# The Evolving Profile of Idiosyncratic Drug-Induced Liver Injury

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**Idiosyncratic drug-induced liver injury (DILI) is an infrequent but important cause of liver disease. Newly identified causes of DILI include the COVID vaccines, turmeric, green tea extract, and immune checkpoint inhibitors. DILI is largely a clinical diagnosis of exclusion that requires evaluation for more common causes of liver injury and a compatible temporal association with the suspect drug. Recent progress in DILI causality assessment includes the development of the semi-automated revised electronic causality assessment method (RECAM) instrument. In addition, several drug-specific HLA associations have been identified that can help with the confirmation or exclusion of DILI in individual patients. Various prognostic models can help identify the 5%–10% of patients at highest risk of death. Following suspect drug cessation, 80% of patients with DILI fully recover, whereas 10%–15% have persistently abnormal laboratory studies at 6 months of follow-up. Hospitalized patients with DILI with an elevated international normalized ratio or mental status changes should be considered for *N*-acetylcysteine therapy and urgent liver transplant evaluation. Selected patients with moderate to severe drug reaction with eosinophilia and systemic symptoms or autoimmune features on liver biopsy may benefit from short-term corticosteroids. However, prospective studies are needed to determine the optimal patients and dose and duration of steroids to use. LiverTox is a comprehensive, freely accessible Web site with important information regarding the hepatotoxicity profile of more than 1000 approved medications and 60 herbal and dietary supplement products. It is hoped that ongoing "omics" studies will lead to additional insight into DILI pathogenesis, improved diagnostic and prognostic biomarkers, and mechanism-based treatments.**

*Keywords:* Drug Hepatotoxicity; Causality Assessment; Acute Liver Failure.

Idiosyncratic drug-induced liver injury (DILI) is an infrequent but important cause of acute and chronic liver disease worldwide. DILI develops largely independent of the dose or duration of medication used, although most cases occur within 6 months of medication initiation. The protean clinical phenotypes observed in patients with DILI makes establishing this diagnosis of exclusion very challenging even for experienced physicians. Furthermore, the lack of reliable animal models, in vitro test systems, and objective, confirmatory blood tests has impeded DILI research and clinical care. Fortunately, a great deal of progress has been made in understanding of the etiologies, natural history, and treatment of DILI over the past 20 years, which is highlighted in this review.

## Epidemiology of Drug-Induced Liver Injury in Western Populations

Population-based studies from France and Iceland estimate the annual incidence of DILI to be 14–19 cases per 100,000 inhabitants. Lower incidence rates have been reported in the United States and higher rates in China.[1-3] The impact of host age, gender, and ethnicity on DILI susceptibility are not well established. Pediatric patients account for 5%–10% of patients with DILI and children seem to be at increased risk for valproate and minocycline hepatotoxicity, whereas the elderly are more susceptible to isoniazid and amoxicillin-clavulanate (AC) hepatotoxicity.[4] Women seem to experience more frequent and severe hepatotoxicity particularly from diclofenac, interferon-$\beta$1a, and nitrofurantoin, whereas men seem to be more susceptible to azathioprine, anabolic steroid, and AC DILI.[5,6] AC is the most common cause of DILI in western patients with an estimated incidence of 1 in every 2500 users of AC.[2] An even higher frequency of DILI was observed in users of azathioprine (1 in 133) and infliximab (1 in 148) in Iceland but the absolute number of exposed patients was substantially smaller.[2] Herbal and dietary supplements (HDS) are the leading cause of DILI in Asian countries, such as China

***Abbreviations used in this paper:*** **AC, amoxicillin-clavulanate; ALF, acute liver failure; ALT, alanine aminotransferase; APAP, acetaminophen; AST, aspartate aminotransferase; DILI, drug-induced liver injury; DILIN, drug-induced liver injury network; FDA, Food and Drug Administration; HDS, herbal and dietary supplement; ICI, immune checkpoint inhibitor; MELD, Model for End-Stage Liver Disease; NAC, *N*-acetylcysteine; RECAM, revised electronic causality assessment method; RUCAM, Rousell Uclaf causality assessment method; ULN, upper limit of normal.**

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and Korea.[3,6] They have also been increasingly reported in western countries, accounting for nearly 20% of cases in the Drug Induced Liver Injury Network (DILIN).[7]

Extracts of green tea that contain variable amounts of catechins are touted to facilitate weight loss and improve energy levels and can be detected in many HDS products without being listed on the product label.[8] Most cases of green tea extract hepatotoxicity present with an acute hepatocellular injury profile and jaundice, which may be severe or even fatal in some cases.[9] Other herbal products widely used in Indian ayurvedic medicine including *Ashwagandha*, *Garcinia cambogia*, and oral formulations of turmeric have been reported to cause DILI.[10-12] Furthermore, oral or parenteral anabolic steroids taken by young men trying to increase muscle strength have been associated with a distinct clinical phenotype of prolonged cholestatic jaundice with severe pruritus.[13,14]

