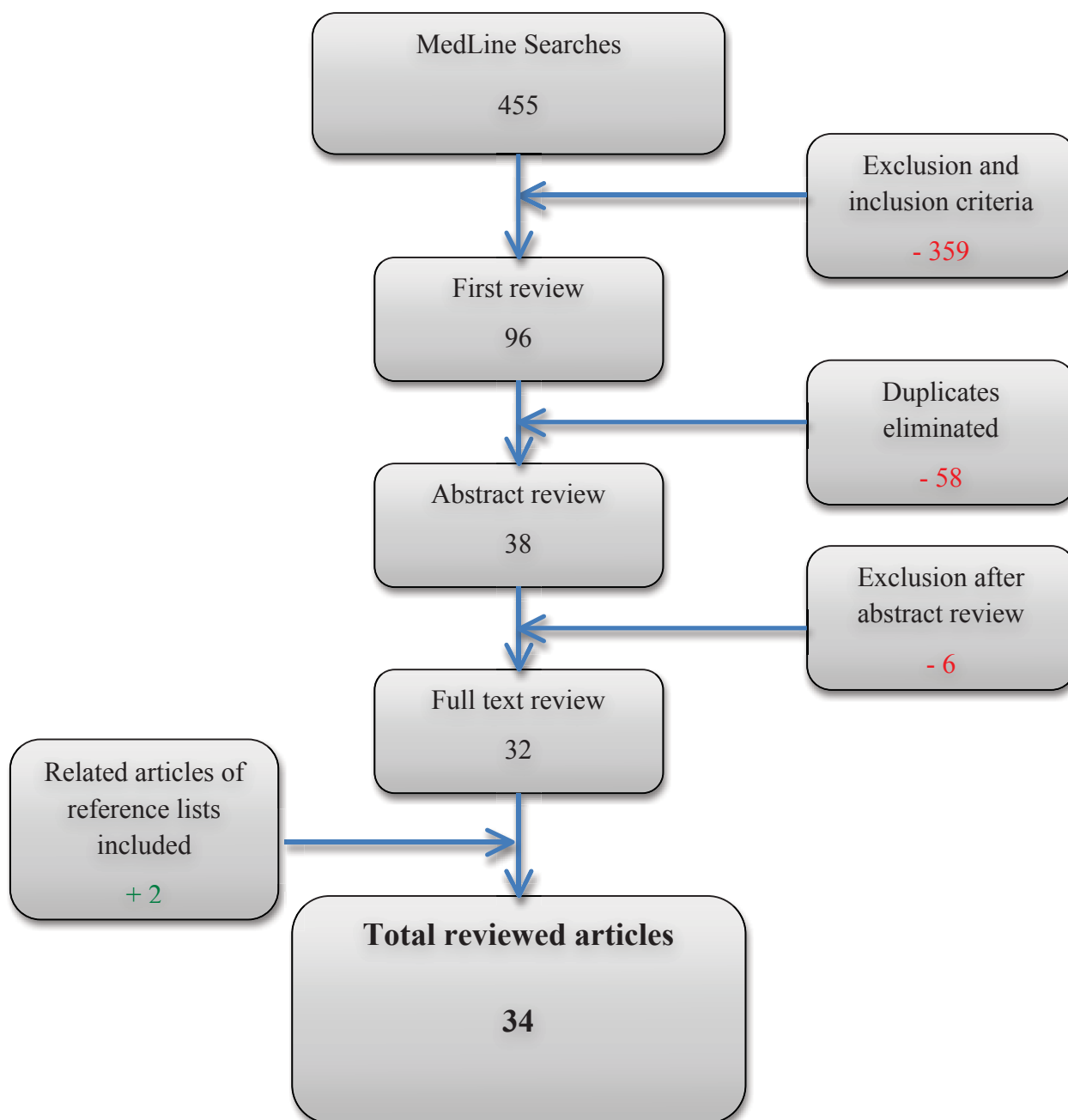
To compare hepatotoxicity in antituberculosis treatment regimens and non-mycobacterial therapy both investigators lastly appointed to include 2 reviews with data content of antituberculous-drug induced hepatotoxicity and, in addition, articles in which RMP was used as single-therapy in latent antituberculosis therapy to assess adverse events of single RMP-therapy. Other articles not matching the criteria were excluded.

2.1 Fusidic acid

Using different subject headings in MedLine (listed below) 455 citations were identified for FA as of 30th November 2011. Considering inclusion and exclusion criteria as described before at first 96 citations were found for FA. In a next step multiple stated citations were subtracted resulting in 38 relevant articles. Six articles did not match the criteria after abstract review and were excluded. After the full text review and following review of potentially relevant related citations in reference lists further 2 articles were included for this literature review. In summary, 34 articles were reviewed in this thesis.

Step	Search details	Citations, no.
1	Fusidic acid and hepatotoxicity	3
2	Fusidic acid and hyperbilirubinemia	12
3	Fusidic acid and icterus	11
4	Fusidic acid and jaundice	10
5	Fusidic acid and liver	72
6	Fusidic acid and side effects and liver	15
7	Fusidic acid and staphylococcal bacteremia	39
8	Fusidic acid and staphylococcal bacteremia and liver	3
9	Fusidic acid and staphylococcal aureus and side effects	46
10	Fusidic acid and staphylococcus aureus and adverse effects	38
11	Fusidic acid and adverse effects	206
Total		455

Table 4. Fusidic Acid - Literature Search Methodology - Flow Chart

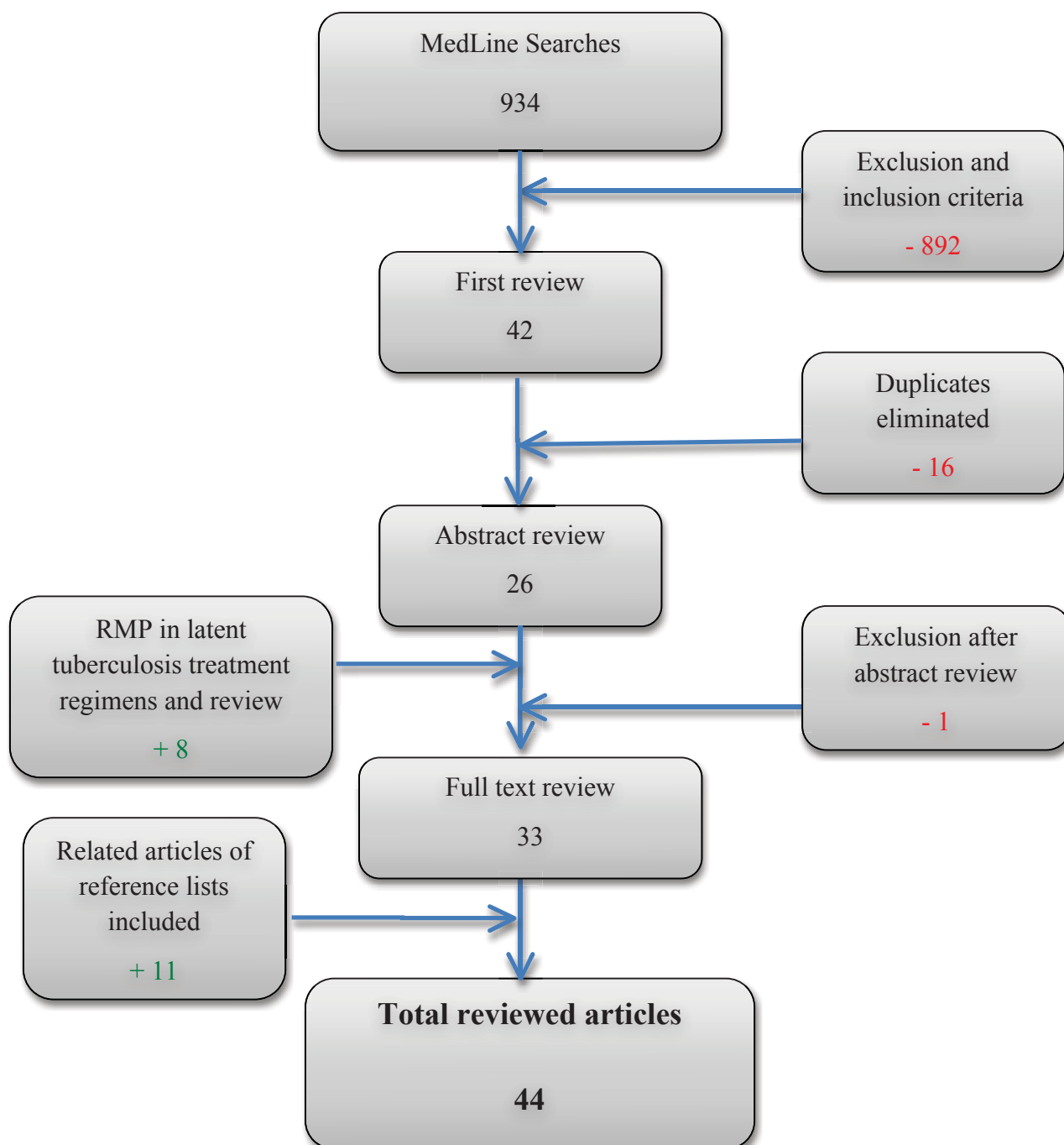


2.2 Rifampin

Using different subject headings in MedLine database (listed below) in total 934 citations were identified for RMP as of 30th November 2011. Considering inclusion and exclusion criteria, as mentioned before, a first review found 42 relevant articles. In a next step multiple stated citations were subtracted resulting in 26 relevant articles. After a following review of MedLine database for RMP in antituberculosis therapy, with limitations as described above, further 8 articles were found matching the inclusion criteria. 33 articles and, in addition, 11 further related articles found in the reference lists and included because of relevancy underwent a full text review. In total, 44 articles were included in this thesis for RMP.

Step	Search details	Citations, no.
1	Rifampin and non-mycobacterial	4
2	Rifampin and nonmycobacterial	4
3	Rifampin and hepatotoxicity	229
4	Rifampicin and hepatotoxicity	290
5	Rifampicin and hyperbilirubinemia	79
6	Rifampin and staphylococcus aureus and hepatotoxicity	3
7	Rifampin and staphylococcal bacteremia	92
8	Rifampin and staphylococcal bacteremia and liver	3
9	Rifampin and jaundice	114
10	Rifampin and icterus	116
Total		934

Table 6. Rifampin - Literature Search Methodology - Flow Chart



3 Results

3.1 Fusidic acid

3.1.1 FA and serum bile acids

FA is shown to be structurally similar to bile salts (40,41). It is converted by the liver to 7 metabolites, including glycodihydrofusidate and taurodihydrofusidate, which are actively secreted into the bile and have micellar properties (6,40). Both derivatives resemble bile salts in terms of structure (42,43) and are noted to inhibit the biliary secretions of bile acids in rats (43), hamsters (44) and rhesus monkeys (42). Narducci et al. found a dose-related increase of serum bile acid levels related to administration of FA in 10 healthy volunteers, furthermore suggesting competing inhibitory effects of FA with bile acids and a common hepatic transport system for both (45,46).

In a study on rat models by Bode et al., investigating whether FA affects the transport across the hepatocyte canalicular membrane, a direct inhibition of Mrp2 and BSEP by competitive interaction of FA was cited. In addition, a downregulation of hepatic Mrp2 protein levels and reduced biliary excretion rates of 17β -D-glucuronosyl estradiol, a Mrp2 substrate which FA resembles structurally, were noted in prolonged treatment with FA (47).

3.1.2 Abnormal liver function in staphylococcal infections due to Fusidic acid

Abnormal liver function tests after administration of FA were first mentioned by Wynn in 1965. A slight elevation of serum bilirubin concentration was shown in 1 of 4 patients, however, not seen in any of the others and, additionally, not in 6 further patients cited in the report. A definite change in liver function due to FA was a delayed and decreased excretion of BSP, but observed to be reversible within 1 to 3 days.

The first case report of hepatic adverse reactions was published by Copperman in 1972, noting a deterioration of hepatic function during therapy in 1 of 3 patients treated with intravenous FA.

Menday and Marsh reviewed 46 cases of intravenous FA in the management of severe staphylococcal infections. 7 patients were children and 39 adults. Progressive jaundice occurred in 2 patients (4.3%) during therapy. 1 patient had been ill for many weeks and already showed jaundice on admission. The second one was a child with treatment for overwhelming post-influenza staphylococcal pneumonia. Jaundice was thought to be due to

the toxemic process of the disease in that case. No further details of laboratory results were given (48).

In a retrospective study by Humble et al., FA was administered in 131 out of 250 patients in treatment of staphylococcal bacteraemia over 10 years. In all patients FA was used in combination with another antibiotic. In addition to FA, Cloxacillin/Flucloxacillin (n=91), Penicillin/Ampicillin (n=17) and Vancomycin (n=11) were used most frequently. 19 patients already had jaundice before FA was started. In 13 of these 19 patients (68%) bilirubin or AP concentration increased further during treatment, but returned to normal after FA was withdrawn. Jaundice occurred in 38 of 112 patients (34%) who were not clinically jaundiced or showed prior normal liver function, compared with 2 of 101 patients, that were treated with other antimicrobials and had normal liver function at baseline (2%) ($p < 0.0001$).

Higher incidences of jaundice were shown in patients given FA intravenously (48%) than orally (13%) ($p < 0.0005$). In 93 % of the cases jaundice developed within 48 hours after administration of FA. However, serum bilirubin concentration fell to normal values within 4 days after FA was withdrawn. Also, cholestatic jaundice was suggested in 6 of 32 patients receiving FA intravenously, since they developed jaundice and had elevated AP levels in addition. AP and AST activity was measured in 91 patients receiving FA. AP became abnormal during treatment in 12 cases, however, 2 patients already had jaundice at baseline. AP rose further during treatment in 4 cases (2 already had jaundice). AST increased during treatment in 16 cases (1 already had jaundice at baseline) and increased further during treatment in 4 cases (49).

Talbot et al. mentioned in a comment 44 cases of jaundice occurring between 1963 and February 1980 (including the 6 cases mentioned below) referred to the Committee on Safety of Medicines. Six cases of jaundice due to the treatment of FA were reported to the West Midlands Adverse Drug Reaction Study Group during four years until 1980. In 5 patients FA was given orally and in 1 patient intravenously. In all cases jaundice developed within a few days and resolved when FA was withdrawn. 3 of 5 patients, of whom full details were available, had normal liver function tests at baseline and no other cause for their jaundice was found. In 2 patients with abnormal liver function tests previous to the administration of FA, bilirubin increased progressively and returned to normal after FA withdrawal. However, Talbot noted that a causal relationship to FA could not be established with certitude (50).

