DRUG INDUCED LIVER INJURY

G-ECHO FELLOW PRESENTATION 19 MAY 2025

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Project ECHO®
Gastroenterology Foundation of sub Saharan Africa

G-ECHO
GI HEPATOLOGY ECHO OF SUB-SAHARAN AFRICA
ESTABLISHED 2020

OUTLINE

- EPIDEMIOLOGY
- DEFINTIONS
- CAUSES
- RISK FACTORS
- CLINICAL PRESENTATION
- DIAGNOSIS
- APPROACH
- MANAGEMENT
- SPECIFIC SCENARIOS

EPIDEMIOLOGY

- Incidence varies per region
- Overall rare: 14-19/100 0000 → 1% of all causes of acute liver injury
- HOWEVER: commonest cause of acute liver failure in West → 10-50% mortality
- Data from SSA lacking
  - Common culprit drugs: anti-tuberculosis and ART

EPIDEMIOLOGY

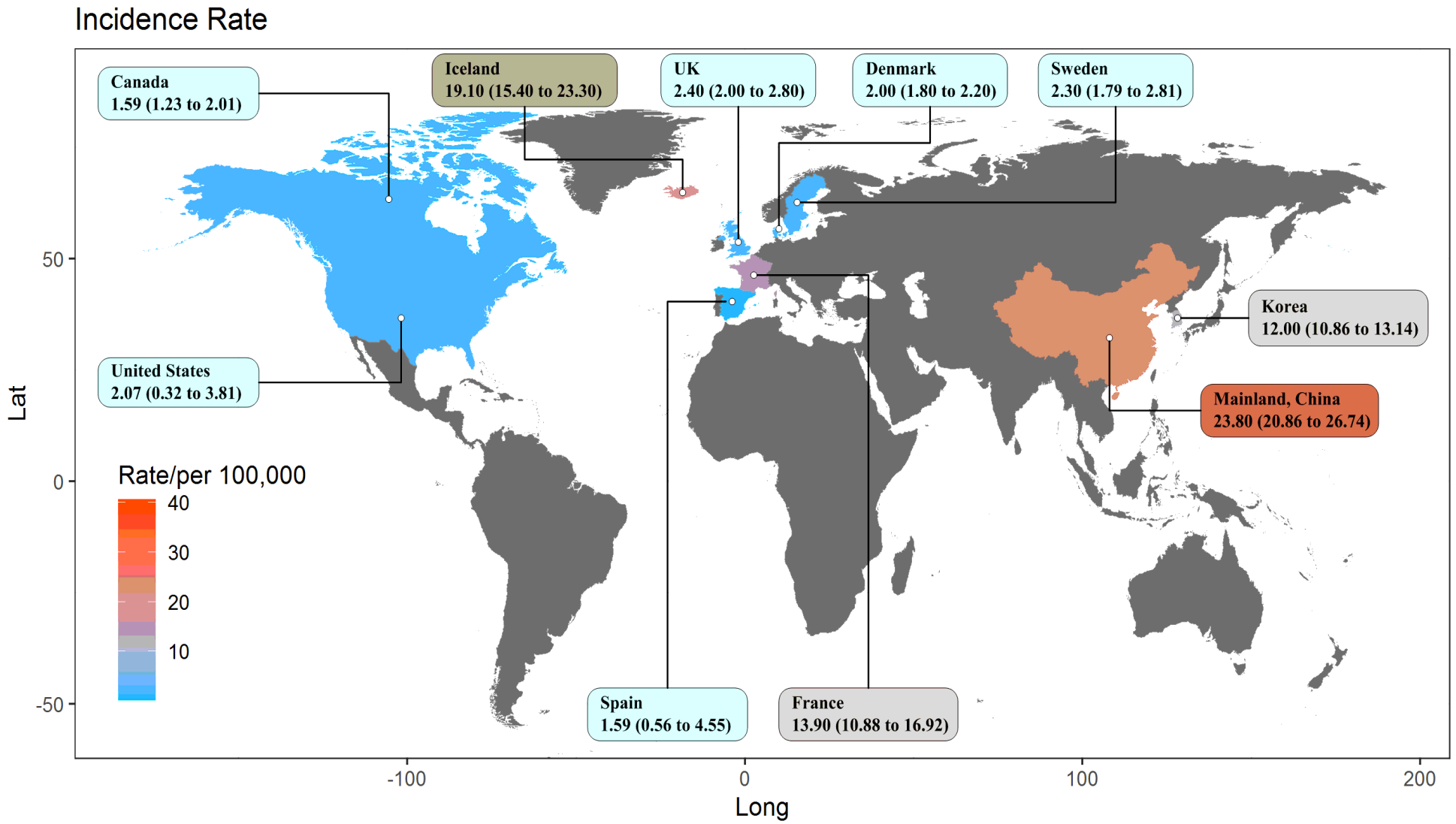


Table 2. Summary of global DILI incidence showing origin, most common offending drug and the population investigated.

	Notable findings	Frequently implicated drugs	Cohort type	Causality assessment	Study
Sweden	19.1 per 100,000	Antibiotics 22% NSAIDs 6%	Severely jaundiced	RUCAM	(Björnsson et al. 2013)
South Korea	12 per 100,000	Herbal – 27.5%	Hospitalized query liver injury	RUCAM	(Suk et al. 2012)
USA (Delaware)	2.7 per 100,000 adult residents	Herbal Dietary Supplements – 43% Antimicrobials – 36%	Surveillance of DILI symptoms from population	RUCAM	(Vega et al. 2017)
France	13.9 (±2.4%) per 100,000	Antimicrobials 19% NSAIDs 16%	Symptomatic drug induced injuries	RUCAM	(Sgro et al. 2002)
Sweden	2.3 per 100,000	Antimicrobials 30% NSAIDs 22%	Suspected DILI diagnosed outpatients	RUCAM	(De Valle et al. 2006)
United Kingdom	2.4 per 100,000	Antimicrobials NAIDs	Retrospective search of GPRD database	None	(De Abajo et al. 2004)
China	-	Chinese herb medicine 53.62%	Confirmed DILI cases	RUCAM	(Lai et al. 2012)
China	92.95 per 100,000 inpatients	Chinese herbal medicine 36.01%	DILI diagnosis at discharge	American College of Gastroenterology Clinical Guidelines	(Ou et al. 2015)
South Africa	-	ART 35% TBT 27%	Patients with liver disfunction	None	(Schutz et al. 2012)
Nigeria	18.2%		Patients prescribed Anti-TB medication	None	(Isa et al. 2016)
China	19.4%	Antimicrobials 32% Glucocorticoids- 24%	Inpatients ALT 10× ULN	RUCAM	(Xu et al. 2012)
India	-	ATT – 49% Anti-epileptic- 12% ART – 10%	Patients with suspected DILI	RUCAM	(Rathi et al. 2017)

