Drug-induced liver injury: a comprehensive review

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***Abstract*:** Drug-induced liver injury (DILI) remains a challenge in clinical practice and is still a diagnosis of exclusion. Although it has a low incidence amongst the general population, DILI accounts for most cases of acute liver failure with a fatality rate of up to 50%. While multiple mechanisms of DILI have been postulated, there is no clear causal relationship between drugs, risk factors and mechanisms of DILI. Current best practice relies on a combination of high clinical suspicion, thorough clinical history of risk factors and timeline, and extensive hepatological investigations as supported by the international Roussel Uclaf Causality Assessment Method criteria, the latter considered a key diagnostic algorithm for DILI. This review focuses on DILI classification, risk factors, clinical evaluation, future biomarkers and management, with the aim of facilitating physicians to correctly identify DILI early in presentation.

Keywords: acute hepatitis, acute liver failure, acute liver injury, DILI, drug-induced liver injury, RUCAM

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Introduction

Drug-induced liver injury (DILI) is an adverse toxic drug reaction resulting in liver injury. It is an uncommon occurrence with an estimated incidence of 14–19 cases per 100,000 population, accounting for less than 1% of acute liver injury (ALI).[1] Nevertheless, DILI is the most common cause of acute liver failure (ALF) in the West, with a case fatality rate of 10–50%, although no definite causative agent has been attributed in several cases.[2] Such potentially fatal events have a critical impact on policymaking to both tighten pharmaceutical restrictions of or, at times, complete market withdrawals of drugs. Between 1998 and 2007, the United States Acute Liver Failure Study Group (ALFSG) network group identified that paracetamol was the commonest cause of ALF (46%), followed by indeterminate DILI (15%) and idiosyncratic DILI (12%). Idiosyncratic DILI was attributed to anti-tuberculous medications, sulpha compounds, phenytoin and herbal and dietary supplements.[3] With an ever-increasing repertoire of pharmaceuticals combined with the changing consumer behaviour towards the use of phytotherapy, it is imperative for physicians to both recognise and effectively manage DILI. This review will outline the classification, risk factors, diagnosis, management and prognosis of DILI.

Classification

DILI is traditionally classified as either intrinsic or idiosyncratic. Intrinsic DILI is typically dose dependent and occurs in a predictable manner with an onset of hepatotoxicity observed within hours to days of exposure. Drugs causing intrinsic DILI are often lipophilic, permitting free access across the hepatocyte's lipid bilayer. They undergo biomodification into reactive metabolites that cause oxidative stress and activate cellular signalling pathways to induce mitochondrial dysfunction and disturbances of bile acid homeostasis.[4] The archetypal drug causing intrinsic DILI is paracetamol, which accounts for half of intrinsic DILI progressing to ALF in both Europe

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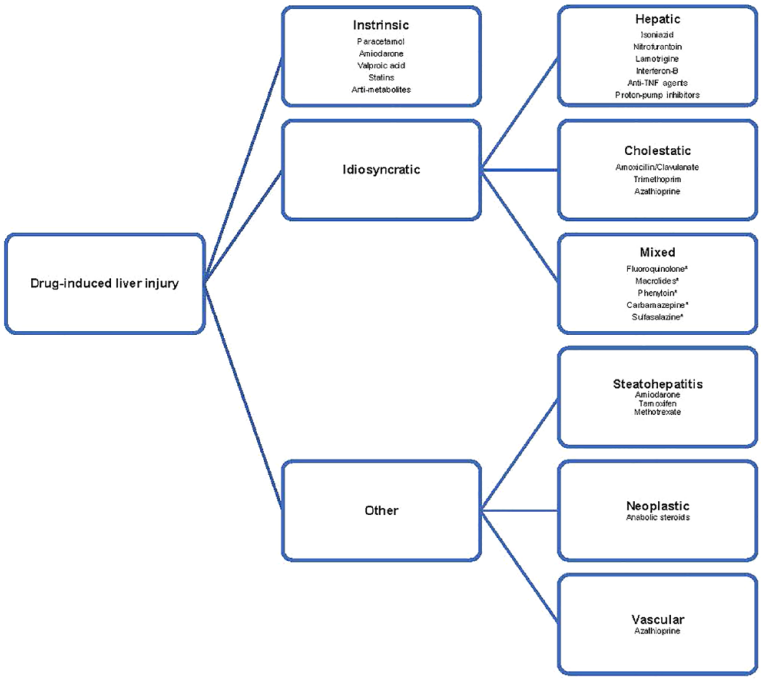

Figure 1. Classification of DILI.
*Medications known to cause hepatocellular, cholestatic or mixed pattern of liver injury.
DILI, drug-induced liver injury.

and Northern America. Other drugs causing intrinsic DILI include amiodarone, valproic acid and statins (Figure 1).[5]

On the contrary, idiosyncratic DILI typically follows an unpredictable course with variable latency of onset of weeks to months.[4] Although it is a rare occurrence typically observed in one in more than 10,000 patients, idiosyncratic DILI accounts for 10–15% of ALF in the United States.[6] Idiosyncratic DILI lacks a clear dose dependence; yet, recent studies suggest a minimum of 50–100 mg per day of the offending drug is required.[4] Although the Roussel Uclaf Causality Assessment Method (RUCAM) criteria can provide a possible causative agent in the case of multiple drug administration, the unpredictability and rarity of idiosyncratic liver injuries and the absence of diagnostic biomarkers make clinical recognition difficult. Severity of idiosyncratic DILI can vary from spontaneous recovery following drug cessation to ALF needing hospitalisation, liver transplantation (LT) or contributing to death. The adaptive immune system and restricted human leukocyte antigen (HLA) have been postulated to play a critical role in the pathogenesis of idiosyncratic DILI in genetically susceptible individuals.[7]