In the United States, the causes of DILI have evolved over the past 20 years with older anticonvulsant drugs, such as phenytoin and carbamazepine, being less commonly reported possibly because of reduced use and increased use of more liver-friendly drugs.[15] Similarly, antitubercular drugs, such as isoniazid, are less frequently causing DILI in western countries presumably from their reduced use. In contrast, biologic agents that impact the host immune system, such as infliximab, have been increasingly recognized as causing DILI, and the immune checkpoint inhibitors (ICIs).[16,17] Although ICIs have revolutionized the treatment of cancer, they are associated with a plethora of immune-related adverse events in 30%–50% of treated patients including dermatitis and colitis followed by pneumonitis, hypophysitis, and hepatitis. Acute hepatocellular injury has been the predominant form of ICI-related liver injury but more recent reports have demonstrated mixed and cholestatic reactions in up to 30% and rare instances of biliary strictures from secondary sclerosing cholangitis.[18]

Drug-induced autoimmune-like hepatitis has historically been described with several drugs, such as nitrofurantoin, minocycline, hydralazine, and methyldopa. Recently, a systematic review revealed that other agents associated with drug-induced autoimmune-like hepatitis include interferons, high-dose methylprednisolone, adalimumab, and imatinib.[19] Khat, a flowering plant with psychogenic stimulant ingredients, and *Tinospora cordifolia* in India were the only HDS products associated with well-documented cases of drug-induced autoimmune-like hepatitis.[20] There have also been recent reports of the COVID mRNA and adenoviral vector vaccines leading to hepatotoxicity with autoimmune features in some.[21,22] Although very infrequent in light of the >12 billion doses administered, most patients presented with an acute hepatocellular injury, 70% were jaundiced, and many had detectable autoantibodies.[21,22] Interestingly, some patients had known established autoimmune hepatitis and required short courses of corticosteroids but fatalities are exceedingly rare (<1%). Finally, abdominal pain and hepatitis were reported in June of 2022 in more than 470 patients shortly after consuming a food supplement called French Lentil and Leek crumbles.[23] The Food and Drug Administration (FDA) is currently investigating this outbreak of a possible direct hepatotoxin linked to the presence of tara flour and the manufacturer has removed the product from the US marketplace.[23] A summary of newer drugs and HDS products associated with DILI is provided in Table 1 including Kratom, an unregulated psychoactive botanical product with opioid agonist features extracted from *Mitragyna speciosia*.[24]

## Establishing a Diagnosis of Drug-Induced Liver Injury

Practice guidelines recommend that a complete medical and medication history, battery of blood tests, and liver imaging be obtained in all patients with suspected DILI (Figure 1).[6,25] Because 10%–20% of the general population have mild liver biochemical abnormalities, patients with suspected DILI should meet minimal laboratory criteria, such as a serum alanine aminotransferase (ALT) >5 times the upper limit of normal (ULN), alkaline phosphatase >2 times the ULN, or total bilirubin >2.5 mg/dL.[26] Calculation of the R-ratio allows one to develop a focused differential diagnosis. Testing for acute hepatitis E virus is recommended in many patients with suspected DILI including older men and those residing in endemic areas.[27] Similarly, universal testing for acute hepatitis C virus infection is recommended in all patients with DILI because of its rising incidence in the general population.[28] A plausible temporal relationship between the suspect medication or HDS product use and liver injury onset that is consistent with prior reports or experience should be present. In most instances, the drug latency is <6 months but notable exceptions include liver injury attributed to minocycline, nitrofurantoin, methotrexate, and tolvaptan.[29] Furthermore, improvement of liver injury following drug discontinuation (dechallenge) is important to assess in suspected DILI cases for diagnostic and prognostic purposes.

Differentiating sporadic autoimmune hepatitis from DILI with autoimmune features continues to be challenging. In those instances and in other ambiguous cases, a liver biopsy may help identify histologic features consistent with idiosyncratic DILI, such as mixed cholestatic hepatitis, necrosis, or intrahepatic eosinophils and granulomas versus an alternative etiology.[30,31] In addition, certain medications are associated with specific histologic patterns that can be confirmed on biopsy. Lastly, useful prognostic information from a biopsy includes the extent of hepatic necrosis, ductular reaction, and hepatic fibrosis, which are all associated with poorer outcomes.

The LiverTox Web site provides an authoritative and comprehensive review of the hepatotoxicity profile of

