World Journal of Hepatology

Submit a Manuscript: http://www.f6publishing.com

World J Hepatol 2017 April 8; 9(10): 491-502

DOI: 10.4254/wjh.v9.i10.491

ISSN 1948-5182 (online)

REVIEW

Drug-induced liver injury: Do we know everything?

Tamara Alempijevic, Simon Zec, Tomica Milosavljevic

Tamara Alempijevic, Simon Zec, Tomica Milosavljevic, University of Belgrade, School of Medicine, 11000 Belgrade, Serbia

Tamara Alempijevic, Tomica Milosavljevic, Clinical Center of Serbia, Clinic for Gastroenterology and Hepatology, 11000 Belgrade, Serbia

Author contributions: All authors contributed equally to the conception, design, literature review, drafting, editing and critical revision of the final manuscript; as a native English speaker, Zec S also provided additional English language polishing.

Conflict-of-interest statement: Authors declare no potential conflicts of interest and no financial support.

Manuscript source: Invited manuscript

Correspondence to: Tamara Alempijevic, MD, PhD, Professor, University of Belgrade, School of Medicine, 2 Dr Koste Todorovica Street, 11000 Belgrade, Serbia. tamara.alempijevic@med.bg.ac.rs
Telephone: +381-11-3628582
Fax: +381-11-3628582

Received: August 25, 2016
Peer-review started: August 26, 2016
First decision: November 11, 2016
Revised: February 28, 2017
Accepted: March 14, 2017
Article in press: March 17, 2017
Published online: April 8, 2017

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 to date, 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 causes 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; Hepatoxicity; Acetaminophen toxicity; Cholestatic injury; Liver biopsy; Pharmacoepidemiology; Herbal-induced liver injury; Hy's law

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

state of the art. The identification of risk factors and predictors of injury, novel mechanisms of injury, refined causality assessment tools, and targeted treatment options have amplified our understanding of the impact of drug-induced liver injury, however gaps in our knowledge still remain.

Alempijevic T, Zec S, Milosavljevic T. Drug-induced liver injury: Do we know everything? *World J Hepatol* 2017; 9(10): 491-502 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i10/491.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i10.491

INTRODUCTION

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[1-5]. 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[6,7]. By the mid-1960s, hepatotoxic agents including halothane, isoniazid (INH), carbamazepine, phenytoin and alpha methyldopa were famously referred to by Popper *et al*[8] as "penalties for progress", and by the mid-1980s close to 1000 drugs were linked to hepatic injury[9]. Even though much of this early work[6,8] 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[10-15].

STATE OF THE ART OF DILI

Clinically, DILI ranges from asymptomatic transaminitis, acute or chronic hepatitis[16] 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[17]. Although severe DILI is rare clinically, drugs have become the overall leading overall cause of ALF in the United States and other western countries[7]. In the United States, approximately 1600 to 2000 people per year develop ALF, with 30% of these patients receiving aggressive therapy including liver transplant[18]. 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[7,19,20]. 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[21]. 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[22]. However, compounds cannot be guaranteed to be totally free of the potential to cause harm and liver injury in preclinical 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[23-25]. The creation of the Evaluation of Drug-Induced Serious Hepatotoxicity plot[26], the "Rule-of-Two"[27,28], FDA Adverse Event Reporting System[29], the Sentinel projects[30], and Liver Toxicity Knowledge Base[31] 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[32], ipilimumab[33,34], and tolvaptan[35,36] and our further understanding of known hepatotoxins including azithromycin[37], duloxetine[38], fluoroquinolones[39], statins[40], telithromycin[41], tyrosine kinase inhibitors[42] and others[43], has broadened.

Additionally, the identification of risk factors, predictors and biomarkers of injury[44-52], and novel mechanisms of injury[53-58], along with refined causality assessment tools[59-61], and targeted treatment options of hepatotoxicity[62-68], 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[69]. 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[70,71], a prospective study with a database containing > 1200 patients with acute DILI caused by approximately 200

Table 1 Summary of drug-induced liver injury guidelines by the American College of Gastroenterology[7,69]

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 hepatocellular injury; 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.

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[7]. In the light of these collective efforts, gaps in our knowledge still undoubtedly remain[2,4,11].

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 1000000 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[90]. 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)[91]. 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].

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].

Herbals 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[80,96]. 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[43,73]. 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[19]. 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[10]. 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[10]. 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 hepatocanalicular 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, antituberculous 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[105] (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[7].

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

	Iceland[78], *n* = 96	India[79], *n* = 313	Spain[76], *n* = 446	Sweden[77], *n* = 784	United States DILIN[72], *n* = 899
Individual drugs (%)					
	Amoxicillin-clavulanate 22.9	INH + anti-TB 57.8	Amoxicillin-clavulanate 13.2	Flucloxacillin 16.5	Amoxicillin-clavulanate 10%
	Diclofenac 6.3	Phenytoin 6.7	INH + anti-TB 6.9	Erythromycin 5.4	INH 5.3%
	Nitrofurantoin 4.2	Dapsone 5.4	Ebrotidine 4.9	Disulfiram 3.4	Nitrofurantoin 4.7%
	Infliximab 4.2	Olanzapine 5.4	Ibuprofen 4	TMP-SMX 2.7	SMX-TMP 3.4%
	Azathioprine 4.2	Carbamazine 2.9	Flutamide 3.8	Diclofenac 2.6	Minocycline 3.1%
	Isotretinoin 3.1	Cotrimoxazole 2.2	Ticlopidine 2.9	Carbamazepine 2.2	Cefazolin 2.2%
	Atorvastatin 2.1	Atorvastatin 1.6	Diclofenac 2.7	Halothane 1.9	Azithromycin 2%
	Doxycycline 2.1	Leflunamide 1.3	Nimesulide 2	Naproxen 1.4	Ciprofloxacin 1.8%
		Ayurvedic 1.3	Carbamazepine 1.8	Ranitidine 1.3	Levofloxacin 1.4%
Drug classes (%)					
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.

Table 3 *R* values[105]

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

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[22,105,106]. 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-hepatitic, 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[107-109]. The most common of these are acute and chronic hepatitic, acute and chronic cholestatic, and mixed hepatitis-cholestatic[107], and are most often associated with fluoroquinolones, nitrofurantoin, methyldopa, and amoxicillin-clavulanate, respectively[10]. 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[76]. Testament to this reasoning is the fact that the histological patterns of DILI are neither pathognomonic nor do they perfectly correlate with the biochemical patterns[10,107]. Indeed, biochemical parameters underestimate the degree of cholestasis and bile duct injury[107], and although hepatocellular damage correlates better, the mixed biochemical pattern overestimates the degree of cholestasis compared to hepatocellular damage[107]. With this in mind, according to the first guidelines for DILI diagnosis and management[69], 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[7,69], 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[72]. For cholestatic DILI the mean peak of ALP was 682 IU/L (6 × ULN)[72]. For idiosyncratic drug-induced ALF the median peak values of ALT were around 500 IU/L[19], incomparable with the record elevations seen in acetaminophen injury[6]. 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[6]. Similarly, the enzyme elevations of acute idiosyncratic DILI are different from those found in alcoholic liver disease[6,7]. With our growing clinical expertise, newly identified viral causes, including hepatitis E virus (HEV), have made clear recognition even more arduous[7]. Mimicry by HEV should therefore be on the clinician's mind when forming a differential diagnosis

Table 4 Classic Clinical Syndromes of drug-induced liver injury and the drugs most commonly associated[6,7,117]

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.

of DILI[7,60].