Iwarson et al. studied adverse reactions to intravenous administration of FA. 6 patients were treated with FA in connection with major bowel surgery and 9 patients treated for

staphylococcal abscess, wound infection and osteomyelitis. Slight hyperbilirubinemia occurred in 3 of the surgical patients during postoperative treatment, but none of the non-operated patients showed abnormal liver function tests. Nevertheless, liver function tests were checked before and during treatment in only 6 of the infected patients and the surgical patients received other doses (0.5 g 4 times daily) in comparison to infected patients (0.5 g 3 times daily). Notably, according to the author, slight hyperbilirubinemia shown in the 3 surgical patients also may be associated with the proceeded major surgery (51).

Kutty et al. published a case report of FA-induced hyperbilirubinemia. In this patient hyperbilirubinemia was shown to be predominantly of the conjugated type. Transient slight increases in AST and AP were noted. Serum bilirubin rapidly fell three days after discontinuation and complete normalization took nearly a month. Other possible causes of hyperbilirubinemia were excluded. A needle liver biopsy was taken additionally and showed findings in light- and electron-microscopy similar to those reported in experimental cholestasis induced by bile acids (52).

Eykyn treated 145 episodes of *S. aureus* bacteraemia with FA. 2 patients had jaundice before FA was started and jaundice increased in both. Jaundice during treatment with FA was found in 12 of 143 patients (8.3%) without evidence of jaundice at baseline. 6 of the 35 (17%) patients receiving FA intravenously and 6 of the 108 patients (6%) receiving FA orally developed jaundice. Nevertheless no detailed information about laboratory results, serum bilirubin or liver enzyme concentration was given (53).

In the study by Portier et al. 49 patients were treated with FA because of severe staphylococcal infections. FA was given alone in 3 cases and in combination with another antibiotic in 46 cases. RMP was administered in combination with FA (500 mg three times daily) in 3 cases. 15 (27.8%) patients showed abnormal liver function tests during treatment, commonly with an elevation of serum bilirubin and/or AP. Clinical jaundice was recorded in 4 (7.4%) cases. In few cases slight elevations of transaminase levels were found, but details about its extent and number of patients were missing. Noteworthy, in 11 of 15 (73.3%) patients that developed abnormal liver function tests during treatment, slightly elevated values were already noted before treatment was started. In these cases, further increases in serum bilirubin or liver enzymes occurred within 5 days. Patients with higher hepatic impairment (defined as AP or bilirubin elevation more than 1.5 times ULN) prior to FA administration were excluded from investigation. Liver function tests tended to normalize, either during continued therapy, or shortly after completing therapy with FA. FA was not withdrawn in any

case because of alterations in liver function tests, but in two patients daily dosage was reduced because of hyperbilirubinemia (54).

Haddad et al. described a case of jaundice associated with the use of FA for treatment of postoperative wound infection. The patient received FA in combination with RMP after initial antibiotic therapy. RMP was not seen as the causative factor. 5 days after treatment was started asymptomatic jaundice developed, with an increase in total bilirubin but normal ALT, AST, γ -GT and AP levels. Both antibiotics were withdrawn and bilirubin concentration returned to normal levels in four days (55).

In a randomized trial Mehtar et al. compared Teicoplanin alone against Flucloxacillin with or without FA in the treatment of serious gram-positive infections, especially *S. aureus* and *S. epidermidis*. Of the 10 patients receiving Flucloxacillin and FA 1 patient showed jaundice and 1 hyperbilirubinemia, both resolving spontaneously. However, FA was discontinued in the patient with hyperbilirubinemia. No exact explanation and definition were given, but the author mentioned that the analysis of laboratory data did not show any other findings than the reported ones mentioned as adverse events (56).

In the study by Drancourt et al. 23 patients received RMP in combination with FA and 23 patients RMP and Ofloxacin for oral treatment of *Staphylococcus* spp. infected orthopaedic implants. No adverse events related to the study regimens were mentioned (57).

In another study published by Aboltins et al. FA and RMP were used besides debridement and prosthesis retention in treatment of staphylococcal prosthetic joint infections. Of 20 patients matching inclusion criteria none showed any episode of hepatotoxicity. Laboratory data were not available for review and no definitions concerning hepatotoxicity were given. 2 patients developed a transient rash and additionally pruritus; however, underlying mechanisms e.g. cholestasis were not investigated or discussed (58).

Table 7 FA in staphylococcal infections					
	Study design	Patient no.	Administered drugs	Jaundice/Hyperbilirubinemia	Other liver enzyme elevation
Menday and Marsh, 1976 (48)	Retrospective case review	46 (7 children 39 adults)	previous AB: Penicillin, Cloxacillin Ampicillin 39 pat.; concurrent AB to iv. FA in 28 pat. (no further data)	Jaundice: 2 (4.3%)*	-
Humble et al., 1980 (49)	Retrospective review	250 (131 FA; 119 in control group)	FA and Cloxacillin/Flucloxacillin, Vancomycin, Penicillin/Ampicillin or others	Jaundice: 38 (34%) of 112 patients without jaundice at baseline further elevation in 13 (68%) of 19 patients already jaundiced at baseline [§]	AP raised during treatment: 12 (31.6%) [§] AST raised during treatment: 16 (42.1%) [§]
Iwarson et al., 1981 (51)	not defined	15	6 surgical p., 9 non-surgical p. FA iv.	Slight Hyperbilirubinemia: 3 (50%) of surgical patients	-
Eykyn et al., 1990 (53)	Restrospective review	145	FA + Flucloxacillin or others	Jaundice: 12 (8.3%) ^{&}	-
Portier et al., 1990 (54)	Multicenter, open clinical trial	49	FA alone (3) FA + Vancomycin (14), Aminoglycoside (21), Quinolone (4), RMP (3), Penicillin, Fosfomycin Pristinamycin (2)	Jaundice: 4 (7.4%)	Abnormal liver function tests: 15 (27.8%) – commonly bilirubin/AP # Slight elevations of transaminase levels: ?

Mehtar et al., 1995 (56)	Comparative randomized trial	56	Teicoplanin (30), Flucloxacillin (16) Flucloxacillin + FA (10)	Jaundice: 1 (10%) Hyperbilirubinemia: 1 (10%)	-
Drancourt et al., 1997 (57)	Prospective clinical trial	46	FA + RMP (23) RMP + Ofloxacin (23)	0	0
Aboltins et al., 2007 (58)	Retrospective cohort analysis	20	FA + RMP	0	0
<p>AB....antibiotics</p> <p>pat.....patients</p> <p>*.... 1 child (due to authors related to toxæmic process of disease), 1 adult (with jaundice at admission); no further data available;</p> <p>\$ increased further during treatment</p> <p>§ % of patients jaundiced during treatment (38 of 112)</p> <p>&..... and 2 who were already jaundiced before treatment</p>					

3.1.3 FA used in treatment of psoriasis

Vickers and Menday published a double-blind cross-over trial comparing FA and placebo in treatment of 33 patients with psoriasis. 17 patients received FA and 16 patients placebo. Liver function tests were conducted before and 4 and 8 weeks after therapy. 4 patients already had raised values before treatment, including bilirubin in 1, AP in 2, AST in 1 and ALT in 3 patients. 1 patient with normal values before treatment showed elevation of AP (5.9%) and 1 patient (5.9%) an elevation in ALT levels after 4 weeks of treatment, however, all elevations resolved after another 4 weeks. Bilirubin remained elevated in the patient who already had elevated bilirubin at baseline. Elevated AP remained elevated in 1 patient and ALT levels in 2 patients with elevated values at baseline (50).

Another report of jaundice due to FA in treatment of pustular psoriasis was noted in the review by Christiansen. An elevation of serum bilirubin developed 3 days after FA was started in 1 patient, however, levels normalized after FA was withdrawn (59).

3.1.4 Pharmacokinetics, tolerability and safety

The study about pharmacokinetics and tolerance of FA, authored by MacGowan et al. in 1989, showed no adverse liver events related to the treatment with FA (60).

In the study by Reimann et al. HIV-infected L-methadone-substituted intravenous drug abusers were treated with FA in 2 of 3 randomized groups for investigating possible effects of fusidic acid on microsomal enzyme activity. Some patients had chronic active hepatitis B and/or hepatitis C also, but all laboratory values had to be within normal ranges to be included into the study. Although FA causes a significant time-dependent activating effect on the CYP P450 enzyme system, no side-effects occurred in any of the patients and no changes in liver function tests, including AST, ALT, γ -GT, bilirubin and AP could be found during 14 and 28 days of therapy with FA (6).

Peter et al. investigated pharmacokinetics of FA and 3-ketofusidic acid in cholestatic and non-cholestatic postoperative patients - recruited in Intensive Care Units - suffering from pneumonia or septicemia and treated with intravenous administration of single and multiple doses of FA. In group I non-icteric patients with normal bilirubin and AP levels were included. Group II included subjects with bilirubin and AP above the upper limits of normal (ULN) and group III included patients with isolated conjugated hyperbilirubinemia. Since FA is highly albumin bound it was suggested that low albumin concentrations, found in all subjects, may lead to increased free fractions of FA and larger and faster distribution of the free drug. Patients in group I and II indeed showed a higher clearance and lower accumulation rates than that in healthy volunteers calculated in another study, which was seen to be due to an increased metabolism and distribution in tissue as a consequence of lower serum albumin concentrations. On the other hand, clearance at steady state in group III patients was lower than that in group I and II patients, although albumin concentrations were low. It has been suggested that high bilirubin concentrations were in competition with FA for participation of limited glucuronidation processes. The authors concluded that FA may be administered in a normal dosage regimen to postoperative patients with hyperbilirubinemia since postoperative serum albumin concentration is generally low (61).

In 2011 Kraus et al. published a safety record of available safety data on FA cited in global literature between 1962 and 2007, containing data on oral FA safety and, in addition, data of the centralized database (VigiBase) of spontaneous safety reports, focussing on skin infections.

In the surveyed literature between 1962 and 2007 7 hepatobiliary events were found in patients with skin infections treated with oral FA. However, hepatotoxicity was not persuasively linked to FA monotherapy in these patients. Elevations in bilirubin and hepatic enzyme levels were explained by the concomitant exposure with known potentially hepatotoxic agents. In a second case elevations in bilirubin and hepatic enzyme levels were interpreted to be due to disease state and/or use of known hepatotoxic drugs, since the patient suffered from AIDS and a concomitant use of potentially hepatotoxic drugs (Sulfadoxine and Pyrimethamine) and CYP 3A4 inhibitors (Ketokonazole) was found. Furthermore, 19 articles on osteomyelitis, including 429 patients, were cited. Adverse events were similar in character to skin infection subjects. All 9 hepatobiliary events were not persuasively linked to oral FA exposure. In 1 patient, for instance, concomitant use of hepatotoxic agents was found and further 4 patients were treated with high-dose FA, with a mean daily dose of 3 g; however, due to limited information critical clinical assessment is not feasible.

The review of VigiBase, a database which is developed and maintained by the Uppsala Monitoring Centre on behalf of the World Health Organization comprising international drug safety data, found in total 1476 adverse events reported among 824 subjects. Adverse events due to FA were cited to be most frequently categorized as hepatobiliary and allergic, as well as hematologic, gastrointestinal or neurologic.

In total 414 hepatobiliary events were noted in 824 patients with primary reference of an adverse event linked to orally administered FA. In detail, in 18 of 50 identified patients treated for skin infections and 4 of 18 identified subjects treated for osteomyelitis hepatobiliary adverse effects were noted. Incidentally, 392 further hepatobiliary events were identified in VigiBase Data extract. Of 13 cited deaths listed as potentially related to FA exposure, 11 were classified to be due to liver and biliary system disorders. However, no convincing association to FA exposure alone was found. The authors stated that hepatotoxic events in literature were lacking significant clinical information to allow critical assessment, were meant to be potentially referred to FA exposure, but not of significant concern (7).

A randomized, double-blinded, placebo-controlled dose escalation study in 2011 conducted in 40 healthy volunteers showed that oral administration of single doses (550 mg, 1100 mg, 1650 mg, 2200 mg), multiple doses (same as single dose, but every 12 hours (Q12h) for 5.5 consecutive days (11 doses)) and loading dose regimens followed by multiple doses (1100 mg Q12h on Day 1, 550 mg Q12h for 6.5 consecutive days (13 doses); or 1650 mg Q12h on Day 1, 825 mg Q12h for 6.5 days) were safe and well-tolerated at all dose levels. No deaths or

serious adverse events were reported and no clinically significant laboratory abnormalities were found for any dose level. Nevertheless, 2 patients who received multiple doses, 2 patients who received loading dose regimens and four subjects who received higher loading dose regimens developed transient, mild and reversible increases in total serum bilirubin, however, considered not to be clinically significant by the authors (62).

Another phase 2, randomized, double-blind, multiple-center study in 2011 conducted in 198 patients with cellulitis or wound infection evaluated FA loading-dose regimen (1500 mg twice per day on day 1 followed by 600 mg twice per day) compared with oral Linezolid. No adverse effects concerning hepatotoxicity, liver enzyme alterations or hyperbilirubinemia were mentioned. Efficacy, safety and tolerability were shown by the authors to be comparable to Linezolid for the treatment of acute gram-positive bacterial skin and skin structure infections (63).

3.2 Rifampin

3.2.1 RMP-induced cholestasis and potential molecular mechanisms

Interference and competition with bilirubin transport and conjugation and hepatic elimination of compounds such as bilirubin, bromosulfophthalein and indocyanine green has been shown for RMP (27,64,65). This metabolic effect may also be seen as a variant of cholestatic injury, resulting in hyperbilirubinemia (64). In the small study by Capelle et al. 5 of 6 patients with normal livers showed an important increase of unconjugated bilirubin and total bilirubin levels after RMP was administered. RMP was noted to inhibit both uptake and excretion of bilirubin in a dose-related manner, leading to an elevation in both conjugated and unconjugated bilirubin plasma levels (64,65). Besides, Capelle et al. noted that the increase in total bilirubin level was clearer in cirrhotic patients, however, none of them showed any clinical signs of intolerance (65).

In the study by Galeazzi et al. the total serum bilirubin concentrations showed a significant - but transient - increase in all patients after administration of RMP considering RMP to inhibit the hepatic transport of bile acids (66). Furthermore, an inhibition of hepatocellular bile salt uptake due to RMP was suggested, since serum bile salt concentrations were elevated in 72 % of patients after the first dose of RMP (27). All interference phenomena with bile acids and bilirubin were categorized to be dose-related and predictable (27,64,65).

