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REVIEW ARTICLE

Drug-Induced Liver Injury: Highlights of the Recent Literature

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Abstract

Drug-induced liver injury (DILI), herbal-induced liver injury, and herbal and dietary supplement (HDS)-induced liver injury are an important aspect of drug safety. Knowledge regarding responsible drugs, mechanisms, risk factors, and the diagnostic tools to detect liver injury have continued to grow in the past year. This review highlights what we considered the most significant publications from among more than 1800 articles relating to liver injury from medications, herbal products, and dietary supplements in 2017 and 2018. The US Drug-Induced Liver Injury Network (DILIN) prospective study highlighted several areas of ongoing study, including the potential utility of human leukocyte antigens and microRNAs as DILI risk factors and new data on racial differences, the role of alcohol consumption, factors associated with prognosis, and updates on the clinical signatures of autoimmune DILI, thiopurines, and HDS agents. Novel data were also generated from the Spanish and Latin American DILI registries as well as from Chinese and Korean case series. A few new agents causing DILI were added to the growing list in the past 2 years, including sodium–glucose co-transporter-2 inhibitors, as were new aspects of chemotherapy-associated liver injury. A number of cases reported previously described hepatotoxins confirmed via the Roussel Uclaf Causality Assessment Method (RUCAM; e.g., norethisterone, methylprednisolone, glatiramer acetate) and/or the DILIN method (e.g., celecoxib, dimethyl fumarate). Additionally, much work centered on elucidating the pathophysiology of DILI, including the importance of bile salt export pumps and immune-mediated mechanisms. Finally, it must be noted that, while hundreds of new studies described DILI in 2017–2018, the quality of such reports must always be addressed. Björnsson reminds us to remain very critical of the data when addressing the future utility of a study, which is why it is so important to adhere to a standardized method such as RUCAM when determining DILI causality. While drug-induced hepatotoxicity remains a diagnosis of exclusion, the diverse array of publications that appeared in 2017 and 2018 provided important advances in our understanding of DILI, paving the way for our improved ability to make a more definitive diagnosis and risk assessment.

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Key Points

While studies regarding the diagnosis and risk assessment of drug-induced liver injury (DILI) and herbal-induced liver injury (HILI) continue to proliferate each year, the field still lacks a pathognomonic diagnostic biomarker.

Many case reports and case series that report possible DILI still lack the requisite minimal number of elements needed to critically assess causality; more widespread use of the Roussel Uclaf Causality Assessment Method (RUCAM) or the methodologies employed by DILI registries, such as the US DILI Network (DILIN) are encouraged.

Many new agents observed to cause hepatotoxicity were reported in 2017–2018, including fimasartan, everolimus, and obeticholic acid, among others.

Interesting new studies of known hepatotoxins included protein adducts as a biomarker for acetaminophen toxicity, new evidence that direct oral anticoagulants may not be as hepatotoxic as previously thought, and a potential new DILI risk assessment tool for direct-acting antivirals for hepatitis C infection.

New guidelines were created by the China Association of Chinese Medicine regarding the evaluation of HILI. An increasing number of articles in the last 2 years concerned Kratom, *Garcinia cambogia*, red yeast rice, and Ayurvedic compounds.

1 Introduction

Drug-induced liver injury (DILI) and herbal and dietary supplement (HDS)-induced liver injury (HILI) are important aspects of drug safety, and knowledge regarding responsible drugs, mechanisms, risk factors, and diagnostic tools continued to grow in the last year, with more than 1800 publications. Many large registries were updated in the past 2 years, including the US DILI Network (DILIN) [1–14], Spanish DILI Registry [15, 16], and Latin American DILI Network. Contributions also came from populations in Iceland [17, 18], China [19], and Korea [20]. Additionally, recognition of HILI and HDS has been increasing and, in this past year, the list of herbal substances causing liver injury continued to increase [21–37].

Much work has been undertaken to refine the diagnostic approach to DILI, as the diagnosis remains one of exclusion. This review briefly provides updates on the diagnosis of DILI, but a more thorough analysis of biomarkers and risk factors for DILI is beyond the scope of this review and is available elsewhere [12, 38–51].

The diagnosis of DILI is important not only in clinical practice but also in its potential broader impact. Reporting cases of possible DILI to the appropriate regulatory authorities is of great importance and has real-world consequences, as it can lead to termination of clinical trials or even force withdrawal of a drug from the market. Recently, a phase III trial of a type 2 diabetes mellitus medication, fasiglifam, was terminated because of an increased incidence of alanine transaminase (ALT) elevations greater than three times the upper limit of normal (ULN), which included several Hy's law cases [52]. Biogen and AbbVie recently voluntarily withdrew the multiple sclerosis drug daclizumab after multiple reports of immune-related conditions, such as encephalitis and severe liver damage, in the postmarket setting, highlighting the importance of postapproval monitoring [53]. In addition, solithromycin, a potential antibiotic for treatment of community-acquired pneumonia did not receive US FDA approval because many patients experienced transaminase elevations, necessitating further investigation [54]. More details on solithromycin are provided later in the manuscript.

This past year, study of the specific mechanisms leading to DILI provided a better understanding for how and why this particular type of liver injury occurs. For example, publications dealing with mechanistic models to study bile salt export pumps and their role in cholestatic liver injury, and the link between the immune system and idiosyncratic DILI, were reviewed. The role of mitochondrial dysfunction and oxidative stress in DILI were also explored [55–59]. The aim of this review is to highlight publications in 2017 and 2018 that provide the clinician with new clinical and translational information regarding the recognition, identification, and mechanisms of DILI and HDS.

2 Methods

We performed an expansive search utilizing the PubMed search engine. We specifically searched for the following terms: DILI, hepatotoxins, mechanisms of DILI, herbal hepatotoxicity, and diagnosing DILI. We included articles that were published from January 2017 through September 2018. As more than 1800 articles appeared, we opted to focus on those specifically pertaining to new reports of established hepatotoxins, new reports of previously unknown hepatotoxins, mechanisms of DILI, and updates in international DILI registries. We limited our review to human studies unless we felt the specific article provided promising results at the forefront of DILI research. In addition, we only included studies written in English. Approximately 170 articles were used in the review process, across a variety of studies, including in vitro/ex vivo studies, case reports, and

randomized controlled trials. Because of the large number of articles published in the last year on DILI, we tried to keep the review succinct, describing what we felt were the most innovative or informative for clinical practice. Articles not included should not be construed as lacking in importance or interest. A large portion of studies involved individual case reports as well as case series, which highlights the importance of the Roussel Uclaf Causality Assessment Method (RUCAM), our primary method of determining DILI due to a specific agent. We strove to only include cases that met a score of at least probable likelihood.

3 Drug-Induced Liver Injury (DILI) Registry Updates

3.1 US DILI Network

Authors from the US DILIN prospective study continued to publish new findings in several areas, including human leukocyte antigen (HLA) associations and other risk factors, differences among races, the effect of alcohol consumption, and updates in terms of diagnosis, prognosis, and several individual drug classes causing DILI, including autoimmune DILI.

De Boer et al. [1] characterized autoimmune hepatitis (AIH) in DILI by analyzing cases secondary to nitrofurantoin, minocycline, methyldopa, or hydralazine. They examined levels of immunoglobulin G (IgG) and titers of antinuclear antibodies (ANAs), smooth muscle antibody, and soluble liver antigen antibody, and derived an autoimmune score based on levels. This scoring system is summarized in Table 1. AIH-associated HLA antigens HLA-DRB1*03:01 and HLA-DRB1*04:01 allele frequencies in these cases were compared with controls. They defined an autoimmune phenotype as having an autoimmune score ≥ 2, which was present in the majority of cases with nitrofurantoin and minocycline (83 and 74%, respectively), whereas it was only seen in about one-half the cases with methyldopa and hydralazine (55 and 43%, respectively). Furthermore, the typical HLA alleles found in AIH (HLA-DRB1*03:01 and HLA-DRB1*04:01) were found at a rate in autoimmune DILI that was similar to that in the general population. In contrast to De Boer et al. [1], Urban et al. [3] found that HLA-B 35:02 was associated with an increased risk of liver injury from minocycline, thus providing a potential diagnostic tool for this type of liver injury.

Table 1 Summary of serum antibody scoring system used by De Boer et al. [1] to define an autoimmune phenotype

Antibody	Scoring system[a]
ANA	Negative (0) Low positive (+1) High positive (+2)
SMA	Negative (0) Low positive (+1) High positive (+2)
SLA	Negative (0) Low positive (+1) High positive (+2)
IgG	0 (≤1600 mg/dL: <ULN) +1 (1600–1760 mg/dL: 1.0–1.1×ULN) +2 (>1760 mg/dL: >1.1×ULN)
Total	Range (0–8)

ANA antinuclear antibody, *IgG* immunoglobulin G, *SLA* soluble liver antigen antibody, *SMA* small muscle antibody, *ULN* upper limit of normal

[a]Autoimmune hepatitis defined a total score of ≥2

Examining other HLA associations, Nicoletti et al. [2] performed a genome-wide association study to identify genetic risk factors for DILI from licensed drugs without previously reported genetic risk factors. They found an association between HLA-A*33:01 and DILI due to terbinafine and possibly fenofibrate and ticlopidine. They also identified the polymorphism rs116561224 on chromosome 18 associated with DILI from statins, along with two non-drug-specific risk factors including a single nucleotide polymorphism (SNP) on the *LRBA* gene and an intergenic SNP on chromosome 2, rs72631567 [2]. Fontana et al. [14] further discussed HLA associations with terbinafine-induced liver injury, which can be found in Sect. 5.2.