**Table 1.** Newly Identified Causes of Idiosyncratic DILI

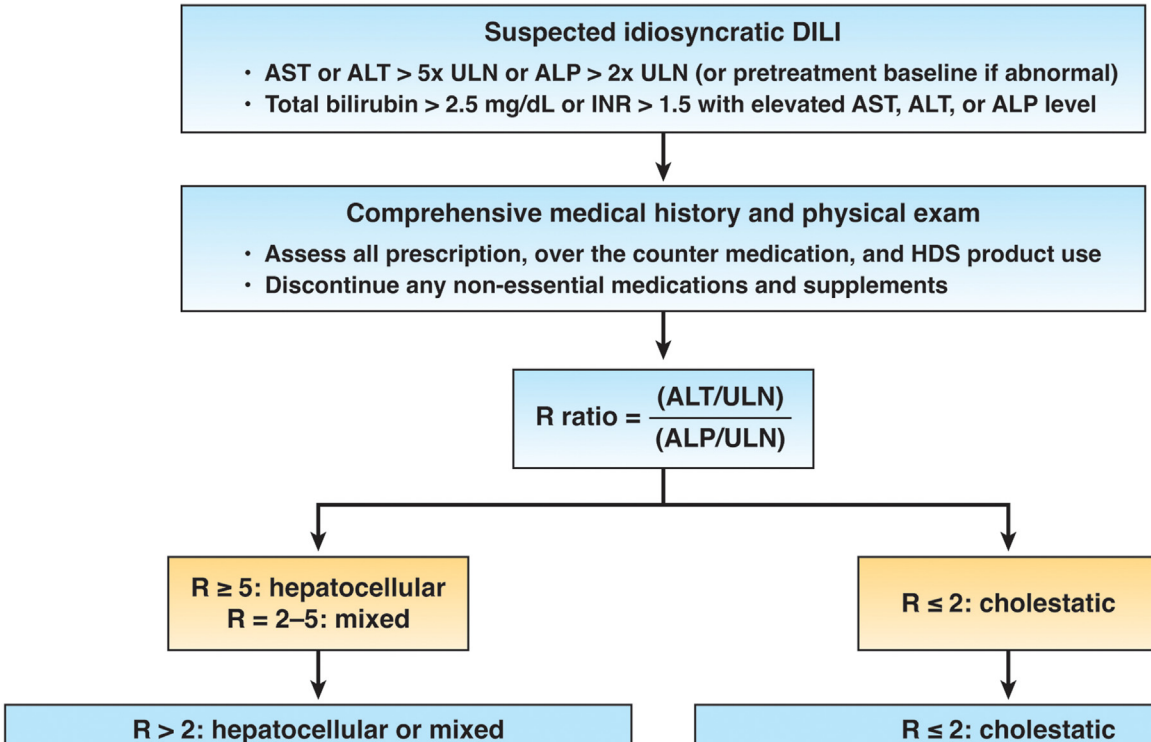
| Agents (ref) | Median age, *y* | Female, % | Latency (range) | Clinical features | Outcome |
|---|---|---|---|---|---|
| Immune checkpoint inhibitors (n = 100) (ref 17) | 60 | 39 | 59 d (8–454) | 70% hepatocellular, some DI-AILH | Deaths mostly caused by malignancy |
| TNF-$\alpha$ inhibitors (n = 36) (ref 16) | 46 | 78 | 110 d (94–144) | Hepatocellular, some DI-AILH and secondary sclerosing cholangitis | Favorable, but transplants reported |
| COVID vaccines (n = 87) (ref 22) | 48 | 63 | 15 d (3–65) | 84% hepatocellular | 1 liver transplant |
| Anabolic steroids (n = 60) (ref 13, 14) | 32 | 1.7 | 73 d | Severe and prolonged cholestasis | No deaths or transplants |
| Green tea extract (n = 40) (ref 9) | 40 | 74 | 5–448 d | 95% hepatocellular | 8% liver transplant |
| *Ashwaganda* (n = 7) (ref 10) | 39 | 43 | 2–12 wk | Cholestatic/hepatocellular jaundice | No deaths or transplants |
| Turmeric (n = 10) (ref 12) | 56 | 80 | 4–24 wk | Hepatocellular jaundice | 1 death |
| *Tinospora cordifola* (n = 43) (ref 20) | 50 | 54 | 46 d | Autoimmune features | Fatality in CLD, liver transplants reported |
| Kratom (n = 11) (ref 24) | 40 | 18 | 14 d | Mixed or cholestatic injury with jaundice | No deaths or transplants |

CLD, chronic liver disease; DI-AILH, drug-induced autoimmune-like hepatitis; DILI, drug-induced liver injury; TNF, tumor necrosis factor.

more than 1000 medications and 60 HDS products. Annotated references and adjudicated case examples are also provided.[32] In cases involving multiple suspect products, the LiverTox likelihood scale for an individual agent ranging from A to E can be useful in identifying which agent is more likely to be causal. The FDA-approved labels of prescription drugs (ie, package insert) can also provide useful information regarding the hepatotoxicity of drugs observed during clinical trials and from postmarketing surveillance. However, there may be substantial discrepancies regarding warnings and advice between FDA and European Medicines Agency recommendations.[33,34]

## Causality Assessment

Causality assessment in DILI is most commonly undertaken using expert opinion–based scaling or various diagnostic instruments. The DILIN expert opinion causality scale ranks the likelihood of a case being caused by an agent on a scale of 1 (definite >95% likelihood) to 5 (unlikely, <25% probability). Advantages of the expert opinion approach include the ability to account for atypical cases, interrupted drug exposure, and synthesis of subtle clues in comparison with the published literature. However, limitations include the lack of generalizability and limited number of DILI experts. In contrast, the modified Rousell Uclaf causality assessment method (RUCAM) and revised electronic causality assessment method (RECAM) are structured causality assessment instruments that provide a numerical score based on points assigned for diagnostic testing, temporal association, and other clinical features that can be used by both expert and practicing clinicians (Table 2; see http://gihep.com/calculators/hepatology/recam/).[35,36] Potential advantages of the RECAM over the RUCAM include the elimination of risk factors; simplification of latency and dechallenge fields; and the ability to incorporate available liver biopsy, other diagnostic testing, or rechallenge data when available. Going forward additional studies regarding the interrater and intrarater reliability of the RECAM are needed.[37] Causality assessment for HDS cases poses additional challenges because many patients ingest more than 1 multi-ingredient HDS product and recent studies have demonstrated significant discrepancies between verified ingredients and product labels.[8] Nonetheless, careful phenotyping of