3.2.1.1 Transporters, pumps and bile acids

The Na⁺/taurocholate cotransporting polypeptide (NTCP) and the bile salt export pump (BSEP) play an important role in the regulation of the concentration of bile acids. In literature NTCP and BSEP were shown to be possible target molecules for cholestatic drugs, such as rifamycin and RMP (29,67).

A recent study by Mita et al. demonstrated inhibitory effects of RMP and rifamycin SV on the basal-apical efflux of taurocholate. The efflux clearance across the apical membrane was calculated and an inhibition of 70 % (RMP) and 44 % (rifamycin SV) of the efflux clearance across the apical membrane was noted, indicating that both drugs inhibited the efflux of taurocholate by BSEP located in the apical membrane. As further target involved, an inhibition of NTCP was suggested for rifamycin SV. However, the possibility of inhibition of NTCP for RMP was not shown but could not be excluded based upon their data (67).

In a study by Fattinger et al. rifamycin SV was shown to inhibit both organic anion transporting polypeptides, Oatp1 and Oatp2, whereas RMP was identified as a selective inhibitor of Oatp2 (27). A following study by Vavricka et al. showed an interference of rifamycin SV and RMP with OATP-mediated substrate transport. BSP uptake was tested and almost completely abolished by rifamycin SV. Additionally, BSP uptake by OATP8 was in comparison to others, such as OATP-C, OATP-B and OATB-A, preferentially inhibited by RMP, indicating that an uptake of RMP is predominantly mediated by OATP8 (68). Fattinger et al. inferred that an inhibition of human liver OATPs shown in their study may explain observed effects of RMP and rifamycin SV on hepatic organic anion elimination (27).

3.2.1.2 Tight junctions

Hepatocyte tight junctions consist of a network of protein strands anchored directly or indirectly to the actin component of the cytoskeleton. Tight junctions generally assist in maintaining the polarity of cells and are the only intercellular barrier, preventing passage of ions and molecules from the canalicular spaces to the sinusoidal spaces. In the study by Chen et al. bilirubin and total bile acid in serum were measured in RMP-induced cholestatic mice. The outcome was a 70-fold increase in total bilirubin and an 82-fold increase in conjugated bilirubin after an administration of RMP for 1 week. Total bile acid levels in serum and total bile acid levels in liver tissue were noted to be elevated, suggesting RMP-induced cholestasis (69). A histology of the liver was taken, showing predominantly steatosis associated with necrosis and inflammation. AP was found to be significantly increased after 7 days of

administration of RMP and some evidence of increased ALT and AST levels was mentioned, but shown to be minor (69). Additionally, a single dose of RMP resulted in slight increases in ALT and AST levels, significantly increased levels of total bilirubin and conjugated bilirubin in serum and reversibly increased levels of total bile acids in serum and liver tissue. However, a single dose of RMP did not show any pathological damage on mouse liver. Chen et al. concluded that both a single dose and an administration of RMP for 1 week cause cholestatic liver damage. Additionally, the observed tortuous and discontinuous (immuno)staining of ZO-1 and occludin and a significant decrease in expression of hepatic zonula occludens (ZO)-1 and ZO-2 mRNA after 7 days of administration of RMP, indicated that RMP-induced cholestasis is associated with altered integrity and intensity of hepatocyte tight junctions (69).

3.2.1.3 RMP-induced cytotoxicity

Nakajima et al. identified the recombinant human arylacetamide deacetylase (AADAC) to be responsible for deacetylation of rifamycins, such as RMP, Rifabutin and Rifapentine. In their study, rifamycins showed potent cytotoxicity to HepG2 cells in a dose-dependent manner, however, RMP showed less toxicity in comparison to Rifabutin and Rifapentine. The 25-deacetylated metabolites showed no or less cytotoxicity and also had no or little inducing potential of CYP3A4. Additionally, rifamycins provoked low cytotoxicity and exhibited low induction potency of CYP3A4 in HepG2 cells infected with a recombinant adenovirus expressing human AADAC, suggesting AADAC would protect against rifamycins-induced cytotoxicity (70).

3.2.1.4 Inflammatory Mediators

Nitric oxide (NO) is known to be a major immune mediator. Its production is controlled by constitutive and inducible isoforms of nitric oxide synthase (NOS). NO itself is associated with many cellular and biochemical functions. It plays an important role in hepatic microcirculation and endothelial integrity. High levels of NO are noted to be either protective or harmful, depending on the kind of injury. NO and IL-8 induce proinflammatory effects in the liver. Moreover, prolonged or massive production of NO is noted to be able to lead to hepatic inflammation and tumor development (38). Recent studies showed that RMP increases the expression of inducible NOS and NO in human alveolar epithelial cells. The study by Yuhas et al. exhibited that RMP may induce proinflammatory mediators and increase cytokine-induced production of NO and IL-8 in HepG2 cells, indicating proinflammatory effects by RMP on the liver. Furthermore, the enhanced NO production caused by RMP may affect the induction of other immunomodulators (38).

3.2.1.5 Oxidative stress

Shen et al. showed RMP-induced hepatotoxicity in gel-entrapped rat hepatocytes. In their study, biomarkers of oxidative stress were assayed, showing a drastic generation of reactive oxygen species (ROS) and a depletion of intracellular glutathione (GSH) after RMP administration, indicating that oxidative stress plays a role in RMP-induced hepatotoxicity. Both GSH enhancers and ROS scavenger were effective in reducing RMP-induced toxicity, confirming the involvement of oxidative stress. Furthermore, Shen et al. detected intracellular lipid accumulation and lipid peroxidation to play a role in RMP-hepatotoxicity (71). In addition, the treatment of rat hepatocytes with CYP 450 inhibitors showed no toxicity and CYP450 inhibitors could not inhibit the toxicity of RMP, suggesting that CYP 450 could be unrelated to RMP-toxicity (71).

3.2.2 RMP in non-mycobacterial infections – clinical trials and reviews

Forrest et al. reviewed data concerning RMP combination therapy for non-mycobacterial infections and concluded that there is a lack of significantly controlled clinical studies. Data supporting RMP combination therapy in non-mycobacterial infections are basically based upon in vitro or in vivo data or retrospective case series, all with major limitations. Two studies published by Riedel et al und Schrenzel et al were reviewed in the article, showing a relation to hepatotoxic adverse effects of RMP (12).

A large literature review by Kissling and Bergamini mentioned 7 cases of jaundice due to RMP in 650 patients reviewed in several trials. After review of the reference list all articles where published in another language than English and not matching inclusion criteria for review of further details. However, it is of interest to note at that point, that 2 cases where defined as subicteric, 3 described patients where alcoholics and in 2 other cases patients already had hepatic dysfunction before RMP-treatment was started. Furthermore, two articles mentioned elevated ALT and AST levels, but one article considered a case report in a 2-month old child and another article was published in French. A further article noted deterioration of preexisting liver impairment in 1 patient and elevation of serum bilirubin values in another patient after administration of RMP. However, this article was found to be published in French and not listed in MedLine (72).

In total, 8 articles concerning RMP in non-mycobacterial infections were found matching inclusion criteria for this thesis: 2 articles investigated RMP in treatment of osteoarticular infections (73,74) and another study analyzed the efficacy and safety of RMP containing

regimen for staphylococcal prosthetic joint infections (75). 2 further studies dealt with RMP in combination therapy of (bacteraemic) infections caused by *S. aureus* (76,77) and the other 3 articles contained RMP therapy of native valve infective endocarditis caused by *S. aureus* (78), right sided-staphylococcal endocarditis in injection drug users (79) and MRSA-Endocarditis (80).

In summary, the incidence of hepatotoxicity due to RMP used in non-mycobacterial infections was low and ranged from 0 to 4.3 %. In 3 studies hepatotoxicity due to RMP was noted and the incidence ranged from 2.8 to 4.3 % (75,77,79). In the other 5 published trials no hepatotoxicity was observed.

In total, 6 articles showed liver enzyme elevations. 4 articles described elevated transaminase levels ranging from 2.9 to 13 of patients % (73,74,77,80). The study population was small in all reviewed articles. There was a lack of information concerning definition, chemistry values and grading in all of them. In only 3 of the reviewed articles exact definition of hepatotoxicity, hepatitis, or transaminase elevation was available (74,78,79).

Table 8. RMP in non-mycobacterial infections						
	Hepatotoxicity Definition	Study design	Patient, no.	Administered drugs	Hepatotoxicity/hepatitis (in%)	Liver enzyme elevation
Cluzel et al., 1984 (73)	Not defined	Not defined	20	RMP + aminoglycosides, mostly Gentamicin (18), + Cephalothin and Amikacin (1), + Cotrimoxazole and Gentamicin (1)	0	1 (5%) slightly raised transaminase levels
Levine et al., 1991 (80)	Not defined	Cohort analysis of a randomized trial	42 Vancomycin 22 Vancomycin + RMP 20	Vancomycin i.v. + RMP 600 mg once daily orally	0	1 (5%)
Heldman et al., 1996 (79)	Hepatotoxicity: serum transaminase	Prospective, randomized, non-blinded	Ciprofloxacin-RMP 36 Oxacillin/Vancomy	Oral: Ciprofloxacin + RMP (600 mg)	1 (2.8 %)	-

	elevation from normal to > 150 IU/l; abnormal baseline to > 3-fold increase;	trial	cin and gentamicin 39	i.v.: Oxacillin/Vancomycin + Gentamicin		
Yzerman et al., 1998 (76)	Not defined	Open study	16	Teicoplanin + RMP (1200 mg) i.v.	0	(?) Slight elevations of AP and GGT
Schrenzel et al., 2004 (77)	Not defined	Multicenter randomized clinical trial	130 (69 Fleroxacin –RMP; 61 flucloxacillin or vancomycin; respectively 68 and 59)	Fleroxacin-rifampicin (600 mg) vs. Flucloxacillin or Vancomycin	3 (4.3)	2 (2.9) increased transaminase levels
Roblot et al., 2007 (74)	RMP-induced hepatotoxicity: ALT > 2 times ULN	Pilot study	46	44 orally, 2 parenterally; 42 patients 600 mg twice daily, 3 600 mg 3 times daily one patient 900 mg twice daily; ALT values obtained before RMP therapy and +/- 3 days around each RMP measurement,	0	6 (13%)# ALT > 1 ULN
Riedel et al., 2008 (78)	Elevation of hepatic transaminase levels > 5 times of ALT/AST baseline levels	Retrospective matched cohort study	84 + RMP 42 - RMP 42	Combinated drug: Vancomycin (81%) Nafcillin (17%) Daptomycin (one patient)	0	9 (21%)

El Helou et al., 2009 (75)	Not defined	Prospective cohort (PC) Retrospective cohort (RC)-with RMP, without RMP	PC -14 RC - 87 (with RMP 31 without RMP 56)	PC (RMP 900 mg + Levofloxacin orally)	0 3 (3.2) *	-
<p>* in retrospective cohort treated with RMP</p> <p># ALT > 1 ULN, 3 (6.5%) already had ALT > 1 ULN at baseline</p> <p>ULN...upper limit of normal</p> <p>§ not impact of study; side note</p>						

In the following sections the articles are reviewed in detail:

Cluzel et al. noted slightly elevated transaminase levels in 1 (5%) of 20 patients treated with RMP-combination-therapy in osteoarticular infections due to staphylococci. But no data concerning liver enzymes, grading or definition were given. In addition, hepatotoxicity due to RMP was not described.

Heldman et al. compared - in a prospective randomized non-blinded trial - oral treatment of Ciprofloxacin and RMP with parenteral therapy of Oxacillin or Vancomycin plus gentamicin in right-sided staphylococcal endocarditis. 1 patient (2.8 %) showed hepatotoxicity. In comparison, 13 (33%) of the patients in the parenteral treated group showed a hepatotoxic reaction (79).

In the study by Yzerman et al. a dosage of 600 mg RMP twice a day in combination with Teicoplanin was administered parenterally in 16 patients with hospital-acquired, bacteraemic *S. aureus* infections. No incidence of hepatotoxicity in patients treated with parenteral administration of RMP was noted. Slight elevation of AP and GGT, but normal aminotransferase levels were observed in some patients, without giving information about the quantity and whether these effects have been reversible or not (76).

Schrenzel et al. analyzed RMP in combination therapy for staphylococcal infections and noted hepatitis in 3 (4.3%) of 69 patients. In 2 cases, RMP was withdrawn because of hepatitis. In addition 2 (2.9%) patients showed elevations in transaminase levels. Nevertheless, no exact

grading, definition or chemistry values were mentioned in this article. The incidence of drug toxicity was shown to be higher in the Fleroxacin-RMP group (600 mg) in comparison to the Flucloxacillin or Vancomycin group (77).

Roblot et al. found no hepatotoxicity, defined as ALT elevation >2 times ULN in their pilot study of 46 patients treated with RMP (in combination with Fluoroquinolones, Trimethoprim-sulfamethoxazole or Glycopeptide) for osteoarticular infections. Nevertheless, 6 (13%) patients showed ALT elevations > 1 time ULN, however, 3 (6.5%) of them already had elevations >1 time ULN at baseline (74).

In a retrospective cohort analysis published by Riedel et al. a higher incidence of hepatic transaminase elevations was noted. 9 (21 %) of 42 patients showed significant hepatic transaminase elevations defined as an elevation of hepatic transaminase (ALT/AST) levels more than 5 times of baseline levels in the group in which *S. aureus* infective endocarditis was treated in addition with RMP. RMP was used in combination with Vancomycin (81%), Nafcillin (17%) and in 1 patient with Daptomycin. In comparison, only 1 (2%) patient in the control group (without RMP) showed a hepatotoxic reaction. Nevertheless, all patients had marginal elevations of hepatic transaminases at baseline and occurred only in patients with hepatitis C virus infection. 50 % of the patients were injection drug users. The highest values were for AST levels in limits of 3 times ULN and ALT levels in limits of 4 times ULN. No exact values of liver enzymes were available for review. Besides, no description of the administered dosage of RMP was given in the article by Riedel et al. The author concluded that RMP should be used with caution, especially in patient with underlying hepatitis C virus infection. In addition, a careful risk-benefit assessment before adding RMP to standard antibiotic therapy was recommended (12,78).

In the prospective cohort study by El Helou et al. none of the 14 patients treated with 900 mg RMP and Levofloxacin orally for staphylococcal prosthetic joint infections showed hepatotoxicity. Data were compared to a historical cohort in which 3 (3.2%) of 31 patients treated with RMP-combination therapy developed hepatotoxicity, however, not defined and graded and no data concerning liver enzymes were available for review. Noteworthy, all patients with hepatotoxicity were in the retrospective cohort and none of the patients of the prospective cohort showed any hepatotoxic reactions (75).