Whritenour et al. [4] attempted to incorporate the lymphocyte transformation test (LTT) into the DILIN framework. The LTT has been proposed as a way to assess hypersensitivity to a specific drug [4, 60]. Although it is not FDA approved, it is used elsewhere, especially in Japan [4, 61]. Suspect drugs are incubated with peripheral blood mononuclear cells (PBMCs), with a positive response seen when [^{3}H]-thymidine is incorporated into new DNA. Using cytokine and granzyme B production, the authors developed a modified LTT (mLTT) and assessed PBMCs of donors with a history of drug hypersensitivity. Their results demonstrated that the mLTT was not a reliable test in diagnosing DILI for the majority of drugs: allopurinol, amoxicillin, carbamazepine, clavulanic acid, nitrofurantoin, isonicotinic acid, levofloxacin, metformin, minocycline, phenytoin, sulfamethoxazole, trimethoprim, and valproic acid. The only exception was isoniazid, where the authors observed that two of four samples elicited a positive mLTT response [4].

While not part of the US DILIN, we thought it was important to also note a similar study by Benesic et al. [62], who developed an in vitro test using monocyte-derived hepatocyte-like (MH) cells to help diagnose DILI in patients taking multiple medications. The premise of their test involved measuring the level of lactate dehydrogenase released from MH cells that had been isolated from a patient's blood sample and incubated with each drug the patient was taking.

Elevated levels of lactate dehydrogenase were considered to be positive for DILI. Their test demonstrated 92.3% sensitivity and 100% specificity. The drugs that tested positive for DILI with their method included amoxicillin–clavulanate, diclofenac, methylprednisolone, atorvastatin, metamizole, pembrolizumab, piperacillin/tazobactam, moxifloxacin, duloxetine, and sertraline. They also noted that a small subset of their patients were accidentally reintroduced to some of these medications, and the MH test correctly reidentified 92% of these drugs as being the culprit for liver injury [62].

US DILIN authors also continued to study microRNAs (miRNAs) for their potential utility as biomarkers for the diagnosis and prognosis of DILI. Russo et al. [5] examined sera from 78 subjects and showed that miRNA-122 combined with a low serum albumin (< 2.8 g/dL) accurately identified mortality within 6 months of acute DILI. If confirmed, this combination may prove useful in identifying patients who are at high risk of death and/or liver transplantation [5].

Bonkovsky et al. [6] examined the clinical presentation and prognosis of liver injury secondary to drugs associated with bile duct loss. By examining the US DILIN database for cases that included a liver biopsy, the authors identified 26 patients (7% of the total registry) with various degrees of bile duct loss (graded as mild, moderate, and severe) on histology. The most common clinical phenotype for these cases was a cholestatic pattern. Amoxicillin–clavulanate, HDS products, and temozolomide were associated with the most bile duct loss and were each implicated in three cases of bile duct loss, followed by azithromycin, fluoroquinolones, and lenalidomide/thalidomide, which were each implicated in two cases. Not surprisingly, patients with bile duct loss were more likely to develop chronic liver injury than were those without such injury (94 vs. 47%). The seriousness of the finding was demonstrated in that 5 of 26 patients died and another two required liver transplantation. The authors concluded that bile duct loss from DILI was indeed an indicator of vanishing bile duct syndrome, which currently has no cure or prevention [6].

Navarro et al. [7] summarized the work of a 2-day research symposium sponsored by the American Association for the Study of Liver Disease and the National Institutes of Health that focused on liver injury from HDS. In the USA, HDS now account for 20% of all hepatotoxicity cases. Challenges that emerged from this symposium included problems in diagnosis, identification of hepatotoxic constituents, regulation of nonprescription products, and developing strategic partnerships among physicians, chemists, toxicologists, and regulators [7]. Vega et al. [8] used the state of Delaware to look more closely at DILI, HILI, and HDS-induced liver injury. Using gastroenterologist-based surveillance data, the authors calculated an incidence of 2.7 cases per 100,000 adults in 2014, marking the first prospective estimate of DILI in the USA [8].

Another interesting area of study is the association of age, sex, and race with DILI. Suzuki et al. [9] examined 212 cases of DILI, studying differences between women aged < 50 years and others to assess the influence of menopause and sex on DILI. They noted that hepatocellular injury was significantly more prevalent in women aged < 50 years, with more severe interface hepatitis noted in these patients than in patients aged > 50 years from both sexes. Additionally, biopsies from female patients had greater plasma cell infiltrates, hepatocyte apoptosis, rosettes, and lobular disarray than those of males but less iron-positive hepatocytes and cholestatic features [9]. Chalasani et al. [10] examined racial differences between African Americans and Caucasians enrolled in the US DILIN prospective study. Drugs causing DILI differed among the two groups, with trimethoprim–sulfamethoxazole being the most common among African Americans and amoxicillin–clavulanate being much more common in Caucasians. More importantly, the authors noted a greater severity of illness in African American patients, defined by peak mean albumin, international normalized ratio (INR), and DILIN severity scores. They also observed higher rates of hospitalization, liver transplantation, and liver-related death at 6 months in acute DILI cases in African Americans compared with Caucasians (Table 2) [10].

Hayashi et al. [11] used the DILIN prospective study to analyze patients who had a fatal outcome within 2 years of acute DILI onset. The authors found that a higher peak bilirubin and the presence of coagulopathy, leukocytosis, and thrombocytopenia were all independently associated with death from DILI. Hayashi et al. [11] also studied a modified Hy's law (nR Hy's law criteria), defined as bilirubin ≥ 2.5 mg/dL and ([ALT/ULN] ÷ [alkaline phosphatase/ULN]) > 5, where aspartate transaminase (AST) is substituted for ALT if the AST yields a greater R ratio [11]. They noted that nR Hy's law yielded a higher positive predictive value for fatality than the original Hy's law (14 vs. 10%). Overall, their investigation found that DILI led to death in 7.6% of cases, either directly or indirectly, which continues to validate the observations of Hy Zimmerman [11]. The importance of this particular study by Hayashi et al. [11], specifically the creation of a modified Hy's law, has been reinforced in a number of commentaries on their findings in the past year [63, 64].

Björnsson et al. [17] contributed to several areas of DILI in 2017, both within the US DILIN and in an Icelandic population. DILI induced by the antimetabolites azathioprine and 6-mercaptopurine was examined in 22 patients with injury from one of these two medications. Median time to onset of liver injury was 75 days. The most common symptoms were jaundice (73%), nausea (64%), and fatigue (50%) [17]. The authors noted that anicteric patients tended to present with a

Table 2 Differences between drug-induced liver injury in African Americans vs. Caucasians in the US Drug-Induced Liver Injury Network [10]

	African Americans	Caucasians	*p* value
Top 3 medications causing DILI	1. Trimethoprim-sulfamethoxazole 2. Isoniazid 3. Phenytoin	1. Amoxicillin–clavulanate 2. Nitrofurantoin 3. Anabolic steroids	
INR (mean peak)	1.9 ± 1.8	1.6 ± 1.5	< 0.001
DILIN Severity Score (controlled for BMI)	Mean score 3.0 OR 1.98 (95% CI 1.42–2.75)	Mean score 2.6	For OR, < 0.001
Hospitalization	77%	56%	< 0.001
Likelihood of death or liver transplantation (controlled for age and BMI)	OR 2.12 (95% CI 1.12–3.9) vs. Caucasians		0.02

BMI body mass index, *CI* confidence interval, *DILI* drug-induced liver injury, *DILIN* DILI Network, *INR* international normalized ratio, *OR* odds ratio

hepatocellular pattern of injury, whereas icteric patients generally had a mixed or cholestatic injury pattern. Median ALT was 210 U/L, alkaline phosphatase was 151 U/L, and bilirubin was 7.4 mg/dL with a peak of 13.4 mg/dL [17]. Most of the 22 patients recovered from their DILI within 3 months, usually by reducing the dose, as long as pre-existing liver disease was not present previously [17].

Björnsson et al. [18] also studied the response to corticosteroids in drug-induced AIH (DIAIH) in 14 Icelandic patients, 13 of whom were women. He noted the difficulties inherent in distinguishing DILI with autoimmune features from idiopathic AIH. In this cohort, 40% of patients had improvement in liver enzymes simply with drug cessation. The rest received corticosteroids at 30 or 40 mg/day for a mean of 4 months [18]. All patients had normalization of aminotransferases after a mean of 154 days [18]. Interestingly, none of the patients who required steroids experienced relapse, even after approximately 4 years of follow-up, which is not typically the case with idiopathic AIH [18].

Dakhoul et al. [12] examined the relationship between heavy alcohol consumption and DILI outcomes of patients enrolled in the US DILIN prospective study. The authors studied the characteristics of 348 patients with DILI (of 601 patients who reported alcohol consumption) who completed a questionnaire regarding alcohol use. They noted that anabolic steroids were the most common cause of DILI in those they defined as "heavy" alcohol drinkers (defined as an average of three drinks per day for men and two drinks per day for women). They did not find a significant difference in liver-associated deaths or need for transplant between heavy drinkers and nondrinkers [12]. However, outcomes were not reported for patients who may have far exceeded the two to three drinks per day minimum describing "heavy" alcohol consumption before or during acute DILI.

Another interesting area of study performed by the US DILIN was on sclerosing cholangitis (SC)-like changes seen on magnetic resonance cholangiopancreatography in patients with suspected DILI. A few studies have demonstrated this potential correlation, but they frequently included only a small number of cases. Ahmad et al. [13] looked at all patients within the US DILIN who underwent magnetic resonance imaging between 2004 and 2014. This initially yielded 233 patients, but imaging was available for only 83 of them. Among these 83, only 56 had imaging that was clear enough to be interpretable. In total, four patients had SC changes (7%). The authors noted they were unsure of why this happens in some cases of DILI, but they did discuss two important correlations, including that those with SC changes had not only more severe initial liver injury but also a higher incidence of chronic liver damage. While these conclusions are informative, their ultimate number of cases was small, despite looking at a 10-year period, so further study in this area is warranted.

3.2 Spanish DILI Registry

Several articles analyzed the Spanish DILI Registry and the Latin American DILI Registry, highlighting several important differences in drug hepatotoxicity outside of the USA. Zoubek et al. [15] examined ibuprofen-induced hepatotoxicity in 21 cases from the Spanish DILI Registry and five cases in the Latin American DILI Registry in comparison with both other nonsteroidal anti-inflammatory drug (NSAID)-induced DILI cases and non-NSAID DILI cases. The authors showed that ibuprofen was the most frequent NSAID known to cause DILI in Spain, but it was only the third-leading hepatotoxic drug in Latin America, behind nimesulide and diclofenac. A total of 29% of NSAID DILI cases were attributed to ibuprofen, and the authors postulated that the higher frequency in Spain compared with that in the USA might be secondary to the dose. In Spain, over-the-counter ibuprofen is available in both 200- and 400-mg formulations, whereas only the 200-mg dose is available in the USA [15].

