Drug-induced liver injury: Do we know everything?

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Abstract
Interest in drug-induced liver injury (DILI) has dramatically increased over the past decade, and it has become a hot topic for clinicians, academics, pharmaceutical companies and regulatory bodies. By investigating the current state of the art, the latest scientific findings, controversies, and guidelines, this review will attempt to answer the question: Do we know everything? Since the first descriptions of hepatotoxicity over 70 years ago, more than 1000 drugs have been identified, however, much of our knowledge of diagnostic and pathophysiologic principles remains unchanged. Clinically ranging from asymptomatic transaminitis and acute or chronic hepatitis, to acute liver failure, DILI remains a leading cause of emergent liver transplant. The consumption of unregulated herbal and dietary supplements has introduced new challenges in epidemiological assessment and clinician management. As such, numerous registries have been created, including the United States Drug-Induced Liver Injury Network, to further our understanding of all aspects of DILI. The launch of LiverTox and other online hepatotoxicity resources has increased our awareness of DILI. In 2013, the first guidelines for the diagnosis and management of DILI, were offered by the Practice Parameters Committee of the American College of Gastroenterology, and along with the identification of risk factors and predictors of injury, novel mechanisms of injury, refined causality assessment tools, and targeted treatment options have come to define the current state of the art, however, gaps in our knowledge still undoubtedly remain.

Key words: Acute liver failure; Drug-induced liver injury; Hepatotoxicity; Acetaminophen toxicity; Cholestatic injury; Liver biopsy; Pharmacoepidemiology; Herbal-induced liver injury; Hy's law

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Core tip: Drug-induced liver injury has gained a great amount of interest in the past decade, raising the question of whether we know everything. Various global registries have been established and the first guidelines for diagnosis and management have come to define the...
Drug-induced liver injury (DILI) is a current hot topic for academics, clinicians, pharmaceutical companies and regulatory bodies, as seen by the increasing number of publications over the past fifteen years. Evidence to the fact is shown in the number of new monographs, revised chapters in textbooks, workshops and single-topic conferences specifically dedicated to DILI. When DILI was the subject of a specific PubMed search, 44738 items were found in the past 5 and a half years (2010 through 2016), a number more than double the total number of items related to DILI published in the preceding decade (2000-2009).

This extensive body of new information leads us to a question that will be the focus of this review. By investigating the current state of the art of DILI, focusing on the latest scientific findings, controversies and guidelines, this review will take a clinician's point of view and attempt to find an answer to the question: Do we know everything?

DILI: A BRIEF HISTORY

Iproniazid, cinchophen, and sulfonamides were amongst the first prototypical hepatotoxins to be identified, paving the way for future histological and clinical descriptions that followed the second world war. By the mid-1960s, hepatotoxic agents including halothane, isoniazid (INH), carbamazepine, phenytoin and alpha methyldopa were famously referred to by Popper et al45 as “penalties for progress”, and by the mid-1980s close to 1000 drugs were linked to hepatic injury. Even though much of this early work has remained the mainstay of diagnostic, and pathophysiologic principles even to this day, DILI remains a significant diagnostic challenge due to the fact that drugs can mirror acute and chronic hepatic diseases, and act through various mechanisms causing injury.