| R > 2: hepatocellular or mixed | |
|---|---|
| **Consider** | **Evaluation** |
| Viral hepatitis (e.g., HAV, HBV, HCV, HEV, CMV, EBV, HSV) | HAV IgM, HBsAg, HCV RNA, HEV IgM, HEV RNA, CMV DNA,EBV DNA,HSV DNA |
| Ischemia | History of hypotension, sepsis, or heart failure; echocardiogram |
| Autoimmune hepatitis | ANA, ASMA, IgG, liver biopsy |
| Alcoholic hepatitis | Clinical hx, AST > 2x ALT, serum PEth, urine ethylgluc |
| Drug/toxin (e.g., mushroom, APAP) | History, urine toxicology, serum APAP |
| Budd-Chiari | Doppler ultrasound (CT or MRI) |
| Wilson disease | Ceruloplasmin, ALP:TB < 4, AST:ALT > 2.2 |
| Alpha-1-antitrypsin deficiency | A1AT level |
| Fatty liver disease | History and imaging features |
| Celiac disease | Anti-TTG IgA |
| Rhabdomyolysis | CPK |
| Hypothyroidism/ thyrotoxicosis | TSH, free T4, T3 |

| R ≤ 2: cholestatic | |
|---|---|
| **Consider** | **Evaluation** |
| Choledocholithiasis | Liver ultrasound |
| Primary biliary cholangitis | AMA, liver biopsy |
| Pancreaticobiliary disease or strictures | CT or MRCP |
| Malignancy or infiltrating cancer | LDH, CT or MRI with contrast |
| TPN cholestasis | History |
| Bone disease | ALP isoenzymes, 5' nucleotidase |
| Chronic passive congestion | Echocardiogram, doppler liver ultrasound |
| Sepsis | Cultures, medical hx |

**Consider liver biopsy if:**
- **Diagnostic uncertainty**
- **Auto-antibodies and persistent liver injury**
- **Moderate to severe ICI hepatitis not responding to steroids**
- **Ongoing injury, possible drug rechallenge**

**Figure 1.** Recommended approach to the patient with suspected DILI. A stepwise evaluation is recommended for all patients with suspected drug and HDS hepatotoxicity. Calculation of the R-value at DILI onset helps guide the evaluation for alternative causes of liver injury. A liver biopsy may be useful in cases of diagnostic uncertainty and when drug-induced autoimmune-like hepatitis is suspected.

cases and application of genome-wide association studies methods have identified *HLA-B * 35:01* as being a significant correlate of high-causality green tea extract, turmeric, and polygonum multiforum hepatotoxicity cases (Table 3).[9,38]

Because of its low incidence in exposed patients (ie, <1 in 1000 to 1 in 100,000), many experts have hypothesized that DILI susceptibility may be caused by rare or common genetic variants in host-drug metabolizing, excretory, or immune response genes. Using genome-wide association studies, a single nucleotide polymorphism in the *PTPN22* gene has been identified and validated as a bona fide DILI risk factor across multiple drugs and patient ethnicities.[39] The exact role of this gene in DILI pathogenesis is unknown but *PTPN22* is also associated with several other immune-mediated conditions. In addition, several drug-specific HLA polymorphisms in various class I and class II alleles have been identified (Table 3). Some of these HLA alleles are infrequent in the general population (ie, carrier frequency <1%), whereas others are present in 10%–20% of population control subjects. Testing for an HLA allele before prescribing a medication is currently not recommended to prevent most instances of DILI because of its low positive predictive value. However, testing for a drug-specific HLA risk allele may prove useful in establishing a diagnosis of DILI. Ongoing studies are now focused on improving the understanding of how these HLA risk alleles and the host adaptive immune response are involved in DILI pathogenesis.

New diagnostic biomarkers that may be more sensitive and specific than serum aspartate aminotransferase (AST) and ALT for early detection of DILI are in development. Serum glutamate dehydrogenase holds promise as a potentially promising diagnostic biomarker and may have particular utility in patients with muscular dystrophy receiving domagrozumab.[40,41] Also, total and caspase cleaved cytokeratin 18, macrophage colony–stimulating factor, and miRNA-122 serum levels show promise as future DILI diagnostic and prognostic biomarkers.[42] Lastly, studies involving the use of human liver organoids as a model system for DILI pathogenesis are underway.[43]

**Table 2.** Datafields of the RUCAM and RECAM Causality Assessment Instruments

| Data field | Modified RUCAM[a] | RECAM |
|---|---|---|
| Chronology (latency) | | |
| 1a Drug start to injury onset | + 1 to + 2 | - 6 to + 4 |
| 1b Drug discontinuation to onset | +1 | - 6 to 0 |
| Dechallenge | | |
| Improvement after stopping | Hepatocellular: -2 to +3<br>Chol/Mix: 0 to +2 | - 6 to + 4 |
| Competing cause of liver injury | | |
| Serologic, molecular, and radiologic testing | - 3 to + 2 | - 6 to 0 |
| Rechallenge | 0 to + 3 | 0 or + 6 |
| Prior reports | 0 to + 2 | 0 to + 3 |
| Risk factors | 0 to + 1 | NA |
| Other medications | - 3 to 0 | NA |
| DILI likelihood categories | | |
| Definite | ➢ 9 | ➢ 8 |
| Probable | 6 to 8 | 4 to 7 |
| Possible | 3 to 5 | - 3 to + 3 |
| Unlikely | 1 to 2 | ≤ -4 |
| Excluded | ≤0 | |