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[7,110], a statement that was termed "Hy's Law" by Robert Temple at the FDA[7,110]. The current, modified definition of Hy's Law[35,110,111] consists of ALT/AST > 3 × ULN in addition to total bilirubin > 2x ULN in the absence of cholestatic injury (ALP < 2 × ULN), with no other identifiable cause[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[112].

BIOMARKERS

In the light of such difficultly in distinguishing DILI from other causes of hepatic injury, researchers have begun investigating potential biomarkers in an attempt at earlier identification[113]. Many possible genetic associations between individual human leukocyte antigens and the potential for DILI have been explored[114-116], however no definitive biomarker has yet been found. Of promise, are microRNAs, cytokeratin-18, and high mobility group box protein 1[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[49,69,107]. Recognising the clinical picture of DILI is therefore paramount[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[7,105]. Although not quite user-friendly, the Roussel Uclaf Causality Assessment Method (RUCAM) remains in widespread use today[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[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[59,118]. Even with more accurate causality tools, the clinical problems in diagnosing DILI in the setting of underlying CLD[69,72], malignancy[119], or congestive heart failure[120] still rests heavily on physician's expertise which cannot easily be substituted by scoring systems[60,69]; a fact which is even more relevant in the face of HILI, because of the unknown and unregulated ingredients often incorporated into HDS[73], again indicating the need for future research in this field[121].

RISK FACTORS AND NATURAL PROGRESSION OF DILI

With the difficulty of establishing diagnosis and causality, an important point to remember is who is at the greatest risk for DILI. The exact pathogenesis of idiosyncratic DILI and HILI is poorly understood, and the risk factors arise from three diverse aspects: (1) clinical host-related; (2) environmental; and (3) drug-related. Non-modifiable risk factors include age and gender[122]; however one must remember discrepancies in DILI reporting when citing one particular age or gender at greatest risk, for example, males have been indicated as high risk patients for DILI associated with systemic antivirals, whereas liver injury and ALF has been reported with higher frequency in children[81,123]. In any case, females have been predominately identified in many registries[71,76-79]. As mentioned above, much research has focused on genome-wide studies[114-116,124], and this is an area where we should be focusing our future attention. Environmental factors are poorly understood, with no definitive studies linking diet, or alcohol and coffee consumption to increased DILI risk, again illustrating a need for answers. The "Rule-of-Two",

Table 5 Drug-induced liver injury network scoring criteria[59,118]

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

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[7]. 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[76,126]. 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-limited 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[7], yet drug substitutions have been reported with non-estolate 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[6,43,69,125]. 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[66], 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[67]; 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

valproic acid related liver injury[146], and increasing hepatic clearance with an enterohepatic washout regimen of cholestyramine for leflunamide associated injury[147]. Plasma exchange and bioartifical liver assist devices such as moleculer absorbant recirculating systems have proven to successfully bridge certain patients to liver transplant, which remains the best therapy for irreversible ALF[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[63], to the humble milk thistle[149]. So one can see that apart from some anecdotal treatment options and of course removal of the offender, we are mostly alone 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.

REFERENCES

1 **Pyrosopoulos NT**, ed. Drug hepatotoxicity. *Clin Liver Dis* 2013; **17**: 507-786
2 **Chalasani N**, Hayashi PH. Slow but steady progress in a field with many knowledge gaps. *Semin Liver Dis* 2014; **34**: 113-114 [PMID: 24879976 DOI: 10.1055/s-0034-1375952]
3 **Kaplowitz N**, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. London: Elsevier/Academic Press, 2013
4 **Watkins PB**, Merz M, Avigan MI, Kaplowitz N, Regev A, Senior JR. The clinical liver safety assessment best practices workshop: rationale, goals, accomplishments and the future. *Drug Saf* 2014; **37** Suppl 1: S1-S7 [PMID: 25352323 DOI: 10.1007/s40264-014-0181-8]
5 **Senior J**, Watkins P, Avigan M, Pauls L. Drug-induced liver injury (DILI) conference XV: the importance of getting it right. [accessed 2016 Aug 17]. Available from: URL: https://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/ucm071471.htm
6 **Zimmerman HJ**. Hepatotoxocity: the adverse effects of drugsand other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, William & Wilkins, 1999
7 **Lewis JH**. The Art and Science of Diagnosing and Managing Drug-induced Liver Injury in 2015 and Beyond. *Clin Gastroenterol Hepatol* 2015; **13**: 2173-2189.e8 [PMID: 26116527 DOI: 10.1016/j.cgh.2015.06.017]
8 **Popper H**, Rubin E, Cardiol D, Schaffner F, Paronetto F. Drug-Induced Liver Disease: A penalty for progress. *Arch Intern Med* 1965; **115**: 128-136 [PMID: 14331990 DOI: 10.1001/archinte.1965.03860140008003]
9 **Stricker BHC**, Spoelstra P. Drug-induced hepatic injury. Amsterdam: Elsevier, 1985
10 **Fisher K**, Vuppalanchi R, Saxena R. Drug-Induced Liver Injury. *Arch Pathol Lab Med* 2015; **139**: 876-887 [PMID: 26125428 DOI: 10.5858/arpa.2014-0214-RA]
11 **Lewis JH**, Kleiner DE. Hepatic injury due to drugs, herbal compounds, chemicals and toxins. In: Burt AD, Portmann BC, Ferrell LD, eds. MacSween's pathology of the liver. 6th ed. Edinburgh: Churchill Livingstone, 2012: 645-760 [DOI: 10.1016/B978-0-7020-3398-8.00013-1]
12 **Chen M**, Suzuki A, Borlak J, Andrade RJ, Lucena MI. Drug-induced liver injury: Interactions between drug properties and host factors. *J Hepatol* 2015; **63**: 503-514 [PMID: 25912521 DOI: 10.1016/j.jhep.2015.04.016]
13 **Luedde T**, Kaplowitz N, Schwabe RF. Cell death and cell death responses in liver disease: mechanisms and clinical relevance. *Gastroenterology* 2014; **147**: 765-783.e4 [PMID: 25046161 DOI: 10.1053/j.gastro.2014.07.018]
14 **Tujios S**, Fontana RJ. Mechanisms of drug-induced liver injury: from bedside to bench. *Nat Rev Gastroenterol Hepatol* 2011; **8**: 202-211 [PMID: 21386809 DOI: 10.1038/nrgastro.2011.22]
15 **Stephens C**, Andrade RJ, Lucena MI. Mechanisms of drug-induced liver injury. *Curr Opin Allergy Clin Immunol* 2014; **14**: 286-292 [PMID: 24915546 DOI: 10.1097/ACI.0000000000000070]
16 **Mayoral W**, Lewis JH, Zimmerman H. Drug-induced liver disease. *Curr Opin Gastroenterol* 1999; **15**: 208-216 [PMID: 17023947 DOI: 10.1097/00001574-199905000-00005]
17 **O'Grady JG**, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. *Lancet* 1993; **342**: 273-275 [PMID: 8101303 DOI: 10.1016/0140-6736(93)91818-7]
18 **Ostapowicz G**, Fontana RJ, Schiødt FV, Larson A, Davern TJ, Han SH, McCashland TM, Shakil AO, Hay JE, Hynan L, Crippin JS, Blei AT, Samuel G, Reisch J, Lee WM. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med* 2002; **137**: 947-954 [PMID: 12484709 DOI: 10.7326/0003-4819-137-12-200212170-00007]
19 **Lee WM**. Drug-induced acute liver failure. *Clin Liver Dis* 2013; **17**: 575-586, viii [PMID: 24099019 DOI: 10.1016/j.cld.2013.07.001]
20 **Reuben A**, Koch DG, Lee WM. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. *Hepatology* 2010; **52**: 2065-2076 [PMID: 20949552 DOI: 10.1002/hep.23937]
21 **Holt MP**, Ju C. Mechanisms of drug-induced liver injury. *AAPS J* 2006; **8**: E48-E54 [DOI: 10.1208/aapsj080106]
22 **Lewis JH**. Drug-induced liver injury throughout the drug development life cycle: where we have been, where we are now and where we are headed - perspectives of a clinical hepatologist. *Pharm Med* 2013; **27**: 165-191 [DOI: 10.1007/s40290-013-0015-5]
23 **Avigan MI**. DILI and drug development: a regulatory perspective. *Semin Liver Dis* 2014; **34**: 215-226 [PMID: 24879985 DOI: 10.1055/s-0034-1375961]
24 **Regev A**. Drug-induced liver injury and drug development: industry perspective. *Semin Liver Dis* 2014; **34**: 227-239 [PMID: 24879986 DOI: 10.1055/s-0034-1375962]
25 **Senior JR**. Evolution of the Food and Drug Administration approach to liver safety assessment for new drugs: current status and challenges. *Drug Saf* 2014; **37** Suppl 1: S9-17 [PMID: 25352324 DOI: 10.1007/s40264-014-0182-7]
26 **Guo T**, Gelperin K, Senior JR. A tool to help you decide (detect potentially serious liver injury). [accessed 2016 Aug 11]. Available from: URL: https://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/ucm076777.pdf
27 **Chen M**, Borlak J, Tong W. High lipophilicity and high daily dose of oral medications are associated with significant risk for drug-induced liver injury. *Hepatology* 2013; **58**: 388-396 [PMID: 23258593 DOI: 10.1002/hep.26208]
28 **Chen M**, Tung CW, Shi Q, Guo L, Shi L, Fang H, Borlak J, Tong W. A testing strategy to predict risk for drug-induced liver injury in humans using high-content screen assays and the 'rule-of-two' model. *Arch Toxicol* 2014; **88**: 1439-1449 [PMID: 24958025 DOI: 10.1007/s00204-014-1276-9]
29 **Brinker AD**, Lyndly J, Tonning J, Moeny D, Levine JG, Avigan MI. Profiling cumulative proportional reporting ratios of drug-induced liver injury in the FDA Adverse Event Reporting System (FAERS) database. *Drug Saf* 2013; **36**: 1169-1178 [PMID: 24178291 DOI: 10.1007/s40264-013-0116-9]

