Drug-related Problems and Dosage Adjustment in Patients with Liver Disease

Inauguraldissertation

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Dekan

“Wer nicht

aufs Kleine schaut,

scheitert am Großen.”

Laotse

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Summary

The liver is essential for the metabolism of medicinal substances. Liver disease, especially liver cirrhosis, may lead to various pharmacokinetic and pharmacodynamic changes, predisposing patients with liver cirrhosis to adverse drug events (ADEs). In contrast to patients with renal failure, where dose adjustment can be performed by means of creatinine clearance, no such surrogate parameter exists for patients with liver disease. Specific dosage recommendations for patients with liver cirrhosis are often not available in the product information.

We contributed to the development of a database that categorizes drugs according to their pharmacokinetic characteristics and allows for specific dosage recommendations for patients with liver disease.

In the first study, we summarized this database for all anti-infective drugs on the Swiss market in 2012. Forty-seven % (N = 49) and 44% (N = 46) of the 104 anti-infectives on the market were primarily eliminated by the liver and the kidney, respectively. For 9 drugs, the elimination pathway could not be elucidated. One fifth of all drugs was eliminated ≥50% by bile. CYP P450 enzymes were involved in the metabolism of 27% of the drugs. For 48% of the anti-infectives, studies on pharmacokinetic alterations in liver disease were found. The Swiss product information provides specific recommendations for patients with liver disease for only 50% of anti-infective drugs.

The aim of the second study was the assessment of diagnoses, medication patterns, adverse drug reactions (ADRs), and potential drug-drug interactions (pDDIs) in cirrhotic patients at hospital admission. For this purpose, we performed a cross-sectional retrospective study including 400 patients with liver cirrhosis. At hospital admission, the 400 patients had 2415 diagnoses (median 6 per patient) and 1999 drugs (median 5 per patient), whereof 68% were predominantly eliminated by the liver. In total, 200 ADRs and 132 pDDIs were detected in 112 (28%) and 86 (21.5%) patients, respectively. Fifteen ADRs were directly caused by 17 DDIs, whereof three resulted in hospital admission. Patients with ADRs were older, had more comorbidities, were treated with more drugs, and had a worse renal function and more pDDIs than patients without ADRs.

In the third study, the medication at hospital admission of the same population described in the second study was analyzed in greater detail with the goal to determine the prevalence of incorrectly dosed drugs (IDDs) and their association with ADRs. The adequacy of the drugs with respect to dosing or prescribing was investigated retrospectively by means of previous publications or the above-mentioned database. Additionally, we calculated potential cost savings associated with IDDs and additional hospital stay due to IDD-induced ADRs. In contrast to the second study, we excluded vitamins and minerals for the analyses. Of the remaining 1653 drugs prescribed (median 4 per patient), 336 (20%) were IDDs in 184 patients. Overall, 198 ADRs (83% preventable) occurred in 110 patients. Sixty-one (31% of all ADRs) were associated with IDDs in 40 patients, whereof 77% were considered to be preventable. Especially non-steroidal anti-inflammatory drugs and psycholeptics were a frequent cause of preventable ADRs. Overall, IDDs were more frequently associated with ADRs than correctly dosed drugs and patients with IDDs were more frequently admitted to the hospital due to ADRs. Hospitalizations due to IDD-induced ADRs resulted in 94 additional hospital days. Potential drug-cost savings as a result of mere dose adjustment in patients with liver cirrhosis was minor, but considerable when taking into account hospitalizations due to preventable ADRs caused by IDDs.

Pharmacotherapy in patients with liver cirrhosis is complex and specific recommendations for dosage adjustment frequently not available. Prescribing physicians should be aware of problematic drugs and the principles of dosage adjustment in patients with liver cirrhosis. Prevention of IDDs and associated ADRs potentially leading to hospital admission can contribute to the reduction of healthcare costs.

By developing a database allowing for specific dosage recommendations in patients with liver disease, we are contributing to a safer drug treatment in patients with liver cirrhosis.

Zusammenfassung

Der Metabolismus von vielen Medikamenten hängt von der Leber ab. Leberinsuffizienz, insbesondere Leberzirrhose, kann zu unterschiedlichen pharmakokinetischen und –dynamischen Änderungen führen, was Patienten mit Leberzirrhose für unerwünschte Arzneimittelereignisse anfällig macht. Im Gegensatz zu Patienten mit Niereninsuffizienz, bei denen die Dosierung gemäss Kreatinin-Clearance angepasst werden kann, gibt es bei Leberkrankheit keinen entsprechenden Surrogatparameter. Zudem stellt die Fachinformation häufig keine konkreten Dosierungsempfehlungen für Patienten mit Leberkrankheit zur Verfügung.

Wir trugen zur Entwicklung einer Datenbank bei, die Medikamente anhand ihrer pharmakokinetischer Parameter einteilt und die dadurch ermöglicht, spezifische Dosisempfehlungen für Patienten mit Lebererkrankungen zu machen.

In der ersten Studie haben wir diese Datenbank für alle Antiinfektiva zusammengefasst, die anfangs 2012 in der Schweiz auf dem Markt waren. Siebenundvierzig % (N = 49) bzw. 44% (N = 46) von den 104 Antiinfektiva auf dem Markt wurden vor allem über die Leber bzw. über die Niere ausgeschieden. Für 9 Medikamente konnte der Eliminationsweg nicht geklärt werden. Ein Fünftel der Medikamente wurde zu ≥50% über die Galle ausgeschieden. CYP P450 Enzyme trugen zum Metabolismus von 27% der Medikamente bei. Für 48% der Antiinfektiva haben wir Studien über pharmakokinetische Änderungen bei Leberkrankheiten gefunden. Die Schweizer Fachinformation stellt nur für 50% der Antiinfektiva konkrete Dosisempfehlungen bei Leberinsuffizienz zur Verfügung.

Die zweite Studie hatte zum Ziel, Diagnosen, Medikation, unerwünschte Arzneimittelwirkungen (UAW) und potentielle Medikamenteninteraktionen (pMIA) von Zirrhose-Patienten bei Spitaleintritt genauer zu erfassen. Dazu haben wir eine retrospektive Querschnittsstudie mit 400 Patienten mit Leberzirrhose durchgeführt. Bei Spitaleintritt hatten die 400 Patienten 2415 Diagnosen (Median 6 pro Patient) und 1999 Medikamente (Median 5 pro Patient), wovon 68% vor allem hepatisch eliminiert wurden. Insgesamt wurden 200 UAW bzw. 132 pMIA in 112 (28%) bzw. 86 (21.5%) Patienten festgestellt. Siebzehn pMIA führten zu 15 UAW, wovon drei zu einer Hospitalisation führten. Verglichen mit Patienten ohne UAW waren

Patienten mit UAW älter, hatten mehr Komorbiditäten, erhielten mehr Medikamente und hatten eine schlechtere Nierenfunktion als auch mehr pMIA.

In der dritten Studie wurde die Medikation derselben Population wie in der zweiten Studie detaillierter analysiert mit dem Ziel, die Prävalenz von inkorrekt dosierten Medikamenten (IDM) und deren Assoziation mit UAW zu bestimmen. Dabei wurde mithilfe von früheren Publikationen oder der oben erwähnten Datenbank retrospektiv untersucht, ob die Medikamente angemessen verschrieben und/oder dosiert wurden. Zusätzlich haben wir mögliche Kostenersparnisse berechnet, die mit IDM oder zusätzlichem Spitalaufenthalt aufgrund von IDM-assoziierten UAW in Zusammenhang stehen. Verglichen mit der zweiten Studie haben wir hier Vitamine und Mineralstoffe für die Analyse ausgeschlossen. Von den verbleibenden 1653 verschriebenen Medikamenten (Median 4 pro Patient), waren 336 (20%) IDM bei 184 Patienten. Insgesamt kamen 198 UAW (davon 83% vermeidbar) bei 110 Patienten vor. Einundsechzig (31% von allen UAW) waren mit IDM bei 40 Patienten assoziiert, wovon wiederum 77% als vermeidbar angesehen wurden. Vor allem nicht-steroidale Antirheumatika und Psycholeptika waren häufig verantwortlich für vermeidbare UAW. Insgesamt waren IDM häufiger mit UAW assoziiert als korrekt dosierte Medikamente und Patienten mit IDM wurden häufiger hospitalisiert aufgrund einer UAW. Hospitalisationen aufgrund von UAW, die durch IDM ausgelöst wurden, führten zu 94 zusätzlichen Spitaltagen. Mögliche Kostenersparnisse lediglich aufgrund von Dosisanpassungen waren minimal, wurden aber beträchtlich, wenn man die zusätzlichen Hospitalisationen aufgrund vermeidbarer UAW, die durch IDM ausgelöst wurden, ebenfalls in Betracht zieht.

Die medikamentöse Therapie bei Patienten mit Leberzirrhose ist komplex und konkrete Empfehlungen für eine Dosisanpassung sind häufig nicht erhältlich. Verschreibende Ärzte sollten sich problematischer Medikamente und den Grundlagen der Dosisanpassung bei Leberzirrhose bewusst sein. Die Vermeidung von IDM und damit verbundenen UAW, die zu einer Spitaleinweisung führen können, kann zur Senkung von Gesundheitskosten beitragen.
Indem wir eine Datenbank entwickeln, die es ermöglicht, spezifische Dosisempfehlungen für Patienten mit Lebererkrankungen zu machen, tragen wir zu einer sichereren Therapie bei Patienten mit Leberinsuffizienz bei.

Abbreviations

ACE	angiotensin converting enzyme
ADEs	adverse drug events
ADRs	adverse drug reactions
ATC	Anatomical Therapeutic Chemical Classification System
AUC	area under the concentration-time curve
CAT	category
CAT1	category 1 (high hepatic extraction drugs)
CAT2	category 2 (intermediate hepatic extraction drugs)
CAT3	category 3 (low hepatic extraction drugs)
CAT4	category 4 (mainly renal elimination drugs)
CAT5	category 5 (drugs with unknown elimination pathway)
CDDs	correctly dosed drugs
CDS	clinical decision support
CL_{hep}	hepatic clearance
CL_{int}	intrinsic hepatic clearance
CL_{sys}	systemic clearance
C_{max}	maximal plasma concentration
COX	cyclooxygenase
CPOE	computerized physician order entry
CYP	cytochrome P450
DDIs	drug-drug interactions
E	hepatic extraction
f_u	unbound fraction of a drug
GABA	γ-aminobutyric acid
GSH	glutathione
HBV	hepatitis B virus
HCV	hepatitis C virus
HSCT	hematopoietic stem cell transplantation
ICSR	individual case safety reports
IDDs	incorrectly dosed drugs
INR	international normalized ratio
MELD	Model for End-Stage Liver Disease
MEs	medication errors

NADs	not assessable drugs
NAPQI	N-acetyl-p-benzoquinoneimine
NSAIDs	non-steroidal anti-inflammatory drugs
OR	odds ratio
pDDIs	potential drug-drug interactions
PDR	Physicians' Desk Reference
Q_0	extrarenal dose fraction
RAAS	renin-angiotensin-aldosterone system
SULT	sulfotransferase
$T_{1/2}$	elimination half-life
UGT	uridine diphosphate glucuronosyltransferase
V_d	volume of distribution

Chapter I

Aims of the thesis

1 Aims of the thesis

The main goal of this PhD thesis is to contribute to a better understanding of the characteristics of patients with liver cirrhosis and to improve drug safety in this patient population.

First, we contributed to the development of a database containing pharmacokinetic and toxicologic data of drugs on the Swiss market. We classified drugs according to their elimination pathway and reviewed the literature and product information for pharmacokinetic changes and dosage recommendations in patients with liver disease. Based on pharmacokinetic as well as pharmacodynamic data, the database provides specific dosage recommendations for patients with impaired hepatic function whenever possible. In collaboration with Documed AG, the development of a clinical decision support (CDS) tool is planned.
With our first study, where we present a part of the database using the example of anti-infective drugs, we aimed at simplifying drug prescription of anti-infectives in patients with liver disease by giving specific recommendations.

The aim of the second study was to identify characteristics and drug-related problems in patients with liver cirrhosis. For this purpose, we included a population of 400 patients with liver cirrhosis. We characterized the patients in respect of their demographic data, comorbidities, prevalent drugs at hospital admission, adverse drug reactions (ADRs), and potential drug-drug interactions (pDDIs). We tried to work out the prevalence of ADRs and pDDIs as well as associated and/or critical drugs in hepatically impaired patients.
By comparing cirrhotic patients with ADRs to those without ADRs, we could identify potential risk factors for ADRs.

The goal of the third study was to investigate the medication (prevalent at hospital admission) of the 400 patients with liver cirrhosis in greater detail. To this end, we judged the adequacy of the administered drugs and their doses according to the recommendations of previous publications or the above-mentioned database. On the one hand, we investigated if there was an association between incorrectly dosed drugs (IDDs) and the rate of ADRs. ADRs associated with IDDs were described in detail. On the other hand, the relationship between a drug's elimination pathway and the occurrence of ADRs was assessed. Furthermore, we calculated potential cost savings associated with IDDs and additional hospital stay due to IDD-induced ADRs.

Chapter II

Introduction

2.1 The liver

2.1.1 Liver anatomy and function

The liver is a gland of approximately 1.5kg situated in the right upper quadrant of the abdomen. It is the central organ for synthesis, storage, and metabolism of important endogenous and exogenous substances. It is divided into four lobes of different size. The histologic units of the liver are the small (1-2mm in diameter) hexagonal liver lobules, whereof about 500'000 exist in the liver [1, 2]. The most important cells of these lobules are the hepatocytes or parenchymal cells, which are organized as one-cell thick plates. Nonparenchymal cells consist of endothelial cells, pit cells (the natural killer cells of the liver), Kupffer cells with phagocytic activity, and the contractile hepatic stellate cells, which contain large amounts of retinoids (95% of body store) [1].

Hepatic blood supply occurs by the portal vein (75-80%) and the hepatic artery (20-25%). Both vessels enter the liver at the porta hepatis at the lower side of the liver, whereas the bile ducts leave the liver at this site. The portal vein drains venous blood from almost the whole gastrointestinal tract [3] and spleen into the liver and serves as a carrier of nutrient-derived or other ingested substances (e.g. drugs). Blood enters the hepatic lobule at the portal triads at the corners of the hexagon, and then passes the hepatic capillaries, which are called sinusoids, unidirectionally towards the middle of the lobule, where it empties into the central vein (Fig. 1) [1, 2].

The sinusoidal wall is made up of endothelial cells and hepatic stellate cells. Instead of being continuous, the sinusoidal wall has pores, so-called fenestrae (1000 Å in diameter). It is separated from the hepatocytes by a small space, the space of Disse [1, 2]. Except for substances with a diameter >1000 Å, certain proteins, soluble compounds, or waste products that are filtered or taken up by the endothelial cells, many blood components can penetrate the sinusoidal wall and interact with the hepatocytes' microvilli, which project into the space of Disse. Uptake into hepatocytes is mediated by various, partially specific (e.g. for bile or amino acids) transport proteins, which may be regulated by different endogenous and exogenous factors such as electrogenic state of the hepatocyte or fasting. Bilirubin is transported by an anion carrier, which is also involved in the transport of hydrophobic anionic drugs, which may lead to hyperbilirubinemia if the transporter is saturated [1].

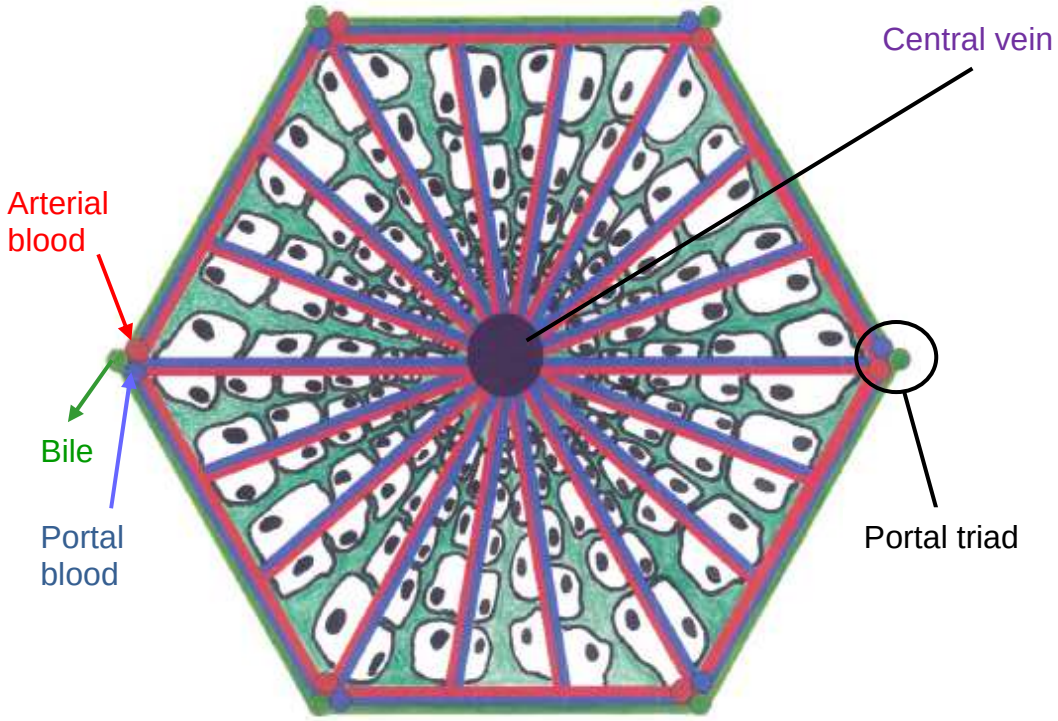

Fig. 1 Schematic illustration of a hepatic lobule. While the portal vein (blue) and the hepatic artery (red) enter the lobule at the portal triad, the biliary tract (green) leaves the lobule there (modified from [2]).

A major purpose of the hepatocytes is the metabolism of endogenous and exogenous substances by activation, inactivation, or detoxification, as well as their elimination (see also section *1.1.2 The role of the liver in drug metabolism*). The hepatocytes are categorized into three zones according to their distance from the afferent blood vessels. Zone 1 cells are located near the portal triad, whereas zone 3 cells are near the central vein, and zone 2 cells are in between. According to their zonation, hepatocytes differ with respect to key enzymes, cell receptors, subcellular structures, and cell matrix interactions. For example, more cytochrome P450 (CYP) enzymes are located in zone 3 hepatocytes compared to zone 1 hepatocytes, whereas the opposite is true for the enzyme sulfotransferase (SULT). Since perfusion along the sinusoid is unidirectional and blood composition changes along the sinusoids, hepatocytes are confronted with heterogeneous microenvironments. Next to basic genetic expressions, various signals from these microenvironments lead to the development of the above mentioned zonation [1].
The hepatocytes play a major role in bile formation. They actively secret bile acids, electrolytes, and organic solutes such as bilirubin. Bile flows in canaliculi along the liver cell plate and forms a countercurrent to the blood flow through the sinusoids

(Fig. 1). Bile serves as an elimination pathway for hydrophobic substances on the one hand, and as a fat emulsifier in the gastrointestinal tract to increase absorption of fat-soluble substances on the other hand [1]. Thereby, bile acids are recycled: they are excreted into the duodenum and reabsorbed in the ileum (so-called enterohepatic circulation) [2].

2.1.2 The role of the liver in drug metabolism

Metabolic enzymes exist in many tissues of the body, however, the liver possesses the highest amount and diversity of enzymes [4]. For example, 90-95% of CYP enzymes are located in the liver and only 1-2% in the gastrointestinal epithelium. Next to the liver, uridine diphosphate glucuronosyltransferase (UGT) is also expressed in the gut, the kidney, the lung, the prostate, the skin, and the brain [5].

Regarding the metabolism of xenobiotics, one differentiates between phase I and II metabolism. During *phase I*, the substances are chemically altered in order to make them more polar. The principal enzymes belong to the CYP family and typically perform N- or O-dealkylation, N- or S-oxidation, aliphatic or aromatic hydroxylation, or deamination [6]. Further enzymes involved in phase I reactions are alcohol and aldehyde dehydrogenases, xanthine oxidases, amine oxidases, esterases, or epoxide hydrolases [5]. During *phase II* metabolism the following conjugation reactions take place: glucuronidation, sulfation, methylation, acetylation, glutathione (GSH) and amino acid conjugation. Involved enzymes are UGT, SULT, N-acetyltransferases, GSH S-transferases, methyl transferases, and catechol O-methyl transferases [6]. These reactions usually contribute to the inactivation of substances and also increase their hydrophilicity, facilitating excretion by the kidney and bile [5]. Exceptionally, metabolism may lead to more active substances compared to the parent compounds or even to toxic products. Examples are morphine-6-glucuronide, which shows a two to four times higher analgesic potency than its parent drug morphine [7], and N-acetyl-p-benzoquinoneimine (NAPQI), a highly reactive metabolite of acetaminophen resulting from N-hydroxylation mainly by CYP2E1 and 1A2 [8, 9]. NAPQI is usually detoxified by GSH conjugation, but can lead to hepatotoxicity if high amounts of acetaminophen are ingested [8] or in GSH-depleted patients [10].

2.1.3 Liver cirrhosis: epidemiology and pathology

Due to the focus on patients with liver cirrhosis in this PhD thesis and the pronounced impact of cirrhosis on liver architecture and function, this section will focus on liver cirrhosis.

In western Europe, the yearly mortality rate due to liver cirrhosis between 1997 and 2001 was between 9.7 (Netherlands) and 43.5 (Austria) per 100,000 males and between 5.6 (Sweden) and 16.7 (Austria) per 100,000 females [11]. In countries with a higher frequency of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, e.g. in Asia or Africa, these numbers are even higher [12].

As a response to chronic liver damage, excess extracellular matrix is produced (fibrogenesis) in order to replace the injuries by regenerative scar tissue. Activated myofibroblasts derived from hepatic stellate cells and fibroblasts are involved in this process [1, 12]. Liver fibrosis develops, which may progress to liver cirrhosis [12, 13]. Histologically, liver cirrhosis presents as regenerative nodules surrounded by fibrous bands [12], leading to an increased intrahepatic blood flow resistance. Consequently, portal hypertension may develop and lead to intra- and extrahepatic portosystemic shunts circumventing the liver [4, 12].

Next to a decreased number of functional hepatocytes in patients with liver cirrhosis [14], altered hepatic architecture impairs normal function of remaining hepatocytes [1, 12]. For example, a process called sinusoidal capillarization (Fig. 2) occurs, where sinusoidal endothelium is replaced by a collagen basement membrane, most of the endothelial fenestrae lost, and the space of Disse filled with scar tissue [1, 12]. Furthermore, the hepatocytes lose their microvilli [1]. As a result, exchange between blood in the sinusoids and the hepatocytes is impaired [1, 4].

Liver cirrhosis represents the terminal stage of many liver diseases of different etiologies. The primary cause for liver cirrhosis in industrial countries is alcohol abuse, followed by HBV and HCV infections [13]. Other possible causes are toxic substances, chronic autoimmune hepatitis, chronic biliary obstruction, non-alcoholic steatohepatitis, hepatic porphyrias, vascular disorders (e.g. Budd Chiari syndrome), or metabolic diseases such as Morbus Wilson or hemochromatosis [2, 12, 13].

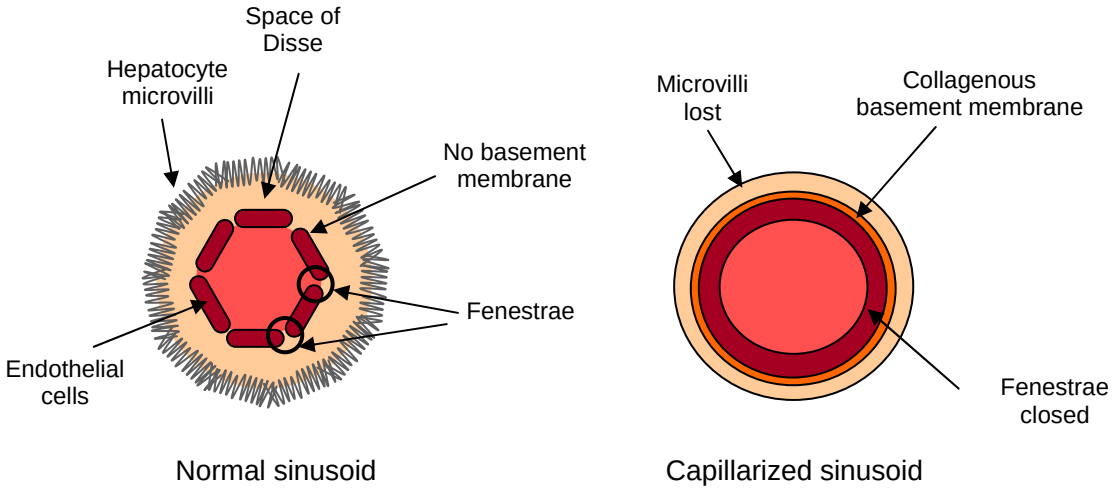

Fig. 2 While blood and solutes can readily interact with the hepatocytes microvilli in a normal sinusoid, this interaction is impaired in capillarized sinusoids due to closed fenestrae, a collagenous basement membrane and lack of microvilli (modified from [1]).

Patients with compensated liver cirrhosis may be asymptomatic or present with unspecific symptoms such as fatigue or gastrointestinal disturbances (anorexia, nausea, diarrhea, obstipation) [12, 13]. More specific symptoms are ascites, jaundice, pruritus, dermatologic changes (spider angioma, palmar erythema), or bleeding tendency [2, 13]. However, it is still common that patients come to clinical attention for the first time due to decompensation of liver cirrhosis with serious complications such as ascites, esophageal variceal bleeding, spontaneous bacterial peritonitis, or hepatic encephalopathy [12, 13].

The combination of clinical and laboratory signs (e.g. increased liver enzymes or bilirubin, or decreased albumin or prothrombin time) and symptoms, a known exposure to a causal agent, and imaging strategies (ultrasonography, computerized tomography, magnetic resonance imaging) frequently allow to suppose the presence of liver cirrhosis. To confirm the diagnosis, however, a liver biopsy is necessary [12].

The therapy of cirrhosis depends on the causal agent. While patients with alcoholic cirrhosis profit from alcohol abstinence, patients with viral hepatitis should be treated with antiviral agents to prevent disease progression and/or hepatocellular carcinoma [12]. Although liver cirrhosis is generally thought to be irreversible, regression of cirrhosis has been reported in patients treated successfully for HCV [15] and HBV [16].

Liver cirrhosis may lead to various complications (Fig. 3). Patients with liver cirrhosis have hemodynamic alterations. Due to portal hypertension followed by

splanchnic vasodilation and arterial hypovolemia, the body counteracts by activation of vasoconstricting systems (sympathetic nervous system and renin-angiotensin-aldosterone system [RAAS]). This leads to sodium and water retention in the kidney, which can compensate for arterial underfilling in the beginning. Additionally, edema and ascites (fluid accumulation in the peritoneal cavity) may develop, causing further sodium and water retention. If disease progresses and vasoconstrictors prevail in the kidney, renal perfusion decreases, eventually resulting in hepato-renal syndrome with renal failure [17].

Spontaneous bacterial peritonitis is a complication where ascitic fluid is spontaneously infected by bacteria, supposedly originating from the gastrointestinal tract. Thereby, decreased phagocytic function of the reticuloendothelial system and decreased anti-microbial activity of the ascitic fluid are risk factors for the development of spontaneous bacterial peritonitis [17].

Hepatic encephalopathy is a term used for neuropsychiatric changes in patients with liver disease. Due to a circumvention of the liver by portosystemic shunts on the one hand and a decreased hepatic clearance (CL_{hep}) on the other hand, a greater amount of potentially toxic substances which are normally detoxified by the liver become systemically available. It is unknown whether such substances (e.g. ammonia) directly lead to neurotoxicity in the brain or induce secondary alterations in brain neurochemistry [18].

Due to the obstructed portal blood flow in patients with liver cirrhosis, blood flow across portosystemic communications increases (e.g. at the cardia of the stomach). As a result, vasodilation occurs in these blood vessels and they become varicose veins. Eventually, rupture of these gastroesophageal varices may cause hemorrhage with a mortality of up to 20-30% [3].

Hemorrhage may be more problematic in cirrhotic patients than in healthy subjects, because synthesis of all coagulation factors except for factor VIII occurs in the liver and may be affected by liver diseases. Another important product affected by impaired hepatic synthesis is the plasma protein albumin [19]. Hypoalbuminemia is a contributing factor to ascites due to a reduced oncotic pressure in plasma [2].

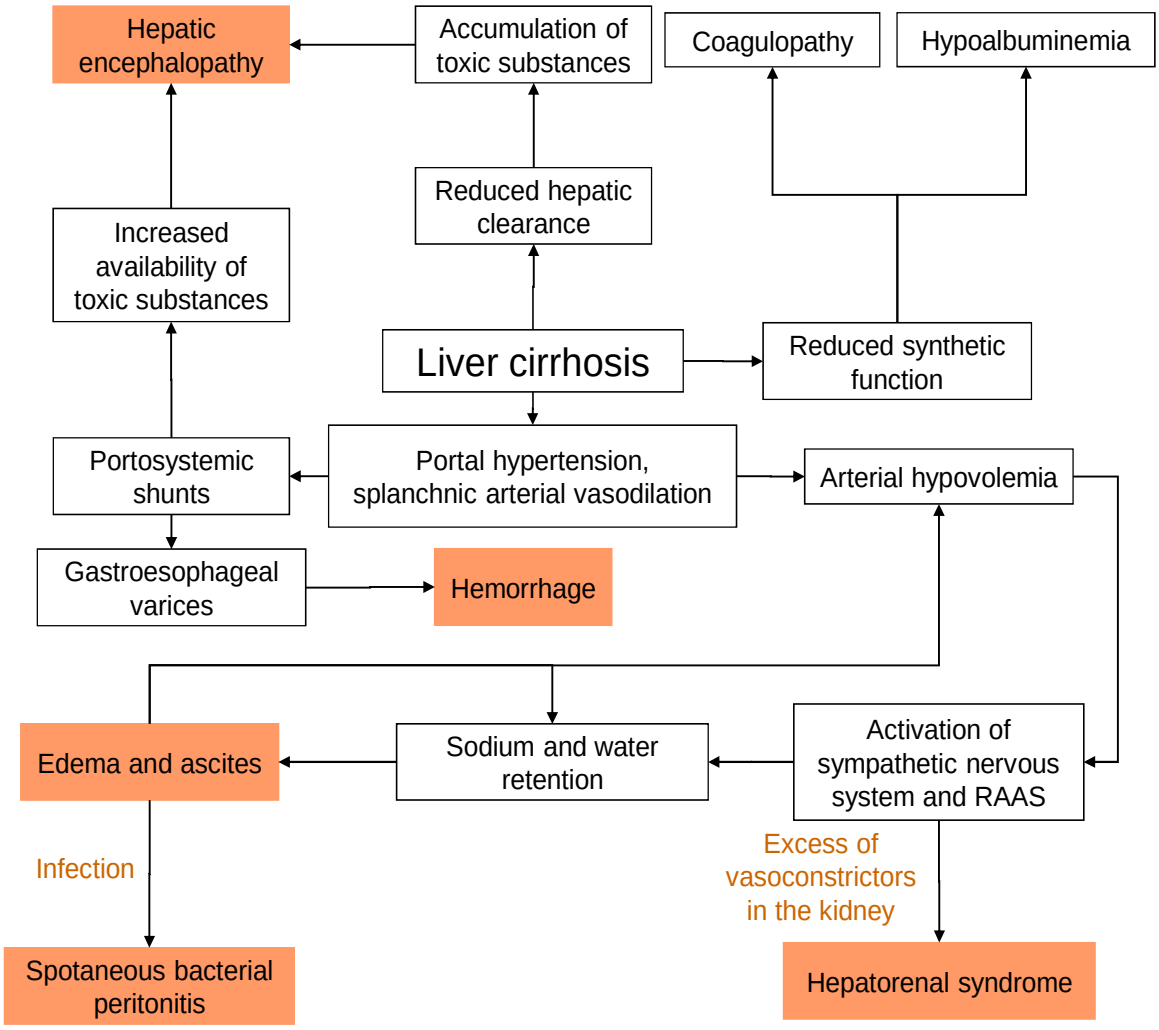

Fig. 3 Liver cirrhosis and the pathophysiology of its complications, complications in orange boxes. Modified from [17, 18]. RAAS = renin-angiotensin-aldosterone system.