Medina-Caliz et al. [16] characterized hepatotoxicity secondary to HDS recorded in the Spanish DILI registry. The authors found 32 patients from 1994 through 2016 with liver injury attributed to HDS. This group represented only 4% of the total registry, which is significantly lower than that found in the US DILIN. Of these 32 cases, 20 were secondary to anabolic steroids. The investigators noted a higher incidence of progression to acute liver failure in patients with HDS-induced liver injury (6%) than in either the anabolic steroid group (0%) or in the conventional drug group (4%) [16].

3.3 China

China has made significant strides to increase DILI awareness since 2014, with the establishment of the HepatoTox website, which is similar to the US LiverTox website and currently includes 400 drugs recorded in its database [19]. In addition, the Chinese Society of Hepatology drafted its own guidelines on the diagnosis and management of DILI [19]. These guidelines provided 16 evidence-based recommendations on the diagnosis, treatment, and prevention of DILI based on current practice in China. These recommendations share similarities to the 13 recommendations from the 2014 American College of Gastroenterology (ACG) clinical guidelines for diagnosing and managing idiosyncratic DILI [65] and incorporate some of the 2009 FDA guidelines for preventing hepatotoxicity in clinical trials (Tables 3, 4) [66].

3.4 Korea

Cho et al. [20] conducted a nationwide study specifically aimed at HILI in Korea. The authors prospectively collected data from April 2013 and January 2016 from 1001 inpatients from ten South Korean tertiary hospitals who were being treated with herbal medications. Of these patients, six were diagnosed with HILI based on RUCAM scores (four probable and two possible cases), although none of the cases had clinical symptoms. All of the patients were women who developed a hepatocellular pattern of HILI, and only one patient met the criteria for Hy's law [20]. Based on these data, they calculated an incidence rate of just 0.6% over a span of nearly 3 years [20].

4 Newly Described Hepatotoxins

Only a few reports linked new drugs to DILI in 2017–2018. It is important to note that DILI is still much less common than other causes of acute liver injury [67]. Teschke and Danan [67] analyzed 22 DILI case series that included 13,335 cases and found that alternative causes were more likely than DILI in 34.2% of cases. Thus, although case reports are important in raising the possibility of DILI, they should not be seen as being conclusive for making a firm association.

Malnick et al. [68] described a case of denosumab-induced submassive hepatic necrosis that resulted from an immune reaction to the monoclonal antibody. Improvement in aminotransferases and gamma-glutamyl transferase (GGT) occurred following treatment with steroids. Namn et al. [69] reported what they described as the first case of acute liver failure from diphenhydramine without the concurrent use with acetaminophen, which developed in a 28-year-old man taking diphenhydramine 400 mg nightly for sleep. Unfortunately, no RUCAM or other causality score was applied in this case. Niijima et al. [70] described a 75-year-old patient with type 2 diabetes mellitus who switched to oral ipragliflozin, a sodium–glucose cotransporter-2 inhibitor, who then experienced cholestatic DILI, which improved after cessation of the medication. Conversely, this same drug is currently being studied to treat nonalcoholic fatty liver disease (NAFLD) and has recently been shown to exert equally beneficial effects as pioglitazone in NAFLD [71].

Patel et al. [72] discussed a case of everolimus-induced liver injury in a 56-year-old male who had received a liver transplant and was being maintained on this drug for immunosuppression. Their full analysis demonstrated a mixed hepatocellular and cholestatic type liver injury. They documented a RUCAM score of 8 (probable). Park et al. [73] reported a case of DILI in fimasartan, an angiotensin-receptor blocker (ARB). While they mentioned that hepatotoxicity was previously associated with other ARBs, there are currently no other published cases of fimasartan-induced liver injury. Workup included exclusion of other liver infections, trending of liver enzymes, and a liver biopsy demonstrating hepatocellular necrosis. The authors calculated a RUCAM score of 11 (highly probable) [73].

The FDA released a safety statement early in 2018 regarding the use of obeticholic acid in primary biliary cirrhosis, noting a significant number of incidences of inappropriate dosing of this particular medication, resulting in liver injury [74, 75]. Specifically, they noted that many patients were receiving supratherapeutic doses and that there were even some reports of liver injury with appropriate dosing of the drug. As a result, a safety statement was released to ensure that physicians pay close attention to the trending of liver enzymes when prescribing this drug [74].

Lugoboni et al. [76] studied the effect of high-dose benzodiazepines on the liver, as this class of drugs is primarily metabolized by the liver. They reviewed 201 cases of patients who had been admitted to an addiction treatment center for sole benzodiazepine misuse. They reviewed liver enzymes at admission and documented potential DILI if Hy's law was met. They found that persistent high-dose benzodiazepine use did not result in significant hepatotoxicity despite its metabolic pathway [76].

Table 3 Chinese Society of Hepatology guidelines [19] (with strength of recommendation and level of evidence) compared with the 2014 American College of Gastroenterology clinical guidelines [66] of DILI diagnosis and management

2017 CSH guidelines	2014 ACG guidelines
1. The clinical diagnosis of DILI remains one of exclusion and requires a history of drug administration, clinical features, changes in liver biochemical tests, response on drug rechallenge, and exclusion of other causes of liver injury (1B)	1. In suspected hepatocellular/mixed DILI, (a) acute viral hepatitis, autoimmune hepatitis, and HCV RNA should be excluded; (b) anti-HEV testing is not recommended; (c) acute CMV, acute EBV, or acute HSV infection should be considered if classical viral hepatitis is excluded or if clinical features are suggestive of other viral hepatitis; (d) Wilson's disease and Budd–Chiari syndrome should be considered when clinically appropriate 2. In suspected cholestatic DILI, (a) abdominal imaging should be performed; (b) testing for primary biliary cholangitis should occur only when abdominal imaging shows no obvious biliary tract pathology; (c) endoscopic retrograde cholangiography should only be considered when imaging cannot exclude biliary stone, primary sclerosing cholangitis, or malignancy
5. For patients with underlying liver disease, frequent monitoring for liver injury should be performed when potentially hepatotoxic drugs are used (1B)	12. The use of potentially hepatotoxic drugs in pts with chronic liver disease should be based upon benefits vs. risks 13. No data to recommend a specific liver test monitoring schedule when a potential hepatotoxic agent is prescribed to pts with chronic liver disease
6. The first general principle for treatment of DILI is prompt discontinuation of the suspected hepatotoxic drug(s) (1A)	5. In suspected DILI, offending agent(s) should be stopped 10. Pts with suspected HDS hepatotoxicity should stop all HDS and be monitored
7. The withdrawal of hepatotoxic drugs may be necessary with any one of the following: (1) ALT or AST > 8 × ULN; (2) ALT or AST > 5 × ULN for 2 weeks; (3) ALT or AST > 3 × ULN, with TBili > 2 × ULN or INR > 1.5; (4) ALT or AST > 3 × ULN, along with gradually aggravated fatigue, digestive tract symptoms, or eosinophilia (> 5%) (1B)	5. In suspected DILI, offending agent(s) should be stopped
8. For early drug-induced ALF in adults, treatment with NAC as early as possible is recommended (2B)	6. No definitive therapies are available for idiosyncratic DILI with or without ALF. NAC may be considered in adults with early-stage ALF 7. NAC is not recommended for children with severe DILI
15. Clinicians should carefully prescribe drugs and strictly obey the principles for drug compatibility and incompatibility. It is necessary to strengthen public education and clinician risk management of DILI (1B)	8. Patients should be encouraged to report use of HDS to their healthcare providers. They should be reminded that supplements are not subject to the same rigorous testing for safety as are prescription medications

Strength of recommendation defined as strong (grade 1), weak (grade 2); quality of evidence defined as high quality (A), moderate quality (B), low quality (C), very low quality (D)

All 2014 ACG recommendations are of low or very low levels of evidence

ACG American College of Gastroenterology, *ALF* acute liver failure, *ALT* alanine transaminase, *AST* aspartate transaminase, *CSH* Chinese Society of Hepatology, *CMV* cytomegalovirus, *DILI* drug-induced liver injury, *EBV* Epstein-Barr virus, *HCV* hepatitis C virus, *HDS* herbal and dietary supplements, *HEV* hepatitis E virus, *HSV* herpes simplex virus, *INR* international normalized ratio, *NAC* N-acetylcysteine, *pts* patients, *TBili* total bilirubin, *ULN* upper limit of normal

4.1 Chemotherapy and DILI

There were several chemotherapeutic agents whose novel hepatotoxic profiles were noted for the first time. Honda et al. [77] described a case of rapidly developing hepatic fibrosis in a patient who received tegafur–uracil, even though administration was only short term. Edwards et al. [78] used multiple cancer center databases to find cases of vismodegib-associated hepatotoxicity. The authors found 94 reported cases in the FDA Adverse Event Reporting System, 35 of which were reported as severe adverse effects [78]. Sakumura et al. [79] described a case of sinusoidal obstruction syndrome (SOS) in a patient who received a non-hematopoietic-stem cell transplant. SOS has previously been described after hematopoietic-stem cell transplant from oxaliplatin-based neoadjuvant chemotherapy in metastatic colon cancer. The authors presented a 58-year-old Japanese man with lymphoma who was treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) and then switched to rituximab, cyclophosphamide, vincristine, doxorubicin, and methotrexate (R-CODOX-M) alternating with ifosfamide, etoposide, and high-dose cytarabine (IVAC) after two cycles. He experienced hepatocellular injury with a serum aminotransferase concentration ten times the ULN after the first cycle of R-CODOX-M. His clinical course deteriorated, and he died

