3rd GLOBAL LIVER HEALTH FORUM

sanofi

# Diagnosis and treatment of drug-induced liver injury: guidelines and practice

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# Disclosures

- No disclosures to declare

# DILI in general population

Prospective studies in general population

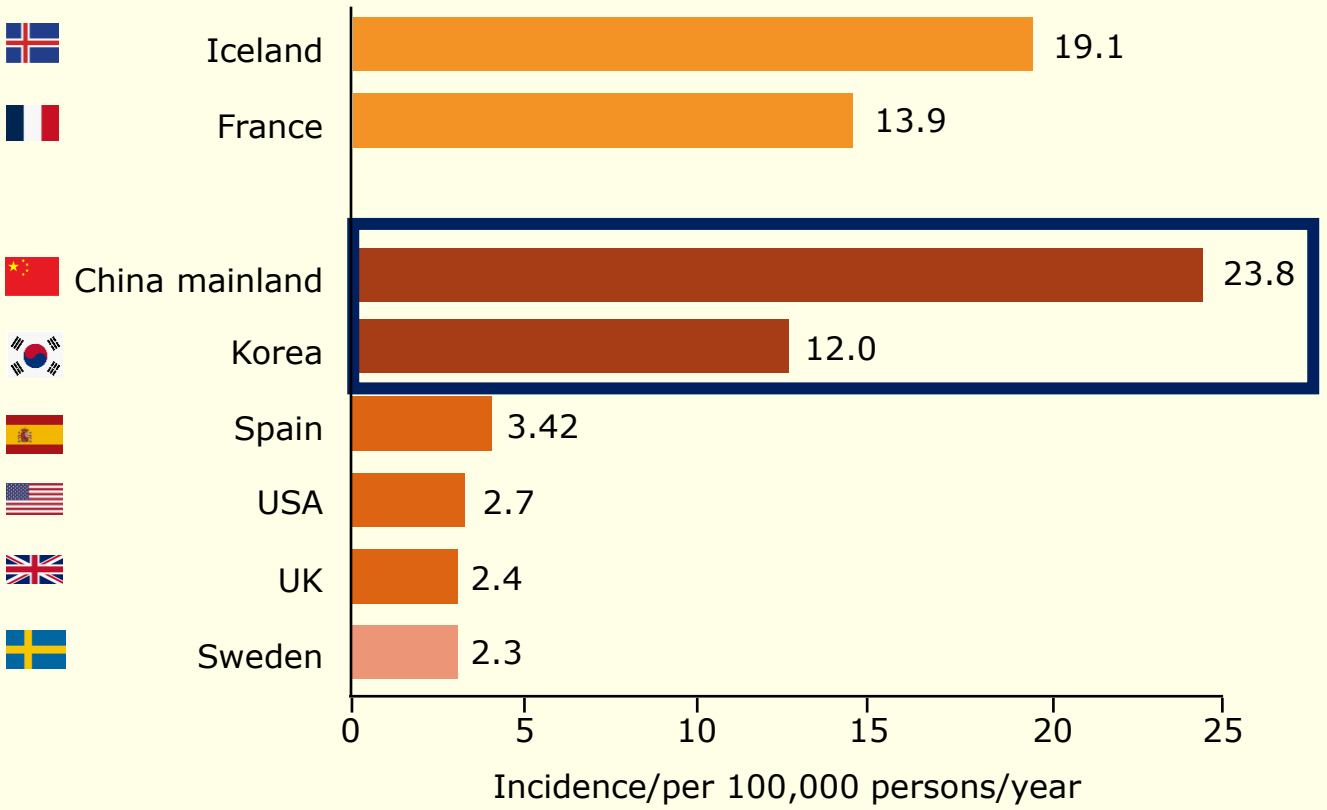
Population-based

Other studies reporting the incidence of DILI in general population

Hospitalised patients

Registry

Outpatients




| Study design |
|---|
| Prospective |
| Prospective |
| Retrospective |
| Prospective |
| Prospective |
| Prospective |
| Retrospective |
| Retrospective |

DILI, drug-induced liver injury

Li X, et al. Liver Int 2022;4:1999–2014

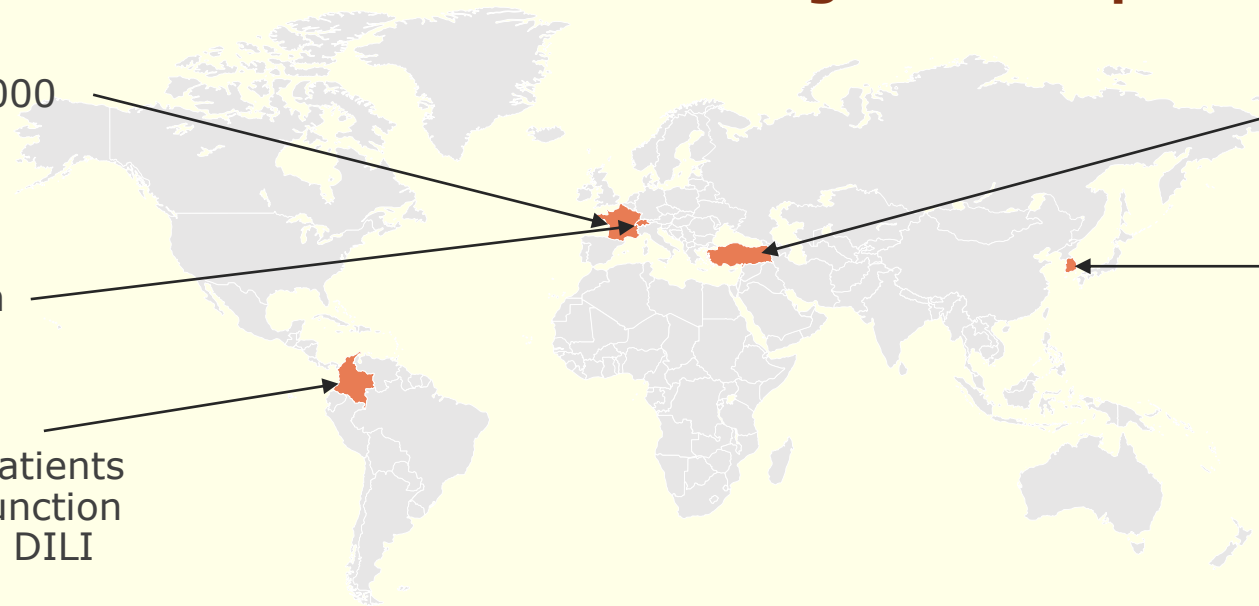
# DILI in hospitalised patients

## Prevalence of DILI tends to be higher in hospitalised patients

**France:**
Rate of DILI: 6.6/1,000 inpatients/week

**Switzerland:**
Prevalence of DILI in inpatients: 1.4%

**Colombia**
6% of hospitalised patients with elevated liver function were diagnosed with DILI



**Turkey:**
Prevalence of DILI in inpatients: 3.1%

**South Korea:**
Prevalence of herbal formulation-induced liver injury: 0.6% in inpatients

**DILI is a common aetiology among patients with unexplained liver conditions**

- Prevalence of DILI in patients with jaundice: ~2–10%
- USA: the prevalence of DILI in patients with new onset non-alcoholic jaundice: ~4% (most cases attributed to APAP)

**The proportion of DILI in the ALF population is increasing**

- DILI caused by APAP and iDILI accounts for >50% of all cases of ALF in the USA
- UK: 57% and 11% of ALF cases were caused by APAP and iDILI, respectively, from 1999–2007

ALF, acute liver failure; APAP, acetaminophen; (i)DILI, (idiosyncratic) drug induced liver injury

Li X, et al. Liver Int 2022;4:1999–2014

# The leading cause of DILI in different countries

## Most frequent causing of DILI (%)

| China | Japan | Korea | Singapore | India | USA | Spain | Iceland | France |
|---|---|---|---|---|---|---|---|---|
| TCM or HDS: 26.81 | Anti-inflammatory drugs: 11 | Herbal medications: 27.5 | Chinese traditional CAM: 55 | Anti-TB drugs: 57.8 | Antimicrobials: 46.5 | Anti-infectious drugs: 37 | Antibiotics: 37 | Anti-infectious drugs: 25 |
| Anti-TB drugs: 21.99 | Antimicrobial drugs: 11 | Prescription or non-prescription medications: 27.3 | Malay CAM: 16 | Phenytoin: 6.7 | HDS: 16.5 | Drugs targeting CNS: 14 | Immune suppressants: 10 | Psychotropic: 22.5 |
| Antineoplastic or immunomodulator: 8.34 | Anticancer drugs: 10 | Health foods or dietary supplements: 13.7 | Anti-TB drugs consisting of isoniazid, ethambutol and rifampicin: 6 | Dapsone: 5.4 | Cardiovascular agents: 10 | Musculoskeletal agents: 11 | Psychotropic drugs: 7 | Hypolipidemic agents: 12.5 |
| Anti-infectious agents: 6.08 | Dietary supplements: 9 | Medicinal herbs or plants: 9.4 | | Olanzapine: 5.4 | Drugs targeting CNS: 9.4 | Drugs targeting CVS: 11 | NSAIDs: 6 | NSAIDs: 10 |
| Psychotropics: 4.90 | Drugs for the gastrointestinal system: 9 | Folk remedies: 8.6 | | Carbamazepine: 2.9 | Antineoplastic agents: 5.6 | Antineoplastic drugs: 8 | Antineoplastic agents: 5 | |

CAM, complementary and alternative medicines; CNS, central nervous system; CVS, cardiovascular system; DILI, drug-induced liver injury; HDS, herbal and dietary supplements; NSAIDs, non-steroidal anti-inflammatory drugs; TB, tuberculosis; TCM, traditional Chinese Medicine