The most common prognostic models used in patients with liver cirrhosis are the Child Pugh score and the Model for End-Stage Liver Disease (MELD). While the MELD [20, 21] includes serum bilirubin, serum creatinine, the international normalized ratio (INR), and the etiology of liver disease for the evaluation of patients with liver cirrhosis, the Child Pugh score [22] includes serum bilirubin, serum albumin, the INR, and the presence of encephalopathy and ascites (Tab. 1). The Child Pugh classification has some limitations [20]. First, some parameters can be interpreted subjectively (e.g. ascites) depending on the observer and the diagnostic method used. Secondly, the measurement of laboratory values (e.g. albumin) may vary between different laboratories. Thirdly, the discriminatory power is limited, e.g. a patient with bilirubin of 3.5mg/dl and one with 20mg/dl both have 3 points for bilirubin (so-called ceiling effect). Furthermore, physical findings used for the classification such as ascites can be influenced by medication. Many of these

problems are circumvented by the MELD, e.g. it bases on objective parameters [20]. However, laboratory values used for the MELD may also vary depending on the methods used (e.g. creatinine) [23]. A systematic review comparing the two prognostic models used in patients with liver cirrhosis has found no superiority of the MELD compared to the Child Pugh model [24].

As liver cirrhosis at the University Hospital Basel is graded by the Child Pugh score, this model was used in our studies.

Tab. 1 Child Pugh Score [22]

Parameters	***Points****		
	1	***2***	***3***
Ascites	absent	slight	moderate
Bilirubin	<2mg/dL	2-3mg/dL	>3mg/dL
Albumin	>3.5g/dL	2.8-3.5g/dL	<2.8g/dL
Prothrombin time prolongation ***or*** ***INR***	1-4s <1.7	4-6s 1.7-2.3	>6s >2.3
Encephalopathy (grade)	none	1 and 2	3 and 4

* By adding up the points a score between 5 and 15 results: patients with a score of 5-6, 7-9, and 10-15 have mild (Child Pugh A), moderate (Child Pugh B), and severe (Child Pugh C) liver cirrhosis, respectively.

2.2 Impact of liver disease on drug distribution and efficacy

2.2.1 Pharmacokinetic alterations in patients with liver disease

In patients with liver cirrhosis, the absorption process may be altered due to potential gastrointestinal dysfunction (e.g. hypertensive gastropathy [25]), whereas the amount absorbed does not seem to be influenced [26].

For hydrophilic drugs, the volume of distribution (V_d) increases in patients with ascites. To achieve effective blood concentrations rapidly, a higher loading dose may be indicated in such cases [4, 27]. According to Eq. 1, applicable for drugs with linear pharmacokinetics [28], an increased V_d leads to a prolonged elimination half-life ($t_{1/2}$), if systemic clearance (CL_{sys}) is unchanged.

$$t_{1/2} = 0.7 * \frac{Vd}{CL_{sys}}$$ (Equation 1)

As described earlier, synthetic function of the liver decreases in patients with liver cirrhosis potentially resulting in decreased production of plasma proteins such as albumin or α_1-acid glycoprotein [4]. Consequently, free fraction and possibly also free concentration of highly protein-bound drugs may be increased in patients with liver cirrhosis [27], leading to a more pronounced pharmacodynamic effect. Additionally, certain endogenous substances binding to plasma proteins such as bilirubin may accumulate in liver disease, potentially competing with drugs for binding sites [4].

Systemic bioavailability may be increased in patients with liver cirrhosis due to portosystemic shunting and reduced hepatic blood flow on the one hand and reduced metabolism on the other hand [4]. Phase I metabolizing enzymes, whose function depends on molecular oxygen, seem to be more sensitive to liver disease than phase II enzymes [4, 27, 29, 30]. In advanced disease stages, glucuronidation seems also to be impaired, but further studies are necessary to clarify the impact of liver disease on glucuronidation [4]. But even within the CYP enzyme family, the observed alteration in functionality was inhomogeneous. For example, CYP2C19 seems to be affected in an earlier disease stage than CYP2D6 [31].

Additionally, the impact of liver disease on a drug's metabolism also depends on the characteristics of the drug itself. For further information see section *2.3 Classification of drugs according to their pharmacokinetic parameters*.

Biliary excretion of drugs may be impaired in patients with liver cirrhosis, even in patients without obvious mechanical biliary obstruction. Potential mechanisms include alterations of the membrane or the cytoskeleton of bile canaliculi, altered activity of transporters or paracellular pathways, or impaired intracellular calcium homeostasis. Intra- and extrahepatic cholestasis may lead to an accumulation of drugs that normally undergo mainly biliary excretion [4]. Enterohepatic cycling may be interrupted [32]. Furthermore, impaired function of hepatic CYP enzymes was reported in patients with cholestasis [4, 27].

Finally, impaired kidney function is often observed in patients with liver cirrhosis (hepato-renal syndrome) [4, 27].

2.2.2 Pharmacodynamic alterations in patients with liver disease

Apart from pharmacokinetic changes, patients with liver disease also have pharmacodynamic alterations.

For diuretics and β-adrenoreceptor antagonists for example, a decreased pharmacodynamic effect was observed, while sensitivity was increased for centrally depressing drugs and non-steroidal anti-inflammatory drugs (NSAIDs) [4, 27].

There is some evidence that β-adrenoreceptors are less sensitive in patients with liver cirrhosis [4, 33]. For diuretics, a higher concentration in the renal tubule is necessary for the excretion of a certain amount of sodium [4, 27]. This was shown for the loop-diuretics torasemide [34, 35], furosemide [35-37], bumetanide [38], and triamterene [39, 40]. For certain substances with hepatic elimination such as torasemide, compensatory increased renal elimination may counterbalance the decreased pharmacodynamic effect [34].

Cirrhotic patients have increased central sensitivity to centrally depressing drugs such as opiates, benzodiazepines, or antipsychotics [4, 27]. These substances may precipitate hepatic encephalopathy in patients with liver cirrhosis. Hypotheses to explain the increased brain sensitivity include altered permeability of the blood-brain barrier, an increased presence of γ-aminobutyric acid (GABA) receptors, or changes in GABA-ergic tone [4, 41].

As described earlier, patients with liver cirrhosis may have impaired kidney function. Renal prostaglandins (mainly prostaglandin E2 [42]) acting as vasodilators contribute to the maintenance of renal perfusion and function in these patients. The administration of NSAIDs, which inhibit prostaglandin synthesis, may precipitate renal failure in patients with liver disease [27, 43].

2.2.3 Classification of drugs according to their pharmacokinetic characteristics and derived recommendations

In contrast to patients with renal failure, where dosage of drugs can be adjusted according to the creatinine clearance, no such surrogate parameter exists in patients with liver disease [27]. By looking at the pharmacokinetic characteristics of a drug, the role of the liver in the elimination of the drug can be estimated.

Fig. 4 shows our classification of drugs into five categories (CAT) with the corresponding recommendations. Additionally, the procedure to find ideal dose recommendations for patients with liver disease is depicted.

First, the extrarenal dose fraction (Q_0) tells us if a drug is mainly eliminated unchanged by the kidney (Q_0<0.5, CAT4) or if it undergoes mainly hepatic elimination (Q_0≥0.5) and is excreted either by the kidney (as metabolites) or by the bile (unchanged and/or as metabolites). Secondly, drugs with mainly hepatic elimination can be further categorized, namely into drugs with low (E<0.3, CAT3), intermediate (E 0.3-0.6, CAT2), or high hepatic extraction (E>0.6, CAT1). Hepatic extraction E is an equivalent to the hepatic first pass effect. Therefore, the lower the value for E the higher the systemic bioavailability after oral administration, provided that gastrointestinal solubility and absorption is good [32]. Finally, CAT5 refers to drugs with unknown Q_0 and/or E.

The CL_{hep} of a drug can be calculated by Eq. 2:

$$Cl_{hep} = Q * E \qquad \text{(Equation 2)}$$

where E is the hepatic extraction of the drug, and Q the hepatic blood flow (~54L/h).

According to the “well-stirred” or “venous equilibrium” model, E can be calculated as shown in Eq. 3 due to its dependence on hepatic blood flow Q, intrinsic hepatic clearance CL_{int}, and the unbound fraction f_u of the drug [4, 27].

$$E = \frac{f_u * CL_{int}}{Q + (f_u * CL_{int})} \qquad \text{(Equation 3)}$$

By replacing E in Eq. 2 by Eq. 3 the following equation for CL_{hep} results.

$$CL_{hep} = \frac{Q * (f_u * CL_{int})}{Q + (f_u * CL_{int})} \qquad \text{(Equation 4)}$$

For drugs with high hepatic extraction (E>0.6), $CL_{int}*f_u >> Q$. Thus, Eq. 4 can be shortened to

$$CL_{hep} \approx Q \qquad \text{(Equation 5)}$$

This indicates that CL_{hep} of drugs with high hepatic extraction, also called “flow-limited” drugs, depends more on hepatic blood flow than on the unbound fraction and CL_{int}. A reduced hepatic blood flow and portosystemic shunts in patients with

liver cirrhosis may have a major impact on oral bioavailability [4, 27]. An example of such a drug is clomethiazole, which has an oral bioavailability of 10% in normal subjects. In patients with liver cirrhosis, the reported oral bioavailability was 100% [44]. For oral administration of drugs with high hepatic extraction, a reduction of the initial and the maintenance dose by ≥ 50% is indicated in patients with liver cirrhosis. With parenteral administration, the hepatic first pass metabolism is avoided and only the maintenance dose has to be reduced.

For drugs with low hepatic extraction (E<0.3), $Q >> (CL_{int} \times f_u)$. Thus, Eq. 4 can be shortened to

$$Cl_{hep} \approx (f_u * Cl_{int}) \qquad \text{(Equation 6)}$$

This indicates that CL_{hep} of drugs with low hepatic extraction depends more on the unbound fraction and the CL_{int} of the drug than on the hepatic blood flow. For these drugs, also called “enzyme-capacity limited” drugs, the reduced CL_{int} in patients with liver disease may result in a prolonged $t_{1/2}$. As a general rule, it is not necessary to reduce the initial dose of low hepatic extraction drugs in patients with liver cirrhosis, but maintenance dose should be reduced by up to 50%. An example for a low hepatic extraction drug is cefixime. An unaltered maximal plasma concentration (C_{max}) with a 2-fold prolonged $t_{1/2}$ was reported in patients with moderate to severe liver cirrhosis [45, 46]. Furthermore, unbound fraction f_u may be increased in patients with liver cirrhosis and hypoalbuminemia. Hence for drugs with a high protein binding and a shown relationship between plasma concentration and response, it is crucial to measure the free plasma concentration to avoid enhanced pharmacodynamic effects. However considering Eq. 6, an opposed effect is also possible for low hepatic extraction drugs with a high protein binding and a linear pharmacokinetic behavior. According to this equation, an increased unbound fraction may result in an unaltered or even increased CL_{hep} [27].

Drugs with an intermediate hepatic extraction (E 0.3 – 0.6) have characteristics of both drugs with high and low hepatic extraction. Their pharmacokinetic behavior in patients with liver cirrhosis depends on all three variables hepatic blood flow, CL_{int}, and unbound fraction [27]. E.g. for rabeprazole, an increase of C_{max} by 50%, of the area under the concentration-time curve (AUC) and $t_{1/2}$ by 100%, and a reduction of the CL_{sys} to 38% was observed in patients with compensated liver cirrhosis [47].

Hence, for intermediate hepatic extraction drugs, an initial dose in the lower range of normal and a reduced maintenance dose by approximately 50% should be administered orally. With parenteral administration, again only the maintenance dose has to be reduced.

For all hepatic extraction categories (CAT1, CAT2, CAT3), adjustment of maintenance dose by means of clinical effect and dose-dependent ADRs is possible.

Additionally, we should be aware of a potential accumulation of drugs with mainly biliary elimination in patients with cholestasis.

Finally, if a drug with a low V_d is administered to patients with ascites, the initial dose should generally be chosen according to body weight and the maintenance dose in the lower range of normal.

Next to pharmacokinetic data of the parent drug in patients with liver cirrhosis, we must not forget to think about possible pharmacokinetic alterations of active or toxic metabolites.

For an optimal dose recommendation for patients with liver cirrhosis, apart from pharmacokinetic considerations, also pharmacodynamic data have to be taken into account.

We can conclude that pharmacotherapy is complex in patients with liver cirrhosis. The more so because interindividual variability of alterations is high in patients with liver disease [4, 27, 32].

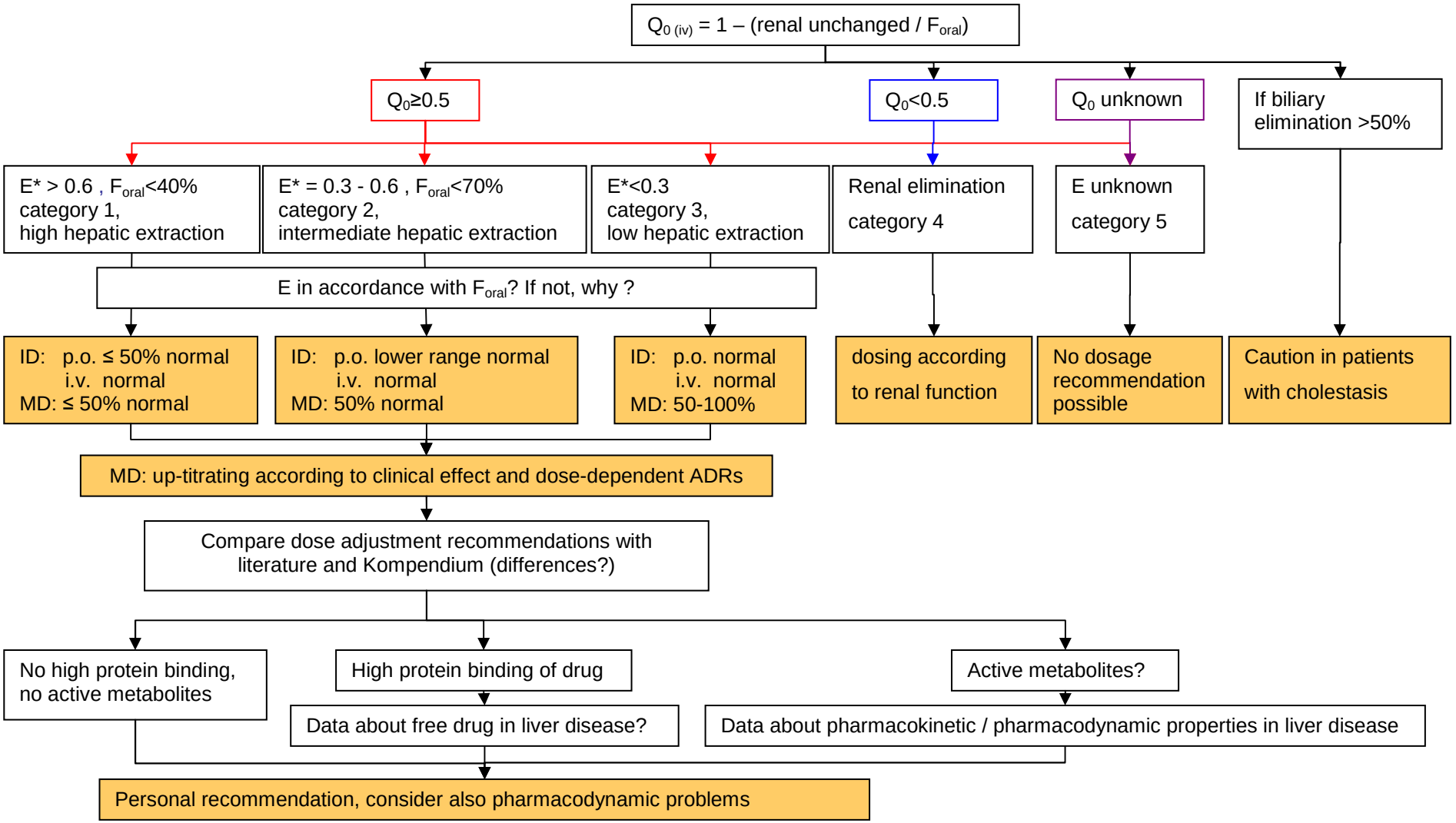

Fig. 4 Classification of drugs according to pharmacokinetic data and corresponding recommendations for patients with liver disease. * E is either obtained from the literature or calculated by $E = Q_0 * CL_{sys}/Q$; ADRs = adverse drug reactions; CL_{sys} = systemic clearance; E = hepatic extraction; F_{oral} = systemic bioavailability after oral administration (good gastrointestinal solubility and absorption assumed); ID = initial dose; MD = maintenance dose; Q = hepatic blood flow (~54L/h); Q_0 = extrarenal dose fraction

2.3 Drug safety

2.3.1 Background

„Dosis sola facit venenum“, as Paracelsus wrote in 1538 [48], refers to the fact that every substance, administered to an organism in high enough amounts, causes damage. This phrase is frequently cited in association with toxic substances, but is also true for medicinal substances. Next to their desired and beneficial effects, drugs may be harmful.

As outlined in the previous section, liver cirrhosis is associated with various pharmacokinetic and –dynamic changes, predisposing patients to untoward drug reactions. This section gives a short overview of the different terms used to describe drug-related problems.

To clarify the meaning of the various drug-related problems explained below, an example will be given from our own results in patients with liver cirrhosis.

Tab. 2 Definitions of most important drug-associated problems

Drug-related problem	“All circumstances involving a patient’s drug treatment that actually, or potentially, interfere with the achievement of an optimal outcome” [49].
Adverse drug event	“Any injury related to the use of a drug, regardless of whether a therapeutically appropriate dosage is used. The causality of this relationship may not be proven” [50].
Adverse drug reaction	“A response to a drug which is noxious and unintended and which occurs at doses normally used in human for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function” [51].
Medication error	“A medication error is a failure in the treatment process that leads to, or has the potential to lead to, harm to the patient” [52].
Drug drug interaction	“The combining of two or more drugs such that the potency or efficiency of one drug is significantly modified by the presence of another” [53].
Lack of efficacy	“Unexpected failure of a drug to produce the intended effect as determined by previous scientific investigation” [51].
Nonadherence	If patients do not take their medication as prescribed by their health care providers [54].
Overdosage	Intake of an excessive amount of drug potentially leading to increased pharmacologic and/or toxic effects. Overdosages may be accidental, intentional, or iatrogenic [55].
Addiction	If patients develop a strong tendency to increase the drug dose or the duration of therapy, whereas the drug is often not or no longer indicated. Addiction is characterized by dependence, tolerance development, and withdrawal reaction [55].

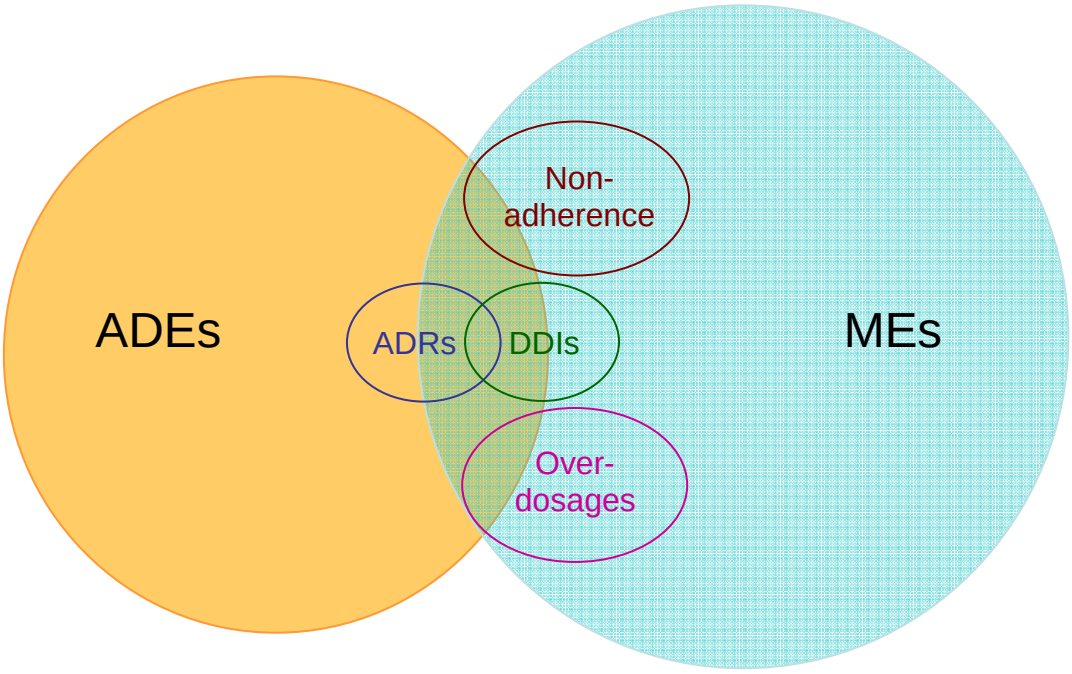

Fig. 5 Correlation between various drug-related problems (modified from [56]). DDIs not associated with ADEs or ADRs are called potential DDIs.
ADEs = adverse drug events; ADRs = adverse drug reactions; DDIs = drug-drug interactions; MEs = medication errors

2.3.2 Definitions

Tab. 2 provides definitions for the most important terms. Fig. 5 shows the correlation of the terms, excluding lack of efficacy and addiction.

2.3.3 Adverse drug events

Any untoward effect related to the use of a drug is classified as adverse drug event (ADE). A causal relationship is not mandatory and the dosage can be appropriate or not (Tab. 2) [50]. Thus, next to ADRs occurring with appropriate dosage and given causality [56], also harm caused by overdosage or lack of efficacy are considered ADE.

ADEs lead to increased morbidity, mortality, duration of hospital stay, and healthcare costs [56-58]. According to a review [56], 6.1% (range 0.17-65%) of all in-patients suffer from ADEs or ADRs. Only 5-15% of ADEs are detected by healthcare professionals [59, 60].

Risk factors for ADEs are polymorbidity, polypharmacy, old age, female sex, but also altered drug elimination due to renal or hepatic impairment [61-63].

An example for an ADE in patients with liver cirrhosis is the administration of diazepam 20mg/day to a patient with severe liver cirrhosis, after which the patient

became confused and fell [64]. Since diazepam is contraindicated in patients with severe liver cirrhosis according to the Physicians' Desk Reference (PDR) [65], the reason for the mentioned ADE is a ME.

2.3.4 Adverse drug reactions

For the definition of ADRs, see Tab. 2.

In the US, severe ADRs are the reason or a contributing factor for 6-7% of hospital admissions [66], leading to a prolonged hospital stay and to costs similar to the drug treatment itself [67]. ADRs are under the top ten death causes in the United States [63].

Risk factors for ADRs are equal to the ones for ADEs [62, 63].

ADRs can be classified as type A or type B. Type A ADRs can be expected considering a drug's pharmacologic profile. Thus, they are dose-dependent and predictable. Frequently, type A ADRs are detected in premarketing trials. Type B ADRs are also called idiosyncratic. They happen unexpectedly and cannot be predicted by the pharmacologic profile of a drug. Since type B ADRs are less frequent than type A ADRs and they possibly occur only in certain susceptible patient populations, they are often only detected after market entry of the drug [63].

Since the recognition of ADRs is not easy [63], many ADRs stay undetected leading to increased healthcare costs due to additional investigations and treatment.

An example for an ADR in patients with liver cirrhosis is the development of hyponatremia after the administration of torasemide 10mg/day to a patient with severe liver cirrhosis [68]. The administered dose is adequate and a possible causal relationship was determined.

2.3.5 Drug-drug interactions

Drug-drug interactions (DDIs) are present if the efficacy or tolerability of a drug is influenced by the presence of one or more other drugs [69]. Three different mechanisms of DDI exist, namely pharmacokinetic, pharmacodynamic, or pharmaceutic DDI [70].

According to a review, less than 5% of all potential DDI result in an ADE. In in-patients, 17% (range 4.8-31%) of all ADE are due to a DDI [56].

It is obvious that an increasing amount of administered drugs results in an increased likelihood for DDIs [70].

An example for a DDI in patients with liver cirrhosis is the development of epistaxis after the administration of ibuprofen and dalteparin. NSAIDs combined with low molecular weight heparins lead to an increased bleeding risk [71]. Additionally, patients with liver cirrhosis may already have coagulopathy (see above).

2.3.6 Medication errors

For a safe drug therapy, five “rights” are essential: The right drug must be given to the right patient at the right dose by the right route at the right time. If there is an error in the medication process, a ME is present. The error can happen at various steps of the medication process, that is during drug prescription, distribution, or administration [49]. According to a review, approximately 6% (range 0.04-56%) of administrations were erroneous in hospitalized patients. Errors at the drug prescription and administration level were most prevalent [56].

Most MEs (>95%) do not result in an ADE [56, 72, 73]. In patients with liver cirrhosis, MEs may be quite frequent, since a significant amount (20%) of drugs is administered incorrectly regarding dosing or prescribing. Of all patients receiving one or more IDD(s), only 22% had an ADE [64].

2.3.7 Preventability of adverse drug events

It was estimated that in the US more than 1.5 Mio preventable ADEs occur every year [74]. As the ADR was reported to be the most frequent type of ADE [69, 75] and most ADRs are type A reactions (80%, range 51-100% [56]), many ADEs could potentially be prevented.

Other aspects for the assessment of preventability are the time-course of the event and the susceptibility of the patient [76]. In dependence of when the ADE occurs after drug administration, different measures can be taken to prevent the ADE. For example, an ADE occurring only after long-term therapy (e.g. tolerance/dependence to benzodiazepines [77]) could be prevented by reducing the duration of therapy. Knowledge about a patient’s susceptibility for a certain ADE can help to increase drug safety. However, we must consider that not every susceptibility factor necessarily results in an ADE. Possibly, only the risk is increased, while the ADE itself rarely develops. For more detailed considerations

regarding preventability of ADEs, the study of Aronson et al. [76] provides a good overview.

A general problem concerning preventability may be that at the moment, ADRs or ADEs are usually diagnosed retrospectively and by exclusion of other causes. Better would be a prospective consideration and recognition of ADRs or ADEs [63].

The following factors can contribute to the prevention of ADEs.

First, education of healthcare professionals regarding prescribing patterns [61], common ADRs and pharmacovigilance is important [62].

Secondly, drug therapy should regularly be reconsidered, especially if polypharmacy is present [62], to prevent DDIs or duplicate prescriptions. For drugs with a small therapeutic window, therapeutic drug monitoring should be considered [69]. In the surveillance of pharmacotherapy, community or clinical pharmacists can play a major role.

Thirdly, characteristics of the individual patient should be taken into account. Risk factors for ADEs should be recognized and preventive measures considered [61]. In this respect, pharmacogenomics identifying genetic risk factors for ADRs may become more and more relevant with the aim to lead to safe and effective therapy for each individual patient [66]. In elderly patients or patients with hepatic or renal impairment, a dosage reduction followed by slow up-titration may be indicated [56, 62].

The patient himself should be informed about the significance of taking his medication as well as about important ADRs [61, 62]. Additionally, caregivers such as nurses should also be informed about preventive measures [61].

Finally, various health information technologies for the improvement of drug safety are being developed. On the one hand, the medical history of patients is recorded electronically, e.g. in integrated electronic medical records including demographic data, medical problems, medications, laboratory and radiologic results [74]. On the other hand, computerized physician order entry (CPOE) improves the legibility and appropriateness of orders [78]. Clinical decision support (CDS) tools, which can be integrated into CPOE, provide information regarding allergies, DDIs, correct prescribing or dosing, e.g. in patients with renal failure. Additional technologies used are bar code medication verification, intravenous infusion safety systems, and electronic medication administration records. For further information see the

publication of Forni et al. [78] or Cheng et al. [74]. It could be shown, that these technologies are effective in preventing MEs and/or ADEs [78].

Regarding patients with liver cirrhosis, to the best of our knowledge, up to now neither CDS-tools for dose adjustment in patients with liver disease nor general studies investigating drug-related problems in patients with liver cirrhosis exist.

2.3.8 Pharmacovigilance

During clinical trials, i.e. before a drug is marketed, often only dose-dependent and frequent ADRs are observed. Furthermore, it is noteworthy that some populations are usually under-represented during clinical trials, such as women, the elderly, children, or patients with various comorbidities. Pharmacovigilance starts at the registration of a drug and is defined as the process of identifying, monitoring, and effectively reducing ADRs [63]. It deals for example with the detection of ADRs that were not observed before market entry. This may be due to a low frequency of these ADRs or because they occur only in special populations, e.g. in children, in patients with renal failure, or in pregnant women [62, 79].

In Switzerland, it is mandatory to document and report serious and/or unexpected ADRs. Such reports of ADRs, so called individual case safety reports (ICSRs), are sent to one of six regional pharmacovigilance centers, which forward the ICSRs to the Swiss Agency for Therapeutic Products, Swissmedic. In case of serious ADRs associated with a specific drug or an abnormal frequency of reported ADRs, Swissmedic can take action, resulting e.g. in altered product information or drug withdrawal from the market [80]. Between 1972 and 1994 in the United Kingdom, approximately 4% of all new approvals were removed from the market due to ADRs [81].

The problem of under-reporting is well-known. A review found that a median of 6% (interquartile range 2-18%) of ADRs are reported to spontaneous reporting systems [82]. Wooten et al. [62] reported the following possible reasons for under-reporting: “takes too much time”, “the form is too difficult to fill out”, “no one’s going to review this anyway”. However, the documentation and reporting of serious and unexpected ADRs is essential to gain more information about a drug’s safety profile. Therefore, all health care professionals should be educated and motivated to document and report ADRs [62, 80].

Chapter III

Results

3.1 Necessity for dose adjustment of anti-infective drugs in patients with liver disease

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3.1.1 Abstract

Introduction: Efficacy of anti-infective therapy is vital, especially in weakened patients. Pharmacokinetic and/or pharmacodynamic changes are prevalent in case of impaired liver function. Up to now, no surrogate parameter allows to estimate the impact of liver disease on the pharmacokinetics of a drug.

Methods: For each anti-infective drug on the Swiss market in 2012, we searched the literature for dose-dependent ADRs, hepatic ADRs, pharmacokinetics, and information about dose adjustment in patients with liver disease. We categorized the drugs according to their Q_0 and hepatic extraction E into five categories.

Results: Of the 104 anti-infectives on the Swiss market in 2012, 32, 13, and 4 drugs underwent low, intermediate, and high hepatic extraction, respectively. Forty-six drugs were mainly renally eliminated and of 9 drugs, the elimination pathway was unknown. CYP P450 enzymes were involved in the metabolism of 27% of all drugs. Biliary elimination affected one fifth of all drugs. The literature search revealed reports on hepatic ADRs for almost all of the drugs (N = 101). Pharmacokinetic alterations in liver disease were reported for 48% of the drugs.