STATE OF THE ART OF DILI

Clinically, DILI ranges from asymptomatic transaminitis, acute or chronic hepatitis to acute liver failure (ALF) or fulminant hepatic failure, defined as sudden and life-threatening liver dysfunction leading to coagulopathy and hepatic encephalopathy within 26 wk of the onset of illness. Although severe DILI is rare clinically, drugs have become the overall leading cause of ALF in the United States and other western countries. In the United States, approximately 1600 to 2000 people per year develop ALF, with 30% of these patients receiving aggressive therapy including liver transplant. Acetaminophen (paracetamol) is the offending drug in 40%-50% of these cases, with a further 11%-12% of ALF cases being caused by herbal compounds and dietary supplements (HDS), equalling the frequency of ALF due to acute viral hepatitis and greater than that seen with all other individually identifiable causes. Indeed, due to this significant morbidity and mortality, DILI remains an important reason for drug withdrawal from the market, with most recent examples including, bromfenac and troglitazone. Due to the significant time and expense involved in bringing a novel drug to market, it should come as no surprise, that identification of potential toxicities early in the development process is paramount. However, compounds cannot be guaranteed to be totally free of the potential to cause harm and liver injury in predclinical stages of development, and as such, tremendous steps have been undertaken in regulatory science, so as to identify DILI in clinical and post-approval settings. The creation of the Evaluation of Drug-Induced Serious Hepatotoxicity plot, the “Rule-of-Two”, FDA Adverse Event Reporting System, the Sentinel projects, and Liver Toxicity Knowledge Base has empowered clinicians to detect and predict DILI as early and successfully as possible. Working in parallel at the bedside, new hepatotoxins have been uncovered including dronedarone, ipilimumab, and tolvaptan and our further understanding of known hepatotoxins including azithromycin, duloxetine, fluoroquinolones, statins, telithromycin, tyrosine kinase inhibitors and others, has broadened.

Additionally, the identification of risk factors, predictors and biomarkers of injury, and novel mechanisms of injury, along with refined causality assessment tools, and targeted treatment options of hepatotoxicity, have come to define the current state of the art.

GUIDELINES AND REGISTRIES

Cumulatively, the aforementioned advances have led to the recent publication of the first guidelines for the diagnosis and management of DILI, offered by the Practice Parameters Committee of the American College of Gastroenterology. The guidelines, as summarized in Table 1, provide key practical advice on all aspects and problems which may be faced in the work-up of a DILI case. This parallels the establishment of the United States DILI Network (US DILIN) in 2004, a prospective study with a database containing > 1200 patients with acute DILI caused by approximately 200

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agents other than acetaminophen, including HDS\(^{72,73}\). As of 2014, DILIN continued to publish analyses from the data in their registry, most notably defining clinical signatures of specific agents; chiefly, a new syndrome was identified to occur after a single intravenous dose of cefazolin, characterised by marked cholestasis and a self-limited moderate to severe clinical course, following a one to three week latency period\(^{74}\). Globally, numerous registries have been formed in the past decade, including those in Australia\(^{75}\), Spain\(^{76}\), Iceland\(^{77,78}\), India\(^{79}\), South Korea\(^{80}\), and Serbia\(^{81}\), amongst others\(^{82-84}\). In addition to DILIN and the other national databases, the United States National Institutes of Health and National Library of Medicine launched LiverTox\(^{85}\) (https://livertox.nlm.nih.gov/) in April 2012. This comprehensive, up-to-date, interactive online resource, with over 650 agents currently listed, projects to expand its role into a virtual textbook on hepatotoxicity\(^{71}\). In the light of these collective efforts, gaps in our knowledge still undoubtedly remain\(^{7,69}\).

**EPIDEMIOLOGICAL ISSUES**

One of the greatest challenges to furthering our understanding of the global epidemiology of DILI is the elusive nature of its clinical presentation. Illustration of the fact can be seen in several studies, which found that DILI is both under-recognized and under reported\(^{83,86-89}\). In one study\(^{86}\), around 50% of the suspected DILI cases investigated were found to be common hepatic disorders when assessed by specialists and DILI experts. In another study from France\(^{83}\), underreporting by clinicians untrained in the recognition of DILI was greater by a factor of 16, when compared to those specifically trained to identify cases.