Herbal and dietary supplements

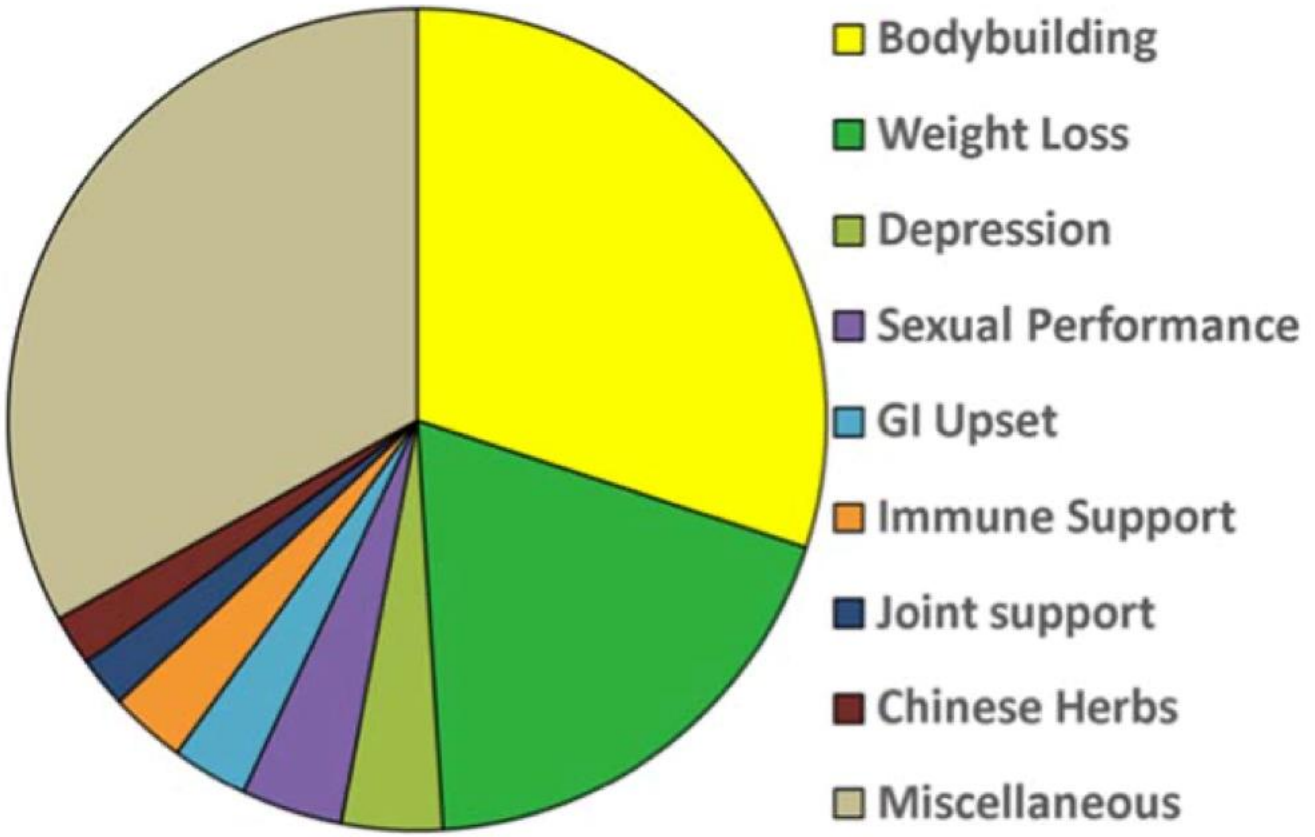


FIG. 2. Distribution of HDS implicated in liver injury in the DILIN.

DEFINITIONS AND CLASSIFICATION

- DIRECT HEPATOTOXICITY
- IDIOSYNCRATIC HEPATOTOXICITY
- INDIRECT HEPATOTOXICITY
- ADAPTATION

DEFINITIONS AND CLASSIFICATION

- DIRECT HEPATOTOXICITY
- IDIOSYNCRATIC HEPATOTOXICITY
- INDIRECT HEPATOTOXICITY
- ADAPTATION
  - Asymptomatic elevation of LFTs when starting a drug
  - Usually resolve without intervention
  - Underlying mechanisms:
    - changes in drug-metabolizing enzyme activity,
    - upregulation of hepatoprotective pathways
    - or downregulation of hypersensitivity reactions to the drug or its metabolites.

DEFINITIONS AND CLASSIFICATION

- DIRECT HEPATOTOXICITY

PARACETAMOL

INTRINSICALLY TOXIC
COMMON
PREDICTABLE
DOSE-DENPENDANT
REPRODUCIBLE IN ANIMAL MODELS
SHORT LATENCY PERIOD

DEFINITIONS AND CLASSIFICATION

- IDIOSYNCRATIC HEPATOTOXICITY

  NITROFURANTOIN INDUCED AIH
  AMIODARONE INDUCED HEPATITIS
  ANTI-TUBERCULOSIS/ART

NO INTRINSIC HEPATOXOCITY
LIVER INJURY IN RARE CIRCUMSTANCES
UNPREDICTABLE
NOT DOSE DEPENDANT
NOT REPRODUCIBLE

DEFINITIONS AND CLASSIFICATION

- INDIRECT HEPATOTOXICITY

PI & STEATOSIS

HEP B REACTIVATION WITH IMMUNOSUPRESSIVE AGENTS

- **CAUSED BY ACTION OF DRUG**
- **PARTIALLY PREDICTABLE**
- **NOT DOSE DEPENDANT**

DEFINITIONS AND CLASSIFICATION

Table 1. Drug-Induced Liver Injury According to Type.*

Variable	Direct Hepatotoxicity	Idiosyncratic Hepatotoxicity	Indirect Hepatotoxicity
Frequency	Common	Rare	Intermediate
Dose-related	Yes	No	No
Predictable	Yes	No	Partially
Reproducible in animal models	Yes	No	Not usually
Latency (time to onset)	Typically rapid (days)	Variable (days to years)	Delayed (months)
Phenotypes	Acute hepatic necrosis, serum enzyme elevations, sinusoidal obstruction, acute fatty liver, nodular regeneration	Acute hepatocellular hepatitis, mixed or cholestatic hepatitis, bland cholestasis, chronic hepatitis	Acute hepatitis, immune-mediated hepatitis, fatty liver, chronic hepatitis
Most commonly implicated agents	High doses of acetaminophen, niacin, aspirin, cocaine, IV amiodarone, IV methotrexate, cancer chemotherapy	Amoxicillin–clavulanate, cephalosporins, isoniazid, nitrofurantoin, minocycline, fluoroquinolones, macrolide antibiotics	Antineoplastic agents, glucocorticoids, monoclonal antibodies (against tumor necrosis factor, CD20, checkpoint proteins), protein kinase inhibitors
Cause	Intrinsic hepatotoxicity when agent given in high doses	Idiosyncratic metabolic or immunologic reaction	Indirect action of agent on liver or immune system

* IV denotes intravenous.

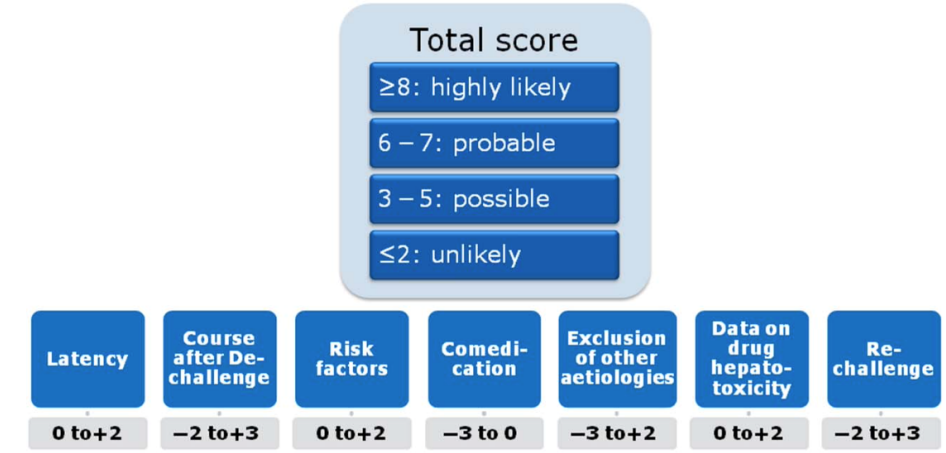
N Engl J Med 2019;381:264-73.
DOI: 10.1056/NEJMra1816149

DETERMINE CAUSALITY

- Various scoring systems
- RUCAM

- ***Latency***
- ***Dechallenge***
- ***Rechallenge***
- ***Drug phenotype and potential to cause hepatotoxicity***