The pattern of liver injury in idiosyncratic DILI can be divided into hepatocellular, cholestatic or mixed according to the liver enzyme derangement profile observed in each individual case.[8,9] Idiosyncratic DILI can be further classified into immune-mediated (allergic) and non-immune-mediated reactions. Immune-mediated idiosyncratic DILI usually presents within 1–6 weeks of drug administration, characterised by fever, rash, eosinophilia, presence of autoantibodies (antinuclear antibody or anti-smooth-muscle antibody) and, in severe cases, Stevens–Johnson syndrome.[10] Minocycline and nitrofurantoin are well-established drugs known to cause drug-induced autoimmune hepatitis (AIH), as verified in DILI cases that have been assessed for causality using RUCAM.[11] Non-immune-mediated idiosyncratic DILI instead does not manifest any of the aforementioned features, with a delayed onset of clinical presentation. Beyond intrinsic and idiosyncratic DILI, other forms of DILI such as steato-hepatitic, neoplastic (anabolic steroid-induced or nodular regenerative hyperplasia) and

vasculitic (azathioprine-induced hepatic sinusoidal obstruction syndrome) variants have been described.[10]

Mortality outcomes vary with the pattern of idiosyncratic DILI. Mixed liver injury has the most favourable prognosis with ALF being a rare adversity. Conversely, patients with hepatocellular injury combined with jaundice have the worst prognosis, with 10% fatality rate.[12] The definition of hepatocellular DILI has been further refined to patients with a ratio of alanine transferase (ALT) to alkaline phosphatase (ALP) of 5 or higher while cholestatic and mixed liver injuries are defined by a ratio of ALT/ALP being equal to or less than 2 and between 2 and 5, respectively.[13]

Although not a drug, the incidence of herb-induced liver injury (HILI) is rising as the use of phytotherapy gains popularity in the West. HILI has been reported worldwide including sub-Saharan Africa, China and Europe.[14] HILI shares common presenting features to DILI and is subclassified into hepatocellular, cholestatic and mixed patterns of liver injury. A recent systematic review by Lin *et al.*[15] reviewed published cases of herb-induced hepatitis using RUCAM liver enzyme derangement patterns as indicators of liver injury and showed that HILI can present in a wide age group from 15 to 78 years with a mean age of presentation of 48 years. There is an overall female predominance with cholestatic patterns of liver injury with the exception of the elderly population where men were more likely to be affected. Hepatocellular and cholestatic liver injury have been reported following the ingestion of products containing tea extracts catechin and germander, greater celandine as a remedy for gastrointestinal disorders, as well as seeds of *Psoralea corylifolia* for asthma, aphrodisiac or anti-inflammatory use. Catha Edulis, also known as khat, consumed in parts of Eastern Africa and Middle East can cause ALI and ALF. Linoleic acid and vitamin A can predispose to hepatocellular hepatitis.[4] The reason why only a small proportion of patients taking herbal products develop HILI is unknown, suggesting the role of a complex interaction between toxic metabolites, contaminants, harmful drug interactions and possibly genetic predisposition in its pathogenesis.[16]

Risk factors

Various risk factors have been implicated in DILI.[17] The propensity of a drug to cause DILI is highly dependent on patient age groups as emphasised by the RUCAM algorithm criteria.[8,9] Younger patients seem to have a higher risk for hepatocellular DILI compared to the elderly. Indeed, aspirin use in children is associated with Reye's syndrome, characterised by increased fatty infiltration into hepatocytes and cerebral oedema.[18] Similarly, valproic acid produces increased reactive oxygen species leading to hepatocyte damage in the young adult population.[19,20] Elderly patients are more prone to cholestatic DILI, with amoxicillin/clavulanate being the classic example.[21] Increasing age is associated with increased hepatotoxicity from anti-tuberculous drugs also, especially isoniazid. The exact pathophysiology is unclear; yet, it is plausibly due to age-related changes in renal and liver function and associated blood flow, defective immune responses to certain drug metabolites or increased presence of reactive oxygen species in hepatocytes.[22,23] The role of polypharmacy in old age and its link with DILI is disputed with little evidence to support an association.[24]

Gender has also been implicated as an important risk factor of DILI. It was long proposed that females have a higher risk for idiosyncratic DILI to drugs such as diclofenac, tetracyclines and nitrofurantoin.[25] Yet, multiple studies show otherwise, demonstrating equal prevalence of DILI in both men and women.[26,27] Nevertheless, Lucena *et al.*[28] reported nearly twice as many women suffering from hepatocellular DILI as well as increased severity and poorer outcomes from DILI. The exact pathophysiology of such variations is unclear but increased genetic susceptibility and increased likelihood of autoimmune-mediated liver injury in females may potentiate this risk.

Drug pharmacodynamics and interactions

Drug metabolism through different isoforms of cytochrome P450 (CYP) plays a critical role in idiosyncratic DILI.[29] Of 3312 cases of idiosyncratic DILI assessed for causality with RUCAM, Tschke *et al.*[30] identified 61.1% of drugs to be metabolised by cytochrome P450 (CYP) isoforms. Among these drugs, almost half (49.1%) were metabolised by CYP 3A4/5 and almost a quarter (24.6%) were metabolised by CYP 2C8/9. The remaining quarter was metabolised by CYP 2E1, CYP 2C19, CRP 1A2 and CYP 2D6. Patients with idiosyncratic DILI had a

higher proportion of drugs metabolised by CYP 2C9 (24.6% *versus* 10%) and CYP 2E1 (13.2% *versus* 2–4%) when compared to the general healthy population. Valproic acid, particularly in young children, is found to cause hepatotoxicity by enhancing 4-ene-valproic acid reactive metabolite formation by inducing CYP 2A6 and CYP 2C9. Furthermore, valproic acid induces β-oxidation leading to impaired mitochondrial DNA repair. Enhanced production of reactive metabolites is also observed in statins, with reduced drug clearance from functional CYP3A4 polymorphisms implicated. Interactions with drugs such as amiodarone, macrolides and fluconazole that inhibit CYP3A4 activity also reduce threshold for statin-induced hepatotoxicity.[31]

The lipophilicity of a drug as a risk factor for idiosyncratic DILI has been a focus of much debate. Due to their high solubility and ability to have increased off-target effects, lipophilic drugs are thought to be able to cross into hepatocytes and undergo metabolism.[32] The latter can produce reactive species which can either injure hepatocytes directly or trigger an immune response due to abnormal protein formation. Various drugs are listed in LiverTox database as to their potential to cause liver injury. Notably, diclofenac forms hepatotoxic reactive amines during its metabolism. Valproic acid toxicity is increased by other anticonvulsants, presumably due to an increased pool of intermediary reactive oxygen species, which would otherwise be cleared by glutathione conjugation and N-acetyl conjugation, a process thought to be reduced with other anticonvulsants present.[19]