Table 4 2017 Chinese Society of Hepatology guidelines [19] (with strength of recommendation and level of evidence) that differ from 2014 American College of Gastroenterology guidelines [66]

2017 CSH guidelines	2014 ACG guidelines
2. RUCAM is recommended to serve as a scoring system for the evaluation of causality of a suspected drug (1B)	3. Liver biopsy should be considered when (a) AIH remains a possibility and immunosuppression is contemplated; (b) liver tests or liver function worsens despite cessation of possible offending agent; (c) if peak ALT level has not fallen by >50% at 30–60 days after onset in cases of hepatocellular DILI, or if peak Alk Phos has not fallen by >50% at 180 days in cases of cholestatic DILI despite stopping the suspected offending agent; (d) expected continued or re-exposure to the implicated drug; (e) liver test abnormalities persist beyond 180 days to evaluate for the presence of chronic liver diseases and chronic DILI
3. Diagnosis of DILI should include the name of the drug, clinical type, acute or chronic course, RUCAM score, and severity (1B)	4. Intentional re-exposure to a drug that likely caused hepatotoxicity is strongly discouraged
4. It is often difficult to differentiate AIH and AIH-like DILI. If necessary, it requires a histological examination of the liver for further differentiation (2C)	9. The same diagnostic approach for DILI applies to suspected HDS-induced liver injury
9. Treatment of DILI with glucocorticoids should involve the cautious consideration of its potential benefits and possible risks (1B)	11. Diagnosis of DILI in pts with chronic liver disease requires exclusion of more common causes of acute liver injury, including exacerbation of the underlying liver disease
10. Magnesium isoglycyrrhizinate can be used to treat acute hepatocellular or mixed DILI (1A)	
11. Patients with mild to moderate hepatocellular and mixed DILI who also have severe liver inflammation may be treated with bicyclol and glycyrrhizic acid (diammonium glycyrrhizinate enteric-coated capsules or compound glycyrrhizin). Those with mild inflammation can be treated with silymarin. Patients with cholestatic DILI can be treated with ursodeoxycholic acid or S-adenosyl methionine (2B)	
12. Combining two or more types of anti-inflammatory and hepatoprotective agents to treat for or prophylactically use to reduce DILI is not recommended (2B). Liver transplantation should be considered in drug-induced ALF and decompensated cirrhosis (1B)	
13. Hy's law is of great value for assessing the safety profile of new drugs (1B)	
14. Adopting different strategies and methods to achieve various goals for the management of DILI risk is advisable (1B)	
16. The use and development of interactive websites such as HepaTox in addition to the most updated version of RUCAM is important and will contribute to better understanding of DILI (1B)	

Strength of recommendation defined as strong (grade 1), weak (grade 2); quality of evidence defined as high quality (A), moderate quality (B), low quality (C), very low quality (D)

All 2014 ACG recommendations are of low or very low levels of evidence

ACG American College of Gastroenterology, *AIH* autoimmune hepatitis, *ALF* acute liver failure, *Alk Phos* alkaline phosphatase, *ALT* alanine transaminase, *CSH* Chinese Society of Hepatology, *DILI* drug-induced liver injury, *HDS* herbal and dietary supplements, *pts* patients, *RUCAM* Roussel Uclaf Causality Assessment Method

of cytomegalovirus pneumonia; on autopsy, he was diagnosed with hepatic SOS, likely secondary to R-CODOX-M [79].

Shah et al. [80] presented a case of an elderly woman who was thought to have developed DILI after receiving imatinib for the treatment of gastrointestinal stromal tumor. Initial laboratory testing showed significantly elevated AST (1450 U/L) and ALT (1632 U/L), with increased total bilirubin (4.9 mg/dL) and alkaline phosphatase (162 U/L). A liver biopsy demonstrated a histologic pattern of acute hepatitis consistent with DILI. Ultimately, discontinuation of imatinib led to recovery in the patient's clinical condition along with normalization of her liver function tests over the next several weeks [80]. However, none of these case reports applied RUCAM or another causality assessment methodology to make the diagnosis of DILI.

SOS has also been linked to antibody–drug conjugates. In a study by McDonald et al. [81], a panel of hepatologists reviewed all subjects with liver abnormalities following

inotuzumab ozogamicin (InO) therapy in patients with hematologic malignancy in two multicenter protocols. Patients ($n = 638$) were randomized to treatment with either InO or standard chemotherapy. The frequency of SOS was 5/328 (1.5%) compared with zero cases among the 310 controls. DILI developed in 26 (7.9%) of those in the treatment arm compared with three (1%) in the control arm. Overall, these data suggest that InO had a relatively low frequency of SOS but a relatively high frequency of DILI. However, for the most part, the manifestations of DILI were transient, with asymptomatic elevations of serum ALT, alkaline phosphatase, or total serum bilirubin. Unfortunately, it cannot be said with certainty whether DILI was related to InO exposure or toxicity from concomitant medications, as most patients in both arms of both protocols received antibiotics, antifungal drugs, and antiviral drugs [81].

4.1.1 Immune-Checkpoint Inhibitors

Tanaka et al. [82] described a case of steroid-refractory ipilimumab hepatotoxicity, which is a well-described adverse effect of immune-checkpoint inhibitors. While this form of liver injury usually responds to steroids alone, these clinicians successfully treated a refractory case with the combination of mycophenolate mofetil along with corticosteroids, which offers an alternative regimen when steroids alone are insufficient—notably, this strategy was initially described by Eigentler et al. [83] in 2016.

With regard to other immune-checkpoint inhibitors, Gelsomino et al. [84] presented what may be the first thoroughly examined case of nivolumab-induced cholangitic liver disease. Prior to this case, nivolumab had only been associated with transient immune-related toxicity without cholestatic injury [84]. Matsubara et al. [85] also reported a case of nivolumab-induced persistent liver injury in a patient with malignant melanoma. This patient experienced grade 3 ALT elevation after the first cycle of nivolumab at week 3, with spontaneous recovery and subsequent recurrent grade 4 ALT elevation after 17 cycles of nivolumab; this contrasts with a prior pooled analysis in which the onset of liver toxicity in nivolumab-treated patients was found to typically occur after 2–6 cycles [86]. Interestingly, liver injury in this patient was sustained for more than 5 months after discontinuing nivolumab therapy [85].

Zarrabi et al. [87] conducted a meta-analysis of 27 clinical trials focusing on potential liver injury associated with nivolumab. They demonstrated a statistically significant increase in incidence of AST and ALT elevations due to nivolumab in a variety of cancers. The authors also found the incidence of DILI was markedly increased when nivolumab was implemented as part of combination therapy, specifically when in conjunction with ipilimumab.

Zen et al. [88] presented a study that aimed to compare clinicopathologic features between checkpoint inhibitor-induced liver injury and acutely presenting AIH or idiosyncratic DILI. Seven patients treated with nivolumab or ipilimumab presented with liver dysfunction a median of 41 days after the initiation of immunotherapy. All patients had elevated liver enzymes; hyperbilirubinemia was less common. None of the patients had ANA or IgG elevations. Stopping the immunotherapy and increasing immunosuppression with additional corticosteroids normalized or decreased liver enzymes in all patients. Histologically, all biopsies showed predominantly lobular hepatitis with milder portal inflammation. Centrilobular confluent necrosis and plasmacytosis were observed in a single case and were less common and milder than those in AIH. One case each of bile duct injury, micro-abscesses, and extramedullary hematopoiesis was also found. Immunostaining revealed the presence of large numbers of cluster of differentiation (CD)-3^+ and $CD8^+$ lymphocytes, whereas $CD20^+$ B cells and $CD4^+$ T cells were fewer in checkpoint inhibitor-induced liver injury than in AIH or DILI. Overall, this histology study demonstrated that, although liver injury caused by cancer immunotherapy shares some features with injury of AIH, there are important differences between the two [88].

4.1.2 Chemotherapy-Associated Liver Injury

Vigano et al. [89] assessed the reversibility of chemotherapy-associated liver injury (CALI), notably in patients with colorectal cancer with liver metastases. CALI is important with regard to resection of liver metastases in metastatic colorectal cancer because of its association with increased postoperative morbidity and mortality [89]. The authors evaluated 429 patients undergoing liver resection for colorectal liver metastases who underwent neoadjuvant therapy with oxaliplatin and/or irinotecan. They noted that sinusoidal dilatation and nodular regenerative hyperplasia improved 9 months after chemotherapy and that an interval of > 270 days between chemotherapy and resection was an independent protective factor against grade 2–3 sinusoidal dilatation. However, steatosis and steatohepatitis were present even after 9 months, suggesting that CALI is only partially reversible [89].

Wakiya et al. [90] studied 64 patients undergoing oxaliplatin-based chemotherapy in three cohorts (< 65 years, 65–74 years, and > 75 years) to examine the effect of age in CALI. They observed no differences in sinusoidal injury or steatohepatitis and concluded that age alone did not play a role [90]. However, the three cohorts were unbalanced in terms of size, with 37 patients in the youngest cohort, compared with only ten in the oldest cohort and 17 in the middle age cohort [90].

4.2 Solithromycin

Solithromycin is a novel macrolide-ketolide specifically developed to combat the macrolide resistance seen in community-acquired bacterial pneumonia (CABP) [54]. It works similarly to other macrolides, binding to the large (50S) ribosomal subunit to inhibit protein synthesis; however, its longer alkyl-aryl side chains provide better anchoring [91].

Unfortunately, solithromycin was observed to cause a significant degree of transient aminotransferase elevations in its clinical trials [54, 92]. Specifically, Buege et al. [54] reported that elevations in ALT in the phase III trial were more than three, five and ten times the ULN in 7.2%, 2.4%, and 0.1%, respectively, of those treated with solithromycin versus 3.6%, 1.0%, and 0.2% of those treated with moxifloxacin as the comparator. Most solithromycin-treated patients had peak ALT values about 4 days after initiation of treatment, but up to 30% of patients developed peak levels following completion of treatment and up to 15 days later. Also noteworthy, the effect was more pronounced in those receiving the intravenous formulation as opposed to the oral formulation [54].