Discussion: With anti-infective therapy in liver disease, an ideal dose should be effective and non-toxic at the same time. Since liver disease does not lead to uniform pharmacokinetic alterations, dosage recommendation is difficult. Categorizing the drugs according to their pharmacokinetic properties and reviewing the literature helps to increase the awareness of the problem and allows for specific recommendations for many drugs.

3.1.2 Introduction

Anti-infective drugs and their early administration play a crucial role in the management of infections. In patients with impaired hepatic function, an effective anti-infective therapy is vital. Hepatic disease may debilitate these patients, predisposing them to increased morbidity due to infections. Moreover, the disease may be caused by a virus.

While dose adjustment in renal failure is possible by means of creatinine clearance, no surrogate parameter allows estimating the severity and the pharmacokinetic impact of liver disease. Various authors have reviewed the

pharmacokinetic and/or pharmacodynamic changes in liver insufficiency [4, 14, 26, 27, 83-86].

An approach to estimate the necessity of dose adjustment in liver disease bases on the pharmacokinetic characterization of drugs [27]. Eq. 4 describes the CL_{hep} of a drug:

$$CL_{hep} = \frac{(f_u * CL_{int}) * Q}{(f_u * CL_{int}) + Q}$$ (Equation 4, see Section 1.2.3 in *Introduction*)

Q is the hepatic blood flow, f_u the free fraction of the drug, and CL_{int} the intrinsic clearance of the drug.

For drugs with high hepatic extraction (E>0.6), where (CL_{int}xf_u)>>Q, we can simplify Eq. 4 to CL_{hep} ≈ Q. CL_{hep} of such drugs depends more on the hepatic blood flow Q than on the free fraction f_u and the CL_{int} of the drug. These drugs have a low bioavailability (<40%). If they are administered orally, a decreased blood flow across the liver, e.g. due to portosystemic shunts in liver cirrhosis, results in profoundly increased bioavailability.

For drugs with low hepatic extraction (E<0.3), where Q>>(CL_{int} x f_u), Eq. 4 can be expressed as CL_{hep} ≈ (f_u x CL_{int}). CL_{hep} depends rather on f_u and CL_{int} than Q. Provided that solubility in the gastrointestinal tract and absorption is good, these drugs have a high bioavailability (>70%) and liver disease causes a problem due to reduced CL_{int} resulting in a prolonged elimination phase.

Drugs with intermediate hepatic extraction (E 0.3 – 0.6) have a bioavailability of 40 - 70%, and their characteristics lie between the other two groups. For further information on this classification see the publication of Delcò et al. [27]

With this work, we aimed at (i) categorizing anti-infective drugs according to their pharmacokinetic data to estimate the necessity of dosage adjustment in patients with liver disease, (ii) reviewing the literature for information about pharmacokinetic alterations and dose adjustment in case of impaired hepatic function, and (iii) providing dosage recommendations for patients with hepatic disease.

3.1.3 Methods

For each anti-infective drug for systemic use (Anatomical Therapeutic Chemical Classification System [ATC] class J) on the Swiss market in the beginning of 2012, we searched for dose-dependent ADRs, hepatic ADRs, pharmacokinetics in general as well as pharmacokinetic alterations in patients with liver disease, and information about dose adjustment in patients with liver disease. For basic data, we consulted the Swiss product information [87], Micromedex® 1.0 [71] and 2.0 System [88], the PDR [65], as well as other standard literature [89-93]. Furthermore, we performed a literature search (MEDLINE, EMBASE) for studies concerning the topics mentioned above using the key terms *pharmacokinetics*, *drug toxicity*, and *liver diseases* combined with the generic name of each drug.

To group the drugs, we modified the classification previously used by Tchambaz et al. [94] and Schlatter et al. [95]. We added one CAT for mainly renally eliminated drugs (CAT4) and used CAT5 for drugs with unknown elimination pathway. We grouped the drugs by means of their Q_0 and E (Fig. 4). We obtained E from the literature or calculated it as follows:

$$E = \frac{Q_0 * CL_{sys}}{Q} \qquad \text{(Equation 7)}$$

E is the hepatic extraction, Q_0 the extrarenal dose fraction, CL_{sys} the systemic clearance (L/h), and Q the hepatic blood flow (54L/h) [94].

We generated a database summarizing pharmacokinetic data, hepatic and dose-dependent ADRs, literature, and product information. Based on this data, we made specific dosage recommendations for patients with liver insufficiency where possible. As a general rule for the different drug CAT, the dosage can be adjusted as shown in Fig. 4. The route of administration of a drug has to be taken into account. In contrast to oral dosing, a reduction of the initial dose of a parenterally administered drug is generally not indicated due to the avoidance of the first liver pass effect with this route of administration. We also considered pathophysiologic alterations in patients with liver disease such as decreased albumin synthesis potentially resulting in a decreased protein binding of highly protein-bound drugs. Additionally, pharmacodynamic alterations were taken into account. All this information taken together allowed us to make specific dose recommendations for many drugs.

To visualize the pharmacokinetic alterations of a drug in patients with liver disease, we generated standard plasma-concentration-time curves for the drug categories with mainly hepatic elimination (CAT1, CAT2, CAT3).

3.1.4 Results

In the beginning of 2012, 104 anti-infective drugs for systemic use (amphotericin and amphotericin liposomal were counted as two drugs) were registered in Switzerland. The major part consisted of antibacterial (N = 50) and antiviral drugs (N = 38), followed by antimycotic (N = 10) and antimycobacterial (N = 5) drugs as well as one immunoglobulin (N = 1). Tab. 3 gives an overview of all the drugs and the corresponding elimination CAT. Fig. 6 shows the distribution of the anti-infectives into the five CAT. A similar amount of drugs underwent mainly hepatic (CAT1, CAT2, CAT3; N = 48; 46.2%) or renal (CAT4; N = 46; 44.2%) elimination. For ten drugs (9.6%), the elimination pathway was unknown.

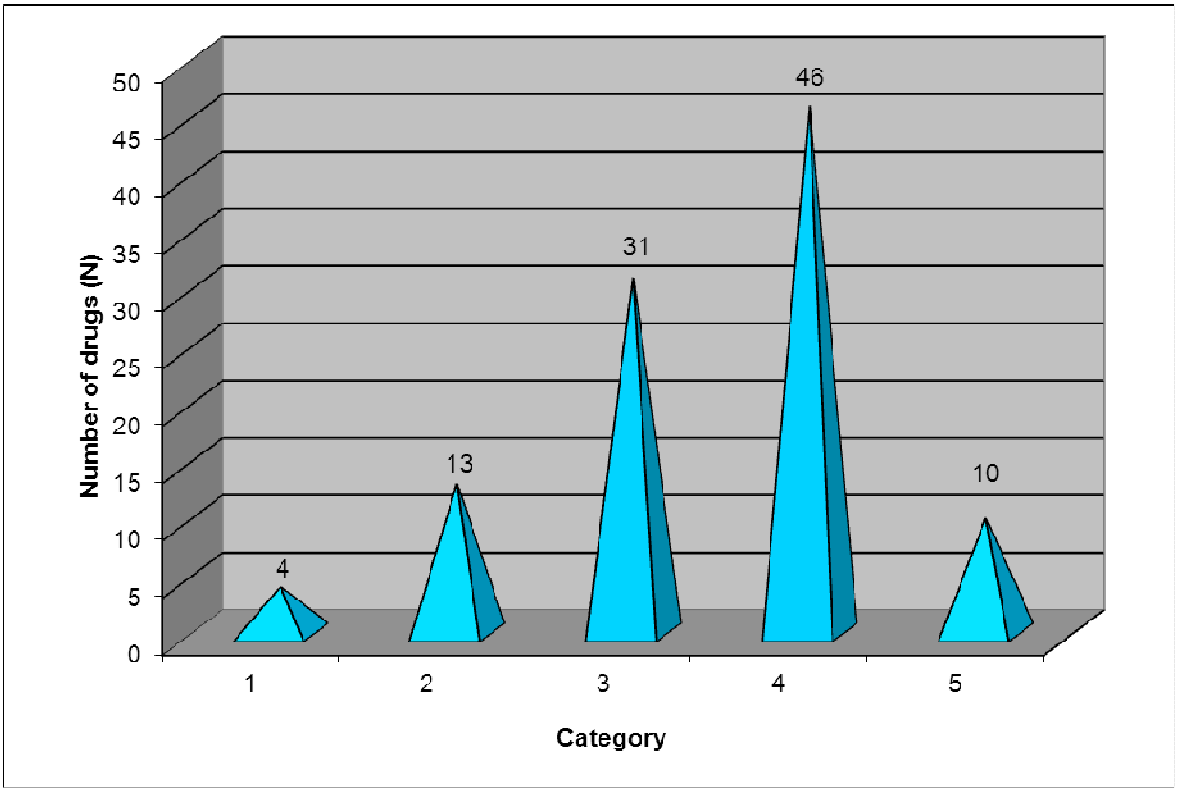

Fig. 6 Number of anti-infective drugs per drug category. Category 1 = high hepatic extraction; category 2 = intermediate hepatic extraction; category 3 = low hepatic extraction; category 4 = mainly renal elimination; category 5 = unknown elimination pathway

The simulated changes in plasma-concentration-time curves in patients with liver cirrhosis for each drug CAT are shown in Fig. 7. As would be expected, most pronounced changes occur in drugs with a high hepatic extraction (CAT1, Fig. 7A). For CAT4 drugs with mainly renal elimination (plasma-concentration-time curve not shown), liver disease does usually not have a significant impact on the pharmacokinetics provided that renal function is normal.

Tab. 3 Anti-infective drugs on the Swiss market at the beginning of 2012 (N = 104) with the corresponding elimination categories.

Elimination category	Drugs
1 (high hepatic extraction), N = 4	Spiramycin, azithromycine, boceprevir, maraviroc
2 (intermediate hepatic extraction), N = 13	Tigecycline, phenoxymethylpenicillin, erythromycin, clarithromycin, itraconazole, posaconazole, isoniazid, ribavirin, indinavir, fosamprenavir, telaprevir, zidovudine, didanosine
3 (low hepatic extraction), N = 31	Doxycycline, minocycline, ceftriaxone, cefixime, ertapenem, sulfamethoxazole, clindamycin, moxifloxacin, fusidic acid, metronidazole, ornidazole, nitrofurantoin, linezolid, daptomycin, amphotericin B, amphotericin B (liposomal), voriconazole, caspofungin, anidulafungin, rifampicin, rifabutin, pyrazinamide, brivudine, ritonavir, lopinavir, tipranavir, darunavir, stavudine, abacavir, nevirapine, efavirenz
4 (mainly renal elimination), N = 46	Limecycline, amoxicillin, benzylpenicillin, flucloxacillin, piperacillin, cefazolin, cefuroxime, cefamandole, cefaclor, cefprozil, ceftazidime, cefpodoxime, ceftibuten, cefepime, aztreonam, meropenem, doripenem, imipenem, trimethoprim, tobramycin, gentamicin, amikacin, ofloxacin, ciprofloxacin, levofloxacin, vancomycin, teicoplanin, colistin, fosfomycin, fluconazole, flucytosine, ethambutol, aciclovir, ganciclovir, famciclovir, valaciclovir, cidofovir, valganciclovir, foscarnet, lamivudine, tenofovir disoproxil, adefovir dipivoxil, emtricitabine, entecavir, zanamivir, oseltamivir
5 (unknown elimination pathway), N = 10	Norfloxacine, ketoconazole, saquinavir, nelfinavir, atazanavir, telbivudine, etravirine, enfuvirtide, raltegravir, palivizumab

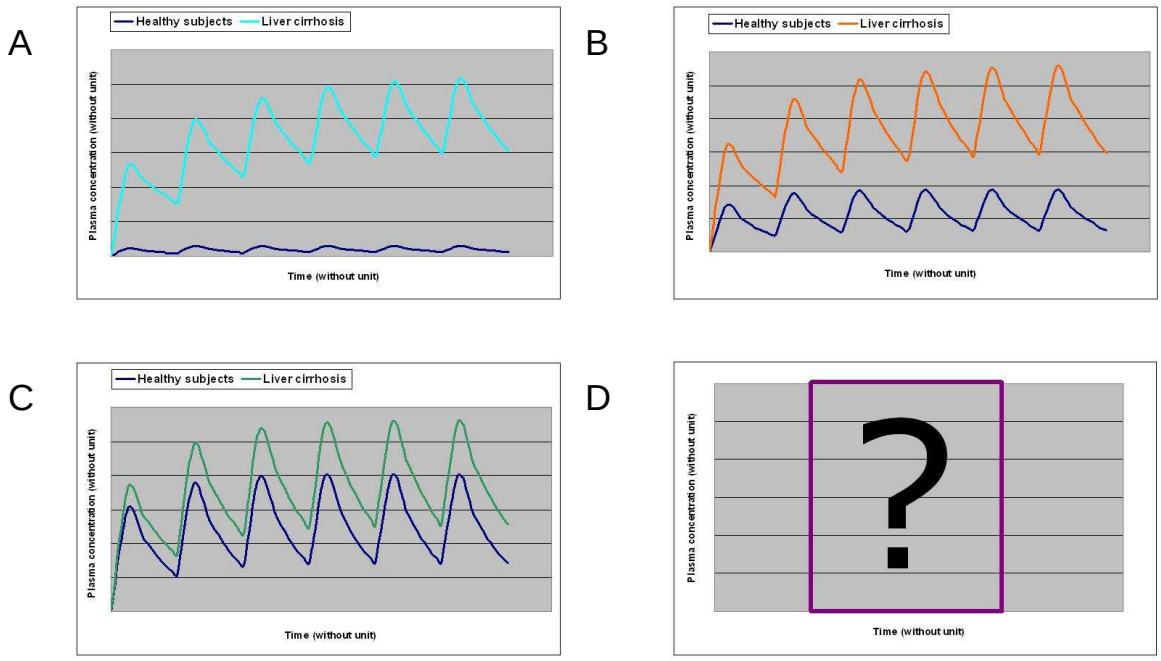

Fig. 7 Expected pharmacokinetic alterations of the plasma-concentration-time curves of the different drug categories in patients with liver cirrhosis. A category 1 (high hepatic extraction); B category 2 (intermediate hepatic extraction); C category 3 (low hepatic extraction); D category 5 (unknown elimination pathway)

Tab. 4 summarizes the database for high hepatic extraction drugs. The database for the rest of anti-infective drugs on the Swiss market is listed in Appendix Tab. 11 (anti-bacterials) or is available from the attached CD (whole database). Regarding the metabolism of all anti-infective drugs, most drugs (55; 52.9%) underwent minimal metabolism. Eighteen (17.3%) were metabolized by CYP P450 enzymes, 8 (7.7%) by other enzymes, 3 (2.9%) by mere conjugation (glucuronidation, sulfation), and 2 (1.9%) by non-enzymatic pathways. Ten (9.6%) drugs underwent CYP P450 metabolism as well as conjugation (glucuronidation). For 8 (7.7%) drugs, we found not enough information about metabolic pathways. Six antiviral drugs, namely tipranavir, darunavir, saquinavir, atazanavir, lopinavir, and fosamprenavir, all protease inhibitors and strongly metabolized by CYP3A4, are usually combined with ritonavir, a strong inhibitor of CYP3A4, to increase their bioavailability.

Biliary elimination of ≥50% affected 22 (21.2%) drugs, while 69 (66.3%) were not excreted by the bile. Of 13 (12.5%) drugs, the amount eliminated by bile could not be defined.

For almost all drugs (N = 101), the literature reported hepatic ADRs. For vancomycin, cidofovir, and zanamivir no hepatic ADRs have been described so far.

Tab. 4 Extract of the database draft summarizing pharmacokinetic data, adverse drug reactions, pharmacokinetic studies, and recommendations in liver disease for anti-infective drugs. Listed are the high hepatic extraction drugs.

Drug (route of application)	*Metabolism*	*Kinetic parameters*	*Hepatic ADRs*	*Potentially dose-dependent ADRs*	*Studies, product information, and dose recommendations*
Spiramycin (oral)	The exact metabolic pathway is unknown. Enterohepatic circulation may occur [87, 90, 96, 97].	Q_0: 0.85 $T_{1/2}$: 5h V_d: 5L/kg PB: 10% F_{oral}: 36% CL_{sys}: 84L/h E: >0.99 BE: major	*Rare:* elevated liver enzymes, hepatitis with and without cholestasis [87].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, paresthesia, cholestatic hepatitis [87, 90]	*Studies:* Hepatic dysfunction appears not to markedly affect the kinetics of spiramycin [90]. It is accepted that no dose reduction is necessary, but patients with liver cirrhosis should be monitored [98-100]. *Product information*: Caution in patients with liver insufficiency due to the risk of cholestatic jaundice [87]. *Recommendation:* According to pharmacokinetic data and literature, initial dose should be chosen in the lower range of normal and maintenance dose adjusted according to clinical effect and dose-dependent adverse drug reactions. Caution in patients with cholestasis.
Azithromycine (oral)	Metabolism mainly by N-demethylation, but also O-demethylation and hydroxylation (metabolites inactive) [87, 90].	Q_0: 0.9 $T_{1/2}$: 50h V_d: 31L/kg PB: 50% F_{oral}: 37% CL_{sys}: 38L/h E: 0.63 BE: major	*Occasionally:* reversible asymptomatic elevations of liver enzymes (>3x ULN). *Rare:* hepatitis, cholestatic jaundice, liver necrosis, liver failure [87, 90].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, ototoxicity, neurotoxicity (headache, dizziness, convulsions, asthenia, paresthesia), palpitations, arrhythmias (QT-prolongation, torsades de pointes), cholestatic hepatitis, neutropenia [65, 87, 90]	*Studies:* Despite its hepatic metabolism, no dose modification seems necessary according to the results from a single dose study with 500mg azithromycin in 16 cirrhotic patients with mild or moderate hepatic impairment (Child-Pugh Class A and B) [101]. No clinical data are available for patients with severe hepatic impairment (Child-Pugh Class C) or in patients with cholestasis. Azithromycin is not recommended in these cases [102]. *Product information:* In cirrhotic patients with Child Pugh A and B no significant differences in pharmacokinetics were observed after a single dose compared to healthy subjects. Renal clearance seems to be increased instead. No data is available for multiple dosing. Caution in patients with liver insufficiency, due to its high hepatic elimination. No dose adjustment seems necessary in patients with mild and moderate liver dysfunction [87]. *Recommendation*: Choose doses in the lower range of normal. Caution in patients with cholestasis.

Tab. 4 (continued)

Drug (route of application)	*Metabolism*	*Kinetic parameters*	*Hepatic ADRs*	*Potentially dose-dependent ADRs*	*Studies, product information, and dose recommendations*
Boceprevir (oral)	Main metabolism by aldo-keto reductase, minor metabolism by CYP3A4/3A5 [65, 71, 87].	Q_0: 0.97 $T_{1/2}$: 3.4h V_d: 11L/kg PB: 75% F_{oral}: n.k. CL_{sys}: 161L/h E: >0.99 BE: major	*Occasionally*: elevated bilirubin. *Rare:* cholecystitis [87].	myelosuppression (anemia, neutropenia, thrombocytopenia, leucopenia), chills, asthenia, decreased appetite, gastrointestinal disturbances, arthralgia, myalgia, neurotoxicity (insomnia, irritability, visual and hearing disturbances, depression, paresthesia), triglyceride elevations, palpitations, chest pain, exanthema [65, 87]	*Studies:* In patients with moderate and severe liver disease compared to patients with normal liver function, the mean AUC of the active diastereomer of boceprevir was 32% and 45% higher, respectively. Mean C_{max} was 28% and 62% higher, respectively. Patients with mild liver disease had unaltered exposure to the active diastereomer of boceprevir [65]. *Product information:* Contraindicated in autoimmune hepatitis. No dosage adjustment necessary in patients with mild, moderate, or severe liver disease. No clinically significant pharmacokinetic alterations observed. The combination with peginterferon and ribavirin is contraindicated in patients with severe liver disease or decompensated liver cirrhosis [87]. No data on safety and efficacy in patients with decompensated liver cirrhosis or HBV co-infection [65]. *Recommendation:* In spite of pharmacokinetic data showing high hepatic extraction, boceprevir can be used as recommended in patients with mild and moderate liver disease due to no evidence for marked pharmacokinetic alterations in liver disease in clinical studies. In patients with severe liver disease, boceprevir in combination with peginterferon alfa and ribavirin is contraindicated. Caution in patients with cholestasis.
Maraviroc (oral)	Oxidation, N-dealkylation by CYP P450 3A4. Major inactive metabolite is a secondary amine [87].	Q_0: 0.78 $T_{1/2}$: 15h V_d: 2.8L/kg PB: 76% F_{oral}: 28% CL_{sys}: 44L/h E: 0.64 BE: n.k.	*Frequent:* elevation of ALT, AST, bilirubin. *Occasionally:* cholestatic jaundice, liver cirrhosis, liver failure, portal vein thrombosis [71, 87].	dizziness, postural hypotension, increased pulse rate, asthenia [65, 87, 103]	*Studies:* Child Pugh A: C_{max} and AUC increased by 11% and 25%, respectively. Child Pugh B: C_{max} and AUC increased by 32% and 46%, respectively. Child Pugh C: No data [87]. *Product information:* Caution in patients with liver disease or HBV or HCV co-infection, risk for hepatotoxicity may be increased. Monitor patients [87]. In Child Pugh A and B generally no dose adjustments are necessary [71]. *Recommendations:* According to product information, start with normal initial dose in patients with Child Pugh A and B cirrhosis (despite high hepatic extraction) and reduce maintenance dose ≥50%. In patients with Child Pugh C cirrhosis, consider reduction of initial dose and reduce maintenance dose ≥50%. Monitor all patients for hepatotoxicity.

Tab. 4 (legend)

ADRs = adverse drug reactions; ALT = alanine aminotransferase; AST = aspartate aminotransferase; AUC = area under the concentration-time curve; BE = biliary elimination; C_{max} = maximal plasma concentration; CL_{sys} = systemic clearance; CYP = cytochrome P450 enzymes; E = hepatic extraction; F_{oral} = systemic bioavailability after oral administration; HBV = hepatitis B virus; HCV = hepatitis C virus; n.k. = not known; PB = protein binding; Q_0 = extrarenal dose fraction; $T_{1/2}$ = elimination half-life; ULN = upper limit of normal; V_d = volume of distribution.

Tab. 5 Information about dosage adjustment in patients with liver disease provided by the Swiss product information [87]

	Number of drugs, N (%)
Total	104 (100)
Specific recommendation[a]	52 (50.0)
No specific recommendation[b]	22 (21.2)
No recommendation	29 (27.9)

[a] Including contraindications or specific dosage recommendations

[b] Including recommendations to reduce dosage (without specification), to use the drug cautiously, or to avoid risk factors

The literature search revealed data on pharmacokinetic alterations in case of liver disease for 50 (48.1%) drugs, whereas no or minimal pharmacokinetic alterations were observed for 27 (26%) drugs. We found no studies for 27 (26%) drugs.

Tab. 5 summarizes the information about dose adjustment provided by the Swiss product information [87]. For 50% of the drugs, specific recommendations are available, while for the other drugs only unspecific (21% of all drugs) or no recommendations (28% of all drugs) are provided. Additional or different recommendations from the Swiss product information [87] were found for 18 (17.3%) drugs in PDR [65], Micromedex® [71, 88], or in studies from the literature.

For many drugs (N = 65; 59.6%), the dosage recommendations / pharmacokinetic observations in the literature coincided with our recommendations made on the basis of pharmacokinetic data. For all CAT1 drugs (spiramycin, azithromycine, boceprevir, maraviroc), for five CAT2 drugs (tigecycline, clarithromycin, ribavirin, telaprevir, didanosine), and for ten CAT3 drugs (cefixime, ertapenem, sulfamethoxazole, clindamycin, linezolid, daptomycin, rifabutin, ritonavir, atazanavir, stavudine) the literature and/or product information proposed a higher dosage than we would recommend according to pharmacokinetic data. For

zidovudine (CAT2), the literature and/or product information proposed a lower initial dose than we would recommend according to pharmacokinetic data. For aztreonam (CAT4), clinical studies suggest pharmacokinetic alterations in patients with alcoholic liver cirrhosis in spite of mainly renal elimination ($Q_0 = 0.2$) and thus, dosage adjustment is considered necessary in such patients. For the remaining 18 (17.3%) drugs, we found not enough literature and/or pharmacokinetic data to allow for a comparison.

There are seven drugs for the treatment of HBV / HCV infection. Three (lamivudine, tenofovir, entecavir) undergo mainly renal elimination, two (telaprevir, ribavirin) undergo intermediate hepatic excretion, and one (boceprevir) high hepatic extraction. The elimination pathway of the remaining drug (telbivudine) is unknown. Biliary elimination is negligible for four drugs (lamivudine, tenofovir, entecavir, ribavirin), major for one drug (boceprevir), and unknown for two drugs (telbivudine, telaprevir). We found pharmacokinetic studies / observations in patients with liver disease as well as reports on hepatic ADRs for all of these drugs. Furthermore, the product information makes specific dosage recommendations for every drug used in the treatment of HBV or HCV.

3.1.5 Discussion

Literature reviews addressing dose adjustment of anti-infective drugs in patients with liver disease are rare. We have only found three studies [32, 104, 105]. In 1988, Davey [104] summarized the significant studies and recommendations in patients with liver disease. He categorized the drugs by means of impaired hepatic elimination, potential toxicity, and changed pharmacodynamics in liver disease. Furthermore, he emphasized to consider the free fraction of a drug in patients with liver disease due to potentially reduced synthesis of albumin or α_1-acid glycoprotein. The second study [105] concerns dosage adjustment of antimicrobial drugs in pediatric cancer patients with impaired hepatic or renal function. It lists many anti-infective drugs outlining their pharmacokinetic properties, hepatotoxicity, nephrotoxicity, and necessity of dosage adjustment in renal or hepatic failure. The work points out that for most substances eliminated primarily by the liver, no exact dosage recommendations are available. The authors recommend avoiding these drugs. If no alternative agent can be found, liver function and, if possible, drug levels in blood should be monitored [105]. Tschida et al. [32] used a classification

similar to the one we use and summarized all available studies investigating pharmacokinetic alterations of anti-infective drugs in patients with liver disease.

More than half of the anti-infective drugs reviewed in our study undergo mainly hepatic metabolism, indicating the importance of considering dose reduction in patients with impaired hepatic function. Furthermore, one fifth of the drugs are mainly (≥ 50%) eliminated by the bile. Their administration requires caution in patients with biliary obstruction to avoid accumulation.

Respective the drugs with mainly renal elimination, we should keep in mind that patients with liver cirrhosis may also have an impaired renal function [4, 27]. CAT4 drugs with a narrow therapeutic index should be used with caution in patients with liver cirrhosis.

Specific recommendations for patients with liver disease are difficult to make due to the diversity and individuality of pharmacokinetic changes in such patients. As a result, the Swiss product information [87] makes specific recommendations for only half of the anti-infective drugs. For the rest, unspecific or no recommendations are provided.

In anti-infective therapy, efficacy is particularly important to avoid aggravation of the infection and to avoid developing resistance. This fact poses a problem to the dosage adjustment in patients with liver disease. The ideal dose should be efficacious and non-toxic at the same time. Such a dose is difficult to define due to the interindividual variability of liver alterations in hepatically impaired patients. In life-threatening infections, initial efficacy may outbalance non-toxicity. Consequently, we felt that for maraviroc and for boceprevir, despite high hepatic extraction, normal initial dose can be administered at least in patients with mild and moderate liver disease.

Fosamprenavir, saquinavir, lopinavir, atazanavir, tipranavir, and darunavir are usually combined with ritonavir, which inhibits liver metabolism by CYP 3A4. Thus, reduced metabolism in liver disease is not relevant. Therefore, usually normal initial dose, at least in mild liver disease, may be used and maintenance dose should be adjusted by means of clinical effect and dose-dependent ADRs. For the combination of ritonavir with saquinavir as well as with atazanavir, we found not enough pharmacokinetic data to make dose recommendations.

3.1.6 Conclusion and Outlook

Since efficacy of anti-infective therapy can save lives, pharmacokinetic implications to reduce dosage can be ignored for some drugs, and normal initial doses can be used to control the infection, especially for short-term treatments. However, for most anti-infective drugs, dose reduction according to pharmacokinetic data is indicated to avoid dose-dependent toxicity. The ideal dose should be chosen between good efficacy and low toxicity, but this is very difficult to define in patients with liver disease due to the variable pharmacokinetic / pharmacodynamic alterations.

By categorizing the drugs according to their pharmacokinetic properties and reviewing the literature, we increase the awareness of the problem and give specific recommendations where possible.

We plan to integrate our data on anti-infective drugs into a software system for electronic drug prescription, allowing the physician to access the information if required.

3.2 Potential drug-drug interactions and adverse drug reactions in patients with liver cirrhosis

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3.2.1 Abstract

Background and aims: Patients with liver cirrhosis may be at risk for pDDIs and/or ADRs due to the severity of their disease and comorbidities associated with polypharmacy.

Methods: We performed a cross-sectional retrospective study including 400 cirrhotic patients and assessed diagnoses, medication patterns, pDDIs and ADRs at hospital admission.

Results: The median (range) age of the patients was 60 (21-88) years; 68.5% were male. They had a total of 2415 diagnoses, resulting in 6 (1-10) diagnoses per patient. Frequent were diagnoses of the digestive system (28.4%), circulatory system (14.2%), blood and blood forming organs (8.7%), and psychiatric disorders (7.5%); 60.7% of the diagnoses were not liver-associated. The median number of drugs per patient was 5 (0-18), whereof 3 (0-16) were predominantly hepatically eliminated. Drugs were primarily indicated for gastrointestinal, cardiovascular, or nervous system disorders, reflecting the prevalent diagnoses. In 112 (28%) patients, 200 ADRs were detected, mainly associated with spironolactone, torasemide, furosemide and ibuprofen. In 86 (21.5%) patients, 132 pDDIs were detected. Seventeen of these pDDIs were the direct cause of 15 ADRs, whereof 3 resulted in hospital admission. Patients with ADRs were older, had more comorbidities, were treated with more drugs, and had a worse renal function and more pDDIs than patients without ADRs.

Conclusions: Pharmacotherapy is complex in cirrhotic patients. Hepatologists should know the principles of dose adjustment in cirrhosis and renal failure, but also the most important pDDIs of the drugs used to treat liver disease and comorbidities in this population.

3.2.2 Introduction

Liver cirrhosis remains a frequent cause of morbidity and mortality in most countries, including countries in Europe. Between 1997 and 2001, the yearly mortality rate due to liver cirrhosis was between 9.7 (Netherlands) and 43.5 (Austria) per 100,000 males and between 5.6 (Sweden) and 16.7 (Austria) per 100,000 females [11].

Since the liver plays a crucial role in the metabolism of endogenous and exogenous substances, impaired hepatic function may influence the pharmacokinetics of drugs used in cirrhotic patients. The absorption process may be altered [27, 106] and bioavailability may be increased due to portosystemic shunting [27, 107]. The free fraction and possibly also the free concentration of highly protein-bound drugs is increased in patients with hypoalbuminemia [27]. Finally, CL_{hep} is usually decreased due to lower hepatic blood flow [27, 108] and decreased activity of phase I enzymes [27, 29, 30]. Pharmacodynamic changes are also prevalent in patients with liver cirrhosis. Increased sensitivity has been shown for central effects of morphine [109] and benzodiazepines [110] and for renal adverse effects of NSAIDs [43].

