Hépatites médicamenteuses
pour REMED, Genève
21.09.2017

Plan

- Critère définissant une hépatite médicamenteuse (DILI)
- Exemple d’une condition à risque
- DILI - > HILI
- Ce qu’on peut retenir

Roussel Uclaf Causality Assessment Method

Prédispositions et Conditions à risque

- Génotype (HLA)
- Métabolisme, Distribution, Elimination
- Co-morbidité
- Lipophilicité
- Doses journalières élevées

Roussel Uclaf Causality Assessment Method

Crit Rev Toxicol 2017 ; 47 (8):633-649

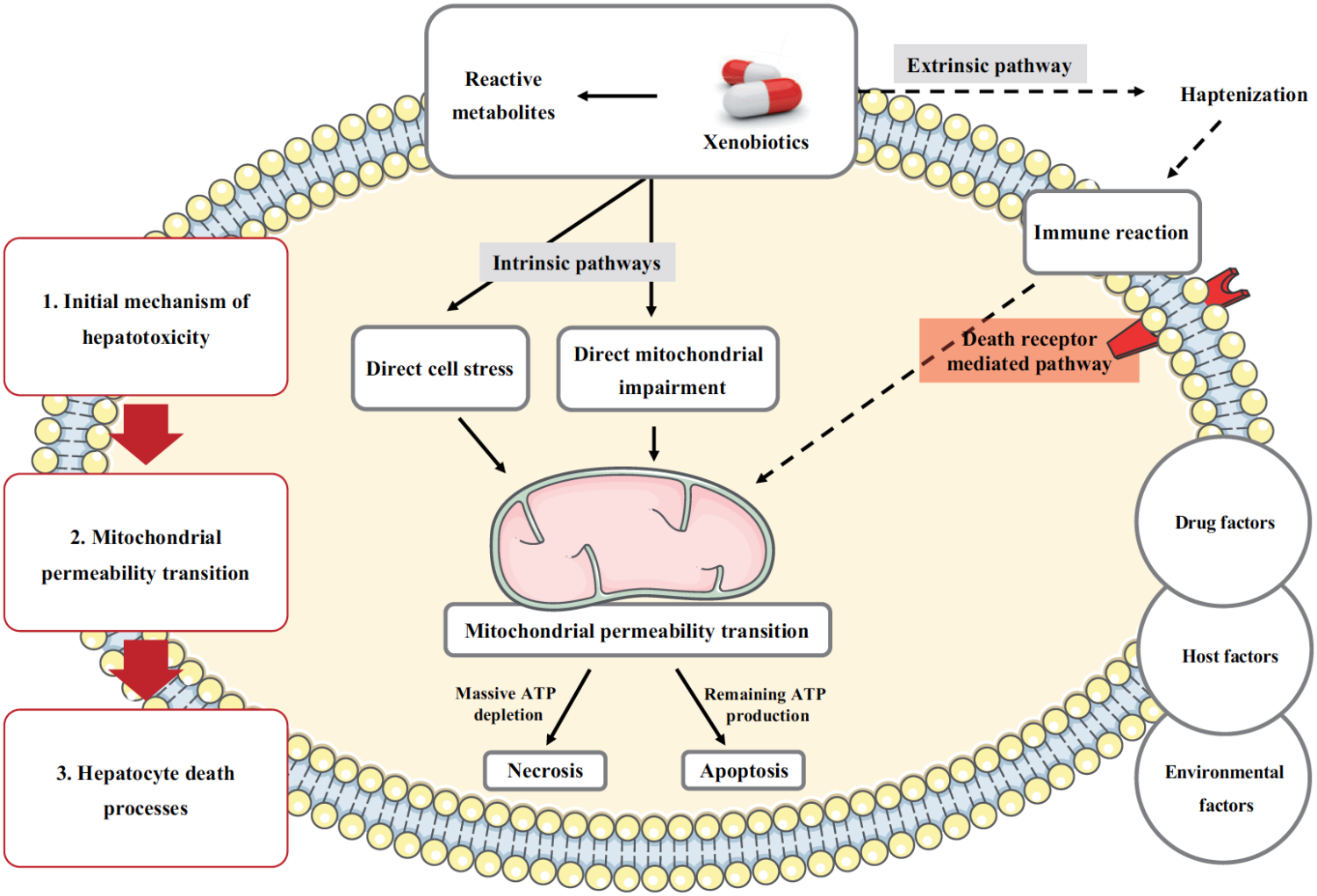


Figure 1. Schematic representation of a three-step mechanistic model of hepatotoxicity. Adapted from Russmann et al. (2009).