3.2.3 Rifampin in antituberculosis therapy – clinical trials and reviews

According to Tostmann et al. the incidence of antituberculosis drug-induced hepatotoxicity (ATDH) depends on the investigator's definition of hepatotoxicity. It is variably reported to be between 2 % and 28 % for standard multidrug antituberculosis therapy, including RMP, Isoniazid and Pyrazinamide. Few data on toxicity rates of antituberculosis drugs as single therapy exist, since active TB is generally treated with multiple drug schedules. Isoniazid was for a long time the only exception because of its prophylactic use in latent tuberculosis infection (LTBI), and therefore more data are available (81). Nevertheless, several studies now compared RMP-single-therapy in comparison to INH-therapy in LTBI and are listed and analyzed below (82-85).

Yew and Leung cited some articles noting that RMP alone is possibly associated with a lower potential for hepatotoxicity than Isoniazid or Pyrazinamide. Further recommendations of the American Thoracic Society/Centers for Disease Control and Prevention/Infectious Disease Society of America note RMP as first drug to be restarted after recovery from antituberculosis chemotherapy-induced hepatitis (80), which may support this argument.

Tostmann et al. cited 2 articles in which RMP-induced hepatotoxicity occurred in about 1-2 % of patients during prophylactic RMP monotherapy, but 1 of these did not match inclusion criteria (81). In their review about antituberculosis drugs and hepatotoxicity Yew and Leung cited an article by Steele et al. about toxic hepatitis with Isoniazid and RMP. This article demonstrated an incidence rate of liver toxicity of 1.1 % with RMP alone, 1.6 % with Isoniazid alone and 2.6 % if both are co-administered (86).

Girling mentioned some articles, noting transient increases in serum transaminase concentrations and other abnormalities of liver function tests, without clinical evidence of hepatitis. 1 study was reported in which RMP was given alone, however, this study was not found in MedLine. In addition, Girling mentioned some articles in which RMP was used in combination with other drugs causing liver function abnormalities, however, after reference review all articles did not match criteria of this thesis since RMP was in multi-drug antituberculosis therapy schedules, mostly published in another language than English, or the impact factor of the journals was less than 1, and therefore not further reviewed. Nevertheless, it is of interest to note that Girling found these abnormalities of liver function to be transient and common, typically occurring during the first few weeks of chemotherapy and self-limiting even if RMP-administration was continued (87).

After abstract review the Australian rifampicin trial by Proust was included in this review (88). 54 patients were included in the trial and, in addition, values of 226 patients outside the trial were analysed. Of 27 patients (Group A) of which complete records of liver function were available 2 patients showed subicteric toxic hepatitis and no one showed jaundice. Of 27 patients in Group B, with incomplete biochemical records but full clinical records, 1 patient showed signs of subicteric toxic hepatitis. Of 226 Australian patients outside the trial 4 developed jaundice and 1 was categorised as subicteric toxic hepatitis. However, it is of interest to note that no exact definition of grading criteria of jaundice or subicteric toxic hepatitis were mentioned by the author. Furthermore, after full text review all patients received multi-drug therapy. All 3 patients in the trial with subicteric toxic hepatitis received RMP and Prothionamide and 1 patient also Pyrazinamide; 1 patient was alcoholic. The subicteric patient outside the trial received RMP in combination with INH. Proust noted that in 16 of 54 patients some evidence of abnormal liver function could be found. Proust described an association of the seven more serious abnormalities (three cases of subicteric toxic hepatitis and four cases in which more than three parameters were altered) with other drugs that were used in combination with RMP, such as Ethionamide, Prothionamide, Pyrazinamide or p-aminosalicylic acid or alcoholism except in 1 case. RMP was continued in 5 of these 7 cases without signs of illness. Nevertheless, in 7 of 9 cases in which 1 or 2 parameters showed abnormalities, RMP was considered as causing factor, however, not further described in the article. Exact values of measured parameter abnormalities were not mentioned and RMP was never used alone. In some cases liver function turned back to normal after suspending RMP and restarting antituberculosis therapy without RMP. Proust concluded that RMP administration may be followed by toxic hepatitis in a small percentage of treated patients. However, Proust noted that the incidence of the described hepatitis seemed to be associated with co-administration of certain drugs, alcoholism and preexisting liver disease (88).

Schonell et al. mentioned a transient rise in AST levels in 1 (5.8%) of 17 patients, however treated for tuberculosis in multidrug-therapy including RMP (9). In another study treatment regimen was planned to be switched from Streptomycin and INH to high-dose (1200 mg) RMP twice weekly in addition to INH. But the high incidence of side effects led to cessation of the intermittent regimen. Hepatotoxicity was not further considered, but the authors stated, that none of the patients showed hepatotoxic reactions. No further data or definitions were available (89).

To summarize data of articles concerning RMP-single therapy in LTBI, there are 8 published clinical trials that are included in this review documenting hepatotoxicity and transaminase elevation of RMP (82-85,90,91). Four of these articles compared hepatotoxicity rates between INH and RMP in latent tuberculosis infection (LTBI) (82-85), 2 further articles discussed the topic RMP in LTBI therapy (90,91) and 1 article was about preventive therapy for tuberculosis infection (92). The incidence of hepatotoxicity in the included and reviewed articles ranged from 0 to 2 %. Five studies showed incidences less than 1%, ranging from 0-0.7% (82,83,85,91,92). However, the study by Fountain et al. (90) noted an incidence of 1.95 % of RMP-induced hepatotoxicity and the recently published study by Fresard et al. (84) an incidence of 2 %, respectively.

In 4 studies hepatotoxicity was defined as transaminase elevation >3 times ULN plus symptoms or an elevation >5 times ULN (82,84,90,91). By Menzies et al. adverse events were graded by the National Cancer institute Common Terminology criteria for adverse events defining hepatotoxicity grade 3 as elevation >3 times ULN plus symptoms respectively 5-10 times ULN and no symptoms and as grade 4 hepatotoxicity > 10 times ULN (83). In the study by Lardizabal et al. (85) no clear definition was given and in study by Villarino et al. (92) hepatotoxicity was not defined, but an elevation of transaminase levels was noted if ALT/AST levels exceeded twice ULN.

Elevated transaminase levels not achieving hepatotoxicity definition criteria were noted in 4 studies (82,83,91,92). Definitions differed, making a comparability difficult. Generally low elevations in transaminase levels (ALT or/and AST more than (>) 1 to less than (<) 3 times ULN) occurred with an incidence ranging from 0.9 to 5% (83,91,93). Elevations >3 to <5 times ULN, but not fitting definition criteria of hepatotoxicity, occurred with an incidence of 0.1-0.5% (82,83,91).

In summary, in only 4 of 8 studies bilirubin levels were measured and in only 1 study further data were available (83,91-93). Nevertheless, in the study of Villarino et al. 4 patients presented with an elevation in total bilirubin, ranging from 2 to 4 mg/dl, but without symptoms (92).

In 2 studies baseline liver function tests and blood levels were only monitored if patients had an increased risk of hepatotoxicity, such as HIV infection, history of hepatitis, chronic liver disease or an history of alcohol use (82,85). In 4 studies baseline values were routinely withdrawn with a range of 6 % to 43 % of missing data concerning ALT/AST levels (82-84,91). In the study of Haley et al. values were routinely controlled each month if baseline

levels were abnormal or new symptoms occurred (91). In the study by Menzies et al. transaminases were routinely monitored only at baseline and after 1 and 2 months of treatment but clinical follow-up conducted for 4 months (83). Fountain et al. noted routine monitoring at baseline and the first 3 months. Nevertheless, ALT levels were only measured in some patients (90). Monthly control was also performed in the study by Villarino et al. (92). A monthly clinical monitoring was performed in 3 studies. In the study of Page et al. (82) a symptomatic review using a list of standard questions was performed and in the study of Lardizabal et al. (85) patients were monitored by nurses during each face-to-face visit. Patients were reviewed for signs and symptoms of RMP-induced adverse effects and active tuberculosis referring to physician evaluation if adverse effects or symptoms were detected (92).

Table 9. RMP in antituberculosis therapy					
	Hepatotoxicity Definition	Patients, no.	Hepato toxicity (Inc.)	ALT/AST elevation (Inc.)	Monitoring schedule
Menzies et al.; 2008 (83)	Grade 3: ALT/AST 3-10 times ULN + symptoms or 5-10 times ULN no symptoms Grade 4: 4 ALT or AST levels >10 times	Total: 840 /847 RMP: 418 /420 screened for serious adverse events respectively analyzed for treatment completion	3 (0.7)	ALT: 22 (5) * AST: 17 (4) * 3 (1) # 1 (0.2) #	Baseline, blood tests first and second month; seen every month for the first 4 months;
Page et al.; 2006 (82)	ALT AST level > 3 ULN with hepatitis symptoms or > 5 times ULN without symptoms elevated transaminase levels = asymptomatic individuals with ALT/ and or AST levels 3 to fewer than 5 times the ULN	Total 2149 RMP: 1379 (1229 for adverse drug reactions measured)	1 (0.08)	ALT or AST 6 (0.5)	Routine measurement only in patients with risk factors for hepatotoxicity

Fountain et al.; 2009 (90)	Hepatotoxicity = AST or ALT > 3 times the ULN with symptoms or > 5 times the ULN without symptoms Moderate hepatotoxicity = AST/ALT 5 to 10 times ULN; Severe hepatotoxicity AST/ALT > 10 times ULN	205 patients (available data)	4 (1.95)	-	Baseline; monitoring AST at 1 moth and 3 months of therapy;
Fresard et al.; 2011 (84)	AST/ALT elevation >_ 5 times ULN or 3 times ULN plus syptoms or clinical hepatitis	426 pat INH (15 switched to RMP), 198 RIF	4 (2)	-	Baseline, monitoring every month (for whole duration)
Haley et al.; 2007 (91)	AST/ALT >5 times ULN > 3times ULN plus hepatitis symptoms	749	3 (0.4)	ALT: 7 (0.9) § respectively 8	Baseline, monitoring if baseline values abnormal or new syptoms
Lardizabal et al.; 2006 (85)	Not defined; clinical hepatotoxicity (?)	474	0	-	Baseline and monitoring if increased risk
Villarino et al.; 1995 (92)	Not defined, AST/ALT elevation = > 2 times ULN Total bilirubin > 1.5 mg/dl	157	0	ALT: 4 (2.5) AST: 2 (1.3) Tot Bil: 4 (2.5)	baseline, at least monthly, supervised by nurses; 2 year follow-up
Lee et al.; 2011/12 (93)	Not defined	87	0 (?)	ALT: (6.9) AST: (3.4)	Baseline, 1, 2 and 3 months of therapy, 2-year follow-up
*1 to 3 times ULN # >3 times ULN § > 2 to <3 of normal					

| 1 (0.2 %) patient was asymptomatic not fitting hepatotoxicity criteria

|| 1 patient (0.1%) of 4 with elevated transaminase levels (ALT/AST >3 <5 times ULN was asymptomatic and therefore not fitting hepatotoxicity criteria)

Inc. - Incidence in %

Tot Bil. - Total Bilirubin (range 2-4 mg/dl)

In the following section the included articles are reviewed in detail:

The 3 patients that developed hepatotoxicity in the study of Haley et al. had normal baseline levels and 2 were symptomatic. None of the patients had known hepatitis risk factors. Nevertheless, HIV and viral hepatitis serology and a screening of potential liver-toxic substances were not performed (91). In the study of Fountain et al. 3 of 4 (1.95%) of the patients with hepatotoxicity had elevated AST/ALT values at baseline. 1 patient had hepatitis C (AST baseline: 112) and 1 had an unconfirmed history of hepatitis (AST baseline: 218). 3 of the 4 patients were asymptomatic and two discontinued RMP-treatment after 1 month (90).

In the study of Fresard et al. 4 (2 %) patients developed hepatotoxicity but all were asymptomatic. It was not mentioned whether the patients had previous baseline elevations. Besides, only 61 % had available baseline values (84). According to the author, the higher rate of hepatotoxicity may be due to the systematic monthly monitoring of AST and ALT. But systematic monthly monitoring was also done in other studies, either for the first 2 to 3 months or for the whole period respectively (83,90,92). In the study by Fresard, however, the occurrence of hepatotoxicity was not mentioned, so the comparability to these studies is not possible.

In the study by Page et al. with a low incidence of 0.08 % of RMP-induced hepatotoxicity data were only evaluated of patients who returned to clinic, making possible that some could have had adverse reactions not evaluated (82).

Exploratory analyses performed in the article by Menzies et al. demonstrated that hepatotoxicity was significantly associated with other comorbid illnesses, such as history of allergy, intravenous drug use but not with age, sex, country of birth, bacille Calmette-Guerin vaccination, reason for treatment, history of smoking or alcohol use, or pretreatment aminotransferase levels (83).

In the study of Menzies et al. 17 (4%) patients had elevated AST levels after 1-2 months of therapy and 22 (5 %) elevated ALT levels (both >1 to <3 times ULN). AST and ALT level changes >3 times ULN were found in 1 (0.2 %), respectively 3 (1%) patients. Therefore 1

patient (0.2 %) must have been asymptomatic and did not fit definition criteria for hepatotoxicity (83).

In the study of Haley et al. 7 (0.9%) patients showed an elevation in transaminase levels >2 to <3 times ULN. Besides, 4 patients (<1 %) showed ALT or AST levels >3 to <5 times ULN, one patient (0.1 %) not being symptomatic and therefore not matching definition-criteria of hepatotoxicity (91).

Page et al. found 6 (0.5%) patients with asymptomatic ALT/AST elevation >3 to <5 times ULN (82). Lee et al. also described asymptomatic rises in ALT values in 6.9 % and AST values in 3.4 % of 87 patients receiving RMP for prophylaxis in a tuberculosis outbreak, which did not require cessation of therapy. All ALT and AST-levels were low and <2 times ULN except of 1 AST-value which was around 125 U/l. All elevations were described as grade I/II toxicity, but no exact definition by the author was found. Besides, of all patients which experienced adverse events none had a previous hepatic disease (93).

Additionally, a meta-analysis by Ziakas and Mylonakis was included to be reviewed, showing that RMP was associated with lower rates of hepatotoxicity (defined as 3 or 4 grade liver failure) in comparison to INH and, moreover, associated with significant reduction in the risk of hepatotoxicity (94).