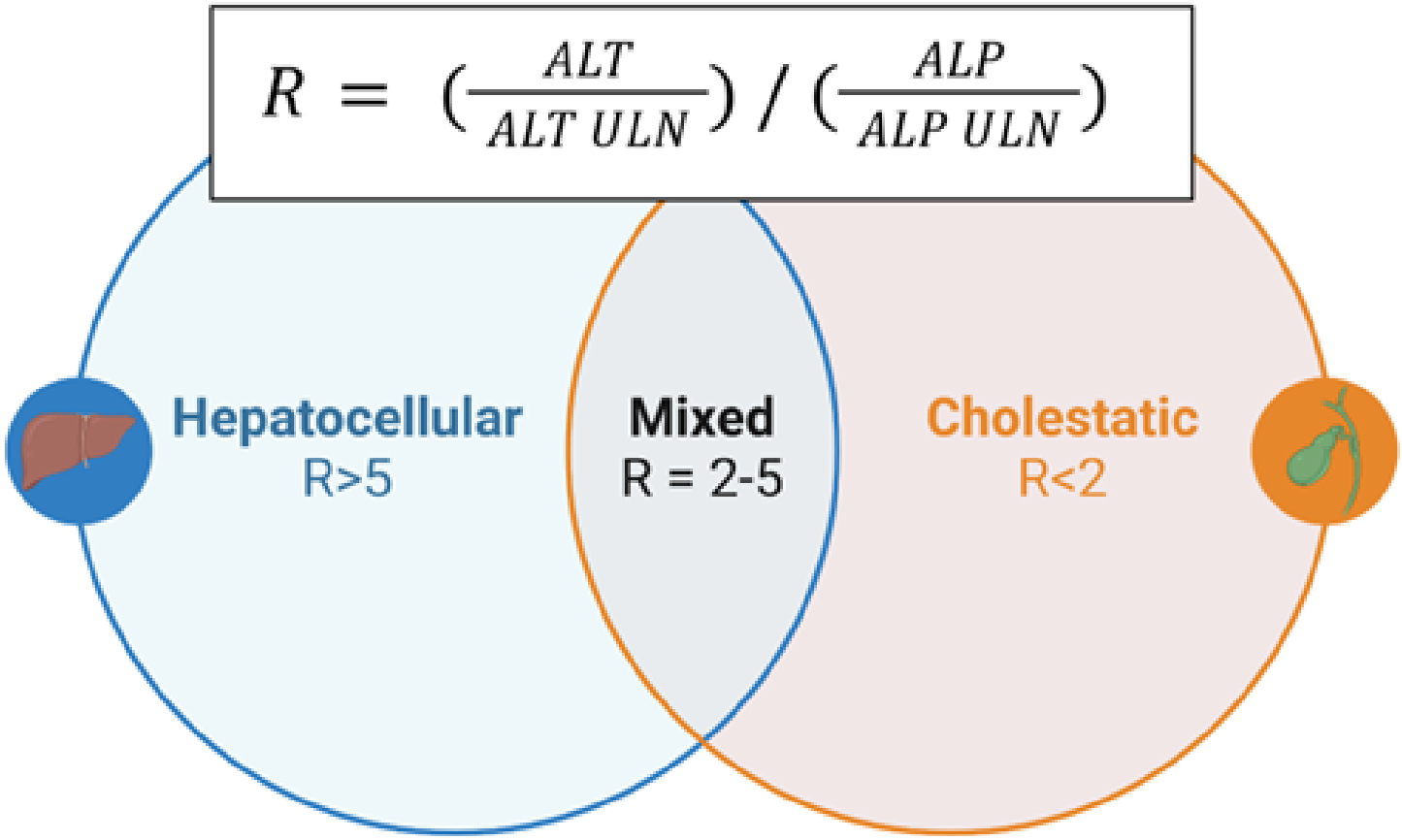
Figure 2 Roussel-Uclaf Causality Assessment Method (RUCAM) diagnostic score.



Kullak-Ublick GA, *et al*. *Gut* 2017;**66**:1154–1164. doi:10.1136/gutjnl-2016-313369

PATTERNS OF IDIOSYNCRATIC DILI

- HEPATOCELLULAR
- CHOLESTATIC
- MIXED



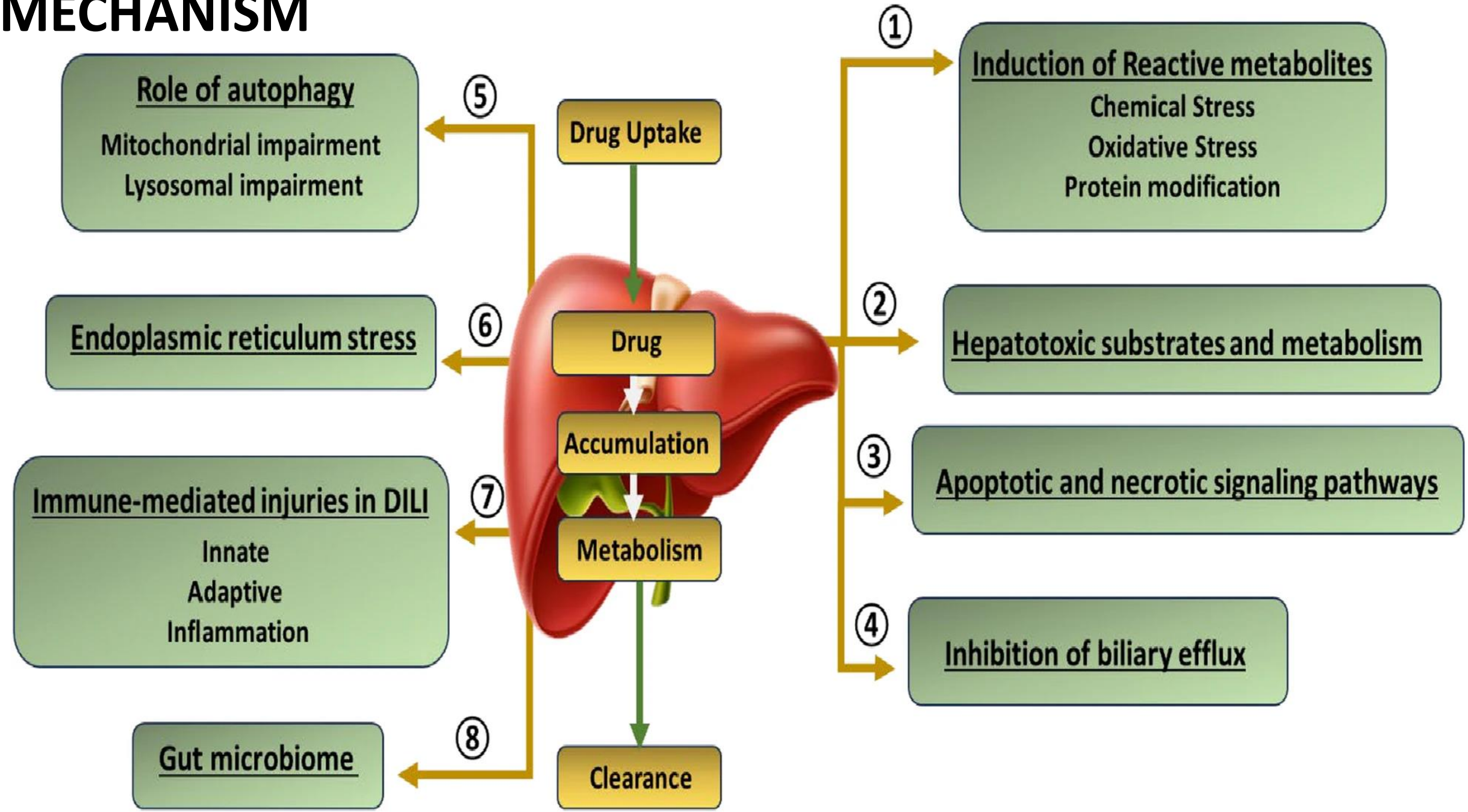
https://www.aasld.org/liver-fellow-network/core-series/back-basics/how-approach-elevated-liver-enzymes

