Hepatotoxicity: A Drug-Induced Cholestatic Pattern

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Abstract

Although drug induced liver disease is a rare condition, it explains 40% to 50% of all cases of acute liver failure. In 20% to 40% of the cases, the pattern is cholestatic and is caused by inhibition of the transporters that regulate bile synthesis. This reduction in activity is directly or indirectly mediated by drugs and their metabolites and/or by genetic polymorphisms and other risk factors of the patient. Its manifestations range from biochemical alterations in the absence of symptoms to acute liver failure and chronic liver damage.

Although there is no absolute test or marker for diagnosis of this disease, scales and algorithms have been developed to assess the likelihood of cholestatic drug induced liver disease. Other types of evidence are not routinely used because of their complexity and cost. Diagnosis is primarily based on exclusion using circumstantial evidence.

Cholestatic drug induced liver disease has better overall survival rates than other patters, but there are higher risks of developing chronic liver disease. In most cases, the patient's condition improves when the drug responsible for the damage is removed. Hemodialysis and transplantation should be considered only for selected cases. The effectiveness of other therapies is unproven.

This article will delve into the pathophysiology, biochemistry, and histopathology and the clinical presentation of the disease and will discuss diagnosis, management and prognosis of this type of cholestasis.

Keywords

Cholestasis, drug, liver disease, drug-induced liver disease.

INTRODUCTION

Drug Induced Liver Injury (DILI) is a rare cause of liver disease in the general population: it accounts for less than 1% of patients hospitalized with jaundice (1,2) and for up to 1% of patients managed by internal medicine (primarily with tuberculostatic and antineoplastic agents). (3) However, this entity accounts for 40% to 50% of cases of acute liver failure, (4) and it is estimated that by 6 months after onset of symptoms one in ten patients has died or required liver transplantation. One out of every five develops chronic liver disease. (5) Clearly, this entity is an important topic for research and drug monitoring. (4,6)

Three patterns of DILI have been identified: cholestatic, hepatocellular and mixed. The cholestatic pattern is characterized by levels of alkaline phosphatase (ALP) greater than twice the upper limit of normal (ULN) and/or less than or equal to 2R (R is the relationship between ALP and ALT as shown in Figure 1). The hepatocellular pattern is defined as ALT levels greater than twice the ULN and/or more than 5R while in the mixed pattern ALT is greater than twice the ULN with R from two to five. (7-10)

The cholestatic pattern accounts for 20% to 40% of DILI, the hepatocellular pattern accounts for 40% to 78%, and the mixed pattern accounts for 12% to 20%. (7,10) Despite the fact that there is a higher survival rate for the cholestatic

presentation, the rate of improvement of patients' biochemical liver profile is low and it has a high risk for development of chronic liver disease. (11)

$$R = \frac{\text{Patient's ALT/UNL of ALT}}{\text{Patient's ALP/UNL of ALP}}$$

Figure 1. Definition of R for DILI patterns. ALP: alkaline phosphatase; ALT: alanine aminotransferase.

In recent decades, multiple studies have been conducted to identify the main risk factors for development of liver toxicity as well as to determine methods of early diagnosis and proper management. This review summarizes the pathophysiological, clinical, diagnostic features of DILI and discusses the most relevant treatments.

PHYSIOLOGY

Bile is secreted through osmosis resulting from concentration of salts and other components in the bile canaliculi. Solute transport of blood to bile occurs by means of transport systems at the surface of the basolateral (sinusoidal) plasma membranes and apical canalicular membranes of hepatocytes. (12)

Basolateral membranes contains the Na+/K+-ATPase (sodium-potassium pump) and voltage-gated potassium channels (VGKCs) which have transmembrane electrical potentials of about -35 mV. This maintains the intracellular and extracellular ion gradients and pH homeostasis. This potential is what allows uptake of conjugated bile salts (bile acids) from the blood primarily by sodium-taurocholate cotransporting polypeptide (NTCP). (13) In contrast, unconjugated bile salts, organic anions and many other components which bind to albumin are transported from the plasma to hepatocytes by independent sodium transport systems such as organic anion-transporting polypeptides (OATPs). (12)

The canalicular excretion of bile acids (the major fraction of organic solutes in bile) is mediated by the family of ATP dependent transporters for bile acids and organic anions. This is the determining step for the rate of bile formation. (14) Osmotic excretion of bile acids is followed by movement of water through aquaporins and tight junctions, a flow which is dependent on bile acid. In addition to osmosis, bile acids promote canalicular secretion of phospholipids and cholesterol for the formation of mixed micelles. (13,18) There are also compounds such as reduced glutathione and bicarbonate that are independent of the flow of bile acids. Both cholangiocytes and hepatocytes secrete and absorb different components that modify the characteristics of bile as it passes through the bile duct. (Figure 2). (15)