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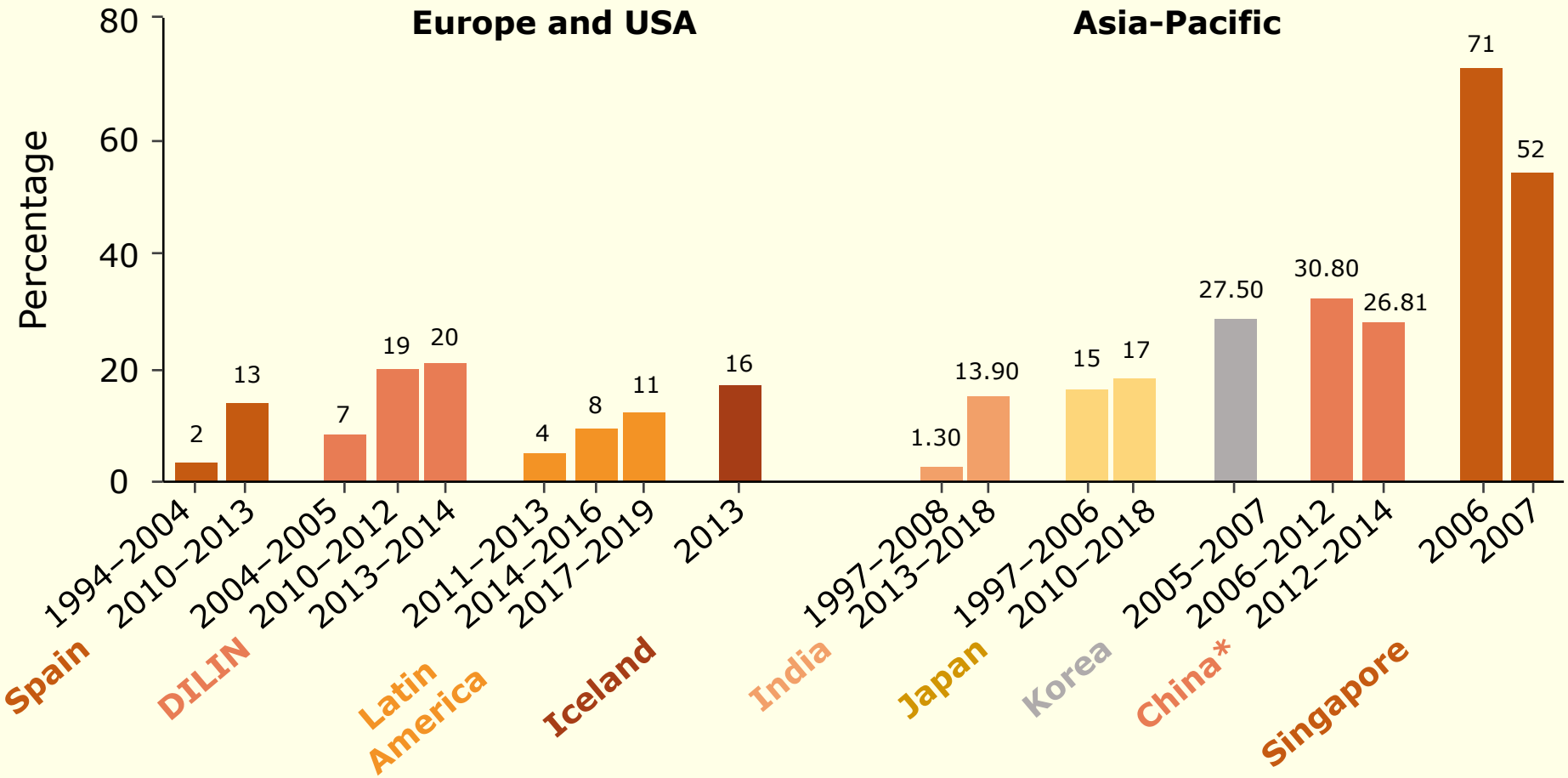
# HDS/TCM-induced liver injury in different countries

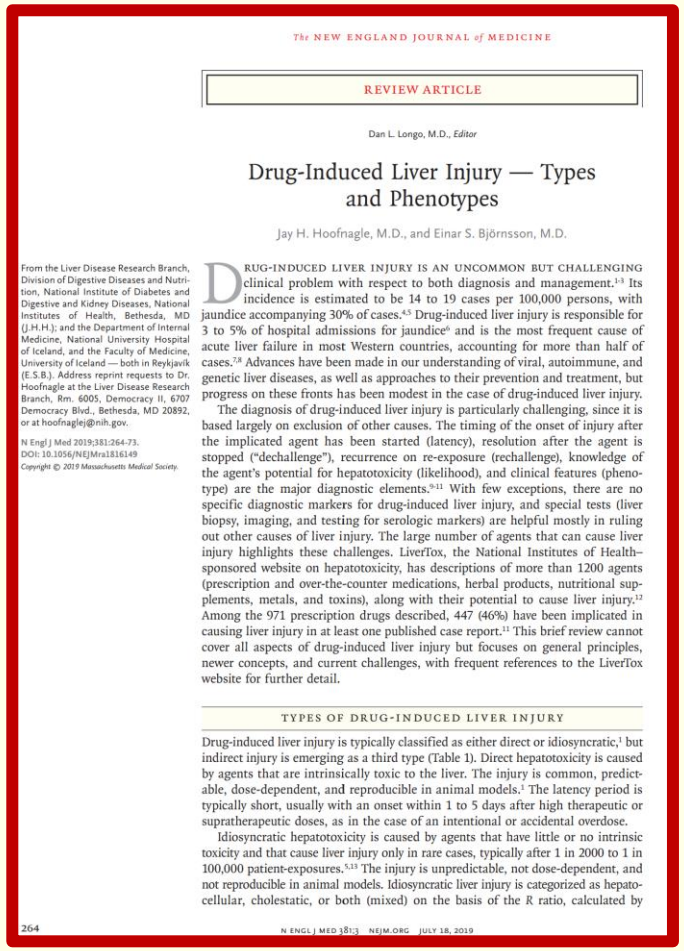
## Selected studies addressing composition ratio of HDS-induced liver injury in DILI




*Mainland China. DILI, drug-induced liver injury; DILIN, drug-induced liver injury network; HDS, herbal and dietary supplements; TCM, traditional Chinese Medicine

Li X, et al. Liver Int 2022;4:1999–2014

# Indirect hepatotoxicity: new challenges in DILI



The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

## Drug-Induced Liver Injury — Types and Phenotypes

Jay H. Hoofnagle, M.D., and Einar S. Björnsson, M.D.

From the Liver Disease Research Branch, Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD (J.H.H.); and the Department of Internal Medicine, National University Hospital of Iceland, and the Faculty of Medicine, University of Iceland — both in Reykjavik (E.S.B.). Address reprint requests to Dr. Hoofnagle at the Liver Disease Research Branch, Rm. 6005, Democracy II, 6707 Democracy Blvd., Bethesda, MD 20892, or at hoofnaglej@nih.gov.

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


DRUG-INDUCED LIVER INJURY IS AN UNCOMMON BUT CHALLENGING clinical problem with respect to both diagnosis and management.[1-3] Its incidence is estimated to be 14 to 19 cases per 100,000 persons, with jaundice accompanying 30% of cases.[4,5] Drug-induced liver injury is responsible for 3 to 5% of hospital admissions for jaundice[6] and is the most frequent cause of acute liver failure in most Western countries, accounting for more than half of cases.[7,8] Advances have been made in our understanding of viral, autoimmune, and genetic liver diseases, as well as approaches to their prevention and treatment, but progress on these fronts has been modest in the case of drug-induced liver injury.

The diagnosis of drug-induced liver injury is particularly challenging, since it is based largely on exclusion of other causes. The timing of the onset of injury after the implicated agent has been started (latency), resolution after the agent is stopped ("dechallenge"), recurrence on re-exposure (rechallenge), knowledge of the agent's potential for hepatotoxicity (likelihood), and clinical features (phenotype) are the major diagnostic elements.[9-11] With few exceptions, there are no specific diagnostic markers for drug-induced liver injury, and special tests (liver biopsy, imaging, and testing for serologic markers) are helpful mostly in ruling out other causes of liver injury. The large number of agents that can cause liver injury highlights these challenges. LiverTox, the National Institutes of Health–sponsored website on hepatotoxicity, has descriptions of more than 1200 agents (prescription and over-the-counter medications, herbal products, nutritional supplements, metals, and toxins), along with their potential to cause liver injury.[12] Among the 971 prescription drugs described, 447 (46%) have been implicated in causing liver injury in at least one published case report.[11] This brief review cannot cover all aspects of drug-induced liver injury but focuses on general principles, newer concepts, and current challenges, with frequent references to the LiverTox website for further detail.

### TYPES OF DRUG-INDUCED LIVER INJURY

Drug-induced liver injury is typically classified as either direct or idiosyncratic,[1] but indirect injury is emerging as a third type (Table 1). Direct hepatotoxicity is caused by agents that are intrinsically toxic to the liver. The injury is common, predictable, dose-dependent, and reproducible in animal models.[1] The latency period is typically short, usually with an onset within 1 to 5 days after high therapeutic or supratherapeutic doses, as in the case of an intentional or accidental overdose.

Idiosyncratic hepatotoxicity is caused by agents that have little or no intrinsic toxicity and that cause liver injury only in rare cases, typically after 1 in 2000 to 1 in 100,000 patient-exposures.[5,13] The injury is unpredictable, not dose-dependent, and not reproducible in animal models. Idiosyncratic liver injury is categorized as hepatocellular, cholestatic, or both (mixed) on the basis of the *R* ratio, calculated by

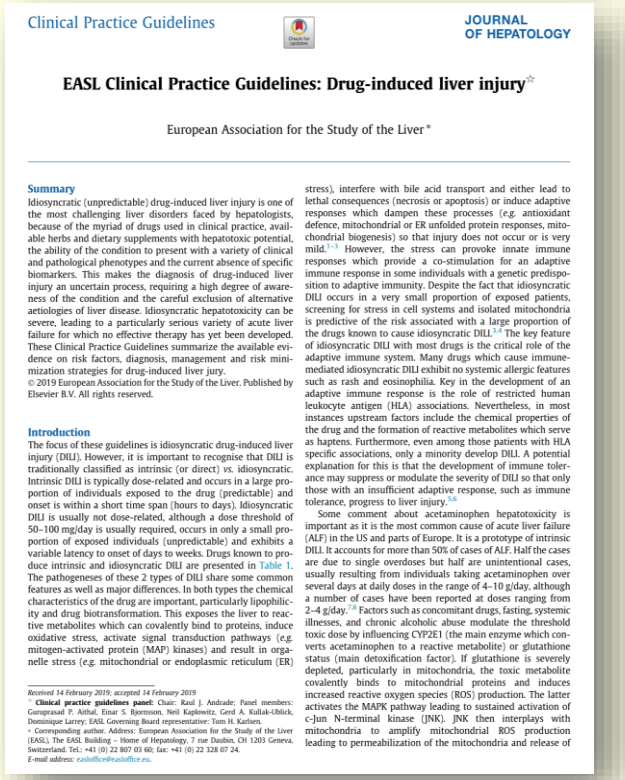


**Table 1. Drug-Induced Liver Injury According to Type.***

| 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 |

DILI, drug-induced liver injury; IV, intravenous
Hoofnagle JH, Bjrnsson ES. N Engl J Med 2019;381:264–73

# International DILI guidelines



Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

**EASL Clinical Practice Guidelines: Drug-induced liver injury**☆

European Association for the Study of the Liver*

**Summary**

Idiosyncratic (unpredictable) drug-induced liver injury is one of the most challenging liver disorders faced by hepatologists, because of the myriad of drugs used in clinical practice, available herbs and dietary supplements with hepatotoxic potential, the ability of the condition to present with a variety of clinical and pathological phenotypes and the current absence of specific biomarkers. This makes the diagnosis of drug-induced liver injury an uncertain process, requiring a high degree of awareness of the condition and the careful exclusion of alternative aetiologies of liver disease. Idiosyncratic hepatotoxicity can be severe, leading to a particularly serious variety of acute liver failure for which no effective therapy has yet been developed. These Clinical Practice Guidelines summarize the available evidence on risk factors, diagnosis, management and risk minimization strategies for drug-induced liver injury.