3.2.4 Case reports

In one reviewed case report RMP was considered responsible for asymptomatic jaundice in a 26-year-old female treated for renal tuberculosis. Jaundice started 12 days after RMP was added to standard therapy of Streptomycin and INH and resolved without change of therapy. Bilirubin levels were 3.5 mg/100ml, transaminase and AP were normal. RMP was considered by the author to be responsible for jaundice in this patient, but no clear reason was found and, moreover, RMP was used in combination with 2 known hepatotoxic agents, INH and Streptomycin (95).

Another reviewed case report described jaundice and severe liver failure after RMP administration in 5 patients with longstanding cirrhosis. In 4 cases jaundice occurred after 6-8 days after RMP was started. The author suggested a relationship between RMP, jaundice and liver failure, since all patients were not seriously ill when RMP was prescribed and drug abuse, blood transfusion, viral hepatitis or alcohol abuse were excluded in history. 3 of them died. No liver biopsy or necropsies were done (96).

4 Discussion

4.1 Fusidic acid

Drug-induced cholestasis and liver injury are frequent forms of acquired liver disease. Functional defects of bile formation, impaired bile secretion and bile flow, bile salt transporter defects or transporter function impairment are some possible causes of cholestasis.

FA and two of its derivatives, glycodihydrofusidate and taurodihydrofusidate resemble bile salts structurally (40,42,43) and were suggested to alter transport and secretion of bile salts and bile pigments (42-46) in early studies. Transport experiments found a direct, however competitive inhibition of BSEP and Mrp2 due to FA (47). BSEP is generally a vulnerable target for inhibition by drugs (35,36). Defects in BSEP expression, or BSEP function result in impaired bile secretion, bile flow and intrahepatic cholestasis due to a retention of bile salts (30,33-36). Consequently, data of Bode et al. possibly confirm prior assumptions and indicate that FA may have cholestatic side effects as a result of retention of bile acids. This might be furthermore confirmed since the main observed adverse hepatobiliary reaction in FA treatment was found to be hyperbilirubinemia, and generally no alteration of other liver enzyme levels, such as transaminase or GGT levels occurred. It is of interest to note that the Dubin-Johnson syndrome, characterized by an absence of Mrp2 in the human hepatocyte canalicular membrane, is associated with isolated conjugated hyperbilirubinemia (97).

Bode et al. also observed a decrease in Mrp2 protein levels, which is commonly found in cholestasis, and diminished biliary excretion rates of 17β -D-glucuronosyl estradiol - a Mrp2 substrate which FA resembles structurally - in prolonged treatment with FA (47). Nevertheless, no changes in plasma bilirubin concentration were found during treatment in the study by Bode et al. (47). This may be due to regulatory processes in the liver to evade hepatotoxic injury, such as the compensatory increase in MRP1 and MRP3 levels, both mediating the sinusoidal efflux of bile salt conjugates and other organic anions (35). It might be of interest in further studies, whether this described process may play a role in reversible hyperbilirubinemia or whether it may explain the lack of hepatobiliary side effects in FA treatment regimens in other clinical trials.

4.1.1 Alterations in liver function

Alterations in liver function are reported in several clinical studies (49,53,56,62,98) and case reports (50,52,55). The main hepatobiliary adverse effect of FA shown in literature is an

isolated hyperbilirubinemia. Incidences of jaundice and elevated bilirubin levels as well as enzyme variations differed. In the study by Humble et al. jaundice occurred in 38 of 112 patients (34%) who were not clinically jaundiced or showed prior normal liver function (49). However, in the study by Portier lower incidences were shown (7.4%) (54). Similar findings were observed in the study by Eykyn et al. in which 12 of 143 patients (8.3%) showed clinical jaundice during FA treatment (53). In the study by Mehtar et al. 2 patients (20%) showed hepatobiliary adverse events, 1 patient jaundiced and 1 had hyperbilirubinemia (56). In a randomized, double-blinded, placebo-controlled dose escalation study 8 of 40 volunteers (20%) were found with increased total serum bilirubin levels, however mild and reversible (62). Differences in administration formulation were found by Humble et al. and Eykyn et al., showing higher incidences of jaundice in patients given the intravenous formulation (48% in the study of Humble et al. and 17% in the study of Eykyn et al.) than in oral treatment (13% and 6%, respectively) (49,53).

Jaundice in FA treatment regimens is commonly reversible and elevations of bilirubin levels transient (49,50,52,53,55,62). A potential explanatory pathogenetic mechanism of this reversibility and transient rise in bilirubin level is the announced direct inhibition of bile salt transport due to competitive interference of FA with MRP2 and BSEP. Structural-similarity of FA with bile acids or compensatory mechanisms of other bile salt transporters, as described before, may play a further role.

Additionally, it was noted in literature that elevations of plasma bile acid levels, however, reversible on cessation of the drug, could be expected during FA treatment, especially in patients with prior liver impairment (41). In the studies by Humble, Eykyn and Portier a significant increase of bilirubin concentrations during FA treatment was shown in patients who had elevated bilirubin levels before treatment was started (49,53,54). It is important to note, that in patients with cholestatic injury a reduced expression of hepatobiliary transport systems for bile acids and other organic anions (NTCP, OATP, BSEP and MRP2) develops (33,37). Furthermore, an inhibition of BSEP leads to acquired cholestasis (99) and cholestasis may be associated with an increase in bile acid levels and an impaired clearance of drugs (33).

FA was shown to inhibit bile acid secretions in animal studies (42-44) and Narducci et al. mentioned FA causing a dose-dependent increase in serum bile acids in man (45). Besides its direct competitive inhibitory effect on BSEP and MRP2, FA also resembles bile salts and is a structural analog of the BSEP substrate cholyltaurine (47). Also, a liver biopsy conducted in 1 patient with transient elevated bilirubin concentration in FA treatment showed changes in

light microscopy and electron microscopy comparable with reported cholestasis induced by bile acids (52). Consequently, FA is susceptible to increase bile acids and bilirubin concentration levels, especially in patients with liver impairment, indicating that an interaction of FA with bile salts, bile salt transport and bile salt excretion may play a certain role in pathogenesis of FA-induced hepatic side effects. Furthermore liver values should be controlled routinely before FA is started and in patients with slight elevations regular laboratory controls are indicated. In patients showing clinical jaundice during FA treatment a cessation of the drug is recommended.

Another potential mechanism of hepatobiliary side effects of FA may be related to the steroid-like structure of FA (2,3). OATPs - especially OATP1A2 - are capable of transporting compounds including steroid conjugates (30). Changes in expression of OATPs under pathological conditions or function defects due to drug inhibition may generally influence transport processes leading to altered accumulation of OATP substrates and furthermore may result in increased toxicity and a higher number of adverse events of drugs. This may contribute to a potential interference of FA with OATPs and suggesting a further possible pathway of FA-induced cholestasis or hyperbilirubinemia. In addition, alterations in BSP levels - another compound of OATP1A2 - were observed during FA treatment in all patients by Wynn et al. (98). Also, Delage et al. found decreased BSP concentration in bile due to glycodihydrofusidate (44).

In contrary, no evidence of adverse effects concerning hepatotoxicity, liver enzyme alterations or hyperbilirubinemia due to FA was found in several clinical studies such as by Drancourt et al. (57), Aboltins et al. (58) and, additionally, in a recent published randomized, double-blind, multiple-center study in 198 patients treated with FA (63). Furthermore, no hepatobiliary side effects due to FA were observed in the study of MacGowan et al. and Reimann et al. (6,60).

4.1.2 Influence of dosage?

Another question is whether higher antibiotic levels in serum due to competitive mechanisms may cause adverse effects to a higher percentage. The labeling specifies a dosage of 500 mg 3 times daily for patients with less than 70 kg, or 4 times daily for patients with more than 70 kg bodyweight respectively (3). This dosage was used in nearly all included and reviewed studies. Kraus found no indication of greater toxicity at higher dose or duration regimens in their safety record, however referred 4 cases of adverse hepatobiliary reaction to be due to high-dose FA treatment (3000 mg). Plasma exposure was found to be higher after multiple

doses versus single doses in the study by Still et al. contributable with accumulation, a mechanism which is currently not fully understood. Additionally, 500-mg-twice daily regimens for treatment of skin and soft-tissue infections was found to be equally effective but noted to be associated with fewer gastrointestinal adverse effects (62). Front-loading strategies (1100 mg every 12 hours (Q12h) on Day 1, followed by 550 mg Q12h maintenance doses for 6.5 days (13 doses) or 1650 mg Q12h (Day 1) followed by 825 mg Q12h maintenance doses for 6.5 days) were investigated and found to be well-tolerated. Nevertheless in patients who received the 1650/825 mg loading-dose regimen in more patients (4 in comparison to 2) a transient, mild, and reversible increase in total serum bilirubin levels was observed. However, these abnormalities were not considered clinically significant by the authors (62).

4.1.3 Hyperbilirubinemia and other potential mechanisms

Besides drug intake, also other reasons should be taken into consideration for elevated bilirubin levels during FA treatment. Iwarson et al. noted that the observed slight hyperbilirubinemia in surgical patients during FA treatment, may also be associated with proceeded major surgery (51). Indeed, several patients developed mild jaundice after major surgery in another study by Peter et al. (61). The authors noted two potential situations for this possible postoperative hyperbilirubinemia and jaundice. On the one hand spontaneous hemolysis leading to isolated increase in conjugated bilirubin or on the other hand intrahepatic cholestasis accompanied by mild signs of hepatic impairment - such as elevated bilirubin and AP levels, as well as a moderate increase in aminotransferase levels - due to fatty liver or preoperative chronic liver disease (61). However, in the reviewed literature and MedLine no evidence of FA inducing hemolysis was found.

In several studies FA was used in treatment for bacteremic infection and adverse reactions such as jaundice or hepatobiliary side effects occurred. Bacteremia was observed in literature to be accompanied by jaundice (100,101). In our reviewed articles 1 case of jaundice was thought to be due to toxæmic processes of the disease (48). Also, Kraus et al. mentioned that hepatobiliary adverse events in some cases were directly associated with skin infections (7). Indeed, an impairment of canalicular organic anion transport in endotoxemic liver was found by Roelofsen et al. (102) and a downregulation in Ntcp expression and Mrp2, as well as Oatp1 and Mrp3 was shown under experimental conditions of sepsis in animal studies, confirming previous findings (34). Severely decreased bilirubin transport into bile in rat livers

after endotoxin administration was observed (103) and endotoxin was shown to decrease bile flow in the rat in another study (104). Trauner and Boyer postulated that in patients with sepsis cholestatic symptoms and particularly conjugated hyperbilirubinemia develop commonly (105). These results may complicate studying drug-associated jaundice and complicate evaluation and interpretation of FA induced adverse hepatobiliary effects in patients treated with FA in septicemia. Therefore, it may relativise data extracted from articles published by Humble et al. and Eykyn et al. in which exclusively patients with staphylococcal bacteraemia were investigated. Also, in the study of Portier et al. 22 of 49 patients were treated with FA for septicemia. However, in the study by Portier et al. it was not determinable if the reported 4 cases of jaundice may be contributable with effects of septicemia since not all patients were treated for septicemia and there was, in addition, a lack of significant information.

Furthermore, these effects of septicemia may influence drug administration, dosage and monitoring in patients with FA containing treatment regimens and especially in patients with preimpairment of the liver.

4.1.4 Data of safety records

The published safety record, focussing on FA treatment in skin infections by Kraus et al. noted several cases of hepatobiliary side effects in FA treatment, found in the reviewed literature. Nevertheless, hepatotoxicity was not persuasively linked to FA exposure in these patients. The included review of the international safety database VigiBase cited hepatobiliary side effects due to FA treatment in patients treated for skin infections and osteomyelitis. Nevertheless, the authors concluded in their safety record that hepatobiliary adverse events in FA treatment were meant to be potentially referred to FA exposure, but not of significant concern and, furthermore, cited that literature was lacking significant clinical information to allow critical clinical assessment (7).

4.1.5 FA in combination therapy

Comparing the incidence of hepatobiliary side effects of FA combination therapy and other antibiotic regimens, FA-including regimens showed higher incidences of hepatobiliary side effects in the study by Humble et al. (38% to 2 % respectively). Drancourt, however, found no differences in adverse events of RMP in combination with FA compared with RMP in combination with Ofloxacin. In the study by Mehtar et al. comparing Teicoplanin alone,

Flucloxacillin alone and Flucloxacillin in combination with FA 1 of 30 patients in the Teicoplanin group jaundiced in comparison to 1 patient with jaundice and 1 patient with hyperbilirubinemia of 16 patients treated with FA. The recent published study of Craft et al. observed no side effects in both Linezolid and FA treatment and noted that the efficacy, safety and tolerability of FA is comparable to Linezolid for the treatment of acute gram-positive bacterial skin and skin structure infections.

FA levels were shown to be supratherapeutic when used with other drugs, such as protease inhibitors. This effect was mentioned to be most likely due to inhibitory effects of protease inhibitors on the CYP P450 enzyme system (6,7,98). Drug interactions of FA and other substrates of the CYP 450 enzyme system should be taken into consideration if FA is added in treatment regimens. Of interest might be an interaction of RMP and FA in combination therapy, since RMP is a potent inducer of both the hepatic and intestinal CYP 450 enzyme system. In addition, both agents are mainly metabolised by the CYP3A4 enzymes and RMP is known to cause an increased hepatic metabolism, diminished or shortened effects or a reduction of serum concentration for substances that are metabolized by the same pathway (8,10,11,18). In this literature review a concomitant use of FA and RMP in treatment of staphylococcal infections was found in 3 included trials (54,57,58). In 2 studies no adverse hepatobiliary events due to combination treatment were observed (57,58). In the other study a combination of RMP and FA was used in 3 of 49 patients, however, an explicit correlation of combination therapy and jaundice or liver enzyme elevation could not be done, since significant information was lacking (54). In another recently published study by Peel et al. RMP was used in 38 of 43 patients in combination with FA for prosthetic joint infection by MRSA. One patient showed an alteration of liver function tests. But it could not be evaluated if due to RMP and FA combination therapy or RMP in combination with another antibiotic, since no data concerning liver laboratory was available and there was a lack of significant clinical information for further critical assessment.

Additionally, both FA and RMP show similar effects in bile acid transport due to their ability of inhibiting bile salt transport. At that point, it will be of further interest whether drug-drug interaction may play a role in lowering hepatobiliary side effects of FA and/or RMP in combination therapy.