30 **Behrman RE**, Benner JS, Brown JS, McClellan M, Woodcock J, Platt R. Developing the Sentinel System--a national resource for evidence development. *N Engl J Med* 2011; **364**: 498-499 [PMID: 21226658 DOI: 10.1056/NEJMp1014427]

31 **Chen M**, Zhang J, Wang Y, Liu Z, Kelly R, Zhou G, Fang H, Borlak J, Tong W. The liver toxicity knowledge base: a systems approach to a complex end point. *Clin Pharmacol Ther* 2013; **93**: 409-412 [PMID: 23486446 DOI: 10.1038/clpt.2013.16]

32 **Felser A**, Blum K, Lindinger PW, Bouitbir J, Krähenbühl S. Mechanisms of hepatocellular toxicity associated with dronedarone--a comparison to amiodarone. *Toxicol Sci* 2013; **131**: 480-490 [PMID: 23135547 DOI: 10.1093/toxsci/kfs298]

33 **Andrews S**, Holden R. Characteristics and management of immunerelated adverse effects associated with ipilimumab, a new immunotherapy for metastatic melanoma. *Cancer Manag Res* 2012; **4**: 299-307 [PMID: 23049279 DOI: 10.2147/CMAR.S31873]

34 **Kleiner DE**, Berman D. Pathologic changes in ipilimumab-related hepatitis in patients with metastatic melanoma. *Dig Dis Sci* 2012; **57**: 2233-2240 [PMID: 22434096 DOI: 10.1007/s10620-012-2140-5]

35 **Stine JG**, Lewis JH. Drug-induced liver injury: a summary of recent advances. *Expert Opin Drug Metab Toxicol* 2011; **7**: 875-890 [PMID: 21510822 DOI: 10.1517/17425255.2011.577415]

36 **Watkins PB**, Lewis JH, Kaplowitz N, Alpers DH, Blais JD, Smotzer DM, Krasa H, Ouyang J, Torres VE, Czerwiec FS, Zimmer CA. Clinical Pattern of Tolvaptan-Associated Liver Injury in Subjects with Autosomal Dominant Polycystic Kidney Disease: Analysis of Clinical Trials Database. *Drug Saf* 2015; **38**: 1103-1113 [PMID: 26188764 DOI: 10.1007/s40264-015-0327-3]

37 **Martinez MA**, Vuppalanchi R, Fontana RJ, Stolz A, Kleiner DE, Hayashi PH, Gu J, Hoofnagle JH, Chalasani N. Clinical and histologic features of azithromycin-induced liver injury. *Clin Gastroenterol Hepatol* 2015; **13**: 369-376.e3 [PMID: 25111234 DOI: 10.1016/j.cgh.2014.07.054]

38 **Vuppalanchi R**, Hayashi PH, Chalasani N, Fontana RJ, Bonkovsky H, Saxena R, Kleiner D, Hoofnagle JH. Duloxetine hepatotoxicity: a case-series from the drug-induced liver injury network. *Aliment Pharmacol Ther* 2010; **32**: 1174-1183 [PMID: 20815829 DOI: 10.1111/j.1365-2036.2010.04449.x]

39 **Orman ES**, Conjeevaram HS, Vuppalanchi R, Freston JW, Rochon J, Kleiner DE, Hayashi PH. Clinical and histopathologic features of fluoroquinolone-induced liver injury. *Clin Gastroenterol Hepatol* 2011; **9**: 517-523.e3 [PMID: 21356330 DOI: 10.1016/j.cgh.2011.02.019]

40 **Russo MW**, Hoofnagle JH, Gu J, Fontana RJ, Barnhart H, Kleiner DE, Chalasani N, Bonkovsky HL. Spectrum of statin hepatotoxicity: experience of the drug-induced liver injury network. *Hepatology* 2014; **60**: 679-686 [PMID: 24700436 DOI: 10.1002/hep.27157]