DILI, drug-induced liver injury; NA, not applicable; RECAM, revised electronic causality assessment method; RUCAM, Rousell Uclaf causality assessment method.
Adapted from references 35 and 36.
[a]The component datafields and the range of possible points for each datafield are provided. Once the data are entered, a total case score is generated and categorized into the DILI likelihood score. The RUCAM has a range of scores varying from –10 to +14; the RECAM scores vary from –6 to +20.

## Natural History and Prognostic Models

In clinical practice, DILI is often suspected in patients with overt acute liver injury that are taking a drug or HDS after other competing causes have been ruled out (Figure 1). In this instance, the prompt interruption of the suspect medication is of paramount importance to prevent further liver injury. Following culprit drug withdrawal, 80% of patients with DILI will fully recover within 6 months, although a small fraction may progress to acute liver failure (ALF) or die from hepatic decompensation or comorbid conditions.[44] Patients with DILI with hepatocellular injury and jaundice (eg, Hy's law) are at greatest risk of serious hepatic outcomes and frequently require hospitalization or serial laboratory monitoring.[45] Patients with DILI with clinical evidence of mental status changes and coagulopathy (ie, international normalized ratio >1.5) have ALF and should be promptly referred to a liver transplant center because their likelihood of spontaneous recovery is less than 30%.[46] Several registries have identified clinical and laboratory variables associated with poor outcomes in the first weeks after DILI onset including female sex, African and Asian American race, older age, preexisting liver disease, and medical comorbidities.[47-50]

Although the height of liver enzymes alone is not sufficient to reflect the severity of liver injury, a high serum AST (>17.1 times the ULN) and total bilirubin (>6.6 times the ULN) levels have been found to be predictive of a higher risk of ALF, liver transplantation, and death.[51] Furthermore, some drugs, such as bardoxolone methyl, can cause ALT elevations by inducing ALT production without any evidence of histologic damage.[52] In addition, low albumin levels are an independent risk

**Table 3.** Examples of Genetic Polymorphisms Associated With Idiosyncratic DILI

| Drug | Gene | Race/ethnicity | Odds ratio (95% CI) | MAF in control subjects |
|---|---|---|---|---|
| Multiple drugs | *PTPN22* | White<br>Black<br>Hispanic | 1.4 (1.2–1.6) | 0.08 |
| Individual drugs | | | | |
| Amoxicillin- clavulanate | *HLA- A * 02:01* | White | 2.3 (1.8–2.9) | 0.28 |
| | *HLA-DRB1 * 15:01* | White | 2.8 (2.1–3.8) | 0.14 |
| Flucloxacillin | *HLA- B * 57:01* | White | 36.6 (26.1–51.2) | 0.04 |
| Minocycline | *HLA-B * 35:02* | White | 29.6 (7.8–89.8) | 0.006 |
| Terbinafine | *HLA-A * 33:01* | White | 40.5 (12.5–131.1) | 0.01–0.03 |
| Trimethoprim-sulfamethoxazole | *HLA- A * 34:02* | White | 47.5 (5.2–320) | 0.001 |
| | *HLA-B * 14:01* | White | 9.2 (3.1–22.3) | 0.009 |
| | *HLA-B * 35:01* | Black | 2.8 | 0.087 |
| Valproic acid | *POLG G* | White | 23.6 (8.4–66) | 0.04–0.08 |
| Herbal and dietary supplements | | | | |
| Green tea extract | *HLA- B * 35:01* | White | 6.8 | 0.06 |
| Polygonum multiforum | *HLA-B * 35:01* | Asian[a] | 30.4 (11.7–77.8) | 0.027 |
| Turmeric | *HLA-B * 35:01* | White | 7 | 0.06 |

CI, confidence interval; DILI, drug-induced liver injury; MAF, minor allele frequency.
[a]Han Chinese.

factor for liver-related death or liver transplantation in the DILIN prospective study.[35,50]

Composite scores have been proposed to predict adverse hepatic outcomes in acute idiosyncratic DILI (Table 4). Hy's law defined by AST or ALT >3 times the ULN and total bilirubin >2 times the ULN (in absence of cholestatic damage with elevated alkaline phosphatase levels) is frequently used by regulatory agencies to identify hepatotoxic drugs in clinical trials and has also shown the ability to predict the risk of liver-related mortality/liver transplantation at DILI onset in registry studies.[45] Relying on the value of high AST as an independent risk factor of serious DILI outcome, the Spanish DILI Registry reformulated Hy's law, the so-called "nR Hy's law" based on a new ratio (nR) defined as [(ALT or AST, whichever is higher/ULN) ÷ (Alk P/ULN)] >5) and total bilirubin >2 times the ULN.[51] The nR Hy's law showed a better area under the receiver operating curve in predicting ALF than the traditional Hy's law (0.77 vs 0.67) and was later validated in an independent cohort.[46] A prognostic algorithm has also been developed by establishing cutoff points of AST, total bilirubin, and AST/ALT ratio, as predictors of mortality/liver transplantation at DILI onset. This algorithm showed better specificity and area under the receiver operating curve in predicting ALF compared with traditional Hy's law and nR Hy's law (area under the receiver operating curve, 0.80),[51] but is still pending external validation. Another prognostic tool used in patients with decompensated cirrhosis but also tested in idiosyncratic DILI is the Model for End-Stage Liver Disease (MELD) score. Indeed, a MELD score >19 showed the highest accuracy for predicting death compared with Hy's law and nR Hy's law.[46]