In 2013, the National Centre for Toxicological Research of the US Food and Drug Administration (FDA)[33] analysed 164 FDA-approved oral medications and coined the 'rule-of-two' where a combination of a defined daily dose (DDD) of $\geqslant$100 mg and high lipophilicity increased the risk of hepatotoxicity (odds ratio: 14.05, $p < 0.001$). Moreover, employing the 'rules of two' increased the positive predictive value for DILI from 85% to 96%, while decreasing the negative predictive value from 55% to 39%. Nevertheless, Weng *et al.*[34] published contrasting results based on a review of 975 oral drugs. Of 49% (478) of the drugs identified to induce hepatotoxicity, a higher DDD of $\geqslant$100 mg and extensive liver metabolism of $\geqslant$50% were associated with hepatic adverse drug reactions. Yet, lipophilicity of an oral drug alone or in combination did not contribute to hepatotoxicity. This study's methodology that was used to derive results was later questioned, as it inappropriately defined 'DILI negatives' as a simple subtraction of 'DILI positives' in a given condition from the total number of drugs. There are significant contradictions in defining 'DILI-negative' drugs across studies, with up to 40% of drugs labelled as 'DILI negative' in one registry and 'DILI positive' in another.[35] To resolve this, McEuen *et al.*[36] established a consensus annotation by cataloguing the majority vote of five selected annotations.[37–41] From analysing 1036 FDA-approved drugs, both lipophilicity and extent of metabolism were found to be weak but independent risk factors for DILI. This study also supported previous findings that DDD of $\geqslant$100 mg and extensive hepatic metabolism of $\geqslant$50% were strongly associated with increased risk of DILI. Regardless, it is important to note that the reference annotations used in this study did not have a consistent methodology in defining DILI, highlighting the need for consistency in using validated scores to better characterise causality in future studies.

Assessment

The clinical presentation of DILI varies extensively, from patients who develop a viral hepatitis-like syndrome to those who are asymptomatic. Some patients with deranged liver biochemistry can develop eosinophilia suggestive of an underlying drug allergy, but this is observed in only a fraction of patients. Furthermore, imaging of the liver and biliary tree is often normal in DILI.[4]

Re-challenge of an implicated drug provides the strongest evidence for DILI. In practice, re-challenge of a drug commonly occurs inadvertently by patients without prior knowledge of the causal relationship between a drug and liver injury. Excluding anti-tuberculous medications, however, re-challenge of an implicated drug can be dangerous and is rarely advocated in clinical practice due to ethical constraints.[4,42]

Identifying deranged liver enzymes, although non-specific, remains the hallmark for diagnosing DILI.[10] Hepatocellular DILI is outlined by an ALT $\geqslant$ 5 times the upper limit of normal (ULN) and ALT/ALP $\geqslant$ 5 times ULN. Cholestatic DILI is denoted by an ALP $\geqslant$ 2 times ULN and ALT/ALP ratio of $\leqslant$2 times ULN. Mixed

DILI is characterised by ALT ⩾ 3 times ULN, ALP ⩾ 2 times ULN and ALT/ALP ratio <5 or >2 times ULN.[13] Liver enzyme derangements combined with clinical history of toxicity including dermal reactions, kidney injury and previous DILI should prompt suspicion of DILI (Figure 2).[4] Investigations include an extensive liver panel as well as imaging of both the liver and the biliary tract using ultrasound, contrast-enhanced computed tomography or magnetic resonance imaging based on clinical context.

On liver biopsy, hepatocellular idiosyncratic DILI involves a high degree of portal inflammation, necrosis and apoptosis that typically involves zone 3. Cholestatic DILI instead involves canalicular and hepatocellular cholestasis.[4] Yet, such features are not pathognomonic of DILI, with mixed subtype of DILI further complicating diagnostic evaluation. Whilst liver biopsy can be useful to identify certain cases of liver injury such as a liver mass of unknown origin, it is not necessarily required for cases of DILI. A stepwise approach to the clinical history, alcohol intake, lists of drugs taken, clinical examination, liver tests, viral screening and relevant imaging is often sufficient to point to the cause of liver injury.

Genetic predisposition to DILI is poorly understood but several gene polymorphisms encompassing cytochrome enzymes, HLA and mitochondrial DNA mutations are thought to contribute to the overall risk of DILI. DILI defined by RUCAM criteria has been strongly associated with HLA loci polymorphisms. Notably, HLADRR1*15:01 was found to be associated with amoxicillin/clavulanate DILI.[43] The presence of HLA-B*57:01 was also found to be associated with an 81-fold increased risk of flucloxacillin-induced hepatotoxicity.[44] Clinical medicine has not yet incorporated regular DNA profiling to identify at-risk individuals and as such is not an easily identifiable trait. Until genomic medicine and technology become widely available and accessible, risk assessment based on genetic make-up is not regularly feasible.

There have been multiple standardised causality assessment scales that have been developed to provide more objective and reproducible criteria. The Council for International Organisations of Medical Sciences endorsed the RUCAM in 1993 to aid clinicians for detection of idiosyncratic DILI.[8,9] Today, the RUCAM scale remains the most widely used tool to confirm or exclude DILI. It uses objective criteria such as time of onset of hepatotoxicity, risk factors, exclusion of alternative non-drug-related causes of ALI, and ALT/ALP levels to establish a possible causal association between a drug and liver injury. A total score ranging from −9 to +15 is derived from seven distinct domains to stratify patients according to their probability of having DILI. When first validated, the RUCAM scale demonstrated a sensitivity of 86%, specificity of 89%, positive predictive value of 93% and negative predictive value of 78%. RUCAM has been widely adopted worldwide due to the ease of clear criteria identification, stepwise approach and easy scoring system which can be independently reassessed by different colleagues. It also went through an international update to its criteria since its inception.[13]

In 2022, a digitised version of RUCAM, known as RECAM (Revised Electronic Version of Causality Assessment Method), was developed. This incorporated a modified criteria for the diagnosis of DILI and was trialled on DILI cases registered on the US DILI Network and Spanish DILI Registry. The results did not show overall improved diagnostic sensitivity or specificity of RECAM over RUCAM.[45] Notably, the study was limited to only 194 US and Spanish cases, most of which were of Caucasian descent which restricts its generalisability. RECAM's validation did not include DILI cases with positive re-challenge, which is considered the gold standard by DILI experts. Moreover, LiverTox scores as a measure of hepatoxicity are not evidence based and are of weak quality. The authors pointed out that RUCAM was unreliable, but this stems mainly from inaccurate use by different users. RUCAM is ingrained in actual cases (published or from databases) and is the most widely used diagnostic tool for DILI due to its objectivity and strong validation based on 81,856 DILI cases. RECAM showed that there could be a path to digitisation of RUCAM to improve accessibility and data acquisition, but the use of such computerised causality assessment method warrants adequate validation and generalisability.[46]