The system of hepatobiliary transporters is regulated at transcriptional and posttranscriptional levels, for example through the activation of nuclear receptor ligands. These positively and negatively regulate bile formation pathways like that of the detoxifying enzymes and pumps that export bile compounds in both pathological and physiological states. (16) Bile components, lipid products, hormones and xenobiotics work together to activate nuclear receptors such as endogenous and exogenous ligands and to modify genes that encode hepatobiliary transporters and phase I and II metabolism enzymes. (16)

There is growing evidence that the activity of nuclear receptors such as the Farnesoid X receptor (FXR) is affected by chromatin remodeling through acetylation of histones. (16) This is important because it is the best defined nuclear receptor and because it is critically involved in reducing bile acid production (CYP7A1) and in both Na + -dependent (NTCP) and Na + independent (OATP1B1 and OATP1B3) bile acid absorption. In addition, it activates monovalent canalicular excretion (BSEP - Bile Salt Export Pump) and divalent canalicular excretion (MRP2 and MDR3) of bile acid and conjugated bilirubin (MRP2) (Figure 3). (15-17, 19)

PATHOPHYSIOLOGY AND MECHANISMS OF CHOLESTASIS

Cholestasis is the basis of liver damage in every manifestation and clinical pattern of DILI. (20) In most cases, drugs cause cholestasis by inhibiting expression and functioning of hepatocellular transporters, but on rare occasion drugs induce vanishing bile duct syndrome (VBDS) which can progress to biliary cirrhosis. (21) Many cases of drug-induced cholestasis result in inhibition of liver functions resulting from the effects of the drug or its metabolites on various transport proteins and pathways. The most frequently affected, especially in cholestatic DILI, is the export of ATP-dependent bile acids via the BSEP pathway. (22) This is inhibited directly and competitively by drugs such as rifampin, cyclosporine, troglitazone and glyburide, and indirectly by metabolites of steroid hormones such as estrogen and progesterone. (23-26) The MRP2 pathway and secretion of phospholipids via the MDR3 pathway are also affected. (27,28)

Genetic alterations in the ATP-binding cassette (ABC) transporter family have also been associated with cholestatic disorders ranging from progressive familial intrahepatic cholestasis and benign recurrent intrahepatic cholestasis,