The fact remains, that acute DILI is a relatively rare clinical entity, and as such, determining the exact incidence from individual drugs is arduous. The estimated incidence of non-acetaminophen-related DILI, reported from a population-based Icelandic study, was found to be 19.1 cases per 100000 inhabitants\(^{78}\), similar to the 13.9 per 100000 found more than ten years prior, in France\(^{83}\). A higher incidence was found in Spain in 2005, with 34.2 per 100000 inhabitants per year, and 16.6 per 1000000 inhabitants per year being serious life-threatening episodes\(^{76}\). In Great Britain, the estimated incidence per 100000 persons was 2.4 in 2004\(^{86}\), however more recent data is unavailable. In the United States, a retrospective cohort study determined an incidence rate of drug-induced ALF of 1.61 events per 1000000 person-years\(^{80}\). By using population-based epidemiological data within the paediatric population, the incidence of acute liver injury was found to be comparable to that of the adult population, with higher incidence in Italy, when compared to the Netherlands (73 and 21 per 100000, respectively)\(^{81}\). Antibiotics were the most frequent offending drugs in this study and others, as comprehensively discussed by Björnsson\(^{89}\), stating that amoxicillin-clavulanic acid and INH in particular, along with other antibiotics and antiepileptics are the most common agents linked to hepatotoxicity. If one takes into account data from the United States Acute Liver Failure Study Group, acetaminophen is the most common overall causative agent for ALF with 45.8%, followed by non-acetaminophen DILI with 11%\(^{19}\), and INH the leading cause of DILI thereafter with 18.8%\(^{20}\).

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**Table 1 Summary of drug-induced liver injury guidelines by the American College of Gastroenterology\(^{72,49}\)**

| Elements necessary for the diagnostic evaluation of DILI |
|------------------------------------------------------------------|
| Known duration of exposure                                      |
| Concomitant medications and diseases                           |
| Response to dechallenge (and rechallenge if performed)          |
| Presence or absence of symptoms, rash, eosinophilia            |

Performing sufficient exclusionary tests (viral serology, imaging, etc.) to reflect the injury pattern and acuteness of liver function tests (e.g., acute viral serology for A, B and C and autoimmune hepatitis when presenting with acute hepatoencephalopathy; routine testing for hepatitis E virus not recommended because of the problems with current commercial assays; Epstein-Barr virus, cytomegalovirus, and other viral serology if lymphadenopathy, atypical lymphocytosis present)

Sufficient time to determine clinical outcome - did the event resolve or become chronic?

Use of liver biopsy

Often not required if the acute injury resolves

Helpful in confirming clinical suspicion of DILI but rarely pathognomonic

Useful to differentiate between Drug-Induced autoimmune hepatitis and idiopathic autoimmune hepatitis

Useful to rule out underlying chronic viral hepatitis, non-alcoholic fatty liver disease, alcoholic liver disease, or other chronic liver disease

Used to exclude DILI where re-exposure or ongoing use of an agent is expected

Rechallenge: Generally best avoided, unless there is no alternative treatment

Use of Causality Assessment Methods

Roussel Uclaf Causality Assessment Method is best considered an adjunct to expert opinion (it should not be the sole diagnostic method)

Consensus opinion

Expert consultation

For patients with chronic viral hepatitis, DILI requires a high index of suspicion, knowledge of a stable clinical course before the new medication, and monitoring of viral loads to rule out flares of the underlying disease

Assigning causality to herbal compounds and dietary supplements can be especially difficult; require knowledge of all ingredients and their purity

DILI: Drug-induced liver injury.
These findings come from large cohorts, however the vast majority of DILI research comes in the form of numerous case reports identifying novel hepatotoxic agents; the most recent example from 2016, being hepatotoxicity in HIV/HCV infected patients receiving ledipasvir/sofosbuvir with or without ribavirin.\(^{92,93}\)

Herbal pose yet another obstacle to our understanding of the epidemiology of DILI. Currently, the absence of regulatory guidelines for the production and sale of herbal compounds, means that the calculation of the true incidence of herbal-induced liver injury (HILI) becomes very difficult. Evidence is emerging from Asia, in particular China, where in a cohort of 21789 patients with DILI found that alternative medicines were one of the two most common etiologies reported.\(^{94}\) It is estimated that 15% of DILI cases may be attributed to herbs and other traditional Chinese medicines.\(^{95}\)