All of these factors can potentially influence the effectiveness of a drug and/or the likelihood that a drug is causing adverse reactions. ADRs may further increase morbidity and mortality in patients with liver disease.

The current study had several aims concerning drug treatment of patients with liver cirrhosis. First, we wanted to find out which drugs are commonly prescribed in this group of patients. Secondly, we investigated the quantity and severity of pDDIs in these patients. Thirdly, we identified the ADRs. For this purpose, we characterized the medication pattern of 400 patients with liver cirrhosis and assessed the prevalence of pDDIs and ADRs at hospital admission.

3.2.3 Methods

3.2.3.1 Patients

In the present cross-sectional, retrospective study, we included 400 patients with liver cirrhosis diagnosed by liver histology and/or typical clinical, sonographic, and computer tomographic signs. They were hospitalized at the University Hospital, Basel, Switzerland, between January 2002 and December 2007. The protocol of the study was accepted by the cantonal Ethics Committee.

3.2.3.2 Data collection

For each patient, demographic and clinical data, diagnoses, drugs administered, characteristics of the drugs administered (dosage and Q_0), and pDDIs and ADRs [56] were collected at hospital admission. Creatinine clearance was calculated by the Cockcroft Gault equation [111]. Severity of liver cirrhosis was classified by the Child Pugh Score [112]. Drugs were grouped according to the ATC code. Drugs

with a $Q_0 \geq 0.5$ were defined as primarily hepatically eliminated. Potential DDIs were determined by screening the drug profiles using the online version of DRUG-REAX (Micromedex® 1.0 Healthcare Series, http://www.micromedex.com). Only pDDIs with moderate or major severity were considered. All ADRs were classified with a definite, probable, or possible causality-rating as described previously [113].

3.2.3.3 Statistical analysis

The data were descriptively analyzed using Excel and/or SPSS (version 15.0). Comparisons between patients with ADRs and those without ADRs were performed using Student's t-test or the chi-squared test without correction for repetitive testing. A significance level of 5% was chosen.

3.2.4 Results

3.2.4.1 Patient characteristics

All patients studied were adults with males being more prevalent than females (Appendix Tab. 12). Most patients were in the Child Pugh classes B and C. The most frequent cause of liver cirrhosis was alcohol (69.8%), followed by viral hepatitis (13.5%) or a combination of both (9.7%). Almost 20% of the patients died during hospitalization, reflecting the severity of this disease.

The patients had a total number of 2415 diagnoses at hospital admission, resulting in a median number of 6 (1-10) diagnoses per patient (Appendix Tab. 13). Most common were diseases of the digestive (28.4% of all diagnoses) or circulatory system (14.2%) as well as diseases of the blood and blood-forming organs (8.7%) and psychiatric disorders (7.5%). Approximately 40% of all diagnoses were associated with liver cirrhosis, e.g., spontaneous bacterial peritonitis, esophageal varices, and variceal bleeding.

3.2.4.2 Medication at hospital admission

The patients had a total of 1999 drugs at hospital admission (Tab. 6). The median number of drugs per patient was 5 (0-18); a median of 3 (0-16) were predominantly hepatically eliminated. Most prevalent were drugs affecting the alimentary tract and metabolism, mainly vitamins and proton pump inhibitors, as well as drugs for the cardiovascular system, primarily potassium-sparing diuretics, loop diuretics, and betablockers. Approximately 10% of all patients were treated with an angiotensin-converting enzyme (ACE) inhibitor. The most frequent drugs

for the nervous system were benzodiazepines and benzodiazepine-related drugs as well as opioids. Eleven percent of the patients were treated with phytomenadione, 7.5% with platelet-aggregation inhibitors, and 5% with oral anticoagulants. Astonishingly, 11% of the patients were treated with a cyclooxygenase (COX) inhibitor (NSAIDs, analgesic aspirin, or COX-2 inhibitor).
About 68% of all administered drugs were eliminated primarily hepatically (Q_0 ≥0.5).

3.2.4.3 pDDIs and ADRs at hospital admission

In 21.5% of all patients, a median of 1 (1-5) pDDI was detected (Tab. 7). Most prevalent possible adverse reactions due to pDDI were hyperkalemia (potassium-sparing diuretics, ACE inhibitors, and potassium chloride), hypoglycemia (betablockers combined with insulin, sulfonylureas, and/or repaglinide), increased bleeding risk (anticoagulants such as dalteparin or phenprocoumon combined with NSAIDs), respiratory depression (benzodiazepines combined with opiates or phenobarbital), and cardiac problems (cardiac depression, QT prolongation). Of all pDDIs, 12.9% resulted in an ADR.
ADRs were detected in 28% of the patients at entry (Tab. 8). Relative to the number of patients in each Child Pugh class, patients in class Child Pugh A were more frequently affected by ADRs (35.7% of patients) than those in class Child Pugh B (26.1%) or Child Pugh C (26.6%). Nonetheless, most ADRs (43.0%) occurred in patients with liver cirrhosis Child Pugh C. The drugs most frequently associated with an ADR were spironolactone, torasemide, furosemide, and ibuprofen. Most frequently, ADRs resulted in metabolic disorders (mainly hyperkalemia or hyponatremia associated with diuretics and/or ACE inhibitors), in gastrointestinal bleeding (associated with the use of NSAIDs or oral anticoagulants), and in urinary system disorders (mainly worsening renal function due to the use of diuretics and/or ACE inhibitors). Five percent of all ADRs affected the liver and/or the biliary system.
Sixteen ADRs (8%) were the cause of hospital admission. These ADRs consisted of gastrointestinal bleeding associated with low dose aspirin, ibuprofen, or phenprocoumon; hyperkalemia associated with spironolactone or perindopril; and worsening renal function or ascites accumulation associated with ibuprofen.

Tab. 6 Drugs at hospital admission for patients with liver cirrhosis (n = 400 patients)

	Number of drugs (% of patients receiving corresponding drug)	Number of drugs with Q_0 ≥0.5[a] (% of patients with corresponding drug)
Number of drugs at hospital admission	1999	1360
Drugs per patient at hospital admission[b]	5 (0-18)	3 (0-16)
Alimentary tract and metabolism[c]	650	255
Vitamins[c]	207	6
Thiamine	89 (22.3%)	0
Proton pump inhibitors	154 (38.5%)	154 (38.5%)
Osmotically acting laxatives	83 (20.8%)	0
Blood glucose lowering drugs (excl. insulins)[c]	65	38
Magnesium	33 (8.3%)	0
Insulins and analogues	27 (6.8%)	27 (6.8%)
Calcium	27 (6.8%)	0
Propulsives	12 (3.0%)	12 (3.0%)
Potassium	11 (2.8%)	0
Cardiovascular system[c]	633	532
Potassium sparing diuretics[d]	160 (40.0%)	160 (40.0%)
Loop diuretics (high ceiling)	157 (39.3%)	127 (31.8%)
Betablockers	146 (36.5%)	134 (33.5%)
Propranolol	78 (19.5%)	78 (19.5%)
ACE inhibitors	34 (8.5%)	8 (2.0%)
Calcium antagonists	25 (6.3%)	25 (6.3%)
Statins	23 (5.8%)	23 (5.8%)
Angiotensin receptor blockers	19 (4.8%)	19 (4.8%)
Thiazides	19 (4.8%)	0
Organic nitrates	12 (3.0%)	12 (3.0%)
Amiodarone	7 (1.8%)	7 (1.8%)
Nervous system[c]	270	257
Benzodiazepines and related drugs	102 (25.5%)	102 (25.5%)
Lorazepam	28 (7.0%)	28 (7.0%)
Zolpidem	27 (6.8%)	27 (6.8%)
Oxazepam	14 (3.5%)	14 (3.5%)
Diazepam	13 (3.3%)	13 (3.3%)
Opioids	58 (14.5%)	58 (14.5%)
Methadone	29 (7.3%)	29 (7.3%)
Antidepressants, excl. SSRI[e]	30 (7.5%)	30 (7.5%)
SSRI	21 (5.3%)	21 (5.3%)
Neuroleptics	17 (4.3%)	15 (3.8%)
Antiepileptics	16 (4.0%)	10 (2.5%)
Dopaminergic agents	8 (2.0%)	8 (2.0%)

Tab. 6 Drugs at hospital admission for patients with liver cirrhosis (n = 400 patients, continued)

	Number of drugs (% of patients receiving corresponding drug)	Number of drugs with Q0 ≥0.5a (% of patients with corresponding drug)
Blood and blood-forming organs[c]	154	96
Phytomenadione	44 (11.0%)	44 (11.0%)
Platelet aggregation inhibitors (incl. aspirin low dose)	30 (7.5%)	30 (7.5%)
Iron	26 (6.5%)	0
Oral anticoagulants	21 (5.3%)	21 (5.3%)
Heparins	15 (3.8%)	2 (0.5%)
Folic acid	13 (3.3%)	0
Musculo-skeletal system[c]	93	89
NSAIDs	28 (7.0%)	28 (7.0%)
Paracetamol	23 (5.8%)	23 (5.8%)
Allopurinol[f]	14 (3.5%)	14 (3.5%)
Aspirin, analgesic	8 (2.0%)	8 (2.0%)
COX-2 inhibitors	7 (1.8%)	7 (1.8%)
Respiratory system[c]	75	43
Anti-infectives for systemic use[c]	63	30
Antivirals[c]	38	20
Antibacterials	25 (6.3%)	10 (2.5%)
Fluoroquinolones	9 (2.3%)	4 (1.0%)
Systemic hormonal preparations, excl. sex hormones and insulins[c]	31	31
Corticosteroids	16 (4.0%)	16 (4.0%)
Thyroid hormones	13 (3.3%)	13 (3.3%)
Antineoplastic and immunomodulating agents[c]	15	10
Genito-urinary system and sex hormones[c]	10	9
Various[c]	5	5

[a] Only drugs with known Q_0 included

[b] Data are presented as median (range)

[c] One individual patient may have >1 drug of the corresponding group, % not calculated

[d] Spironolactone accounts for 97.5% of this group. It is mainly converted to active metabolites (the two major ones being canrenone and 7-alpha-thiomethylspironolactone), which are primarily renally eliminated

[e] Including tri-, tetracyclic antidepressants, and venlafaxine

[f] Allopurinol is rapidly converted by the liver to the slightly less active oxypurinol, which is renally eliminated. Dosage adjustment is necessary in both patients with liver and renal insufficiency

Tab. 7 Major and moderate pDDIs in patients with liver cirrhosis (n = 400 patients)

DDI/potential outcome	Number of pDDI	Interacting drugs (number of cases)
Total pDDIs	132 (100%)	
Major pDDIs	56 (42.1%)	
Moderate pDDIs	76 (57.9%)	
Number of different pDDIs	91	
Number of patients with ≥1 pDDI	86 (21.5% of all patients)	
pDDI per patient[a, b]	1 (1-5)	
DDIs resulting in an ADR	17 (12.9% of all pDDIs)	
Hyperkalemia + risk for nephrotoxicity	24 (18.2%) 9 (6.8%)	*Major*: Potassium-sparing diuretics + ACE inhibitors (9), potassium chloride + spironolactone (4), potassium chloride + lisinopril (1) *Moderate:* Spironolactone + valsartan (1) *Moderate*: Potassium-sparing diuretics + NSAID (9)
Hypoglycemia	23 (17.4%)	*Moderate:* Betablocker + insulin (14), betablocker + sulfonylureas (8), betablocker + repaglinide (1)
Increased bleeding risk	17 (12.9%)	*Major:* Dalteparin + acetylsalicylic acid (low dose) (1), dalteparin + clopidogrel (1), dalteparin + phenprocoumon (1), dalteparin + ibuprofen (1); acetylsalicylic acid (low dose) + phenprocoumon (2), acetylsalicylic acid (low dose) + venlafaxine (1) *Moderate:* Phenprocoumon + allopurinol (3), phenprocoumon + amiodarone (3), phenprocoumon + diclofenac (1); acetylsalicylic acid (low dose) + verapamil (2), acetylsalicylic acid (low dose) + ibuprofen (1)
Respiratory depression	10 (7.6%)	*Major:* Benzodiazepines + opiates (7), benzodiazepines + phenobarbital (2); fentanyl + hydrocodone (1)
Cardiac depression	9 (6.8%)	*Major:* Betablocker + calcium antagonist (4), betablocker + amiodarone (2) *Moderate:* Digoxin + betablocker (3)
QT prolongation	7 (5.3%)	*Major*: Amitriptyline + sulfamethoxazole, trimethoprim (2); ciprofloxacin + propafenone (1); fluoxetine + haloperidol (1), fluoxetine + methadone (1); risperidone + tramadol (1); trimipramine + venlafaxine (1)

Tab. 7 Major and moderate pDDIs in patients with liver cirrhosis (n = 400 patients, continued)

DDI/potential outcome	Number of pDDI	Interacting drugs (number of cases)
Digoxin toxicity	6 (4.5%)	*Major:* Digoxin + hydrochlorothiazide (2), digoxin + spironolactone (2), digoxin + amiodarone (1) *Moderate:* Digoxin + furosemide (1)
Altered methadone exposure	6 (4.5%)	*Moderate:* Methadone + HIV protease inhibitor (4), methadone + efavirenz (2)
Serotonin syndrome	4 (3.0%)	*Major*: Mirtazapine + fluoxetine (1), mirtazapine + tramadol (1), mirtazapine + venlafaxine (1); tramadol + venlafaxine (1)
Reduced efficacy of levodopa	4 (3.0%)	*Moderate:* Levodopa + iron (2), levodopa + levomepromazine (1), levodopa + olanzapine (1)
Other	22 (16.7)	

[a] Referring to the patients with one or more pDDI (n = 86)

[b] Data are presented as median (range)

Fifteen ADRs (7.5%) resulted from a DDI; among them five patients with bleeding disorders (gastrointestinal bleeding, epistaxis, anemia), four patients with hyperkalemia, three patients with cardiovascular disorders (hypotension, bradycardia, torsade de pointes) as well as one patient each with a psychiatric disorder, somnolence, and collapse. Three DDI-associated ADRs were the reason for hospital admission, namely gastrointestinal bleeding due to the combination of aspirin (100 mg/day) and phenprocoumon, symptomatic bradycardia due to the combination of amiodarone and propranolol, and hyperkalemia due to the combination of spironolactone and perindopril.

The 36 NSAIDs prescribed (NSAIDs and analgesic aspirin) were associated with 24 ADRs in 18 patients (50% of all patients with a NSAID) (Fig. 8). The most prevalent ADRs due to NSAIDs were gastrointestinal bleeding (14/24), bleeding-associated anemia (3/24), exacerbation of ascites (2/24), and thrombocytopenia (2/24). The 53 ACE inhibitor or sartan prescriptions resulted in 20 ADRs in 10 patients (19% of patients treated with an ACE inhibitor or sartan, Fig. 8). Symptoms observed were worsening renal function (6/20), syncope (4/20), hyperkalemia (3/20), hyponatremia (3/20), and hypotension (2/20). In contrast, of 146 betablocker prescriptions, only 12 ADRs (hypotension, syncope, confusion) were identified in 9 patients (6% of all patients with a betablocker, Fig. 8).

Tab. 8 Prevalence of ADRs with a definite, probable, or possible causality rating in 400 patients with liver cirrhosis

ADR	Number of ADRs (total; according to Child Pugh A, B, C)	Drugs associated with ADR[a] (cases according to Child Pugh A, B, C)[b]
Total ADR Child Pugh A Child Pugh B Child Pugh C	200 (100.0%) 46 (23.0%) 68 (34.0%) 86 (43.0%)	Spironolactone (9, 11, 30), torasemide (5, 7, 20), furosemide (4, 1, 10), ibuprofen (1, 4, 6)
Number of ADR per patient[c,d] Child Pugh A Child Pugh B Child Pugh C	1 (1-5) 1 (1-5) 1 (1-5) 1.5 (1-5)	
Patients with ≥1 ADR Child Pugh A Child Pugh B Child Pugh C	112 (28% of all patients) 25 (35.7% of Child Pugh A patients) 41 (26.1% of Child Pugh B patients) 46 (26.6% of Child Pugh C patients)	
ADR with definite/probable causality rating	24 (12.0%) (8, 11, 5)	Spironolactone (3, 1, 1), phenprocoumon (0, 4, 0), ibuprofen (0, 1, 3), acetylsalicylic acid low dose (1, 3, 0)
ADRs with possible causality rating	176 (88.0%) (38, 57, 81)	Spironolactone (6, 10, 29), torasemide (3, 7, 19), furosemide (3, 1, 10), propranolol (2, 2, 3)
ADRs as a reason for hospital admission	16 (8.0%) (6, 5, 5)	Spironolactone (3, 0, 1), acetylsalicylic acid low dose (1, 2, 0), ibuprofen (0, 0, 3), torasemide (2, 0, 1), perindopril (2, 0, 0), phenprocoumon (0, 2, 0)
ADRs due to ≥1 DDI	15 (7.5%) (6, 7, 2)	*Major:* Spironolactone + ACE inhibitors (1, 0, 1), opiates + benzodiazepines (1, 1, 0), acetylsalicylic acid low dose + dalteparin (0, 1, 0), acetylsalicylic acid low dose + phenprocoumon (0, 1, 0), dalteparin + ibuprofen (1, 0, 0), diltiazem + betablockers (2, 0, 0), amiodarone + propranolol (0, 1, 0)
ADR due to DDI causing hospital admission	3 (2.0%) (1, 2, 0)	Acetylsalicylic acid low dose + phenprocoumon (0, 1, 0), perindopril + spironolactone (1, 0, 0); amiodarone + propranolol (0, 1, 0)

Tab. 8 Prevalence of ADRs with a definite, probable, or possible causality rating in 400 patients with liver cirrhosis (continued)

ADR	Number of ADRs (total; according to Child Pugh A, B, C)	Drugs associated with ADR[a] (cases according to Child Pugh A, B, C)[b]
ADR according to system organ class		
Metabolic and nutritional disorders	54 (27.0%) (13, 13, 28)	Spironolactone (4, 6, 17), torasemide (1, 2, 6), furosemide (3, 0, 3), hydrochlorothiazide (1, 2, 0), chlortalidone (3, 0, 0), amiloride (0, 3, 0), ramipril (0, 0, 2), enalapril (0, 2, 0)
Gastro-intestinal system disorders	30 (15.0%) (6, 13, 11)	Acetylsalicylic acid low dose (1, 4, 0) and analgetic (1, 1, 1), ibuprofen (0, 2, 3), mefenamic acid (1, 2, 1), iron (0, 2, 1), spironolactone (0, 0, 3), phenprocoumon (0, 2, 0)
Urinary system disorders	25 (12.5%) (3, 9, 13)	Torasemide (2, 3, 8), spironolactone (2, 2, 6), furosemide (0, 1, 4), enalapril (0, 1, 1), lisinopril (1, 0, 1)
Cardiovascular disorders, general	16 (8.0%) (6, 3, 7)	Furosemide (1, 0, 2), amlodipine (2, 0, 1), diltiazem (2, 0, 0), ramipril (0, 1, 1), spironolactone (1, 0, 1), torasemide (0, 0, 2)
Central and peripheral nervous system disorders	15 (7.5%) (1, 6, 8)	Zolpidem (1, 0, 2), oxazepam (0, 1, 1), propranolol (0, 0, 2), ropinirole (0, 2, 0), spironolactone (0, 1, 1), torasemide (0, 1, 1)
Liver and biliary system disorders	10 (5.0%) (1, 3, 6)	Spironolactone (1, 1, 1), enalapril (0, 1, 1)
Psychiatric disorders	10 (5.0%) (4, 4, 2)	Midazolam (1, 0, 1), oxazepam (0, 2, 0), propranolol (1, 1, 0), zolpidem (1, 0, 1)
Platelet, bleeding and clotting disorders	10 (5.0%) (3, 5, 2)	Spironolactone (1, 0, 1), torasemide (1, 0, 1)
Red blood cell disorders	8 (4.0%) (2, 2, 4)	Ibuprofen (0, 1, 2), torasemide (1, 0, 2)
Heart rate and rhythm disorders	4 (2.0%) (1, 2, 1)	[e]
Other	18 (9.0%) (6, 8, 4)	[e]

Tab. 8 Legend

[a] Most frequent drugs associated with ADR mentioned

[b] Sum of cases may exceed the number of ADRs (more than one drug can cause the same ADR)

[c] Referring to the patients with one or more ADRs (n = 112)

[d] Data are presented as median (range)

[e] No drug responsible for more than one case

Tab. 9 Cirrhotic patients with one or more ADRs in comparison with cirrhotic patients without an ADR

Characteristics	Patients with ADR (n = 112)	Patients without ADR (n = 288)	p-value
Age (years)[a]	61 (35-88)	58 (21-87)	0.017
Male	77 (68.8%)	197 (68.4%)	0.947
Creatinine clearance (mL/min)[a, b]	64 (9-290)	92 (9–280)	0.001
BMI (kg/m^2)[a, c]	24.3 (16.0-42.0)	24.9 (13.5-47.2)	0.997
Child Pugh classification			0.282
Child Pugh A	25 (22.3%)	45 (15.6%)	
Child Pugh B	40 (35.7%)	117 (40.6%)	
Child Pugh C	47 (42.0%)	126 (43.8%)	
Diagnoses per patient[a]	6 (3-10)	6 (1-10)	0.036
Drugs per patient	6 (0-15)	4 (0-18)	<0.001
Drugs with Q_0 ≥0.5 per patient	4 (0-12)	3 (0-16)	<0.001
Patients with ≥1 hepatically eliminated drug	111 (99.1%)	235 (81.6%)	<0.001
Number of pDDIs per patient	0 (0-5)	0 (0-5)	0.012
Patients with ≥1 pDDI	35 (31.3%)	51 (17.8%)	0.004
Length of hospital stay (days)[a]	12 (1-77)	14 (2-116)	0.984
Patients died during hospitalization	23 (20.5%)	44 (15.3%)	0.233
Cause of cirrhosis			0.056
Alcohol	87 (77.7%)	192 (66.7%)	
Viral Hepatitis	9 (8.0%)	45 (15.6%)	
Both	7 (6.3%)	32 (11.1%)	

[a] Data are presented as median (range)

[b] Due to incomplete data (body weight, serum creatinine), n = 107 and 279 for patients with and without ADR, respectively

[c] Due to incomplete data (body weight, height), n = 63 and 186 for patients with and without ADR, respectively

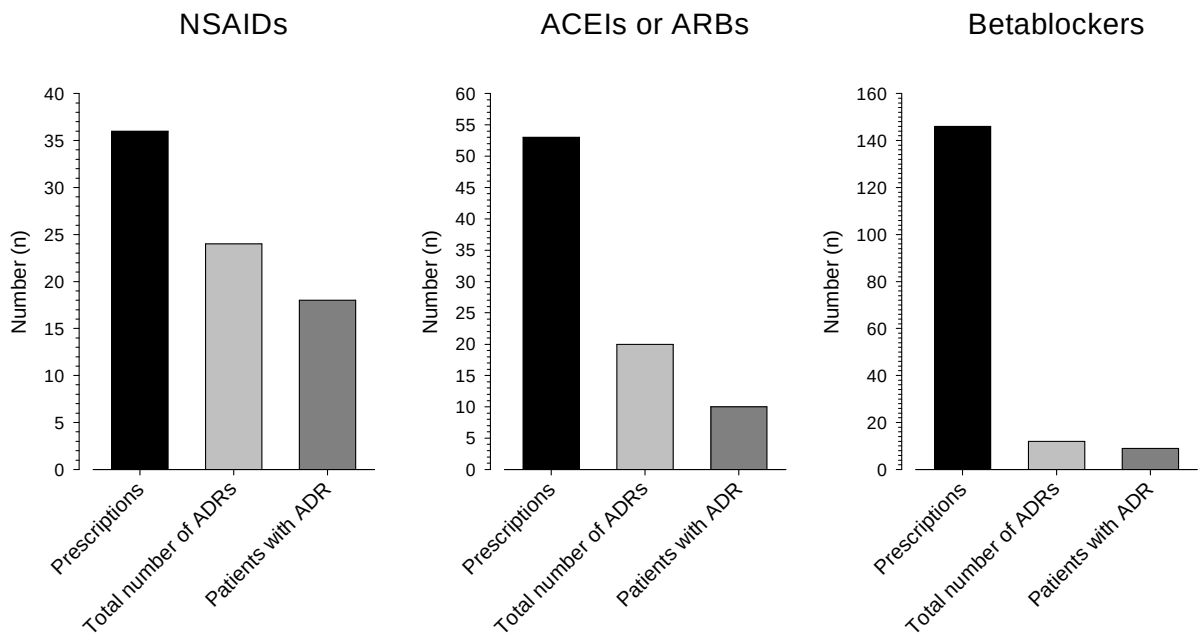

Fig. 8 Number of prescriptions, adverse drug reactions (ADRs), and patients with ADRs for specific drug classes. *NSAIDs* Nonsteroidal anti-inflammatory drugs, *ACEIs* angiotensin-converting enzyme inhibitors, *ARBs* angiotensin receptor blockers

3.2.4.4 Cirrhotic patients with one or more ADR compared with cirrhotic patients without an ADR

When comparing patients with ADRs to those without ADRs (Tab. 9), patients with ADRs were significantly older than those without ADRs (61 vs. 58 years, $p<0.05$), had a lower creatinine clearance (64.3 vs. 91.6mL/min, $p<0.001$), had more total diagnoses (6.38 vs. 5.91, $p<0.05$), as well as more non-liver-associated diagnoses (4.20 vs. 3.77, $p<0.05$). They had more drugs prescribed (6 vs. 4, $p<0.001$), as well as more drugs with predominantly hepatic elimination (4 vs. 3, $p<0.001$). Patients with ≥1 hepatically eliminated drug were more prevalent in the ADR group (99.1 vs. 81.6%, $p<0.001$). The same was true for patients with ≥1 pDDI at hospital admission (31.3 vs. 17.8%). Furthermore, pDDIs were more prevalent in patients with ADRs than in the control group (0.50 vs. 0.26 per patient, $p<0.05$).

3.2.5 Discussion

Studies on patients with liver cirrhosis focusing on drug therapy and drug-related problems are scarce in the literature. Lucena et al. investigated prescribing patterns and drug use in patients with liver cirrhosis [114, 115]. To prevent or treat complications of cirrhosis, diuretics, anti-ulcer drugs, laxatives, and vitamin K were the drugs prescribed most often [114]. Frequent medications for nonhepatic

comorbidities consisted of insulin, oral antidiabetics, cardiovascular drugs (calcium antagonists, ACE inhibitors, angiotensin receptor blockers), as well as drugs for the nervous (anxiolytics, hypnotics) and respiratory system [115]. The medication pattern of the patients in our study was similar to the patients reported by Lucena et al. [114, 115], suggesting that these studies reliably reflect the medication pattern in cirrhotic patients.

Every fifth patient in our study population had a pDDI, every fourth had an ADR, and 8% of the patients were hospitalized due to an ADR. This is in line with the 5-10% prevalence for ADR-related hospitalizations found in the meta-analysis by Lazarou et al. [116], but slightly more than the 5.1-6.5% reported in a retrospective cohort study [117] and in a prospective observational study [118]. Compared to patients without ADRs, patients with ADRs had more diagnoses and more drugs prescribed, received more drugs eliminated hepatically, had more pDDIs, and had a more compromised renal function.

Polypharmacy is a known risk factor for ADRs [56, 60, 119] and DDIs [120, 121]. Our data indicate that cirrhotic patients who have more comorbidities have more drugs prescribed and are therefore at a higher risk for ADRs. The relationship between number of diagnoses and number of drugs prescribed is well established [121]. The resulting polypharmacy is a risk factor for pDDIs [120, 121] and also for ADRs [56, 60, 119], which may be related to DDIs.

Our data suggest also that treatment with drugs with predominantly hepatic elimination is a risk factor for ADRs. More than 50% of the drugs used in our study fall into this category. Patient exposure to such drugs may be increased mostly due to elevated oral bioavailability and/or decreased CL_{hep}, possibly leading to an increased incidence of dose-dependent ADRs [27]. Astonishingly, systematic publications focusing on hepatically eliminated drugs as a risk factor for ADRs in patients with liver disease are lacking. The drugs with predominantly hepatic elimination associated with ADRs in our population were mostly cardiovascular drugs (torasemide, spironolactone, propranolol, amlodipine, diltiazem), NSAIDs (ibuprofen, acetylsalicylic acid, mefenamic acid), phenprocoumon, and benzodiazepines or related agents (midazolam, oxazepam, zolpidem). If possible, such drugs should be started at a low dose with careful up-titration until reaching a satisfactory drug response or toxicity.

A further risk factor for ADRs is impaired renal function. Impaired glomerular filtration is a well-known risk factor for ADRs also in other populations such as the

elderly [56, 122]. In our study, patients with ADRs had a lower creatinine clearance as compared to patients without ADRs. Impaired glomerular filtration may be associated with decreased renal clearance and increased exposure to drugs with a predominantly renal excretion. Importantly, patients with liver cirrhosis and ascites can have a creatinine clearance <60mL/min in spite of a normal serum creatinine [123], mostly due to impaired hepatic formation of creatine and increased tubular secretion of creatinine [27, 124]. Since the Cockcroft formula may overestimate the creatinine clearance in cirrhotic patients, drugs with predominantly renal elimination and dose-dependent ADRs should be dosed very carefully in cirrhotic patients [27].

Another important risk factor for ADRs is the presence of pDDIs. In our study, 7.5% of all ADRs were due to a DDI and 12.9% of the DDIs resulted in an ADR. In a recent review of hospitalized patients on different wards, 17% (range 5 - 31%) of all ADRs were reported to be due to DDIs [56]. In patients with hematopoietic stem cell transplantation (HSCT), 16% of the ADRs were caused by a DDI and 33% of all DDIs resulted in an ADR [113]. A comparison of the findings in patients with liver cirrhosis suggests that the DDIs in cirrhotics are less severe compared to DDIs in patients with HSCT. This is due to the fact that imidazole and triazole antimycotics used in patients with HSCT are CYP inhibitors interacting with immunosuppressants such as cyclosporin and tacrolimus, which are used routinely in HSCT patients. Nevertheless, pDDIs possibly resulting in severe ADRs are present also in cirrhotic patients; they are known and should be avoided.

The drugs most frequently involved in ADRs and pDDIs in our patients were ACE inhibitors, diuretics, NSAIDs, and oral anticoagulants. ACE inhibitors predispose cirrhotic patients for electrolyte disturbances and renal ADRs. The risk for hyperkalemia in cirrhotic patients treated with ACE inhibitors is increased 5.2-fold compared to patients without liver disease [125]. Patients with liver cirrhosis and portal hypertension have an activation of the RAAS and of the sympathetic nervous system, leading to renal vasoconstriction, impaired renal perfusion and glomerular filtration [126], and increased sodium retention [127]. Since drugs interfering with the RAAS such as ACE inhibitors or sartans can further impair glomerular filtration due to reduced filtration pressure, they should be used very cautiously in cirrhotic patients. Nevertheless, ACE inhibitors and sartans are prescribed frequently in cirrhotic patients [115].