Table 2. Phenotypes of Drug-Induced Liver Injury.*

Phenotype	Type of Liver Injury	Latency	Enzyme Pattern	Typical Agents	Comments
Acute hepatic necrosis	Direct	Days	Marked, abrupt ALT elevations; mild Alk P and bilirubin elevations	Acetaminophen, aspirin, niacin, "Ecstasy"	Often due to overdose
Enzyme elevations	Direct	Days to months	Mild-to-moderate ALT or Alk P elevations	Many agents	Usually transient and asymptomatic
Acute hepatitis	Idiosyncratic, indirect	Days to months	High ALT elevations, modest Alk P elevations	Isoniazid, diclofenac	High death rate
Cholestatic hepatitis	Idiosyncratic	Weeks to months	High Alk P elevations, modest ALT elevations	Amoxicillin–clavulanate, cefazolin	Pruritus, early and prominent
Mixed hepatitis	Idiosyncratic	Days to months	Moderate ALT and Alk P elevations	TMP-SMZ, phenytoin	Usually benign, self-limited
Chronic hepatitis	Idiosyncratic, indirect	Months to years	Moderate ALT elevations with bilirubin elevations	Diclofenac, nitrofurantoin, minocycline	Insidious onset; may require glucocorticoids
Bland cholestasis	Unknown, possibly idiosyncratic	Months	Moderate ALT elevations, mild Alk P elevations	Anabolic steroids, estrogens	Pruritus, prominent and prolonged
Acute fatty liver, lactic acidosis, and hepatic failure	Direct	Days to months	Lactic acidosis, modest ALT elevations, hepatic failure	Stavudine, linezolid, aspirin (Reye's syndrome)	Mitochondrial failure, pancreatitis
Nonalcoholic fatty liver	Indirect, direct	Months	Mild ALT and Alk P elevations	Glucocorticoids, tamoxifen, haloperidol	Asymptomatic; fatty liver seen on ultrasound
Sinusoidal obstruction syndrome	Direct	Weeks	Variable enzyme elevations	Cancer agents, busulfan, gemtuzumab	Hepatomegaly, weight gain, edema, ascites
Nodular regenerative hyperplasia	Direct	Years	Minimal ALT and Alk P elevations	Thioguanine, azathioprine, oxaliplatin	Noncirrhotic portal hypertension

* The phenotypes are listed very generally in order of frequency; there is some overlap between idiosyncratic and indirect forms of injury. Alk P denotes alkaline phosphatase, ALT alanine aminotransferase, and TMP-SMZ trimethoprim–sulfamethoxazole.

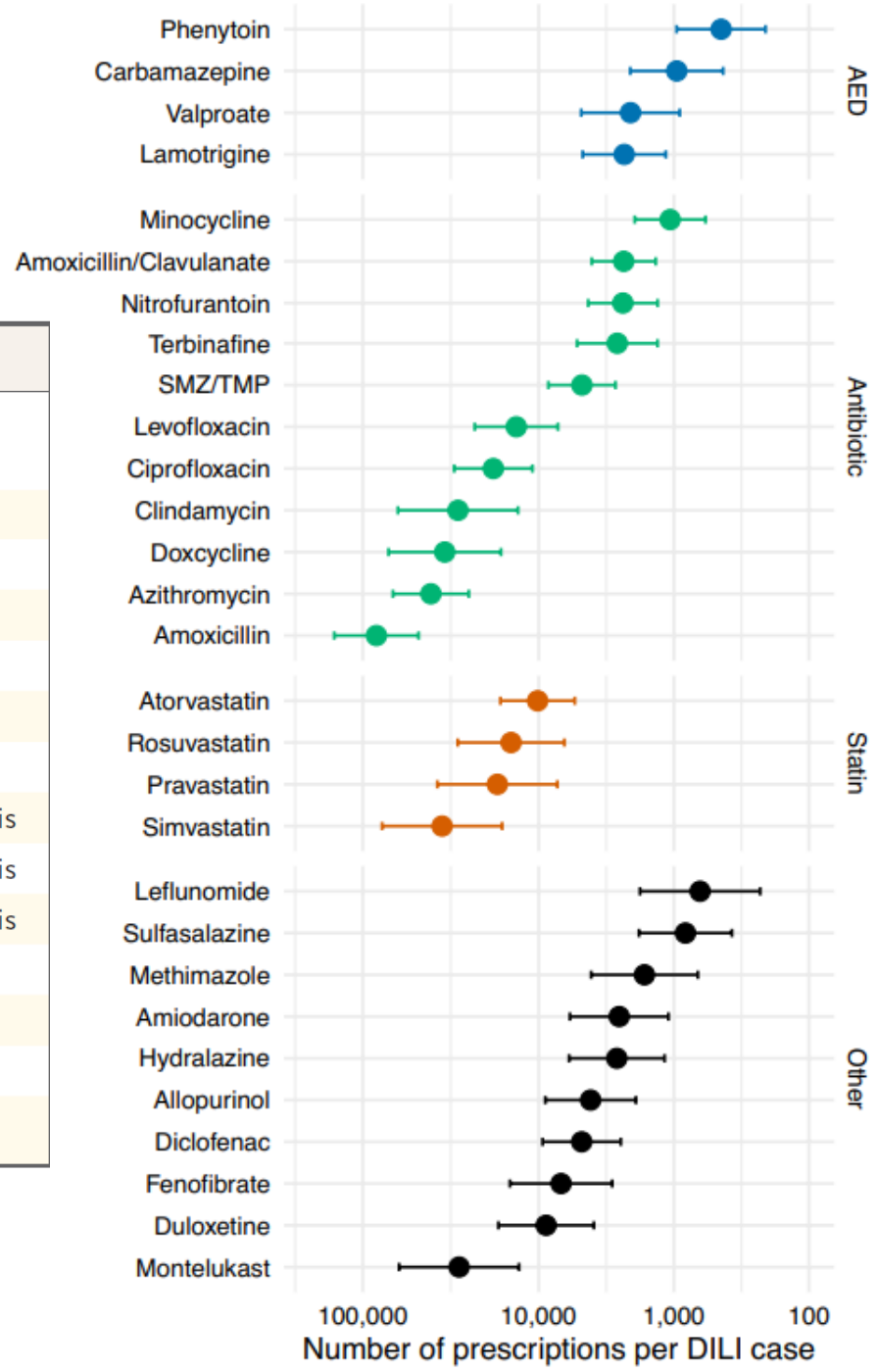
MECHANISM


Role of autophagy
Mitochondrial impairment
Lysosomal impairment
5
Drug Uptake
1
Induction of Reactive metabolites
Chemical Stress
Oxidative Stress
Protein modification
Endoplasmic reticulum stress
6
Drug
2
Hepatotoxic substrates and metabolism
Accumulation
3
Apoptotic and necrotic signaling pathways
Immune-mediated injuries in DILI
Innate
Adaptive
Inflammation
7
Metabolism
4
Inhibition of biliary efflux
Gut microbiome
8
Clearance