**Introduction**

The focus of these guidelines is idiosyncratic drug-induced liver injury (DILI). However, it is important to recognise that DILI is traditionally classified as intrinsic (or direct) vs. idiosyncratic. Intrinsic DILI is typically dose-related and occurs in a large proportion of individuals exposed to the drug (predictable) and onset is within a short time span (hours to days). Idiosyncratic DILI is usually not dose-related, although a dose threshold of 50–100 mg/day is usually required, occurs in only a small proportion of exposed individuals (unpredictable) and exhibits a variable latency to onset of days to weeks. Drugs known to produce intrinsic and idiosyncratic DILI are presented in Table 1. The pathogeneses of these 2 types of DILI share some common features as well as major differences. In both types the chemical characteristics of the drug are important, particularly lipophilicity and drug biotransformation. This exposes the liver to reactive metabolites which can covalently bind to proteins, induce oxidative stress, activate signal transduction pathways (*e.g.* mitogen-activated protein (MAP) kinases) and result in organelle stress (*e.g.* mitochondrial or endoplasmic reticulum (ER) stress), interfere with bile acid transport and either lead to lethal consequences (necrosis or apoptosis) or induce adaptive responses which dampen these processes (*e.g.* antioxidant defence, mitochondrial or ER unfolded protein responses, mitochondrial biogenesis) so that injury does not occur or is very mild.[1–3] However, the stress can provoke innate immune responses which provide a co-stimulation for an adaptive immune response in some individuals with a genetic predisposition to adaptive immunity. Despite the fact that idiosyncratic DILI occurs in a very small proportion of exposed patients, screening for stress in cell systems and isolated mitochondria is predictive of the risk associated with a large proportion of the drugs known to cause idiosyncratic DILI.[1,3] The key feature of idiosyncratic DILI with most drugs is the critical role of the adaptive immune system. Many drugs which cause immune-mediated idiosyncratic DILI exhibit no systemic allergic features such as rash and eosinophilia. Key in the development of an adaptive immune response is the role of restricted human leukocyte antigen (HLA) associations. Nevertheless, in most instances upstream factors include the chemical properties of the drug and the formation of reactive metabolites which serve as haptens. Furthermore, even among those patients with HLA specific associations, only a minority develop DILI. A potential explanation for this is that the development of immune tolerance may suppress or modulate the severity of DILI so that only those with an insufficient adaptive response, such as immune tolerance, progress to liver injury.[3,6]

Some comment about acetaminophen hepatotoxicity is important as it is the most common cause of acute liver failure (ALF) in the US and parts of Europe. It is a prototype of intrinsic DILI. It accounts for more than 50% of cases of ALF. Half the cases are due to single overdoses but half are unintentional cases, usually resulting from individuals taking acetaminophen over several days at daily doses in the range of 4–10 g/day, although a number of cases have been reported at doses ranging from 2–4 g/day.[7,8] Factors such as concomitant drugs, fasting, systemic illnesses, and chronic alcoholic abuse modulate the threshold toxic dose by influencing CYP2E1 (the main enzyme which converts acetaminophen to a reactive metabolite) or glutathione status (main detoxification factor). If glutathione is severely depleted, particularly in mitochondria, the toxic metabolite covalently binds to mitochondrial proteins and induces increased reactive oxygen species (ROS) production. The latter activates the MAPK pathway leading to sustained activation of c-Jun N-terminal kinase (JNK). JNK then interplays with mitochondria to amplify mitochondrial ROS production leading to permeabilization of the mitochondria and release of

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☆ **Clinical practice guidelines panel:** Chair: Raul J. Andrade; Panel members: Guruprasad P. Aithal, Einar S. Björnsson, Neil Kaplowitz, Gerd A. Kullak-Ublick, Dominique Larrey; EASL Governing Board representative: Tom H. Karlsen.

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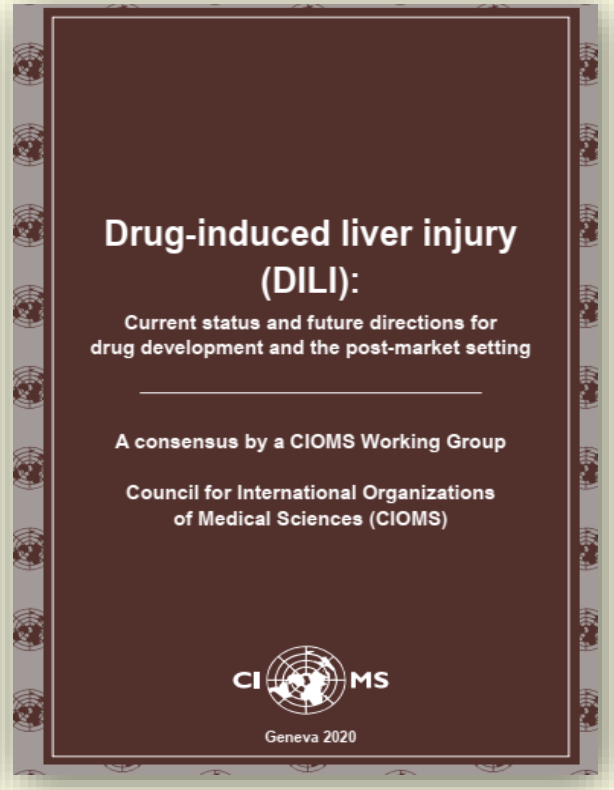

**Drug-induced liver injury (DILI):**

**Current status and future directions for drug development and the post-market setting**

**A consensus by a CIOMS Working Group**

**Council for International Organizations of Medical Sciences (CIOMS)**

CIOMS

Geneva 2020

Hepatology International
https://doi.org/10.1007/s12072-021-10144-3

CONSENSUS

**Drug-induced liver injury: Asia Pacific Association of Study of Liver consensus guidelines**

**Harshad Devarbhavi[1] · Guruprasad Aithal[2] · Sombat Treeprasertsuk[3] · Hajime Takikawa[4] · Yimin Mao[5] · Saggere M. Shasthry[6] · Saeed Hamid[7] · Soek Siam Tan[8] · Cyriac Abby Philips[9] · Jacob George[10] · Wasim Jafri[7] · Shiv K. Sarin[6] on behalf of on behalf of the Asia Pacific Association of Study of Liver**

Received: 9 December 2020 / Accepted: 16 January 2021


**Abstract**

Idiosyncratic drug-induced liver injury mimics acute and chronic liver disease. It is under recognized and underrecognised because of the lack of pathognomonic diagnostic serological markers. Its consequences may vary from being asymptomatic to self-limiting illness to severe liver injury leading to acute liver failure. Its incidence is likely to be more common in Asia than other parts of the world, mainly because of hepatotoxicity resulting from the treatment of tuberculosis disease and the ubiquitous use of traditional and complimentary medicines in Asian countries. This APASL consensus guidelines on DILI is a concise account of the various aspects including current evidence-based information on DILI with special emphasis on DILI due to antituberculosis agents and traditional and complementary medicine use in Asia.

**Keywords** APASL · DILI · Consensus · Guidelines · Hepatotoxicity · Drug-induced liver injury · Medications · Risk factors · Tuberculosis · Antituberculosis drugs · Monitoring · Treatment · Traditional and complimentary medicine

**Introduction**

Drug-induced liver injury (DILI) is an underdiagnosed and underappreciated causal or contributing factor to liver injury. DILI can mimic features of the entire spectrum of acute and chronic liver disease. The diagnosis of DILI is challenging not only by the lack of specific objective diagnostic tests but also by the low incidence and suspicion for the diagnosis in the first place. Furthermore, several diseases that need treatment are themselves capable of producing liver test abnormalities which complicate causality; hence, exclusion of a host of diseases by blood tests constitutes a critical part of the diagnosis of DILI.

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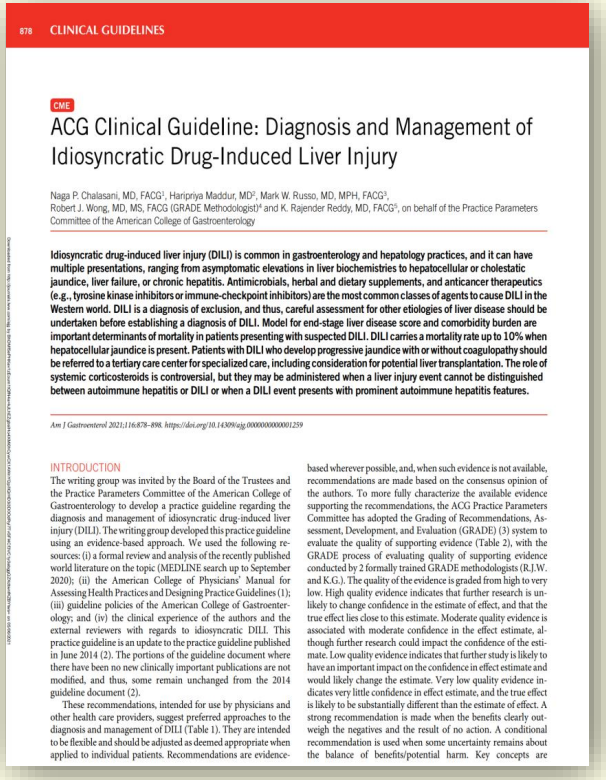




CME

**ACG Clinical Guideline: Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury**

Naga P. Chalasani, MD, FACG[1], Haripriya Maddur, MD[2], Mark W. Russo, MD, MPH, FACG[3], Robert J. Wong, MD, MS, FACG (GRADE Methodologist)[4] and K. Rajender Reddy, MD, FACG[5], on behalf of the Practice Parameters Committee of the American College of Gastroenterology

**Idiosyncratic drug-induced liver injury (DILI) is common in gastroenterology and hepatology practices, and it can have multiple presentations, ranging from asymptomatic elevations in liver biochemistries to hepatocellular or cholestatic jaundice, liver failure, or chronic hepatitis. Antimicrobials, herbal and dietary supplements, and anticancer therapeutics (e.g., tyrosine kinase inhibitors or immune-checkpoint inhibitors) are the most common classes of agents to cause DILI in the Western world. DILI is a diagnosis of exclusion, and thus, careful assessment for other etiologies of liver disease should be undertaken before establishing a diagnosis of DILI. Model for end-stage liver disease score and comorbidity burden are important determinants of mortality in patients presenting with suspected DILI. DILI carries a mortality rate up to 10% when hepatocellular jaundice is present. Patients with DILI who develop progressive jaundice with or without coagulopathy should be referred to a tertiary care center for specialized care, including consideration for potential liver transplantation. The role of systemic corticosteroids is controversial, but they may be administered when a liver injury event cannot be distinguished between autoimmune hepatitis or DILI or when a DILI event presents with prominent autoimmune hepatitis features.**

*Am J Gastroenterol 2021;116:878–898. https://doi.org/10.14309/ajg.0000000000001259*

INTRODUCTION

The writing group was invited by the Board of the Trustees and the Practice Parameters Committee of the American College of Gastroenterology to develop a practice guideline regarding the diagnosis and management of idiosyncratic drug-induced liver injury (DILI). The writing group developed this practice guideline using an evidence-based approach. We used the following resources: (i) a formal review and analysis of the recently published world literature on the topic (MEDLINE search up to September 2020); (ii) the American College of Physicians' Manual for Assessing Health Practices and Designing Practice Guidelines (1); (iii) guideline policies of the American College of Gastroenterology; and (iv) the clinical experience of the authors and the external reviewers with regards to idiosyncratic DILI. This practice guideline is an update to the practice guideline published in June 2014 (2). The portions of the guideline document where there have been no new clinically important publications are not modified, and thus, some remain unchanged from the 2014 guideline document (2).