Novel biomarkers

Biomarkers including metabolic enzymes, microRNA and cellular proteins have been a focus of research for diagnostic and prognostic evaluation

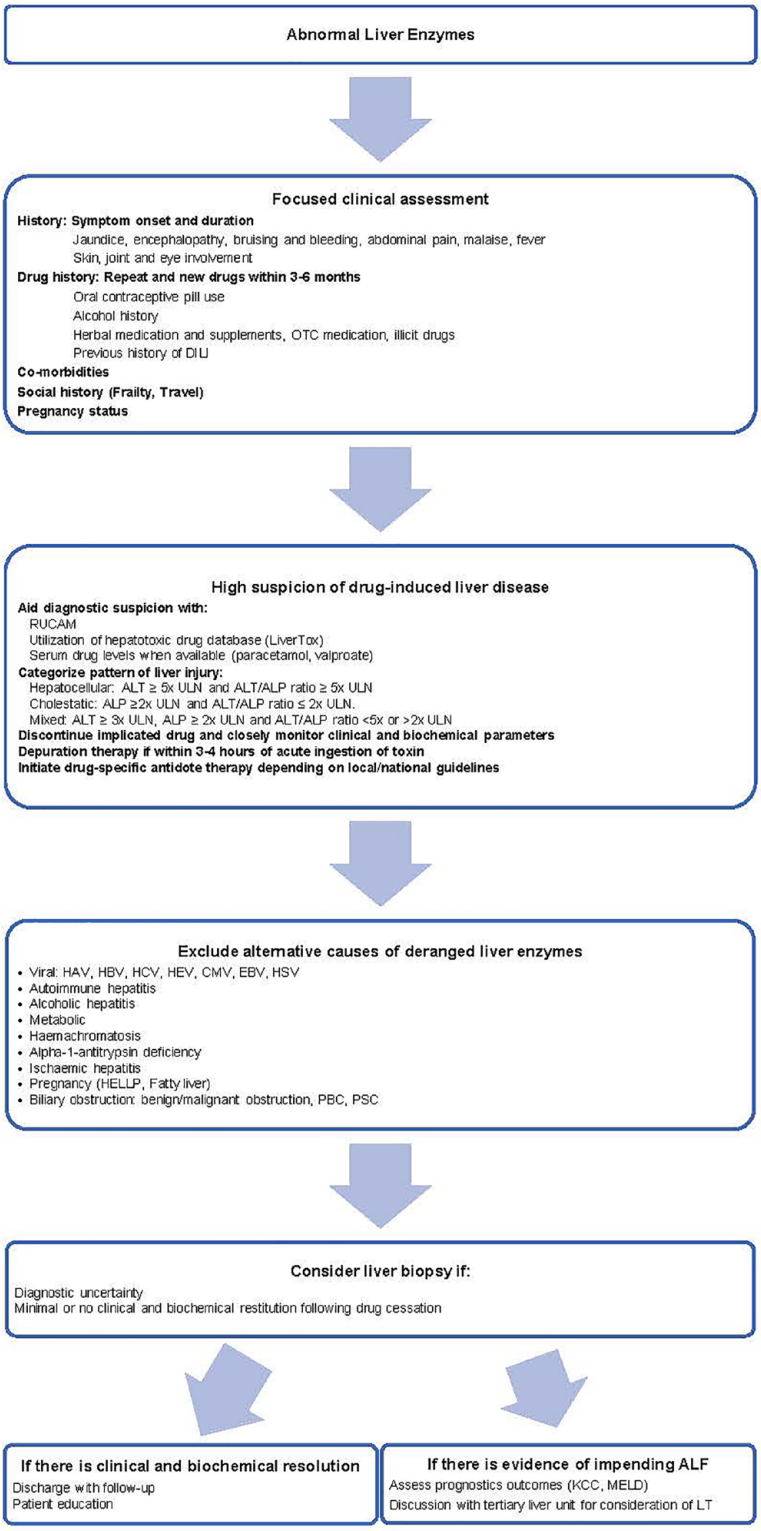

Figure 2. Clinical algorithm for suspected DILI.
ALP, alkaline phosphatase; ALT, alanine transaminase; CMV, cytomegalovirus; DILI, drug-induced liver injury; EBV, Epstein-Barr virus; HAV, Hepatitis A virus; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HEV, Hepatitis E virus; HSV, herpes simplex virus; KCC, King College Criteria; LT, liver transplantation; MELD, Model For End-Stage Liver Disease; OTC, Over-the-counter; RUCAM, Roussel Uclaf Causality Assessment Method; ULN, upper limit of normal.

of DILI. Fatty acid binding protein 1 (FABP-1) is found abundantly in the liver and is involved in fatty acid metabolism, storage and transport.[47] Mikus *et al.*[48] found that FABP-1 increased early in drug-mediated liver injury compared to ALT. Once treatment was over, FABP-1 levels decreased to baseline whilst ALT elevation persisted. Additionally, increased FABP-1 was found to be associated with poorer outcomes in paracetamol hepatotoxicity.[49] However, FABP-1 levels also change in other diseases such as cancer, diabetes and metabolic disorders; as such, its kinetics and variation in illness need to be studied to determine its sensitivity and specificity in detecting DILI.

Due to the lack of sensitive molecular markers in predicting or prognosticating DILI, there was much excitement following the identification of High Mobility Group Box-1 and microRNA-122 as possible diagnostic biomarkers specific to DILI cases. However, the results of the validation experiments came under scrutiny and were later retracted due to lack of scientific robustness. Hence, new innovative and robust methods need to be designed to properly identify the true biomarkers of liver injury. These should be validated in RUCAM-defined cases of DILI to enhance their credibility and reliability for clinical practice.[50]

Identifying new biomarkers comes with pitfalls, and the advent of proteomics is gaining new insight into new potential protein biomarkers for DILI.[51] The ideal biomarker should be sensitive to pick up early liver injury and specific to avoid other confounding illnesses. Until specific biomarkers are available in clinical practice, a case-by-case expert judgement with a systematic approach using a combination of liver biopsy, immune-allergic features and standardised causality assessment scales is therefore recommended for early diagnosis and management of DILI.