In South Korea, DILI incidence was 12 per 100000 persons, with 70% due to herbal and folk remedies.\(^{96,97}\) According to the DILIN registry, HDS were responsible for DILI in 16% of cases, second only to antimicrobials.\(^{72}\) What is potentially worrying is that patients with chronic liver disease (CLD) have been increasingly using HDS,\(^{97}\) leading to an increase in safety alerts from the FDA and other regulatory bodies.\(^{93,73}\) The most recent HDS to receive hepatotoxicity warning labels were the muscle building, fat burning product OxyELITE Pro\(^ {97}\) (USP Labs LLC, Dallas, Texas) and the weight loss supplement Herbalife\(^ {98}\). Other causes of HILI include anabolic steroids, black cohosh, green tea, Hydroxycut (Iovate Health Sciences Inc, Oakville, Ontario, Canada), and kava\(^ {99}\), and therefore HDS should also be on one’s mind in any case of suspected liver injury.

**DEFINING, RECOGNISING AND PREDICTING DILI**

At this stage, it may be helpful to remind one that DILI is initially defined as either intrinsic (predictable, dose-dependent) or idiosyncratic (unpredictable and non-dose dependent). By far the most common intrinsic cause of DILI is acetaminophen.\(^ {100}\) Twenty billion doses of non-prescription acetaminophen are sold annually in the United States, with $87 million dollars spent treating complications of overdose.\(^ {100,101}\) The intrinsic nature of acetaminophen hepatotoxicity stems from the production of N-acetyl-p-benzoquinone imine; excessive accumulation of this reactive metabolite leads to a depletion of intracellular glutathione, in turn leading to zone 3 centrilobular necrosis of the hepatocytes.\(^ {102,103}\) This predictable course of acetaminophen toxicity led to the introduction of N-acetylcysteine (NAC) as an antidote in 1977,\(^ {104}\) remaining the drug of choice for overdose treatment today.\(^ {100}\)

The mechanisms of idiosyncratic DILI on the other hand, have a far more complex nature and are the focus of the majority of current research. Broadly speaking they may be divided into two categories, hypersensitivity-type reactions (also known as immunologic), and metabolic types of injuries.\(^ {105}\) Hypersensitivity-type reactions, occurring due to reactive metabolites covalently binding proteins, forming drug-protein adducts, and thus triggering immune-mediated reactions or direct hepatic toxicity,\(^ {12}\) account for 23%-37% of all idiosyncratic DILI cases.\(^ {106}\) In addition, lipophilicity combined with dose, also known as the “rule-of-two,”\(^ {27,28}\) is known to enhance the risk of developing DILI, due to increased blood uptake into hepatocytes, forming greater amounts of reactive metabolites and subsequently interacting with hepatocanaliculare transport and mitochondrial membranes.\(^ {12}\) As such, metabolic mechanisms include oxidative stress, mitochondrial liability and inhibition of hepatobiliary transporters.\(^ {12}\) In the case of INH induced DILI, hepatocellular injury may result from the creation of covalent drug-protein adducts, leading to hapten formation and an immune response, and/or through direct mitochondrial injury by INH or its metabolites, leading to mitochondrial oxidant stress and energy homeostasis impairment.\(^ {54}\) If such mitochondrial deficiencies are already present, even non-toxic concentrations of INH, may trigger marked hepatocellular injury, due to underlying impairment of complex I function.\(^ {54}\) Other examples of mitochondrial injury include: Impaired beta-oxidation, and mitochondrial respiration, membrane disruption and mtDNA damage, usually caused by tamoxifen, valproic acid, diclofenac and tacrine, respectively.\(^ {12}\)

Indeed, hundreds of offending drugs have been identified thus far, with the list constantly growing. However, according to the DILIN registry,\(^ {72}\) the top 10 drugs account for greater than one-third of all idiosyncratic DILI cases. The most common causative agents and drug classes, according to various registries, are summarized in Table 2. The lists are rather heterogenic, however, antibiotics amoxicillin-clavulanate and INH top most registries as individual agents. Unsurprisingly, antibiotic agents top the list of severe and often fatal DILI in India, where acetaminophen use is rare and tuberculosis is prevalent.\(^ {79}\) Of the drug classes, antibiotics are the most common agents amongst the registries investigated with the exceptions of Spain and Sweden, where “other” drugs are most common with 44% and 69%, respectively. Collectively, these data illustrate that DILI cases and the drugs responsible vary from country to country, based on the overall prevalence of certain diseases within each healthcare system.