Définition « DILI »

- Idiosyncratic drug-induced liver injury
  an adverse hepatic reaction that is unexpected on the basis of the pharmacological action of the drug administered
- 7-15 % des hépatites aiguës (EU & USA)
  hors surdosage volontaire au paracétamol
- Retrait du marché des médicaments
- Critères classiques d'imputabilité en pharmacovigilance

DILI

Table 1. Common drugs implicated in idiosyncratic drug-induced liver injury according to studies from different countries

Iceland[6]	American DILIN[7]	Spanish registry[8]	UK[9]
Amoxicillin-clavulanate	Amoxicillin-clavulanate	Amoxicillin-clavulanate	Amoxicillin-clavulanate
Diclofenac	Isoniazid	Isoniazid	Diclofenac
Azathioprine	Nitrofurantoin	Combined anti-tuberculous therapy	Tricyclic antidepressants
Infliximab	Trimethoprim-sulfamethoxazole	Flutamide	Macrolides
Nitrofurantoin	Minocycline	Ibuprofen	Chlorpromazine

DILIN = drug-induced liver injury network

Clin Med 2016 ; 16 (6) : s104-s109

DILI

TABLE 1. Epidemiology of Drug-Induced Liver Injury

Group	N	F (%)	Age (y) (mean)	Drug (or class) no. 1	Drug (or class) no. 2	Drug (or class) no. 3	Herbal	Death	LTx	Chronicity
China (2013)	24,112	46	-	Tuberculosis medications 31%	CAMs (19%)	Antibiotics (10%)	19%	3%	-	-
France (2002)	34	65	M: 51 F: 58	Amoxicillin/clavulanate (12%)	NSAIDs (12%)	Nevirapine (9%)	-	6%	0	0
Iceland (2013)	96	56	55	Amoxicillin/clavulanate (22%)	Diclofenac (6%)	Azathioprine (4%)	16%	1%	0	(7) 7%
Korea (2012)	371	63	49	Antifungal (% not available)	-	-	63%[b]	-	(2) 1%	(3) 1%
Spain (2005)	461	49	53	Amoxicillin/clavulanate (13%)	T-2: Ebrotidine (5%) T-2: INH/rifampin/pyrazinamide (5%)	Ibuprofen (4%)	2%	5%	(8) 2%	(46) 10%
United States (2008)	300	60	48	Amoxicillin/clavulanate (8%)	Nitrofurantoin (4%)	T-3: Isoniazid (4%) T-3: Trimethoprim-sulfamethoxazole (4%)	9%	8%	(9) 2%	14%

[a]CAM = complementary and alternative medicine; F = female; M = male; NSAID = nonsteroidal anti-inflammatory drug; LTx = liver transplantation; T = tie.
[b]Includes herbal medicines, health foods and dietary supplements, medicinal herbs or plants, folk remedies, and herbal preparations.

Mayo Clin Proc 2014 ; 89(1) : 95-106

Définition « DILI »

- Sans perturbation préalable des enzymes hépatiques :
  - **ALAT > 5 x** limite supérieure de référence
  - **ph. alcaline > 2 x**
  - **bilirubine > 2 x et ALAT > 3 x**
- Avec perturbation préalable
  - remplacer la référence par la moyenne des tests hépatiques connus

Définition « DILI »

- Limitations :
  - Tableau spécifique tel que
    méthotrexate
        (fibrose, hyperplasie régénérative nodulaire)
    valproate
        (toxicité mitochondriale)
    tamoxifene
        (steatose)
  - Élévation isolée ASAT, gammaGT ou Bili
    pas suffisantes

Définition « DILI »

- Rapport taux de variation ALAT divisé

  Rapport taux de variation ph. Alc.

  (ALAT/réf) ÷ (ph. alc./réf) = **R**

- **Hépatocellulaire : R ≥ 5**
- **Atteinte mixte : 2‹ R › 5**
- **Cholestatique : R ≤ 2**

Définition « DILI »

Box 3 DILI severity index

Category	Severity	Description
1	Mild	Elevated alanine aminotransferase/ alkaline phosphatase (ALT/ALP) concentration reaching criteria for DILI* but bilirubin concentration <2× upper limit of normal (ULN)
2	Moderate	Elevated ALT/ALP concentration reaching criteria for DILI* and bilirubin concentration ≥2× ULN, or symptomatic hepatitis
3	Severe	Elevated ALT/ALP concentration reaching criteria for DILI*, bilirubin concentration ≥2× ULN, and one of the following: • International normalized ratio ≥1.5 • Ascites[73] and/or encephalopathy, disease duration <26 weeks, and absence of underlying cirrhosis[31] • Other organ failure considered to be due to DILI
4	Fatal or transplantation	Death or transplantation due to DILI