41 **Brinker AD**, Wassel RT, Lyndly J, Serrano J, Avigan M, Lee WM, Seeff LB. Telithromycin-associated hepatotoxicity: Clinical spectrum and causality assessment of 42 cases. *Hepatology* 2009; **49**: 250-257 [PMID: 19085949 DOI: 10.1002/hep.22620]

42 **Iacovelli R**, Palazzo A, Procopio G, Santoni M, Trenta P, De Benedetto A, Mezi S, Cortesi E. Incidence and relative risk of hepatic toxicity in patients treated with anti-angiogenic tyrosine kinase inhibitors for malignancy. *Br J Clin Pharmacol* 2014; **77**: 929-938 [PMID: 23981115 DOI: 10.1111/bcp.12231]

43 **Chalhoub WM**, Sliman KD, Arumuganathan M, Lewis JH. Drug-induced liver injury: what was new in 2013? *Expert Opin Drug Metab Toxicol* 2014; **10**: 959-980 [PMID: 24746272 DOI: 10.1517/17425255.2014.909408]

44 **Daly AK**, Day CP. Genetic association studies in drug-induced liver injury. *Drug Metab Rev* 2012; **44**: 116-126 [PMID: 21913872 DOI: 10.3109/03602532.2011.605790]

45 **Urban TJ**, Daly AK, Aithal GP. Genetic basis of drug-induced liver injury: present and future. *Semin Liver Dis* 2014; **34**: 123-133 [PMID: 24879978 DOI: 10.1055/s-0034-1375954]

46 **Chen R**, Zhang Y, Tang S, Lv X, Wu S, Sun F, Xia Y, Zhan SY. The association between HLA-DQB1 polymorphism and antituberculosis drug-induced liver injury: a Case-Control Study. *J Clin Pharm Ther* 2015; **40**: 110-115 [PMID: 25250564 DOI: 10.1111/jcpt.12211]

47 **Visschers RG**, Luyer MD, Schaap FG, Olde Damink SW, Soeters PB. The gut-liver axis. *Curr Opin Clin Nutr Metab Care* 2013; **16**: 576-581 [PMID: 23873346 DOI: 10.1097/MCO.0b013e32836410a4]

48 **Possamai LA**, McPhail MJ, Khamri W, Wu B, Concas D, Harrison M, Williams R, Cox RD, Cox IJ, Anstee QM, Thursz MR. The role of intestinal microbiota in murine models of acetaminophen-induced hepatotoxicity. *Liver Int* 2015; **35**: 764-773 [PMID: 25244648 DOI: 10.1111/liv.12689]

49 **Hawkins MT**, Lewis JH. Latest advances in predicting DILI in human subjects: focus on biomarkers. *Expert Opin Drug Metab Toxicol* 2012; **8**: 1521-1530 [PMID: 22998122 DOI: 10.1517/17425255.2012.724060]

50 **Bell LN**, Vuppalanchi R, Watkins PB, Bonkovsky HL, Serrano J, Fontana RJ, Wang M, Rochon J, Chalasani N. Serum proteomic profiling in patients with drug-induced liver injury. *Aliment Pharmacol Ther* 2012; **35**: 600-612 [PMID: 22403816 DOI: 10.1111/j.1365-2036.2011.04982.x]

51 **Steuerwald NM**, Foureau DM, Norton HJ, Zhou J, Parsons JC, Chalasani N, Fontana RJ, Watkins PB, Lee WM, Reddy KR, Stolz A, Talwalkar J, Davern T, Saha D, Bell LN, Barnhart H, Gu J, Serrano J, Bonkovsky HL. Profiles of serum cytokines in acute drug-induced liver injury and their prognostic significance. *PLoS One* 2013; **8**: e81974 [DOI: 10.1371/journal.pone.0081974]

52 **Welch MA**, Köck K, Urban TJ, Brouwer KL, Swaan PW. Toward predicting drug-induced liver injury: parallel computational approaches to identify multidrug resistance protein 4 and bile salt export pump inhibitors. *Drug Metab Dispos* 2015; **43**: 725-734 [PMID: 25735837 DOI: 10.1124/dmd.114.062539]

53 **Aleo MD**, Luo Y, Swiss R, Bonin PD, Potter DM, Will Y. Human drug-induced liver injury severity is highly associated with dual inhibition of liver mitochondrial function and bile salt export pump. *Hepatology* 2014; **60**: 1015-1022 [PMID: 24799086 DOI: 10.1002/hep.27206]

54 **Boelsterli UA**, Lee PK. Mechanisms of isoniazid-induced idiosyncratic liver injury: emerging role of mitochondrial stress. *J Gastroenterol Hepatol* 2014; **29**: 678-687 [DOI: 10.1111/jgh.12516]

55 **Ribeiro MP**, Santos AE, Custódio JB. Mitochondria: the gateway for tamoxifen-induced liver injury. *Toxicology* 2014; **323**: 10-18 [PMID: 24881593 DOI: 10.1016/j.tox.2014.05.009]

56 **Webb GJ**, Adams DH. Modeling idiosyncrasy: a novel animal model of drug-induced liver injury. *Hepatology* 2015; **61**: 1124-1126 [PMID: 25418789 DOI: 10.1002/hep.27617]

57 **Metushi IG**, Cai P, Zhu X, Nakagawa T, Uetrecht JP. A fresh look at the mechanism of isoniazid-induced hepatotoxicity. *Clin Pharmacol Ther* 2011; **89**: 911-914 [PMID: 21412230 DOI: 10.1038/clpt.2010.355]

58 **Fontana RJ**. Pathogenesis of idiosyncratic drug-induced liver injury and clinical perspectives. *Gastroenterology* 2014; **146**: 914-928 [PMID: 24389305 DOI: 10.1053/j.gastro.2013.12.032]

59 **Rockey DC**, Seeff LB, Rochon J, Freston J, Chalasani N, Bonacini M, Fontana RJ, Hayashi PH. Causality assessment in drug-induced liver injury using a structured expert opinion process: comparison to the Roussel-Uclaf causality assessment method. *Hepatology* 2010; **51**: 2117-2126 [PMID: 20512999 DOI: 10.1002/hep.23577]

60 **Lewis JH**. Causality assessment: which is best—expert opinion or RUCAM? *Clinical Liver Dis* 2014; **4**: 4-8 [DOI: 10.1002/cld.365]

61 **Regev A**, Seeff LB, Merz M, Ormarsdottir S, Aithal GP, Gallivan J, Watkins PB. Causality assessment for suspected DILI during clinical phases of drug development. *Drug Saf* 2014; **37** Suppl 1: S47-S56 [PMID: 25352327 DOI: 10.1007/s40264-014-0185-4]

62 **Teo YL**, Ho HK, Chan A. Formation of reactive metabolites and management of tyrosine kinase inhibitor-induced hepatotoxicity: a literature review. *Expert Opin Drug Metab Toxicol* 2015; **11**: 231-242 [PMID: 25400226 DOI: 10.1517/17425255.2015.983075]