4.2 Rifampin

4.2.1 RMP in non-mycobacterial infections

In contrary to FA, RMP showed less likely elevations in bilirubin in serum, however, was associated more likely with transaminase elevations, indicating hepatocellular injury. The incidence of hepatotoxicity due to RMP used in non-mycobacterial infections, however, was low and ranged from 0 to 4.3 % (73-80). In 3 studies it ranged from 2.8 to 4.3 % (75,77,79). In the other 5 published trials no hepatotoxicity was noted. In 6 of 8 articles liver enzyme elevations were shown. In 1 article slight elevations of AP and GGT, but normal ALT and AST levels were mentioned, however, without giving detailed information (76). Four articles described elevated transaminase levels ranging from 2.9 to 13 % not matching criteria of hepatotoxicity (73,74,77,80). Noteworthy, 3 of 6 patients with liver enzyme elevations in the study by Roblot et al. already had elevated levels at baseline (74). The elevations were mentioned to be slight in most cases, however, not defined or graded.

In 1 article 9 of 42 (21%) patients were found with significantly elevated hepatic transaminase levels, however, all of them had a hepatitis C virus infection and marginal transaminase elevations at baseline (78). Accordingly, Forrest et al. and Riedel et al. concluded that RMP should be used with caution in patients with underlying hepatitis C virus infection (12,78). A careful risk-benefit assessment in patients with co-existing chronic liver disease should be considered (8). In conclusion, transaminase elevations were observed in 2.8 to 21 % of the cases, if rates of hepatotoxicity - commonly defined as transaminase elevation over a certain extent - and transaminase elevation rates in RMP treatment of non-mycobacterial infections, were combined. Therefore, these data suggest that transaminase alterations are quite common. Nevertheless, it is important to mention that data concerning incidences are needed to be relativized, since they often depend on the investigator's definition of hepatotoxicity and transaminase alterations and several patients, additionally, had elevated baseline levels.

The study population was small in all reviewed articles. There was a lack of information concerning definition, chemistry values and grading in all of them. In only 3 of the reviewed articles exact definition of hepatotoxicity, hepatitis, or transaminase elevation was available (74,78,79). Therefore, RMP-induced hepatic adverse effects, withdrawal of RMP because of hepatic adverse effects and liver enzyme elevations may have been omitted in some reports. Transaminase elevations, hepatic adverse effects or hepatotoxicity due to RMP were often not graded or further described. Possibly due to the fact that it was often not the main aim of the

study or mentioned as side note (73,80), making a lack of information in some cases reasonable.

4.2.2 RMP in mycobacterial infections

To compare hepatotoxicity in antituberculosis treatment regimens and non-mycobacterial therapy this review also included studies and trials concerning RMP monotherapy in LTBI. The incidence of hepatotoxicity ranged from 0 to 2 %. 5 studies showed incidences less than 1%, ranging from 0-0.7% (82,83,85,91,92). However, the study by Fountain et al. (90) noted an incidence of 1.95 % of RMP-induced hepatotoxicity and the recently published study by Fresard et al. (84) an incidence of 2 %, respectively. Generally, low elevations in transaminase levels (ALT or/and AST >1 < 3 times ULN) occurred with an incidence ranging from 0.9 to 5 % (83,91,93). Transaminase elevations in the limits of >3 to <5 ULN, but not fitting definition criteria of hepatotoxicity occurred with an incidence of 0.1-0.5% (82,83,91). Nevertheless, Lee et al. described rises in ALT and AST values in a greater number of patients (6.9 % and 3.4%) (93). Combining incidences of hepatotoxicity - defined as transaminase elevation - and incidences of transaminase elevations in general, transaminase elevations occurred in 0.1 to 6.9 % of the cases treated with RMP for LTBI.

Not all, but some patients with transaminase elevations in RMP treatment regimens were noted to be clinically asymptomatic (82,83,91,93). In 1 study all patients that developed hepatotoxicity were found to be asymptomatic (84). In addition, Girling mentioned articles showing increases in serum transaminase concentrations and other abnormalities of liver function tests, without clinical evidence of hepatitis (87). Also, Schonell et al. found a transient rise in AST levels in 1 (5.8%) of 17 patients treated for tuberculosis but in multidrug-therapy including RMP (9).

The true incidence of RMP-induced liver injury, hepatotoxicity, hyperbilirubinemia or liver enzyme elevation in mycobacterial infections is generally difficult to establish, since RMP is mostly used in combination with other drugs that have known hepatotoxic potential, such as Isoniazid, or Pyrazinamide (81,86). Notably, Isoniazid co-administration is seen to be a serious risk factor for developing hepatotoxicity (16,64,81). Hydrazine, a metabolite of Isoniazid, is suggested to be most likely the cause of Isoniazid-induced hepatotoxicity in recent studies. Hepatotoxicity induced by RMP in combination with Isoniazid may be due to additive or synergistic effects. One potential mechanism is the suggested involvement of RMP in enzyme induction generating hydrolysis of Isoniazid leading to increasing Hydrazine

production that may explain the higher toxicity in co-administration of RMP and Isoniazid (86,106). Hepatotoxicity as adverse side effect of antituberculosis treatment with RMP in combination with INH and Pyrazinamide is noted in many clinical studies, in vitro studies, case reports (88,95,107,108) and trials which are mentioned in reviews (81,86) included in this thesis. However, it is of interest to note that Yew et al. stated in their concise up-to date review about antituberculosis drug-induced hepatotoxicity, that RMP is possibly associated with a lower potential of hepatotoxicity than Isoniazid or Pyrazinamide (86). Supportingly recommendations by the American Thoracic Society/Centers for Disease Control and Prevention/Infectious Disease Society of America suggest RMP to be the drug restarted first after recovery from antituberculosis drug-induced hepatitis (86). On the contrary, a recent study showed that INH, RMP and Pyrazinamide can be safely reintroduced simultaneously at full dosage after antituberculosis treatment-induced hepatotoxicity (109).

In conclusion, RMP-induced hepatotoxicity in treatment of LTBI was found to be rare, elevated transaminase levels in patients were often noted to be transient and patients were often not clinically symptomatic. In some cases elevated liver values normalized, although therapy was continued. Nevertheless, in patients with baseline elevation and preimpairment of the liver a risk-benefit assessment is recommended.

4.2.3 Potential pathomechanisms of RMP-induced hyperbilirubinemia

Pathomechanisms of RMP-induced hepatobiliary adverse effects or cholestatic injury are still not fully explained. In some studies significant metabolic effects such as interference and competition of RMP in bilirubin transport, conjugation and hepatic elimination of compounds such as bilirubin and BSP were found (27,64,65,68), which may be associated with cholestatic injury, possibly explaining hyperbilirubinemia. The in vitro study by Chen et al. showed a significant increase in total bilirubin and conjugated bilirubin levels, indicating RMP-induced cholestasis due to altered integrity and intensity of hepatocyte tight junctions after RMP administration (69). Most notably RMP was shown to cause both elevated conjugated and unconjugated bilirubin plasma levels. All interference phenomena of RMP with bile acids and bilirubin were categorized to be dose-related and predictable (27,64,65). Capelle et al. noted that the increase in total bilirubin level was clearer in cirrhotic patients, however, none of them showed any clinical signs of intolerance (65). Transient increases in total serum bilirubin concentrations after administration of RMP were mentioned (66). These observations may reflect the results of Chen et al. who found significantly increased levels of

total bilirubin and conjugated bilirubin in serum and reversibly increased levels of total bile acids in serum and liver tissue (69).

In experimental studies RMP and Rifamycin inhibited transport activity of the bile salt export pump (BSEP) (29,67). As mentioned in the discussion of FA-treatment, that may explain intrahepatic cholestasis due to a retention of bile salts. As further target involved, an inhibition of NTCP was suggested for rifamycin SV. An inhibition of NTCP could not be shown for RMP, but also not excluded (67). An interference of RMP with organic anion transporting polypeptides (OATP) was shown in several studies (27,68). OATP transporters are thought to play an important role in drug disposition and may play a role in drug-drug interaction. In a recent study Oatp1a/1b are noted to play an important role in hepatic reuptake of conjugated bilirubin, uptake of unconjugated bile acids and the hepatic uptake of drugs. RMP was found to be an inhibitor of Oatp1a/1b transporters (110), which may explain hyperbilirubinemia in RMP treatment. In line with these data Fattinger et al. demonstrated in a previous study that Rifamycin SV inhibits both organic anion transporting polypeptides, Oatp1 and Oatp2. In addition, in this study, RMP was identified to be a selective inhibitor of Oatp2 (27). Function defects in these transporters due to drug inhibition may lead to altered accumulation of OATP substrates, such as bile acids and bilirubin, resulting in hyperbilirubinemia. An increased toxicity and a higher number of adverse events, also of co-administered drugs which may influence the same pathway, should be taken into consideration. Concerning drug-drug interaction van de Steed et al. stated that coadministration of specific OATP inhibitors may be used to increase systemic exposure and therefore as well oral availability of drugs with generally high hepatic uptake via OATP1A/1B transporters. Furthermore, it will be of interest whether a therapeutical inhibition of OATP1A/1B transporters may be used to limit hepatic toxicity of several drugs (110).

Zhang et al. performed a study to investigate a potential association between SLCO1B1 polymorphism (gene that encodes OATP1B1) and serum bilirubin levels (42 healthy volunteers) and in addition effects of low-dose RMP (450 mg once daily) on serum bilirubin levels in different SLCO1B1 genotypes (24 healthy volunteers). Patients with SLCO1B1*15 haplotype showed higher baseline serum levels of unconjugated bilirubin, total bilirubin and direct bilirubin, compared with other haplotypes. In addition, RMP was found to increase significantly serum bilirubin levels, however, no association with SLCO1B1 genotype was observed for RMP (26). In contrary, a further recent published trial investigated a potential association between OATP1B1 polymorphisms and RMP hepatotoxicity. OATP1B1*15

haplotype was found to be susceptible to DILI, particularly of the cholestatic/mixed type. In this haplotype bile acid uptake was markedly decreased and the inhibition of RMP greater in comparison to the other haplotypes, suggesting OATP1B1*15 haplotype as an important predisposing factor for RMP-induced liver injury (111).

These results may explain hyperbilirubinemia due to RMP. Nevertheless, it is of interest to note, that only in 4 of the included and reviewed clinical studies variations of bilirubin levels were mentioned, but only in 1 study further data were available (83,91-93). In this study 4 patients presented with an elevation in total bilirubin, ranging from 2 to 4 mg/dl, however, without clinical symptoms (92). The low incidence of alterations in bilirubin values might be due to a lack of significant information, or due to the fact that hyperbilirubinemia was not a defined point of interest in several studies or that no clinically significant hyperbilirubinemia was observed during RMP treatment. In addition, future investigations may also consider potential effects of the hepatoprotective mechanisms of increased MRP1 and MRP3 levels by increasing the efflux of bile salt conjugates and other anions (35), possibly explaining low and lower incidences of hyperbilirubinemia or its absence.

4.2.4 Potential pathomechanisms of RMP-induced hepatotoxicity

Generally, toxic hepatocellular damage can be divided into two groups, predictable injury due to direct chemical reactions and unpredictable injury – also known as idiosyncratic reaction (20,21). The predictable injury due to direct interaction of the drug or its metabolites is, therefore, the favorable pathogenetic pathway concerning RMP-induced liver injury so far. This is furthermore supported by findings concerning oxidative stress, glutathione depletion and lipid peroxidation.

Oxidative stress is a glutathione dependent process and contributes to many pathological conditions and diseases. It is associated with an imbalance between oxidants and antioxidants. In the detoxification of reactive oxygen species several processes such as non-enzymatic scavengers (antioxidants) as well as enzymatic systems (e.g. glutathione conjugation) play an important role. Generally, mitochondria dysfunction caused by reactive metabolites formed during drug metabolism and overwhelming oxidative stress are main pathways of hepatocyte death caused by drugs. In addition, recent studies have also suggested that activated or inhibited signal transduction pathways during oxidative stress play an important role in drug-induced liver injury (112). Mitochondria have been shown to play an important role in aerobic life and cell death and to be important cellular targets for many hepatotoxicants. Changes in

mitochondrial function lead to an impairment of cellular energy and lipid metabolism and, furthermore, a release of mediators of cell death (113). Fernandez et al. showed that mitochondrial glutathione modulates cell death. Its regulation, therefore, may be an important target to influence disease progression and drug-induced cell death (114). Shen et al. showed RMP-induced hepatotoxicity in gel-entrapped rat hepatocytes. Biomarkers of oxidative stress were assayed, showing a drastic generation of reactive oxygen species (ROS) and a depletion of intracellular glutathione after RMP administration, indicating that oxidative stress plays a role in RMP-induced hepatotoxicity. Both GSH enhancers and ROS scavenger were effective in reducing RMP-induced toxicity, confirming the involvement of oxidative stress (71). In addition, Shen et al. also detected that intracellular lipid accumulation and lipid peroxidation play a role in RMP-induced hepatotoxicity (71). Furthermore, Yew et al. stated in their review that INH- and RMP-induced hepatotoxicity are mediated through oxidative damage, since an altered profile of antioxidants with increased lipid peroxidation was found in other reviewed studies (86).

Chowdhury et al. showed that INH and RMP co-administration causes steatosis, increased apoptosis of hepatocytes and hepatic oxidative stress (106). Interestingly, after an administration of INH or Hydrazine to rats reduced glutathione levels and reduced activity of glutathione-S transferase, catalase and superoxide dismutase were found indicating an involvement of oxidative stress in INH-induced hepatotoxicity (81,106,115). Treatment with INH or RMP alone also caused significant depletion of hepatic glutathione content, indicating oxidative stress. Hepatic oxidative stress was shown by Chowdbury to be caused particularly in the mitochondrial fraction (106), which is known to play an important role in disease progression and drug-induced cell death.

Also, alcohol leads to a depletion of hepatoprotective mitochondrial glutathione stores (114). Therefore, these persons may be more susceptible to toxicity of drugs. Moreover, persons with AIDS, persons who are malnourished, and persons who are fasting may be more susceptible to adverse drug reactions, especially in the liver, because of low glutathione stores (21). Consequently and considering a potential involvement of oxidative stress and alterations in glutathione stores during RMP treatment, recommendations for patients with co-existing chronic liver disease, alcoholism or malnutrition consider a careful risk-benefit assessment or a consequent control of liver function if a therapy with RMP is indicated (8). In conclusion, some evidence of an involvement of oxidative stress in the pathogenesis of RMP-induced liver toxicity could be found. Nonetheless, whether oxidative stress is generally involved in

RMP-induced hepatotoxicity is still matter of debate and the need for further controlled studies remains.