Management

Prompt discontinuation of the implicated drug remains the most important step to managing DILI. Cessation of the causative agent often leads to spontaneous recovery in days to weeks and does not require any further therapeutic interventions. Yet, the trajectory of clinical and biochemical resolution is not always predictable. Protraction of or deterioration in hepatic function despite cessation of the culprit drug can generate significant clinical uncertainty, leading to alternative causes being missed and appropriate therapy not being administered. Moreover, biochemical resolution of liver tests may not always connote clinical improvement, with decreasing ALT observed in patients with reducing hepatic reserve from liver necrosis.[4,10] Active surveillance with frequent blood tests is critical for this patient cohort. Spontaneous recovery from paracetamol-induced ALF is observed in 65% of cases.[3] In contrast, recovery from idiosyncratic drug-induced ALF is uncommon, with 27.1% of patients surviving longer than 3 weeks.[52] Consequently, early involvement of a hepatologist and transfer to a gastroenterology ward are paramount to patient survival. With LT improving overall survival to 66%, any signs of ALF including coagulopathy [international normalized ratio (INR) $>$ 1.5], ascites and encephalopathy should prompt transfer to intensive care and urgent referral to a tertiary liver unit.[3,13]

Two treatment approaches have been endorsed to manage patients who develop drug-induced ALF. One is through rapid depuration of the toxic drug to limit its absorption and dose-dependent hepatotoxic effects. Activated charcoal is widely used to treat drug overdoses such as paracetamol, phenobarbital and carbamazepine.[53–55] As its therapeutic benefit is restricted to within 3–4 h of acute ingestion of the toxin, the efficacy of depuration therapy is highly dependent on prompt admission of patients for assessment, recognition of potential DILI by physicians and healthcare resource availability.[4] Consequently, depuration therapy is often limited to drugs that cause an intrinsic pattern of DILI and has shown to be of little benefit in idiosyncratic DILI and HILI. Previous uses of whole bowel irrigation and gastric lavage have largely been superseded by activated charcoal depuration but can sometimes be used in cases of acute poisoning with iron, lithium, sustained release tablets and body packing.

The second treatment approach widely endorsed is the administration of a drug-specific antidote to counter the hepatotoxic effects of a toxin. Hepatoprotective medications including N-acetylcysteine (NAC) and L-carnitine have been widely used in ALI secondary to overdoses of paracetamol and valproic acid, respectively.[10] The hepatoprotective role of NAC in idiosyncratic DILI,[56] however, remains controversial. In a prospective,

double-blind trial by Lee *et al.*,[57] a total of 173 patients with non-paracetamol-induced ALF were randomised to receive a 72-h infusion of either NAC or placebo. Overall, no significant survival benefit was demonstrated using NAC therapy. Nevertheless, subgroup analysis demonstrated that patients with early stages of ALF with Grade I–II encephalopathy had a significant improvement in non-transplant survival using NAC. In a separate retrospective cohort study, Borlak *et al.*[58] evaluated the effectiveness of concomitant NAC infusion and corticosteroid therapy in severe idiosyncratic DILI secondary to flupirtine. The study suggested that the use of NAC with prednisolone resulted in quicker recovery of ALT, AST and INR compared to untreated patients. Conclusions could not be made however as the retrospective study involved a very small cohort of 21 patients compared to an external control, did not use RUCAM criteria to identify DILI cases of flupirtine and was mainly aimed at liver injury secondary to flupirtine only. This therefore did not include other causes of idiosyncratic DILI. As such, the authors recommended that a proper randomised controlled trial would be more suitable to assess the efficacy of this treatment.

Evidence for therapies including corticosteroids for immune-mediated reactions and ursodeoxycholic acid for cholestatic liver injury remain sparse, and their use today is widely off-license.[10] Of note, a recent retrospective analysis of autoimmune, indeterminate and drug-induced ALF by Karkhanis *et al.*[59] in conjunction with ALFSG concluded that corticosteroid therapy had no prognostic benefit in drug-induced ALF. Moreover, they demonstrated that corticosteroid use was associated with poorer prognosis in patients with higher Model For End-stage Liver Disease (MELD) scores. Benefits of corticosteroids are therefore limited to immune-mediated DILI or drug-induced AIH. Immune-mediated DILI typically requires a short course of corticosteroids to achieve therapeutic benefit. On the contrary, long duration of corticosteroid therapy is usually required for drug-induced AIH.[10]

Immune-checkpoint inhibitor (ICI)-hepatitis is rare, with incidence increasing on the use of combination therapy with other ICI or chemotherapy drugs.[60,61] ICIs such as programmed cell death protein 1 antagonists (nivolumab and pembrolizumab) and cytotoxic T-lymphocyte-associated protein 4 antagonists (ipilimumab) adversely induce hepatitis as a sequela to over-activating the immune system in response to the tumour.[62] Identification of deranged liver tests with thorough evaluation of aetiologies including cancer progression, alcohol misuse and opportunistic viral infections is warranted. The Common Terminology Criteria for Adverse Events can be used to assess the severity of ICI-hepatitis. Severity is graded by the level of ALT and AST: Grade 1 (>ULN to 3 times ULN), Grade 2 (>3–5 times ULN), Grade 3 (>5–20 times ULN) and Grade 4 (>20 times ULN). Consensus from the Innovation and Quality DILI Immunotherapy Working Group has not recommended the use of RUCAM to diagnosis immunotherapy-induced DILI. This may be due to difficulty achieving scores to categorise patients as having 'probable' or 'highly probable' DILI without previous exposure or re-exposure to the immunotherapy, which is not safe to do in patients with cancer.[63] Nevertheless, we recommend clinicians to actively exclude alternative causes of DILI, such as antibiotic use in immunosuppressed oncological patients following opportunistic infections, especially when considering the prognostic implications in discontinuing immunotherapy. The use of the updated RUCAM score may therefore be of benefit to clinicians as a tool to exclude alternative causes of DILI. The American Gastroenterological Association[64] provides a useful guideline in managing ICI-induced hepatitis. For patients with Grade 1 ICI-hepatitis, defined by AST/ALT elevated ⩽3 times ULN and bilirubin elevated ⩽1.5 times ULN, continuing immunotherapy whilst close monitoring of symptoms with weekly or biweekly blood tests may be sufficient. Grade 2 ICI-hepatitis, defined by rises in AST/ALT of up to 3–5 times ULN and bilirubin of up to 1.5–3 times ULN, should prompt clinicians to consider liver biopsy, hold the culprit ICI and initiate 0.5–1 mg/kg/day oral prednisolone. Resumption of ICI should be considered in patients showing improvement in LTs to ⩽Grade 1 hepatitis following a slow taper of corticosteroid over a month. Permanent discontinuation of ICI with admission to hospital for liver biopsy and 1–2 mg/kg/day IV methylprednisolone therapy is recommended in patients with Grade 3 or 4 ICI-hepatitis (defined by an AST/ALT > 5 times ULN and bilirubin > 3 times ULN). Slow tapering of steroids over 1 month following Grade 3–4 hepatitis is recommended if improvement in LTs is seen. Nevertheless, it is important to highlight