Given the hepatotoxicity risk, the FDA did not approve solithromycin for CABP, instead recommending a large safety study as they felt the risk of hepatotoxicity had not been adequately characterized [93]. The FDA asserted that, although a number of clinical trials were performed with this drug, not enough patients were included to fully understand the extent of the adverse side effects; they have requested a study including at least 9000 patients. In addition, the FDA noted that, if this future study finds no adverse effects, the availability of solithromycin to patients will still need to be limited, and it will not be used as a first-line option [92].

Of note, and although not the purpose of this paper, solithromycin is also being studied for its potential benefit in nonalcoholic steatohepatitis (NASH). One pilot study showed solithromycin improved NASH histologically, and these patients also saw a reduction in hepatic stiffness scores when measured by fibroscan [94]. We will continue to watch new developments with this agent to see how the difference between hepatotoxicity and hepatoprotection plays out and ultimately affects its approval and marketing.

5 New Reports of Established Hepatotoxins

5.1 Acetaminophen

While acetaminophen DILI is regularly studied, relatively few articles in the past 2 years provided significant advances in our understanding of intrinsic hepatotoxicity. Wong et al. [95] analyzed the accuracy of the paracetamol–aminotransferase multiplication product (APAP concentration [mg/L]) × ALT [IU/L]) as it pertains to modified-release paracetamol overdoses. The paracetamol–aminotransferase multiplication product has typically been studied and confirmed with immediate-release paracetamol [95–97]; this study used the modified-release formulation. They specifically noted that a multiplication product above 10,000 mg/L × IU/L was highly predictive of developing hepatotoxicity, whereas products < 1500 mg/L × IU/L were much less likely to cause acute liver injury [95].

Heard et al. [98, 99] studied acetaminophen protein adducts as a potential diagnostic biomarker of acetaminophen-induced liver injury in both children and adults. They performed a cross-sectional study in 100 children aged 1–12 years [98]. Of those whose caregivers confirmed they had received acetaminophen within the previous 2 weeks, 52% tested positive for the presence of the protein adduct, whereas 100% of those who denied acetaminophen use within the previous 2 weeks tested negative for the protein adduct [98]. Similarly, this same group of researchers studied the acetaminophen protein adduct in an adult population [99]. The study included 230 patients, with 42% of those who confirmed taking acetaminophen in the previous 2 weeks testing positive for the protein adduct and 99% of those who denied acetaminophen ingestion within the previous 2 weeks testing negative [99]. Both studies found a positive correlation between the serum level of the protein adduct and the time of ingestion and dose of the acetaminophen [98, 99]. For further information on the utility of acetaminophen protein adducts and the future of SNPs linked to acetaminophen-induced liver injury, the reader is directed to a thorough review by Heruth et al. [100].

On a similar note, Roberts et al. [101] developed a point-of-care test, called AcetaSTAT, for serum levels of the acetaminophen protein adduct and compared the results against those from a standard highly specific and sensitive quantitative assay. Their study included 19 patients with no exposure to acetaminophen, 29 patients with therapeutic dosing of acetaminophen, and 33 patients with acute liver injury due to acetaminophen. They observed a high level of concordance between the two assays. For patients with acute liver injury, the AcetaSTAT had 100% sensitivity, 86.2% sensitivity, 89.2% positive predictive value, and 100% negative predictive value [101].

5.2 Antifungals

Dob et al. [102] looked at the hepatotoxicity profiles of five major antimycotics used in invasive fungal disease, including caspofungin, liposomal amphotericin B, anidulafungin, fluconazole, and voriconazole. They used human hepatocytes with a previously established in vitro cytotoxicity screening model to analyze synthetic liver function at varying clinical doses of these antifungals. More specifically, they measured the following parameters: viability of cells,

synthesis of albumin, cytochrome 1A2 activity, and cell death. They found that liposomal amphotericin B, caspofungin, and anidulafungin all demonstrated mild levels of hepatotoxicity. However, as drug concentrations increased, anidulafungin was associated with severe liver injury, and both fluconazole and voriconazole demonstrated dose-dependent liver injury. The mechanisms by which these drugs caused hepatotoxicity have not been fully delineated. This study confirmed that therapeutic drug monitoring is recommended for any patient who requires 'azole' therapy and already has some degree of hepatic dysfunction and that close monitoring is advised for any patient who requires treatment with anidulafungin [102].

In contrast to the findings of Dob et al. [102], Pettit et al. [103] specifically found that therapeutic drug monitoring may not be necessary for patients receiving posaconazole. However, their study was retrospective in nature, involving individuals who required therapy with posaconazole, such as those who underwent bone marrow transplant, and Pettit et al. [103] did not analyze varying doses. Their goal was therapeutic dosing, and while they did not observe any relationship between the posaconazole serum concentration and a linear change in liver enzymes, they did note that increases in the liver enzymes were seen predominantly in patients who were or had been receiving concomitant hepatotoxic medications.

Gayam et al. [104] reported a single case of DILI in an individual receiving intravenous fluconazole for sepsis due to inguinal candidiasis. After initiation of the antifungal, the patient subsequently had a rise in AST and ALT to 25,000 IU/L and 6500 IU/L, respectively, on day 3 of hospitalization [104]. The fluconazole was promptly discontinued, and the AST/ALT trended down within 3 days. This patient had no underlying kidney or liver impairment. The authors confirmed this was an adverse drug reaction (ADR) using the Naranjo algorithm, which yielded a score of 10, suggesting definite ADR. To establish causality, a RUCAM score of 11 was calculated, indicating highly probable. Notably, the patient did report having had elevated liver enzymes approximately 1 year prior after receiving oral fluconazole for candiduria. This case not only highlights the importance of a detailed history but also shows how a positive response when re-exposed to a particular medication can help establish causality through RUCAM [104].

As discussed, new genotypic polymorphisms continue to be identified as risk factors for DILI. Fontana et al. [14] discussed specific HLA polymorphisms in regard to the antifungal drug, terbinafine, that may predispose patients to liver injury. After reviewing a small population of patients with terbinafine-associated hepatotoxicity (determined by the DILIN causality committee), the authors found that HLA-A*33:01, HLA-B*14:02, and HLA-C*08:02 were significantly overrepresented in these particular patients. More specifically, these haplotypes were present in 91% of study patients with European ancestry but 1.6% of those in the control group with European ancestry. Molecular docking studies strengthened the association. In short, the authors obtained the sequences of HLA-A*33:01, HLA-A*33:03, HLA-B*14:02, and HLA-C*08:02 and generated atomic models. Their research found terbinafine had the potential to interact with all four haplotypes with moderate affinities. This highlights the increasing importance of identifying genetic risks factors for DILI [14].

5.3 Tolvaptan

Tolvaptan is a vasopressin receptor antagonist used for the short-term treatment of hyponatremia and long-term treatment of adult polycystic kidney disease (ADPKD) to reduce cyst burden. DILI has only been demonstrated in those with ADPKD taking the drug long term [105]. The mechanism by which DILI occurs is unknown, as the initial animal models in which tolvaptan was tested did not demonstrate any evidence of hepatotoxicity [106]. Mosedale et al. [107] utilized a collaborative cross mouse line to help delineate the mechanism of liver damage. This line is unique in that it has been found to be superior to the traditional mouse models [108, 109]. Indeed, Mosedale et al. [107] found that hepatotoxicity was induced by oxidative stress, with downstream immune system activation in addition to disruption of bile acid homeostasis. Moreover, they found that altering the bile acid composition actually led to the largest increase in ALT levels. Finally, they also found a potential biomarker linked to tolvaptan-induced liver injury in the form of elevated levels of secretory leukocyte peptidase inhibitor messenger RNA [107].

In a different study, Mosedale et al. [110] used primary human hepatocytes for further study into the mechanism of tolvaptan-induced liver injury. They treated the hepatocytes with various doses of the drug and then measured the miRNA-122 levels. They found that the highest level of miRNA-122 correlated with increased incidence of cell death. Early increases of miRNA-122 correlated with increased apoptosis and oxidative stress. Notably, at each of these drug concentrations, there was no significant increase in alanine aminotransferase levels. The significance of this is that therapeutic levels of tolvaptan could potentially induce serious liver injury via the immune system before any significant change in liver transaminases occurs [110].

In addition, tolvaptan has been the subject of a number of studies utilizing quantitative systems pharmacology (QSP) over the last 2 years [111, 112]. An in silico model known as DILIsym® has been gaining more recognition as a diagnostic tool for idiosyncratic DILI and has previously been applied to tolvaptan. The reader is directed to a number of articles further addressing tolvaptan and QSP [111–113].

5.4 Enalapril

Enalapril is an angiotensin-converting enzyme (ACE) inhibitor most frequently used in cardiovascular disease. Overall, the incidence of DILI with ACE inhibitors is considered low, although the VigiBase (World Health Organization (WHO) individual case safety report database) contains reports of several hundred cases, although it must be noted that the quality of some of these reports is questionable [114, 115]. Table 5 demonstrates the number of reported cases of DILI associated with each ACE inhibitor. It is important to note that the number of DILI cases associated with each of the drugs listed in Table 5 may fluctuate according to how frequently it is prescribed [115]. Currently, the mechanism of DILI induced by enalapril is unknown. Shirai et al. [116] utilized a mouse model and hypothesized that the mechanism of DILI was centered on oxidative stress in livers with existing hepatic steatosis. While this has not yet been confirmed in humans, such information may be clinically useful when prescribing ACE inhibitors to a patient with pre-existing fatty liver disease.

5.5 Direct-Acting Oral Anticoagulants

Direct-acting oral anticoagulants (DOACs), also known as non-vitamin K antagonists, have become increasingly popular and are commonly used for prevention of stroke in patients with nonvalvular atrial fibrillation. The possibility of increased hepatotoxicity has been raised as a concern, with multiple cases of liver injury thought to be related to this class of drugs [117, 118]. To examine this further, Alonso et al. [119] analyzed 113,000 patients and found a decreased incidence of liver injury when directly comparing DOACs and warfarin. The results from this study were later confirmed by Douros et al. [120], who studied a population of 52,000 patients from the Canadian health database from 2011 to 2014. They found no association of increased liver injury in two populations, including those with and without a previous history of liver disease. Current European Heart Rhythm Association guidelines recommend checking liver enzymes once per year for patients receiving a DOAC [121]; however, the usefulness of such arbitrary monitoring can certainly be questioned. Douros et al. [120] emphasize that the status of any liver disease should not preclude the use of a DOAC if it would otherwise be the best available option for that patient.