*Criteria for DILI are defined in **Box 1**

Level of evidence: 1b (inception cohort studies)

Clinical Pharmacol Ther 2011 ; 89 (6) : 806-815

Définition « DILI »

- Durée :
  « hépatite médicamenteuses persistante »
  cytolytique ou mixte > 3 mois
  cholestatique > 6 mois

  « hépatite médicamenteuse chronique »
  > 12 mois

RUCAM

- Check-list et Scores atteintes hépatocellulaires
- idem mixtes ou cholestatiques

  score d'imputabilité :

≥ 9	hautement probable
6-8	probable
3-5	possible
1-2	improbable
≤0	exclu

- Sens 86 % - Spéc 89 % - VPP 93 % - VPN 78 %

Items for Hepatocellular Injury	Score	Result
1. Time to onset from the beginning of the drug/herb		
• 5–90 days (rechallenge: 1–15 days)	+2	☐
• <5 or >90 days (rechallenge: >15 days)	+1	☐
Alternative: Time to onset from cessation of the drug/herb		
• ⩽15 days (except for slowly metabolized chemicals: >15 days)	+1	☐
2. Course of ALT after cessation of the drug/herb		
Percentage difference between ALT peak and N		
• Decrease ⩾ 50% within 8 days	+3	☐
• Decrease ⩾ 50% within 30 days	+2	☐
• No information or continued drug use	0	☐
• Decrease ⩾ 50% after the 30th day	0	☐
• Decrease < 50% after the 30th day or recurrent increase	−2	☐
3. Risk factors		
• Alcohol use (current drinks/d: >2 for women, >3 for men)	+1	☐
• Alcohol use (current drinks/d: ⩽2 for women, ⩽3 for men)	0	☐
• Age ⩾ 55 years	+1	☐
• Age < 55 years	0	☐
4. Concomitant drug(s)/herb(s)		
• None or no information	0	☐
• Concomitant drug/herb with incompatible time to onset	0	☐
• Concomitant drug/herb with compatible or suggestive time to onset	−1	☐
• Concomitant drug/herb known as hepatotoxin and with compatible or suggestive time to onset delete marking right side above	−2	☐
• Concomitant drug/herb with evidence for its role in this case (positive rechallenge or validated test)	−3	☐
5. Search for alternative causes	Tick if negative	Tick if not do
Group I (7 causes)		
• HAV: Anti-HAV-IgM	☐	☐
• Hepatobiliary sonography / colour Doppler	☐	☐
• HCV: Anti-HCV, HCV-RNA	☐	☐
• HEV: Anti-HEV-IgM, anti-HEV-IgG, HEV-RNA	☐	☐
• Hepatobiliary sonography/colour Doppler sonography of liver vessels/ endosonography/CT/MRC	☐	☐
• Alcoholism (AST/ALT ⩾ 2)	☐	☐
• Acute recent hypotension history (particularly if underlying heart disease)	☐	☐
Group II (5 causes)		
• Complications of underlying disease(s) such as sepsis, metastatic malignancy, autoimmune hepatitis, chronic hepatitis B or C, primary biliary cholangitis or sclerosing cholangitis, genetic liver diseases	☐	☐
• Infection suggested by PCR and titer change for		
◦ CMV (anti-CMV-IgM, anti-CMV-IgG)	☐	☐
◦ EBV (anti-EBV-IgM, anti-EBV-IgG)	☐	☐
◦ HSV (anti-HSV-IgM, anti-HSV-IgG)	☐	☐
◦ VZV (anti-VZV-IgM, anti-VZV-IgG)	☐	☐
Evaluation of groups I and II		
• All causes-groups I and II—reasonably ruled out	+2	☐
• The 7 causes of group I ruled out	+1	☐
• 6 or 5 causes of group I ruled out	0	☐
• Less than 5 causes of group I ruled out	-2	☐
• Alternative cause highly probable	-3	☐
6. Previous hepatotoxicity of the drug/herb		
• Reaction labelled in the product characteristics	+2	☐
• Reaction published but unlabelled	+1	☐
• Reaction unknown	0	☐
7. Response to unintentional reexposure		
• Doubling of ALT with the drug/herb alone, provided ALT below 5N before reexposure	+3	☐
• Doubling of ALT with the drug(s)/herb(s) already given at the time of first reaction	+1	☐
• Increase of ALT but less than N in the same conditions as for the first administration	−2	☐
• Other situations	0	☐
Total score for the case		☐