Due to the large number of different causative agents, further division of idiosyncratic DILI is classically determined on three biochemical patterns of liver injury: Hepatocellular, cholestatic and mixed, and based on the ratio of alanine aminotransferase (ALT) to alkaline phosphatase (ALP) defined as an R value (Table 3). The prognosis of each case is greatly dependant on which pattern of injury has occurred, and although bilirubin is not incorporated into the R value, it remains a central prognostic marker in calculating the Model for End-Stage Liver Disease score along with defining Hy’s law.\(^ {27}\)
The cornerstone of any liver assessment rests on ALT and aspartate aminotransferase (AST) elevations indicating hepatocellular injury, however in the case of DILI, these indicators are neither sensitive nor specific and cannot predict the pattern of injury because they are elevated after injury has already occurred. This brings into question the role of liver biopsy. The United States DILIN has recognized 18 distinct histological categories of damage: Acute hepatitis, chronic hepatitis, acute cholestatic, chronic cholestatic, cholestatic-hepatic, granulomatous, macrovesicular steatotic, microvesicular steatotic, steatohepatitic, zonal necrosis, nonzonal necrosis, vascular injury, hepatocellular alteration, nodular regenerative hyperplasia, mixed or unclassified injury, minimal nonspecific changes, absolutely normal, and massive necrosis. The most common of these are acute and chronic hepatitis, acute and chronic cholestatic, and mixed hepatitis-cholestatic, and are most often associated with fluoroquinolones, nitrofurantoin, methylidopa, and amoxicillin-clavulanate, respectively. Although useful in narrowing the differential diagnosis to a specific drug or class, liver biopsy is not required for the clinical evaluation and diagnosis of idiosyncratic DILI, and is performed in less than half of suspected cases.

Table 2 The most common individual drugs and classes responsible for idiosyncratic drug-induced liver injury according to various Global Registries

| Drug classes (%) | Iceland (n = 96) | India (n = 313) | Spain (n = 446) | Sweden (n = 784) | United States DILIN (n = 899) |
|------------------|-----------------|----------------|----------------|-----------------|-----------------------------|
| Antibiotics      | 37              | 65             | 32             | 27              | 45.4                        |
| HDS              | 16              | 1.3            | 2              | NS              | 16.1                        |
| CNS              | 7               | 12             | 17             | 3               | 9.8                         |
| Hypolipidemic    | 3.1             | 1.6            | 5              | 1               | 3.7                         |
| Others           | 37              | 20             | 44             | 69              | 25.7                        |

United States DILIN: United States Drug-Induced Liver Injury Network; INH: Isoniazid; SMX: Sulfamethoxazole; TMP: Trimethoprim; TB: Tuberculosis; HDS: Herbal and dietary supplements; CNS: Central nervous system; NS: Not specified.

Calculation of R value
ALT/AST value divided by its ULN = fold elevation/fold elevation above ULN for alkaline phosphatase

Definitions
Hepatocellular injury = R > 5
Cholestatic injury = R < 2
Mixed injury = R > 2 < 5

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ULN: Upper limit of normal.

Table 3 R values

The most common patterns of DILI are neither pathognomonic nor do they perfectly correlate with the biochemical patterns. Indeed, biochemical parameters underestimate the degree of cholestasis and bile duct injury, and although hepatocellular damage correlates better, the mixed biochemical pattern overestimates the degree of cholestasis compared to hepatocellular damage. With this in mind, according to the first guidelines for DILI diagnosis and management, liver biopsy is integral in differentiating drug-induced autoimmune hepatitis (DI-AIH) from idiopathic autoimmune hepatitis (AIH) (Table 1). Histopathological evidence of portal neutrophils, and intracellular cholestasis, favours the diagnosis of DI-AIH over AIH, and therefore one may employ biopsy in such cases.