63 **Momen-Heravi F**, Bala S, Bukong T, Szabo G. Exosome-mediated delivery of functionally active miRNA-155 inhibitor to macrophages. *Nanomedicine* 2014; **10**: 1517-1527 [PMID:

24685946 DOI: 10.1016/j.nano.2014.03.014]
64 **Lexmond WS**, Van Dael CM, Scheenstra R, Goorhuis JF, Sieders E, Verkade HJ, Van Rheenen PF, Kömhoff M. Experience with molecular adsorbent recirculating system treatment in 20 children listed for high-urgency liver transplantation. *Liver Transpl* 2015; **21**: 369-380 [PMID: 25366362 DOI: 10.1002/lt.24037]
65 **Liu CT**, Chen TH, Cheng CY. Successful treatment of drug-induced acute liver failure with high-volume plasma exchange. *J Clin Apher* 2013; **28**: 430-434 [PMID: 23922237 DOI: 10.1002/jca.21291]
66 **Wree A**, Dechêne A, Herzer K, Hilgard P, Syn WK, Gerken G, Canbay A. Steroid and ursodesoxycholic Acid combination therapy in severe drug-induced liver injury. *Digestion* 2011; **84**: 54-59 [PMID: 21304237 DOI: 10.1159/000322298]
67 **Singh S**, Hynan LS, Lee WM. Improvements in hepatic serological biomarkers are associated with clinical benefit of intravenous N-acetylcysteine in early stage non-acetaminophen acute liver failure. *Dig Dis Sci* 2013; **58**: 1397-1402 [PMID: 23325162 DOI: 10.1007/s10620-012-2512-x]
68 **Squires RH**, Dhawan A, Alonso E, Narkewicz MR, Shneider BL, Rodriguez-Baez N, Olio DD, Karpen S, Bucuvalas J, Lobritto S, Rand E, Rosenthal P, Horslen S, Ng V, Subbarao G, Kerkar N, Rudnick D, Lopez MJ, Schwarz K, Romero R, Elisofon S, Doo E, Robuck PR, Lawlor S, Belle SH. Intravenous N-acetylcysteine in pediatric patients with nonacetaminophen acute liver failure: a placebo-controlled clinical trial. *Hepatology* 2013; **57**: 1542-1549 [PMID: 22886633 DOI: 10.1002/hep.26001]
69 **Chalasani NP**, Hayashi PH, Bonkovsky HL, Navarro VJ, Lee WM, Fontana RJ. ACG Clinical Guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. *Am J Gastroenterol* 2014; **109**: 950-966; quiz 967 [PMID: 24935270 DOI: 10.1038/ajg.2014.131]
70 **Hoofnagle JH**. Drug-induced liver injury network (DILIN). *Hepatology* 2004; **40**: 773 [PMID: 15382161 DOI: 10.1002/hep.20445]
71 **Fontana RJ**, Watkins PB, Bonkovsky HL, Chalasani N, Davern T, Serrano J, Rochon J. Drug-Induced Liver Injury Network (DILIN) prospective study: rationale, design and conduct. *Drug Saf* 2009; **32**: 55-68 [PMID: 19132805 DOI: 10.2165/00002018-200932010-00005]
72 **Chalasani N**, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, Watkins PB, Navarro V, Barnhart H, Gu J, Serrano J. Features and Outcomes of 899 Patients With Drug-Induced Liver Injury: The DILIN Prospective Study. *Gastroenterology* 2015; **148**: 1340-1352.e7 [PMID: 25754159 DOI: 10.1053/j.gastro.2015.03.006]
73 **Navarro VJ**, Barnhart H, Bonkovsky HL, Davern T, Fontana RJ, Grant L, Reddy KR, Seeff LB, Serrano J, Sherker AH, Stolz A, Talwalkar J, Vega M, Vuppalanchi R. Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network. *Hepatology* 2014; **60**: 1399-1408 [PMID: 25043597 DOI: 10.1002/hep.27317]
74 **Alqahtani SA**, Kleiner DE, Ghabril M, Gu J, Hoofnagle JH, Rockey DC. Identification and Characterization of Cefazolin-Induced Liver Injury. *Clin Gastroenterol Hepatol* 2015; **13**: 1328-1336.e2 [PMID: 25528012 DOI: 10.1016/j.cgh.2014.11.036]
75 **Sistanizad M**, Peterson GM. Drug-induced liver injury in the Australian setting. *J Clin Pharm Ther* 2013; **38**: 115-120 [PMID: 23350857 DOI: 10.1111/jcpt.12039]
76 **Andrade RJ**, Lucena MI, Fernández MC, Pelaez G, Pachkoria K, García-Ruiz E, García-Muñoz B, González-Grande R, Pizarro A, Durán JA, Jiménez M, Rodrigo L, Romero-Gomez M, Navarro JM, Planas R, Costa J, Borras A, Soler A, Salmerón J, Martin-Vivaldi R. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. *Gastroenterology* 2005; **129**: 512-521 [PMID: 16083708 DOI: 10.1016/j.gastro.2005.05.006]
77 **Björnsson E**, Olsson R. Outcome and prognostic markers in severe drug-induced liver disease. *Hepatology* 2005; **42**: 481-489 [PMID: 16025496 DOI: 10.1002/hep.20800]
78 **Björnsson ES**, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. *Gastroenterology* 2013; **144**: 1419-1425, 1425.e1-3; quiz e19-20 [PMID: 23419359 DOI: 10.1053/j.gastro.2013.02.006]
79 **Devarbhavi H**, Dierkhising R, Kremers WK, Sandeep MS, Karanth D, Adarsh CK. Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. *Am J Gastroenterol* 2010; **105**: 2396-2404 [PMID: 20648003 DOI: 10.1038/ajg.2010.287]
80 **Suk KT**, Kim DJ, Kim CH, Park SH, Yoon JH, Kim YS, Baik GH, Kim JB, Kweon YO, Kim BI, Kim SH, Kim IH, Kim JH, Nam SW, Paik YH, Suh JI, Sohn JH, Ahn BM, Um SH, Lee HJ, Cho M, Jang MK, Choi SK, Hwang SG, Sung HT, Choi JY, Han KH. A prospective nationwide study of drug-induced liver injury in Korea. *Am J Gastroenterol* 2012; **107**: 1380-1387 [PMID: 22733303 DOI: 10.1038/ajg.2012.138]
81 **Petronijevic M**, Ilic K. Associations of gender and age with the reporting of drug-induced hepatic failure: data from the VigiBase™. *J Clin Pharmacol* 2013; **53**: 435-443 [PMID: 23440959 DOI: 10.1002/jcph.3]
82 **Montastruc F**, Scotto S, Vaz IR, Guerra LN, Escudero A, Sáinz M, Falomir T, Bagheri H, Herdeiro MT, Venegoni M, Montastruc JL, Carvajal A. Hepatotoxicity related to agomelatine and other new antidepressants: a case/noncase approach with information from the Portuguese, French, Spanish, and Italian pharmacovigilance systems. *J Clin Psychopharmacol* 2014; **34**: 327-330 [PMID: 24561328 DOI: 10.1097/JCP.0000000000000094]
83 **Sgro C**, Clinard F, Ouazir K, Chanay H, Allard C, Guilleminet C, Lenoir C, Lemoine A, Hillon P. Incidence of drug-induced hepatic injuries: a French population-based study. *Hepatology* 2002; **36**: 451-455 [PMID: 12143055 DOI: 10.1053/jhep.2002.34857]
84 **de Abajo FJ**, Montero D, Madurga M, García Rodríguez LA. Acute and clinically relevant drug-induced liver injury: a population based case-control study. *Br J Clin Pharmacol* 2004; **58**: 71-80 [PMID: 15206996 DOI: 10.1111/j.1365-2125.2004.02133.x]
85 **Hoofnagle JH**, Serrano J, Knoben JE, Navarro VJ. LiverTox: a website on drug-induced liver injury. *Hepatology* 2013; **57**: 873-874 [PMID: 23456678 DOI: 10.1002/hep.26175]
86 **Aithal GP**, Rawlins MD, Day CP. Accuracy of hepatic adverse drug reaction reporting in one English health region. *BMJ* 1999; **319**: 1541 [PMID: 10591713 DOI: 10.1136/bmj.319.7224.1541]
87 **Meier Y**, Cavallaro M, Roos M, Pauli-Magnus C, Folkers G, Meier PJ, Fattinger K. Incidence of drug-induced liver injury in medical inpatients. *Eur J Clin Pharmacol* 2005; **61**: 135-143 [PMID: 15726344 DOI: 10.1007/s00228-004-0888-z]
88 **Leise MD**, Poterucha JJ, Talwalkar JA. Drug-induced liver injury. *Mayo Clin Proc* 2014; **89**: 95-106 [PMID: 24388027 DOI: 10.1016/j.mayocp.2013.09.016]
89 **Björnsson ES**. Epidemiology and risk factors for idiosyncratic drug-induced liver injury. *Semin Liver Dis* 2014; **34**: 115-122 [PMID: 24879977 DOI: 10.1055/s-0034-1375953]
90 **Goldberg DS**, Forde KA, Carbonari DM, Lewis JD, Leidl KB, Reddy KR, Haynes K, Roy J, Sha D, Marks AR, Schneider JL, Strom BL, Corley DA, Lo Re V. Population-representative incidence of drug-induced acute liver failure based on an analysis of an integrated health care system. *Gastroenterology* 2015; **148**: 1353-1361.e3 [PMID: 25733099 DOI: 10.1053/j.gastro.2015.02.050]
91 **Ferrajolo C**, Verhamme KM, Trifirò G, 't Jong GW, Giaquinto C, Picelli G, Oteri A, de Bie S, Valkhoff VE, Schuemie MJ, Mazzaglia G, Cricelli C, Rossi F, Capuano A, Sturkenboom MC. Idiopathic acute liver injury in paediatric outpatients: incidence and signal detection in two European countries. *Drug Saf* 2013; **36**: 1007-1016 [PMID: 23591830 DOI: 10.1007/s40264-013-0045-7]
92 **Marchan-Lopez A**, Dominguez-Dominguez L, Kessler-Saiz P, Jarrin-Estupiñan ME. Liver failure in human immunodeficiency virus - Hepatitis C virus coinfection treated with sofosbuvir, ledipasvir and antiretroviral therapy. *J Hepatol* 2016; **64**: 752-753 [PMID: 26682727 DOI: 10.1016/j.jhep.2015.10.033]