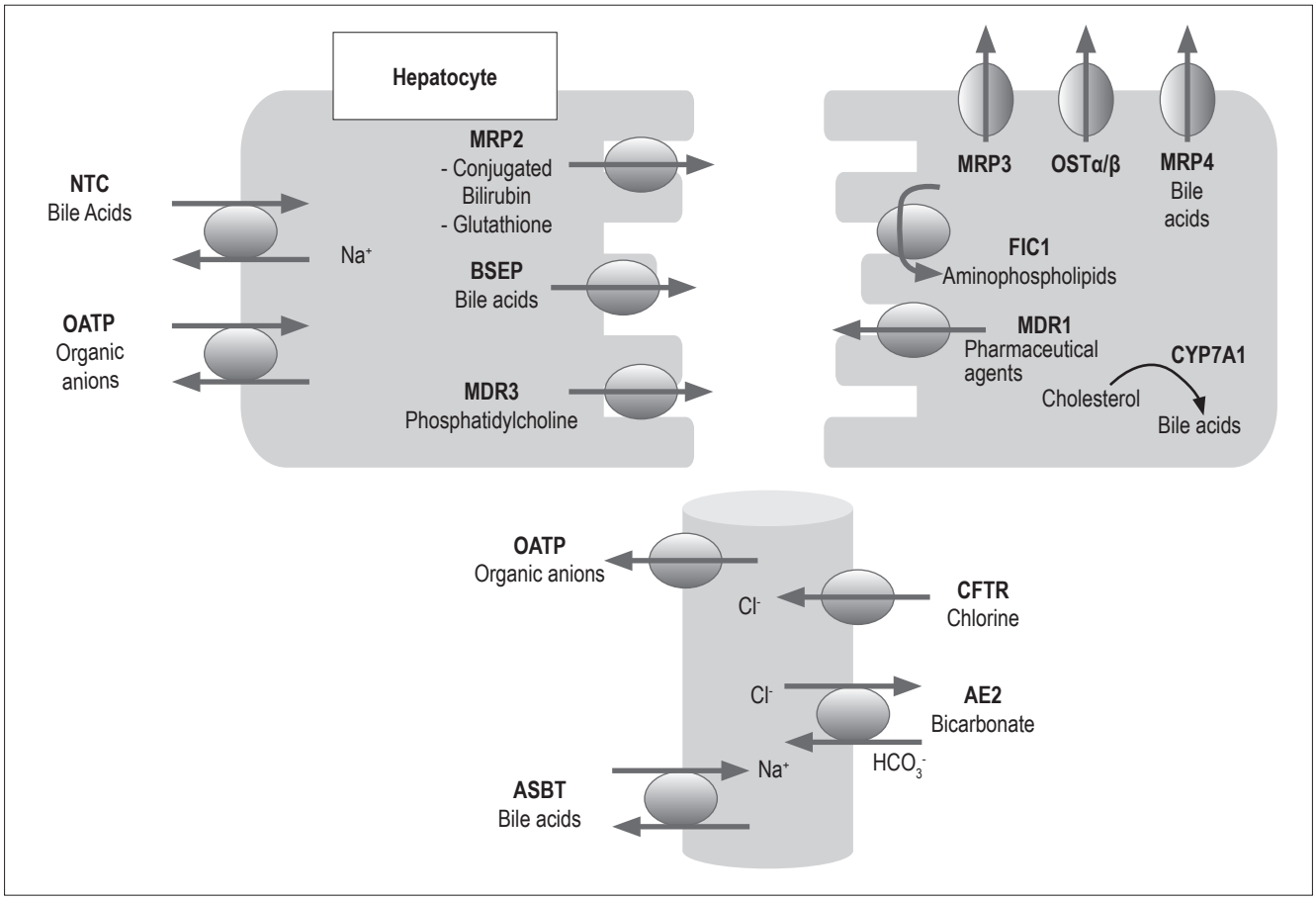

Figure 2. Bile acid transporters. Hepatocellular bile acids from cholesterol and from de novo synthesis pathway CYP7A1 replaces that lost in feces (3% -5% daily). Hepatocellular uptake of bile acids from sinusoidal blood in the enterohepatic circulation also occurs. It is mediated by the high affinity transporter sodium taurocholate (NTCP) and the family of multispecies organic anion transporters (OATP). Canalicular excretion of bile components via ATP dependent transporters determines the speed of the bile synthesis. The canalicular membrane contains a bile salt export pump (BSEP) for monovalent bile acids. A pump for export of conjugated bilirubin (MRP2) mediates the excretion of various organic anions such as bilirubin and bile acids. The phospholipid (MDR3) export pump removes phosphatidylcholine which forms mixed bile acid and cholesterol micelles. Cationic drugs are excreted by the multidrug export pump (MDR1). In addition, the canalicular membrane contains FIC1, a P-type ATPase which is a flippase aminophospholipid. MRP3 and MRP4 are additional bile acid pumps in the basolateral membrane. The soluble organic heterodimer transporter OSTα/β reinforces sinusoidal bile acid export. Under normal conditions, this transport system is expressed at very low levels, but can be induced by cholestatic conditions or medications. Cl(-)-HCO3- exchanger isoform AE2 mediates the biliary excretion of bicarbonates from both hepatocytes and cholangiocytes. The cystic fibrosis transmembrane conductance regulator (CFTR) drives bicarbonate excretion via AE2 exclusively in cholangiocytes. The biliary epithelium is also involved in the reabsorption of bile acids through Apical sodium dependent bile acid transporter (ASBT) and its counterpart basolateral OSTα/β. Modified from Wagner M, et al. 2009.

to intrahepatic cholestasis of pregnancy, drug-induced cholestasis, intrahepatic cholelithiasis and biliary cirrhosis.

Homozygous alterations cause great impacts variants that result in cholestatic syndromes at early ages. (29-32) Heterozygous defects in transporters predispose to the acquisition of cholestasis through drugs, hormones and inflammation that cause decompensation of slight to moderate defects. (32)

CLINICAL, BIOCHEMICAL AND HISTOLOGICAL FEATURES

Clinical

Drug-induced cholestasis can be classified according to the anatomical site and the biochemical and histopathological pattern of the injury. These range from liver disorders that

