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REVIEW

Drug-Induced Liver Injury

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Abstract

Drug hepatoxicity can be nonidiosyncratic (predictable), as in the case of acetaminophen, or idiosyncratic (unpredictable). This review article focuses primarily on idiosyncratic drug-induced liver injury (DILI). New epidemiologic data suggest that approximately 20 new cases of DILI per 100,000 persons occur each year. Idiosyncratic DILI accounts for 11% of the cases of acute liver failure in the United States. Risk factors for DILI include medication dose, drug lipophilicity, and extent of hepatic metabolism. There is mixed evidence to support the role of host factors such as age, sex, and chronic liver disease in the development of DILI. For specific drugs, a genetic predisposition appears to be a risk factor for DILI. Suspected cases of idiosyncratic DILI should be categorized as hepatitic, cholestatic, or mixed on the basis of the degree/ratio of abnormalities in the alanine aminotransferase and alkaline phosphatase. A careful evaluation for other causes of liver disease should be performed, though a liver biopsy is rarely needed. There is evidence that some patients with DILI may actually have hepatitis E and this diagnosis should be considered. Amoxicillin/clavulanate isoniazid, and nonsteroidal anti-inflammatory drugs are among the most common causes of DILI. Drug discontinuation or dechallenge should lead to an improvement in liver biochemistries in most patients, though a bilirubin value of more than 3 g/dL is associated with mortality of at least 10%. New biomarkers for DILI using proteomics and micro RNA appear promising but require further study. New studies on drugs with potential for causing DILI are reviewed herein, including tumor necrosis factor-alpha antagonists, fluoroquinolones, tyrosine kinase inhibitors, statins, and supplements. PubMed was used with search terms of drug induced liver injury OR DILI with filter settings of "English language" and "humans" and custom date range of "January 1, 2000." The authors also manually searched bibliographies from key references and included seminal references before the year 2000.

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The true incidence of drug-induced liver injury (DILI) is difficult to discern because of an unknown denominator of individuals receiving a drug, lack of a simple objective test for the diagnosis of DILI, lack of consensus on what liver test abnormalities constitute DILI, difficulty in attribution of causation to a single drug in those on many medicines, and lack of systematic reporting. Multiple studies have attempted to address the epidemiology of DILI, which are summarized in Table 1.[1-6] It is important to note that the main cause of DILI in 4 of the 6 studies was amoxicillin/clavulanate and that isoniazid and nonsteroidal anti-inflammatory drugs were also one of the top 3 culprits across studies.

A recent study by Bjornsson et al[5] helped to define the incidence of idiosyncratic DILI by prospectively examining a population-based cohort in Iceland. Overall prescription medication consumption in this population was documented through linkage to nationwide pharmaceutical databases for outpatient prescriptions and inpatient medication use. This is the most recent population-based study (2013) on DILI, with the only other population-based study coming from France (2002).[1] In Iceland, 96 cases of DILI were identified between 2010 and 2011, and the crude annual incidence was 19.1 (95% CI, 1.54-23.3) cases per 100,000 inhabitants. This incidence is higher than that in the French study, which reported an annual incidence of 13.9 cases per 100,000 inhabitants. It is notable that the French study used a lower liver test threshold to define DILI cases, included acetaminophen cases, and did not examine inpatients. In the United States, the Drug Induced Liver Injury Network (DILIN) reported on 300 idiosyncratic DILI cases on which information was collected prospectively by the National Institute of Health at 5 academic medical centers.[3] In these 300 cases, the mean age was 48 years, 60% were women, and the largest 2 categories were antimicrobial agents and central nervous system (CNS) agents. Eight percent of the patients died,

ARTICLE HIGHLIGHTS

- In the most recent and well-executed population-based study, the crude annual incidence of drug-induced liver injury was 19.1 (95% CI, 1.54-23.3) cases per 100,000 persons.
- The most common drug causing drug-induced liver injury is amoxicillin/clavulanate.
- The most common class of drug responsible for acute liver failure from drug-induced liver injury is antibiotic medications, with isoniazid, sulfur antibiotics (trimethoprim-sulfamethoxazole), and nitrofurantoin being the most common individual drugs.
- Hepatitis E can masquerade as a drug-induced liver injury in 3% to 13% of the cases.
- Drug-induced autoimmunelike hepatitis responds to steroids and generally does not recur after a steroid taper.
- Drug-induced liver injury with predominant elevations in aminotransferase levels (hepatocellular pattern) in those who develop jaundice has a mortality of approximately 10% (Hy's law).
- N-Acetylcysteine should be considered for patients with non-acetaminophen drug-induced acute liver failure, because it has been shown to improve transplant-free mortality in a randomized controlled trial.