NSAIDs and COX-2 inhibitors block renal production of prostaglandins, possibly leading to impaired renal perfusion and glomerular filtration, sodium retention and increase in ascites [27, 43]. Furthermore, NSAIDs may be associated with bleeding from esophageal varices and/or gastrointestinal ulcers due to their toxic effects on gastrointestinal epithelia and inhibition of thrombocyte function. In a case-control study including patients with esophageal varices with or without variceal bleeding, the use of NSAIDs in the week prior to the index day was significantly more common in bleeding patients (OR = 2.8) [128]. Taking into account the risks for gastrointestinal bleeding, deterioration of renal function and increase of ascites, it is astonishing that 7% of our patients used NSAIDs and 2% analgesic aspirin. A clearer communication of the risks associated with the use of these drugs and of the analgesic alternatives in this population is therefore necessary.

Our study has several limitations. A first limitation is the retrospective character of the study. The elaborated data were therefore limited to the information provided in the medical records, and it was sometimes not possible to obtain more information on the patient‘s situation or drug history prior to hospitalization. A second limitation is the limited sample size, which resulted in relatively small numbers of ADRs and DDIs. Nevertheless, we are convinced that the study provides important safety data in patients with liver cirrhosis and helps in identifying medication risks.

From the data of our study, we conclude that patients with liver cirrhosis have many comorbidities predisposing them to polypharmacy, which is associated with pDDIs and ADRs. Besides polypharmacy, important risk factors for ADRs in cirrhotic patients are lack of dose adjustment of drugs eliminated predominantly by the liver or by the kidney and certain pDDIs. Hepatologists should therefore not only know the principles of dose adjustment in patients with liver and/or renal failure, but also the most important DDIs of the drugs used to treat liver disease and comorbidities in this population.

3.3 Dose adjustment in patients with liver cirrhosis: impact on drug safety and healthcare costs

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3.3.1 Abstract

Background & Aims: To assess drug-related problems in patients with liver cirrhosis by investigating the prevalence of IDDs and their association with ADRs and costs.

Methods: Cross-sectional retrospective study assessing the dose adequacy of drug treatment of 400 cirrhotic patients at the day of hospital admission based on previous own studies and standard literature. We also determined the prevalence of total and preventable ADRs and potential drug-cost savings by dose adjustment and additional hospital stay due to preventable ADRs.

Results: Of all 1653 drugs prescribed (median 4 per patient), 336 (20%) were IDDs in 184 patients. In total, 198 ADRs (83% preventable) occurred in 110 patients. Sixty-one (31% of all ADRs) were associated with IDDs in 40 patients, whereof 77% were preventable. Especially NSAIDs and psycholeptics were a frequent cause of preventable ADRs associated with IDDs. IDDs were more frequently associated with ADRs than correctly dosed drugs (CDDs) and patients with IDDs were more frequently admitted to the hospital due to ADRs. Hospitalization of patients with IDDs causing preventable ADRs resulted in 94 additional hospital days, costing 151,000 Euros. Potential drug-cost savings (averaging approximately 400 Euros per hospitalized patient) result mainly from hospitalizations due to preventable ADRs and to a lesser extent from consequent dose adjustment.

Conclusion: IDDs in patients with liver cirrhosis are associated with an increased frequency of ADRs, hospital admissions, and costs. Education of prescribing physicians concerning problematic drugs in patients with liver cirrhosis should be improved.

3.3.2 Introduction

The elimination of the majority of drugs on the market depends on liver function. About two thirds of the drugs on the Swiss market have a Q_0>0.5 and are thus cleared mainly by the liver. Most patients with liver cirrhosis have an impaired hepatic handling of such drugs, depending on the severity of cirrhosis [4, 27].

In patients with liver cirrhosis, hepatic extraction can be impaired, leading to a substantial increase in bioavailability of drugs that have a high hepatic extraction in

healthy subjects. This is mainly due to an impaired exposure of the hepatocytes to blood because of extra- and intrahepatic shunts [14]. Furthermore, the access of drugs to hepatocytes may be diminished in cirrhotic livers due to capillarization of the sinusoidal endothelium [129].

In addition to increased bioavailability, CL_{hep} of most drugs mainly metabolized and/or excreted by the liver is reduced in patients with liver cirrhosis. For drugs with a high hepatic extraction, this is mainly due to impaired blood flow across the liver [4, 27, 108, 130]. For drugs with a low hepatic extraction, metabolism by phase I enzymes, in particular CYPs, is the critical factor [27]. Several investigations have shown that the enzyme content and/or the activity of the most important CYPs are reduced in cirrhotic livers [4, 27, 31]. CYPs appear to be more sensitive to liver cirrhosis than phase II enzymes such as UGT [4].

Beside pharmacokinetic alterations, pharmacodynamic aspects must also be considered as a potential reason for ADRs in this patient population. For example, NSAIDs should be avoided due to the risk for impaired renal perfusion, eventually leading to renal failure [27]. Similarly, the susceptibility to central adverse effects of opiates such as morphine [109] and of benzodiazepines [110] is increased in patients with liver cirrhosis.

We recently published a cross-sectional retrospective study presenting demographic data, medication patterns, pDDIs, and ADRs in 400 patients with liver cirrhosis admitted to the University Hospital of Basel [68]. We found that 28% of the patients had at least one ADR and 21.5% of the patients at least one pDDI at hospital admission. In the current study, we focused on the quality of dose adjustment in this population and we estimated the excess of ADRs, hospitalization days and costs in patients with IDDs at hospital admission.

3.3.3 Patients and Methods

The study is based on the same population described previously [68]. The study design, patients included, data collection, and previous descriptive analyses regarding patients, diagnoses, and medication are described in detail in this earlier study.

3.3.3.1 Drug categorization

The drugs were classified by means of their Q_0 and their hepatic extraction (E) into five CAT. Drugs with a Q_0 ≥0.5 were considered to undergo mainly hepatic elimination. For drugs with Q_0 ≥0.5, E was either obtained from the literature or calculated using Eq. 7:

$$E = \frac{Q_0 * CL_{sys}}{Q} \qquad \text{(Equation 7)}$$

where CL_{sys} is the systemic clearance (L/h), Q_0 the extrarenal dose fraction of a specific drug, and Q the hepatic blood flow (~54L/h).

The drugs were further categorized according to E into the three categories high hepatic extraction drugs (CAT1), intermediate hepatic extraction drugs (CAT2), and low hepatic extraction drugs (CAT3). Drugs with a Q_0<0.5 are excreted mainly by the kidney (CAT4). CAT5 refers to drugs with an unknown Q_0 and/or E. For further information regarding this classification, see Fig. 4 and the publications of Delco et al. [27], Tchambaz et al. [94], and Schlatter et al. [95].

3.3.3.2 Dose assessment and ADRs

The patients' dose at hospital admission was compared to published dosing recommendations in patients with liver cirrhosis (Fig. 4 and [27, 94, 95]) and judged using a prototypal internal drug database. This database has been constructed as described in our previous publications about medication in liver cirrhosis [27, 94, 95]. The recommendations concerning dosing in patients with liver cirrhosis within this database are based on published kinetic studies for individual drugs and on the recommendations provided in the PDR [65], Micromedex® [71] and/or the Swiss drug register (Arzneimittel-Kompendium) [87].

All patients included in the study were on long-term medication and used their maintenance dose at hospital entry; initial doses were therefore not considered. According to the general recommendations [27, 94, 95], maintenance dose for CAT1, CAT2, and CAT3 drugs should generally be reduced by 50-75%, approximately 50%, or 0-50%, respectively, in patients with liver cirrhosis (Fig. 4). Since up-titration according to clinical effect and tolerability is recommended for most drugs, doses that exceeded the general recommendations had to be judged individually using the recommendations of the internal database described above. This database provides dosing recommendations adjusted to the severity of liver

disease (according to the Child class). Accordingly, for each dose assessed, characteristics of the individual patient (in particular the severity of liver disease), as well as of the drug administered were taken into account. For drugs which can be monitored by specific tests (e.g. INR for phenprocoumon, blood glucose for insulin and oral antidiabetics, serum levels), these values were taken into account for defining the correct dose.

All drugs contraindicated or prescribed in an incorrect dose according to this database (IDDs) were further analyzed. We assessed how many patients received IDDs and which CAT and ATC codes were involved. We identified the ADRs associated with IDDs and classified each ADR as type A (dose-dependent, and thus preventable) or type B (dose-independent, considered to be not preventable) ADR. We then assessed the prevalence of total as well as preventable ADRs per drug CAT. Furthermore, we investigated the impact of IDDs and/or ADRs on mortality. Finally, the discontinuation rate of drug treatments at hospital entry was assessed as well as the reasons for discontinuation, in particular IDDs and ADRs.

3.3.3.3 Risk assessment for incorrectly administered drugs

To investigate whether IDDs are associated with an increased risk for ADRs, we calculated the relative risk for developing ADRs according to the ATC code in patients with IDDs compared to patients without IDDs and expressed it as an odds ratio (OR). A significance level of 5% was chosen.

3.3.3.4 Contraindicated drugs

The PDR [65] was consulted to check if the prescribed drugs were formally contraindicated in patients with liver disease. Drugs not listed in the PDR were checked in Micromedex® [71] and drugs listed neither in the PDR nor in Micromedex® were judged by means of our internal database which bases on published studies. According to our database, NSAIDs are contraindicated in patients with liver cirrhosis due to an increased risk for ADRs, in particular gastrointestinal bleeding and/or renal failure [27, 43, 131]. This judgment is supported by the results of our previous study, showing a bad tolerability of these drugs by patients with liver cirrhosis [68]. We also investigated the question whether ADRs were more frequently associated with contraindicated than with not contraindicated drugs.

3.3.3.5 Excess hospitalization days and potential cost savings

For IDDs that were continued during hospital stay, the cost difference between administered and recommended dose was calculated as Euros per cirrhotic patient and day. For preventable ADRs associated with IDDs, the excess hospitalization days and costs for the hospitalizations were also calculated.

3.3.4 Results

3.3.4.1 Drug categories at hospital admission

At hospital admission, the 400 patients with liver cirrhosis had 1653 prescriptions (median 4 drugs per patient, range 0-15), vitamins and minerals excluded. Considering drug CAT, most abundant were drugs with a low (29.4%) or high (27.4%) hepatic extraction, followed by drugs with intermediate hepatic extraction (19.2%), and drugs with mainly renal (12.3%) or unknown elimination (11.7%) (Appendix Fig. 11). Details to the drugs with hepatic elimination, e.g. individual drug classes, were published in our previous work [68].

3.3.4.2 Dose assessment and ADRs

Overall, 336 (20.3%) of all drugs (47.6% of CAT2; 20.1% of CAT4; 18.1% of CAT3; 10.6% of CAT1; 4.1% of CAT5; Appendix Fig. 11) were judged to be IDDs in 184 patients. Thirty-six of these drugs were contraindicated in patients with liver cirrhosis and 300 were dosed inadequately high. The majority of drugs (68.4% of all drugs; 89.4% of CAT1; 81.7% of CAT3; 80.0% of CAT4; 51.7% of CAT2; 2.5% of CAT5) were dosed correctly (CDDs) and 11.1% of all drugs (93.3% of CAT5; 0.6% of CAT2; 0.2 of CAT3; 0% of CAT1 and 4) could not be judged regarding dosing (not assessable drugs, NADs). According to the ATC-code, drugs for the alimentary tract and metabolism (ATC A; n=137), for the nervous system (ATC N; n=80), for the cardiovascular system (ATC C; n=62), and for the musculo-skeletal system (ATC M; n=31) were most frequently IDDs (Fig. 9). Most often involved drug classes were drugs for acid related disorders (A02), oral blood glucose lowering drugs (A10B), non-steroidal anti-inflammatory and antirheumatic products (M01A), hypnotics and sedatives (N05C), and other analgesics and antipyretics (N02B).

In total, 198 ADRs (164 preventable reactions, 82.8% of all ADRs) occurred in 110 patients (27.5%) (median 1 [range 1-5] per affected patient). Of all ADRs, 61 (30.8% of all ADRs; 47 [77%] of them preventable) were associated with IDDs in

40 (10%) patients. ADRs associated with IDDs are listed in Tab. 10. As shown in the Table, especially NSAIDs and psycholeptics were frequently involved in these ADRs. Low, intermediate, and high hepatic extraction drugs were associated with 27, 22, and 8 IDD-associated ADRs, respectively. Seven of the ADRs were due to a drug-drug interaction.

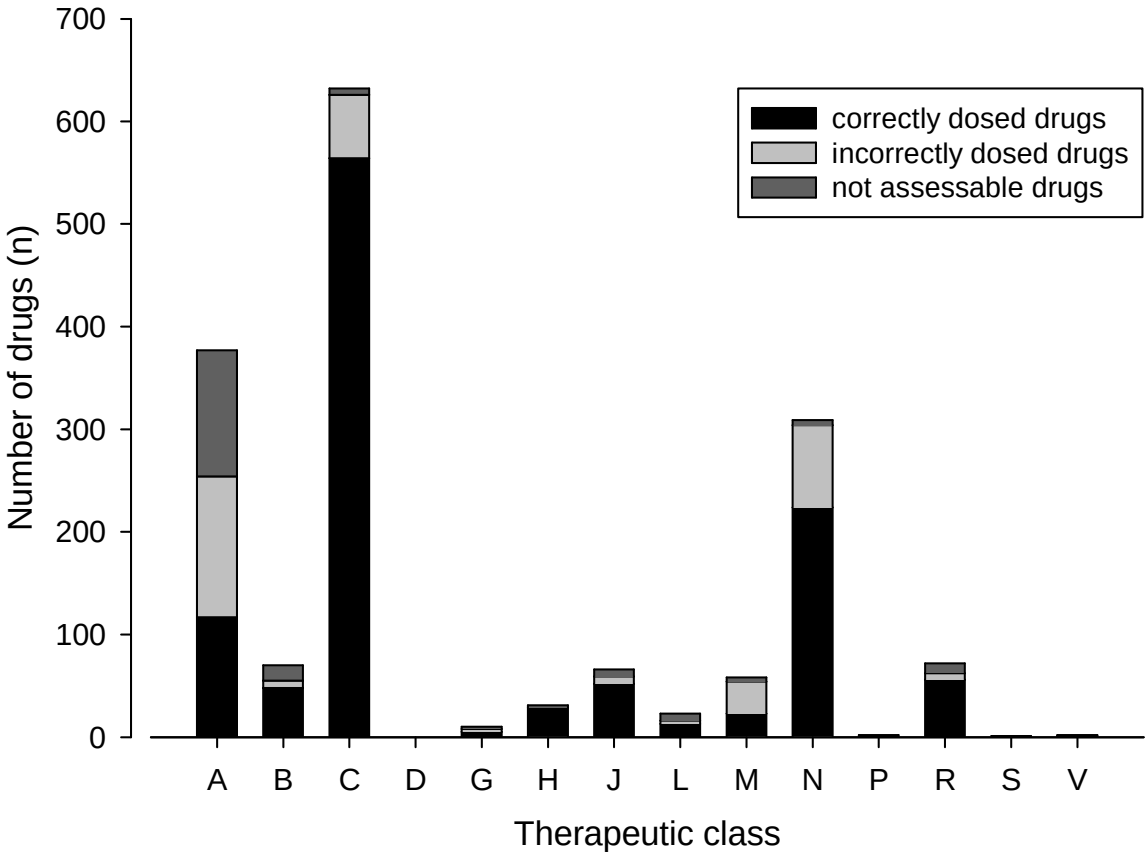

Fig. 9 Fraction of each drug class (ATC-code) with correctly (CDDs) and incorrectly (IDDs) dosed drugs. A = alimentary tract and metabolism; B = blood and blood forming organs; C = cardiovascular system; D = dermatologicals; G = genito-urinary system and sex hormones; H = systemic hormonal preparations (excl. sex hormones and insulin); J = antiinfectives for systemic use; L = antineoplastic and immunomodulating agents; M = musculo-skeletal system; N = nervous system; P = antiparasitic products, insecticides and repellents; R = respiratory system; S = sensory organs; V = various; NADs = not assessable drugs.

Tab. 10 Adverse drug reactions (ADRs) associated with incorrectly dosed drugs (IDDs)

Drug class (ATC-code)	Drugs (n ADR)	Type A ADR (n)	Other ADR (n)
Anti-inflammatory and antirheumatic products (M01)	ibuprofen (11*), diclofenac (7*), mefenamic acid (6*), piroxicam (1*)	gastrointestinal hemorrhage/ulcer (12*; 1 DDI), anemia (3*), worsening of ascites (2*), hyperkalemia (1*; 1 DDI), reduction of creatinine clearance (1*), psychomotor agitation (1*), epistaxis (1*; 1 DDI)	thrombocytopenia (2*), leucopenia (1*)
Psycholeptics (N05)	zolpidem (6), diazepam (2*, 1), midazolam (2), pipamperon (1)	somnolence (3), confusion (1*, 2), gait disorder (1), mental retardation (1; 1 DDI), fall (1*)	somnambulism (1), elevated ALT (1)
Diuretics (C03)	spironolactone (6), torasemide (2)	reduction of creatinine clearance^ (3), hyperkalemia (2; 1 DDI), hyponatremia (1)	anemia (1), diarrhea (1)
Drugs used in diabetes (A10)	metformin (3), rosiglitazone (2)	loss of appetite (1), diarrhea (1), heart failure (1)	thrombocytopenia (1), hyperbilirubinemia (1)
Calcium channel blockers (C08)	amlodipine (4)	edema (2), dyspnea (1)	hyperbilirubinemia (1)
Agents acting on the RAAS (C09)	ramipril (2), losartan (2)	syncope (1), hyperkalemia (1), hypotension (1)	eosinophilia (1)
Drugs for acid related disorders (A02)	lansoprazole (1)		elevated ALT (1)
Antithrombotic agents (B01)	phenprocoumon (1)	INR increased (1)	
Antineoplastic agents (L01)	doxorubicin (1)	neutropenic fever (1; 1 DDI)	
Analgesics (N02)	acetylsalicylic acid (1*)	gastrointestinal ulcer (1*)	
Other nervous system drugs (N07)	Methadone (1)	torsade de pointes (1; 1 DDI)	

ADR = adverse drug reaction; ALT = alanine transaminase; AP = alkaline phosphatase; ATC = anatomical therapeutic chemical classification system; DDI = drug-drug interaction (n); RAAS = renin-angiotensin-aldosterone system

^partly type A ADR

*contraindicated drug/ADRs associated with contraindicated drug

As reported in our previous study [68], 16 ADRs were the reason for hospital admission. Noticeably, patients with IDDs were more frequently admitted to hospital due to an ADR than patients with CDDs/NADs (7.1% and 1.4% of all patients with and without IDDs, respectively). In six cases, the IDD was the direct cause for the ADR (coma due to midazolam [1], worsening of ascites due to ibuprofen [1], gastrointestinal ulcer/hemorrhage due to diclofenac [1], ibuprofen [2] or the combination piroxicam-acetylsalicylic acid [1]). As shown in Fig. 10, ADRs were overall more frequent for IDDs compared to CDDs (overall in 18.2% vs. 13.1% of the prescribed drugs; preventable 14.0% vs. 10.6%). Surprisingly, this was not the case for all drug CAT. For instance, ADRs were less frequent in CAT1 drugs that were dosed incorrectly (16.7% vs. 20.0%; Fig. 10). The same was true for primarily renally eliminated drugs (CAT4), where the frequency of ADRs was 12.2% for IDDs and 25.2% for CDDs (Fig. 10). In the other drug categories (CAT2, 3, 5), more ADRs occurred for IDDs compared to CDDs. The difference was most pronounced in CAT3 drugs (30.7% vs. 13.9%, Fig. 10) followed by CAT2 (14.6% vs. 10.4%; Fig. 10). For CAT5, we compared the drugs which are contraindicated or not recommended in liver cirrhosis with the other drugs in this group (CDDs and NADs). ADRs were more frequent for drugs that are contraindicated/not recommended in liver cirrhosis (12.5% vs. 4.9%; Fig. 10).

The only ATC group associated with a statistically significant increased risk for ADRs in case of IDDs was the musculo-skeletal system group (ATC M; OR 11.1, 95% CI 2.5-66.5; Appendix Fig. 12), which contains the NSAIDs.

At hospital admission, IDDs associated with an ADR were more likely to be stopped (total 36/42 [85.7%]; CAT4 and 5 100%; CAT2 92.9%; CAT3 84.2%; CAT1 60.0%) than CDDs associated with an ADR (total 96/127 [75.6%]; CAT4 88.5%; CAT2 78.6%; CAT1 77.6%; CAT3 62.2%; CAT5 100%). IDDs without ADRs were less often stopped at hospital admission (total 90/294 [30.6%]; CAT5 57.1%; CAT2 34.3%; CAT4 28.9%; CAT3 26.1%; CAT1 23.3%).

An increased mortality rate was observed in patients with ADRs (see below). Correct dosing, however, had only a minor influence on mortality. In patients with ADRs, mortality was similar in patients with IDDs as compared to patients with CDDs/NADs (20.0% versus 21.7%, respectively). In comparison, in patients without ADRs, mortality rates were 15.2% and 15.1% in patients with IDDs and CDDs/NADs, respectively.

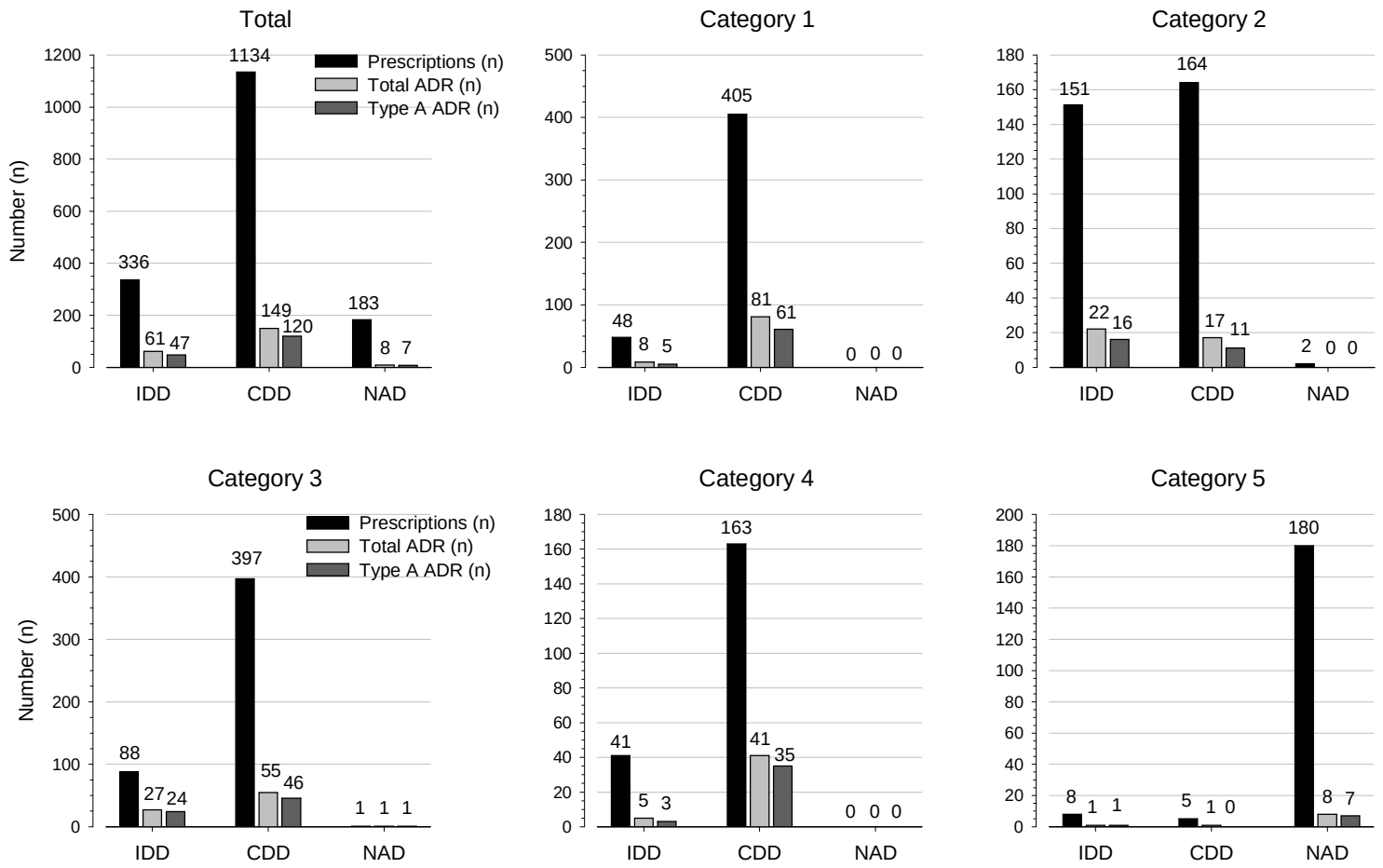

Fig. 10 Number of prescriptions, total number ADRs and number of preventable (Type A) ADRs stratified per drug category. Within each drug category, prescriptions and ADRs are classified further per adequacy of dose adjustment (CDDs: correctly dosed drugs; IDDs: incorrectly dosed drugs; NAD: non-assessable drugs). The sum of the ADRs can exceed the total number of ADRs, since ADRs caused by more than one drug (e.g. one IDD and one CDD) were counted more than once.

3.3.4.3 Contraindicated drugs

Of all drugs, 36 (2.2%) were contraindicated in patients with liver disease (ibuprofen (12), diclofenac (9), mefenamic acid (5), diazepam (3), atorvastatin (2), acemetacin (1), piroxicam (1), acetylsalicylic acid (1), methyldopa (1), pravastatin (1)). Drug CAT involved were CAT1 with high (acetylsalicylic acid, atorvastatin, pravastatin), CAT2 with intermediate (diclofenac), and CAT3 with low hepatic extraction (acemetacin, ibuprofen, piroxicam, diazepam, zopiclone, methyldopa), as well as CAT5 with unknown elimination (mefenamic acid).

In total, these drugs caused 28 ADRs; these ADRs are marked with a star (*) in Tab. 10. The most frequent ADRs were gastrointestinal hemorrhage/ulcer associated with NSAIDs. Related to prescriptions, approximately 7 times more ADRs (7.7 times more preventable ADRs) occurred due to treatment with contraindicated drugs as compared to non-contraindicated drugs.

3.3.4.4 Potential cost savings

Direct potential drug cost savings from dose adjustment was minor with <1 Euro per cirrhotic patient and day or 30 Euro per hospitalized patient with liver cirrhosis.

However, 6 patients were admitted to the hospital due to a preventable ADR directly caused by an IDD. Taken together, these patients stayed in hospital for 94 days, resulting in total costs of 151’575 Euros or 379 Euros per hospitalized cirrhotic patient. For the remaining 41 preventable ADRs associated with IDDs, the excess hospital stay and costs could not be estimated, since the patients were hospitalized for other reasons. In total, for every hospitalized cirrhotic patient, at least 409 Euros are spent due to IDDs.

3.3.5 Discussion

In the current study, we assessed drug dosing in 400 cirrhotic patients at hospital entry using our own recommendations [27, 94, 95] in combination with Micromedex® [71] and the respective product information [65].

Approximately three quarters of all drugs (excl. vitamins and minerals) used in this population have a predominantly non-renal elimination, in most cases involving the liver. Approximately 20% of the prescriptions were considered to be inappropriate, in most cases too high or contraindicated. IDDs were more frequently associated with ADRs (18.2% of prescriptions) compared to CDDs (13.1% of prescriptions). Patients with IDDs were more frequently admitted to hospital due to an ADR (7.1%

vs. 1.4%) than patients with CDDs/NADs. Since most IDDs associated with ADRs were recognized and eliminated at hospital entry, duration of hospitalization and mortality rates were not different between patients with or without IDD.

To the best of our knowledge, there is so far no study in the literature, in which dosage adjustment in patients with liver cirrhosis was investigated systematically. A major problem may be that, in contrast to impaired renal function, no concrete dose recommendations exist for patients with impaired liver function. Particularly for older drugs, recommendations in the product information are often lacking or not helpful (e.g. “drug should be used with caution”), shifting the problem to the prescribers.

In comparison to our previous publication involving the same group of patients [68], the number of prescriptions and ADRs are lower in the current study. This is due to the exclusion of vitamins and minerals for the current investigation. Since precise pharmacokinetic data for vitamins and minerals are usually not available, most of these substances would belong to CAT5 with unknown elimination pathway, resulting in an inadequate overestimation of this drug CAT (in our previous study, 17% of all prescriptions were vitamins and minerals [68]). Taking into account the generally good tolerability of vitamins and minerals, we feel that their exclusion from our analysis is acceptable.

In our study, 20.3% of all prescriptions were dosed incorrectly in relation to liver function, and IDDs were more frequently associated with ADRs than CDDs. This could be expected taking into account the fact that most ADRs are dose-dependent. Surprisingly, IDD-associated ADRs were not more frequent for drugs with a high hepatic extraction (CAT1) or predominant renal elimination (CAT4) compared to CDD-associated ADRs. It appears, therefore, that physicians are aware of the high risk drugs in these patients and of the necessity for dose adjustment in patients with liver cirrhosis. A contributing factor may be that the maintenance dose of such drugs can be adjusted according to clinical effect and tolerability in each individual patient. For certain drugs, the actual maintenance dose may therefore be higher than suggested by the recommendations. This is for example the case for betablockers, which were the most frequent CAT1 drugs in our population (e.g. propranolol and metoprolol). Therefore, the dosage of CAT1 betablockers was judged only rarely as an inappropriate (in 3 of 109 CAT1 betablocker prescriptions).

The IDDs in CAT4 were mainly due to the prescription of metformin and the dosage of ramipril. Metformin should be avoided in patients with liver cirrhosis due to an increased risk for lactic acidosis and ramipril should be used at a low dose, since hemodynamic changes in patients with liver cirrhosis predispose them for renal hypoperfusion and/or hypofiltration possibly leading to renal failure [27].

In our study, 82.8% of all ADRs and 77% of IDD-associated ADRs were classified as potentially preventable. These numbers correspond well with the frequencies reported in a review published in 2007 [56], stating that 80% (51-100%) of ADEs in hospitalized patients are potentially preventable. Prevention of such events could be achieved by using the lowest effective dose and by the elimination of DDIs and other MEs [56].

NSAIDs were by far the most often prescribed contraindicated drugs in this population. Of the 36 contraindicated drugs, 28 were NSAIDs. NSAIDs caused a total 25 ADRs, 21 of them were considered to be preventable and 5 were a reason for hospitalization. Cirrhotic patients treated with a NSAID had a 50% probability to develop a severe ADR. In total, patients treated with a contraindicated drug (including NSAIDs) had 7-fold higher risk to suffer from an ADR than patients without contraindicated drugs. These figures highlight the importance of avoiding contraindicated drugs in this population, in particular NSAIDs. Interestingly, NSAIDs are not contraindicated in cirrhotic patients by the PDR and Micromedex®, but by the Swiss “Arzneimittel-Kompendium”. Taking into account the high frequency of mostly severe ADRs caused by NSAIDs (leading to hospitalization and potentially death), NSAIDs should be considered to be contraindicated in cirrhotic patients.

Interestingly, IDD-associated ADRs were most frequently related to drugs causing pharmacodynamic alterations in patients with liver cirrhosis; drug classes most often involved were NSAIDs, sedatives/hypnotics, and oral antidiabetics. While CNS-depressing drugs bear an increased risk for hepatic encephalopathy [27], oral antidiabetics may induce hypoglycemia due to impaired drug metabolism and possibly also impaired gluconeogenesis in patients with decompensated liver cirrhosis [132].

Overall, potential cost savings by avoiding incorrect drug dosing per cirrhotic patient and hospitalization were at least 409 Euro in our study. These savings result mainly from six patients admitted to the hospital due to an ADR, which was directly caused by an IDD. The costs for the corresponding hospital stays (151’575

Euros) could have been prevented by not using IDDs in cirrhotic patients. The costs of the remaining 41 ADRs associated with IDDs present at hospital entry could not be calculated, since the ADRs were not the cause for hospital admission.