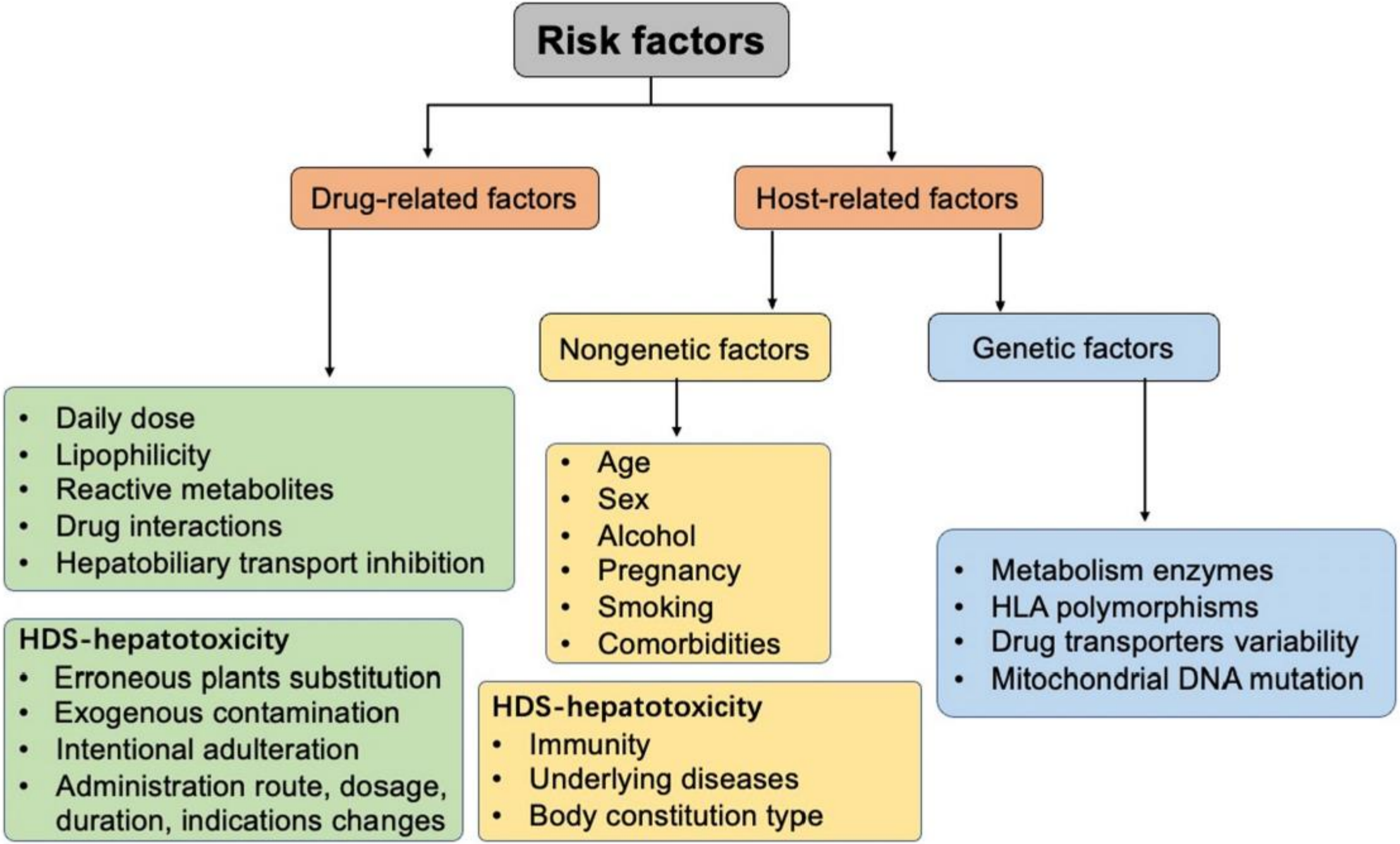
CAUSES

Table 3. Most Frequent Causes of Idiosyncratic Prescription Drug–Induced Liver Injury.*

Rank	Agent	Year of FDA Approval	No. (%)†	Major Phenotypes
1	Amoxicillin–clavulanate	1984	91 (10.1)	Cholestatic or mixed hepatitis
2	Isoniazid	1952	48 (5.3)	Acute hepatocellular hepatitis
3	Nitrofurantoin	1953	42 (4.7)	Acute or chronic hepatocellular hepatitis
4	TMP-SMZ	1973	31 (3.4)	Mixed hepatitis
5	Minocycline	1971	28 (3.1)	Acute or chronic hepatocellular hepatitis
6	Cefazolin	1973	20 (2.2)	Cholestatic hepatitis
7	Azithromycin	1991	18 (2.0)	Hepatocellular, mixed, or cholestatic hepatitis
8	Ciprofloxacin	1987	16 (1.8)	Hepatocellular, mixed, or cholestatic hepatitis
9	Levofloxacin	1996	13 (1.4)	Hepatocellular, mixed, or cholestatic hepatitis
10	Diclofenac	1988	12 (1.3)	Acute or chronic hepatocellular hepatitis
11	Phenytoin	1946	12 (1.3)	Hepatocellular or mixed hepatitis
12	Methyldopa	1962	11 (1.2)	Hepatocellular or mixed hepatitis
13	Azathioprine	1968	10 (1.1)	Cholestatic hepatitis



1. N Engl J Med 2019;381:264-73.
2. Drug Safety (2025) 48:151–160


Risk factors
Drug-related factors
Host-related factors
Nongenetic factors
Genetic factors
• Daily dose
• Lipophilicity
• Reactive metabolites
• Drug interactions
• Hepatobiliary transport inhibition
HDS-hepatotoxicity
• Erroneous plants substitution
• Exogenous contamination
• Intentional adulteration
• Administration route, dosage, duration, indications changes
• Age
• Sex
• Alcohol
• Pregnancy
• Smoking
• Comorbidities
HDS-hepatotoxicity
• Immunity
• Underlying diseases
• Body constitution type
• Metabolism enzymes
• HLA polymorphisms
• Drug transporters variability
• Mitochondrial DNA mutation

CLINICAL PRESENTATION

- DIVERSE CLINICAL PHENOTYPE
- MIMIC ALL FORMS OF ACUTE AND CHRONIC LIVER DISEASE
- ASYMPTOMATIC WITH LIVER ENZYME ELEVATION → ACUTE LIVER FAILURE

DIAGNOSIS

- DIAGNOSIS OF EXCLUSION

- DETAILED MEDICAL & MEDICATION HISTORY
  - PRESCRIPTION
  - OVER THE COUNTER
  - HOME REMEDIES
  - HERBAL SUPPLEMENTS

DIAGNOSIS

- DIAGNOSIS OF EXCLUSION

- DETAILED MEDICAL & MEDICATION HISTORY
  - START & STOP DATES
  - DOSE CHANGE
  - PRIOR USE
  - DECHALLENGE AND RECHALLENGE EVENTS

DIAGNOSIS

- DIAGNOSIS OF EXCLUSION
- DETAILED MEDICAL & MEDICATION HISTORY HISTORY
- INITIAL LAB ASSESSMENT → CALCULATE R VALUE
- EXCLUDE OTHER POTENTIAL CAUSES
  - VIRAL HEPATITIDES
  - AIH
  - METABOLIC LIVER DISEASE
  - PANCREATIICOBILIARY CAUSES

DIAGNOSIS

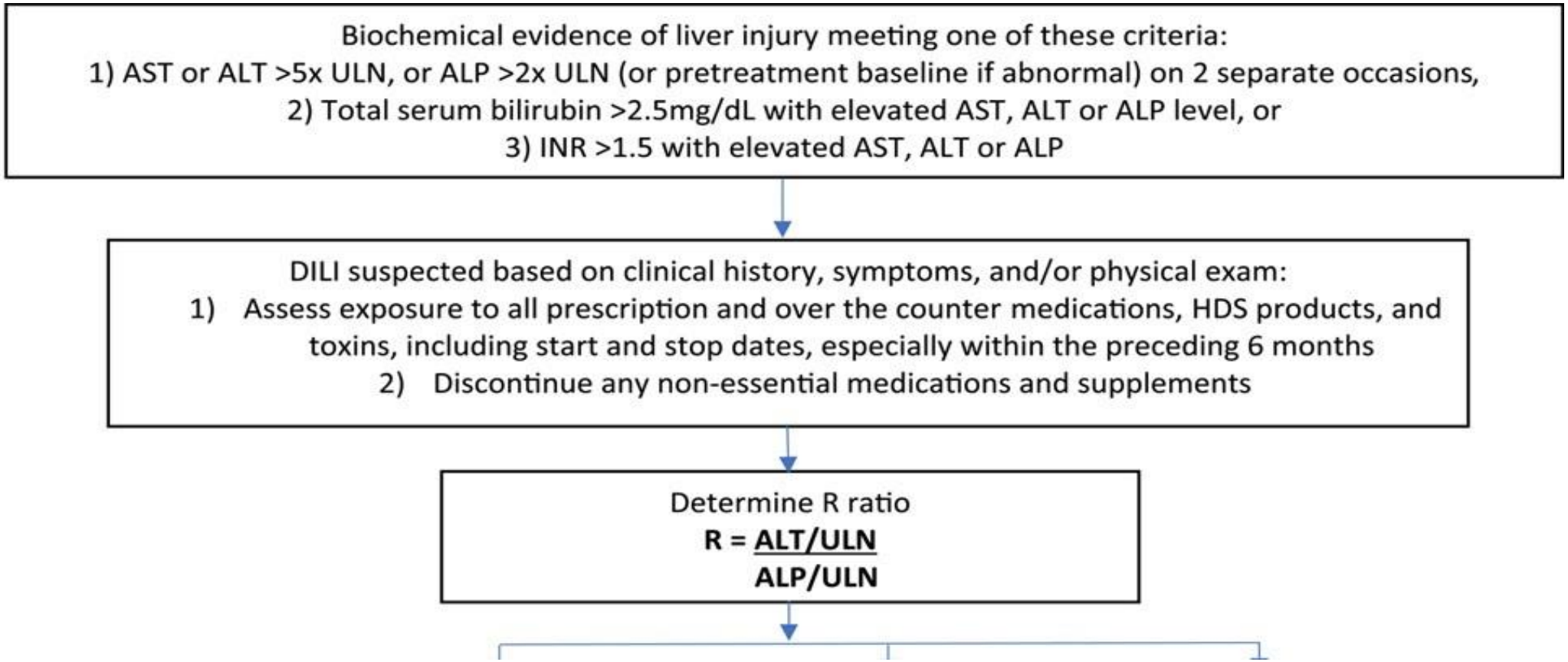
- DIAGNOSIS OF EXCLUSION
- DETAILED MEDICAL & MEDICATION HISTORY HISTORY
- INITIAL LAB ASSESSMENT → CALCULATE R VALUE
- EXCLUDE OTHER POTENTIAL CAUSES
- LOOK FOR SPECIFIC DRUG “SIGNATURES”
- LIVERTOX WEBSITE