93 **Dyson JK**, Hutchinson J, Harrison L, Rotimi O, Tiniakos D, Foster GR, Aldersley MA, McPherson S. Liver toxicity associated with sofosbuvir, an NS5A inhibitor and ribavirin use. *J Hepatol* 2016; **64**: 234-238 [PMID: 26325535 DOI: 10.1016/j.jhep.2015.07.041]

94 **Zhou Y**, Yang L, Liao Z, He X, Zhou Y, Guo H. Epidemiology of drug-induced liver injury in China: a systematic analysis of the Chinese literature including 21,789 patients. *Eur J Gastroenterol Hepatol* 2013; **25**: 825-829 [PMID: 23510965 DOI: 10.1097/MEG.0b013e32835f6889]

95 **Teschke R**, Zhang L, Long H, Schwarzenboeck A, Schmidt-Taenzer W, Genthner A, Wolff A, Frenzel C, Schulze J, Eickhoff A. Traditional Chinese Medicine and herbal hepatotoxicity: a tabular compilation of reported cases. *Ann Hepatol* 2015; **14**: 7-19 [PMID: 25536637]

96 **Oh SJ**, Cho JH, Son CG. Systematic review of the incidence of herbal drug-induced liver injury in Korea. *J Ethnopharmacol* 2015; **159**: 253-256 [PMID: 25460587 DOI: 10.1016/j.jep.2014.11.027]

97 **Roytman MM**, Pörzgen P, Lee CL, Huddleston L, Kuo TT, Bryant-Greenwood P, Wong LL, Tsai N. Outbreak of severe hepatitis linked to weight-loss supplement OxyELITE Pro. *Am J Gastroenterol* 2014; **109**: 1296-1298 [PMID: 25091255 DOI: 10.1038/ajg.2014.159]

98 **Elinav E**, Pinsker G, Safadi R, Pappo O, Bromberg M, Anis E, Keinan-Boker L, Broide E, Ackerman Z, Kaluski DN, Lev B, Shouval D. Association between consumption of Herbalife nutritional supplements and acute hepatotoxicity. *J Hepatol* 2007; **47**: 514-520 [PMID: 17692424 DOI: 10.1016/j.jhep.2007.06.016]

99 **Raschi E**, De Ponti F. Drug- and herb-induced liver injury: Progress, current challenges and emerging signals of post-marketing risk. *World J Hepatol* 2015; **7**: 1761-1771 [PMID: 26167249 DOI: 10.4254/wjh.v7.i13.1761]

100 **Williamson K**, Wahl MS, Mycyk MB. Direct comparison of 20-hour IV, 36-hour oral, and 72-hour oral acetylcysteine for treatment of acute acetaminophen poisoning. *Am J Ther* 2013; **20**: 37-40 [PMID: 23299230 DOI: 10.1097/MJT.0b013e318250f829]

101 **Krenzelok EP**. The FDA Acetaminophen Advisory Committee Meeting - what is the future of acetaminophen in the United States? The perspective of a committee member. *Clin Toxicol* (Phila) 2009; **47**: 784-789 [PMID: 19735211 DOI: 10.1080/15563650903232345]

102 **Hinson JA**, Roberts DW, James LP. Mechanisms of acetaminophen-induced liver necrosis. *Handb Exp Pharmacol* 2010; **196**: 369-405 [PMID: 20020268 DOI: 10.1007/978-3-642-00663-0_12]

103 **Mitchell JR**, Jollow DJ, Potter WZ, Davis DC, Gillette JR, Brodie BB. Acetaminophen-induced hepatic necrosis. I. Role of drug metabolism. *J Pharmacol Exp Ther* 1973; **187**: 185-194 [PMID: 4746326]