Concerning further possible pathways of RMP-induced hepatobiliary effects, another study, published by Yuhas et al. (38) showed that RMP may induce proinflammatory mediators and increase cytokine-induced production of NO and IL-8, indicating proinflammatory effects by RMP on the liver. NO regulates the expression of many genes. Therefore, it may alterate the production of many other mediators in the immune system (38). Consequently, it may be of further interest, whether co-administration of RMP with other drugs inducing NO should be prevented, and whether anti-inflammatory agents may reduce RMP-induced liver toxicity, elevations in NO levels and other inflammatory processes.

Another potential pathomechanism of RMP-induced hepatotoxicity might be direct cytotoxicity due to RMP or its metabolites. Indeed, a potent direct cytotoxicity of rifamycins was found in HepG2 cells by Nakajima et al. This direct cytotoxicity was shown to be dose-dependent and RMP was associated with less toxicity in comparison to Rifabutin and Rifapentine. The 25-deacetylated metabolites, showed no or less cytotoxicity (70). Noteworthy, currently no reactive toxic metabolite of RMP has been described.

4.2.5 RMP improving symptoms of pruritus and liver injury?

It is of further interest to note, that RMP is used therapeutically to improve symptoms of pruritus and biochemical markers of liver injury in situations of chronic cholestasis and cholestatic liver disease (116,117). In several small trials RMP showed an improvement of pruritus (118-121) and in primary biliary cirrhosis RMP significantly decreased levels of total bile salts (118,120), transaminase values, AP and GGT levels (120). In a metaanalysis of prospective randomized-controlled trials RMP was identified to be safe and effective for treatment of pruritus due to chronic cholestasis and stated to be associated with a low risk of hepatotoxicity in short treatment regimens (122). RMP is seen to be an important noninvasive therapeutic option of acute cholestatic attacks in patients with benign recurrent intrahepatic cholestasis (123). Studying possible molecular mechanisms of RMP in treatment of cholestatic patients showed decreased bilirubin levels in serum, enhanced bile acid detoxification, bilirubin conjugation and increased expression of CYP3A4, UGT1A1 – the gene encoding the bilirubin-uridine-diphosphoglucuronate glucuronosyltransferase - and MRP2 due to RMP (117). In addition, a recent study showed that the co-administration of RMP and Ursodeoxycholic acid - last-mentioned with complementary effects in

comparison to RMP in treatment of cholestatic liver disease - significantly stimulated bile acid and bilirubin detoxification due to CYP3A4. Furthermore it increased the conjugation of bile acid and bilirubin via UGT1A1 and enhanced the elimination of bile acid and bilirubin by MRP2 and stimulated bile acid synthesis (124).

RMP was used with a dosage of 600 mg daily in several trials (117,121,125), however, also lower dosages, such as 150 mg twice daily were found (122,126). Therefore, it may be of interest whether different doses may have different effects in bile acid detoxification, bilirubin conjugation and other hepatobiliary processes, since higher doses are indicated in treatment of tuberculosis and bacteraemia. Furthermore these data may relativise recommended treatment adaptations in patients with preimpairment of the liver and especially in cholestatic patients.

4.2.6 Recommendations

Latest recommendations stated that a single report of moderate transaminase elevations does not induce therapy interruption of RMP. A second repeated liver enzyme evaluation should be done for decision making if values are elevated. Nonetheless, the severity in relation to complaints, clinical status and progress of the patients over time and progress of evaluated parameters should be considered and RMP withdrawn if necessary. An increase in transaminase values more than 100 U/l, an increase in bilirubin concentration or clinical symptoms indicate an immediate withdrawal of RMP (8).

Moreover, since RMP shows a potential of hepatotoxic side effects a routine control of bilirubin and liver enzyme values is recommended for every patient treated with RMP. Liver enzymes should be examined before initiating therapy and depending on the values every 2-4 weeks during therapy (8).

RMP may aggravate effects of other hepatotoxic substances. Since RMP interacts with antiretroviral drugs such as Saquinavir/Ritonavir and affects the plasma levels of these drugs and the risk of hepatotoxicity, a co-administration of RMP and Saquinavir/Ritonavir is contraindicated (81,127).

The hepatic clearance of RMP depends upon the extent of dosage, the frequency of administration and the patient's liver status (8,10). In patients with impaired liver function, plasma concentration and urinary excretion increases. Therefore, a careful risk-benefit assessment or otherwise a consequent monitoring of liver function during therapy in patients with co-existing chronic liver disease, alcoholism or malnutrition is recommended (8,65).

Furthermore, a moderate dosage reduction can be considered since efficient blood concentrations would be achieved with small doses in case of preimpairment of the liver (65).

According to Forrest et al. and Riedel et al. RMP should be used with caution in patients with underlying hepatitis C virus infection (12,78). In addition, for patients exhibiting the slow acetylation phenotype a close monitoring for changes in serum aminotransferases was recommended by Westphal et al. (64).

In patients with severe liver disease, occluding icterus, hepatitis or liver cirrhosis RMP should not be administered.

4.2.7 Lack of information

In most studies of RMP in non-mycobacterial and mycobacterial treatment critical data evaluation was difficult due to a remarkable lack of information concerning grading, definition, liver enzyme values or further details for review like existing hepatitis infection, HIV infection, and in some cases possible baseline elevations or usage of other hepatotoxic medications. More detailed information was available and a higher number of patients were included in reviewed articles about RMP in LTBI. It is of further interest to note that a high incidence of differences in definition of hepatotoxicity was found in the studies concerning RMP in mycobacterial infections, complicating in addition critical data assessment.

5 Conclusion

5.1 Fusidic acid

The review of available literature demonstrates that the mechanism of potential FA-associated jaundice is not fully known. Experimental studies showed evidence of interference with bile salts and a direct competitive inhibition of bile salt transporter MRP2 and BSEP. In surveyed data a lack of significant clinical information regarding other potential confounders, definition criteria and laboratory data was commonly found, making a critical assessment difficult.

FA was announced in several studies to be responsible for hepatobiliary side effects, whereas the mainly found adverse hepatobiliary event was reversible isolated hyperbilirubinemia (4.3-38%). On the contrary, other studies showed no hepatobiliary side effects due to FA in monotherapy, combination therapy or combination therapy with RMP. Jaundice and hyperbilirubinemia were largely found to be transient, mild and reversible on cessation of FA, which would account for the noted competitive inhibitory mechanism on bile salt transport.

In patients with impaired liver function FA should be used with caution and a consequent monitoring of bilirubin and transaminase levels is indicated. A further increase in liver enzymes should lead to cessation of the drug.

The prognosis of patients with hepatobiliary adverse events was principally found to be good. The efficacy, safety and tolerability of FA were stated to be comparable to other antibiotic treatment regimens. Nevertheless, the need for future randomized controlled clinical trials and further safety studies concerning FA in monotherapy and in combined treatment regimens, as well as experimental studies to investigate potential pathomechanisms of hepatobiliary adverse effects, remains.

5.2 Rifampin

This is the first literature review so far analyzing data concerning potential pathomechanisms of RMP-induced liver alterations and RMP-induced hepatotoxicity, hyperbilirubinemia or liver enzyme variations in in vitro and in vivo studies including data of non-mycobacterial infections, especially staphylococcal infections, and existing data of hepatotoxicity in RMP single-therapy of LTBI.

The pathomechanisms of RMP-induced liver injury, possible hepatic side effects, transaminase elevations or cholestatic injury are still not fully explained. In contrary to FA, the main hepatobiliary adverse reaction due to RMP is more likely an elevation of transaminase levels, indicating hepatocellular injury. Nevertheless, the incidence of hepatotoxicity due to RMP was generally low or absent in several clinical studies. It ranged from 0.08 to 2 % in LTBI therapy and 2.8 to 4.3 % in studies concerning non-mycobacterial infections, respectively. Elevations in transaminase levels, not matching criteria of hepatotoxicity, occurred with differing incidences in reviewed literature, however to a higher extent. Combining incidence rates of hepatotoxicity, that is commonly defined as transaminase elevation over a certain extent, and transaminase elevations not matching criteria of hepatotoxicity, result in an incidence of transaminase elevation in RMP treatment of 0.1 to 21 % (RMP in non-mycobacterial and mycobacterial treatment - LTBI).

In surveyed literature a remarkable lack of information concerning grading, definition, liver enzyme values or further potentially relevant information like coexisting hepatitis infection, HIV infection, baseline elevations in some cases or usage of other hepatotoxic medications was found in most studies of RMP in non-mycobacterial and mycobacterial treatment. Therefore, evaluation of the data and a critical assessment was difficult. An international standard grading of drug induced hepatotoxicity and standardized guidelines for further comparative studies might be necessary.

In patients with co-existing chronic liver disease, hepatitis C virus infection, alcoholism or malnutrition, a careful risk-benefit assessment, vigilance in monitoring transaminases and/or a consequent control of liver function during therapy with moderate dosage reduction is recommended. For patients exhibiting the slow acetylation phenotype, a close monitoring for changes in serum aminotransferases is necessary. In patients with severe liver disease, including icterus, hepatitis or liver cirrhosis RMP should not be administered.

Priorities for future studies include basic studies to elucidate the mechanisms of RMP-induced hepatotoxicity and further controlled clinical studies to impact the clinical use of RMP in patients with staphylococcal infections.

6 Key facts for clinicians

6.1 Fusidic acid

- The main adverse hepatobiliary event is a reversible isolated hyperbilirubinemia.
- The mechanisms of FA-associated jaundice/hyperbilirubinemia are not fully known (direct competitive inhibition of bile salt transporters?).
- Jaundice and hyperbilirubinemia are generally transient, mild and reversible on cessation of FA.
- CAVE: In case of (pre-)impaired liver function → consequent monitoring of bilirubin and transaminase levels necessary.
- Significant increase in liver enzymes or symptomatic jaundice → cessation of the drug recommended.

6.2 Rifampin

- The main hepatobiliary adverse reaction is an elevation of transaminase levels.
- The pathomechanisms of RMP-induced liver injury and hepatic side effects are not fully explained (bile salt transporter, tight junctions, oxidative stress etc. ?).
- The incidence of hepatotoxicity due to RMP is generally low.
- Control liver enzymes before treatment started.
- Low transaminase elevations during therapy indicate a second repeated evaluation (withdrawal indication in relation to complaints, clinical status and progress!).
- An increase in transaminase values more than 100 U/l, an increase in bilirubin concentration or clinical symptoms indicate an immediate withdrawal of RMP.
- CAVE: Chronic liver disease, hepatitis C virus infection, alcoholism or malnutrition → careful risk-benefit assessment, consequent control of liver function (e.g. transaminases, bilirubin) during therapy, eventually moderate dosage reduction.
- CAVE: Slow acetylation phenotype → close monitoring for changes in serum aminotransferases indicated.
- CAVE: Severe liver disease (icterus, hepatitis or liver cirrhosis) → no administration!

7 Appendix

Appendix 1. Reviewed Literature Citations – Fusidic acid		
No	Year	Citation
1	1965	Wynn V. Metabolic effects of the steroid antibiotic fusidic acid. <i>Br Med J</i> 1965;1(5447):1400-4.
2	1975	Beaudoin M, Carey MC, Small DM. Effects of taurodihydrofusidate, a bile salt analogue on bile formation and biliary lipid secretion in the rhesus monkey. <i>J Clin Invest</i> 1975; 56:1431-1441.
3	1976	Ziv E, Stratman W. The in vivo stimulation of phosphorylation of rat liver proteins by fusidic acid. <i>FEBS Lett</i> 1976;68(1):86-8.
4	1976	Menday AP, Marsh BT. Intravenous fusidic acid ('Fucidin') in the management of severe staphylococcal infections: a review of 46 cases. <i>Curr Med Res Opin</i> 1976;4(2):132-8.
5	1976	Montet JC, Montet AM, Gerolami A, Arnic J, Hauton JC. Glycodihydrofusidate: Biliary excretion and its effect on biliary secretion of the rat. <i>Lipids</i> 1976;11:408-411.
6	1976	Delage Y, Dumont M, Erlinger S. Effect of glycodihydrofusidate on sulfobromophthalein transport maximum in the hamster. <i>Am J Physiol</i> 1976; 231:1875-1878.
7	1977	Montet JC, Gerolami A, Durbec JP, Crotte C, Montet AM, Hauton JC. Hepatic uptake and biliary excretion of a bile salt analog: Glycodihydrofusidate. <i>Biomedicine</i> 1977; 26:60-64.
8	1978	Anwer MS, Hegner D. Interaction of fusidates with bile acid uptake by isolated rat hepatocytes. <i>Naunyn Schmiedebergs Arch Pharmacol</i> 1978;302(3):329-32.
9	1980	Fusidic acid and jaundice. <i>Br Med J</i> . 1980 Jul 26;281(6235):308.
10	1980	Humble MW, Eykyn S, Phillips I. Staphylococcal bacteraemia, fusidic acid, and jaundice. <i>Br Med J</i> 1980;280(6230):1495-8.
11	1980	Anderson JD. Fusidic acid: new opportunities with an old antibiotic. <i>Can Med Assoc J</i> 1980;122(7):765-9.
12	1981	Iwarson S, Fasth S, Olaison L, Hultén L. Adverse reactions to intravenous administration of fusidic acid. <i>Scand J Infect Dis</i> 1981;13(1):65-7.