These recommendations, intended for use by physicians and other health care providers, suggest preferred approaches to the diagnosis and management of DILI (Table 1). They are intended to be flexible and should be adjusted as deemed appropriate when applied to individual patients. Recommendations are evidence-based wherever possible, and, when such evidence is not available, recommendations are made based on the consensus opinion of the authors. To more fully characterize the available evidence supporting the recommendations, the ACG Practice Parameters Committee has adopted the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) (3) system to evaluate the quality of supporting evidence (Table 2), with the GRADE process of evaluating quality of supporting evidence conducted by 2 formally trained GRADE methodologists (R.J.W. and K.G.). The quality of the evidence is graded from high to very low. High quality evidence indicates that further research is unlikely to change confidence in the estimate of effect, and that the true effect lies close to this estimate. Moderate quality evidence is associated with moderate confidence in the effect estimate, although further research could impact the confidence of the estimate. Low quality evidence indicates that further study is likely to have an important impact on the confidence in effect estimate and would likely change the estimate. Very low quality evidence indicates very little confidence in effect estimate, and the true effect is likely to be substantially different than the estimate of effect. A strong recommendation is made when the benefits clearly outweigh the negatives and the result of no action. A conditional recommendation is used when some uncertainty remains about the balance of benefits/potential harm. Key concepts are

**2019** **2020** **2021**

DILI, drug-induced liver injury

1. EASL Clinical Guidelines: Drug-induced liver injury 2019; 2. CIOMS Working group 20201. 3. Devarbhavi H, et al. Hepatol Int 2021;15:258–82; 4. Chalasani N, et al. Am J Gastroenterol 2021;116:878–98.

# Highlights in different guidelines

| | ACG, 2021[1] | APASL, 2021[2] | EASL, 2019[3] | CIOMS, 2020[4] | CSH, 2015[5] |
|---|---|---|---|---|---|
| TCM/HDS-DILI | + | + | + | + | – |
| AT-DILI | – | + | – | + | – |
| ICIs-DILI | + | – | + | + | – |
| DILI in children | + | – | – | – | – |
| DILI with pre-existing liver disease | + | + | – | – | – |
| Specific phenotype | – | + | + | – | – |

AT, anti-tubercular; DILI, drug-induced liver injury; HDS, herbal and dietary supplements; ICI, immune checkpoint inhibitor; TCM, traditional Chinese Medicine

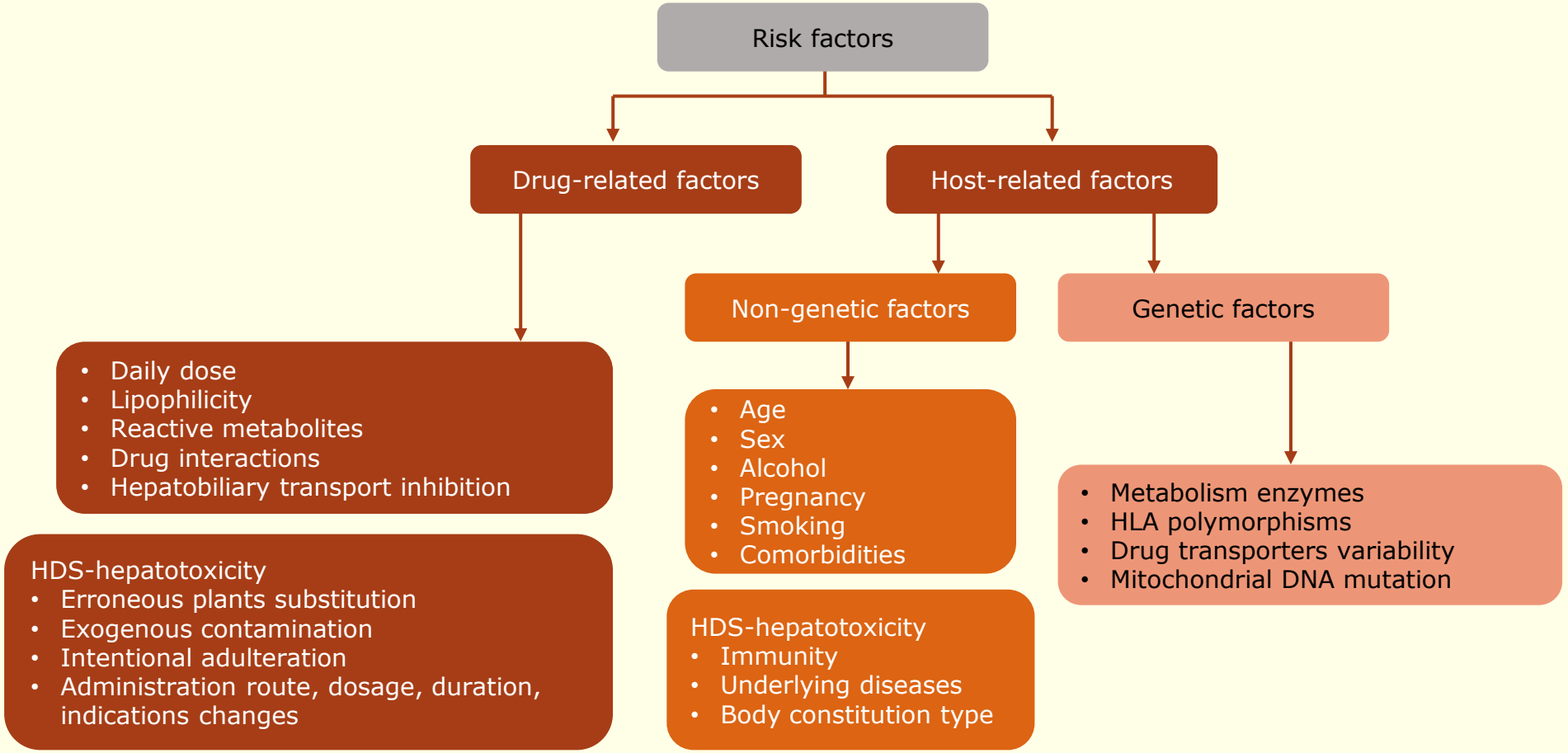
1. Chalasani N, et al. Am J Gastroenterol 2021;116:878–98; 2. Devarbhavi H, et al. Hepatol Int 2021;15:258–82; 3. EASL Clinical Guidelines: Drug-induced liver injury 2019; 4. CIOMS Working group 2020. Available from: https://cioms.ch/wp-content/uploads/2020/06/CIOMS_DILI_Web_16Jun2020.pdf ; 5. Yu YC, et al. Hepatol Int 2017;11:221–41

# Which of the following is not a host-related risk factor of DILI?

1. Age
2. Height
3. Pregnancy

DILI, drug-induced liver injury

# Risk factors of DILI




**There are no confirmed risk factors for all-cause DILI. Certain risk factors may contribute to the risk of DILI in a drug-specific manner**

DILI, drug-induced liver injury; DNA, deoxyribonucleic acid; HDS, herbal and dietary supplements; HLA, human leucocyte antigen

Li X, et al. Liver Int 2022;4:1999–2014

# DILI and selected HLA allele associations

| Study | Cases (n) | Drug | Variant | Ethnicity | OR |
|---|---|---|---|---|---|
| O'Donohue et al. (2000) | 20 patients<br>134 controls | Amoxicillin-clavulanate | DRB1*15:01 | Caucasian | 9.25 |
| Nicoletti et al. (2019) | 12 patients<br>8,438 controls | Carbamazepine | A*31:01 | Caucasian | 7.3 |
| McCormack et al. (2011) | 22 patients<br>3,987 controls | Carbamazepine | A*31:01 | Northern European | 12.41 |
| Stephens et al. (2013) | 11 patients<br>50 controls<br><br>18 patients<br>163 controls | Amoxicillin-clavulanate | A*3002<br><br>B*1801 | Spanish | 6.7<br><br>2.9 |
| Sharma et al. (2002) | 56 patients<br>290 controls | Isoniazid-rifampicin-pyrazinamide | DQB1*0201 | Indian | 1.9 |
| Nicoletti et al. (2016) | 6 patients with flupirtine-DILI<br>614 patients with other DILI<br>10,588 controls | Flupirtine | DRBI*16:01-DQB1*05:02 | German | 18.7 |
| Fontana et al. (2018) | 15 patients with terbinafine-DILI | Terbinafine | A*33:01 | Caucasian | – |
| Hoofnagle et al. (2021) | 36 patients with green tea supplements – DILI<br>15,094 controls | Green tea | B*35:01 | – | – |

DILI, drug-induced liver injury; HLA, human leucocyte antigen; OR, odds ratio

Li X, et al. Liver Int 2022;4:1999–2014

# Non-HLA variants may be potential risk factors for DILI

HHS Public Access
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*Gastroenterology*. 2019 May ; 156(6): 1707–1716.e2. doi:10.1053/j.gastro.2019.01.034.

**A Missense Variant in *PTPN22* is a Risk Factor for Drug-induced Liver Injury**

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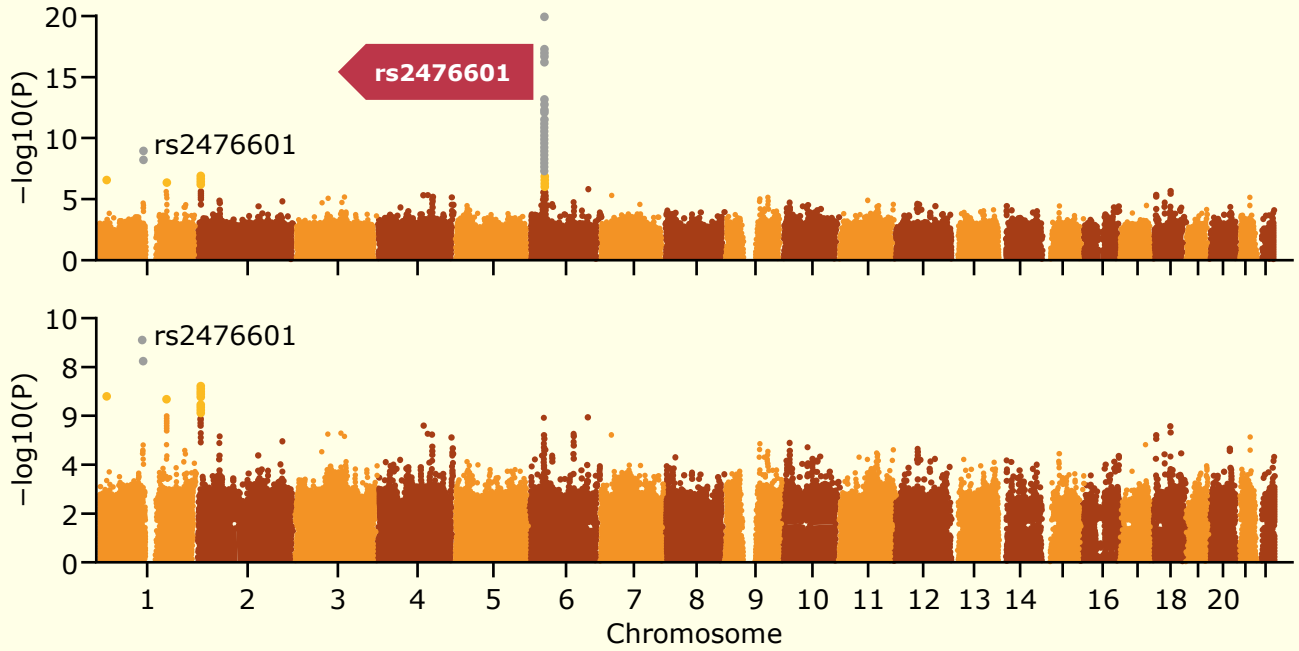