DIAGNOSIS

- LIVER BIOPSY
  - USEFUL TO EXCLUDE OTHER CAUSES OR CONCOMITANT CAUSES
    - IE CO-EXISTING MASLD
  - UNUSUAL DRUG INJURY PATTERN IE. NODULAR REGENERATIVE HYPERPLASIA
  - CHOLESTATIC PICTURE
    - ALLOWS EVALUATION OF BILE DUCT INJURY
    - FEATURES OF DUCTOPENIA OR VANISHING BILE DUCT SYNDROME
  - PERSISTENT ELEVATION OF LIVER BIOCEHMISTRY OR SYMPTOMS ON DISCONTINUATION OF PRESUMED CULPRIT DRUG
  - USEFUL PROGNOSTIC INFORMATION AND ASSESS CHRONICITY

Hepatology. 2023;77:1036–1065

DIAGNOSIS



AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

DIAGNOSIS

Search for injury patterns in LiverTox®, PubMed:

1) Latency (time to onset)
2) Dechallenge (time to recovery)
3) Clinical phenotype (See **Table 4**)

R ≥ 5: Hepatocellular

R value 2-5: Mixed

R ≤ 2: Cholestatic

R >2: Hepatocellular or Mixed

Other Etiologies to Consider	Evaluation
Viral hepatitis (e.g., HAV, HBV, HCV, HEV, CMV, EBV, HSV)	HAV IgM, HBsAg, HCV RNA, HEV IgM, CMV PCR, EBV PCR, HSV PCR
Ischemia	History of hypotension, sepsis, or heart failure; echocardiogram
Autoimmune hepatitis	ANA, ASMA, IgG, liver biopsy
Alcoholic hepatitis	Clinical history, AST >2x ALT, serum PEth, urine ethylglucuronide
Drug/toxin (e.g. mushroom, APAP)	History, urine toxicology, serum APAP
Budd-Chiari	Doppler ultrasound (or CT or MRI)
Wilson disease	Ceruloplasmin, ALP :TB <4, AST:ALT >2.2
Alpha-1-antitrysin deficiency	A1AT level
Hereditary hemochromatosis	Ferritin, transferrin saturation
Fatty liver disease	History and imaging features
Celiac disease	Anti-TTG IgA
Rhabdomyolysis	CPK
Hypothyroidism/ Thyrotoxicosis	TSH, free T4, T3

R ≤ 2: Cholestatic

Other Etiologies to Consider	Evaluation
Choledocholithiasis	Doppler ultrasound
Primary biliary cholangitis	AMA, liver biopsy
Biliary strictures (e.g. primary sclerosing cholangitis)	Cholangiography
Pancreaticobiliary tumors	CT or MRI
Malignancy/infiltrating cancer (e.g. lymphoma)	LDH, imaging
TPN cholestasis	History
Bone disease	ALP isoenyzmes

Exclusion of other causes of liver injury (Underlined tests should be done in most cases; some conditions may present in atypical manner)

Consider liver biopsy if symptoms persist, dechallenge does not progress as expected, suspected autoimmune hepatitis, or atypical presentation

MANAGEMENT

- STOP OFFENDING DRUG
- GENERAL SUPPORTIVE MEASURES
  - ANTI-EMETICS
  - ANALGESICS
  - ANTIPRURITICS
  - PARENTERAL HYDRATION
- TRANSFER TO HEPATOLOGY SERVICE
  - ANY EVIDENCE OF ACUTE LIVER FAILURE
  - INR >1.5
  - ASCITES
  - ENCEPHALOPATHY

MANAGEMENT

- N-ACETYLCYSTEINE
  - SOME BENEFIT IN TRANSPLANT FREE SURVIVAL
  - INCONCULSIVE IN TERMS OF OVERALL SURVIVAL
  - AASLD: 3-DAY COURSE OF NAC CONSIDERED IN DILI-RELATED ALF
    - FEW SIDE EFFECTS
    - IMPROVED 3 WEEK OUTCOMES IN TRANSPLANT FREE SURVIVAL PARTICULARLY IN EARLY ENCEPHALOPATHY (GRADE I-II)
- NOT RECOMMENDED IN PAEDIATRIC CASES

frontiers | Frontiers in Pharmacology

SYSTEMATIC REVIEW
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N-Acetylcysteine for the Management of Non-Acetaminophen Drug-Induced Liver Injury in Adults: A Systematic Review

Judith Sanabria-Cabrera[1,2,3†], Sara Tabbai[1,2], Hao Niu[1,3†], Ismael Alvarez-Alvarez[3,4], Anna Licata[5], Einar Björnsson[6,7], Raul J. Andrade[3,4‡] and M. Isabel Lucena[1,2,3‡]*

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OPEN ACCESS

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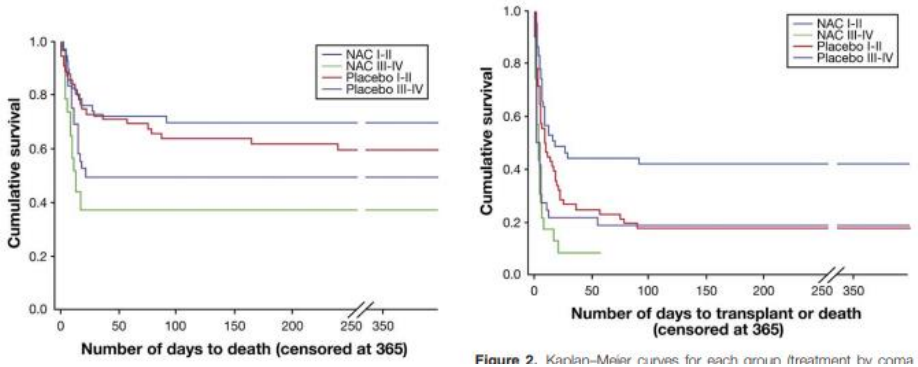


Figure 2. Kaplan–Meier curves for each group (treatment by coma

GASTROENTEROLOGY 2009;137:856 – 864

MANAGEMENT

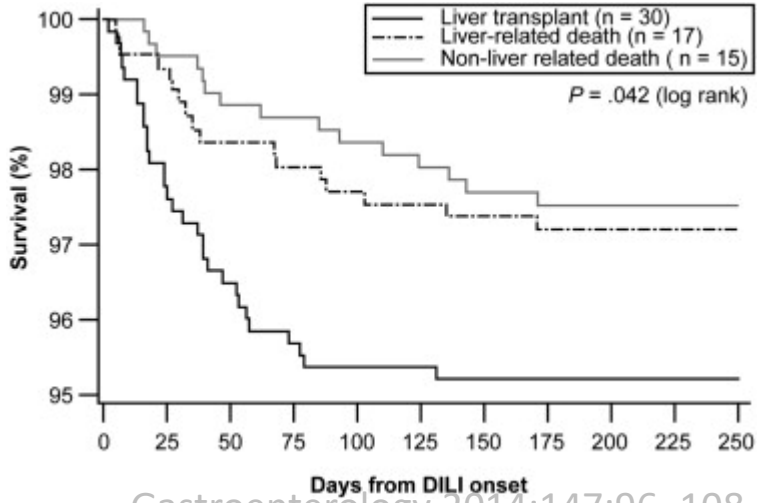
- CORTICOSTEROIDS
  - AUTOIMMUNE FEATURES ON BIOPSY
  - SEVERE HYPERSENSITIVITY REACTIONS (IE. DRESS)
  - IMMUNE CHECKPOINT INHIBITOR AND TYROSINE KINASE INHIBITOR DILI
- OPTIMAL DOSE AND DURATION UNCERTAIN