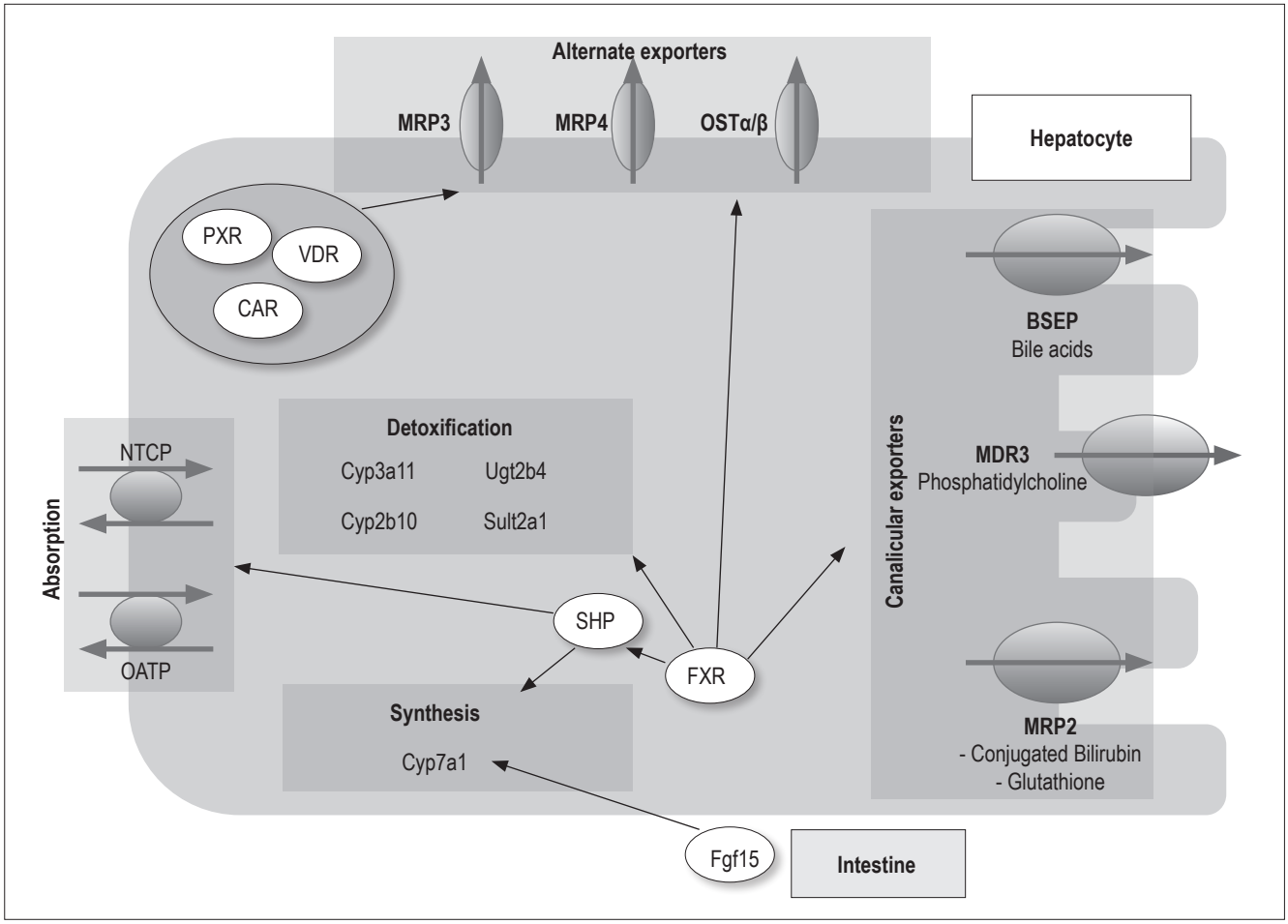

Figure 3. General principles of regulation of enzymes and hepatobiliary bile acid transporters dependent on nuclear receptors (diagram of a rodent model). The principal transcriptional processes in humans are similar although they have been studied much less. FXR, the most important nuclear receptor involved in the regulation of bile formation, is activated by bile acids. This regulates the metabolism of bile acids both directly and indirectly. Direct regulation occurs through stimulation of canalicular export of bile acid by BSEP and MRP2 and through export of phospholipids by MDR2. Indirectly, SHP inhibits Na+ dependent basolateral transporters [NTCP], Na+ independent basolateral transporters [OATP] and absorption and synthesis of bile acids on the CYP7A1 initiated pathway. In addition, Fgf15 derived from ileal enterocytes strongly down regulates transcription of CYP7A1 which functions as an intestinal sensor for bile acid requirements. Except for OSTα/β, which is also regulated by FXR, the alternate exporter systems operate independently of this gene. PXR and VDR upregulate MRP3 while CAR upregulates both MRP3 and MRP4. Phase I metabolism (Cyp3a11 and Cyp2b10) and Phase II (Sult2A1) metabolism are stimulated by PXR and CAR, but FXR is capable of stimulating detoxification of phase I through Cyp3a11 and glucuronidation and sulfation of phase II via Sult2a1 Ugt2b4. Modified from Wagner M, et al. 2009.

interfere with synthesis of bile to changes in bile ducts that impede excretion. (33, 34)

Usually, drug-induced cholestasis is an acute disease that quickly disappears once the agent provoking the condition is suspended. (33) It is clinically characterized by jaundice, pruritus, anorexia, malaise, nausea and fatigue. It may also have other manifestations depending on the causal mechanism and on extrahepatic drug toxicity. (35) In hypersensitive forms, systemic manifestations such as fever, rashes or eosinophilia can be seen. It is important to consider that this condition can present through a spectrum of symptoms ranging from asymptomatic biochemical abnormalities to acute liver failure. (33, 34)

Some medications cause chronic cholestasis with characteristics similar to primary biliary cirrhosis (PBC). These include xanthomas, itching and melanoderma. (35) These

forms of cholestasis are considered benign because they rarely progress and can be differentiated from PBC by the absence of microsomal antibodies, acute onset of symptoms, and atypical histopathological features and clinical presentations. (33)

Biochemistry

As in other forms of cholestatic damage, primarily biochemical assessment shows elevated levels of alkaline phosphatase (ALP) and gamma glutamyl transpeptidase (GGT). (33) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) may be normal or slightly elevated. Although bilirubin concentrations are usually high, they depend on the injury mechanism of the drug. (35)

Histopathology

Histologically, drug-induced cholestasis may occur as an acute or chronic injury which may or may not compromise the parenchyma of the liver. (35) There are two classifications of acute forms, which are more common than chronic forms.