The clinician is therefore left with their experience and knowledge of mimickers of DILI, when distinguishing between drug and non-drug causes of hepatic injury. Employing R values and the absolute height of liver enzymes are helpful in ruling DILI in or out. In the latest DILIN series, the mean values of ALT were 825 IU/L overall, approximately 20 × the upper limit of normal (ULN), with mean peaks of 1510 IU/L. For cholestatic DILI the mean peak of ALP was 682 IU/L (6 × ULN). For idiosyncratic drug-induced ALF the median peak values of ALT were around 500 IU/L, incomparable with the record elevations seen in acetaminophen injury. Simply put, for values of ALT or AST > 7500 IU/L, the differential diagnosis is essentially shock liver, toxic mushroom or other chemical poisoning, and acetaminophen overdose, and not idiosyncratic DILI. Similarly, the enzyme elevations of acute idiosyncratic DILI are different from those found in alcoholic liver disease. With our growing clinical expertise, newly identified viral causes, including hepatitis E virus (HEV), have made clear recognition even more arduous. Mimicry by HEV should therefore be on the clinician’s mind when forming a differential diagnosis...
of DILI\cite{7,100}.

As early as 1978, Hyman Zimmerman stated that drugs causing acute hepatocellular injury with jaundice were associated with a case-fatality rate of 10% or higher\cite{7,110}, a statement that was termed “Hy’s Law” by Robert Temple at the FDA\cite{7,110}. The current, modified definition of Hy’s Law\cite{7,5,110,111} consists of ALT/AST > 3 × ULN in addition to total bilirubin > 2 × ULN in the absence of cholestatic injury (ALP < 2 × ULN), with no other identifiable cause\cite{69,111}. Of such importance is this law that it remains a key element in determining whether DILI is present or not, and may in fact be the sole reason for abandonment of a drug’s development\cite{112}.

BIOMARKERS

In the light of such difficulty in distinguishing DILI from other causes of hepatic injury, researchers have begun investigating potential biomarkers in an attempt at earlier identification\cite{113}. Many possible genetic associations between individual human leukocyte antigens and the potential for DILI have been explored\cite{114-116,113}, however no definitive biomarker has yet been found. Of promise, are microRNAs, cytokeratin-18, and high mobility group box protein 1\cite{113}.

DIAGNOSING, AND ESTABLISHING CAUSALITY

So, with no particularly sensitive or specific biomarker, and little use of liver biopsy, DILI essentially remains a diagnosis of exclusion\cite{49,69,107}. Recognising the clinical picture of DILI is therefore paramount\cite{6,117} (Table 4). With such diverse presentation and because many individual cases of DILI are presented as case reports or case series, it is essential for the clinician to establish solid causality when suspecting DILI. Nearly 25 years ago, an international meeting of hepatologists convened in an attempt to create an objective causality assessment tool for DILI\cite{7,105}. Although not quite user-friendly, the Roussel Uclaf Causality Assessment Method (RUCAM) remains in widespread use today\cite{60}. It is based on expert consensus, and thus scoring requires extensive knowledge, and along with its many omissions, RUCAM is under much scrutiny in clinical practice, with a re-evaluation and revision far overdue\cite{60}. As such, it is not the only causality tool employed by the DILIN, which has created its own additional criteria based on expert opinion incorporated into RUCAM, as illustrated in Table 5\cite{59,118}. Even with more accurate causality tools, the clinical problems in diagnosing DILI in the setting of underlying CLD\cite{60,72}, malignancy\cite{119}, or congestive heart failure\cite{120} still rests heavily on physician’s expertise which cannot easily be substituted by scoring systems\cite{50,60}, a fact which is even more relevant in the face of HILI, because of the unknown and unregulated ingredients often incorporated into HDS\cite{73}, again indicating the need for future research in this field\cite{121}.