MANAGEMENT

- OTHER SPECIFIC TREATMENTS:
  - URSODEOXYCHOLIC ACID
    - SAFE
    - NOT ESTABLISHED THERAPEUTIC AGENT
    - IMPROVEMENT IN BIOCHEMISTRY
  - CHOLESTYRAMINE
    - SPECIFIC CASES MIGHT BE OF USE
    - LONG HALF LIFE AND EXTENSIVE ENTEROHEPATIC CIRCULATION eg LEFLUNAMIDE
  - L-CARNITINE
    - CHILDREN WITH HYPERAMMONEMIA DUE TO VALPROATE TOXICITY

NATURAL HISTORY AND PROGNOSIS

- MAJORITY HAVE COMPLETE RECOVERY
- 10% MORTALITY OR REQUIRE LIVER TRANSPLANT
- 5-10% MAY HAVE EVIDENCE OF CHRONICITY
  - ONGOING INJURY AT 6-12 MONTHS (BIOCHEM/RADIOLOGICAL/HISTOLOGICAL)
  - MINORTY (<1%) → PROGRESSIVE LOSS OF INTRAHEPATIC BILE DUCTS (VANISHING BILE DUCT SYNDROME)
- RISK FACTORS FOR WORSE OUTCOMES:
  - HIGHER TOTAL BILIRUBIN
  - ELEVATED INR LEVELS
  - LOWER SERUM ALBUMIN LEVELS
  - PRE-EXISITING LIVER DISEASE



Gastroenterology 2014;147:96–108

PROGNOSTICATION - HY'S LAW

- Hy's Law
  - Generally used for drugs in development
  - Can be used as a predictor of a drug's ability to cause severe DILI
    - **>3 x ULN ALT & >2x ULN T bili (without significant rise in ALP)**
- New Hy's Law
  - **nR [(ALT or AST/ULN)/(ALP/ULN)] >5 & T Bili >2 ULN**
  - **Similar sensitivity 90%, but improved specificity 63% (vs44%)**

NATURAL HISTORY AND PROGNOSIS

TABLE 8 Prognostic indices for patients with idiosyncratic DILI

Model/parameter	Model components	Proposed thresholds for liver transplant/death	Comments
MELD score[143]	Bilirubin, INR, and creatinine	AUROC = 0.83	Developed for cirrhosis patients
Hy's law[145]	ALT > 3× ULN and bilirubin > 2.5 mg/dl	PPV = 8%–20%	ALP should be < 2× ULN; not applicable to mixed/ cholestatic cases
Modified Hy's law[144]	R-value > 5 and bilirubin > 2.5 mg/dl	PPV = 12%; AUROC = 0.73	
Charlson Comorbidity Index and labs[146]a	MELD score, albumin, Charlson > 2	AUROC = 0.89	Discovery and validation cohort used for 6-month mortality

PARACETAMOL

- DIRECT DILI
- IN NORTH AMERICA: 50 000 EC VISITS, 500 DEATHS ANNUALLY

TABLE 10 Diagnosis and management of APAP hepatotoxicity

Recommendation	Intentional overdose	Unintentional overdose
Diagnostic approach		
Time of ingestion	Single time point	Several days of repeated use
Dose	Supratherapeutic (typically > 4 g over 24 h)	Repeated therapeutic (up to 4 g per day) or supratherapeutic dosing
Presence of coingestants	Diphenhydramine and other sedatives can lead to central nervous system depression	Opioids often used in combination
Liver injury parameters	From time of ingestion: 24–72 h: rapid rise in ALT to > 1000 IU/L associated with variable rise in INR; total bilirubin is typically < 10 mg/dl. 72–96 h: Biochemical elevations peak, and can progress to acute liver failure or rapid and full recovery	Presentation is often delayed, but still see rapid rise in ALT to > 1000 IU/L, associated with rise in INR. Comorbid conditions, such as alcohol use, can affect total bilirubin levels. Eventually, liver injury can progress to acute liver failure or recovery
Serum APAP level	Use modified Rumack-Matthew nomogram to estimate risk of hepatotoxicity	Often undetectable at initial presentation. APAP-protein adducts useful but assay not commercially available
Excluding other causes of acute liver injury	Review clinical history to exclude risk factors for hepatic ischemia and perform tests for acute viral hepatitis	
Management		
GI decontamination	Activated charcoal (1 g/kg, max dose 50 g) if within 4 h of ingestion. Gastric lavage also used in some cases[175]	Usually not helpful nor recommended
N-acetylcysteine	Oral dosing: 140 mg/kg load followed by 70 mg/kg every 4 h; antiemetics as needed. Intravenous dosing[176]: preferred if intolerant of oral intake/ileus or pregnant; telemetry monitoring recommended 150 mg/kg load over 15–60 min, followed by 50 mg/kg (12.5 mg/kg/h) over the next 4 h then 100 mg/kg (6.25 mg/kg/h) over 16 h thereafter (total 300 mg/kg over 24 h). For those with evidence of liver injury, treatment is extended at 6.25 mg/kg/h until ALT is decreasing and INR is < 2	
Evidence of acute liver failure (coagulopathy and encephalopathy)	Close monitoring in intensive care unit and consider prompt referral to a liver transplant center	

Abbreviation: GI, gastrointestinal.

PARACETAMOL

- INDICATIONS FOR LIVER TRANSPLANT

Criteria 1	Criteria 2 (all three required)
pH < 7.3, irrespective of grade of encephalopathy	Prothrombin time > 100 seconds AND
	Serum creatinine >3.4 mg/dL (300 micromol/L AND
	Grade III or IV encephalopathy

DILI IN TUBERCULOSIS

- OCCURS IN 5-33% OF PATIENTS RECEIVING ANTI-TUBERCULOSIS THERAPY
- ELEVATED LFTS AT BASELINE NOT A CONTRAINDICATION – NEEDS TO BE MONITORED

DILI IN TUBERCULOSIS

- Stop TB treatment, ART, and other hepatotoxic drugs (e.g. cotrimoxazole, fluconazole) immediately if :
  1. ALT > 120 IU/L and symptomatic OR
  2. ALT > 120 IU/L and jaundiced OR
  3. ALT > 120 IU/L and total bilirubin > 40 IU/L OR
  4. ALT > 200 IU/L regardless of symptoms or bilirubin OR
  5. ALT > 2x baseline ALT in patients with existing liver disease
- INTIATE BACKGROIUND REGIMEN
  - levofloxacin (15-20mg/kg daily, max 1000mg)
  - ethambutol (800-1200mg daily)
  - linezolid (600mg daily if weight ≥ 36 kg; 300mg daily if weight 30-35.9 kg
- EXCLUDE OTHER CAUSES
  - HEPATOCELLULAR: VIRAL HEPATITIS (A,B,C), HSV
  - CHOLESTATIC: OBSTRUCTIVE CAUSES, SEPSIS, HIV CHOLANGIOPATHY, IRIS, CHRONIC ALCOHOL ABUSE

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DILI IN TUBERCULOSIS

- GENERAL MEASURES
- MEDICINE LIST RECONCILIATION
- STOP TB DRUGS
- CONFIRM TB DIAGNOSIS
- ASSESS SEVERITY
  - *Mild*: no symptoms of hepatitis with INR < 1.5.
  - *Moderate*: symptoms of hepatitis with INR < 1.5.
  - *Severe*: INR > 1.5, regardless of symptoms
- FURTHER INVESTIGATIONS AND SUPPORTIVE MEASURES
  - ULTRASOUND >> CHOLESTATIC PICTURE
  - NAC NOT ROUTINELY USED

TABLE 1: The effect of anti-tuberculous drugs on the liver.

Drug	Pattern of injury	Mechanism of injury	Note
Pyrazinamide	• Hepatocellular†	• Drug extensively metabolised by liver. • Dose-related injury suggesting direct toxic effect of drug or its metabolites.	• May cause asymptomatic transient elevation in transaminases during hepatic adaptation.
Isoniazid	• Hepatocellular† • Onset varies from early (days to weeks) to late	• Accumulation of toxic metabolites. • Immune-mediated component.	• May cause asymptomatic transient elevation in transaminases during hepatic adaptation. • Risk increases with age. • Rash, fever, and eosinophilia rarely.
Rifampicin	• Hepatocellular†, cholestatic‡ or mixed • Typically, within 1–6 weeks of initiation • Associated jaundice	• Drug extensively metabolised by liver. • Direct toxic effect of RIF metabolites. • Immune-mediated component	• May cause asymptomatic transient elevation in transaminases during hepatic adaptation. • Isolated increase in serum bilirubin can occur during first weeks of therapy. • Fever, rash, arthralgias, and eosinophilia rarely.
Moxifloxacin, levofloxacin	• Hepatocellular†, cholestatic‡ or mixed	• Immune-mediated component	• May cause asymptomatic transient elevation in transaminases during hepatic adaptation. • Severe liver injury is rare. • Fever, rash, and eosinophilia rarely.