- Pure or soft cholestasis in which clots of biliary pigment are found in canaliculi which appear to be distended. Pigment accumulates in hepatocytes and Kupffer cells without inflammation or hepatocellular injury. This is more prominent in zone 3 (centrilobular area). (35, 36). Medications that cause this type include anabolic steroids, oral contraceptives and warfarin. (34, 37)
- Cholestatic hepatitis (cholangiolitis or cholestasis due to hypersensitivity) is characterized by hepatocellular compromise which is also expressed in the liver biochemistry. (35) It may be accompanied by proliferation of ducts. cholangiolitis has developed, neutrophils, lymphocytes and eosinophils will be found. (36) This pattern is common in erythromycin and chlorpromazine toxicity. (34, 35, 37)

Chronic forms of the disease last more than 6 months. Pseudoxanthomatosis develops and has a foamy appearance due to the accumulation of bile acids in hepatocytes especially in periportal regions. (33) Copper content can also be demonstrated increased with special stains and there is occasionally evidence of Mallory bodies. (37) There are also two classifications of chronic cholestasis.

- **Vanishing bile duct syndrome (VBDS)** initially presents as hepatocellular and bile duct inflammation but leads to ductopenia and in some cases to cirrhosis when the drug causing the condition is not suspended. It is one of the most severe presentations and can be triggered by carbamazepine, chlorpromazine, ibuprofen, amoxicillin, and clindamycin. Differential diagnosis must be done to rule out PBC and obstructive disease (35,49).
- **Biliary sclerosis** can occur when there is an ischemic injury of intrahepatic or extrahepatic ducts. This can simulate radiological or histological primary sclerosing cholangitis. (35,36) Medications associated with this presentation include 5-fluorodexiuridine (for the treatment of liver metastases of colorectal cancer) and formaldehyde. (35,36)

Portal area edema, infarcts and biliary lakes are late expressions of mechanical obstruction of the ducts which rarely develop in cases of DILI. (33) Nevertheless, since early histopathological presentation of biliary obstruction is indistinguishable from drug-induced cholestasis, differential diagnosis is very important. (35-38)

Table 1 summarizes the most common biochemical and histopathological features of the cholestatic patterns described. Table 2 shows drugs associated with cholestatic patterns of liver toxicity.

RISK FACTORS

Among risk factors for DILI is age which may be explained by changes in the expression of receptors and transporters, in percentage of body fat, in volume distribution or in hormonal status. (7,36) Although there are no significant differences in the incidence of DLI between genders, it has been related to changes in presentation and prognosis. The cholestatic pattern is most common among men, but the development of the disease is less favorable among women. (39) Polymorphisms and genetic factors for drug metabolism have also been identified. These include human leukocyte antigen (HLA) B * 5701, -DRB and -DRBQ haplotypes, and the MDR3/BSEP polymorphism which is associated with predisposition for pregnancy and steroid induced cholestasis. (36, 40, 50)

Alcohol use, liver disease (including steatohepatitis) and HIV infection (by a yet unknown mechanism) have also been described as risk factors. (7)

DILI has also been associated with factors dependent on increased drug strength including composition, dosage and metabolism. Examples include steroids with substitutions in C-17 (particularly alkylation or methylation), (36) doses over 50 mg/day and concomitant use of several drugs affecting the hepatic metabolism. (36, 39, 41)

DIAGNOSIS

There are no tests or markers that are absolute indicators of DILI, so diagnosis depends primarily on exclusion based on circumstantial evidence. The approach when DILI is

Table 1. Types of cholestasis induced by drugs. The table shows histological and biochemical characteristics that identify and differentiate cholestatic drug induced liver injury (DILI) patterns. Modified from R. Mohiuddin et al. 2004

	Morphological term (clinical term)				
	Canalicular pattern (mild jaundice)	**Hepatocanalicular pattern (cholestatic hepatitis)**	**Ductal pattern (cholangial)**	**Vanishing bile duct syndrome**	**Secondary sclerosing cholangitis**
Histological features					
Bile pigment	+	+	+++	+	+
Portal inflammation	0	++[o]	+/-	+	+
Hepatocellular necrosis	-	+	+/-	+	+
Destruction of ducts	0	+	+/-	+++	+++
Cholangitis	-	+/-	+	+	+
Peliosis	+	+	-	-	-
Hypersensitivity	No	Frequent	No	No	No
Biochemical characteristics					
Bilirubin	+++	+++	+++	+/+++	+/+++[a]
Alkaline phosphatase	<3 times ULN	3-10 times ULN	> 3 times ULN	> 3 times ULN	> 3 times ULN
AST/ALT	1-8 times ULN	2-10 times ULN	2-10 times ULN	2-10 times ULN	2-10 times ULN
Cholesterol	+/-	++	+/-	+++	+++
Examples	ACO, anabolic steroids	Chlorpromazine, erythromycin	Benoxaprofen	Paraquat, chlorpromazine	Infusion of floxuridine, scolicidal agents

[o]: usually early
[a]: usually 3-6 months

suspected should begin with a detailed medical history including thorough questioning about medical factors, risk factors, use of prescription drugs, self-medication, and use of unconventional substances such as alternative and herbal medicine. The physician should also inquire about alcohol and other psychoactive substances. Many times this questioning should include the patient's family. All these data should include the time of first use for temporal association with liver damage especially in patients with polypharmacy.