Int J Mol Sci 2016 ; 17 : 14

Items for Cholestatic or Mixed Liver Injury	Score	Result
1. Time to onset from the beginning of the drug/herb		
• 5–90 days (rechallenge: 1–90 days)	+2	▫
• <5 or >90 days (rechallenge: >90 days)	+1	▫
Alternative: Time to onset from cessation of the drug/herb		
• (except for slowly metabolized chemicals: ⩽30 days)	+1	▫
2. Course of ALP after cessation of the drug/herb		
Percentage difference between ALP peak and N		
• Decrease ⩾ 50% within 180 days	+2	▫
• Decrease < 50% within 180 days	+1	▫
• No information, persistence, increase, or continued drug/herb use	0	▫
3. Risk factors		
• Alcohol use current drinks/d: >2 for women, >3 for men)	+1	▫
• Alcohol use (current drinks/d: ⩽2 for women, ⩽3 for men)	0	▫
• Pregnancy	+1	▫
• Age ⩾ 55 years	+1	▫
• Age < 55 years	0	▫
4. Concomitant use of drug(s)/herb(s)		
• None or no information	0	▫
• Concomitant drug/herb with incompatible time to onset	0	▫
• Concomitant drug/herb with compatible or suggestive time to onset	−1	▫
• Concomitant drug/herb known as hepatotoxin and with compatible or suggestive time to onset	−2	▫
• Concomitant drug/herb with evidence for its role in this case (positive rechallenge or validated test)	−3	▫
5. Search for alternative causes	Tick if negative	Tick if not done
Group I (7 causes)		
• HAV: Anti-HAV-IgM	▫	▫
• HBV: HBsAg, anti-HBc-IgM, HBV-DNA	▫	▫
• HCV: Anti-HCV, HCV-RNA	▫	▫
• HEV: Anti-HEV-IgM, anti-HEV-IgG, HEV-RNA	▫	▫
• Hepatobiliary sonography/colour Doppler sonography of liver vessels/endosonography/CT/MRC	▫	▫
• Alcoholism (AST/ ALT ⩾ 2)	▫	▫
• Acute recent hypotension history (particularly if underlying heart disease)	▫	▫
Group II (5 causes)		
• Complications of underlying disease(s) such as sepsis, metastatic malignancy, autoimmune hepatitis, chronic hepatitis B or C, primary biliary cholangitis or sclerosing cholangitis, genetic liver diseases	▫	▫
• Infection suggested by PCR and titer change for		
• CMV (anti-CMV-IgM, anti-CMV-IgG)	▫	▫
• EBV (anti-EBV-IgM, anti-EBV-IgG)	▫	▫
• HSV (anti-HSV-IgM, anti-HSV-IgG)	▫	▫
• VZV (anti-VZV-IgM, anti-VZV-IgG)	▫	▫
Evaluation of group I and II		
• All causes—groups I and II—reasonably ruled out	+2	▫
• The 7 causes of group I ruled out	+1	▫
• 6 or 5 causes of group I ruled out	0	▫
• Less than 5 causes of group I ruled out	−2	▫
• Alternative cause highly probable	−3	▫
6. Previous hepatotoxicity of the drug/herb		
• Reaction labelled in the product characteristics	+2	▫
• Reaction published but unlabelled	+1	▫
• Reaction unknown	0	▫
7. Response to unintentional reexposure		
• Doubling of ALP with the drug/herb alone, provided ALP below 2N before reexposure	+3	▫
• Doubling of ALP with the drugs(s)/herbs(s) already given at the time of first reaction	+1	▫
• Increase of ALP but less than N in the same conditions as for the first administration	−2	▫
• Other situations	0	▫
Total score for the case		▫

Int J Mol Sci 2016 ; 17 : 14

Missed diagnoses as alternatives to drug induced liver injury	Missed diagnoses as alternatives to herb induced liver injury
Hepatitis B	Hepatitis E
Hepatitis C	Hepatitis by EBV
Hepatitis E	Hepatitis by HSV
Hepaits by CMV	Hepatitis by VZV
Hepatitis by EBV	Giant cell hepatitis
Virus hepatitis	Infection with hepatic involvement
Autoimmune hepatitis	Autoimmune hepatitis
Hemochromatosis	LKM positive autoimmune hepatitis
Wilson's disease	SMA positive autoimmune hepatitis
Ischemic hepatitis	Primary biliary cirrhosis
Cardiac hepatopathy	Overlap syndrome
Liver cirrhosis	Alcoholic liver disease/cirrhosis
Fatty liver	Non-alcoholic liver cirrhosis
Non alcoholic steatohepatitis	Previous gastric bypass operation
Alcoholic liver disease	Cardiac hepatopathy
Past liver transplantation	Polytrauma
Unknown liver disease	Preexisting liver diseases/cirrhosis
Gilbert's syndrome	Questionable liver disease
Benign recurrent intrahepatic cholestasis	Liver injury by co-medication
Bile duct diseases	Non-alcoholic steatohepatitis
Tumors	Hyperthyroid hepatopathy
Lymphoma	Biliary diseases
Systemic sepsis	Pancreatitis
Chlamydial infection	Rhabdomyolysis by statin
Thyroid disease	
Postictal state	
Polymyositis	

Int J Mol Sci 2016 ; 17 : 14

Int J Mol Sci 2017 ; 18 : 803

Table 2. Frequency of specified alternative causes of idiosyncratic DILI.