that the use of corticosteroids in ICI-hepatitis is based on longitudinal studies and there are no randomised controlled trials that have validated its effect. Treatment with immunomodulators including azathioprine, mycophenolate mofetil or tacrolimus is recommended in patients where a drop in transaminases by ⩾50% within 3–5 days. The use of anti-thymocyte globulin is reserved for patients with fulminant hepatitis due to its potential pro-oncogenic properties.[65]

In the UK and globally, the King's College Criteria (KCC)[66] devised in 1989 continues to be widely used to determine early deteriorations in patients with ALF in patients with paracetamol toxicity. For ALF induced by idiosyncratic DILI, however, several prognostic scoring systems (KCC, Clichy criteria, ALFSG Index, Japanese criteria and MELD) have been proposed[66–70]; yet, none of these are optimal, and more sensitivity and specific prognostic scoring systems are necessary.[71] Although most patients recover from DILI, 11.7% of patients who develop DILI-induced hepatocellular jaundice either require a LT or die.[12]

Due to the low incidences of idiosyncratic DILI, most studies dichotomise outcomes of DILI based on whether they are paracetamol induced or non-paracetamol induced. Paracetamol toxicity has the most favourable prognosis largely due to robust diagnostics and use of NAC. A retrospective study by Wei *et al.*[72] from Sweden demonstrated that among patients with paracetamol toxicity with a MELD score of <30 who did not fulfil the KCC had a high negative predictive value of 94% for graft-free mortality. ALF secondary to idiosyncratic DILI comparatively has a poorer outcome with a transplant-free survival rate of 21.7% at 3 weeks. Both MELD score >29 and Grade 3–4 encephalopathy are poor prognostic factors indicative of high risk of mortality without LT.[52]

A study of the European Liver Transplant Registry database of 4903 patients between 1988 and 2009 demonstrated that the overall graft survival at 1, 3, 5 and 10 years for patients with ALF listed for LT were 63%, 59%, 57% and 50%, respectively.[73] No statistically significant difference in graft survival was detected between different aetiologies of ALF. The major contributing cause of death and graft failure was infection, irrespective of the cause of ALF. Graft rejection rates of paracetamol and non-paracetamol aetiologies were 9.5% and 9.4%, respectively, which was statistically lower than that of viral (10.1%) or cryptogenic (12.5%) causes. Suicide and non-adherence rates of immunosuppressive medications were highest amongst patients receiving liver grafts following paracetamol toxicity. Of the 203 patients with idiosyncratic DILI receiving LT, only 1% developed disease recurrence.

Early detection of coagulopathy and hepatic encephalopathy and referral for consideration for LT is paramount to improving the overall survival rate of patients with suspected idiosyncratic DILI. Nevertheless, 25% of patients listed for LT die whilst waiting for a suitable graft.[74] Current evidence to delineate spontaneous recovery from idiosyncratic DILI-induced ALF is scarce, especially in those already listed for LT. Consequently, a robust multidisciplinary approach involving a hepatologist, surgeon, anaesthetist and psychiatrist is critical to reducing mortality of transplant candidates and avoiding unnecessary LT.

Conclusion

DILI is an uncommon but potentially fatal adverse reaction to a drug with significant heterogeneity in both latency and pattern of liver injury. Clinical suspicion with history of previous DILI together with liver enzyme derangement remains the hallmark for the diagnosis of DILI. Judicious assessment with both an extensive liver panel and imaging as well as consideration for a liver biopsy is necessary to exclude alternative diagnosis of liver pathology. Spontaneous recovery is seen in most patients with DILI; nonetheless, close clinical and biochemical monitoring is vital, with clinical presentations of ALF prompting urgent referral to intensive therapy unit and referral to tertiary liver units for consideration of LT. Both genetic testing and biomarkers have been newly incorporated into clinical practice to aid early diagnosis of drug toxicity as well as to risk stratify patients who will need immunosuppressive therapy following LT.[4] Extrapolating genetic testing to risk stratify patients with chronic diseases needing long-term medical therapy may be a future strategy to reduce the incidence of DILI.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication
Not applicable.

Author contribution(s)
Tom Hosack: Writing – original draft.

Djamil Damry: Writing – original draft.

Sujata Biswas: Writing – review & editing.