**Association with rs2476601 for drugs with ≥3 case carriers in the European cohort and OR >1**

| Drugs | Cases (n) | AF | OR | 95% CI | p |
|---|---|---|---|---|---|
| Amoxicillin/clavulanic acid | 444 | 0.13 | **1.62** | **1.3–1.98** | **0.000004** |
| Terbinafine | 15 | 0.20 | **3.23** | 1.29–8.1 | **0.01** |
| Sulfamethoxazole/trimethoprim | 42 | 0.17 | 2.07 | 1.16–3.71 | 0.01 |
| Methotrexate | 9 | 0.22 | 3.34 | 1.09–10.16 | 0.03 |
| Rofecoxib | 6 | 0.25 | 4.08 | 1.05–15.82 | 0.04 |
| Valproic acid | 16 | 0.18 | 2.43 | 0.99–5.95 | 0.05 |
| **Flupirtine** | 6 | 0.25 | **4.43** | **0.98–20.05** | **0.05** |
| Fenofibrate | 10 | 0.20 | 2.93 | 0.97–8.87 | 0.06 |
| Erythromycin | 11 | 0.18 | 2.89 | 0.95–8.78 | 0.06 |
| Doxycycline | 6 | 0.25 | 3.21 | 0.85–12.1 | 0.09 |
| Pravastatin | 6 | 0.25 | 3.21 | 0.83–12.47 | 0.09 |
| Nimesulide | 20 | 0.12 | 2.10 | 0.81–5.41 | 0.12 |
| Cefuroxime | 4 | 0.25 | 3.45 | 0.69–17.28 | 0.13 |
| Ethinylestradiol/levonorgestrel | 7 | 0.21 | 2.53 | 0.71–9.05 | 0.15 |
| Isoniazid | 43 | 0.13 | 1.59 | 0.84–3.02 | 0.16 |
| Celecoxib | 9 | 0.17 | 2.37 | 0.69–8.19 | 0.17 |
| **Flucloxacillin** | **195** | **0.11** | **1.24** | **0.90–1.71** | **0.18** |
| Nitrofurantoin | 74 | 0.12 | 1.40 | 0.85–2.32 | 0.19 |
| Piroxicam | 5 | 0.20 | 2.85 | 0.60–13.68 | 0.19 |
| Gabapentin | 5 | 0.20 | 2.79 | 0.58–13.39 | 0.2 |
| Cefazolin | 21 | 0.14 | 1.59 | 0.67–3.8 | 0.3 |
| Mercaptopurine | 10 | 0.15 | 1.72 | 0.50–5.97 | 0.39 |
| Imatinib | 8 | 0.12 | 1.70 | 0.38–7.56 | 0.49 |
| **Ticlopidine** | **5** | **0.10** | **2.01** | **0.24–16.73** | **0.52** |
| Atorvastatin | 29 | 0.10 | 1.32 | 0.56–3.09 | 0.53 |
| **Minocycline** | **32** | **0.11** | **1.29** | **0.58–2.86** | **0.53** |
| Interferon beta-1a | 4 | 0.12 | 1.90 | 0.21–16.79 | 0.57 |
| Amiodarone | 5 | 0.20 | 1.64 | 0.28–9.73 | 0.59 |
| Diclofenac | 66 | 0.10 | 1.17 | 0.67–2.04 | 0.59 |
| Ibuprofen | 15 | 0.10 | 1.36 | 0.41–4.52 | 0.62 |
| Herbal and dietary products | 58 | 0.10 | 1.19 | 0.65–2.17 | 0.58 |
| Disulfiram | 8 | 0.12 | 1.40 | 0.32–6.13 | 0.65 |
| All other therapeutic products | 9 | 0.11 | 1.33 | 0.30–5.93 | 0.71 |
| Nicotinic acid | 4 | 0.12 | 1.45 | 0.17–12.17 | 0.73 |
| Lisinopril | 5 | 0.10 | 1.45 | 0.17–12.17 | 0.74 |
| Phenytoin | 10 | 0.10 | 1.18 | 0.27–5.11 | 0.82 |
| Rosuvastatin | 4 | 0.12 | 1.27 | 0.14–11.29 | 0.83 |

**rs2476601 variant in PTPN22 increased the risk of DILI caused by multiple drugs**

AF, allele frequency; CI, confidence interval; DILI, drug-induced liver injury; HLA, human leucocyte antigen; OR, odds ratio
Cirulli ET, et al. Gastroenterology 2019;156:1707–16.e2

# Patterns and specific phenotype

## Specific phenotype

| Phenotype | Manifestations | Typical agents |
|---|---|---|
| Acute hepatic necrosis | Initially, abrupt AST and ALT elevation with mild ALP or TB elevation ± jaundice. Later marked AST and ALT and bilirubin elevation | APAP, isoniazid |
| Bland cholestasis | Marked and prolonged jaundice, pruritus. Moderate ALT and ALP elevation | Anabolic steroids, oestrogens |
| Cholestatic hepatitis | Marked pruritus and jaundice with high ALP elevation, mild ALT elevation | Amoxicillin-clavulanate, cephalosporins |
| Drug-induced AIH | Acute DILI with serologic tests ± histology compatible with idiopathic AIH | Nitrofurantoin, minocycline, diclofenac, statins |
| Acute fatty liver | Non-specific symptoms to ALF. Moderate ALT elevation and lactic acidosis | Didanosine, stavudine, aspirin and valproate |
| Drug-associated fatty liver disease | Non-alcoholic fatty liver disease due to specific drugs. Mild ALT ± ALP elevation | Tamoxifen, glucocorticoids |
| Granulomatous hepatitis | Moderate to high ALP elevation ± jaundice | Isoniazid, allopurinol, carbamazepine, sulfa drugs |
| Nodular regenerative hyperplasia | Non-cirrhotic portal hypertension, minimal ALT and ALP elevations | Azathioprine, oxaliplatin, didanosine |
| Sinusoidal obstruction syndrome | Abdominal pain, hepatomegaly ± jaundice. Variable enzyme variations | Busulfan, cyclophosphamide, gemtuzumab ozogamicin |
| Vanishing bile duct syndrome | Persistent pruritus and jaundice with prolonged ALP and bilirubin elevation | Amoxicillin/clavulanate, penicillins, sulfa drugs, NSAIDs |
| Liver tumours | Liver mass(es) | Androgenic steroids, oestrogens |

AIH, autoimmune hepatitis; ALF, acute liver failure; ALP, alkaline phosphatase; ALT, alanine transaminase; APA, acetaminophen; AST, aspartate transaminase; NSAIDs, non-steroidal anti-inflammatory drugs; TB, tuberculosis

Devarbhavi H, et al. Hepatol Int. 2021;15:258-82

# Diagnosis: DILI related information is important

| Element | Comments |
|---|---|
| Sex | Particularly pertinent for competing disorders (e.g., PBC) |
| Age | Particularly pertinent for competing disorders (e.g., HEV) |
| Race/ethnicity | Particularly pertinent for competing disorders (e.g., sarcoidosis, sickle cell–related biliary stone disease, and oriental sclerosing cholangitis) |
| Indication for use of drug or HDS | |
| Concomitant diseases | Particularly pertinent disorders may include sepsis, heart failure, hypotension episodes, recent general anesthesia, parenteral nutrition, and cancer |
| Presence of rechallenge | Give timing of rechallenge if performed |
| History of other drug reactions | Certain cross-reactivities may exist (e.g., antiepileptics) |
| History of other liver disorders | Chronic viral hepatitis, NAFLD, hemochromatosis, alcoholic liver disease, PSC, PBC, and liver cancer |
| History of alcohol use | Past vs present; estimated grams per day; sporadic vs binge drinking vs regular (daily or weekly) |
| Exposure time (latency) | Start and stop dates or total number of days, weeks, or months taken |
| Symptoms and signs | Presence or absence, time of onset, type (fatigue, weakness, abdominal pain, nausea, dark urine, icterus, jaundice, pruritus, fever, and rash) |
| Physical findings | Fever, rash, hepatomegaly, hepatic tenderness, and signs of chronic liver disease |
| Medications and HDS products | Complete list of medications or HDS products with particular attention to those started in the previous 6 mo |
| Laboratory results | Day of first abnormal liver biochemistry, liver biochemistries, and eosinophil counts at presentation |
| Viral hepatitis serologies | Anti-HAV IgM, HBsAg, anti-HBc IgM, anti-HCV, and HCV RNA |
| Autoimmune hepatitis serologies | ANA, anti-smooth muscle antibody, and IgG level |
| Imaging | US +/− Doppler, CT, or MRI +/− MRCP |
| Histology if available | Timing of biopsy in relation to enzyme elevation and onset |
| Washout (dechallenge) data | Follow-up liver biochemistries |
| Clinical outcome | Resolution, transplant, death, and timing of each |

## Recommended minimal elements of a diagnostic evaluation in the work-up of suspected DILI[1]

**Recommendation 1** Suspected drug-induced liver injury patients should be evaluated completely which includes obtaining a thorough history of intake of drugs and assessment of the pattern of liver injury based on serum biochemical tests and exclusion of other causes of liver disease. Knowledge of potential drug-related adverse effects on the liver and a high degree of awareness of DILI would enhance the precision of history taking.

Grading of evidence: A. Grading of recommendation: strong (1).