and 2% required liver transplantation (LTx). Interestingly, 14% had continued liver test abnormalities at 6 months, regarded as "long-term DILI" in this study. Although this ongoing study provided data for US cases of DILI, it did not define the incidence of the condition. DILI also contributes significantly to the burden of acute liver failure (ALF) in the United States. In a prospective study of ALF in the United States (n=308), 13% of the ALF cases were thought to be caused by idiosyncratic DILI while 39% of the ALF cases were due to acetaminophen toxicity.[7] Between 1990 and 2002, 270 patients underwent LTx in the United States for drug hepatoxicity (49% from acetaminophen toxicity and 51% were idiosyncratic). More recent estimates suggest that idiosyncratic DILI is responsible for 11% of all cases of ALF in the United States. The most common agent in a US registry was isoniazid, followed by sulfur antibiotics (trimethoprim-sulfamethoxazole), nitrofurantoin, antifungals, antiepilepsy (especially phenytoin), and complementary-alternative medications (11%). Transplant-free, 3-week survival for this group is poor (27%).[8]

CLASSIFICATION

DILI is a broad term applied to any injury to the liver by a prescribed medication, over-the-counter medication, herb, or dietary supplement manifesting as a spectrum from asymptomatic liver test elevations to ALF. Epidemiologic studies and prospective registries use different, arbitrary liver biochemical thresholds to define what constitutes DILI. The first step in describing DILI is to differentiate idiosyncratic (unpredictable) DILI from intrinsic (predictable) DILI. The most common example of a drug causing predictable DILI is acetaminophen. This type of drug injury has a short latency period, is dose related, and is the most common form of DILI observed. On the contrary, idiosyncratic DILI is unpredictable, has longer/variable latency, and is less common. Examples of idiosyncratic DILI include those related to amoxicillin/clavulanate, nonsteroidal anti-inflammatory drugs, and isoniazid.

The second distinction to make is in regard to the pattern of drug injury. DILI can be categorized as hepatitic (hepatocellular injury), cholestatic, or mixed on the basis of liver biochemical parameters. Common examples of each pattern are given in Table 1. Formulas defined by the Council for International Organizations of Medical Sciences and modified by the Food and Drug Administration (FDA) determine the R ratio, which is a ratio of the alanine aminotransferase (ALT) to the alkaline phosphatase relative to their respective upper limits of normal (ULN).[9] The R ratio for hepatitic DILI is more than 5, for cholestatic DILI is less than 2, and for mixed DILI is between 2 and 5. The formulas are as follows: (1) Hepatitic DILI: ALT $\geq$3ULN and (ALT/ULN)/(alkaline phosphatase/ULN) $\geq$5; (2) Cholestatic DILI: alkaline phosphatase $\geq$2ULN and (ALT/ULN)/(alkaline phosphatase/ULN) $\leq$2; (3) Mixed DILI: ALT $>$3ULN and alkaline phosphatase $>$2ULN and (ALT/ULN)/(alkaline phosphatase/ULN) between 2 and 5. These formulas can be applied in practice to narrow down the differential diagnosis in patients in whom DILI is plausible yet multiple possible offending agents exist. Although many medications responsible for DILI produce stereotypical

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TABLE 1. Epidemiology of Drug-Induced Liver Injury