Because medical comorbidities may contribute to mortality in patients with DILI, the Charlson comorbidity index was integrated into a prognostic model that also included MELD and albumin levels (DILI-CAM) (Table 4). This model performed well in a discovery cohort of 306 patients (C statistic of 0.89) and a validation cohort of 254 patients (C statistic of 0.91). Moreover, the authors have developed a Web-based DILI mortality calculator that can be applied in daily practice (http://gihep.com/calculators/hepatology/dili-cam/).[50]

In a collaborative international study, osteopontin showed a strong association with death/transplant (area under the curve, 0.86) and was just slightly behind international normalized ratio (area under the curve, 0.92).[40] The combination of serum cytokeratin-18 and macrophage colony stimulating factor receptor levels with MELD scores in the range of 20 to 29, improved the specificity in predicting death/liver transplant compared with using MELD score ≥20 alone (89% vs 74%).[40]

Histologic features also have prognostic value, which supports the use of liver biopsy for predicting outcome in DILI. In the DILIN prospective study, extensive necrosis and ductular reaction were associated with a higher risk of fatal outcome, whereas the presence of eosinophils in the infiltrate and granuloma were predictive of spontaneous recovery.[30]

Readministration of the hepatotoxic agent (rechallenge) usually occurs inadvertently because of the failure to recognize that the liver injury was a hepatotoxic

**Table 4.** Models of Adverse Outcomes in Idiosyncratic DILI

| Prognostic model (ref) | Fatalities/population, n/n (%)[a] | Model variables | Model performance | End point comments |
|---|---|---|---|---|
| Hy's law (ref 45) | NA | ALT >3 × ULN and T. bilirubin >2 × ULN | 90% sensitivity 44% specificity AUROC = 0.67 | Developed by FDA in clinical trials |
| nR Hy's law (ref 40, 45) | 34/771 (4.4) | (ALT or AST, /ULN))/(Alk P/ ULN)] >5) and T. bilirubin >2 × ULN | 90% sensitivity 63% specificity AUROC = 0.77 | Externally validated in 1089 DILIN cases |
| MELD (ref 40) | 107/1089 (9.8) | Albumin, T. bilirubin, creatinine | HR, 1.2 (95% CI, 1.1–1.2) AUROC = 0.83 (MELD >19) | Fatalities within 2 y of DILI onset |
| Prognostic algorithm (ref 45) | 34/771 (4.4) | AST >17.3 × ULN, T. bilirubiin >6.6 × ULN | 80% sensitivity 82% specificity AUROC = 0.80 | Validated in 97 LATAM DILI cases (5.1% fatalities) |
| DILI CAM (ref 50) | 26/306 (8.5) | Albumin, MELD, and Charlson comorbidity index | AUROC = 0.89 (discovery) AUROC = 0.91 (validation) | Fatalities within 6 mo of DILI onset |
| Serum osteopontin (ref 40) | 15/98 (15.3) | Biomarker of inflammation, regeneration | AUROC = 0.86 (95% CI, 0.76–0.96) | Fatalities within 6 mo of DILI onset |
| MELD, K-18-MCSFR-1 (ref 40) | 15/98 (15.3) | MELD 20–29; K-18 ≥7.98; MCSFR-1 ≥6.94 | 93% sensitivity 89% specificity AUROC = 0.80 vs 0.74 using MELD alone | Fatalities within 6 mo of DILI onset |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUROC, area under the receiver operating curve; CI, confidence interval; DILI, drug-induced liver injury; DILIN, drug-induced liver injury network; FDA, Food and Drug Administration; HR, hazard ratio; LATAM, Latin America; MCSFR, macrophage colony stimulating factor receptor; MELD, Model for End-Stage Liver Disease; NA, not available; T. bilirubin, total bilirubin; ULN, upper limit of normal.
[a]Fatalities include all deaths and liver transplants.

reaction or patient's misuse of a previously identified hepatotoxic drug. However, rechallenge may be deliberately undertaken for essential medications, such as antituberculosis drugs and the ICIs used in oncology patients experiencing a clinical response. In most other circumstances where alternative treatments are available, rechallenge is discouraged because it may result in a more rapid or severe reaction.[6]

In some DILI cases the liver biochemistry abnormalities take a long time to normalize. The incidence of chronic DILI varies between 8% and 21% in prospective studies depending on the definition used with most relying on abnormal laboratory studies rather than liver histology.[53,54] Although the DILIN group considers 6 months of liver biochemical elevations to define chronic DILI, a 3-year prospective study undertaken by the Spanish Registry suggested that a 1-year cutoff point of persistent laboratory abnormalities may be more useful.[54] Other clinical features associated with chronicity include older age, African-American race, cholestatic damage, greater severity at presentation, and dyslipidemia.[53] Although clinical sequelae in patients with chronic DILI are uncommon, a minority may develop progressive fibrosis, cirrhosis, or manifestations of portal hypertension.[55] The long-term follow-up of chronic DILI remains poorly defined but serial laboratory monitoring every 6 months and annual liver elastography would be prudent.