**Recommendation on obtaining DILI history[2]**

ANA, antinuclear antibodies; CT, computerised tomography; DILI, drug-induced liver injury; HAV, hepatitis A virus; HDS, herbal and dietary supplements; HCV, hepatitis C virus; HEV, hepatitis E virus; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; MRCP, Magnetic resonance cholangiopancreatography MRI, magnetic resonance imaging; NAFLD, non-alcoholic fatty liver disease; RNA, ribonucleic acid. 1. Naga C, et al. Am J Gastroenterol 2021;116:878–98; 2. Devarbhavi H, et al. Hepatol Int 2021;15:258–82

# Diagnosis of DILI

Abnormal liver enzymes

↓

Thorough history and physical
Complete review of medications and herbals and dietary supplements

↓

Calculate *R*-value
*R*-value = serum (ALT/ALT ULN) ÷ (ALP/ALP ULN)

| *R*-value ≥5 (hepatocellular) | <2 *R*-value <5 (mixed) | *R*-value ≤2 (cholestatic) |
|---|---|---|
| **First-line tests:** Acute viral hepatitis serologies, HCV RNA, and AIH serologies, imaging studies (e.g. abdominal ultrasound)<br>**Second-line tests on a case-by-case basis:** ceruloplasmin, serologies for less common viruses (HEV, CMV, and EBV), liver biopsy | **First-line tests:** Acute viral hepatitis serologies, HCV RNA, and AIH serologies, imaging studies (e.g. abdominal ultrasound)<br>**Second-line tests on a case-by-case basis:** ceruloplasmin, serologies for less common viruses (HEV, CMV, and EBV), liver biopsy | **First-line tests:** Imaging studies (abdominal ultrasound)<br>**Second-line tests on a case-by-case basis:** Cholangiography (either endoscopic or MR based), serologies for primary biliary cirrhosis, liver biopsy |

↓

Assessment of data, causality assessment, and diagnosis:
1. Assessment of data:
   a. Completeness
2. b. Literature review by use of LiverTox and PubMed
3. Clinical judgement for final DILI diagnosis
4. Expert consultation if doubt persists


878 CLINICAL GUIDELINES

CME

ACG Clinical Guideline: Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury

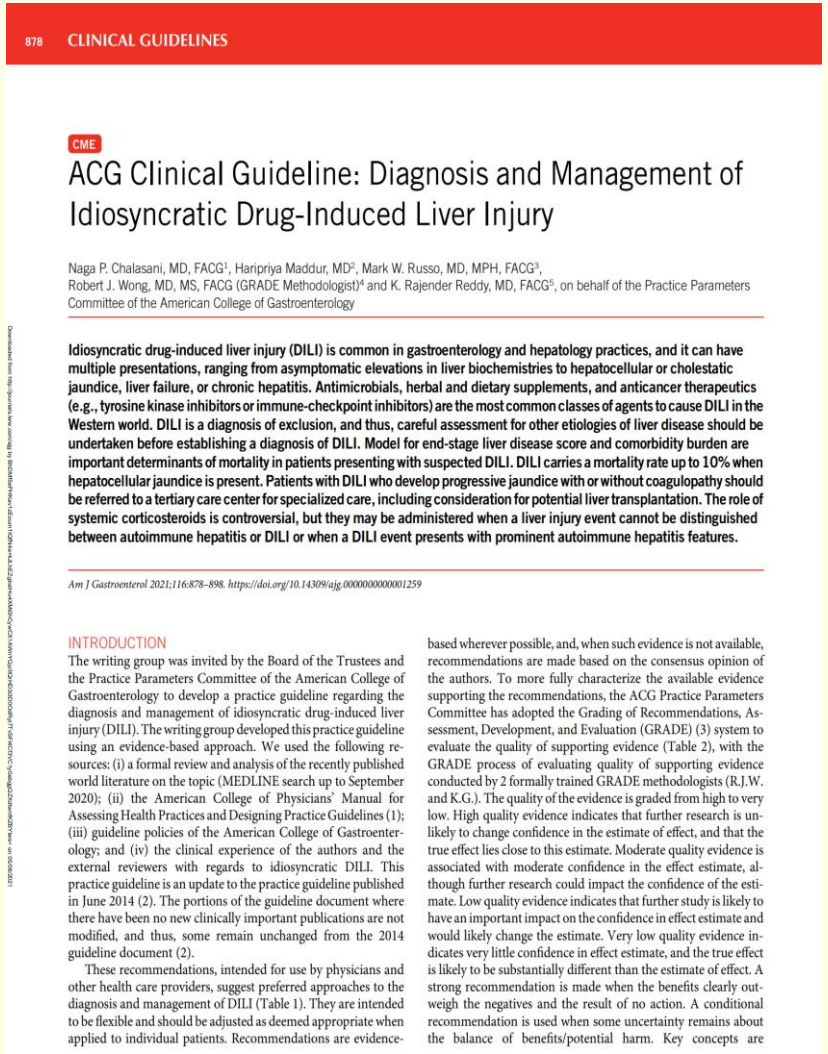
Naga P. Chalasani, MD, FACG[1], Haripriya Maddur, MD[2], Mark W. Russo, MD, MPH, FACG[3], Robert J. Wong, MD, MS, FACG (GRADE Methodologist)[4] and K. Rajender Reddy, MD, FACG[5], on behalf of the Practice Parameters Committee of the American College of Gastroenterology

- Exclusion of other possible causes of liver injury based on clinical history, blood tests, liver imaging and/or biopsy is the strategy for the diagnosis of DILI

AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; CMV, cytomegalovirus; DILI, drug-induced liver injury; EBV, Epstein-Barr virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HSV, herpes simplex virus; MR, magnetic resonance; RNA, ribonucleic acid; ULN, upper limit of normal

Naga C, et al. Am J Gastroenterol 2021;116:878–98

# When to consider a liver biopsy?



878 CLINICAL GUIDELINES

CME

## ACG Clinical Guideline: Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury

Naga P. Chalasani, MD, FACG[1], Haripriya Maddur, MD[2], Mark W. Russo, MD, MPH, FACG[3], Robert J. Wong, MD, MS, FACG (GRADE Methodologist)[4] and K. Rajender Reddy, MD, FACG[5], on behalf of the Practice Parameters Committee of the American College of Gastroenterology

**Idiosyncratic drug-induced liver injury (DILI) is common in gastroenterology and hepatology practices, and it can have multiple presentations, ranging from asymptomatic elevations in liver biochemistries to hepatocellular or cholestatic jaundice, liver failure, or chronic hepatitis. Antimicrobials, herbal and dietary supplements, and anticancer therapeutics (e.g., tyrosine kinase inhibitors or immune-checkpoint inhibitors) are the most common classes of agents to cause DILI in the Western world. DILI is a diagnosis of exclusion, and thus, careful assessment for other etiologies of liver disease should be undertaken before establishing a diagnosis of DILI. Model for end-stage liver disease score and comorbidity burden are important determinants of mortality in patients presenting with suspected DILI. DILI carries a mortality rate up to 10% when hepatocellular jaundice is present. Patients with DILI who develop progressive jaundice with or without coagulopathy should be referred to a tertiary care center for specialized care, including consideration for potential liver transplantation. The role of systemic corticosteroids is controversial, but they may be administered when a liver injury event cannot be distinguished between autoimmune hepatitis or DILI or when a DILI event presents with prominent autoimmune hepatitis features.**

*Am J Gastroenterol 2021;116:878–898. https://doi.org/10.14309/ajg.0000000000001259*

INTRODUCTION

The writing group was invited by the Board of the Trustees and the Practice Parameters Committee of the American College of Gastroenterology to develop a practice guideline regarding the diagnosis and management of idiosyncratic drug-induced liver injury (DILI). The writing group developed this practice guideline using an evidence-based approach. We used the following resources: (i) a formal review and analysis of the recently published world literature on the topic (MEDLINE search up to September 2020); (ii) the American College of Physicians' Manual for Assessing Health Practices and Designing Practice Guidelines (1); (iii) guideline policies of the American College of Gastroenterology; and (iv) the clinical experience of the authors and the external reviewers with regards to idiosyncratic DILI. This practice guideline is an update to the practice guideline published in June 2014 (2). The portions of the guideline document where there have been no new clinically important publications are not modified, and thus, some remain unchanged from the 2014 guideline document (2).

These recommendations, intended for use by physicians and other health care providers, suggest preferred approaches to the diagnosis and management of DILI (Table 1). They are intended to be flexible and should be adjusted as deemed appropriate when applied to individual patients. Recommendations are evidence-based wherever possible, and, when such evidence is not available, recommendations are made based on the consensus opinion of the authors. To more fully characterize the available evidence supporting the recommendations, the ACG Practice Parameters Committee has adopted the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) (3) system to evaluate the quality of supporting evidence (Table 2), with the GRADE process of evaluating quality of supporting evidence conducted by 2 formally trained GRADE methodologists (R.J.W. and K.G.). The quality of the evidence is graded from high to very low. High quality evidence indicates that further research is unlikely to change confidence in the estimate of effect, and that the true effect lies close to this estimate. Moderate quality evidence is associated with moderate confidence in the effect estimate, although further research could impact the confidence of the estimate. Low quality evidence indicates that further study is likely to have an important impact on the confidence in effect estimate and would likely change the estimate. Very low quality evidence indicates very little confidence in effect estimate, and the true effect is likely to be substantially different than the estimate of effect. A strong recommendation is made when the benefits clearly outweigh the negatives and the result of no action. A conditional recommendation is used when some uncertainty remains about the balance of benefits/potential harm. Key concepts are

3. When to consider a liver biopsy?

(a) We recommend performing a liver biopsy if AIH remains a competing etiology and if immunosuppressive therapy is contemplated (strong recommendation, low quality of evidence).

(b) We suggest performing a liver biopsy if there is unrelenting rise in liver biochemistries or signs of worsening liver function despite stopping the suspected offending agent (conditional recommendation, very low quality of evidence).

(c) We suggest performing a liver biopsy if peak ALT level has not fallen by >50% at 30–60 days after onset in cases of hepatocellular DILI or if peak Alk P has not fallen by >50% at 180 days in cases of cholestatic DILI despite stopping the suspected offending agent (conditional recommendation, very low quality of evidence).

(d) We suggest performing a liver biopsy in cases of DILI where continued use or re-exposure to the implicated agent is contemplated (conditional recommendation, very low quality of evidence).

(e) We suggest considering liver biopsy if liver biochemistry abnormalities persist beyond 180 days, especially if associated with symptoms (e.g., itching) or signs (e.g., jaundice and hepatomegaly), to evaluate for the presence of chronic liver diseases (CLDs) and chronic DILI (conditional recommendation, very low quality of evidence).

AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine transferase; DILI, drug-induced liver injury

Naga C, et al. Am J Gastroenterol 2021;116:878–98

# Causality assessment

## RECAM was recommended by guidelines[1,2]

| Criteria enzyme pattern exposure | Hepatocellular | | | Cholestatic or mixed | | |
|---|---|---|---|---|---|---|
| | Initial exposure | Subsequent exposure | Pts | Initial exposure | Subsequent exposure | Pts |
| Timing from<br>Drug start<br><br>Drug stop | <br>5–90 days<br><5, >90 days<br>≤15 days | <br>1–15 days<br>>15 days<br>≤15 days | <br>+2<br>+1<br>+1 | <br>5–90 days<br><5, >90 days<br>≤30 days | <br>1–90 days<br>>90 days<br>≤30 days | <br>+2<br>+1<br>+1 |
| **Course** | **Difference between peak ALT and ULN value** | | | **Difference between peak ALP (or bili) and ULN** | | |
| After drug stop | Decrease ≥50% in 8 days<br>Decrease ≥50% in 30 days<br>Decrease ≥50% in >30 days<br>Decrease <50% in >30 days | | +3<br>+2<br>0<br>−2 | Decrease ≥50% in 180 days<br>Decrease <50% in 180 days<br>Persistence or increase or no information | | +2<br>+1<br>0 |
| Risk factor | Ethanol: yes<br>Ethanol: no | | +1<br>0 | Ethanol or pregnancy: yes<br>Ethanol or pregnancy: no | | +1<br>0 |
| Age | ≥50 years<br><50 years | | +1<br>0 | ≥50 years<br><50 years | | +1<br>0 |
| Other drugs | None or no information<br>Drug with suggestive timing known hepatotoxin w/suggestive timing<br>Drug w/other evidence for a role (e.g. + rechallenge) | | −1<br>−2<br><br>−3 | None or no information<br>Drug with suggestive timing known hepatotoxin w/suggestive timing<br>Drug w/other evidence for a role (e.g. + rechallenge) | | 0<br>−1<br><br>−2 |
| Competing causes | All group I and II ruled out<br>All of group I ruled out<br>4–5 of group I ruled out<br><4 of group I ruled out<br>Non-drug causes highly probable | | +2<br>+1<br>0<br>−2<br>−3 | All group I[a] and II[b] ruled out<br>All of group I ruled out<br>4–5 of group I ruled out<br><4 of group I ruled out<br>Non-drug causes highly probable | | +2<br>+1<br>0<br>−2<br>−3 |
| Previous information | Reaction in product label<br>Reaction published; no label<br>Reaction unknown | | +2<br>+1<br>0 | Reaction in product label<br>Reaction published; no label<br>Reaction unknown | | +2<br>+1<br>0 |
| Rechallenge | Positive<br>Compatible<br>Negative<br>Not performed or not interpretable | | +3<br>+1<br>−2<br>0 | Positive<br>Compatible<br>Negative<br>Not performed or not interpretable | | +3<br>+1<br>−2<br>0 |