Table 5 Number of reports of drug-induced liver injury for various angiotensin-converting enzyme inhibitors in LiverTox and VigiBase [114, 115]

Name	LiverTox (*n*)	VigiBase (*n*)
Enalapril	25	706
Captopril	16	643
Lisinopril	14	378
Ramipril	4	–
Fosinopril	3	–
Benazepril	2	–

5.6 Antivirals

In 2016, a number of studies warned of the potential hepatotoxic nature of direct-acting antivirals (DAAs) in regard to treatment of hepatitis C virus (HCV) infection and the potential risk of hepatic decompensation or reactivation of hepatitis B with this class of drugs [122]. Mishra et al. [123] provided an updated commentary on HCV DAAs. They reviewed the previously established 'rule-of-2' model (Ro2) [124] and its potential as a DILI risk assessment tool specifically with HCV DAAs. The Ro2 model states that increased lipophilicity ($\log P > 3$) and high daily drug dose (> 100 mg/day) may result in an increased risk of DILI. In applying this model to the 12 DAAs currently available for HCV treatment, they found that the Ro2 model correctly identified those with known increased risk for hepatotoxicity (e.g., paritaprevir, dasabuvir, and simeprevir) when compared with each drug's initial clinical trial results. The specificity of the Ro2 model was high (~95%), suggesting it may be a good screening tool for DAA selection. With that said, Mishra et al. [123] noted that further research is necessary to further confirm the potential utility of this model, including larger prospective studies.

Segamwenge et al. [125] presented a case series looking at the effects of antiretroviral therapy, specifically efavirenz, on the liver. They presented four patients with potential DILI secondary to efavirenz. All four were found to have a hepatocellular-type liver injury as evidenced by their R ratios being > 5, and a causality score was calculated for all patients using RUCAM. Three of the cases were found to be probable and one unlikely. See Table 6 for more details. The authors argued that hepatotoxicity as a result of efavirenz was not as rare as suggested in the literature and advocated for regular monitoring of liver enzymes while receiving this medication [125].

5.7 Antiarrhythmics

Although amiodarone-induced liver injury (AILI) has been extensively documented, less is known about patient-specific risk factors for this type of injury. Diab et al. [126] created a prospective case–control trial with 180 patients from intensive care units receiving intravenous amiodarone. The study found that the presence of the following factors were most predictive for the development of AILI: cardiomyopathy, congestive hepatomegaly, increasing baseline total

Table 6 Patients receiving efavirenz-based antiretroviral therapy with subsequent drug-induced liver injury

Case	*R* ratio[a]	RUCAM causality score	Interpretation	Pattern of liver injury	Clinical improvement post-withdrawal of drug?
1	10.17	6	Probable	Hepatocellular	Yes
2	5.22	6	Probable	Hepatocellular	Yes
3	20.33	3	Unlikely	Hepatocellular	No
4	8.36	8	Probable	Hepatocellular	Yes

ALT alanine transaminase, *ALP* alkaline phosphatase, *RUCAM* Roussel Uclaf Causality Assessment Method, *ULN* upper limit of normal

[a]*R* ratio: (ALT/ULN)/(ALP/ULN)

bilirubin, direct current cardioversion, and increasing dose of amiodarone. These were all found to be independent predictors for AILI and all were statistically significant. Risk factors for severe AILI (AST or ALT more than five times the ULN) included the use of inotropic support, presence of congestive hepatomegaly, increasing baseline total bilirubin, and increasing dose of amiodarone. The authors recommend considering these risk factors before initiating intravenous amiodarone, especially for non-life-threatening conditions such as mild, uncomplicated atrial fibrillation [126].

Grimaldi-Bensouda et al. [127] also contributed to our understanding of the effects of amiodarone on the liver as part of their study examining the effects of all classes of antiarrhythmics on acute liver injury. They were inspired after the European Medicines Agency received several reports of acute liver injury following dronedarone administration a few years prior. To summarize, they found that only class III antiarrhythmics were statistically associated with an increased risk of acute liver injury (3.61; 95% confidence interval (CI) 1.56–8.35), of which amiodarone had the largest effect (odds ratio (OR) 5.90; 95% CI 1.74–20.00). Dronedarone also yielded an increased risk for acute liver injury, but the results were not statistically significant (OR 3.1; 95% CI 0.7–14.8). Classes I, II, and IV also did not show statistically meaningful associations. The authors acknowledged the wide CIs and attributed them to the overall low exposure of class III antiarrhythmics [127].

5.8 Antituberculosis Drugs

The typical therapeutic regimen for treating tuberculosis (rifampicin, isoniazid, pyrazinamide, and ethambutol) has been suggested to be associated with elevated liver enzymes in patients who possess a unique genotype of *NAT2* [128]. However, when Zhang et al. [129] reviewed the literature, they noted inconsistent conclusions about the association between *NAT2* polymorphisms and antituberculosis drug-induced liver injury (ATDILI). To better clarify the role of *NAT2* polymorphisms in ATDILI, they performed a meta-analysis of 37 studies and found an overall OR of 3.15 ($p < 0.005$) for slow acetylators and risk of ATDILI. They also recognized this association was more or less pronounced depending on the patient population, with an OR of 6.42 for West Asian populations and 2.32 for European populations. The association between slow acetylators and ATDILI was further confirmed when results were consistent and independent of study design and genotyping methods [129].

Also new in 2018 was the identification of a subset of slow acetylators who are at even higher risk for liver injury, namely the ultra-slow acetylators. Using a meta-analysis, Suvichapanich et al. [128] identified that *NAT2*6A* and *NAT2*7B* genotypes were particularly susceptible to ATDILI. They found *NAT2* ultra-slow acetylators and slow acetylators were at increased risk of ATDILI, with ORs of 3.6 and 2.80, respectively, when each were compared with fast acetylators. When directly comparing ultra-slow acetylators with slow acetylators, the increased risk of ATDILI continued, with an OR of 1.33 [128].

Zhang et al. [129] went on to propose the potential future implications of acetylator status on patient care and treatment of tuberculosis. They specifically discussed that physicians are given a unique opportunity to provide personalized medicine by tailoring dosing of medication according to the speed of specific *NAT2* polymorphisms as a means to reducing overall adverse events, including ATDILI [129].

5.9 Steroids

Relapses and flares of many autoimmune conditions are often treated with high doses of corticosteroids. While most of the evidence for steroid-induced DILI is in the form of case reports, Nociti et al. [130] carried out a prospective study to further evaluate the incidence, severity, and risk factors for DILI, specifically in patients with multiple sclerosis treated with intravenous steroids. They included 175 patients who were treated with pulsed methylprednisolone during a 12-month period. Liver enzymes were checked 2 weeks after intravenous steroid therapy and were found to be elevated in 21 cases, six of which were regarded as severe elevations of ALT according to Hy's law. The following causality assessment tools were used to determine the

etiology of liver injury in these patients: the Naranjo scale, the WHO—Uppsala Monitoring Centre (UMC) causality assessment, RUCAM, and the Autoimmune Hepatitis Scoring System (IAHG). Ultimately, three patients received a diagnosis of possible, probable, or highly probable for DILI, and the other three were probable or definite AIH. This study highlighted the importance of deciphering between the toxic effects of steroids and novel presentations of AIH, as the difference has significant implications not only for treatment of the liver injury but also for subsequent management of the autoimmune condition [130].

Bresteau et al. [131] and Dumortier et al. [132] discussed similar cases. Both sets of authors demonstrated cases of DILI in patients receiving high-dose methylprednisolone for multiple sclerosis. Bresteau et al. [131] specifically discussed a 35-year-old woman whose ALT and AST peaked at 1512 IU/L and 778 IU/L, respectively. A RUCAM assessment was applied, with a result of 8, indicating probable DILI. The authors reviewed 12 previously published cases of methylprednisolone-induced liver injury in patients with multiple sclerosis. In all cases in which the appropriate information was available, *R* ratios were > 5 and RUCAM scores were suggestive of DILI [131]. Dumortier et al. [132] discussed a case of methylprednisolone-induced liver injury in addition to four other cases reported by the French pharmacovigilance center of Lyon. Their patient demonstrated evidence of acute hepatitis on liver biopsy. All five cases scored between 6 and 10 on the RUCAM scale, indicating probable to highly probable DILI. Three of the five patients had positive re-challenges to confirm causality [132].

5.10 Antidepressants

Billioti et al. [133] attempted to quantify the association between observed liver injury and antidepressants, specifically comparing risks between classes. Using data from the French National Health Insurance Database, the authors identified nearly 5 million patients who were initiated on an antidepressant from 2010 to 2015. Of these, 382 serious liver injuries were identified, all attributed to various classes of antidepressants and occurring with a mean of approximately 2 months after initiation of therapy. Age- and sex-adjusted incidence rates were 19.2, 22.2, 12.6, and 32.8 per 100,000 person-years for selective serotonin reuptake inhibitors (SSRIs), including venlafaxine, duloxetine, and mirtazapine, respectively. When compared specifically with SSRIs, no other classes of antidepressants were significantly associated with an increased risk of DILI. The authors did note that some antidepressants, namely duloxetine, have previously been identified in premarketing clinical trials as causing liver injury so are contraindicated in patients with liver disease, and as such could explain the lack of observed differences from this trial [133].

Ferrajolo et al. [134] presented a case–control series of 17 patients with liver injury due to antidepressants. The 17 exposed patients were matched to 99 controls. While the authors did not apply any specific causality scoring system to the cases, they did calculate a statistically significant OR of 1.84 (95% CI 1.02–3.32) for increased risk of liver injury associated with current use of antidepressants. Notably, citalopram, an SSRI, was observed to have an increased incidence of elevations in ALT compared with other antidepressants [134].