## Treatment of Idiosyncratic Drug-Induced Liver Injury

A key aspect in the initial management of DILI involves the withdrawal of the potentially causative or suspect drug. The only medical therapy with some benefit in uncontrolled studies and in highly selected patients, is short-term corticosteroids (Table 5).[6,56] Corticosteroids have demonstrated efficacy in those with severe immune-mediated hypersensitivity reactions, including drug reaction with eosinophilia and systemic symptoms.[56] Less commonly a 1- to 3-month course of corticosteroids may accelerate improvement of liver biochemistry abnormalities in those with an autoimmune phenotype and a liver biopsy with a predominance of plasma cells.[56] However, empiric use of corticosteroids is not recommended in all patients with DILI and particularly in those with a cholestatic presentation or ALF wherein prior studies of the latter have demonstrated no net benefit and even potential harm.[57]

Nearly 20%–30% of patients receiving an ICI either alone or in combination with other agents for cancer

**Table 5.** Potential Treatments for Selected Patients With DILI

| Intervention | Indication | Recommended dose and duration | Evidence level[a] | Comments |
|---|---|---|---|---|
| Corticosteroids | DRESS | 40–60 mg/d oral prednisone; taper over 3–6 mo | ++ | Comanaged with dermatology |
| | Drug-induced autoimmune-like hepatitis | 40–60 mg/d oral prednisone; taper over 1–3 mo | ++ | Not indicated for patients with DILI with ALF |
| | ICI hepatitis | | ++ | Hold ICI if ALT 3–5 x ULN |
| | Grade 2-3 | 0.5–1.0 mg/kg oral prednisone; taper over 1–3 mo or when DILI resolves | + | Permanently discontinue ICI if ALT >5 x ULN |
| | Grade 3-4 | 1 mg/kg intravenous methylprednisolone with oral prednisone taper | | Liver imaging with contrast and liver biopsy recommended before escalation |
| | | Azathioprine (1–2 mg/kg) or mycophenolate mofetil (500–1000 mg BID) in steroid-refractory or persistent DILI | | |
| Ursodeoxycholic acid | Severe pruritus | 10–15 mg/kg in BID dosing until pruritus abates | +/- | No established efficacy in cholestatic DILI (ref 66) |
| *N*-acetylcysteine | APAP hepatotoxicity | Intravenous or oral for 72 h[b] | +++ | • IV formulation requires telemetry; AEs in 10%; avoid if known sulfa allergy |
| | Non-APAP ALF with grade 1/2 encephalopathy | Consider intravenous or oral NAC for 72 h | ++ | • NAC studied in prevention of antitubercular DILI (ref 64) |
| | | | | • RCT of NAC in non-APAP ALF (ref 63) |
| Drug-specific therapies | | | | |
| L-carnitine | Valproate hepatotoxicity with hyperammonemia | 100 mg/kg oral or IV load then 50 mg/kg (to 3 g/dose max) every 8 h; continue until ammonia decrease or clinical improvement | + | Limited data in children with hyperammonemia and seizure disorders |
| Cholestyramine | Leflunomide hepatotoxicity | 1 packet every 6–8 h for 14 d | +/- | Reduces bioavailability of long half-life, agent; reserved for persistent cholestasis |
| Defibrotide | Sinusoidal obstruction syndrome | 6.25 mg/kg every 6 h for 21–60 d | +++ | FDA approved in adult and pediatric hematopoietic stem cell patients; contraindicated with systemic anticoagulant or fibrinolytic therapy; common AEs of hypotension, diarrhea, vomiting, nausea, and epistaxis |
| Liver transplantation | DILI-related ALF | Inpatient transfer to LT center | +++ | Spontaneous survival 30% with supportive care in DILI-ALF; list as status 1 |
| | Chronic DILI with vanishing bile duct syndrome, progressive fibrosis, or portal hypertension | Outpatient LT evaluation | +++ | Chronic patients with DILI selected on individual basis; list with MELD score |

AE, adverse event; ALF, acute liver failure; ALT, alanine aminotransferase; APAP, acetaminophen; DILI, drug-induced liver injury; DRESS, drug reaction with eosinophilia and systemic symptoms; FDA, Food and Drug Administration; ICI, immune checkpoint inhibitor; IV, intravenous; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; NAC, *N*-acetylcysteine; RCT, randomized controlled trial; ULN, upper limit of normal.

[a]Evidence level: +/-, equivocal; +, low; ++, moderate; +++, strong. Level of evidence assigned based on consensus expert opinion of the authors considering the quality and number of observations, the frequency of the clinical condition, and outcomes observed. There is a paucity of randomized interventional trials in a rare condition with heterogeneity in presentation and clinical course and as such we cannot apply the rigorous methodologic criteria for evidence-based recommendations.