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DILI IN TUBERCULOSIS

- RECHALLENGE
  - 20-90% TOLERATE RECHALLENGE WITHOUT RECURRENCE
  - RECURRENCE STRONGLY ASSOCIATED WITH PZA
    - TYPICALLY ONLY RECOMMENDED FOR TBM
  - MILD-MOD DILI
    - INH AND RIF SHOULD BE RECHALLENGED

BOX 2: Suggested approach to rechallenging anti-tuberculous treatment in adult PWH.

- **Day 1:**
  - Start INH 300mg daily.
  - Stop linezolid, clofazimine or terizidone (if prescribed) during the recovery phase.
- **Day 3:**
  - Check ALT: if increased, consider INH the cause of AT-DILI. If not, proceed.
- **Day 4:**
  - Add RIF 600 mg daily.
- **Day 7:**
  - Check ALT: if increased, consider RIF the most likely cause of AT-DILI.† If not, proceed.
- **Day 8:**
  - Add PZA if TBM or unsuccessful rechallenge of INH/RIF.
  - Stop levofloxacin if it is being used.
- **Day 10:**
  - Check ALT: if increased, consider PZA the most likely cause of AT-DILI.† If not, proceed.
- Check ALT weekly for 4 weeks after rechallenge.

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3.2.3 MODIFYING TB TREATMENT REGIMEN

If one of the TB drugs are not tolerated during rechallenge in the INTENSIVE PHASE

RIFAMPICIN rechallenge not tolerated

Start shorter regimen for rifampicin resistant TB treatment i.e. **BPaL-L** (bedaquiline, pretomanid, linezolid, levofloxacin) for **6 months**

If uncertain discuss with an expert or call the hotline (0800 212 506)

ISONIAZID rechallenge not tolerated

If pyrazinamide rechallenged successfully:
Continue rifampicin, ethambutol, levofloxacin (preferred) / moxi-floxacin, and pyrazinamide for a total of **6-9 months***

OR

Pyrazinamide not rechallenged:
Continue rifampicin, ethambutol and levofloxacin (preferred) / moxifloxacin for a total of **9 - 12 months***

*Subtract duration of TB treatment received prior to DILI

PYRAZINAMIDE not rechallenged or not tolerated

Confirm isoniazid susceptibility

If susceptible, continue rifampicin, isoniazid and ethambutol for a total of **9 months***

If not susceptible, refer to expert or call the hotline (0800 212 506)

*Subtract duration of TB treatment received prior to DILI

Monitor ALT weekly for 4 weeks after rechallenge

Refer to an expert or call the hotline (0800 212 506) if patient is in the continuation phase of TB treatment, if more than one TB drug is not tolerated during rechallenge, or if unsure about the duration of TB treatment after rechallenge

DILI ON ART

- NNRTI'S
  - EFAVIRENZ
    - USUALLY 3-6 MONTHS AFTER INITIATION
    - MONTHS TO NORMALISE
- DOLUTEGRAVIR
  - - GENERLALY HEPATOCELLULAR PATTERN, 1-8 MONTHS AFTER INITATION
- PROTEASE INHIBITORS
  - USUALLY WITHIN 8 WEEKS, VAIRIABLE PATTERNS
  - ATAZANAVIR CAN CAUSE RISE OF UNCONJUGATED HYPERBILIRUBINEMIA – CLINICALLY NOT SIGNIFICANT

DILI ON ART

- Mild ALT elevations occur commonly and in general are transient.
- ALT elevations > 5X the upper limit of normal (ULN) are significant in the absence of symptoms.
- In the presence of symptoms of hepatitis, ALT elevations > 2.5X ULN are also significant

TABLE 26: Guidelines for managing hepatotoxicity.

Elevation	ULN[†]		
	< 2.5 × ULN	2.5–5 × ULN	> 5 × ULN
ALT	Repeat at 1–2 weeks	Repeat at 1 week	Discontinue relevant drug(s)
Bilirubin	Repeat at 1 week	Discontinue relevant drug(s)	Discontinue relevant drug(s)

IMMUNE CHECKPOINT INHIBITOR HEPATITIS

- Prescribed for approx. 50% of oncology patients with solid organ tumours
- Incidence of IMH 1-15%
- 3 main ICI's:
  - anti-programmed cell death protein (PD)-1 agents
  - anti-PD ligand (L)-1 agents
  - anti-CTLA-4 agents
- Block inhibitory receptors on the T-cell membrane and reverse T-cell exhaustion
  - Loss of self-tolerance

Table 1. Grading assessment of immune-mediated hepatitis according to the Common Terminology Criteria of Adverse Events (CTCAE) and Drug-Induced Liver Injury Network (DILIN) criteria.

DILIN	CTCAE	Grade
Elevated serum ALT and/or ALP; TBil < 2.5 mg/dL; INR < 1.5; with or without symptoms (fatigue, weakness, nausea, anorexia, right upper abdominal pain, jaundice, pruritus, rash, or weight loss)	ALT/AST < 3× ULN; ALP/GGT > 1–2.5× ULN; TBili < 1.5× ULN	1
Elevated serum ALT and/or ALP; TBil ≥ 2.5 mg/dL or INR ≥ 1.5 without elevated TBil; symptoms may be aggravated	AST/ALT 3–5× ULN; ALP/GGT > 2.5–5× ULN; TBili 2–3× ULN	2
Elevated serum ALT and/or ALP; TBil ≥ 5 mg/dL with or without INR ≥ 1.5; symptoms are further aggravated; indication for hospitalization or prolonged hospitalization	AST/ALT 5–20× ULN; ALP/GGT > 5–20× ULN; TBili > 3× ULN	3
Elevated serum ALT and/or ALP; TBil ≥ 10 mg/dL or daily elevation ≥ 1.0 mg/dL; INR ≥ 1.5 with ascites, encephalopathy, or other organ dysfunction	AST/ALT > 20× ULN; ALP/GGT > 20× ULN; TBili > 10× ULN	4
Death	Death due to hepatoto×icity	5

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; TBil, total bilirubin; INR, international normalized ratio; ULN, upper limit of normal.

IMMUNE CHECKPOINT INHIBITOR HEPATITIS

- Injury related to excessive immune response to tissue
- Similar picture to AIH
  - Several phenotypes

- Clinical presentation varies
  - Majority asymptomatic
  - Fatigue
  - RUQ pain
  - Jaundice
  - Fever

IMMUNE CHECKPOINT INHIBITOR HEPATITIS

- Exclude other causes
- Imaging to rule out progression of underlying malignancy
- MDT management
- 1st line = steroids
- Refractory disease
  - Azathioprine
  - MMF
  - Tacrolimus
  - Case reports of tocilizumab (anti-IL6)

Table 2. Management algorithm for IMH.

Continue ICI; Check LT 1–2 Times Week	Grade 1
Hold ICI; check LT every 3 days; consider liver biopsy; if no improvement start steroid therapy (0.5–1 mg/kg/day of prednisone)	Grade 2
Hold ICI; check LT every 2 days; consider liver biopsy; if no improvement start steroid therapy (1–2 mg/kg/day of prednisone)	Grade 3
Hold ICI; check LT every 1 day; consider liver biopsy; if no improvement start steroid therapy (2 mg/kg/day of prednisone)	Grade 4

ICI: immune checkpoint inhibitors; LT: liver test.

TAKE HOME POINTS

- Detailed medication history (incl. OTC, herbal supplements etc)
- Exclude other causes
- Pattern of liver injury helps categorize potential causes
- Stop culprit drug
- Rechallenge in certain circumstances
- Liver biopsy
  - Degree of damage
  - Cofactors
  - Atypical patterns