In contrast, drug-cost savings by dose reduction in patients with liver cirrhosis appear to be minimal according to our results. In a study assessing dosage adjustment in patients with renal impairment, dose reduction resulted in drug-cost savings of 2250 US$ for four months in 300 patients [133]. If calculated per day and patient, this number is similar to our results. We should keep in mind, however, that dose-dependent ADRs frequently lead to prolongation of hospital stay and extra costs due to additional investigations or treatment. According to a review [56], each ADR in hospitalized patients increases the hospital stay by 3.4 (1.2-8.5) days. Accordingly, the additional costs per ADR ranged between 1400 US$ and approximately 5000 US$ [56]. Since we do not have data on ADRs occurring during hospital stay in our patients, we cannot calculate associated costs.

Our study has several limitations. The retrospective character only allowed us to include the data documented in the medical records, which might not always be complete. Furthermore, the population size is quite small, resulting sometimes in large confidence intervals and possibly in non-significant results.

In conclusion, our study shows that approximately 20% of the prescriptions in patients with liver cirrhosis are inappropriate for dose and/or contraindication. Patients with inappropriate prescriptions, especially those treated with contraindicated drugs, are at a high risk for ADRs, leading to a higher hospitalization rate due to ADRs with high costs. Careful dosing taking into account the clinical effect and dose-related ADRs and avoiding contraindicated drugs is mandatory in this group of patients.

Chapter IV

Discussion, Conclusion, and Outlook

4.1 Discussion

Drug therapy in patients with liver cirrhosis is complex. First, no surrogate parameter exists for dosage adjustment in patients with liver disease [27]. Secondly, various non-uniform pharmacokinetic and pharmacodynamic alterations may be present in this patient population, making it difficult to estimate what impact liver disease has on a specific drug. Individualized dose adjustment according to clinical effect and dose-dependent ADRs should be considered. Dose recommendations in the product information for patients with liver disease are often lacking or unspecific (e.g. “drug should be used with caution”), for instance due to lack of studies. It is therefore not surprising that up to now neither a CDS-tool giving dose recommendations for patients with liver cirrhosis nor studies systematically investigating dosage adjustment in patients with liver cirrhosis exist. To the best of our knowledge, apart from few general studies focusing on drug therapy in patients with liver cirrhosis [114, 115], general studies focusing on drug-related problems in patients with liver cirrhosis are lacking in the literature.

By categorizing drugs according to their pharmacokinetic parameters, we estimated the extent by which a certain drug is eliminated by the liver. Depending on this categorization, dosage recommendations for patients with liver disease can be derived. Additionally, pharmacodynamic changes must also be taken into account. Based on these considerations, we made specific dosage recommendations for patients with liver disease whenever possible. We summarized these recommendations in a database, together with the pharmacokinetic and toxicologic profile of a drug, studies on pharmacokinetic alterations in patients with liver disease, and available recommendations for this patient population. This database is the first step for the development of a CDS-tool. Indeed, a software implementation of the database is planned in collaboration with Documed AG. Currently, preliminary tests are performed. Next to the information in the database, plasma-concentration-time curves as presented in section 3.1.4 will be provided, giving an overview on the impact liver cirrhosis has on the pharmacokinetics of a drug.

In our first study, we resumed the above-mentioned database for the anti-infective drugs on the Swiss market at the beginning of 2012.

Forty-seven % of the 104 anti-infectives on the Swiss market in 2012 are mainly eliminated by the liver. Additionally, studies reported pharmacokinetic alterations in liver disease for 48% of all anti-infectives, indicating the importance of considering dose reduction in patients with impaired hepatic function. Moreover, 27% of the anti-infectives were at least partly metabolized by CYP P450 enzymes, which are more affected by liver cirrhosis than phase II enzymes [4, 27, 29, 30].

Forty-four % of the drugs were mainly eliminated by the kidney. In this respect, it is important to remember that liver cirrhosis may be associated with renal impairment (hepato-renal syndrome) [4, 27]. Biliary elimination ≥50% affected one fifth of all drugs. In patients with intra- or extrahepatic cholestasis, these drugs should be used with caution to avoid accumulation.

We could confirm that specific dosage recommendations for patients with liver cirrhosis are often not available in the product information. In the Swiss product information [87], specific recommendations for patients with liver disease are only available for 50% of all anti-infective drugs. In line with this finding, specific recommendations were also frequently unavailable for antineoplastic and psychotropic drugs [94, 95]. In clinical practice, this leads to difficulties in choosing an adequate, effective, and safe dose for hepatically impaired patients. Therefore, the elaboration of a CDS-tool is crucial.

In our second and third study, we first characterized 400 patients with liver cirrhosis in respect of their demographic data, diagnoses, medication at hospital admission, and the prevalence of ADRs and pDDIs. We found that 28% and 21.5% of cirrhotic patients were affected by ADRs and pDDIs, respectively. Cirrhotic patients with ADRs showed the typical risk factors for ADRs/ADEs [61-63], they were older, had more comorbidities, more drugs prescribed, more pDDIs, and worse renal function than cirrhotic patients without ADRs. Most ADRs were considered dose-dependent and thus potentially preventable. Of all 1653 drugs prescribed excluding vitamins and minerals, 20% were IDDs in 184 patients. IDDs were more frequently associated with ADRs than CDDs and patients with IDDs were more frequently admitted to the hospital due to ADRs than patients with CDDs/NADs (7.1% vs. 1.4%). This number is higher compared to the median ADR prevalence of 5.3% (interquartile range 2.7-9%) at hospital admission in a review

assessing the prevalence of ADR-associated hospitalizations [134]. Potential drug-cost savings as a result of mere dose adjustment in patients with liver cirrhosis was minor, but considerable when taking into account hospitalizations due to preventable ADRs caused by IDDs. In the out-patient setting, IDDs may result in increased morbidity and additional costs. Besides the costs, IDDs may lead to an additional burden to the individual patient due to further morbidity and sequelae.

Our results with a high prevalence of ADRs, pDDIs, and IDDs in cirrhotic patients demonstrate that pharmacotherapy is problematic in patients with liver cirrhosis. A CDS-tool giving dosage recommendations for patients with liver disease may help to improve drug safety in patients with liver cirrhosis. On the one hand, it would help prescribing physicians to choose an adequate dose. On the other hand, a reduction of IDDs would naturally lead to less ADRs, less ADR-associated morbidity in the out-patient setting, and less ADR-associated hospitalizations. Thus, a CDS-tool has the potential to reduce healthcare costs and patient morbidity.

A limiting factor in the second and third studies is the retrospective nature of the chart review, not allowing for communication with the involved patients and healthcare professionals for further information. Our recorded data are based on the medical records, which might not always be complete. Another limitation is the limited population size, which resulted in relatively small numbers of ADRs, DDIs, and sometimes statistically non-significant results.
The reason why we chose a cross-sectional study design is because it is a good design to determine prevalences. Additionally, cross-sectional studies are usually not associated with ethical difficulties, since exposure to a risk factor or treatment are not chosen deliberately [135].

We are convinced that our studies provide important information on the principles of dosage adjustment in patients with liver disease as well as improve the awareness of problematic drugs and relevant safety data in patients with liver cirrhosis. We published the first study with a systematic investigation of dosage adjustment in patients with liver cirrhosis. Furthermore, we are going to contribute to the first CDS-software for patients with liver disease.

4.2 Conclusion

Since data on drug-related problems or systematic investigations of dosage adjustment in patients with liver cirrhosis are lacking in the literature, our studies provide important information for a better understanding of the characteristics of patients with liver cirrhosis and for the improvement of drug safety in this patient population.

We can conclude, that

- Specific dosage recommendations for patients with liver disease are frequently not provided by the product information.
- Elaboration of pharmacokinetic parameters of drugs allows for drug categorization and is the basis for dose recommendations.
- About two thirds of the drugs prescribed to cirrhotic patients are primarily eliminated by the liver.
- Drug-related problems are prevalent in patients with liver cirrhosis at hospital admission. Twenty-eight % and 21.5% of the patients in our study were affected by ADRs and pDDIs, respectively.
- Twenty % of drugs prescribed to cirrhotic patients are incorrectly dosed or prescribed.
- ADRs are more frequent with IDDs than with CDDs.
- Most ADRs are considered dose-dependent and could be prevented, e.g. by dose adjustment to liver function.
- Especially NSAIDs and psycholeptics were a frequent cause of preventable ADRs.
- Patients with IDDs are more frequently admitted to hospital due to an ADR than patients with CDDs/NADs.
- Potential cost savings due to mere dose adjustment in patients with liver cirrhosis is minor, but significant when taking into account additional hospitalizations due to preventable ADRs caused by IDDs.

These findings suggest that a CDS-tool providing dose recommendations for patients with liver disease is strongly needed to improve drug safety and to reduce healthcare costs in patients with liver disease. Our database, allowing for specific dose recommendations for patients with liver disease for many drugs, is the cornerstone for a CDS-software.

4.3 Outlook

In collaboration with Documed AG, our database is about to be implemented into a CDS-software. The marketing of the first version of this software is planned for autumn of 2012. This software will show an information box about the pharmacokinetics of a drug and is additionally will focus mainly on dosage recommendations given by the Swiss product information on the one hand and on our recommendations derived from pharmacokinetic and pharmacodynamic data on the other hand. Additionally, the plasma-concentration-time curves are going to be shown. The first version of the software only allows for the integration of single agent drugs and is will contain approximately 600 of 1000 systemically available drugs on the Swiss market.

Based on this project, additional work can be done for further versions of the software:

- Further development of the database
    - Elaboration of the remaining systemically available drugs on the Swiss market (approximately 400)
    - Additional considerations for the inclusion of combination products
- Validation of the database
    - Ask opinion of physicians using the CDS by questionnaire, regarding for example the clinical relevance and helpfulness of the CDS
    - Prospective follow-up study, where patients with liver cirrhosis could either be treated by physicians using the CDS or they could be treated as usual.
        - Study in in-patients with liver cirrhosis, since the CDS-tool may probably not be available in the out-patient setting in the near future

- Prospective consideration and recognition of ADRs, e.g. by clinical pharmacists
- Analysis of the impact the CDS-tool has on different parameters such as the occurrence of ADRs or healthcare costs
- Validate usefulness of the recommendations in the database by investigation of the prevalence of IDDs in the cases and controls

Chapter V

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Chapter VI

Appendix

6 Appendix

Tab. 11 Draft of the database summarizing pharmacokinetic data, adverse drug reactions, pharmacokinetic studies, and recommendations in liver disease for anti-infectives for systemic use. All the antibacterials, exclusively the high hepatic extraction drugs (see section 3.1.4 Tab. 4), are listed according to the therapeutic groups. The whole database for all anti-infective drugs studied is available on the attached CD.

Drug (route of application)	*Metabolism*	*Kinetic parameters*	*Hepatic ADRs*	*Potentially dose-dependent ADRs*	*Studies, product information, and dose recommendations*
<u>Antibacterials for systemic use</u> Tetracyclines					
Doxycycline (oral, parenteral)	No significant metabolism. Enterohepatic cycling. A part is inactivated by chelation (Ca2+, Mg2+) in the intestine [87, 90, 136].	Q_0: 0.70 $T_{1/2}$: 23h V_d: 0.75L/kg PB: 85% F_{oral}: 95% CL_{sys}: 2.2L/h E: 0.03 BE: n.k. CAT: 3	*Rare:* hepatitis, cholestatic liver injury [87, 92]. *Case report:* microvesicular steatosis [137].	gastrointestinal disturbances, esophageal ulcerations, intestinal overgrowth by non-susceptible organisms, discoloration of teeth, decreased plasma prothrombin activity, benign intracranial hypertension, rise in BUN [87, 90]	*Studies:* No clinical studies available in patients with liver disease. *Product information*: Caution in patients with severe liver dysfunction. No pharmacokinetic data in patients with liver disease [87]. *Recommendation:* According to pharmacokinetic data, start with normal initial doses. Reduce maintenance dose by up to 50%. Adjust maintenance dose according to clinical effect and dose-dependent ADRs.
Lymecycline (oral)	Prodrug of tetracycline. The data reported refer to tetracycline. About 5% of tetracycline is metabolized by C-4 epimerization [90]. Enterohepatic circulation.	Q_0: 0.40 $T_{1/2}$: 10h V_d: 1.5L/kg PB: 60% F_{oral}: n.k. CL_{sys}: 7L/h E: 0.05 BE: minor CAT: 4	*Rare:* liver function disturbances, jaundice, steatosis of the liver [71, 87].	gastrointestinal disturbances, esophageal ulcerations, discoloration of teeth, intestinal overgrowth by non-susceptible organisms, decreased plasma prothrombin activity, neuromuscular blockade, increase in BUN, benign intracranial hypertension, dizziness, convulsions [71, 87, 90]	*Studies:* No clinical studies available in patients with liver disease. *Product information*: Caution in patients with liver disease [87]. *Recommendation:* According to pharmacokinetic data, no dose adjustment seems necessary in patients with liver disease. Choose normal initial dose and adjust maintenance dose by means of creatinine clearance. Due to the risk for hepatic adverse effects, better alternatives may be chosen.

Tab. 11 (continued)

Drug (route of application)	*Metabolism*	*Kinetic parameters*	*Hepatic ADRs*	*Potentially dose-dependent ADRs*	*Studies, product information, and dose recommendations*
Minocycline (oral)	20% excreted unchanged by the feces. Metabolism to a significant degree to 9-hydroxyminocycline and demethylated derivatives (all inactive) [87, 136].	Q_0: 0.85 $T_{1/2}$: 15h V_d: 1.4L/kg PB: 68% F_{oral}: 95% CL_{sys}: 5L/h E: 0.08 BE: major CAT: 3	*Rare:* liver enzyme elevation, hepatic failure, autoimmune hepatitis, hypersensitivity reaction (with hepatitis), hyperbilirubinemia, macrovesicular steatosis [87, 92, 138].	gastrointestinal disturbances, esophageal ulcerations, vestibular disorders (dizziness, vertigo, ataxia, tinnitus), intestinal overgrowth by non-susceptible organisms, decreased plasma prothrombin activity, benign intracranial hypertension, discoloration of teeth, rise in BUN [65, 87, 90]	*Studies:* Serum $t_{1/2}$ independent of hepatic dysfunction [139]. *Product information*: Contraindicated in patients with severe liver disease. Minocycline is excreted significantly by biliary tract. In the case of cholestatic liver disease, accumulation may occur. Caution in patients with liver dysfunction or if combined with other hepatotoxic drugs [87]. *Recommendation:* According to pharmacokinetic data, start with normal initial dose and reduce maintenance dose by up to 50%. Adjust maintenance dose according to clinical effect and dose-dependent ADRs. Monitor liver function for adverse hepatic reactions. Caution in patients with cholestasis due to significant BE.
Tigecycline (parenteral)	Minor metabolism by glucuronidation, N-acetylation [65, 87].	Q_0: 0.78 $T_{1/2}$: 42h V_d: 8L/kg PB: 80% F_{oral}: n.k. CL_{sys}: 24L/h E: 0.35 BE: major CAT: 2	*Frequent:* elevated AST, ALT, AP, elevated bilirubin. *Occasionally:* liver injury (mainly cholestatic), jaundice. *Post-marketing:* liver insufficiency [71, 87, 140].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, decreased plasma prothrombin activity, pseudotumor cerebri, discoloration of teeth, rise in BUN, QT prolongation, pancreatitis [65, 87, 90]	*Studies:* In patients with liver cirrhosis Child Pugh A, B, and C compared to healthy subjects (CL = 29.8L/h), mean tigecycline CL was 31.2L/h, 22.1L/h, and 13.5L/h, respectively [141]. *Product information*: Pharmacokinetics unchanged in patients with mild liver disease. In patients with moderate or severe liver disease, CL_{sys} prolonged by 25% and 55% and $t_{1/2}$ by 23% and 43%, respectively. No dosage adjustment necessary in patients with mild and moderate liver disease. Reduction of maintenance dose to 25mg/12h recommended in patients with severe liver disease [87]. *Recommendation:* According to pharmacokinetic data and product information, use normal doses in patients with mild and moderate liver disease. In patients with severe liver disease, reduce maintenance dose by 50%. Adjust maintenance dose by means of clinical effect and dose-dependent ADRs. Caution in patients with cholestasis due to significant BE.

Tab. 11 (continued)

Drug (route of application)	*Metabolism*	*Kinetic parameters*	*Hepatic ADRs*	*Potentially dose-dependent ADRs*	*Studies, product information, and dose recommendations*
Beta-lactam antibacterials, penicillins *Penicillins with extended spectrum*					
Amoxicillin (oral, parenteral)	10-25% is metabolized in the liver by hydrolysis of the β-lactam ring to penicilloic acid, which is excreted in the urine. Enterohepatic circulation occurs [87, 90].	Q_0: 0.15 $T_{1/2}$: 1.5h V_d: 0.3L/kg PB: 18% F_{oral}: 89% CL_{sys}: 15L/h E: 0.04 BE: minor CAT: 4	*Rare:* transient elevations of liver enzymes, hyperbilirubinemia, cholestatic liver injury, acute hepatic dysfunction, hepatitis [87, 92].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, crystalluria, neurotoxicity (agitation, anxiety, confusion, convulsions) [65, 87]	*Studies:* A single dose study of combined amoxicillin/clavulanic acid (1000/200mg) in cirrhotic patients showed an increased $t_{1/2}$ of amoxicillin (274 min in ascitic vs. 53 min in non-ascitic subjects) probably due to increased V_d in patients with ascites. However, no dose recommendations were made. Monitoring of patients might be advisable [142]. *Product information*: Monitor liver function during long-term treatment [87]. *Recommendation:* According to pharmacokinetic data, choose normal initial dose and adjust maintenance dose and/or dosage interval according to creatinine clearance. In patients with ascites: adjust initial dose according to body weight and adjust maintenance dose according to creatinine clearane.
Beta-lactamase sensitive penicillins					
Benzyl-penicillin (parenteral)	Mainly renal elimination, but also partially metabolized to inactive benzylpenicilloic acid by hydrolysis of the lactam ring [90].	Q_0: 0.3 $T_{1/2}$: 0.8h V_d: 0.4L/kg PB: 55% F_{oral}: n.k. CL_{sys}: 30L/h E: 0.17 BE: minor CAT: 4	*Rare:* cholestasis and/or hepatitis, elevated AST, often in combination with idiosyncratic reactions [71, 87, 143].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, neurotoxicity (agitation, anxiety, confusion, visual disturbances, convulsions), hematological disturbances (e.g. neutropenia) [87, 90, 93]	*Studies:* After 1g aztreonam i.v. (single dose), $t_{1/2}$ was 1.82 h in healthy volunteers, 6.6 h in cirrhotic patients with ascites, and 8.87 h in patients with cirrhosis, ascites and renal failure [144]. *Product information*: No recommendation provided. *Recommendation:* According to pharmacokinetic data, choose normal initial dose and adjust maintenance dose and/or dosage interval by means of creatinine clearance. In patients with ascites: adjust initial dose according to body weight and adjust maintenance dose according to creatinine clearane.

Tab. 11 (continued)

Drug (route of application)	*Metabolism*	*Kinetic parameters*	*Hepatic ADRs*	*Potentially dose-dependent ADRs*	*Studies, product information, and dose recommendations*
Phenoxy-methyl-penicillin (oral)	Metabolism to phenoxymethylpenicilloic acid and small amounts of 6-amino penicilloic acid; enterohepatic cycling [87, 90].	Q_0: 0.6 $T_{1/2}$: 0.5h V_d: 0.5L/kg PB: 80% F_{oral}: 50% CL_{sys}: 29L/h E: 0.32 BE: minor CAT: 2	*Rare:* transient increase of liver enzymes, hepatotoxic reactions [87].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, neurotoxicity (agitation, anxiety, confusion, visual disturbances, convulsions), encephalopathy [87, 90]	*Studies:* No clinical studies available in patients with liver disease. *Product information*: Generally no dose reduction is necessary in patients with mild to moderate liver insufficiency because of its low toxicity. Caution in patients with severe liver disease. $T_{1/2}$ may be prolonged in patients with severe liver disease and concomitant renal impairment [87]. *Recommendation:* According to pharmacokinetic data and product information, no dose modification seems necessary in patients with liver disease if renal function is normal. Adjust maintenance dose by means of clinical effect and dose-dependent ADRs. In patients with ascites: adjust initial dose according to body weight and choose maintenance dose in the lower range of normal.
Beta-lactamase resistant penicillins					
Flucloxacillin (oral, parenteral)	Mainly renal elimination. Metabolism to active 5-hydroxymethylfloxacillin and inactive penicilloic acid [87].	Q_0: 0.3 $T_{1/2}$: 1h V_d: 0.15L/kg PB: 95% F_{oral}: 55% CL_{sys}: 5L/h E: 0.03 BE: minor CAT: 4	*Rare:* transient increase of liver enzymes, hepatitis, cholestatic liver injury (onset may be delayed, protracted liver dysfunction has been observed following withdrawal of therapy) [71, 87].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, neurotoxicity (convulsions) [87]	*Studies:* No clinical studies available in patients with liver disease. *Product information*: Contraindicated in patients with anamnestic jaundice or liver dysfunction associated with flucloxacillin. The active metabolite contributes up to 10% to the total activity. Due to its possible hepatotoxicity, flucloxacillin should be used with caution in patients with hepatic insufficiency [87]. *Recommendation:* According to pharmacokinetic data, choose normal initial dose and adjust maintenance dose and/or dosage interval by means of creatinine clearance. Monitoring of liver function is recommended. In patients with ascites: Adjust initial dose according to body weight and adjust maintenance dose according to creatinine clearance. Use with caution in patients with hypoalbuminemia due to decreased PB.

Tab. 11 (continued)

Drug (route of application)	*Metabolism*	*Kinetic parameters*	*Hepatic ADRs*	*Potentially dose-dependent ADRs*	*Studies, product information, and dose recommendations*
Combinations of penicillins, incl. beta-lactamase inhibitors					
Amoxicillin / Clavulanic acid (oral, parenteral)	*Amoxicillin:* 10-25% is metabolized in the liver by hydrolysis of the β-lactam ring to penicilloic acid, which is excreted in the urine. Enterohepatic circulation occurs [87, 90]. *Clavulanic acid:* 35-60% metabolized to inactive metabolites [87].	Q_0: 0.15/0.55 $T_{1/2}$: 1.5/1h V_d: 0.3/0.23L/kg PB: 18/25% F_{oral}: 89/70% CL_{sys}: 15/13L/h E: 0.04/0.13 BE: minor/minor CAT: 4/3	*Rare:* transient elevations of liver enzymes, hyperbilirubinemia, cholestatic liver injury (believed to be principally related to clavulanic acid moiety), acute hepatic dysfunction, hepatitis [87, 92].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, crystalluria, neurotoxicity (agitation, anxiety, confusion, convulsions) [65, 87]	*Studies:* A single dose study of combined amoxicillin/clavulanic acid (1000/200mg) in cirrhotic patients showed an increased $t_{1/2}$ of amoxicillin (274 min in ascitic vs. 53 min in non-ascitic subjects) and clavulanic acid (200 min in ascitic vs. 54 min in non-ascitic subjects) probably due to increased V_d in patients with ascites. However, no dose recommendations were made [142]. *Product information*: Contraindicated in patients with anamnestic jaundice or liver dysfunction associated with the combination of amoxicillin/clavulanic acid. Caution in patients with liver disease. Monitor liver function during long-term treatment [87]. *Recommendation:* According to pharmacokinetic data, choose normal initial dose and adjust maintenance dose according to creatinine clearance. In patients with ascites: adjust initial dose according to body weight and adjust maintenance dose according to creatinine clearance.
Piperacillin / Tazobactam (parenteral)	*Piperacillin:* Mainly renal elimination. 10-20% are excreted unchanged into the bile. Some metabolism to desethylpiperacillin (inactive). *Tazobactam:* Mainly renal elimination. Some metabolism to an inactive metabolite [71, 87].	Q_0: 0.3/0.2 $T_{1/2}$: 1/0.7h V_d: 0.2/0.2L/kg PB: 19/23% F_{oral}: n.k. CL_{sys}: 10/22L/h E: 0.06/0.08 BE: minor/minor CAT: 4/4	*Occasionally:* elevated AST, ALT. *Rare:* elevated bilirubin, GGT, AP, hepatitis, cholestatic liver disease [71, 87].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, neurotoxicity (agitation, headache, hallucination, confusion, convulsion), hematological disturbances (e.g. leukopenia, thrombocytopenia) [65, 87, 90]	*Studies: Piperacillin:* Plasma $t_{1/2}$ of piperacillin was prolonged in cirrhotic patients compared to controls and even longer in those with ascites (1.95h vs. 0.91h; $p<0.01$) [145]. All patients had normal creatinine values. Total body CL was reduced in cirrhotics (not statistically significant). Mean V_d was similar in both groups. *Tazobactam:* No clinical studies available in patients with liver disease. *Product information*: The excretion of piperacillin/tazobactam is decreased in patients with liver dysfunction, but no dose reduction is necessary [87]. *Recommendation:* According to pharmacokinetic data, choose normal initial dose and adjust dose according to creatinine clearance. In patients with ascites: adjust initial dose according to body weight and adjust maintenance dose according to creatinine clearance.

Tab. 11 (continued)

Drug (route of application)	*Metabolism*	*Kinetic parameters*	*Hepatic ADRs*	*Potentially dose-dependent ADRs*	*Studies, product information, and dose recommendations*
Other beta-lactam antibacterials *First-generation cephalosporins*					
Cefazolin (parenteral)	80-100% is excreted unchanged in the urine [87].	Q_0: 0.06 $T_{1/2}$: 2h V_d: 0.13L/kg PB: 80% F_{oral}: n.k. CL_{sys}: 3L/h E: 0.01 BE: minor CAT: 4	*Occasionally:* elevation of liver enzymes and bilirubin. *Rare:* hepatitis, cholestatic jaundice [71, 87].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, neurotoxicity (agitation, confusion, seizures), encephalopathy [90, 93]	*Studies:* Elimination $t_{1/2}$ of cefazolin was significantly shorter (1.82h vs. 2.57h) and plasma PB of cefazolin was significantly reduced by 18.4% in cirrhosis compared to healthy volunteers. No dose reduction is necessary in severe hepatic impairment [146]. In patients with obstructive biliary disease, cefazoline bile levels are considerably lower than serum levels (<1.0 µg/mL) [71]. *Product information*: No dose recommendations provided. Cefazoline can cause coagulation disorders, monitor quick values in patients with an elevated risk for bleedings (e.g. liver disease) [87]. *Recommendation:* According to pharmacokinetic data, choose normal initial dose and adjust maintenance dose and/or dosage interval by means of creatinine clearance. In patients with ascites: adjust initial dose according to body weight and adjust maintenance dose according to creatinine clearance.
Second-generation cephalosporins					
Cefuroxime (oral, parenteral)	After p.o. application, cefuroxime axetil (prodrug) is hydrolyzed in the intestine to cefuroxime. Cefuroxime is mainly renally eliminated [71, 87, 90]. The pharmacokinetic data refer to cefuroxime.	Q_0: 0.1 $T_{1/2}$: 1.5h V_d: 0.2L/kg PB: 33% F_{oral}: 50% CL_{sys}: 25L/h E: 0.05 BE: minor CAT: 4	*Frequent:* increase in ALT, AST. *Occasionally:* increase in AP and bilirubin. *Rare:* hepatitis, cholestatic jaundice [71, 87].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, neurotoxicity (headache, dizziness, seizures) [65, 87, 90, 93]	*Studies:* Pharmacokinetics were not affected in cirrhotic patients without ascites compared to healthy volunteers [147]. *Product information*: Monitor hemogram, liver and renal function during long-term treatment [87]. *Recommendation:* According to pharmacokinetic data, choose normal initial dose and adjust maintenance dose and/or dosage interval by means of creatinine clearance. In patients with ascites: adjust initial dose according to body weight and adjust maintenance dose according to creatinine clearance.

Tab. 11 (continued)

Drug (route of application)	*Metabolism*	*Kinetic parameters*	*Hepatic ADRs*	*Potentially dose-dependent ADRs*	*Studies, product information, and dose recommendations*
Cefamandole (parenteral)	No metabolism occurs. Mainly renal elimination [87, 90].	Q_0: 0.04 $T_{1/2}$: 0.9h V_d: 0.24L/kg PB: 70% F_{oral}: n.k. CL_{sys}: 10L/h E: 0.01 BE: minor CAT: 4	*Unknown frequency:* liver enzyme elevations (ALT, AST, AP), increase in bilirubin, hepatitis, cholestatic jaundice [71, 87].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, neurotoxicity (agitation, confusion, seizures), encephalopathy [87, 90, 93]	*Studies:* No clinical studies available in patients with liver disease. *Product information*: In case of treatment with cefamandole 50mg/kg over a few days, liver and renal function should be monitored, as well as hemogram [87]. *Recommendation:* According to pharmacokinetic data, choose normal initial dose and adjust maintenance dose and/or dosage interval by means of creatinine clearance. In patients with ascites: adjust initial dose according to body weight and adjust maintenance dose according to creatinine clearance.
Cefaclor (oral)	Mainly renal elimination. Up to 15% are metabolized or otherwise degraded [87, 90].	Q_0: 0.25 $T_{1/2}$: 0.75h V_d: 0.35L/kg PB: 25% F_{oral}: 95% CL_{sys}: 30L/h E: 0.14 BE: minor CAT: 4	*Occasionally:* liver enzyme elevations (AST, ALT, AP). *Rare:* hepatitis, cholestatic liver injury with jaundice [71, 87].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, neurotoxicity (agitation, confusion, seizures) [87, 90, 93]	*Studies:* No clinical studies available in patients with liver disease. *Product information*: Monitor hemogram, liver and renal function during long-term treatment [87]. *Recommendation:* According to pharmacokinetic data, choose normal initial dose and adjust maintenance dose by means of creatinine clearance. In patients with ascites: adjust initial dose according to body weight and adjust maintenance dose according to creatinine clearance.
Cefprozil (oral)	Mainly renal elimination [71, 87, 90].	Q_0: 0.35 $T_{1/2}$: 1.3h V_d: 0.23L/kg PB: 36% F_{oral}: 90% CL_{sys}: 12.6L/h E: 0.08 BE: minor CAT: 4	*Frequent:* increased ALT, AST. *Occasionally:* increase of AP. *Rare:* increase of bilirubin, cholestatic jaundice [71, 87]. *Case report:* hepatitis [148].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, neurotoxicity (headache, dizziness, confusion) [87, 90]	*Studies:* Beside a moderate prolongation of elimination $t_{1/2}$ of cefprozil (27-37%), no statistically significant difference was observed between subjects with hepatic impairment and healthy volunteers [149]. *Product information:* The pharmacokinetics are not significantly affected in the presence of hepatic impairment. No dosage adjustment is required in patients with hepatic dysfunction [87]. *Recommendation:* According to pharmacokinetic data, choose normal initial dose and adjust maintenance dose by means of creatinine clearance. In patients with ascites: adjust initial dose according to body weight and adjust maintenance dose according to creatinine clearance.