5.11 Antitumor Necrosis Factor-α Inhibitors

Kok et al. [135] reported a case series of anti-tumor necrosis factor (TNF)-α-associated acute liver failure; four cases were reported, with an additional five identified on literature review. The majority of individuals affected were female (eight of nine cases). The most common anti-TNF-α agent associated with acute liver failure was infliximab ($n = 8$). The latency between initial drug exposure and acute liver failure ranged from 3 days to over a year. Of the nine cases, six required emergency liver transplantation. Liver biopsy was obtained in seven cases; cholestatic–hepatic features were frequently found on pretransplant and explant histology; none of the biopsies showed clear autoimmune features, which is more typical of anti-TNF-α acute liver injury. Further, only three of the nine cases demonstrated hepatocellular injury, which is in contrast with previous literature documenting this as the more common anti-TNF-α-associated acute liver injury pathology. The authors concluded that anti-TNF-α-associated acute liver failure displays somewhat different characteristics than less serious acute liver injury. RUCAM scores were ascertained in four of the cases, and all four were deemed to have at least probable causality from the anti-TNF-α agent (RUCAM scores 6–7) [135].

Table 7 lists the other drugs reported to cause DILI in 2017 as well as in other recent summaries [136]. The causality assessment methodology used to diagnose DILI is provided when stated by the authors.

6 Herbal and Dietary Supplement (HDS)-Induced Liver Injury

A number of reports involving liver injury from HDS are discussed earlier in this review [7]. Alongside registry data, various individual case reports and other work appeared in 2017–2018 that add to the growing list of HILI and HDS-induced liver injury agents. Continued understanding of HDS that can cause liver damage is important, as the incidence is ever-increasing and has a significant impact on health. Wong et al. [137] discussed that, in the Asia-Pacific region especially, the incidence has been as high as 81%

Table 7 Miscellaneous case reports and case series of previously described medications causing drug-induced liver injury

Drug	Type of liver injury	Cases (*n*)	Causality score used	Causality score
Albendazole [159]	–	1	RUCAM	10 (highly probable)
Atorvastatin + ezetimibe [160]	HC	1	RUCAM	9–10 (highly likely)
Celecoxib [161]	HC (6), M (5), C (4), UK (3)	18	DILIN	3 (mod-severe in 12 cases); 4 (severe in 2 cases); 5 (fatal/transplant in 2 cases)
Dimethyl fumarate [162]	HC	14	FDA/DILIN	Probable (11 cases), possible (3 cases)
Iopamidol [163]	HC	1	RUCAM	5 (possible)
Fenofibrate [164]	HC (2), M (2), C (3)	7	DILIN/RUCAM	DILIN (probable in 2 cases; highly likely in 5 cases); RUCAM (possible in 2 cases; probable in 5 cases)
Glatiramer acetate [165]	–	1	RUCAM	Probable
Mosapride [166]	HC	2	DDW-J 2004	9 (highly probable), 8 (highly probable)
Norethisterone [167]	–	3	RUCAM	10 (highly probable), 8 (probable), 7 (probable)
Pirfenidone [168]	HC	1	RUCAM	10 (highly probable)

C cholestatic injury, *DDW-J 2004* Digestive Disease Week Japan 2004 scale, *DILIN* Drug-Induced Liver Injury Network, *HC* hepatocellular injury, *M* mixed injury, *RUCAM* Roussel Uclaf Causality Assessment Method, *UK* unknown

of DILI cases. Wang et al. [138] discovered that, in China, traditional Chinese medicine (TCM) accounted for almost 26% of DILI cases. In contrast, the incidence of HILI in the USA was significantly lower. In China, Liu et al. [139] attempted to create a database to organize the data on HILI into a format that could easily be used to study and evaluate and therefore prevent future cases of liver injury from herbal medications, which helps to fulfill the recommendations of Wong et al. [137].

To help standardize the process of identifying HILI, another group of authors from the China Association of Chinese Medicine (CACM) created a set of nine recommendations, which are summarized in Table 8 [140].

Jing et al. [141] reiterate the importance of recommendation 1 in the proposed CACM guidelines for evaluation of HILI as Chinese medicine (CM)/herbal medicine (HM) are very different from synthetic drugs. Both sets of authors discuss that CM/HM are typically composed of multiple ingredients as opposed to synthetic drugs, which are made of a single agent [140, 141]. In addition, the actual incidence of HILI from CM is much lower than that of DILI. Further, Jing et al. [141] found that various analyses indicated other key features differentiated CM-HILI from DILI and as such, they should continue to be treated as separate entities.

Melchart and Teschke [21] reported on a large prospective, hospital-based study involving over 21,000 patients at the Hospital for TCM in Bad Kötzting, Germany, from 1994 to 2015. This study was the first to evaluate HILI at a single institution of such magnitude. They noted ALT increases of more than five times the ULN were seen in only 0.12% of patients, most being classified as "possible" HILI by RUCAM assessment, with the most common herbal

Table 8 China Association of Chinese Medicine guidelines for evaluation of herbal-induced liver injury [140]

Recommendation 1	Identify culprit drug by the following: (1) Chinese medicine (CM)/ Herbal medicine (HM) vs. synthetic vs. biologic (2) therapeutic use (3) compare CM/HM with synthetic drug (reference article for description on what differentiates CM/HM from synthetic and biologic drugs)
Recommendation 2	Sub-classify based on pathology of liver damage, timing of liver damage, mechanism of liver damage and type of CM syndrome (reference article for list of CM theories)
Recommendation 3	Level of injury should be labeled as: mild, moderate, moderate to severe, severe, fatal
Recommendation 4	As with DILI, HILI is a diagnosis of exclusion and should therefore rule out all other causes of liver damage (reference article for full list of exclusions)
Recommendation 5	Label HILI as either suspected diagnosis vs. clinical diagnosis vs. confirmed diagnosis (reference article for inclusion criteria for each classification)
Recommendation 6	Attain all details of culprit drug usage history (reference article for sample questionnaire)
Recommendation 7	Physically verify the culprit drug
Recommendation 8	Re-challenging with culprit drug is not recommended
Recommendation 9	No new treatment recommendations—follow treatment path for DILI

CM Chinese medicine, *DILI* drug-induced liver injury, *HILI* herbal-induced liver injury, *HM* herbal medicine

medications implicated being *Bupleuri radix* and *Scutellariae radix* [21].

In addition to the herbal medications more well-known to cause liver injury, some newer agents are increasingly being reported, including Kratom (*Mitragyna speciosa*), *Garcinia cambogia,* red yeast rice, and Ayurvedic compounds.

Kratom, a tropical tree typically found in Southeast Asia and Africa, has been identified as an opiate receptor agonist, with a number of cases linking its abuse with cholestatic liver injury [26, 27]. Tayabali et al. [26] described a case of Kratom-induced HILI that scored an 8 via RUCAM (highly probable). For confirmation of their RUCAM scoring, they used liquid mass chromatography spectrometry [26]. The FDA has since made the use of Kratom illegal, as it appears to be fostering the opiate crisis with its similar physiologic effects, relatively easy accessibility, and lower cost than true opiates [26, 28].

Garcinia cambogia is an herbal supplement that is being used as a weight loss aid. Its active ingredient is hydroxycitric acid. No standard guidelines exist on how to safely take this supplement [29]. Initially, no concrete evidence existed to prove this supplement was directly causing hepatotoxicity, as it typically comes in a form combined with many other supplements. However, within the last 2 years, the number of people who have taken 'purified' *G. cambogia* and experienced associated hepatotoxicity has increased. In 2018, Sharma et al. [30] described a case of potential *G. cambogia*-induced liver injury. The authors used RUCAM to assess for causality, and the analysis yielded an 11, equating to highly probable. This supplement primarily causes hepatocellular liver injury with a wide range of observed clinical presentations, from acute hepatitis to acute liver failure requiring transplantation [29–33].

Red yeast rice is a Chinese herbal medication used as an adjunct for dyslipidemia that has been reported to cause liver injury [37]. Mazzanti et al. [37] used the Italian Surveillance System of Natural Products to review the incidence of liver injury associated with red yeast rice from 2002 to 2015 and found ten documented cases. The majority of these cases resulted in acute hepatitis requiring hospitalization. While the authors noted ten cases, RUCAM had only been applied to two, only one of which provided a significant association (7, probable). For seven of the other cases, the authors applied the WHO method for causality assessment, which yielded six "probable" case and one "unlikely" case. For the tenth case, not enough information was available to use any type of causality assessment. A more commonly seen side effect noted by the authors was an elevation of the creatine phosphokinase and general gastrointestinal reactions, including nausea and emesis [37].

Finally, reports of Ayurvedic compounds causing various forms of liver injury have been increasing [22, 34, 35]. Phillips et al. [34] studied a population of patients from South India and attempted to characterize the histopathologic patterns of Ayurvedic-induced liver injury. Based on RUCAM scoring, they found 33 patients. Their results demonstrated that males had a higher incidence of liver injury, unlike the incidence of DILI in the Western world. Chronic hepatitis was the most common type of inflammation seen on histology. In addition, they found that heavy metals and hepatotoxic volatile organic compounds were present in > 70% of the compounds. Like many of the authors in the last year studying Chinese herbal medication-induced liver injury, Phillips et al. [34] and Devarbhavi [35] stressed that a larger governmental process regulating use and production of these compounds is necessary.

Table 9 lists other case reports of agents causing HILI in the last 1.5 years.

Wang et al. [36] further studied *Polygonum multiflorum*, a Chinese herbal medication used for anti-aging effects, in a case series of 29 patients in an attempt to discover more about the mechanism of liver injury. They noted that the majority of patients experienced severe hepatitis. After withdrawal from the herbal medication, most patients had resolution of liver injury, although the authors noted that some patients did progress to chronic disease.