17.425 Q1 > Hepatology. 2022 Jan 11. doi: 10.1002/hep.32327. Online ahead of print.

**A revised electronic version of RUCAM for the diagnosis of DILI**

Paul H Hayashi [1], M Isabel Lucena [2 3], Robert J Fontana [4], Einar S Bjornsson [5 6], Guruprasad P Aithal [7], Huiman Barnhart [8], Andres Gonzalez-Jimenez [2 3], Qinghong Yang [8], Jiezhun Gu [8], Raul J Andrade [2 3], Jay H Hoofnagle [9]

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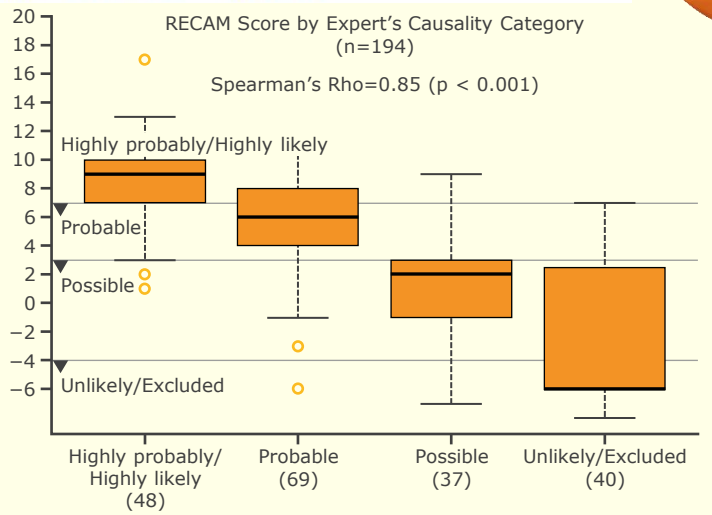


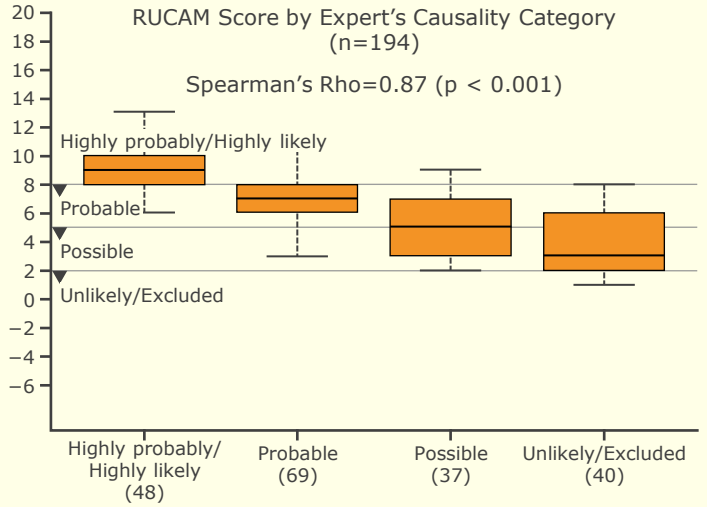


**RECAM is at least as capable as RUCAM in diagnosing DILI, is more aligned with expert opinion and has better sensitivity to detect extreme diagnostic categories[2]**

ALP, alkaline phosphatase; Pts, patients; RUCAM, Roussel Uclaf Causality Assessment Method

1. Zhonghua Gan Zang Bing Za Zhi 2015;23(11):810-20; 2. Hayashi P, et al. Hepatology 2022;76:18–31

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# Recommendations on treatment of DILI

| | ACG, 2021[1] | APASL, 2021[2] | EASL, 2019[3] | CIOMS, 2020[4] | CSH, 2015[5] |
|---|---|---|---|---|---|
| Withdrawal offending drug | + | + | + | + | + |
| **Recommended drug therapies** | | | | | |
| NAC | +（adult ALF） | +（adult ALF） | +（adult ALF） | +（adult ALF） | +（adult ALF） |
| Corticosteroid | DILI patients with AIH-like features | - | Routine use may not be substantiated | DILI patients with AIH-like features | Patients with immuno-allergic or autoimmune features |
| Cholestyramine | – | Leflunomide-DILI | Leflunomide and terbinafine-DILI | – | – |
| Carnitine | – | Valproate-DILI | Valproate-DILI | – | – |
| UDCA | – | DILI with cholestasis | Efficacy may not be substantiated | Need further research | DILI with cholestasis |
| Magnesium isoglycyrrhizinate | – | + | – | + | + |
| Liver-protected agents | – | – | – | Need further research | +，need further research |

ACG, American College of Gastroenterology; AIH, autoimmune ALF; ALF, acute liver failure; APASL, Asian Pacific Association for the Study of the Liver; CIOMS, Council for International Organizations of Medical Sciences; CSH, Chinese Society of Hepatology; DILI, drug-induced liver injury; EASL, European Society for the Study of the Liver; NAC, N-acetylcysteine; UDCA, Ursodeoxycholic acid

1. Chalasani N, et al. Am J Gastroenterol 2021;116:878–98; 2. Devarbhavi H, et al. Hepatol Int 2021;15:258–82; 3. EASL Clinical Guidelines: Drug-induced liver injury 2019; 4.CIOMS Working group 2020. Available from: https://cioms.ch/wp-content/uploads/2020/06/CIOMS_DILI_Web_16Jun2020.pdf; 5. Yu YC, et al. Hepatol Int 2017;11:221–41

# Steroid use in ALF

**Steroid use in Acute Liver Failure**

Jamuna Karkhanis[1], Elizabeth C. Verna[1], Matthew S. Chang[1], R. Todd Stravitz[2], Michael Schilsky[3], William M Lee[4], Robert S Brown Jr[1], and the Acute Liver Failure Study Group

3rd GLOBAL LIVER HEALTH FORUM

## Retrospective analysis of autoimmune, indeterminate, and drug-induced ALF patients in the Acute Liver Failure Study Group from 1998 to 2007

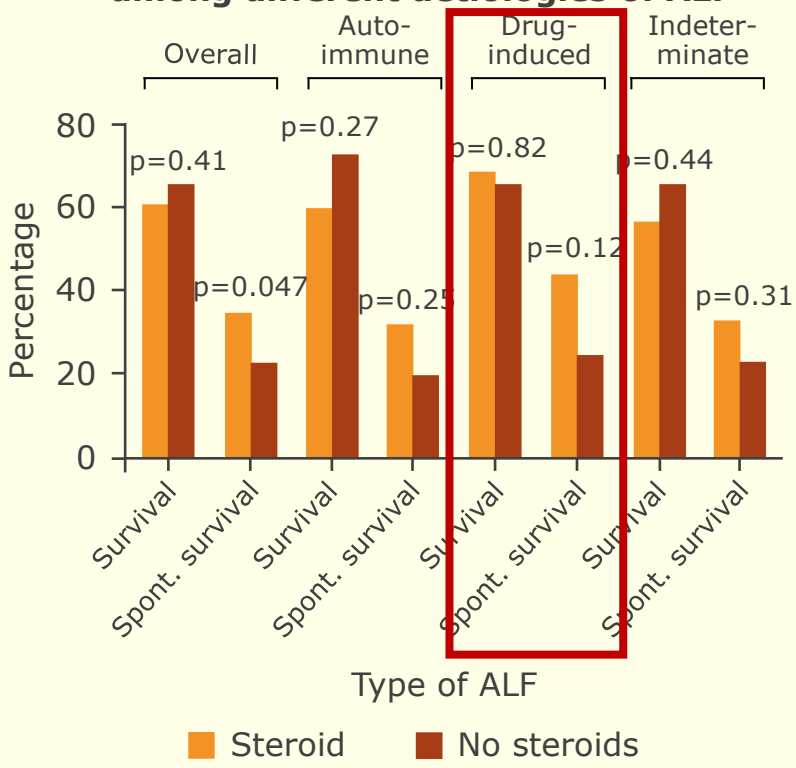
### N=361 patients with ALF

| | AIH (n=66) | Indeterminate ALF (n=164) | DILI (n=131) |
|---|---|---|---|
| Patients treated with steroids, n | 25 | 21 | 16 |

### Uni- and multivariable analysis to predict spontaneous survival

| Variable | Univariate OR | Univariate p value | Multivariate OR | Multivariate p value |
|---|---|---|---|---|
| Steroid treatment | 1.80 | 0.049 | 1.80 | 0.12 |
| Diagnosis | | | | |
| AI-ALF | – | – | – | – |
| DI-ALF | 1.18 | 0.63 | 1.49 | 0.33 |
| Indeterminate | 1.00 | 0.98 | 1.36 | 0.46 |
| Male gender | 1.58 | 0.07 | – | – |
| Coma grade | | | | |
| 1 | – | – | – | – |
| 2 | 0.56 | 0.05 | | |
| 3 | 0.50 | 0.04 | | |
| 4 | 0.22 | <0.001 | | |
| Ventilatory support | 0.24 | <0.001 | 0.21 | <0.001 |
| MELD | 0.93 | <0.001 | 0.93 | <0.001 |
| INR | 0.84 | 0.01 | – | – |
| ALT (per 100 U/L) | 1.02 | <0.001 | 1.04 | <0.001 |
| AST (per 100 U/L) | 1.01 | 0.004 | – | – |
| Bilirubin | 0.93 | <0.001 | – | – |
| pH <7.4 | 0.60 | 0.13 | – | – |

### Overall and spontaneous survival among different aetiologies of ALF




**Steroid use did not improve overall or spontaneous survival in patients with ALF, highlighting the need for effective therapies to treat ALF and DILI**

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AIH, autoimmune hepatitis; ALF, acute liver failure; ALT, alanine transferase; AST, aspartate transferase; DILI, drug-induced liver injury; INR, international normalised ratio of prothrombin time; MELD, Model for Endstage Liver Disease; OR, odds ratio; Spont., spontaneous