Alternative Causes	*n*	Frequency %
Biliary diseases	39	11.89
Autoimmune hepatitis	35	10.67
Hepatitis B or C	28	8.54
Hepatic tumor	26	7.93
Ischemic hepatitis	24	7.32
Hepatitis E	20	6.10
Sepsis	20	6.10
Liver injury due to comedication	19	5.79
Viral Hepatitis	18	5.49
Past liver transplantation	17	5.18
Alcoholic liver disease	16	4.88
Fatty liver	9	2.44
Non-alcoholic steatohepatitis	9	2.44
Hepatitis C	6	1.83
Cardiac hepatopathy	5	1.52
Thyroid hepatopathy	4	1.22
Primary biliary cholangitis	3	0.92
Primary sclerosing cholangitis	3	0.92
Gilbert syndrome	3	0.92
CMV Hepatitis	2	0.61
EBV Hepatitis	2	0.61
Hemochromatosis	2	0.61
Wilson disease	2	0.61
Paracetamol overdose	2	0.61
Postictal state	2	0.61
Bone disease	2	0.61
Lymphoma	2	0.61
Preexisting liver cirrhosis	2	0.61
Hepatitis B	1	0.31
Benign recurrent intrahepatic cholestasis	1	0.31
Rhabdomyolysis	1	0.31
Polymyositis	1	0.31
Chlamydial infection	1	0.31
HIV infection	1	0.31
Total	328	100%

Among the study cohort, clearly defined alternative diagnoses were available for 328 patients. Updated details from previous reports [8,9]. Abbreviations: CMV, Cytomegalovirus; DILI, Drug induced liver injury; EBV, Epstein Barr virus; HIV, Human immunodeficiency virus.

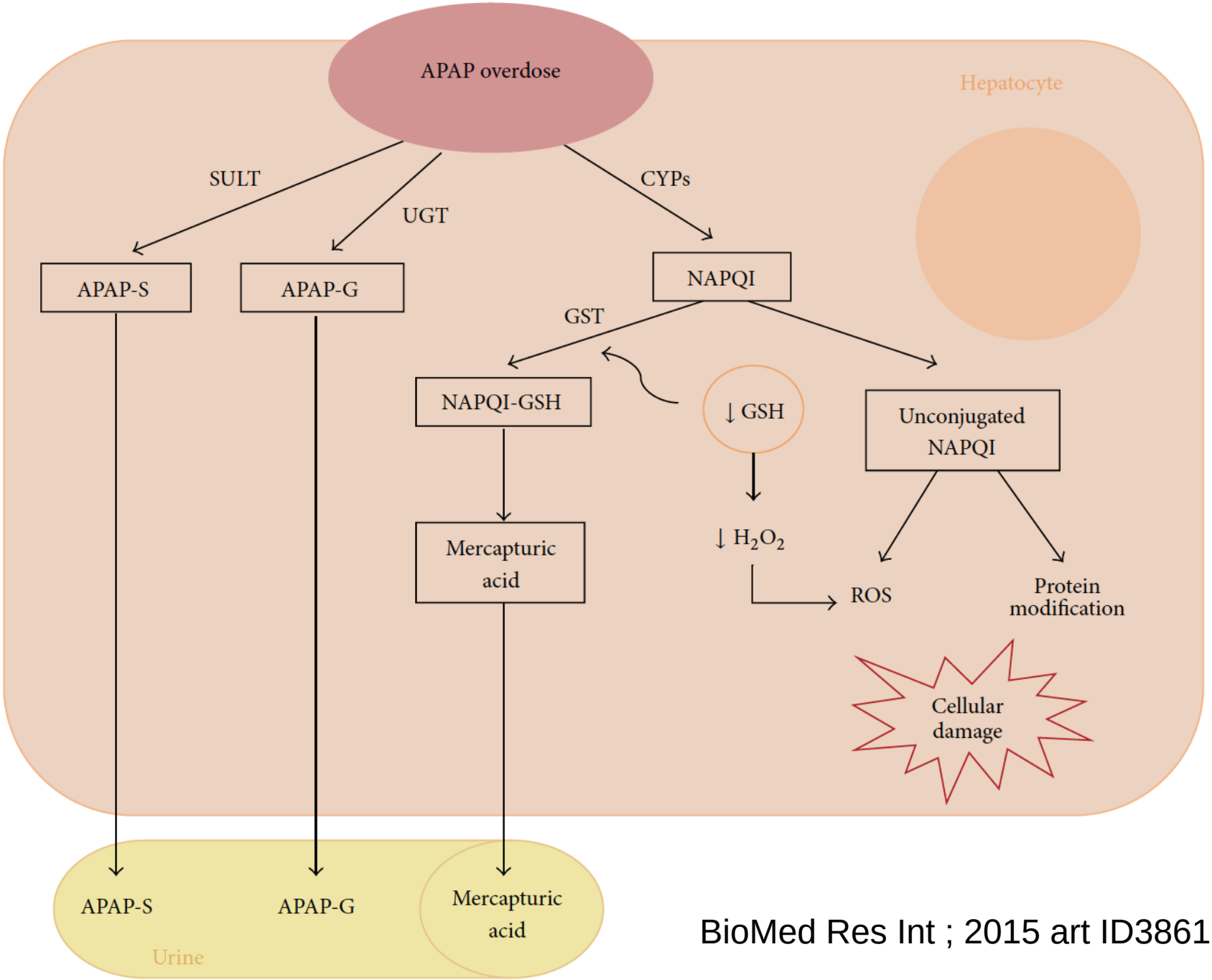
Bio-marqueurs ?