13	1982	Narducci F, Pelli MA, Vedovelli A, Morelli A, Fedeli L, Fiorucci MG et al. Elevation of serum bile acids induced by sodium fusidate administration in man. <i>Dig Dis Sci</i> 1982;27(3):283-4.
14	1987	Kutty KP, Nath IV, Kothandaraman KR, Barrowman JA, Perkins PG, Ra MU et al. Fusidic acid-induced hyperbilirubinemia. <i>Dig Dis Sci</i> 1987;32(8):933-8.
15	1987	Muñoz R, Ferreras JM, Alonso P, Vaquera J, Girbés T. Polyvalent inhibitory action of fusidic acid in isolated rat liver cells. <i>Biochem Int</i> 1987;15(5):1013-9.
16	1989	MacGowan AP, Greig MA, Andrews JM, Reeves DS, Wise R. Pharmacokinetics and tolerance of a new film-coated tablet of sodium fusidate administered as a single oral dose to healthy volunteers. <i>J Antimicrob Chemother</i> 1989;23(3):409-15.
17	1990	Eykyn SJ. Staphylococcal bacteraemia and endocarditis and fusidic acid. <i>J Antimicrob Chemother</i> 1990;25 Suppl B:33-8.
18	1990	Portier H. A multicentre, open, clinical trial of a new intravenous formulation of fusidic acid in severe staphylococcal infections. <i>J Antimicrob Chemother</i> 1990;25 Suppl B:39-44.
19	1993	Haddad M, Shabat S, Koren A, Stelman E, Zelikovski A. Fusidic acid induced jaundice. <i>Eur J Clin Microbiol Infect Dis</i> 1993;12(9):725-6.
20	1993	Peter JD, Jehl F, Pottecher T, Dupeyron JP, Monteil H. Pharmacokinetics of intravenous fusidic acid in patients with cholestasis. <i>Antimicrob Agents Chemother</i> 1993;37(3):501-6.
21	1994	Westphal JF, Vetter D, Brogard JM. Hepatic side-effects of antibiotics. <i>J Antimicrob Chemother</i> 1994;33(3):387-401.
22	1994	Sesso R, Parisio K, Dalboni A, Rabelo T, Barbosa D, Cendoroglo M et al. Effect of sodium fusidate and ofloxacin on <i>Staphylococcus aureus</i> colonization and infection in patients on continuous ambulatory peritoneal dialysis. <i>Clin Nephrol</i> 1994;41(6):370-6.
23	1995	Mehtar S, Drabu Y, Wilson AP, Grüneberg RN. A comparative study between teicoplanin alone and flucloxacillin, plus or minus fusidic acid, in the treatment of serious infections caused by methicillin-susceptible gram-positive bacteria. <i>Chemotherapy</i> 1995;41(5):412-9.
24	1997	Nicoletti F, Beltrami B, Raschi E, Di Marco R, Magro G, Grasso S et al. Protection from concanavalin A (Con A)-induced Tcell-dependent hepatic lesions and modulation of cytokine release in mice by sodium fusidate. <i>Clin Exp Immunol</i> 1997;110(3):479-84.

25	1997	Drancourt M, Stein A, Argenson JN, Roiron R, Groulier P, Raoult D. Oral treatment of Staphylococcus spp. infected orthopaedic implants with fusidic acid or ofloxacin in combination with rifampicin. <i>J Antimicrob Chemother</i> 1997;39(2):235-40.
26	1999	Christiansen K. Fusidic acid adverse drug reactions. <i>Int J Antimicrob Agents</i> 1999;12 Suppl 2:3-9.
27	1999	Reimann G, Barthel B, Rockstroh JK, Spatz D, Brockmeyer NH. Effect of fusidic acid on the hepatic cytochrome P450 enzyme system. <i>Int J Clin Pharmacol Ther</i> 1999;37(11):562-6.
28	1999	Whitby M. Fusidic acid in septicaemia and endocarditis. <i>Int J Antimicrob Agents</i> 1999;12 Suppl 2:17-22.
29	2002	Bode KA, Donner MG, Leier I, Keppler D. Inhibition of transport across the hepatocyte canalicular membrane by the antibiotic fusidate. <i>Biochem Pharmacol</i> 2002;64(1):151-8.
30	2007	Aboltins CA, Page MA, Buising KL, Jenney AW, Daffy JR, Choong PF et al. Treatment of staphylococcal prosthetic joint infections with debridement, prosthesis retention and oral rifampicin and fusidic acid. <i>Clin Microbiol Infect</i> 2007;13(6):586-91.
31	2011	Still JG, Clark K, Degenhardt TP, Scott D, Fernandes P, Gutierrez MJ. Pharmacokinetics and safety of single, multiple, and loading doses of fusidic acid in healthy subjects. <i>Clin Infect Dis</i> 2011;52 Suppl 7:504-12.
32	2011	Craft JC, Moriarty SR, Clark K, Scott D, Degenhardt TP, Still JG et al. A randomized, double-blind phase 2 study comparing the efficacy and safety of an oral fusidic acid loading-dose regimen to oral linezolid for the treatment of acute bacterial skin and skin structure infections. <i>Clin Infect Dis</i> 2011;52 Suppl 7:520-6.
33	2011	Kraus CN, Burnstead BW. The safety record of fusidic acid in non-US markets: a focus on skin infections. <i>Clin Infect Dis</i> 2011;52 Suppl 7:527-37.
34	2011	Fernandes P, Pereira D. Efforts to support the development of fusidic acid in the United States. <i>Clin Infect Dis</i> 2011;52 Suppl 7:542-6.

Appendix 2. Reviewed Literature Citations - Rifampin

No	Year	Citation
1	1971	Proust AJ. The Australian rifampicin trial. <i>Med J Aust</i> 1971;2(2):85-94.
2	1971	Poole G, Stradling P, Worlledge S. Potentially serious side effects of high-dose twice-weekly rifampicin. <i>British Medical Journal</i> 1971; 3:343-347.
3	1971	Gabriel R. Rifampicin jaundice. <i>Br Med J</i> 1971;3(5767):182.
4	1972	Capelle P, Dhumeaux D, Mora M, Feldmann G, Berthelot P. Effect of rifampicin on liver function in man. <i>Gut</i> 1972;13(5):366-71.
5	1972	Schonell M, Dorken E, Grzybowski S. Rifampin. <i>Can Med Assoc J</i> 1972;106(7):783-6.
6	1977	Girling DJ. Adverse reactions to rifampicin in antituberculosis regimens. <i>J. Antimicrob. Chemother</i> 1977; 3:115-32.
7	1977	Miguet JP, Mavier P, Soussy CJ, Dhumeaux D. Induction of hepatic microsomal enzymes after brief administration of rifampicin in man. <i>Gastroenterology</i> 1977 May;72(5 Pt 1):924-6.
8	1978	Di Piazza S, Cottone M, Craxi A, Gatto G, Pinzelle G, Pagliaro L. Severe rifampicin-associated liver failure in patients with compensated cirrhosis. <i>Lancet</i> 1978;1(8067):774.
9	1979	Nessi R, Fowst G. Clinical use of rifampicin in combination for non-mycobacterial infections: a survey of published evidence. <i>J Int Med Res</i> 1979;7(3):179-86.
10	1980	Galeazzi R, Lorenzini I, Orlandi F. Rifampicin-induced elevation of serum bile acids in man. <i>Dig Dis Sci</i> 1980; 25:108-112.
11	1981	Kissling M, Bergamini N. Rifampicin in free combination with other antimicrobial drugs in non-Tb infections. Clinical data on 650 patients (a review). <i>Chemotherapy</i> 1981;27(5):368-402.
12	1982	Kissling M, Bergamini N, Xilinas M. Parenteral rifampicin in tuberculous and severe non-mycobacterial infections. Clinical data on 237 patients. <i>Chemotherapy</i> 1982;28(3):229-39.
13	1983	Grosset J, Leventis S. Adverse effects of rifampin. <i>Rev Infect Dis</i> 1983;5 (Suppl 3):440-50.
14	1984	Cluzel RA, Lopitiaux R, Sirot J, Rampon S. Rifampicin in the treatment of osteoarticular

		infections due to staphylococci. <i>J Antimicrob Chemother</i> 1984; 13 (Suppl C):23-29.
15	1991	Levine DP, Fromm BS, Reddy BR. Slow response to vancomycin or vancomycin plus rifampicin in methicillin-resistant staphylococcus aureus endocarditis. <i>Ann Int Med</i> 1991; 115:674-680.
16	1993	Morris AB, Brown RB, Sands M. Use of rifampin in nonstaphylococcal, nonmycobacterial disease. <i>Antimicrob Agents Chemother</i> 1993;37(1):1-7.
17	1994	Westphal JF, Vetter D, Brogard JM. Hepatic side-effects of antibiotics. <i>J Antimicrob Chemother</i> 1994;33(3):387-401.
18	1996	Heldman AW, Hartert TV, Ray SC, Daoud EG, Kowalski TE, Pompili VJ et al. Oral antibiotic treatment of right-sided staphylococcal endocarditis in injection drug users: prospective randomized comparison with parenteral therapy. <i>Am J Med.</i> 1996;101(1):68-76.
19	1997	Villarino ME, Ridzon R, Weismuller PC. Rifampin preventive therapy for tuberculosis infection: experience with 157 adolescents. <i>Am J Respir Crit Care Med</i> 1997; 155:1735-1738.
20	1998	Vesely JJ, Pien FD, Pien BC. Rifampin, a useful drug for nonmycobacterial infections. <i>Pharmacotherapy</i> 1998;18(2):345-57.
21	1998	Yzerman EP, Boelens HA, Vogel M, Verbrugh HA. Efficacy and safety of teicoplanin plus rifampicin in the treatment of bacteraemic infections caused by <i>Staphylococcus aureus</i> . <i>J Antimicrob Chemother</i> 1998;42(2):233-9
22	2000	Fattinger K, Cattori V, Hagenbuch B, Meier PJ, Stieger B. Rifamycin SV and rifampicin exhibit differential inhibition of the hepatic rat organic anion transporting polypeptides, OATP1 and OATP2. <i>Hepatotology</i> 2000; 32:82-86.
23	2002	Vavricka SR, Van Montfoort J, Ha HR, Meier PJ, Fattinger K. Interacts of rifamycins SV and rifampin with organic anion uptake systems of human liver. <i>Hepatology</i> 2002; 36: 164-72.
24	2004	Schwalm JD, El-Helou P, Lee CH. Clinical outcome with oral linezolid and rifampin following recurrent methicillin-resistant <i>Staphylococcus aureus</i> bacteremia despite prolonged vancomycin treatment. <i>Can J Infect Dis</i> 2004;15(2):97-100.
25	2004	Schrenzel J, Harbarth S, Schockmel G, Genné D, Bregenzer T, Flueckiger U et al. Swiss Staphylococcal Study Group. A randomized clinical trial to compare fleroxacin-rifampicin with flucloxacillin or vancomycin for the treatment of staphylococcal

		infection. Clin Infect Dis 2004;39(9):1285-92.
26	2006	Page KR, Sifakis F, Montes de Oca R, Cronin WA, Doherty MC, Federline L et al. Improved adherence and less toxicity with rifampin vs isoniazid for treatment of latent tuberculosis: a retrospective study. Arch Intern Med 2006;166(17):1863-70.
27	2006	Yew WW, Leung CC. Antituberculosis drugs and hepatotoxicity. Respirology 2006;11:699-707.
28	2006	Larzibal A, Passannante M, Kojakali F, Hayden C, Reichmann LB. Enhancement of treatment completion for latent tuberculosis infection with 4 months of rifampin. Chest 2006;130:1712-7.
29	2007	Roblot F, Besnier JM, Giraudeau B, Simonnard N, Jonville-Bera AP, Coipeau P et al. Lack of association between rifampicin plasma concentration and treatment-related side effects in osteoarticular infections. Fundam Clin Pharmacol 2007;21(4):363-9.
30	2007	Zhang W, He YJ, Gan Z, Fan L, Li Q, Wang A et al. OATP1B1 polymorphism is a major determinant of serum bilirubin level but not associated with rifampicin-mediated bilirubin elevation. Clin Exp Pharmacol Physiol 2007;34(12):1240-4.
31	2008	Tostmann A, Boeree MJ, Aarnoutse RE, de Lange WC, van der Ven AJ, Dekhuijzen R. Antituberculosis drug-induced hepatotoxicity: concise up-to-date review. J Gastroenterol Hepatol 2008;23(2):192-202.
32	2008	Menzies D, Long R, Trajman A, Dion MJ, Yang J, Al Jahdali H et al. Adverse events with 4 months of rifampin therapy or 9 months of isoniazid therapy for latent tuberculosis infection: a randomized trial. Ann Intern Med 2008;149(10):689-97.
33	2008	Riedel DJ, Weekes E, Forrest GN. Addition of rifampin to standard therapy for treatment of native valve infective endocarditis caused by Staphylococcus aureus. Antimicrob Agents Chemother 2008 Jul;52(7):2463-7.
34	2008	Haley CA, Stephan S, Vossell LF, Sherfy EA, Laserson KF, Kainer MA. Successful use of rifampicin for hispanic foreign-born patients with latent tuberculosis infection. Int J Tuberc Lung Dis 2008; 12:160-7.
35	2009	Ziakas PD, Mylonakis E. 4 months of rifampin compared with 9 months of isoniazid for the management of latent tuberculosis infection: a meta-analysis and cost-effectiveness study that focuses on compliance and liver toxicity. Clin Infect Dis 2009;49(12):1883-9.
36	2009	Chen X, Zhang C, Wang H, Xu J, Duan ZH, Zhang Y et al. Altered integrity and decreased expression of hepatocyte tight junctions in rifampicin-induced cholestasis in

		mice. <i>Toxicol Appl Pharmacol</i> 2009;240(1):26-36.
37	2009	Shen C, Cheng X, Li D, Meng Q. Investigation of rifampicin-induced hepatotoxicity in rat hepatocytes maintained in gel entrapment culture. <i>Cell Biol Toxicol</i> 2009;25(3):265-74.
38	2009	Fountain FF, Tolley EA, Jacobs AR, Self TH. Rifampin hepatotoxicity associated with treatment of latent tuberculosis infection. <i>Am J Med Sci</i> 2009;337 (5):317-20.
39	2010	El Helou OC, Berbari EF, Lahr BD, Eckel-Passow JE, Razonable RR, Sia IG et al. Efficacy and safety of rifampin containing regimen for staphylococcal prosthetic joint infections treated with debridement and retention. <i>Eur J Clin Microbiol Infect Dis</i> 2010;29(8):961-7.
40	2010	Forrest GN, Tamura K. Rifampin combination therapy for nonmycobacterial infections. <i>Clin Microbiol Rev</i> 2010;23(1):14-34.
41	2010	Frésard I, Bridevaux PP, Rochat T, Janssens JP. Adverse effects and adherence to treatment of rifampicine 4 months vs isoniazid 6 months for latent tuberculosis: a retrospective analysis. <i>Swiss Med Wkly</i> 2011;141:w13240.doi:10.4414/smw.2011.13240.
42	2011	Nakajima A, Fukami T, Kobayashi Y, Watanabe A, Nakajima M, Yokoi T. Human arylacetamide deacetylase is responsible for deacetylation of rifamycins: Rifampicin, rifabutin, and rifapentine. <i>Biochem Pharmacol.</i> 2011;82(11):1747-56.
43	2011	Yuhas Y, Berent E, Ashkenazi S. Effect of Rifampin on Production of Inflammatory Mediators in HepG2 Liver Epithelial Cells. <i>Antimicrob Agents Chemother</i> 2011;55(12):5541-6.
44	2011	Lee SH, Yim JJ, Kim HJ, Shim TS, Seo HS, Cho YS, Lee HK, Lee YM, Lee EJ, Lew WJ. Adverse events and development of tuberculosis after 4 months of rifampicin prophylaxis in a tuberculosis outbreak. <i>Epidemiol Infect</i> 2011,11:1-8.

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