Table 4  Classic Clinical Syndromes of drug-induced liver injury and the drugs most commonly associated\cite{4,7,112}

| Acute viral hepatitis-like: e.g., INH: Absence of hypersensitivity symptoms; present with malaise, fatigue, anorexia, nausea, vomiting, right upper quadrant pain |
| Hypersensitivity syndrome: Fever, rash, and/or eosinophilia seen in 25%-30% of DILI cases, usually with short latency and prompt rechallenge response (e.g., amoxicillin-clavulanate, phenytoin, carbamazepine, SMX-TMP, halothane) |
| Sulfone syndrome: e.g., dapsone, fever, exfoliative dermatitis, lymphadenopathy, atypical lymphocytosis, eosinophilia, hemolytic anemia, methemoglobinemia |
| Pseudomononucleosis syndrome: e.g., phenytoin, dapsone, sulfonamides: Hypersensitivity syndrome with atypical lymphocytosis, lymphadenopathy, and splenomegaly |
| DILI associated with severe skin injury: Stevens-Johnson syndrome, toxic epidermal necrolysis, e.g., beta-lactam antibiotics, allopurinol, carbamazepine |
| Autoimmune hepatitis associated with positive autoantibodies: e.g., nitrofurantoin, minocycline, methyldopa |
| Immune-mediated colitis with autoimmune hepatitis: e.g., ipilimumab |
| Acute cholecystitis-like: e.g., erythromycin estolate |
| Reye syndrome-like: e.g., valproic acid: Hepatocellular injury, acidosis, hyperammonemia, encephalopathy, abdominal pain, nausea, vomiting, paradoxical worsening of seizure activity, microvesicular steatosis on biopsy |

INH: Isoniazid; SMX: Sulfamethoxazole; TMP: Trimethoprim; DILI: Drug-induced liver injury.
defined as increased DILI risk with higher lipophilicity and drug dose or greater degrees of hepatic metabolism\(^{27,28}\), is a known risk factor. It accurately predicted liver injury in 14 of 15 drugs withdrawn due to hepatotoxicity, with a warning affixed to the final drug, and successfully predicted hepatotoxicity in multidrug regimens\(^{27}\). In spite of this success, upon multivariate logistic regression analysis, high lipophilicity was not a significant factor\(^{27}\), suggesting a redefinition may be necessary.

If a drug causes acute DILI, it is generally accepted that discontinuation will lead to a resolution of any injury within a few weeks\(^{125}\), and this is definitely true for hepatocellular injury\(^{26,126}\). In the case of cholestatic injury, often caused by antimicrobials, this process of resolution may take months, and can even persist after drug discontinuation\(^{126}\); in fact mimicry of primary biliary cholangitis and the development of portal hypertension has occurred\(^{127}\). Chronically administered drugs such as methyldopa, minocycline and nitrofurantoin have been associated with an insidious and self-limiting autoimmune hepatitis, which resolves after discontinuation of the offender\(^{128}\). As such, the United States DILIN follows patients for a minimum of 6 mo after any case of DILI\(^{72}\). However, as of August 2016, Medina-Caliz et al\(^{129}\) on behalf of the Spanish DILI registry, defined a new cut-off for chronic DILI of 1 year, suggesting that ALP and total bilirubin measurements in the second month after acute injury may help predict chronicity. Furthermore, statins were implicated as distinctly related to chronicity\(^{129}\). Therefore, it is prudent to consider acute DILI transforming into chronic DILI in certain patients.

### PREVENTION AND TREATMENT OPTIONS

The saying goes, the best treatment is prevention, and in the case of DILI this sentiment holds true. Liver injury may be caused by most drugs, and labels often carry a warning to lower the dose in the setting of CLD\(^{124}\). However, there is little evidence to support this reducing the risk for DILI\(^{130}\). As such, liver enzyme monitoring has been proposed as an option in all drugs with a high risk of hepatotoxicity\(^{131}\). An example is bosentan, however, even after stringent risk evaluation, adherence remained an issue\(^{132}\), and therefore, testing for CYP2C9 prior to administration may prove effective\(^{133}\). Similarly, statins were recommended to be followed with regular enzyme monitoring based on animal toxicity\(^{134}\), however again compliance was sub-optimal\(^{135}\) and hence, ALT monitoring was dropped by the FDA\(^{134}\). Nevertheless, in CLD patients ALT monitoring of patients receiving statins in the first months is sensible, given the fact that potential benefits may outweigh risks\(^{134}\). The fact that INH remains a major cause of DILI and drug-induced ALF, illustrates that monitoring is not as effective as one would hope\(^{79}\). Whether ALT finger stick testing, such as in the case of glucose, could become a global standard practice and positively influence monitoring regimens, remains to be answered in the not too distant future\(^{136,137}\).