Table 2. The most common combinations and concentration fluctuations of urinary metabolites associated with different manifestations of hepatic lesions.

Potential urinary metabolite biomarkers	Histological damage	Example of drugs	References
(↓) TCA intermediates	Multiple types of damage	APAP, Isoniazid, Fenofibrate, Pravastatin, Monocrotaline, Pentamethylchromanol, Bay 41-4109, ANIT, GalN, BHT, Hydrazine	(Beckwith-Hall et al. 1998; Waters et al. 2001; Bollard et al. 2005a; Lenz et al. 2007; Shi et al. 2007; Sun et al. 2008; Ohta et al. 2009; Sumner et al. 2010; Bando et al. 2011; Parman et al. 2011; Conotte & Colet 2014)
(↓) Hippurate	Multiple types of damage	APAP, Isoniazid, Valproic acid, Pravastatin, Monocrotaline, Methotrexate, Pentamethylchromanol, GalN, BHT, Methylene dianiline, Hydrazine, Thioacetamide	(Beckwith-Hall et al. 1998; Bollard et al. 2005a; Ishihara et al. 2006; Lenz et al. 2007; Sun et al. 2008; Sumner et al. 2010; Parman et al. 2011; Kim JW et al. 2013; Conotte & Colet 2014; Kyriakides et al. 2014; Wei et al. 2014; Zhang et al. 2014)
(↑) Lactate	Multiple types of damage	APAP, Z24, Isoniazid, Fenofibrate, Bay 41-4109, ANIT, GalN, Methylene dianiline, Hydrazine	(Beckwith-Hall et al. 1998; Bollard et al. 2005a; Ishihara et al. 2006; Wang et al. 2006; Shi et al. 2007; Ohta et al. 2009; Sumner et al. 2010; Fukuhara et al. 2011)
(↑) Ketone bodies	Multiple types of damage	Isoniazid, Bay 41-4109, GalN, Methylene dianiline, Thioacetamide	(Ishihara et al. 2006; Shi et al. 2007; Sumner et al. 2010; Wei et al. 2014)
(↑) Taurine	Steatosis	ANIT, Hydrazine	(Waters et al. 2001; Bollard et al. 2005a)
(↑) Taurine and Creatine	Necrosis	Isoniazid, Pravastatin, ANIT, GalN, BHT	(Beckwith-Hall et al. 1998; Lenz et al. 2007; Sumner et al. 2010)
(↓) Taurine	Necrosis	Z24, Thioacetamide	(Wang et al. 2006; Wei et al. 2014)
(↓) Taurine and (↑) Creatine	Cholestasis with necrosis	Monocrotaline, GalN, Methylene dianiline	(Ishihara et al. 2006; Conotte & Colet 2014)
(↓) Valine and Methyl malonate	Cholestasis	Cyclosporine A	Ishihara et al. (2009)
(↑) Bile acids, Valine and Methyl malonate	Cholestasis	4,4′-Methylene dianiline, ANIT	Ishihara et al. (2009)

(↑) indicates increased metabolite level in urine, (↓) indicates decreased metabolite level in urine.
ANIT: alpha-naphthylisothiocyanate; APAP: N-acetyl-p-aminophenol, Acetaminophen; BHT: butylated hydroxytoluene; GalN: galactosamine.