This should be complemented with the usual liver biochemical tests, standard coagulation tests, serum markers and routine imaging of bile ducts to rule out other more common causes of cholestasis (Table 3). (7, 36, 42) Other tests for autoimmune and infectious diseases may be useful for differential diagnosis. While not always necessary, a liver biopsy may be essential in selected cases, especially to assess the patient's prognosis. (36)

Situations most suggestive of DILI include initiation of treatment with a new drug in the previous three months, a rash or eosinophilia, mixed type liver disease (hepatocellular and cholestatic commitment), cholestasis without alterations in imaging, acute chronic hepatitis without autoantibodies and without hypergammaglobulinemia, and patients with risk factors. The absence of any or all of these factors does not rule out the possibility of drug-induced cholestasis or any other form of DILI, but taking them into account can facilitate earlier diagnosis. (7)

Of the several scales developed to assess the likelihood of DILI, the most widely used and best validated is the CIOMS/RUCAM scale proposed by Danan and Benichou at the International Consensus Meeting of 1990. (8) It allows classification of DILI diagnoses into definite, probable, possible, unlikely and discarded according to the pattern of liver damage (hepatocellular or cholestatic/mixed) chronological criteria, course of disease, risk factors, available information on hepatotoxicity of a drug , exclusion of other causes and response to the re-administration of the drug. This last criterion should not be used because of risks to the patient. Table 4 shows the DILI probability scale for the cholestatic pattern. Additional tests that are useful for diagnosis include the drug-lymphocyte stimulation test (DLST) and the leukocyte migration test (LMT). The first has a sensitivity of 50% and cannot unambiguously link a drug to liver damage. (43) The LMT has proven to be most useful for identifying offending substances. (44) These and other tests of this type are useful for identifying the specific drug that has caused damage, but because they are complex and expensive they are not recommended for routine use. (7)

Table 2. Medications associated with cholestatic injury. Modified from R. Mohiuddin et al. 2004

Medications associated with cholestatic injury		
Antimicrobial agents	**Anti-inflammatory agents**	**Statins**
Antifungals	Benoxaprofen	Pravastatin
Griseofulvin	Celecoxib	**Steroids and their inhibitors**
Itraconazole	Diclofenac	Anabolic steroids
Ketoconazole	Ibuprofen	Oral Contraceptives
Terbinafine	Gold salts	Danazol
Thiabendazole	Indomethacin	Estradiol
Cephalosporins	Infliximab	Tamoxifen
Macrolides	Meloxicam	**Others**
Azithromycin	Piroxicam	Allopurinol
Clarithromycin	**Anticonvulsants**	Beta Carotene
Erythromycin	Carbamazepine	Dapsone
Quinolones	**Cardiovascular Agents**	Floxuridine
Ciprofloxacin	ACE inhibitor	HAART
Norfloxacin	Captopril	Herbal Remedies
Penicillins	Fosinopril	Mesalamine
Amoxicillin-clavulanate	ARBs	Propafenone
Dicloxacillin	Irbesartan	Tacrolimus
Flucloxacillin	Centrally acting sympatholytics	Terfenadine
Oxacillin	Methyldopa	Total parenteral nutrition
Others	Diuretics	
Nitrofurantoin	Thiazides	
Tetracyclines	Anticoagulants and antiplatelet agents	
Trimethoprim-sulfamethoxazole	Heparin	
Rifampin	Clopidogrel	
Psychotropics	Warfarin	
Antipsychotics	**Immunosuppressants**	
Chlorpromazine	Azathioprine	
Haloperidol	Cyclophosphamide	
Risperidone	6-Mercaptopurine	
Sedatives	**H2-receptor antagonists**	
Barbiturates	Cimetidine	
TCAs	Ranitidine	
Imipramine	**Hypoglycemic agents**	
Amitriptyline	Glimepiride	
SSRIs	Metformin	
Sertraline	Pioglitazone	

TREATMENT

In most cases, the patient will improve when the drug responsible for the damage is removed. However, it has been found that some patients have improved even without suspension. For this reason, it is necessary to correlate the severity of the clinical picture with the importance of the use of the drug. (7)

Although there are no definitive criteria for suspension of a drug, the following have been proposed for cases of suspected cholestatic DILI because of their associations with liver damage. (7, 45)

- Bilirubin more than three times ULN.
- INR over 1.5.