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References

1. Sgro C, Clinard F, Ouazir K, *et al*. Incidence of drug-induced hepatic injuries: a French population-based study. *Hepatology* 2002; 36: 451–455.
2. United States Food and Drug Administration. Drug-induced liver injury:premarketing clinical evaluation, FDA-2008-D-0128, https://www.fda.gov/regulatory-documents/drug-induced-liver-injury-premarketing-clinical-evaluation (2009, accessed 20 December 2020).
3. Lee WM. Drug-induced acute liver failure. *Clin Liver Dis* 2013; 17: 575–586.
4. Andrade RJ, Aithal GP, Björnsson ES, *et al*. EASL clinical practice guidelines: drug-induced liver injury. *J Hepatol* 2019; 70: 1222–1261.
5. Chalasani NP, Hayashi PH, Bonkovsky HL, *et al*. ACG clinical guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. *Am J Gastroenterol* 2014; 109: 950–966.
6. Koch DG, Speiser JL, Durkalski V, *et al*. The natural history of severe acute liver injury. *Am J Gastroenterol* 2017; 112: 1389–1396.
7. Dara L, Liu Z-X and Kaplowitz N. Mechanisms of adaptation and progression in idiosyncratic drug induced liver injury, clinical implications. *Liver Int* 2016; 36: 158–165.
8. Danan G and Benichou C. Causality assessment of adverse reactions to drugs—I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *J Clin Epidemiol* 1993; 46: 1323–1330.
9. Benichou C, Danan G and Flahault A. Causality assessment of adverse reactions to drugs—II. An original model for validation of drug causality assessment methods: case reports with positive rechallenge. *J Clin Epidemiol* 1993; 46: 1331–1336.
10. Katarey D and Verma S. Drug-induced liver injury. *Clin Med* 2016; 16: s104–s109.
11. Castiella A, Zapata E, Lucena MI, *et al*. Drug-induced autoimmune liver disease: a diagnostic dilemma of an increasingly reported disease. *World J Hepatol* 2014; 6: 160–168.
12. Andrade RJ, Isabel Lucena M, Carmen Fernández M, *et al*. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. *Gastroenterology* 2005; 129: 512–521.
13. Danan G and Teschke R. RUCAM in drug and herb induced liver injury: the update. *Int J Mol Sci* 2015; 17: 14.
14. Teschke R, Frenzel C, Glass X, *et al*. Herbal hepatotoxicity: a critical review. *Br J Clin Pharmacol* 2013; 75: 630–636.
15. Lin NH, Yang HW, Su YJ, *et al*. Herb induced liver injury after using herbal medicine: a systemic review and case-control study. *Medicine (Baltimore)* 2019; 98: e14992.
16. Bell LN and Chalasani N. Epidemiology of idiosyncratic drug-induced liver injury. *Semin Liver Dis* 2009; 29: 337–347.
17. Chalasani N and Björnsson E. Risk factors for idiosyncratic drug-induced liver injury. *Gastroenterology* 2010; 138: 2246–2259.
18. Schrör K. Aspirin and Reye syndrome: a review of the evidence. *Paediatr Drugs* 2007; 9: 195–204.
19. Bryant AE and Dreifuss FE. Valproic acid hepatic fatalities. III. U.S. experience since 1986. *Neurology* 1996; 46: 465–469.

20. Parra J, Iriarte J and Pierre-Louis SJ. Valproate toxicity. *Neurology* 1996; 47: 1608.
21. Herrlinger C and Klotz U. Drug metabolism and drug interactions in the elderly. *Best Pract Res Clin Gastroenterol* 2001; 15: 897–918.
22. Wynne HA, Cope LH, Mutch E, *et al*. The effect of age upon liver volume and apparent liver blood flow in healthy man. *Hepatology* 1989; 9: 297–301.
23. Cotreau MM, von Moltke LL and Greenblatt DJ. The influence of age and sex on the clearance of cytochrome P450 3A substrates. *Clin Pharmacokinet* 2005; 44: 33–60.
24. Larrey D. Epidemiology and individual susceptibility to adverse drug reactions affecting the liver. *Semin Liver Dis* 2002; 22: 145–155.
25. Ortega-Alonso A, Stephens C, Lucena MI, *et al*. Case characterization, clinical features and risk factors in drug-induced liver injury. *Int J Mol Sci* 2016; 17: 714.
26. Björnsson ES, Bergmann OM, Björnsson HK, *et al*. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. *Gastroenterology* 2013; 144: 1419–1425.
27. Chalasani N, Bonkovsky HL, Fontana R, *et al*. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN prospective study. *Gastroenterology* 2015; 148: 1340–1352.e7.
28. Lucena MI, Andrade RJ, Kaplowitz N, *et al*. Phenotypic characterization of idiosyncratic drug-induced liver injury: the influence of age and sex. *Hepatology* 2009; 49: 2001–2009.
29. Yu K, Geng X, Chen M, *et al*. High daily dose and being a substrate of cytochrome P450 enzymes are two important predictors of drug-induced liver injury. *Drug Metab Dispos* 2014; 42: 744–750.
30. Teschke R and Danan G. Idiosyncratic drug induced liver injury, cytochrome P450, metabolic risk factors and lipophilicity: highlights and controversies. *Int J Mol Sci* 2021; 22: 3441.
31. Chen Y, Mao J and Hop CE. Physiologically based pharmacokinetic modeling to predict drug-drug interactions involving inhibitory metabolite: a case study of amiodarone. *Drug Metab Dispos* 2015; 43: 182–189.
32. Chen M, Borlak J and Tong W. High lipophilicity and high daily dose of oral medications are associated with significant risk for drug-induced liver injury. *Hepatology* 2013; 58: 388–396.
33. Chen IL. FDA summary of adverse events on electronic cigarettes. *Nicotine Tob Res* 2013; 15: 615–616.
34. Weng Z, Wang K, Li H, *et al*. A comprehensive study of the association between drug hepatotoxicity and daily dose, liver metabolism, and lipophilicity using 975 oral medications. *Oncotarget* 2015; 6: 17031–17038.
35. Chen M, Borlak J and Tong W. A model to predict severity of drug-induced liver injury in humans. *Hepatology* 2016; 64: 931–940.
36. McEuen K, Borlak J, Tong W, *et al*. Associations of drug lipophilicity and extent of metabolism with drug-induced liver injury. *Int J Mol Sci* 2017; 18: 1335.
37. Chen M, Suzuki A, Thakkar S, *et al*. DILIrank: the largest reference drug list ranked by the risk for developing drug-induced liver injury in humans. *Drug Discov Today* 2016; 21: 648–653.
38. Greene N, Fisk L, Naven RT, *et al*. Developing structure-activity relationships for the prediction of hepatotoxicity. *Chem Res Toxicol* 2010; 23: 1215–1222.
39. Zhu X and Kruhlak NL. Construction and analysis of a human hepatotoxicity database suitable for QSAR modeling using post-market safety data. *Toxicology* 2014; 321: 62–72.
40. Sakatis MZ, Reese MJ, Harrell AW, *et al*. Preclinical strategy to reduce clinical hepatotoxicity using in vitro bioactivation data for >200 compounds. *Chem Res Toxicol* 2012; 25: 2067–2082.
41. Xu JJ, Henstock PV, Dunn MC, *et al*. Cellular imaging predictions of clinical drug-induced liver injury. *Toxicol Sci* 2008; 105: 97–105.
42. Mushin WW, Rosen M and Jones EV. Post-halothane jaundice in relation to previous administration of halothane. *Br Med J* 1971; 3: 18–22.
43. Lucena MI, Molokhia M, Shen Y, *et al*. Susceptibility to amoxicillin-clavulanate-induced liver injury is influenced by multiple HLA class I and II alleles. *Gastroenterology* 2011; 141: 338–347.
44. Monshi MM, Faulkner L, Gibson A, *et al*. Human leukocyte antigen (HLA)-B*57:01-restricted activation of drug-specific T cells provides the immunological basis for flucloxacillin-induced liver injury. *Hepatology* 2013; 57: 727–739.