Crit Rev Toxicol 2017 ; 47 (8):633-649



BioMed Res Int ; 2015 art ID386186

FIGURE 1: Hepatotoxicity of APAP. APAP: acetaminophen; SULT: sulfotransferase; UGT: glucuronosyltransferase; CYPs: P450 cytochromes; APAP-S: APAP-sulfonate; APAP-G: APAP-glucuronide; NAPQI: N-acetyl-p-benzoquinone imine; GST: glutathione S-transferase; GSH: glutathione; ROS: reactive oxygen species.

co-risques

- NAFLD : nonalcoholic fatty liver disease associé à obésité

  décrit avec : halothane, isoflurane
  paracétamol ?
  corticoides
  irinotecan
  methotrexate
  rosiglitazone

co-risques

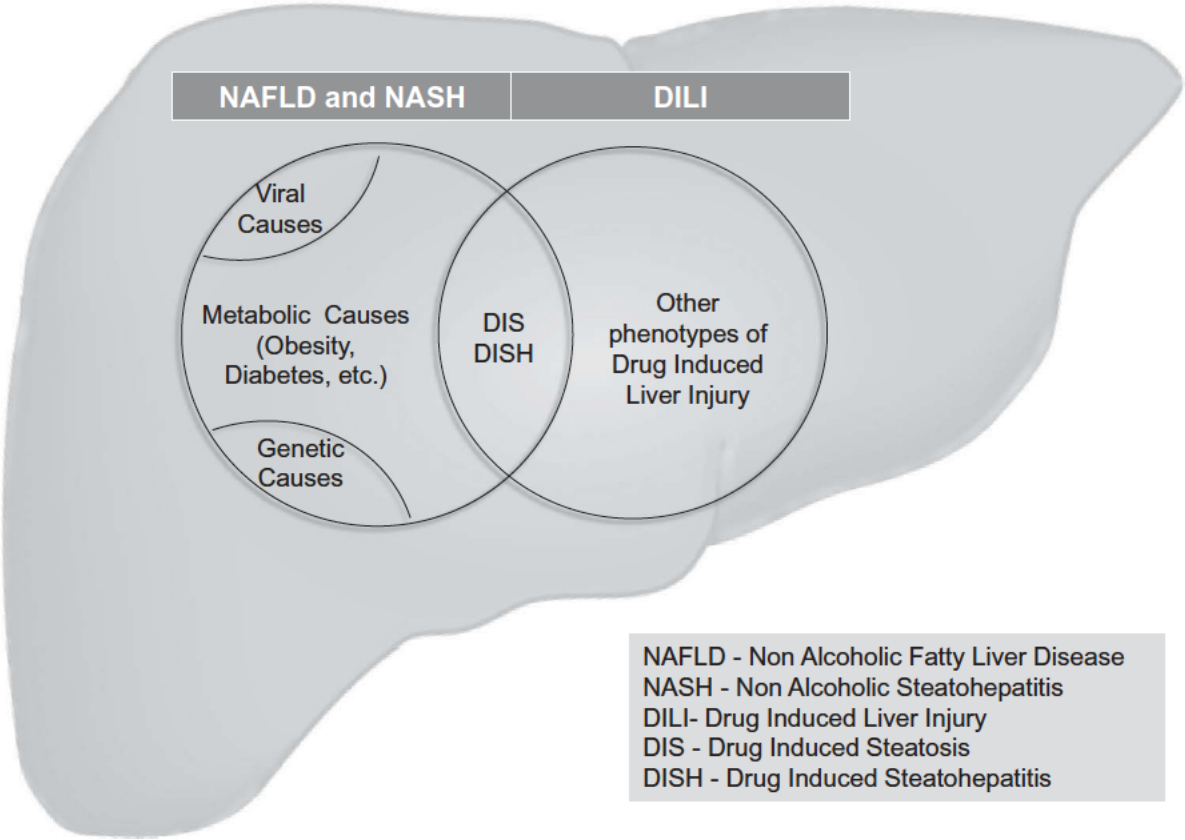


Figure 1. Drug Induced Steatohepatitis (DISH) is a form of drug induced liver injury (DILI) that shares pathological features characterized by lipid accumulation and inflammatory changes, similar to non alcoholic steatohepatitis arising due to other causes.

Exp Opinion Drug Metabol Toxicol 2017 ; 13(2) : 193-204)

co-risques

Table 1. Comparison of some steatohepatitic drugs.