104 **Peterson RG**, Rumack BH. Treating acute acetaminophen poisoning with acetylcysteine. *JAMA* 1977; **237**: 2406-2407 [PMID: 576943 DOI: 10.1001/jama.1977.03270490046025]

105 **Danan G**, Benichou C. Causality assessment of adverse reactions to drugs--I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *J Clin Epidemiol* 1993; **46**: 1323-1330 [PMID: 8229110 DOI: 10.1016/0895-4356(93)90101-6]

106 **Senior JR**. Monitoring for hepatotoxicity: what is the predictive value of liver "function" tests? *Clin Pharmacol Ther* 2009; **85**: 331-334 [PMID: 19129750 DOI: 10.1038/clpt.2008.262]

107 **Kleiner DE**, Chalasani NP, Lee WM, Fontana RJ, Bonkovsky HL, Watkins PB, Hayashi PH, Davern TJ, Navarro V, Reddy R, Talwalkar JA, Stolz A, Gu J, Barnhart H, Hoofnagle JH. Hepatic histological findings in suspected drug-induced liver injury: systematic evaluation and clinical associations. *Hepatology* 2014; **59**: 661-670 [PMID: 24037963 DOI: 10.1002/hep.26709]

108 **Kleiner DE**. The pathology of drug-induced liver injury. *Semin Liver Dis* 2009; **29**: 364-372 [PMID: 19826970 DOI: 10.1055/s-0029-1240005]

109 **Kleiner DE**, Gaffey MJ, Sallie R, Tsokos M, Nichols L, McKenzie R, Straus SE, Hoofnagle JH. Histopathologic changes associated with fialuridine hepatotoxicity. *Mod Pathol* 1997; **10**: 192-199 [PMID: 9071726]

110 **Temple R**. Hy's law: predicting serious hepatotoxicity. *Pharmacoepidemiol Drug Saf* 2006; **15**: 241-243 [PMID: 16552790 DOI: 10.1002/pds.1211]

111 **Senior JR**. How can 'Hy's law' help the clinician? *Pharmacoepidemiol Drug Saf* 2006; **15**: 235-239 [PMID: 16552792 DOI: 10.1002/pds.1210]

112 **Guidance for industry**. Drug-induced liver injury: premarketing clinical evaluation. Silver Spring, MD: Food and Drug Administration, July 2009. [accessed 2016 Aug 20]. Available from: URL: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm174090.pdf

113 **Weiler S**, Merz M, Kullak-Ublick GA. Drug-induced liver injury: the dawn of biomarkers? *F1000Prime Rep* 2015; **7**: 34 [PMID: 25926985 DOI: 10.12703/P7-34]

114 **Donaldson PT**, Daly AK, Henderson J, Graham J, Pirmohamed M, Bernal W, Day CP, Aithal GP. Human leucocyte antigen class II genotype in susceptibility and resistance to co-amoxiclav-induced liver injury. *J Hepatol* 2010; **53**: 1049-1053 [PMID: 20800921 DOI: 10.1016/j.jhep.2010.05.033]

115 **Singer JB**, Lewitzky S, Leroy E, Yang F, Zhao X, Klickstein L, Wright TM, Meyer J, Paulding CA. A genome-wide study identifies HLA alleles associated with lumiracoxib-related liver injury. *Nat Genet* 2010; **42**: 711-714 [PMID: 20639878 DOI: 10.1038/ng.632]

116 **Mallal S**, Nolan D, Witt C, Masel G, Martin AM, Moore C, Sayer D, Castley A, Mamotte C, Maxwell D, James I, Christiansen FT. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet* 2002; **359**: 727-732 [PMID: 11888582 DOI: 10.1016/S0140-6736(02)07873-X]

117 **Ishak KG**, Zimmerman HJ. Morphologic spectrum of drug-induced hepatic disease. *Gastroenterol Clin North Am* 1995; **24**: 759-786 [PMID: 8749898]

118 **Senior JR**. New biomarkers for drug-induced liver injury: are they really better? What do they diagnose? *Liver Int* 2014; **34**: 325-327 [PMID: 25839081 DOI: 10.1111/liv.12384]

119 **Ulcickas Yood M**, Bortolini M, Casso D, Beck JG, Oliveria SA, Wells KE, Woodcroft KJ, Wang LI. Incidence of liver injury among cancer patients receiving chemotherapy in an integrated health system. *Pharmacoepidemiol Drug Saf* 2015; **24**: 427-434 [PMID: 25683797 DOI: 10.1002/pds.3757]

120 **Ambrosy AP**, Vaduganathan M, Huffman MD, Khan S, Kwasny MJ, Fought AJ, Maggioni AP, Swedberg K, Konstam MA, Zannad F, Gheorghiade M. Clinical course and predictive value of liver function tests in patients hospitalized for worsening heart failure with reduced ejection fraction: an analysis of the EVEREST trial. *Eur J Heart Fail* 2012; **14**: 302-311 [PMID: 22357577 DOI: 10.1093/eurjhf/hfs007]

121 **Seeff LB**, Bonkovsky HL, Navarro VJ, Wang G. Herbal products and the liver: a review of adverse effects and mechanisms. *Gastroenterology* 2015; **148**: 517-532.e3 [PMID: 25500423 DOI: 10.1053/j.gastro.2014.12.004]

122 **Iasani N**, Björnsson E. Risk factors for idiosyncratic drug-induced liver injury. *Gastroenterology* 2010; **138**: 2246-2259 [PMID: 20394749 DOI: 10.1053/j.gastro.2010.04.001]

123 **Hunt CM**, Yuen NA, Stirnadel-Farrant HA, Suzuki A. Age-related differences in reporting of drug-associated liver injury: data-mining of WHO Safety Report Database. *Regul Toxicol Pharmacol* 2014; **70**: 519-526 [PMID: 25236535 DOI: 10.1016/j.yrtph.2014.09.007]

124 **Bjornsson ES**, Jacobsen EI, Einarsdottir R, Chalasani N. Discrepancies in liver disease labeling in the package inserts of commonly prescribed medications. *Gastroenterology* 2015; **148**: 269-273 [PMID: 25527971 DOI: 10.1053/j.gastro.2014.12.007]

125 **Marino G**, Zimmerman HJ, Lewis JH. Management of drug-induced liver disease. *Curr Gastroenterol Rep* 2001; **3**: 38-48 [PMID: 11177693 DOI: 10.1007/s11894-001-0039-y]

126 **Aithal PG**, Day CP. The natural history of histologically proved drug induced liver disease. *Gut* 1999; **44**: 731-735 [PMID: 10205214 DOI: 10.1136/gut.44.5.731]

127 **Mohi-ud-din R**, Lewis JH. Drug- and chemical-induced cholestasis. *Clin Liver Dis* 2004; **8**: 95-132, vii [PMID: 15062196