Considerations for drug withdrawal in all patterns of DILI are (46):

- ALT or AST> 8 times ULN
- ALT or AST> 5 times the upper limit of normal for more than 2 weeks.
- ALT or AST> 3 times ULN with total bilirubin> 2 times the upper limit of normal or with INR> 1.5.
- ALT or AST> 3 times ULN with fatigue, nausea, vomiting, abdominal pain in the right upper quadrant, fever, rash and/or eosinophilia> 5%.

Using other medicines for managing cholestatic DILI is not supported in the literature. Although treatment with UDCA (ursodeoxycholic acid) and corticosteroids (in patients with suspected hypersensitivity) has been used, controlled clinical trials have not proven the efficacy of these treatments. (7, 46, 47, 51) Hemodialysis is rarely indicated, but whenever there is any indication of acute liver failure the patient should be hospitalized and considered for liver transplantation. (46, 47) An algorithm proposed for diagnosis and management of cholestatic DILI is shown in Figure 4.

Table 3. Initial diagnostic tests for DILI. The table lists tests that may be useful for assessing DILI. An asterisk * indicates those that should be done initially. Modified from Tajiri, et al. 2008

Initial diagnostic tests for DILI	
Test	**Clinical utility**
Blood tests*	
Complete blood count (including eosinophils)	Hypersensitivity reactions
Biochemical*	
AST/ALT Lactate dehydrogenase Gamma glutamyl transpeptidase Alkaline phosphatase	Definition of pattern of liver damage
Total and direct bilirubin Albumin	Severity of injury
Coagulation*	
Prothrombin INR	Severity of injury
Serological (autoimmune)*	
IgG, IgA, IgM Antinuclear antibodies (ANA) Antimitochondrial antibodies (AMA)	Differential Diagnosis CMV IgM (request in accordance with clinical suspicion)
Viral Serology	
IgM anti-HA* HBsAg*, IgM-HBc*, Anti-HBc, HBV-DNA Anti-HCV*, HCV-RNA Anti-HDV, HDV-DNA Anti-HEV, HEV-RNA IgM-EBV IgM-CMV	Differential Diagnosis (request in accordance with clinical suspicion)
Imaging	
Transabdominal ultrasound	Differential Diagnosis (request in accordance with clinical suspicion)

ALT: alanine aminotransferase, AST: aspartate aminotransferase, CMV, cytomegalovirus, HA: hepatitis A, HBc: Hepatitis B core, HBsAg: Hepatitis B surface antigen, IgA: Immunoglobulin A, IgG: Immunoglobulin G, IgM: Immunoglobulin M, EBV: Epstein-Barr virus, HCV: hepatitis C, VHD: hepatitis D virus, HEV: hepatitis E.

PROGNOSIS

Information on the outcome of the cholestatic and mixed presentations is limited. It was Previously believed that the cholestatic pattern of DILI was associated with a better prognoses, but recent literature shows that 5% to 13% of these patients develop chronic liver disease (more common than in patients with hepatocellular pattern), and that 5% to 14% die or require transplantation. (36, 48)

The long-term prognosis for DILI generally depends on the clinical presentation and initial biochemistry of the patient. Aminotransferase and total bilirubin are the best predictors of mortality. Those who present ALT greater than or equal to three times ULN and jaundice (total bilirubin two or more times ULN) have a mortality rate of between 10% and 50%. This is known as the Hy's Law. (48,52)

Table 4. CIOMS/RUCAM score for assessment of DILI. Result interpretation: greater than 8 definitive, 6-8 probable, 3-5 possible, 1-2: unlikely; less than or equal to 0 discarded. Modified from G. Danan G et al. 2014

CIOMS/RUCAM						
Liver injury type	**Hepatocellular**		**Score**	**Cholestatic/mixed**		**Score**
Chronological criteria	**First exposure**	**Second exposure**		**First exposure**	**Second exposure**	
Duration of administration of medication from onset of symptoms	5-90 days	1-15 days	2	5-90 days	1-90 days	2
	<5 or >90 days	>15 days	1	<5 or >90 days	> 90 days	1
When to suspend administration following onset of symptoms	<15 days	≥15 days	1	≤30 days	≤30 days	1
Course of disease	**Difference between ULN of ALT and maximum**			**Difference between ULN of ALP and maximum**		
To suspension of medication	Improvement > 50% in 8 days		3	Improvement > 50% in 180 days		2
	Improvement > 50% in 30 days		2	Improvement > 50% in 180 days		1
	Insufficient information or no improvement		0	Insufficient information or no improvement		0
	Worsening or improvement <50% in 30 days		-1			
Risk factors	Age (≥55 years)		1	Age (≥55 years)		1
	Alcohol consumption		1	Alcohol consumption or pregnancy		1
Concomitant treatment	None or unknown		0	None or unknown		0
	Drug with suggestive contribution		-1	Drug with suggestive contribution		-1
	Known liver toxin, suggestive contribution		-2	Known liver toxin, suggestive contribution		-2
	Proven role in the case		-3	Proven role in the case		-3
	No information available		0	No information available		0
Exclusion of other non-drug causes	Discarded		2	Discarded		2
	Possibly not investigated		-2 to 1	Possibly not investigated		-2 to 1
	Other probable cause		-3	Other probable cause		-3
Previous Information about hepatotoxicity	Unknown reaction		0	Unknown reaction		0
	Published but not included on label		1	Published but not included on label		1
	Included in information on label		2	Included in information on label		2
Response to readministration of medication	Positive		3	Positive		3
	Compatible		1	Compatible		1
	Negative		-2	Negative		-2
	Not available or not interpretable		0	Not available or not interpretable		0
	Plasma concentrations known to be toxic		3	Plasma concentrations known to be toxic		3
Validated laboratory tests with good positive predictive	Positive		3	Positive		3
	Negative		-3	Negative		-3
	Not available or not interpretable		0	Not available or not interpretable		0