A rather controversial issue is that of desensitization-rechallenge. Generally it is discouraged\(^{69,131}\) for fear of an even more severe reaction or ALF, and death\(^{138}\). Nevertheless, for life-threatening diseases including active tuberculosis where no other therapy is adequate, rechallenge has been successfully carried out\(^{139}\). Studies investigating the effects of switching drugs within one class or between different classes with similar effects are sparse\(^{97}\), yet drug substitutions have been reported with non-esterolate salts of erythromycin\(^{127}\), statins\(^{140}\), and thiazolidinediones\(^{141}\). Albeit more likely to cause liver injury, cephalosporins are good substitutes for penicillin\(^{142}\), though it should go without saying that if the benefits do not outweigh the risks, desensitization-rechallenge ought to be avoided.

Even though our ability to detect, diagnose and prevent acute idiosyncratic DILI has had many advances, treatment has largely remained unchanged, with removal of the offending drug as soon as possible being the only undisputable option\(^{69,131}\). This may at times place the patient at risk for not receiving efficacious and essential medications, and hence, alternatives and adjuvants to the removal of responsible agents have been investigated. Circumstantial success has been achieved in some patients with cholestatic DILI with the use of ursodesoxycholic acid and steroids\(^{166}\), however a targeted treatment for hepatocellular idiosyncratic DILI remains to be found. In the case of intrinsic DILI, acetaminophen overdose is and has been prevented and managed with NAC for decades\(^{100,104,143}\) with the identification of patients at high risk for anaphylactoid reactions to NAC being essential for optimal treatment\(^{144}\). For non-acetaminophen drug-induced ALF, NAC has been shown to be of benefit in adults in the early stages of disease, however, once liver coma sets in, the use of NAC is futile\(^{167}\), and it is virtually useless in children with ALF\(^{68}\). Other treatments have shown some benefits for specific agents including: Folic acid in the case of methotrexate toxicity\(^{145}\), carnitine supplementation in children for

| Causal relationship | Percentage of likelihood | Definition |
|---------------------|--------------------------|------------|
| Unlikely            | < 25                     | Clear evidence that an etiology other than the drug is responsible |
| Possible            | 25-49                    | Evidence for the drug is present but equivocal |
| Probable            | 50-75                    | Preponderance of the evidence links the drug to the injury |
| Highly likely       | 75-95                    | Evidence for the drug causing injury is clear and convincing but not definite |
| Definite            | < 95                     | Evidence of the drug being causal is beyond any reasonable doubt |

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Table 5 Drug-induced liver injury network scoring criteria\(^{[29,118]}\)

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valproic acid related liver injury\cite{137}, and increasing hepatic clearance with an enterohepatic washout regimen of cholestryamine for leflunamide associated injury\cite{137}. Plasma exchange and bioartificial liver assist devices such as molecular absorbant recirculating systems have proven to successfully bridge certain patients to liver transplant, which remains the best therapy for irreversible ALF\cite{20,64,65,148}. The search for novel treatment options broadly ranges from the use of nanotechnology to deliver hepatoprotective agents directly to the liver\cite{63} to the humble milk thistle\cite{149}. So one can see that apart from some anecdotal treatment options and of course removal of the offender, we are mostly along in the dark and in need of further advances.

CONCLUSION

Our knowledge of DILI has come a long way in the past 60 years. We have an extensive amount of knowledge about which drugs are responsible and how to detect them, our understanding of the various mechanisms involved is constantly expanding, and we are identifying which patients are most at risk, however our knowledge is far from complete. In keeping with our oath, Primum non nocere, the quintessential question should not be “do we know everything?”, but rather: do we know enough to successfully prevent, accurately diagnose, and safely treat all of our patients.

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