DOI: 10.1016/S1089-3261(03)00124-7]
128 **Licata A**, Maida M, Cabibi D, Butera G, Macaluso FS, Alessi N, Caruso C, Craxì A, Almasio PL. Clinical features and outcomes of patients with drug-induced autoimmune hepatitis: a retrospective cohort study. *Dig Liver Dis* 2014; **46**: 1116-1120 [PMID: 25224696 DOI: 10.1016/j.dld.2014.08.040]
129 **Medina-Caliz I**, Robles-Diaz M, Garcia-Muñoz B, Stephens C, Ortega-Alonso A, Garcia-Cortes M, González-Jimenez A, Sanabria-Cabrera JA, Moreno I, Fernandez MC, Romero-Gomez M, Navarro JM, Barriocanal AM, Montane E, Hallal H, Blanco S, Soriano G, Roman EM, Gómez-Dominguez E, Castiella A, Zapata EM, Jimenez-Perez M, Moreno JM, Aldea-Perona A, Hernández-Guerra M, Prieto M, Zoubek ME, Kaplowitz N, Lucena MI, Andrade RJ. Definition and risk factors for chronicity following acute idiosyncratic drug-induced liver injury. *J Hepatol* 2016; **65**: 532-542 [PMID: 27184533 DOI: 10.1016/j.jhep.2016.05.003]
130 **Lewis JH**, Stine JG. Review article: prescribing medications in patients with cirrhosis - a practical guide. *Aliment Pharmacol Ther* 2013; **37**: 1132-1156 [PMID: 23638982 DOI: 10.1111/apt.12324]
131 **Lewis JH**. Drug-induced liver disease. *Med Clin North Am* 2000; **84**: 1275-1311, x [PMID: 11026929 DOI: 10.1016/S0025-7125(05)70287-X]
132 **Blanchette CM**, Nunes AP, Lin ND, Mortimer KM, Noone J, Tangirala K, Johnston S, Gutierrez B. Adherence to risk evaluation and mitigation strategies (REMS) requirements for monthly testing of liver function. *Drugs Context* 2015; **4**: pii: 212272 [PMID: 25709706 DOI: 10.7573/dic.212272]
133 **Markova SM**, De Marco T, Bendjilali N, Kobashigawa EA, Mefford J, Sodhi J, Le H, Zhang C, Halladay J, Rettie AE, Khojasteh C, McGlothlin D, Wu AH, Hsueh WC, Witte JS, Schwartz JB, Kroetz DL. Association of CYP2C9*2 with bosentan-induced liver injury. *Clin Pharmacol Ther* 2013; **94**: 678-686 [PMID: 23863877 DOI: 10.1038/clpt.2013.143]
134 **Lewis JH**. Clinical perspective: statins and the liver--harmful or helpful? *Dig Dis Sci* 2012; **57**: 1754-1763 [PMID: 22581301 DOI: 10.1007/s10620-012-2207-3]
135 **Leaver H**, Keng Lim T, Thomson P, Leaver J, Choy AM, Lang CC. Compliance to recommended liver function monitoring in patients on statin therapy. *Cardiovasc Ther* 2009; **27**: 96-100 [PMID: 19426246 DOI: 10.1111/j.1755-5922.2009.00082.x]
136 **Pollock NR**, Colby D, Rolland JP. A point-of-care paper-based fingerstick transaminase test: toward low-cost "lab-on-a-chip" technology for the developing world. *Clin Gastroenterol Hepatol* 2013; **11**: 478-482 [PMID: 23466712 DOI: 10.1016/j.cgh.2013.02.022]
137 **Pollock NR**, McGray S, Colby DJ, Noubary F, Nguyen H, Nguyen TA, Khormaee S, Jain S, Hawkins K, Kumar S, Rolland JP, Beattie PD, Chau NV, Quang VM, Barfield C, Tietje K, Steele M, Weigl BH. Field evaluation of a prototype paper-based point-of-care fingerstick transaminase test. *PLoS One* 2013; **8**: e75616 [PMID: 24098705 DOI: 10.1371/journal.pone.0075616]
138 **Papay JI**, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, Hunt CM. Drug-induced liver injury following positive drug rechallenge. *Regul Toxicol Pharmacol* 2009; **54**: 84-90 [PMID: 19303041 DOI: 10.1016/j.yrtph.2009.03.003]
139 **Thong BY**, Chia FL, Tan SC, Tan TC, Leong KP, Tan JW, Tang CY, Hou JF, Chan GY, Chng HH. A retrospective study on sequential desensitization-rechallenge for antituberculosis drug allergy. *Asia Pac Allergy* 2014; **4**: 156-163 [PMID: 25097851 DOI: 10.5415/apallergy.2014.4.3.156]
140 **Charles EC**, Olson KL, Sandhoff BG, McClure DL, Merenich JA. Evaluation of cases of severe statin-related transaminitis within a large health maintenance organization. *Am J Med* 2005; **118**: 618-624 [PMID: 15922693 DOI: 10.1016/j.amjmed.2005.02.008]
141 **Lebovitz HE**. Differentiating members of the thiazolidinedione class: a focus on safety. *Diabetes Metab Res Rev* 2002; **18** Suppl 2: S23-S29 [PMID: 11921435 DOI: 10.1002/dmrr.252]
142 **Stine JG**, Lewis JH. Hepatotoxicity of antibiotics: a review and update for the clinician. *Clin Liver Dis* 2013; **17**: 609-642, ix [PMID: 24099021 DOI: 10.1016/j.cld.2013.07.008]
143 **Bari K**, Fontana RJ. Acetaminophen overdose: what practitioners need to know. *Clinical Liver Dis* 2014; **4**: 17-21 [DOI: 10.1002/cld.373]
144 **Schmidt LE**. Identification of patients at risk of anaphylactoid reactions to N-acetylcysteine in the treatment of paracetamol overdose. *Clin Toxicol* (Phila) 2013; **51**: 467-472 [PMID: 23697458 DOI: 10.3109/15563650.2013.799677]
145 **Shea B**, Swinden MV, Ghogomu MT, Ortiz Z, Katchamart W, Rader T, Bombardier C, Wells GA, Tugwell P. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. *J Rheumatol* 2014; **41**: 1049-1060 [PMID: 24737913 DOI: 10.3899/jrheum.130738]
146 **Russell S**. Carnitine as an antidote for acute valproate toxicity in children. *Curr Opin Pediatr* 2007; **19**: 206-210 [PMID: 17496767 DOI: 10.1097/MOP.0b013e32805e879a]
147 **Aventis Pharmaceuticals**. Prescribing information for Arava® (leflunomide). [accessed 2016 Aug 19]. Available from: URL: https://www.fda.gov/downloads/safety/MedWatch/Safetyinformation/safetyalertsforhumanmedicalproducts/ucm168409.pdf
148 **Bañares R**, Catalina MV, Vaquero J. Molecular adsorbent recirculating system and bioartificial devices for liver failure. *Clin Liver Dis* 2014; **18**: 945-956 [PMID: 25438293 DOI: 10.1016/j.cld.2014.07.011]
149 **Abenavoli L**, Capasso R, Milic N, Capasso F. Milk thistle in liver diseases: past, present, future. *Phytother Res* 2010; **24**: 1423-1432 [PMID: 20564545 DOI: 10.1002/ptr.3207]

P- Reviewer: Grieco A, Gong ZJ, Jaeschke H, Silva CR, Shimizu Y
S- Editor: Kong JX **L- Editor**: A **E- Editor**: Li D

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com