45. Hayashi PH, Lucena MI, Fontana RJ, *et al.* A revised electronic version of RUCAM for the diagnosis of DILI. *Hepatology* 2022; 76: 18–31.

46. Danan G and Teschke R. Letter to the editor: electronic RUCAM: major pitfalls call for caution and proper validation. *Hepatology* 2022; 76: E27.

47. Fan H and Zhu JH. FABP1 as a novel potential biomarker for predicting mortality in acetaminophen-induced acute liver failure. *Hepatology* 2017; 66: 670.

48. Mikus M, Drobin K, Gry M, *et al.* Elevated levels of circulating CDH5 and FABP1 in association with human drug-induced liver injury. *Liver Int* 2017; 37: 132–140.

49. Karvellas CJ, Speiser JL, Tremblay M, *et al.* Elevated FABP1 serum levels are associated with poorer survival in acetaminophen-induced acute liver failure. *Hepatology* 2017; 65: 938–949.

50. Teschke R, Eickhoff A, Brown AC, *et al.* Diagnostic biomarkers in liver injury by drugs, herbs, and alcohol: tricky dilemma after EMA correctly and officially retracted letter of support. *Int J Mol Sci* 2019; 21: 212.

51. Dragoi D, Benesic A, Pichler G, *et al.* Proteomics analysis of monocyte-derived hepatocyte-like cells identifies integrin beta 3 as a specific biomarker for drug-induced liver injury by diclofenac. *Front Pharmacol* 2018; 9: 699.

52. Reuben A, Koch DG, Lee WM, *et al.* Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. *Hepatology* 2010; 52: 2065–2076.

53. Fontana RJ. Acute liver failure including acetaminophen overdose. *Med Clin North Am* 2008; 92: 761–794, viii.

54. Goldberg MJ and Berlinger WG. Treatment of phenobarbital overdose with activated charcoal. *JAMA* 1982; 247: 2400–2401.

55. Brahmi N, Kouraichi N, Thabet H, *et al.* Influence of activated charcoal on the pharmacokinetics and the clinical features of carbamazepine poisoning. *Am J Emerg Med* 2006; 24: 440–443.

56. Sanabria-Cabrera J, Tabbai S, Niu H, *et al.* N-acetylcysteine for the management of non-acetaminophen drug-induced liver injury in adults: a systematic review. *Front Pharmacol* 2022; 13: 876868.

57. Lee WM, Hynan LS, Rossaro L, *et al.* Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. *Gastroenterology* 2009; 137: 856–864.

58. Borlak J, van Bömmel F and Berg T. N-acetylcysteine and prednisolone treatment improved serum biochemistries in suspected flupirtine cases of severe idiosyncratic liver injury. *Liver Int* 2018; 38: 365–376.

59. Karkhanis J, Verna EC, Chang MS, *et al.* Steroid use in acute liver failure. *Hepatology* 2014; 59: 612–621.

60. Reynolds K, Thomas M and Dougan M. Diagnosis and management of hepatitis in patients on checkpoint blockade. *Oncologist* 2018; 23: 991–997.

61. Pelster MS and Amaria RN. Combined targeted therapy and immunotherapy in melanoma: a review of the impact on the tumour microenvironment and outcomes of early clinical trials. *Ther Adv Med Oncol* 2019; 11: 1758835919830826.

62. Regev A, Avigan MI, Kiazand A, *et al.* Best practices for detection, assessment and management of suspected immune-mediated liver injury caused by immune checkpoint inhibitors during drug development. *J Autoimmun* 2020; 114: 102514.

63. Clinton JW, Kiparizoska S, Aggarwal S, *et al.* Drug-induced liver injury: highlights and controversies in the recent literature. *Drug Saf* 2021; 44: 1125–1149.

64. Dougan M, Wang Y, Rubio-Tapia A, *et al.* AGA clinical practice update on diagnosis and management of immune checkpoint inhibitor colitis and hepatitis: expert review. *Gastroenterology* 2021; 160: 1384–1393.

65. Spänkuch I, Gassenmaier M, Tampouri I, *et al.* Severe hepatitis under combined immunotherapy: resolution under corticosteroids plus anti-thymocyte immunoglobulins. *Eur J Cancer* 2017; 81: 203–205.

66. O'Grady JG, Alexander GJ, Hayllar KM, *et al.* Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989; 97: 439–445.

67. Bernuau J. Selection for emergency liver transplantation. *J Hepatol* 1993; 19: 486–487.

68. Fontana RJ, Ellerbe C, Durkalski VE, *et al.* Two-year outcomes in initial survivors with acute liver failure: results from a prospective, multicentre study. *Liver Int* 2015; 35: 370–380.

69. Mochida S. Indication criteria for liver transplantation for acute liver failure in Japan. *Hepatol Res* 2008; 38: S52–S55.

70. Kamath PS, Wiesner RH, Malinchoc M, *et al*. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; 33: 464–470.

71. Biolato M, Araneo C, Marrone G, *et al*. Liver transplantation for drug-induced acute liver failure. *Eur Rev Med Pharmacol Sci* 2017; 21: 37–45.

72. Wei G, Bergquist A, Broomé U, *et al*. Acute liver failure in Sweden: etiology and outcome. *J Intern Med* 2007; 262: 393–401.

73. Germani G, Theocharidou E, Adam R, *et al*. Liver transplantation for acute liver failure in Europe: outcomes over 20 years from the ELTR database. *J Hepatol* 2012; 57: 288–296.

74. Ostapowicz G, Fontana RJ, Schiødt FV, *et al*. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med* 2002; 137: 947–954.