Tab. 11 (continued)

Drug (route of application)	*Metabolism*	*Kinetic parameters*	*Hepatic ADRs*	*Potentially dose-dependent ADRs*	*Studies, product information, and dose recommendations*
Third-generation cephalosporins					
Ceftazidime (parenteral)	Mainly renal elimination [87, 90].	Q_0: 0.1 $T_{1/2}$: 1.8h V_d: 0.23L/kg PB: 10% F_{oral}: n.k. CL_{sys}: 6.9L/h E: 0.01 BE: minor CAT: 4	*Frequent:* liver enzyme elevations (ALT, AST, GGT, AP). *Rare:* increase of bilirubin, jaundice.[65, 71, 87].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, neurotoxicity (headache, dizziness, paresthesia, seizures, myoclonia), encephalopathy [65, 87, 90]	*Studies:* In a single dose study of 1g i.v. in patients with cirrhosis and ascites, $t_{1/2}$ was significantly prolonged probably due to slow return from the ascitic compartment. Nevertheless, the overall CL did not differ significantly [150]. Hepatic dysfunction had no effect on the pharmacokinetics of ceftazidime in individuals administered 2 g i.v. every 8 hours for 5 days [65]. *Product information*: Dose adjustment is not necessary in patients with hepatic dysfunction, provided renal function is not impaired [65]. *Recommendation:* According to pharmacokinetic data, choose normal initial dose and adjust maintenance dose and/or dosage interval by means of creatinine clearance. In patients with ascites: adjust initial dose according to body weight and adjust maintenance dose according to creatinine clearance.
Ceftriaxone (parenteral)	40-50% are excreted unchanged in the bile, where it is metabo-lized by the intestinal flora into inactive metabolites [87, 90].	Q_0: 0.5 $T_{1/2}$: 8h V_d: 0.14L/kg PB: 90% F_{oral}: n.k. CL_{sys}: 1L/h E: 0.01 BE: minor CAT: 3 Non-linear pharmaco-kinetics	*Frequent:* liver enzyme elevations (AST, ALT, AP), precipitation of calcium salts in the gallbladder (children), reversible cholelithiasis (children), increased bilirubin. *Rare:* jaundice, reversible biliary pseudolithiasis, gallbladder sludge [65, 87, 90, 151].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, neurotoxicity (headache, dizziness, seizures), biliary pseudolithiasis, nephrolithiasis [65, 87, 90]	*Studies:* In patients with chronic liver damage (alcoholic fatty liver, cirrhosis with and without ascites), pharmacokinetics were similar to healthy subjects after 1g ceftriaxone (single dose). V_d was significantly increased in cirrhotics with ascites, but $t_{1/2}$ was not different, probably because of lower PB [152-155]. Similar results were seen in another study [156]. One study showed increase in f_u up to 320% in patients with cirrhosis and ascites compared to healthy controls [154]. Due to the wide therapeutic range, no dose adjustment is necessary in chronic liver disease [154], but indicated in patients with concomitant renal and hepatic impairment [153, 157]. *Product information*: In patients with impaired hepatic function, pharmacokinetics of ceftriaxone are minimally altered. Renal route of elimination may increase. Thus, no dose adjustment is necessary provided that renal function is normal [87]. *Recommendation:* According to pharmacokinetic data and clinical studies, dosage adjustment is only needed in patients with concomitant liver and renal impairment. In patients with ascites: adjust initial dose according to body weight and choose maintenance dose in the lower range of normal.

Tab. 11 (continued)

Drug (route of application)	*Metabolism*	*Kinetic parameters*	*Hepatic ADRs*	*Potentially dose-dependent ADRs*	*Studies, product information, and dose recommendations*
Cefixime (oral)	No metabolic pathways have yet been identified [87, 90].	Q_0: 0.5 $T_{1/2}$: 3.5h V_d: 0.24L/kg PB: 65% F_{oral}: 45% CL_{sys}: 5.5L/h E: 0.05 BE: minor CAT: 3	*Rare:* mild and transient elevations in liver enzymes, hepatitis, cholestatic jaundice [87, 92].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, neurotoxicity (headache, dizziness, agitation) [87, 90, 93]	*Studies:* In a single dose study with 200mg in patients with moderate to severe cirrhosis, $t_{1/2}$ was significantly increased (6.4h) due to an increased V_d. Renal CL (+43%) was also increased significantly (possibly because of reduced extra-renal CL), AUC and C_{max} remained unchanged. Despite a twofold increase in $t_{1/2}$, modification of kinetics was judged as modest. No dose adjustment was considered necessary in patients with moderate to severe cirrhosis [45, 158]. *Product information*: Citation of the same results as reported in clinical studies [87]. *Recommendation:* According to pharmacokinetic data and clinical studies, start with normal initial dose. Reduce maintenance dose by up to 50%. Adjust maintenance dose according to clinical effect and dose-dependent ADRs. In patients with ascites: adjust initial dose according to body weight and choose maintenance dose in the lower range of normal.
Cefpodoxime (oral)	Cefpodoxime proxetil is a prodrug and hydrolyzed presystemically in the small intestine to the active cefpodoxime. Cefpodoxime is mainly renally eliminated [71, 87, 90]. The kinetic data refer to cefpodoxime.	Q_0: 0.2 $T_{1/2}$: 2.4h V_d: 0.45L/kg PB: 25% F_{oral}: 50% CL_{sys}: 14.4L/h E: 0.05 BE: minor CAT: 4	*Occasionally:* moderate and transient increase in AST, ALT, AP. *Rare:* elevated bilirubin [87].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, neurotoxicity (headache, dizziness, tinnitus, paresthesia), asthenia [87, 90, 93]	*Studies:* Pharmacokinetics in cirrhotic patients are only minimally altered [87]. No effect of ascites on the pharmacokinetics of the drug [90]. *Product information*: Dosage adjustment is not necessary in cirrhotic patients [87]. *Recommendation:* According to pharmacokinetic data, choose normal initial dose and adjust maintenance dose and/or dosage interval by means of creatinine clearance. In patients with ascites: adjust initial dose according to body weight and adjust maintenance dose according to creatinine clearance.

Tab. 11 (continued)

Drug (route of application)	*Metabolism*	*Kinetic parameters*	*Hepatic ADRs*	*Potentially dose-dependent ADRs*	*Studies, product information, and dose recommendations*
Ceftibuten (oral)	Mainly renal elimination [71, 87, 159]. The trans isomer is also active.	Q_0: 0.25 $T_{1/2}$: 2.5h V_d: 0.21L/kg PB: 65% F_{oral}: 90% CL_{sys}: 4.6L/h E: 0.03 BE: minor CAT: 4	*Occasionally:* elevated liver enzymes and bilirubin. *Case reports:* jaundice [71, 87].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, neurotoxicity (dizziness, paresthesia, seizure) [87, 93]	*Studies:* The pharmacokinetics do not change significantly in patients with chronic active hepatitis, liver cirrhosis, alcoholic hepatopathy, or other necrotic liver diseases [87]. *Product information*: No recommendation provided. *Recommendation:* According to pharmacokinetic data, choose normal initial dose and adjust maintenance dose or dosage interval by means of creatinine clearance. In patients with ascites: adjust initial dose according to body weight and adjust maintenance dose according to creatinine clearance.
Fourth-generation cephalosporins					
Cefepime (parenteral)	Mainly renal elimination. 7% is metabolized to methyl-pyrrolidine oxide (tertiary amine) [71, 87].	Q_0: 0.2 $T_{1/2}$: 2h V_d: 0.26L/kg PB: 16% F_{oral}: n.k. CL_{sys}: 7.2L/h E: 0.03 BE: minor CAT: 4	*Frequent:* increases in liver enzymes and bilirubin [71, 87].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, neurotoxicity (blurred vision, tinnitus, paresthesia, seizures), encephalopathy [65, 87]	*Studies:* Pharmacokinetics of cefepime were unaltered in patients with impaired hepatic function who received a single 1 g dose (n=11) [87]. *Product information*: No dosage adjustments are necessary for patients with hepatic dysfunction in case of normal renal function [87]. *Recommendation:* According to pharmacokinetic data, choose normal initial dose and adjust maintenance dose and/or dosage interval by means of creatinine clearance. In patients with ascites: adjust initial dose according to body weight and adjust maintenance dose according to creatinine clearance.

Tab. 11 (continued)

Drug (route of application)	*Metabolism*	*Kinetic parameters*	*Hepatic ADRs*	*Potentially dose-dependent ADRs*	*Studies, product information, and dose recommendations*
Monobactams					
Aztreonam (parenteral)	About 20% are metabolized in the liver by hydrolytic opening of the β-lactam ring [87, 90, 160].	Q_0: 0.2 $T_{1/2}$: 1.7h V_d: 0.18L/kg PB: 56% F_{oral}: n.k. CL_{sys}: 5.5L/h E: 0.02 BE: minor CAT: 4	*Frequent:* elevations of liver enzymes and bilirubin. *Rare:* hepatitis, jaundice [71, 87].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, neurotoxicity (headache, dizziness, paresthesia, seizures) [87, 90, 93]	*Studies:* After 1g aztreonam i.v. (single dose), $t_{1/2}$ was 1.82 h in healthy volunteers, 6.6 h in cirrhotic patients with ascites, and 8.87 h in patients with cirrhosis, ascites and renal failure [144]. $T_{1/2}$ was significantly longer (+68%) and serum CL decreased (-27%) in alcoholic cirrhotics compared to normal subjects [161]. Patients with primary biliary cirrhosis had only a longer $t_{1/2}$ (+16%). *Product information:* Dose reduction of 20-25% recommended during long-term therapy in patients with alcoholic cirrhosis. For patients with stable biliary tract cirrhosis or other chronic liver disease, dose adjustment is not necessary, provided that renal function is normal [87]. In patients with hepatic impairment monitoring of liver function is recommended [87, 90] *Recommendation:* According to pharmacokinetic data and clinical studies, choose normal initial dose and adjust maintenance dose by means of creatinine clearance. For patients with alcoholic cirrhosis, see Swiss product information. In patients with ascites: adjust initial dose according to body weight and adjust maintenance dose according to creatinine clearance.
Carbapenems					
Meropenem (parenteral)	25% are metabolized by dehydro-peptidase-I to an inactive derivative [71, 87, 162].	Q_0: 0.3 $T_{1/2}$: 1h V_d: 0.3L/kg PB: 2% F_{oral}: n.k. CL_{sys}: 16.8L/h E: 0.09 BE: minor CAT: 4	*Frequent:* liver enzyme elevations (ALT, AST, AP, GGT). *Occasionally:* increased bilirubin. *Rare:* cholestatic jaundice [71, 87].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, neurotoxicity (headache, paresthesia, seizures) [65, 87, 90]	*Studies:* No difference in pharmacokinetics were found between subjects with stable alcoholic cirrhosis and eight matched controls with normal liver function [163]. *Product information:* A pharmacokinetic study in patients with hepatic impairment has shown no effects of liver disease on the pharmacokinetics of meropenem. No dosage adjustment is needed in patients with liver impairment. Monitor liver function regularly in patients with liver disease [87]. *Recommendation:* According to pharmacokinetic data and clinical studies, choose normal initial dose and adjust maintenance dose and/or dosage interval by means of creatinine clearance. In patients with ascites: adjust initial dose according to body weight and adjust maintenance dose according to creatinine clearance.

Tab. 11 (continued)

Drug (route of application)	*Metabolism*	*Kinetic parameters*	*Hepatic ADRs*	*Potentially dose-dependent ADRs*	*Studies, product information, and dose recommendations*
Ertapenem (parenteral)	Hydrolysis by the renal dehydropeptidase enzyme [71, 87]. About 10% of a dose excreted into the feces.	Q_0: 0.6 $T_{1/2}$: 4h V_d: 0.12L/kg PB: 90% F_{oral}: n.k. CL_{sys}: 1.8L/h E: 0.02 BE: minor CAT: 3	*Frequent:* elevated ALT, AST, AP. *Occasionally:* elevated bilirubin. *Rare:* cholecystitis, jaundice, elevated urobilinogen [71, 87].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, confusion, hallucination, dizziness, tremor, seizure [71, 87]	*Studies:* No clinical studies available in patients with liver disease. *Product information:* No studies available. However, because metabolism in the liver seems negligible, no major change in pharmacokinetics is expected in patients with liver disease. No dose adjustment required in patients with impaired liver function [87]. *Recommendation:* According to pharmacokinetic data, start with normal initial dose and reduce maintenance dose by up to 50%. Adjust maintenance dose according to clinical effect and dose-dependent ADRs. In patients with ascites: adjust initial dose according to body weight and choose maintenance dose in the lower range of normal.
Doripenem (parenteral)	Dehydropeptidase I [71, 87].	Q_0: 0.3 $T_{1/2}$: 1h V_d: 0.24L/kg PB: 8.1% F_{oral}: n.k. CL_{sys}: 15.9L/h E: 0.09 BE: minor CAT: 4	*Frequent:* elevated liver enzymes [71, 87].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, neurotoxicity (headache seizures), rash [87, 164]	*Studies:* No clinical studies available in patients with liver disease. *Product information:* No studies available. Since there is no evidence for hepatic metabolism of doripenem, liver insufficiency is not expected to influence the drugs pharmacokinetics. No dosage adjustment is necessary [87]. *Recommendation*: According to pharmacokinetic data and clinical results, monitor creatinine clearance and adjust dose accordingly. In patients with ascites: adjust initial dose according to body weight and adjust maintenance dose according to creatinine clearance.

Tab. 11 (continued)

Drug (route of application)	*Metabolism*	*Kinetic parameters*	*Hepatic ADRs*	*Potentially dose-dependent ADRs*	*Studies, product information, and dose recommendations*
Imipenem / Cilastatin (parenteral)	*Imipenem:* Imipenem would be extensively metabolized in the kidney by the dehydropeptidase-1 if administered without cilastatin, a dehydropeptidase-1-inhibitor. *Cilastatin:* 10% metabolized to active N-acetyl metabolite [71, 87].	Q_0: 0.3/0.3 $T_{1/2}$: 1/0.9h V_d: 0.2/0.2L/kg PB: 20/15% F_{oral}: n.k. CL_{sys}: 12/12L/h E: 0.07/0.07 BE: minor CAT: 4/4	*Frequent:* elevated ALT, AST, AP. *Occasionally:* elevated bilirubin. *Rare:* jaundice, hepatitis, liver failure [71, 87].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, neurotoxicity (dizziness, paresthesia, hallucinations, confusion, seizures), encephalopathy [65, 87, 90]	*Studies:* No clinical studies available in patients with liver disease. *Product information:* Monitoring of hematopoietic, renal and hepatic function recommended during long-term treatment. No dose recommendations provided [87]. *Recommendation*: According to pharmacokinetic data, monitor creatinine clearance and adjust dose accordingly. In patients with ascites: adjust initial dose according to body weight and adjust maintenance dose according to creatinine clearance.
Sulfonamides and trimethoprim *Combinations of sulfonamides and trimethoprim, incl. derivatives*					
Sulfamethoxazole / Trimethoprim (oral, parenteral)	*Sulfamethoxazole:* N-acetylation (N-acetylsulfamethoxazole) and glucuronidation. *Trimethoprim:* Metabolism to 1- and 3- oxides, 3'- and 4'-hydroxyderivatives (active) [87, 90].	Q_0: 0.8/0.45 $T_{1/2}$: 11/10h V_d: 0.2/1.3L/kg PB: 66/46% F_{oral}: 90/90% CL_{sys}: 1.2/6L/h E: 0.02/0.05 BE: minor/minor CAT: 3/4	*Rare:* liver necrosis, elevated liver enzymes, hepatitis, hyperbilirubinemia, cholestasis, jaundice, vanishing bile duct syndrome [87, 165].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, neurotoxicity (headache, dizziness, ataxia, convulsions, vertigo, tinnitus, hallucinations), crystalluria, hypoglycemia, hypokalemia, folate deficiency, hematological disturbances (leukopenia, agranulocytosis, thrombocytopenia) [65, 87, 90]	*Studies:* In patients with alcoholic liver cirrhosis (incl. Child C) no significant difference in pharmacokinetics was observed after a single dose of 800mg sulfamethoxazole (SMX)/160mg trimethoprim (TMP) compared to healthy subjects. Sporadic increases of $t_{1/2}$ of TMP up to 2-fold have been observed in cirrhotics, but also in healthy subjects. No dose adjustment was considered necessary [166]. After multiple doses (800mg SMX/160mg TMP every 12 hours for 7 days) differences in kinetics disappeared after the third day of administration, suggesting that no dose adjustment is required [167]. *Product information:* Contraindicated in patients with marked parenchymal liver injury. Risk for severe adverse effects may be increased in patients with liver disease. Caution with high doses in patients with severe hepatic insufficiency, even though kinetics are not considerably altered [87]. *Recommendation:* According to pharmacokinetic data and clinical studies, no dose adjustment seems necessary in patients with liver cirrhosis. Caution in patients with severe liver disease.

Tab. 11 (continued)

Drug (route of application)	*Metabolism*	*Kinetic parameters*	*Hepatic ADRs*	*Potentially dose-dependent ADRs*	*Studies, product information, and dose recommendations*
Macrolides, lincosamides and streptogramins *Macrolides*					
Erythromycin (oral, parenteral)	Inactivation by N-demethylation by CYP 3A to des-N-methyl-erythromycin. Enterohepatic cycling [87, 90].	Q_0: 0.9 $T_{1/2}$: 1.5h V_d: 1.1L/kg PB: 60% F_{oral}: 40% CL_{sys}: 26L/h E: 0.41 BE: major CAT: 2	*Rare:* cholestatic hepatitis, jaundice (10-14 days after the start of treatment), associated with raised AST/ALT levels and eosinophilia [87, 90].	gastrointestinal disturbances, increased gut motility, intestinal overgrowth by non-susceptible organisms, ototoxicity, convulsions, paresthesia, ataxia, psychosis, cholestatic jaundice, arrhythmia (QT-prolongation, torsades de pointes), aggravation of myasthenia gravis [65, 87, 90, 93]	*Studies:* AUC and C_{max} were higher (no significance) and $t_{1/2}$ significantly longer (3.2h vs. 2h) in patients with alcoholic liver disease compared to normal subjects [168, 169]. Clinical significance unknown. In patients with alcoholic cirrhosis (Child B and C), f_u (58.3% vs. 30.5%; due to decreased levels of alpha1-acid glycoprotein) and V_d (86L vs. 58L) were significantly increased, CL of unbound erythromycin was significantly reduced (42.2L/h vs. 113.2L/h) [170]. Because of a large therapeutic index of erythromycin, dosage adjustment probably not necessary. *Product information:* Contraindicated in patients with severe liver insufficiency. Use with caution in patients with impaired hepatic function. Maximal daily dose 1g in patients with liver insufficiency. Monitoring for oto- and hepatotoxic adverse effects [87]. *Recommendation:* According to product information, reduce maximal daily dose to 1g and adjust maintenance dose according to clinical effect and dose-dependent ADRs. Caution in patients with cholestasis.
Clarithromycin (oral, parenteral)	N-demethylation, hydroxylation to 14-hydroxy-clarithromycin (active; Q_0 0.9, $t_{1/2}$ 5.5h). Substrate of CYP P450 3A4 [87, 90].	Q_0: 0.65 $T_{1/2}$: 3.5h V_d: 3L/kg PB: 72% F_{oral}: 55% CL_{sys}: 37L/h E: 0.45 BE: minor CAT: 2 Non-linear elimination	*Frequent:* elevated AST, ALT. *Rare:* hepatocellular and/or cholestatic hepatitis, with or without jaundice, liver failure [87, 90, 92].	gastrointestinal disturbances, taste perversion, intestinal overgrowth by non-susceptible organisms, ototoxicity, neurotoxicity (headache, dizziness, convulsions, hallucinations, paresthesia, ataxia), arrhythmias (QT-prolongation, torsades de pointes), cholestatic hepatitis [65, 87, 90]	*Studies:* No differences in pharmacokinetics of clarithromycin observed in cirrhotic patients (Child A, B and C) compared to healthy controls [171-173], but AUC of 14-(R)-hydroxyclarithromycin was significantly lower in patients with severe liver cirrhosis [171, 172]. Caution if the hydroxy-metabolite is necessary for antimicrobial activity (e.g. haemophilus influenzae) [172, 174]. *Product information:* No changes in kinetics observed in patients with mild liver disease. Concentration of the active metabolite was generally lower in these patients. Because of its high hepatic metabolism, monitoring of patients with severe liver disease is recommended [87]. No dosage adjustment necessary in the presence of hepatic impairment in case of normal renal function [65] *Recommendation*: According to clinical studies, normal initial dose can be used in patients with liver disease. Adjust maintenance dose by means of clinical effect and dose-dependent ADRs.

Tab. 11 (continued)

Drug (route of application)	*Metabolism*	*Kinetic parameters*	*Hepatic ADRs*	*Potentially dose-dependent ADRs*	*Studies, product information, and dose recommendations*
Spiramycin → CAT1, see Tab. 4, p. 35 Azithromycin → CAT1, see Tab. 4, p. 35					
Lincosamides					
Clindamycin (oral, parenteral)	N-demethylation, sulfoxidation (by CYP 3A4), hydrolysis to some active metabolites [87, 90, 175].	Q_0: 0.9 $T_{1/2}$: 2.5h V_d: 0.85L/kg PB: 65% F_{oral}: 90% CL_{sys}: 12L/h E: 0.2 BE: major CAT: 3	*Frequent:* 40-50% of patients develop elevated liver enzymes which may return to normal despite continuation of the treatment. *Occasionally*: jaundice. *Rare*: hepatocellular toxicity, exacerbation of pre-existing liver disease [87, 92, 176].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, hypotension, cardiac arrest (after too rapid injection), liver enzyme elevations, jaundice [87, 90]	*Studies:* Studies revealed 1.2-5 fold increase in $t_{1/2}$ in patients with severe liver disease (hepatitis, cirrhosis, obstructive jaundice) [177, 178], one study only in cirrhotics but not in those with hepatitis [179]. Concentration after 5h was 3 times higher in patients with moderate to severe hepatic dysfunction compared to normal controls [180]. Positive correlation between $t_{1/2}$, serum concentration and AST [177, 178, 180] or indirect bilirubin [181] found in some reports, but not in others [179, 181]. Monitoring of drug level and liver function recommended [179]. *Product information:* $T_{1/2}$ is increased in patients with severe liver dysfunction, but dose adjustment not necessary in patients with mild and moderate liver disease. Use with caution and monitor clindamycin levels in case of high dose regimen [87]. *Recommendation:* According to pharmacokinetic data, start with normal initial dose and reduce maintenance dose by up to 50%. Adjust maintenance dose according to clinical effect and dose-dependent ADRs. Monitoring of liver function recommended. Caution in patients with cholestasis.

Tab. 11 (continued)

Drug (route of application)	Metabolism	Kinetic parameters	*Hepatic ADRs*	Potentially dose-dependent ADRs	*Studies, product information, and dose recommendations*
Aminoglycoside antibacterials *Other aminoglycosides*					
Tobramycin (inhalative, parenteral)	Mainly renal elimination [87].	Q_0: 0.02 $T_{1/2}$: 2.5h V_d: 0.25L/kg PB: 10% F_{oral}: n.k. CL_{sys}: 5.6L/h E: 0.01 BE: minor CAT: 4	*Occasionally:* increased liver enzymes (ALT, AST, AP) and bilirubin [71, 87].	ototoxicity, vestibular toxicity, neurotoxicity (paresthesia, convulsions), lethargy, confusion, neuromuscular blockade (aggravation of myasthenia gravis, postoperative respiratory distress), nephrotoxicity [87, 90, 93]	*Studies:* While no significant effect was observed for CL and $t_{1/2}$ in cirrhotics, V_d was significantly larger when ascites was present (0.32 vs. 0.26 L/kg) [182]. *Product information:* No studies in patients with liver disease. Since minor metabolism of tobramycin occurs, liver disease is not expected to have an impact on tobramycin exposure [87]. *Recommendation:* Aminoglycosides are considered contraindicated in liver cirrhosis. If no other possibilities exist, use weight-adapted initial dose and adjust maintenance dose by therapeutic drug monitoring. Monitor renal function.
Gentamicin (parenteral, sponge)	Mainly renal elimination [71, 87].	Q_0: 0.1 $T_{1/2}$: 2h V_d: 0.25L/kg PB: 30% $F_{oral:}$ 0.2% CL_{sys}: 4L/h E: 0.01 BE: minor CAT: 4	*Occasionally:* elevations of liver enzymes and bilirubin, transient hepatomegaly [87].	ototoxicity, vestibular toxicity, neurotoxicity (hallucinations, encephalopathy, convulsions), pseudotumor cerebri, visual disturbances, neuromuscular blockade (aggravation of myasthenia gravis, postoperative respiratory distress), nephrotoxicity [87, 90, 93]	*Studies:* The $t_{1/2}$ and effect of jaundice on excretion was evaluated in neonates. The presence of icterus or hyperbilirubinemia did not delay excretion in any patient [183]. *Product information:* No specification. *Recommendation:* Aminoglycosides are considered contraindicated in liver cirrhosis. If no other possibilities exist, use weight-adapted initial dose and adjust maintenance dose by therapeutic drug monitoring. Monitor renal function.

Tab. 11 (continued)

Drug (route of application)	Metabolism	Kinetic parameters	*Hepatic ADRs*	Potentially dose-dependent ADRs	*Studies, product information, and dose recommendations*
Amikacin (parenteral)	No metabolism. 90-98% is excreted unchanged in the urine [71, 87].	Q_0: 0.02 $T_{1/2}$: 2h V_d: 0.3L/kg PB: 4% F_{oral}: n.k. CL_{sys}: 6L/h E: 0.01 BE: minor CAT: 4	*Rare:* liver enzyme elevations (ALT, AST, AP), elevated bilirubin, hepatomegaly, hepatic necrosis [71, 87].	ototoxicity, vestibular toxicity, neurotoxicity (convulsions, hallucination, encephalopathy), visual disturbances, neuromuscular blockade (aggravation of myasthenia gravis, postoperative respiratory distress), nephrotoxicity, hypomagnesaemia [87, 93]	*Studies:* No clinical studies available in patients with liver disease. *Product information:* No specification. *Recommendation*: Aminoglycosides are considered contraindicated in liver cirrhosis. If no other possibilities exist, use weight-adapted initial dose and adjust maintenance dose by therapeutic drug monitoring. Monitor renal function.
Quinolone antibacterials *Fluoroquinolones*					
Ofloxacin (oral, parenteral)	Less than 10% is metabolized by glucuronidation, demethylation and N-oxidation to inactive metabolites [90].	Q_0: 0.1 $T_{1/2}$: 6h V_d: 1.6L/kg PB: 25% F_{oral}: 95% CL_{sys}: 16L/h E: 0.07 BE: minor CAT: 4	*Rare:* elevations of liver enzymes and bilirubin, cholestatic jaundice, hepatitis, severe liver injury [71, 87].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, neurotoxicity (dizziness, confusion, insomnia, seizures, hearing disturbances, visual disturbances, paresthesias), depression, psychotic reaction, hallucination, tremor, tendinitis [87, 90, 93]	*Studies:* $T_{1/2}$ and V_d were significantly increased by 55% and 33%, respectively, in cirrhotic patients (Child A) compared to controls [185]. A reduction in renal CL was observed (32%; not significant), although renal function was apparently normal. $T_{1/2}$ was also increased by 66% in another study, probably related to impairment of tubular secretion [186]. No dose adjustment seems necessary in patients with cirrhosis and ascites [187]. *Product information:* A dose of 400 mg per day should not be exceeded in patients with severe liver function disorders such as cirrhosis with ascites. The excretion of ofloxacin in these patients may be reduced [87]. *Recommendation:* Based on pharmacokinetic data, use normal initial dose and adjust maintenance dose and/or dosage interval according to creatinine clearance. Maximum dose of 400 mg daily is recommended.

Tab. 11 (continued)

Drug (route of application)	Metabolism	Kinetic parameters	*Hepatic ADRs*	Potentially dose-dependent ADRs	*Studies, product information, and dose recommendations*
Ciprofloxacin (oral, parenteral)	About 16% are eliminated unchanged by the feces, enterohepatic circulation has been suggested. Metabolism to active and inactive metabolites [65, 87, 90].	Q_0: 0.4 $T_{1/2}$: 4h V_d: 2.5L/kg PB: 25% F_{oral}: 75% CL_{sys}: 30L/h E: 0.22 BE: minor CAT: 4	*Occasionally:* elevated liver enzymes and bilirubin. *Rare:* hepatic necrosis, hepatitis, cholestatic jaundice [71, 87, 90, 92].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, neurotoxicity (dizziness, tremor, confusion, hallucinations, seizures), depression, psychotic reaction, vision and hearing disturbances [65, 87, 90]	*Studies:* Various studies showed no difference in pharmacokinetics between patients with liver cirrhosis (Child A, B and C) and healthy controls [188, 189], except one study [190]. Patients with Child C had higher C_{max}, $t_{1/2}$ and AUC. In one study, significant smaller quantities of oxociprofloxacin were found, probably due to decreased hepatic metabolism [191]. Pharmacokinetics were impaired in cirrhotics with moderate renal insufficiency [189]. Administration at usual doses in cirrhotics with normal renal function seems safe [188, 189, 191]. *Product information:* In patients with liver disease, elimination of ciprofloxacin is only minimally altered. According to its metabolism, accumulation in patients with liver disease seems unlikely. Dose adjustment is not necessary, provided that renal function is normal [87]. *Recommendation*: According to pharmacokinetic data and clinical studies, use normal initial dose and adjust maintenance dose according to creatinine clearance. Clinical monitoring recommended.
Norfloxacin (oral)	Metabolites derived from chemical substitutions on the piperazine ring and glucuronidation. Main metabolite oxo-piperazine. Active metabolites with less antimicrobial potency than norfloxacin. A possible first pass effect and enterohepatic circulation is discussed [71, 87, 90, 192].	Q_0: 0.7 $T_{1/2}$: 3.5h V_d: 2.8L/kg PB: 12.5% F_{oral}: 35% CL_{sys}: n.k. E: n.k. BE: minor CAT: 5	*Frequent:* elevated liver enzymes. *Rare:* hepatocellular injury, cholestatic jaundice, hepatitis, hepatic failure (including fatalities) [71, 87, 90, 92].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, neurotoxicity (dizziness, confusion, insomnia, seizures, hearing disturbances, visual disturbances, paresthesias), depression, hallucination, psychotic reactions, crystalluria, tendinitis [65, 87, 90]	*Studies:* A single dose study (400mg) has reported that serum $t_{1/2}$ and AUC were only slightly and not significantly altered in patients with moderate hepatic dysfunction (patients recovering from acute HBV infection) [193]. It is uncertain whether or not the liver is a major site of excretion of norfloxacin [192, 194]. No dose adjustment is probably necessary for patients with mild to moderate hepatic insufficiency. In cirrhotics norfloxacin may be indicated as prophylaxis of spontaneous bacterial peritonitis at a dose of 400mg once or twice daily in cirrhotic patients with gastrointestinal bleeding [195]. *Product information:* No information provided. *Recommendation:* No specific dosage recommendations can be made due to lack of pharmacokinetic data. However, dose of 400mg up to twice daily is used for prophylaxis of spontaneous bacterial peritonitis in cirrhotics [195].