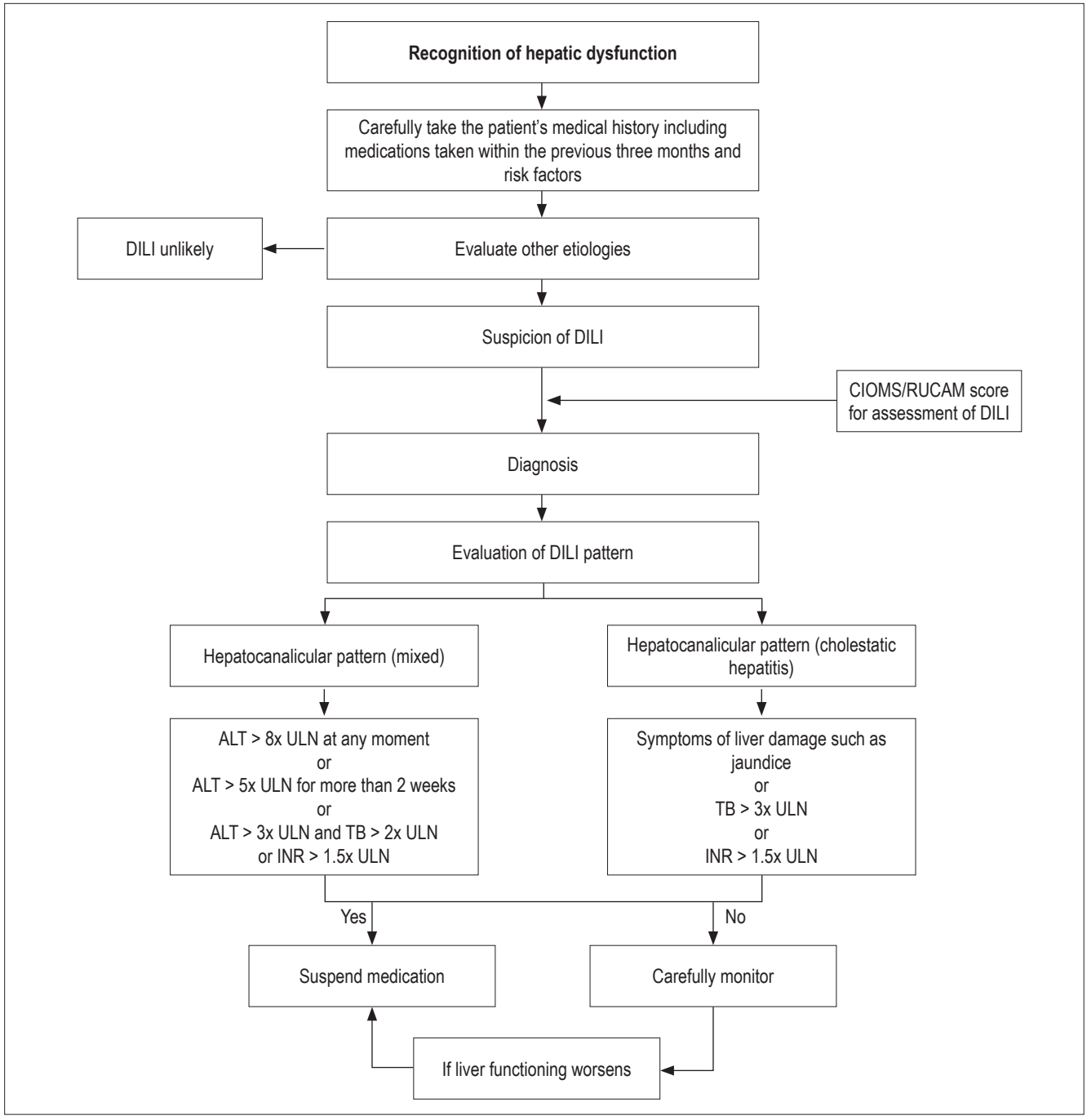

Figure 4. Algorithm for addressing DILI. TB: total bilirubin; ULN: upper limit of normal. Modified from Tajiri, et al. 2008.

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