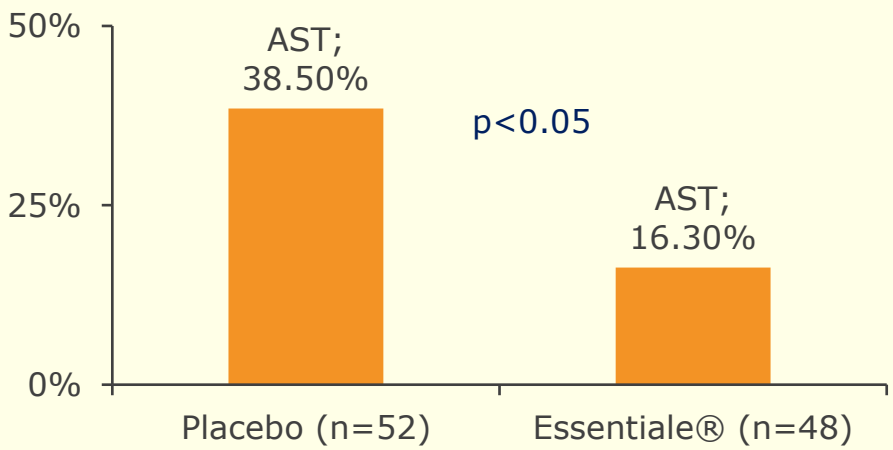
Karkhanis J, et al. Hepatology 2014;59:612–21

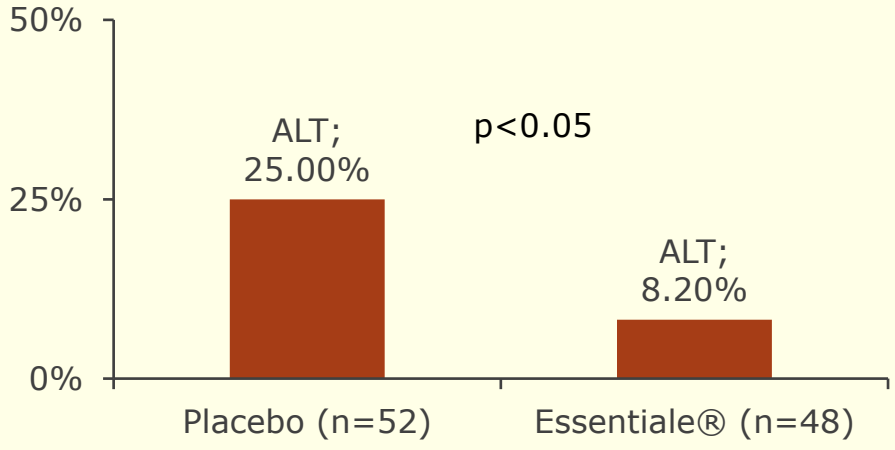
# Pivotal data of Essentiale® in DILI due to AT-drugs

- **Randomised, double-blind study** in pulmonary tuberculosis
- 120 patients with pulmonary tuberculosis received rifampicin, isoniazid and ethambutol for 12 weeks; 101 patients were evaluable and were randomised to receive:
  - Essentiale®, 600 mg, t.i.d. (n=49)
  - Placebo (n=52)

➢ **Significantly more patients receiving placebo showed elevated values for ALT (≥47 units/L) or AST (≥35 units/L) during the study (p<0.05)**

**Percentage of patients with an increase in serum AST and ALT activities during anti-tuberculous treatment and receiving preventative treatment with Essentiale® or placebo**



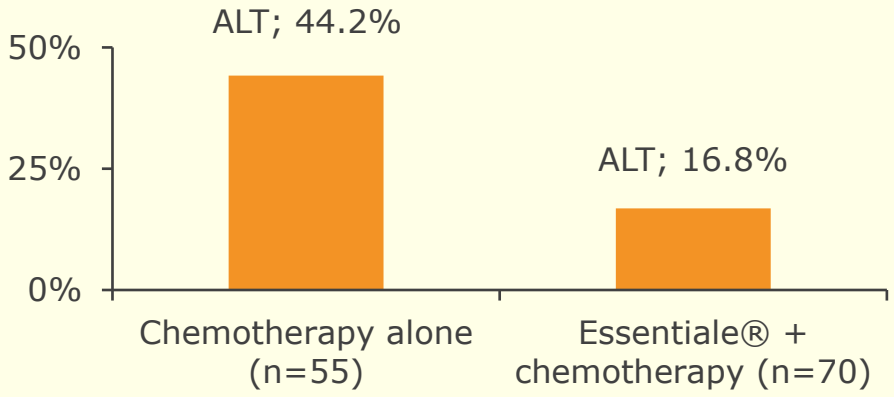

ALT, alanine transaminase; AT, AT, anti-tubercular; AST, aspartate transaminase; DILI, drug-induced liver injury; t.i.d., three times a day; WHO, World Health Organization
Marpaung B et al. Therapiewoche 1988;38:734–40

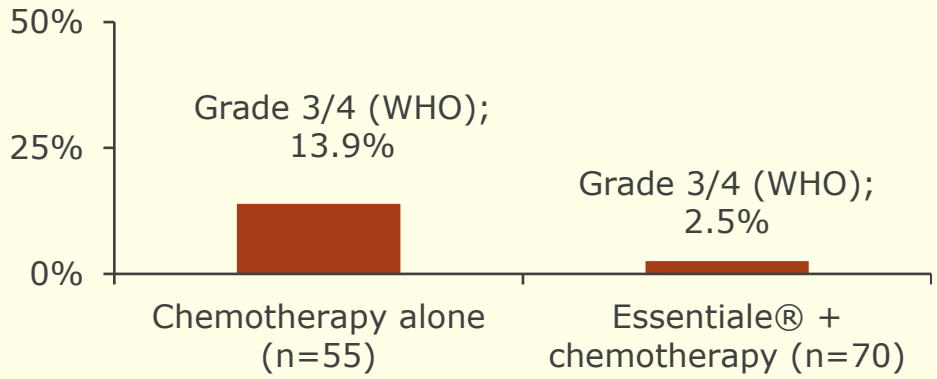
# Data of Essentiale® in DILI due to chemotherapeutic agents

- **Open-label, controlled study** in solid malignant tumours patients
- 150 patients with solid malignant tumours received chemotherapeutic agents for 3 weeks in combination with:
  - Essentiale®, 600 mg, t.i.d (n=70) (chemotherapy 202 episodes)
  - Chemotherapy alone (n=55) (chemotherapy 231 episodes)

➢ **Lower incidence of liver dysfunction with Essentiale® after chemotherapy (16.8% vs 44.2%, p<0.0001) and lower hepatoxicity grade (2.5% vs 13.9%, p<0.0001)**

**Percentage of patients with an increase in serum ALT activities and Grade 3/4 liver function (WHO) impairment during chemotherapy in combination with Essentiale®**




ALT, alanine transaminase; DILI, drug-induced liver injury; t.i.d., three times a day; WHO, World Health Organization

Wu M, et al. Chin J Clin Oncol 1998;25:663–5

# DILI can be seen in patients with COVID-19

**The aim of this systematic review was to characterise the role of conventional drugs in causing DILI in patients with COVID-19, and to define characteristic features of these patients**

## Patient characteristics

| Patient characteristic | Patients with DILI and COVID-19 (N=393) |
|---|---|
| Mean or median age, years | 54.3–56 |
| Male:female ratio | 1.8–3.41 |

## Key results

The most common cause of DILI was **anti-viral drugs** given empirically for their known therapeutic efficacy in other viral infections

Hepatocellular injury was more often reported than cholestatic or mixed injury*

Maximum ALT levels reported **1.541 U/L**

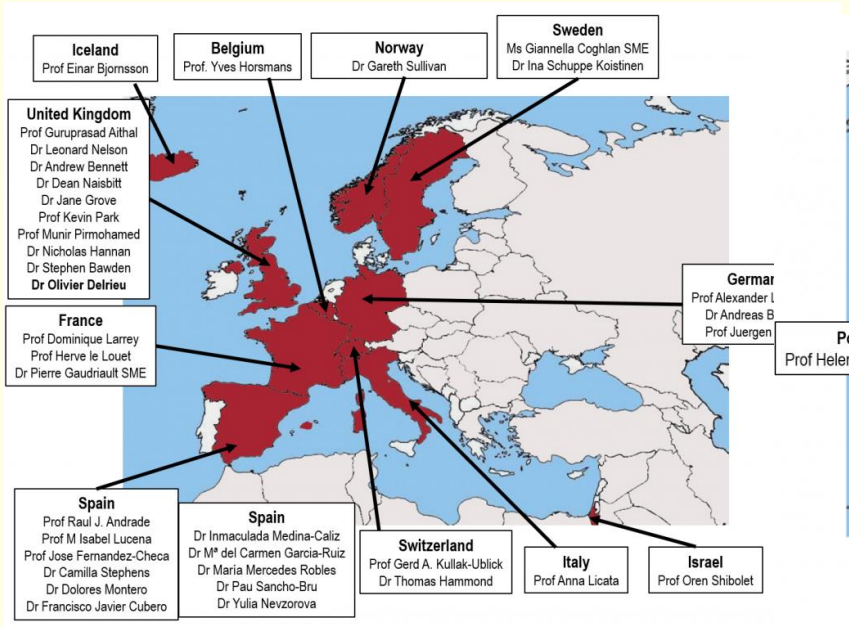
Maximum AST levels reported **1.079 U/L**

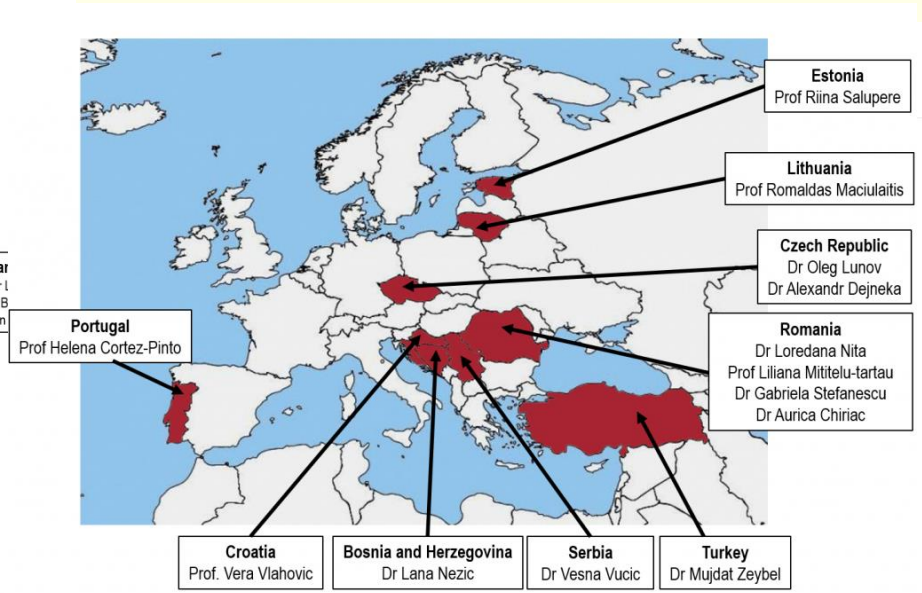
ALT:AST ratio range **0.4–1.4**

**Clinical improvement was seen in most patients, likely due to quick cessation of drugs; however, one patient died**

*Based on Roussel Uclaf Causality Assessment Method criteria using ALT and ALP as diagnostic parameters
ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; COVID-19, coronavirus disease 2019; DILI, drug-induced liver injury
Teschke R, et al. Int J Mol Sci 2022;23:4828

# Global cooperation





**European countries**

**Inclusiveness target countries**

**International partner countries**

**COST ACTION**

PRO-EURO DILI NETWORK
Prospective European Drug-induced Liver Injury Network

sanofi

# Thanks

www.hepatox.org