[b]Oral dosing: 140 mg/kg load then 70 mg/kg every 4 hours. Intravenous dosing preferred if intolerant of oral intake/ileus or pregnant: intravenous 150 mg/kg load over 15–60 minutes, followed by 50 mg/kg (12.5 mg/kg/h) over the next 4 hours, then 100 mg/kg (6.25 mg/kg/h) over 16 hours thereafter (total 300 mg/kg over 24 hours).

develop liver biochemistry abnormalities. However, multiple series have demonstrated that metastatic cancer with intrahepatic or boney metastases is responsible for the liver injury in most of these patients and particularly in those with a mixed/cholestatic injury.[58,59] Therefore, contrast-enhanced imaging of the liver with magnetic resonance imaging or computed tomography is recommended in these cases and liver biopsy in cases of diagnostic uncertainty. Furthermore, magnetic resonance cholangiopancreatography is recommended for those with severe cholestatic liver injury or progressive jaundice to look for rare cases of secondary sclerosing cholangitis from ICIs, which usually does not respond to immunosuppression.[18] The liver injury pattern is hepatocellular in 50%–70% of ICI hepatotoxicity cases and fortunately severe or fatal ICI hepatotoxicity is uncommon.[58-60] Oral corticosteroids at a dose of 0.5–1 mg/kg are frequently prescribed by the treating oncologist in patients with grade II ICI hepatotoxicity (ALT 3–5 times the ULN and/or total bilirubin 1.5–3 times the ULN) that do not improve with drug discontinuation.[56,61] In patients with grade III hepatotoxicity (ALT >5 times the ULN with/or without bilirubin >3 times the ULN), the ICI should be permanently discontinued and many of these patients are hospitalized and receive intravenous methylprednisolone if they do not respond to oral corticosteroids. Although many hepatologists recommend a liver biopsy in cases of uncertain etiology and grade II to III hepatotoxicity, only a minority of patients undergo biopsy in clinical practice.[62] Antimetabolites, such as azathioprine or mycophenolate, have been used in patients with persistent ALT elevations after 3–4 weeks of corticosteroids but the criteria, dose, and duration of these agents is not well established or standardized.

The role of *N*-acetylcysteine (NAC) in acute liver injury or ALF following acetaminophen (APAP) hepatotoxicity is well established.[2] However, the role of NAC in non-APAP severe acute liver injury is less well established. A randomized study on the use of intravenous NAC for 72 hours in adults with non-APAP ALF, including DILI, noted that there was no overall survival benefit but there was a significant improvement in transplant-free survival from 27% to 58% in those with early stage encephalopathy and DILI.[63] Intravenous NAC has also been tested in those with antitubercular DILI and was associated with a reduced length of stay but with no survival benefit.[59,64] Therefore, oral or intravenous NAC treatment can be considered in selected adults with early stage DILI-related ALF.[6] However, NAC is not recommended for children with non-APAP ALF in light of poorer survival compared with placebo in a pediatric trial.[65]

Ursodeoxycholic acid is a synthetic bile acid that is FDA approved for patients with primary biliary cholangitis. It is also often used in patients with severe pruritus associated with cholestatic DILI. It may help the symptom of pruritus but does not seem to have a role in hastening laboratory resolution of DILI. A systematic review concluded that there was no overall benefit from ursodeoxycholic acid in resolution of DILI but it was generally safe to administer and well-tolerated.[66]

L-carnitine therapy has been tested in children with hyperammonemia caused by valproate hepatotoxicity and seems to reduce serum ammonia levels and hasten clinical improvement but large randomized controlled trials are needed to determine the optimal dose and duration of therapy.[67] The bile acid binding agent, cholestyramine, is frequently used in patients with moderate to severe pruritus. It may also be helpful in those with leflunomide hepatotoxicity that are not improving despite drug discontinuation because of its prolonged half-life and enterohepatic circulation.[68] Defibrotide is a complex mixture of single-stranded polydeoxy ribonucleotides derived from porcine intestine that has antithrombotic and profibrinolytic activity. Defibrotide treatment has been associated with improved survival in patients with severe sinusoidal obstruction syndrome following hematopoietic stem cell transplantation.[69] Plasma exchange or plasmapheresis has been used in DILI-related acute liver injury but there is no proven benefit from these interventions in facilitating resolution of DILI.[70] Several other potential interventions to help prevent or hasten DILI resolution have been evaluated.[71,72] In a systematic review and meta-analysis of 22 randomized controlled trials there were 12 on prevention (n = 2471 patients) and 10 on management (n = 797) of DILI/non-APAP-related ALF. The interventions evaluated included silymarin, bicyclol, magnesium isoglycyrrhizinate, tiopronin, and traditional Chinese medicines. Although there was limited efficacy observed in the prevention and management of DILI, the safety profile of many of these agents was generally favorable.[72]

Liver transplantation is an effective lifesaving procedure for those with ALF caused by DILI who have <30% chance of spontaneous survival with supportive medical management.[73] Therefore, it is recommended that any hospitalized DILI patient with an elevated international normalized ratio who develops mental status changes be urgently referred to an liver transplantation center.[6] In addition, patients with chronic DILI and particularly those with a clinical and histologic phenotype of vanishing bile duct syndrome or progressive portal hypertension may need to be considered for liver transplantation.

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