7 Causality Assessment of DILI and HDS Cases

The RUCAM remains the most widely used assessment tool specifically developed for DILI. It was updated by Danan and Teschke [142] in 2016, and its value was reinforced by Teschke et al. [38] in their recent review on biomarkers and their role in causality assessment. While RUCAM has a significant number of advantages over other less liver-specific methodologies, including a stepwise, structured format that has been consistently validated and can be tailored to individual patients, a number of limitations remain. Björnsson and Hoofnagle [115] discussed the importance of knowing the quality of the data in published studies. DILI remains a diagnosis of exclusion [115]. As mentioned, RUCAM continues to be the most reliable method of determining causality, although numerous published reports of suspected or alleged DILI still appear without calculating a liver-specific causality assessment score such as RUCAM. In 2010, Agarwal et al. [143] found that most published studies fell far short of a true diagnosis of DILI. Björnsson et al. [115] analyzed reports of DILI listed on the LiverTox website and found that only 53% of 671 agents demonstrated enough evidence to make a diagnosis of DILI. More recently, Barnhill et al. [168] evaluated case reports and case series from the 2017 literature to see whether the use of causality assessment methodologies had improved since 2010. Perhaps not surprisingly, they found that many publications still did not

Table 9 Case reports of miscellaneous herbal and dietary supplements linked to liver injury with the causality assessment methodology used

Herbal/dietary supplement	Causality score used	Score	Comments
Punarnaya mandur, Kanchnar guggulu [22]	RUCAM	5 (possible)	
Garlic [23]	RUCAM	4 (possible)	
Polygonum multiflorum [25]	RUCAM	9 (highly probable)	Ultra-high-performance liquid chromatography used to confirm RUCAM analysis [25]
Lepidium meyenii (Maca) [24]	RUCAM	9 (highly probable)	

RUCAM Roussel Uclaf Causality Assessment Method

contain the minimally necessary information to diagnose and accurately assess DILI.

As no specific diagnostic marker exists for DILI, we rely on the literature to provide us accurate reports as DILI is a diagnosis of exclusion and many other diseases can mimic it. Ganger et al. [135] found in the Acute Liver Failure Study Group (ALFSG) registry that 11% of the cases (303 patients) were listed as indeterminate etiology. The authors performed a more thorough investigation of each of these cases and found "highly likely" versus "probable" etiologies for 142 of the cases. Interestingly, they determined that 11 of the cases did not even meet the criteria for acute liver failure [144]. Such difficulties in proving causation have spurred the ongoing research efforts to identify a pathognomonic diagnostic blood (or other tissue) biomarker for DILI. In the meantime, as echoed by Björnsson and Hoofnagle [115], it is imperative that authors (and, we would add, reviewers and journal editors) follow a standardized method for diagnosing DILI to prevent poorly or undocumented cases from contaminating the literature.

In 2017, Scalfaro et al. [145] attempted to modify the RUCAM score and apply it to pharmacovigilance data (PV-RUCAM), which are often imperfectly documented. This new scoring system was developed from the original RUCAM, whose purpose was to standardize the process of confirming DILI in cases where it was suspected. This new system was found to have 100% sensitivity, and 91% specificity, with 25% positive predictive value and 100% negative predictive value. Although the authors acknowledged that more prospective research is necessary to confirm the utility of this modified scoring method, we would agree it represents an advance in how postmarketing surveillance for DILI is currently being performed.

Over the past 2 years, significant research has continued in the area of miRNAs and their potential to diagnose or predict the severity of DILI. The reader is directed to several sources for more in-depth reviews of the newly described miRNAs in 2017 and 2018 [113, 145–148]. Several studies confirmed the increased sensitivity and specificity of miRNA-122, specifically with DILI due to acetaminophen and amoxicillin–clavulanate [5, 148–151].

Similarly, DILI risk factors, particularly HLAs and other potential biomarkers where the continued focus of study in the past year, and the interested reader is referred to any number of recent reviews on this important topic [12, 39–51].

8 Updates in the Mechanisms of DILI

Much remains to be discovered in terms of the mechanisms of DILI, particularly that of idiosyncratic DILI. Mosedale et al. [42] and Cho et al. [152] reviewed the key components that lead to DILI, including changes within bile acid homeostasis, oxidative stress, and mitochondrial dysfunction. Similarly, Dakhoul et al. [153] provided a succinct review of various pathologic phenotypes of DILI with associated causative agents and histologic findings. Overall, many studies were published in 2017–2018 regarding DILI mechanisms—a select number of which have been selected for closer review as they provide important conclusions on this topic (Table 10).

8.1 Bile Salt Export Pumps

Bile salt export pumps have become an important area of study as they are a primary mechanism for cholestatic DILI. Multidrug-resistance-associated protein 3 (MRP3) is a specific type of bile salt export pump that is emerging as a primary constituent in cholestatic liver injury [154]. Ali et al. [155] created a model that specifically addressed cholestasis by predicting agents that would potentially inhibit this transporter. Using their model, they confirmed MRP3 inhibition at the cellular level, utilizing three MRP3 inhibitors: fidaxomicin, suramin, and dronedarone.

Table 10 Updates in the mechanisms of drug-induced liver injury

Mechanism	Drugs tested
Bile salt export pumps	
MRP3	Fidaxomicin, suramin, dronedarone [165]
Immune mediated	
Antigen-specific T cells	Flucloxacillin, amoxicillin, isoniazid [166]
TNFα, IFNγ	Flucloxacillin, amoxicillin, isoniazid [55]
Ceramides	Nimesulide, nefazodone, trovafloxacin, aspirin, buspirone, levofloxacin [56]
DAMPs	Amodiaquine, nevirapine [57]
Mitochondria	Acetaminophen [59]
Lipophilicity	DILIrank dataset[a] [168]

DAMPs damage-associated molecular patterns, *IFN* interferon, *MRP3* multidrug-resistance-associated protein 3, *TNF* tumor necrosis factor

[a]DILIrank dataset is a dataset of 1036 drugs FDA approved prior to 2010. They compared drugs that were withdrawn from the market due to DILI or severe DILI warning given to the drug and compared them to drugs that were found to have no causality link with DILI

8.2 DILI and the Immune System

Ogese et al. [156] described a novel mechanism for DILI involving antigen-specific T cells, noting that these types of cells were found to be upregulated with DILI. Roth et al. [55] observed that cytokines are also upregulated with DILI, specifically, TNF-α and interferon (IFN)-γ, based on a model using human hepatocytes with the known hepatotoxic agents flucloxacillin, amoxicillin, and isoniazid. Based on these in vitro studies, they postulated that IFN-γ likely induces the formation of TNF-α, causing a cascade of cellular injury and eventuating in cell death. Their results suggest that these two molecules may be acting synergistically, but further data are needed. Similarly, Jian et al. [56] found that ceramide, an intracellular molecule, is upregulated when the immune system is activated and specifically induces hepatocyte apoptosis.

Kato and Uetrecht [57] expanded the knowledge that damage-associated molecular patterns (DAMPs) activate the immune system and are released by reactive metabolites, creating an inflammatory response within the liver and subsequently eliciting liver damage. These investigators hypothesized that drugs associated with idiosyncratic DILI could be tracked based on whether they released these DAMPs. They proved their theory by studying two drugs highly associated with idiosyncratic DILI (amodiaquine and nevirapine) and measuring high levels of DAMPs when either drug was given [57].

Mitochondrial dysfunction has also been linked to idiosyncratic DILI, specifically with acetaminophen toxicity [58]. Ramachandran and Jaeschke [59] reviewed that more progress has been made on the role of the innate immune system in acetaminophen toxicity, particularly regarding oxidative stress created by mitochondria. However, some controversy remains over the role of both neutrophils and some proinflammatory mediators, including interleukin (IL)-1β. They echo that more research is warranted on this topic [59].

Goda et al. [157] discovered that lipophilicity, an inherent pharmacologic property of drugs themselves, can be linked to mitochondrial dysfunction progressing to liver dysfunction. McEuen et al. [158] specifically looked at the DILIrank dataset with 1036 FDA-approved drugs to assess the relationship between lipophilicity and DILI. Their analysis confirmed that increased lipophilicity was associated with DILI. While this result was technically statistically significant, they did note it was not a strong association and requires further research. The authors also echoed results from previous studies that lipophilic drugs can be metabolized to toxic forms due to the extensive distribution within the body and that these toxic forms can cause oxidative stress via mitochondria and a subsequent inflammatory immune response [158].

9 Conclusions

Drug-induced liver injury and hepatic injury secondary to HDS continues to be a major area of study in the field of drug safety. Investigators continued to broaden our knowledge base of DILI, HILI, and HDS in the past year. This included work from the DILIN prospective study and other international registries. While only a few new cases of DILI and HILI were reported in the literature in 2017–2018, there were numerous publications concerning liver injury secondary to known agents, including a few important differences between DILI affecting Caucasians and African Americans, and the genetic and environmental risk factors affecting DILI. In addition, many authors reinforced the concept that herbal medications require more regulation as reports of associated liver injury are increasing. An analysis of alcohol intake in the US DILIN prospective study found no differences in outcome between nondrinkers and "heavy" drinkers who developed acute DILI, although anabolic steroid use was more likely to be the cause among those drinking the most, perhaps reflecting a lifestyle choice among these individuals. Whether or not alcoholics are at greater risk was not specifically addressed in their results, as "heavy drinking" was not further characterized. Acetaminophen protein adducts continue to demonstrate their utility with high positive and negative predictive values. Immune-checkpoint inhibitors in addition to antivirals for HCV and HIV treatments continue to pose an increasing risk of liver injury and require continuous liver enzyme monitoring. Finally, the roles of bile salt export pumps and the immune system as they relate to the pathophysiology of DILI continued to be

a subject of interest this past year. As investigators continue to work on increasing our understanding of DILI and injury secondary to HDS, we look forward to the time when the clinician's ability to diagnose and manage DILI will become a much more simplified task.

Compliance with Ethical Standards

Ethical approval There was no need for ethical approval.

Conflict of interest Mark Real, Michele Barnhill, Cory Higley and Jessica Rosenberg have no conflicts of interest that are directly relevant to the content of this study. James Lewis has received fees for participation in review activities such as data monitoring boards, etc., for Otsuka, Allergan, GSK, Zydus, Shire, BMS but otherwise has no other conflicts of interest.

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