Drug	Chemical class	Indication	Primary mechanism of action	Histological type of injury	DISH mechanisms involved
Amiodarone	Benzofuran	Antianginal, antiarrhythmic (Class III)	Prolongs myoardial action potential, Antagonism of α- and β-adrenergic receptors	Microvesicular, macrovesicular, steatohepatitis	1, 2, 3, 4
Cocaine	Alkaloid ester	Local anesthetic	Blockade of the dopamine transporter protein	Microvesicular	2
5-Fluorouracil	Fluoropyrimidine	Antineoplastic,	Inhibits thymidylate synthase	Macrovesicular	2
Glucocorticoids	Steroid	Antiinflammatory, immunosupression	Glucocorticoid receptor agonist	Microvesicular, macrovesicular	1,2
Methotrexate	Pteridine	Antirheumatic, antineoplastic, antimetabolite	Inhibits dihydrofolate reductase, Immune modulation	Macrovesicular, steatohepatitis	2
Nucleoside reverse transcriptase inhibitors (NRTIs)	Multiple	HIV	Inhibits reverse transcriptase	Microvesicular	1,2,3
Perhexiline	Piperidine	Antianginal	Inhibits carnitine palmitoyltransferase I		2, 4
Tamoxifen	Stilbene	Antineoplastic	Selective estrogen receptor modulator	Macrovesicular, steatohepatitis	1, 2, 3
Tetracycline	Tetracylcine	Broad spectrum antibiotic	Inhibition of bacterial protein synthesis	Microvesicular	2,3
Valproic acid	Fatty acyl	Antiepileptic, mood stabilizer	Increased brain concentrations of GABA	Microvesicular	2

DISH mechanisms: 1: increased fatty acid synthesis; 2: decreased fatty acid β-oxidation; 3: decreased lipoprotein export; 4: increased mobilization and uptake of fatty acids.

Exp Opinion Drug Metabol Toxicol 2017 ; 13(2) : 193-204)

co-risques

HLA and non-HLA genes associated with drug induced liver injury (DILI) (modified from Daly [79]).

HLA associated genes				
	Pattern of reaction	Drugs	HLA loci	
Liver	Hepatocellular/Cholestatic type	Amoxicillin–clavulanate	DRB1*1501-DQB1*0602 A*0201	
	Cholestatic type	Flucloxacillin	B*5701	
	Hepatocellular type	Ximelagatran	DRB1*0701-DQA1*0201	
	Cholestatic type	Ticlopidine	A*3303	
	Cholestatic type	Lumiracoxib	DRB1*1501-DQB1*0602	
	Hepatocellular/Mixed type	Nimesulide	DRB1*0708-DQB1*0204 DRB1*0713-DQB1*0206	
	Hepatocellular type	Ketoprofen	DRB1*0413-DQB1*0306	
	Hepatocellular type	Green Tea	DRB1*0103-DQB1*0205	
Non-HLA associated genes				
Drug metabolism and transporters (ATP binding cassette)		Liver injury		Phase II
			Isoniazid	NAT2
			Diclofenac	UGT2B7
				UGT1A
		Myopathy/Liver injury	Simvastatin	Transporters SLCO1B1
		Liver injury	Diclofenac	ABCB11 ABCC2
		Hepatocellular		1549
		Cholestatic		1774
Immune and inflammatory system		Liver injury	Diclofenac	IL-4 C590A
				IL-10 C627A
		Liver injury	Anti tubercular drugs	IL-6
		Liver injury	Amoxicillin–clavulanate	STAT-4
			Flucloxacillin	STAT3
			Anti tubercular drugs	ST6GAL1

Eur J Int Medl 2016 ; 28 : 9-16

HILI

- Identification précise de la plante (confusions)
- Adjuvants ou contaminants larvés (métaux lourds, médecine ayurvedique)
- Impuretés (aflatoxine)
- 9 à 24 % des DILI (USA ---CHI)
- Étude multicentrique prospective coréenne a mesuré une incidence de 0,6 % chez des usagers de plante (6 / 1001)

HILI

- Cimicifuga racemosa (ménaupose) – hépatite auto-immune
- Symphyti radix (Consoude) (arthrose)
  (alcaloide pyrrazolidine racine>feuille) – hépatite véno-occlusive
- Germandrée (amaigrissant) – hépatite
  (interdit en F dès 1992)
- Kava (sédatif) – plusieurs cas de Tx hépatique en Eu
- Chelidoine (troubles digestifs) – EMA : évaluation négative (2012)
- Médecine traditionnelle chinoise (CHM)

Ce qu'on peut retenir

- https://livertox.nlm.nih.gov/index.html
- DILI et HILI sont des diagnostics d'exclusion (bio-marqueurs…)
  - Pharmacovigilance
  - RUCAM
    Labo : **R** (cytolytique vs mixte-cholestatique) + check liste et scores
- Critères : Patient – Agent – Environnement
  - NALD / obésité ; HLA ; phénotype

Références

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