Tab. 11 (continued)

Drug (route of application)	Metabolism	Kinetic parameters	*Hepatic ADRs*	Potentially dose-dependent ADRs	*Studies, product information, and dose recommendations*
Levofloxacin (oral, parenteral)	Only minor metabolism to desmethyl-levofloxacin and levofloxacin N-oxide. Less than 4% is excreted into the feces [71, 87].	Q_0: 0.15 $T_{1/2}$: 7h V_d: 1.36L/kg PB: 35% F_{oral}: 99% CL_{sys}: 10.6L/h E: 0.05 BE: minor CAT: 4	*Frequent:* elevations of liver enzymes. *Occasionally:* elevations of serum bilirubin. *Rare:* hepatitis, liver failure, hepatic necrosis, jaundice [71, 87].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, neurotoxicity (dizziness, hearing disturbances, tremors, confusion, seizures, asthenia, visual disturbances), hallucination, depression, torsade de pointes, hypoglycemia, tendinitis [65, 87]	*Studies:* No clinical studies available in patients with liver disease. *Product information:* Due to the limited extent of levofloxacin metabolism, no dosage adjustment is necessary in patients with impaired liver function [87]. *Recommendation*: According to pharmacokinetic data, use normal initial dose and adjust maintenance dose and/or dosage interval according to creatinine clearance.
Moxifloxacin (oral, parenteral)	Liver metabolism does not involve CYP P450 system but phase II metabolism (sulfation, glucuronidation) generating inactive metabolites [87, 196].	Q_0: 0.8 $T_{1/2}$: 12h V_d: 2L/kg PB: 45% F_{oral}: 90% CL_{sys}: 12L/h E: 0.18 BE: major CAT: 3	*Frequent:* elevated ALT, AST. *Occasionally:* increase in other liver enzymes (≤3 ULN). *Rare:* acute liver failure, cholestatic hepatitis, jaundice, hepatic necrosis [71, 87, 197, 198].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, neurotoxicity (dizziness, asthenia, somnolence, confusion, insomnia, seizures, paresthesias, tremors), hallucination, depression, psychotic reaction, tendinitis, torsade de pointes, QT-prolongation [65, 87]	*Studies:* Pharmacokinetics were similar in cirrhotics and healthy subjects [199-201]. AUC of moxifloxacin was 23% lower in cirrhotics (Child A and B), AUC of the sulfo-metabolite was 4 times higher compared to healthy controls [199, 200]. No dose adjustment necessary [199-201]. *Product information:* No significant difference of pharmacokinetics of moxifloxacin in cirrhotics compared to healthy controls. AUC of the sulfo-metabolite was up to 6-fold higher, AUC of the glucuronide metabolite was 1.5-fold higher in cirrhotics Child B compared to healthy subjects. No dose adjustment necessary in patients with mild liver disease. Contraindicated in patients with cirrhosis Child C or transaminase elevations >5 ULN [87]. *Recommendation:* According to pharmacokinetic data and clinical studies, start with normal initial dose and reduce maintenance dose by up to 50%. Adjust maintenance dose according to clinical effect and dose-dependent ADRs. Caution in patients with cholestasis.

Tab. 11 (continued)

Drug (route of application)	Metabolism	Kinetic parameters	*Hepatic ADRs*	Potentially dose-dependent ADRs	*Studies, product information, and dose recommendations*
Other antibacterials *Glycopeptide antibacterials*					
Vancomycin (oral, parenteral)	Metabolism negligible [87, 90].	Q_0: 0.1 $T_{1/2}$: 5h V_d: 0.6L/kg PB: 50% F_{oral}: 0% CL_{sys}: 4L/h E: 0.01 BE: minor CAT: 4		ototoxicity, nephrotoxicity, gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, neutropenia, agranulocytosis [87, 90, 93]	*Studies:* Mean $t_{1/2}$ in patients with different liver diseases and normal renal function was 7.8h (no controls). Renal CL was enhanced due to a reduction in PB and nonrenal CL was reduced, resulting in liver disease having no effect on total CL [202]. *Product information:* No information provided. *Recommendation:* Parenteral administration: Based on pharmacokinetic data, adjust maintenance dose according to creatinine clearance. Monitoring of plasma concentration recommended (reference values: C_{min} 5-10 mg/l, C_{max} <40 mg/l [203]. In patients with ascites: adjust initial dose according to body weight and choose maintenance dose according to plasma concentration monitoring. Oral administration: Use normal dose since oral absorption is low. Monitor dose-dependent toxicity. Determine serum concentration in case of possible toxicity.
Teicoplanin (oral, parenteral)	No absorption takes place if given orally and thus serves as local therapy in the intestine. There is no evidence for extensive hepatic metabolism of the drug [71, 87].	Q_0: 0.3 $T_{1/2}$: 90h V_d: 1.1L/kg PB: 90% F_{oral}: 0% CL_{sys}: 0.95L/h E: 0.01 BE: minor CAT: 4	*Occasionally:* elevated liver enzymes. *Rare:* cholestatic hepatitis [87].	ototoxicity, nephrotoxicity, gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, neurotoxicity (headache, drowsiness, seizures, rigor), fever, thrombocytopenia [87, 90]	*Studies:* No clinical studies available in patients with liver disease. *Product information:* No information provided. Periodic hematological studies, renal, liver and auditory function tests are advised during prolonged treatment. Monitoring C_{min} (reference value: 5-15mg/l) [87]. *Recommendation:* Based on pharmacokinetic data, use normal initial dose and adjust maintenance dose and/or dosage interval according to creatinine clearance. Monitoring of serum levels recommended. Use with caution in patients with hypoalbuminemia due to decreased PB.

Tab. 11 (continued)

Drug (route of application)	Metabolism	Kinetic parameters	*Hepatic ADRs*	Potentially dose-dependent ADRs	*Studies, product information, and dose recommendations*
Polymyxins					
Colistin (inhalative)	Colistimethate sodium is a prodrug and hydrolyzed to the active principle colistin [71]. The pharmacokinetic data refer to colistin.	Q_0: 0.4 $T_{1/2}$: 3h V_d: 0.34L/kg PB: low F_{oral}: low CL_{sys}: n.k. E: n.k. BE: minor CAT: 4	Can exacerbate porphyrias [87].	nephrotoxicity, neurotoxicity (paresthesia, muscle weakness), oral candidiasis, bronchospasm [87, 90]	*Studies:* No clinical studies available in patients with liver disease. *Product information:* No recommendations provided. *Recommendation:* According to pharmacokinetic data, no dosage adjustment seems necessary in patients with liver disease. Adjust maintenance dose to renal function.
Steroid antibacterials					
Fusidic acid (oral)	Metabolism in the liver to glucuronic acid conjugates, dicarboxylic acid metabolite, hydroxy metabolite [87, 90]. Metabolites have weak or no bioactivity.	Q_0: 1 $T_{1/2}$: 11h V_d: 0.3L/kg PB: 98.5% F_{oral}: 91% CL_{sys}: 2L/h E: 0.04 BE: major CAT: 3	*Rare:* liver enzyme elevations, hyperbilirubinemia, reversible cholestatic jaundice, hepatorenal syndrome [87, 90, 92, 204, 205]. Jaundice may be due to intrahepatic cholestasis because of competition with the excretory pathways of hepatic bile acids related to the steroid-like structure of the drug [206]	gastrointestinal disturbances, hyperbilirubinemia, jaundice, liver enzyme elevations, hematological reactions (neutropenia, granulocytopenia, agranulocytosis), lethargy, drowsiness, fatigue [87, 90]	*Studies:* In patients with hypoalbuminemia with no cholestasis, cholestasis or hyperbilirubinemia, CL was higher compared to values in normal subjects because of increased free fraction. In patients with bilirubinemia, this effect was offset by competition for the glucuronidation step by bilirubin [206]. *Product information:* No data in patients with liver disease. Caution in patients with liver disease and/or impaired bilirubin transport or metabolism [87]. Caution in patients with mild and moderate liver disease and bile duct obstruction. Fusidic acid should not be used in patients with severe hepatic failure. Monitoring of liver function recommended [90]. *Recommendation:* According to pharmacokinetic data, start with normal intial dose and reduce maintenance dose by up to 50%. Adjust dosage according to clinical effect and dose-dependent ADRs. Monitoring of liver function necessary. In patients with ascites: adjust initial dose according to body weight and choose maintenance dose in the lower range of normal. Caution in patients with cholestasis due to significant BE. Use with caution in patients with hypoalbuminemia due to decreased PB.

Tab. 11 (continued)

Drug (route of application)	Metabolism	Kinetic parameters	*Hepatic ADRs*	Potentially dose-dependent ADRs	*Studies, product information, and dose recommendations*
Imidazole derivatives					
Metronidazole (oral, parenteral)	30-60% metabolized in the liver by side-chain-oxidation (active hydroxy metabolite $t_{1/2}$ 10h; acetic acid metabolite), glucuronide conjugation. Enterohepatic circulation [87, 90, 93].	Q_0: 0.85 $T_{1/2}$: 7h V_d: 0.74L/kg PB: 20% F_{oral}: 90% CL_{sys}: 5L/h E: 0.08 BE: minor CAT: 3	*Rare:* abnormal liver function tests, hepatocellular and cholestatic hepatic injury [87, 92].	gastrointestinal disturbances, metallic taste, intestinal overgrowth by non-susceptible organisms, peripheral neuropathy, confusion, hallucination, seizures, encephalopathy, paresthesia, ataxia, visual disturbances, discoloration of urine, hematological reactions [87, 90]	*Studies:* No significant alterations of kinetics in patients with decompensated liver cirrhosis or schistosomiasis in one study [207]. Decompensated liver disease: $t_{1/2}$ 152% higher, V_d and CL 21% and 66% lower compared to healthy controls [208]; significant reduction in C_{max} and AUC of hydroxy metabolite [209]. $T_{1/2}$ prolonged 2-fold in patients with hepatic and partly renal insufficiency compared to controls [210]. Alcoholic liver disease: $t_{1/2}$ 18.3h, V_d 0.77L/kg, and CL_{sys} 0.51mL/min per kg (equivalent to 2.1L/h) [211]. Elimination more affected in patients with obstructive liver disease than in patients with hepatocellular liver injury [212]. $T_{1/2}$ increased with severity of liver disease [213]. Decompensated liver disease: recommended to administer 0.5g i.v. 2x instead of 3x a day; oral dose 200mg 4x a day [209]. Alcoholic liver disease: recommended to reduce intravenous dosage from 500mg every 6h to every 12h [211]. *Product information:* Dosage reduction and monitoring of drug levels recommended in patients with severe liver disease. Caution in patients with hepatic encephalopathy [87]. 50% dose reduction in patients with liver insufficiency [90]. *Recommendation:* According to pharmacokinetic data and clinical studies, start with normal intial dose and reduce maintenance dose by up to 50%. Adjust maintenance dose by means of clinical effect and dose-dependent ADRs.

Tab. 11 (continued)

Drug (route of application)	Metabolism	Kinetic parameters	*Hepatic ADRs*	Potentially dose-dependent ADRs	*Studies, product information, and dose recommendations*
Ornidazole (oral, parenteral)	Over 90% are metabolized in the liver by oxidative pathway and hydrolysis [87, 214]. The two major metabolites ($t_{1/2}$ 5-6h) have almost the same activity as the parent compound.	Q_0: 0.95 $T_{1/2}$: 13h V_d: 0.9L/kg PB: 15% F_{oral}: 90% CL_{sys}: 3L/h E: 0.05 BE: minor CAT: 3	*Case reports:* hepatitis, autoimmune hepatitis, cholestatic jaundice [215-218].	gastrointestinal disturbances, metallic taste, intestinal overgrowth by non-susceptible organisms, central and peripheral neuropathy (confusion, dizziness, drowsiness, seizures, paresthesia, ataxia, tremor, rigidity), discoloration of urine, hematological reactions [71, 87]	*Studies:* Single 500mg i.v. dose in patients with alcoholic liver cirrhosis: significant increase of $t_{1/2}$ (22 vs. 14 h) and decrease of plasma CL (35 vs. 51 mL/min) [219]. The interval between repeated doses could be doubled. Patients with hepatitis, noncholestatic cirrhosis and extrahepatic cirrhosis: CL decreased by 26-48% and $t_{1/2}$ increased by 19-38% compared to healthy volunteers. No clear difference could be established between the different patient groups. Plasma concentration of active metabolites increased as a result of reduced elimination including decreased biliary excretion [158]. *Product information:* Compared to healthy subjects $t_{1/2}$ is prolonged and CL decreased. Dosage interval should be doubled in patients with severe liver impairment. The ampullas contain alcohol, caution in patients with liver disease [87]. *Recommendation:* According to pharmacokinetic and clinical data, start with normal initial dose. Adjust maintenance dose or dosage interval by means of clinical effect and dose-dependent ADRs. In patients with severe liver disease, double dosage interval.
Other antibacterials					
Fosfomycin (oral)	No metabolism. Enterohepatic circulation observed [87, 90].	Q_0: 0.1 $T_{1/2}$: 4h V_d: 2L/kg PB: 3% F_{oral}: 50% CL_{sys}: 11L/h E: 0.02 BE: minor CAT: 4	*Case report:* acute fatty liver (steatosis) [220].	gastrointestinal disturbances, dizziness, vertigo, asthenia [87, 90]	*Studies:* No clinical studies available in patients with liver disease. *Product information:* No specification in the Swiss product information. Fosfomycin is not metabolized and dosing adjustments are not required in patients with hepatic insufficiency [71]. *Recommendation:* Based on the pharmacokinetic data, no dosage adjustment seems necessary in patients with liver insufficiency. Adjust maintenance dose according to creatinine clearance.

Tab. 11 (continued)

Drug (route of application)	Metabolism	Kinetic parameters	*Hepatic ADRs*	Potentially dose-dependent ADRs	*Studies, product information, and dose recommendations*
Linezolid (oral, parenteral)	Metabolism to inactive ring-open metabolites probably by slow non-enzymatic morpholine-ring oxidation mediated by reactive oxygen species [87, 221]. About 9% of the dose are excreted as metabolites into the feces [87].	Q_0: 0.65 $T_{1/2}$: 6h V_d: 0.64L/kg PB: 31% F_{oral}: 100% CL_{sys}: 8L/h E: 0.1 BE: minor CAT: 3	*Frequent:* abnormal liver function tests [87]. *Case report:* elevated bilirubin [222], severe cholestatic liver injury (with concomitant lactic acidosis) [223].	gastrointestinal disturbances, metallic taste, intestinal overgrowth by non-susceptible organisms, neurotoxicity (dizziness, insomnia, vertigo, paresthesia, seizure, peripheral and optic neuropathy), hematological reactions [71, 87]	*Studies:* In patients with mild to moderate liver disease by Child-Pugh scores, AUC and $t_{1/2}$ both increased about 1.3-fold, while renal CL decreased by a factor of 1.3 compared to healthy volunteers. Urinary excretion of the two major metabolites was decreased [224]. Therapeutic drug monitoring is recommended for patients with severe liver disease [225]. *Product information:* No dosage adjustment is necessary in patients with cirrhosis Child-Pugh A and B. Linezolid pharmacokinetics in patients with severe hepatic failure have not been evaluated. Due to limited data available, linezolid should only be given to patients with liver disease if the benefit outweighs the risk [87]. *Recommendation:* According to pharmacokinetic data and clinical study, start with normal initial dose. In patients with severe liver disease, maintenance dose should be reduced by up to 50%. Adjust maintenance dose according to clinical effect and dose-dependent ADRs. In patients with ascites: adjust initial dose according to body weight and choose maintenance dose in the lower range of normal.
Daptomycin (parenteral)	In vitro studies showed no metabolism of daptomycin by CYP P450 enzymes [87].	Q_0: 0.5 $T_{1/2}$: 7.8h V_d: 0.1L/kg PB: 90% F_{oral}: n.k. CL_{sys}: 0.6L/h E: 0.01 BE: minor CAT: 3	*Frequent:* elevations of liver enzymes. *Occasionally:* jaundice [87].	gastrointestinal disturbances, intestinal overgrowth by non-susceptible organisms, peripheral neuropathy, paresthesia, dizziness, insomnia, anxiety, elevations of creatine phosphokinase incl. myositis, muscle pain, muscle weakness and rhabdomyolysis, nephrotoxicity [71, 87]	*Studies:* Pharmacokinetics of daptomycin (single i.v. dose 6mg/kg total body weight) in subjects with moderate hepatic liver disease (Child-Pugh B) were similar compared to healthy volunteers matched by weight, age, and sex [226]. *Product information:* No difference in pharmacokinetics in patients with liver insufficiency (Child B) compared to matched normal controls. No dose adjustment indicated in patients with moderate liver impairment. Caution in patients with liver cirrhosis Child C, because the safety has not been studied in this group of patients [87]. *Recommendation:* According to pharmacokinetic data, start with normal intial dose. Adjust maintenance dose according to clinical effect, dose-dependent ADRs, and/or serum levels. In patients with ascites: Adjust initial dose according to body weight and choose maintenance dose in the lower range of normal. Use with caution in patients with hypoalbuminemia due to decreased PB.

Tab. 11 (legend)

ADRs = adverse drug reactions; ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; AUC = area under the concentration-time curve; BE = biliary elimination; BUN = blood urea nitrogen; CAT = drug category; CL = clearance; CL_{sys} = systemic clearance; C_{max} = maximal plasma concentration; C_{min} = minimal plasma concentration; CYP = cytochrome P450 enzymes; E = hepatic extraction; F_{oral} = systemic bioavailability after oral administration; GGT = gamma-glutamyltransferase; HBV = hepatitis B virus; HCV = hepatitis C virus; n.k. = not known; PB = protein binding; Q_0 = extrarenal dose fraction; $T_{1/2}$ = elimination half-life; ULN = upper limit of normal; V_d = volume of distribution.

Tab. 12 Demographic and clinical characteristics of 400 patients with liver cirrhosis.

Characteristics	Patients (n = 400)
Age (years)[a]	60 (21-88)
Male	274 (68.5%)
Creatinine clearance (mL/min)[a, b]	82.8 (9-290)
BMI (kg/m^2)[a, c]	24.8 (13.5-47.2)
Child Pugh classification	
Child Pugh A	70 (17.5%)
Child Pugh B	157 (39.3%)
Child Pugh C	173 (43.2%)
Causes of liver cirrhosis	
Alcohol	279 (69.8%)
Viral Hepatitis	54 (13.5%)
Both	39 (9.7%)
Other	28 (7.0%)
Length of hospital stay (days)[a]	13 (1-116)
Patients died during hospitalization	67 (18.6%)

BMI = body mass index; ADE = adverse drug event; DDI = drug-drug interaction

[a] Data are presented as median (range)

[b] n = 386 patients due to lack of data (body weight and/or serum creatinine)

[c] n = 248 patients due to lack of data (body weight and/or height)

Tab. 13 Diagnoses in 400 patients with liver cirrhosis

Diagnosis	Patients (n = 400)
Number of diagnoses, total	2415
Diagnoses per patient[a]	6 (1-10)
Number of not liver associated diagnoses, total	1467
Not liver associated diagnosis per patient[a]	4 (0-8)
Diseases of the digestive system, total diagnoses[b]	687
Alcoholic liver disease (including cirrhosis)	268 (67.0%)
Non alcoholic fibrosis or cirrhosis of the liver	147 (36.8%)
Esophageal varices	61 (15.3%)
Gastrointestinal bleeding	49 (12.3%)
Gastritis and/or duodenitis	28 (7.0%)
Hepatic failure	22 (5.5%)
Spontaneous bacterial peritonitis	18 (4.5%)
Diseases of the cardiovascular system, total diagnoses[b]	343
Hypertension	80 (20.0%)
Ischemic heart diseases	46 (11.5%)
Atrial fibrillation	17 (4.2%)
Cerebrovascular diseases	16 (4.0%)
Diseases of the blood and blood-forming organs, total diagnoses[b]	211
Anemia	139 (34.8%)
Thrombocytopenia	40 (10.0%)
Psychiatric disorders, total diagnoses[b]	182
Mental and behavioral disorders due to use of alcohol	74 (18.5%)
Mental and behavioral disorders due to multiple drug use and/or use of other psychoactive substances	29 (7.3%)
Depression	27 (6.8%)
Mental and behavioral disorders due to use of tobacco	22 (5.5%)
Endocrine, nutritional and metabolic diseases, total diagnoses[b]	170
Diabetes mellitus	84 (21.0%)
Disorders of fluid and electrolyte balance	24 (6.0%)
Diseases of the genitourinary system, total diagnoses[b]	126
Renal failure	81 (20.3%)
Urinary tract infection	26 (6.5%)

Tab. 13 Diagnoses in 400 patients with liver cirrhosis (continued)

Diagnosis	Patients (n = 400)
Infectious diseases, total diagnoses[b]	124
Viral hepatitis	40 (10.0%)
Sepsis	32 (8.0%)
HIV	16 (4.0%)
Neoplasms, total diagnoses[b]	117
Liver and intrahepatic bile ducts	45 (11.3%)
Gastro-intestinal (other than liver)	16 (4.0%)
Diseases of respiratory system, total diagnoses[b]	111
COPD	43 (10.8%)
Pneumonia	18 (4.5%)
Diseases of musculoskeletal system, total diagnoses[b]	58
Diseases of the nervous system, total diagnoses[b]	54
Epilepsy	15 (3.8%)
Alcoholic polyneuropathy	10 (2.5%)

[a]Data are presented as median (range).

[b]One individual patient may have >1 diagnosis of the corresponding group, % not calculated.

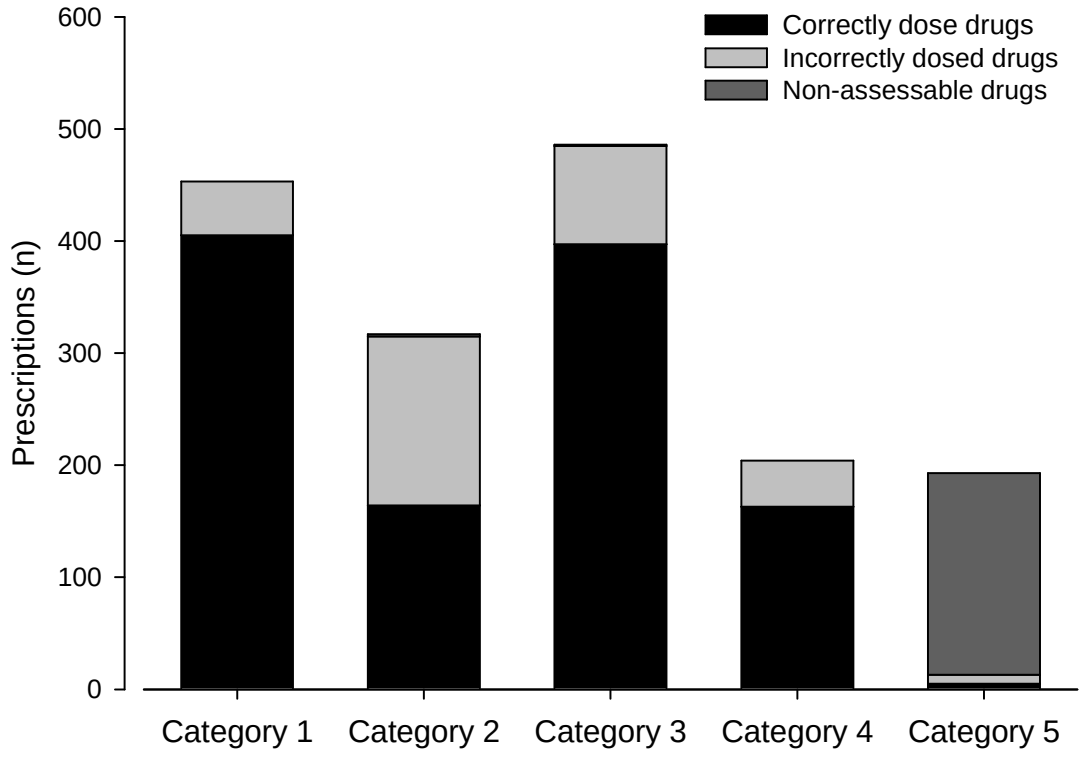

Fig. 11 Number of drugs at hospital admission, categorized according to their elimination pathway (category) and fraction of each category with incorrect dosing. Category 1 = high hepatic extraction drugs; category 2 = intermediate hepatic extraction drugs; category 3 = low hepatic extraction drugs; category 4 = renal elimination drugs; category 5 = drugs with unknown elimination pathway.

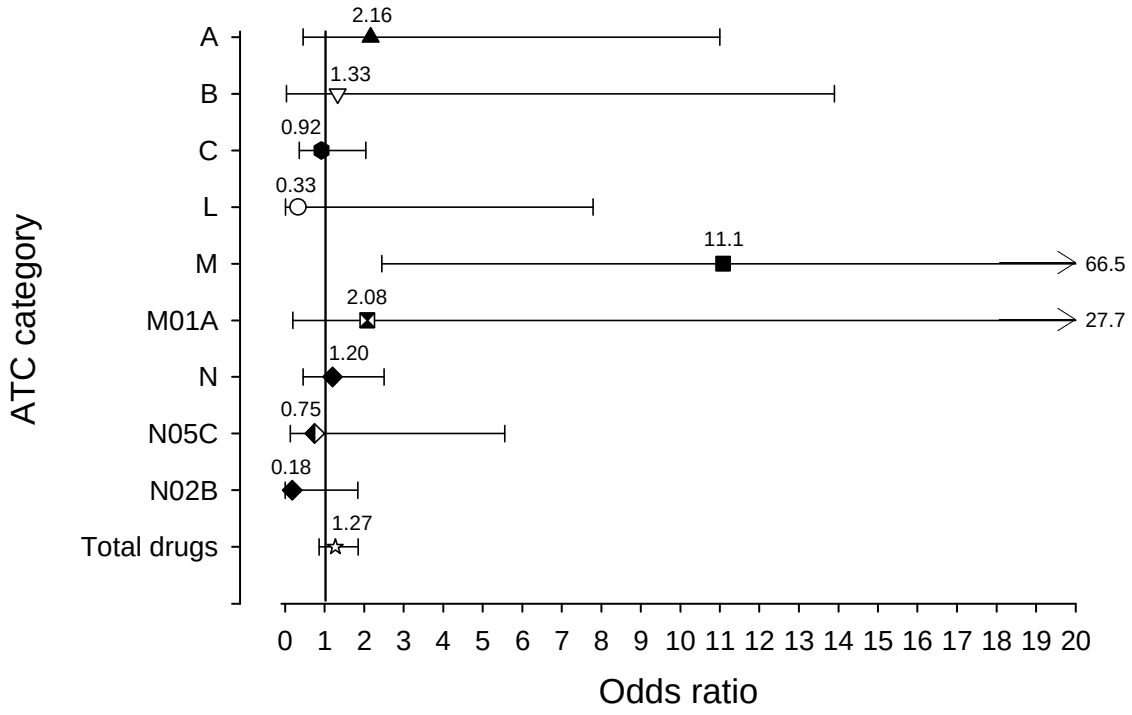

Fig. 12 Odds ratios (with 95% confidence intervals) for the development of ADRs associated with IDDs for the different drug classes (ATC-code). Odds ratios for not listed ATC-codes could not be calculated. A = alimentary tract and metabolism; ATC = anatomical therapeutic chemical classification system; B = blood and blood forming organs; C = cardiovascular system; CI max = upper value of 95% confidence interval; L = antineoplastic and immunomodulating agents; M = musculo-skeletal system; M01A = anti-inflammatory and antirheumatic products, non-steroids; N = nervous system; N05C = hypnotics and sedatives; N02B = other analgesics and antipyretics

Chapter VII

Curriculum vitae

7 Curriculum vitae

Personal Data

Name	Carmen Carina Franz
Date of birth	November 30th, 1983
Hometown	Liesberg, BL
Marital status	unmarried
Address	Strohackerstrasse 20, CH-5013 Niedergösgen
Mobile	0041 78 943 27 68
e-mail	carmen.franz@bluewin.ch

Education

2009-2012	PhD thesis at the Division of Clinical Pharmacology & Toxicology, University Hospital Basel, Switzerland Title: 'Drug-related Problems and Dosage Adjustment in Patients with Liver Disease' Supervised by Prof. Dr. Dr. Stephan Krähenbühl and Dr. Alexandra Rätz Bravo.
2003-2008	Study of Pharmacy with Swiss Federal Diploma at the University of Basel, Switzerland March to July 2007: Master thesis at the Division of Clinical Pharmacology & Toxicology, University Hospital Basel, Switzerland Title: 'Prevalence of Potential Adverse Drug Events as a Reason for Hospital Admission“
2002-2003	Study of Translation at the Zürcher Hochschule Winterthur (zhaw), study abandoned
1998-2002	Matura L (literary), Kantonsschule Olten, Switzerland

Work Experience

2009-2012	Assistance in Regional Pharmacovigilance Center at the Division of Clinical Pharmacology & Toxicology, University Hospital Basel, Switzerland Supervision of two master theses of pharmacy students Titles: '[Relationship between dosage and adverse drug events as well as potential cost savings in patients with liver cirrhosis]' written by Carole Hildbrand (2010) '[Prevalence and possible causes of muscle disorders at the University Hospital Basel]' written by Anna Sabina Zwahlen (2011) Organisation and supervision of a workshop in therapeutic drug monitoring for pharmacy students
	Pharmacist at the DorfApotheke, Zuchwil, the HelvetiaplatzApotheke, Zürich, and the Hammer Apotheke, Olten, Switzerland For one or two Saturdays per month and additional days if required
10/2008-12/2008	Pharmacist at the ZehntenhausApotheke, Zürich Affoltern, Switzerland, and other pharmacies of the Topwell-Apotheken AG if required (full-time job)
2007-2008	Assistant pharmacist at the Hammer Apotheke, Olten, Switzerland
2007	Assistance in Migros Gourmessa, Zürich Altstetten, Switzerland
2004-2007	Office assistance (pension fund)

Major Lectures

2009-2012

- University of Basel, Switzerland: Seminars on Drug Discovery and Development, Biostatistics I, Scientific Writing, Research Seminar in Clinical Pharmacology & Toxicology
- 'Pharmathemen' (organized by the Division of Clinical Pharmacology & Toxicology, University Hospital Basel, Switzerland)
- Various courses for pharmacists
- Various hospital-internal courses

Attendance and Presentations at Congresses

2012

- SGIM Jahresversammlung, Basel, Switzerland, Poster and Poster Presentation
  Title: 'Importance of Dosage Adjustment in Patients with Liver Cirrhosis: Influence on Safety and Healthcare Costs'

2011

- European Association of Hospital Pharmacists (EAHP), Vienna, Austria

2010-2012

- Annual Research Meeting, University of Basel, Switzerland
  Poster 1: 'Prevalence of Drug-Drug Interactions and Adverse Drug Events in Patients with Liver Cirrhosis'
  Poster 2: 'Necessity for Dosage Adjustment in Patients with Liver Disease – Development of a Drug Database'
  Poster 3: 'Prevalence of and Possible Reasons for Myopathies at the University Hospital Basel'

Language Skills

German	first language
English	advanced knowledge in reading, writing, and speaking
Spanish	advanced knowledge in reading, writing, and speaking
French	basic knowledge in reading, writing, and speaking
Chinese	basic knowledge in reading, writing, and speaking
Portuguese	basic knowledge in reading, writing, and speaking

Computer skills

Microsoft office	Word, Excel, Powerpoint
Pharmacy programs	Propharma, Golden Gate
Statistical programs	Stata 10

Interests

Sports (biking, jogging, swimming, hiking, karate, pilates, yoga), nature, animals, travelling, reading, cooking, music

Publications

- Franz CC, Bruggisser M, Krähenbühl S, Rätz Bravo AE. [Rhabdomyolysis associated with atorvastatin combined with amiodarone and fluconazole]. Praxis (Bern 1994). 2011 Mar 2;100(5):273-84.
- Franz CC, Egger S, Born C, Rätz Bravo AE, Krähenbühl S. Potential drug-drug interactions and adverse drug reactions in patients with liver cirrhosis. Eur J Clin Pharmacol. 2012 Feb;68(2):179-88.