Group	N	F (%)	Age (y) (mean)	Drug (or class) no. 1	Drug (or class) no. 2	Drug (or class) no. 3	Herbal	Death	LTx	Chronicity
China (2013)	24,112	46	-	Tuberculosis medications 31%	CAMs (19%)	Antibiotics (10%)	19%	3%	-	-
France (2002)	34	65	M: 51 F: 58	Amoxicillin/clavulanate (12%)	NSAIDs (12%)	Nevirapine (9%)	-	6%	0	0
Iceland (2013)	96	56	55	Amoxicillin/clavulanate (22%)	Diclofenac (6%)	Azathioprine (4%)	16%	1%	0	(7) 7%
Korea (2012)	371	63	49	Antifungal (% not available)	-	-	63%[b]	-	(2) 1%	(3) 1%
Spain (2005)	461	49	53	Amoxicillin/clavulanate (13%)	T-2: Ebrotidine (5%) T-2: INH/rifampin/ pyrazinamide (5%)	Ibuprofen (4%)	2%	5%	(8) 2%	(46) 10%
United States (2008)	300	60	48	Amoxicillin/clavulanate (8%)	Nitrofurantoin (4%)	T-3: Isoniazid (4%) T-3: Trimethoprim-sulfamethoxazole (4%)	9%	8%	(9) 2%	14%

[a]CAM = complementary and alternative medicine; F = female; M = male; NSAID = nonsteroidal anti-inflammatory drug; LTx = liver transplantation; T = tie.
[b]Includes herbal medicines, health foods and dietary supplements, medicinal herbs or plants, folk remedies, and herbal preparations.

biochemical signatures, it should be noted that different biochemical patterns could be caused by the same medication. Another pitfall to the biochemical classification is that there is no standardized time period in which the drug injury pattern should be categorized. For instance, in a DILIN (n=192) analysis, many were reclassified from one pattern to another when measured at the time of diagnosis of DILI (hepatocelluar, 57%; cholestatic, 22%; mixed, 21%) vs later in the evolution of the drug injury (hepatocellular, 45%; cholestatic, 37%; mixed, 17%).[10]

DILI can also be categorized as immune or nonimmune. Immune-related DILI has also been referred to as an allergic reaction or a hypersensitivity reaction. Immune-related DILI can be recognized by its presentation with fever, rash, eosinophilia, and autoantibodies. Other specific forms of immune-mediated drug reaction include Stevens-Johnson syndrome, toxic epidermolysis necrosis syndrome, and drug rash, eosinophilia and systemic symptoms syndrome. Other features of immune-mediated DILI include its early onset (1-6 weeks) and rapid reinjury with reintroduction of the drug. Common examples of drugs that can cause immune-mediated DILI include angiotensin-converting enzyme inhibitors, allopurinol, phenytoin, diclofenac, amoxicillin/clavulanate, and tricyclic antidepressants. Nonimmune-mediated DILI typically has a later onset of action (up to 1 year), lacks the systemic features of immune DILI, and is not associated with rapid reinjury with rechallenge.

Drug-induced autoimmunelike hepatitis (DI-AIH) can be the predominant pattern of DILI. Drug-induced AIH is important to identify because it can be treated with corticosteroids. In this scenario, patients present with elevated levels of aminotransferases along with elevated levels of gammaglobulins and antinuclear and/or anti—smooth muscle antibodies. Common medications that precipitate DI-AIH include minocycline and nitrofurantoin.[11] More recently, fluoroquinolones and anti—tumor necrosis factor (TNF) alpha inhibitors have also been implicated as causes of DI-AIH.[12,13] Differentiating DI-AIH from true autoimmune hepatitis is difficult. Histologic findings can be helpful when no chronicity is identified, but this remains a clinical challenge.[14] To date, the absence of AIH relapse after the resolution of liver injury with or without immunosuppressive therapy can distinguish DI-AIH from idiopathic AIH.

DILI may also be classified by histologic features, though a liver biopsy is not required to diagnose most cases of DILI. Various histologic findings can be seen with different types of drug injury, including hepatitis, drug-induced autoimmune hepatitis, nodular regenerative hyperplasia, cholestasis, bland steatosis, steatohepatitis, fibrosis, sinusoidal damage, granuloma formation, and vanishing bile duct syndrome. Table 2 lists some of these histologic types and their associated drugs. Unfortunately, many of the histologic findings can be seen with multiple drugs and/or other disease states and therefore are not very helpful in making a specific diagnosis.

TABLE 2. Liver Test Abnormalities, Histologic Patterns, and Associated Drugs

	Associated Drugs
Liver Test abnormalities	
Hepatocellular	Acetaminophen, aspirin, allopurinol, amiodarone, baclofen, bupropion, ciprofloxacin, HAART, imatinib isoniazid, ketoconazole, lisinopril, losartan, methotrexate, NSAIDs, rifampin, statins, tetracyclines, valproic acid
Cholestasis	Amoxicillin/clavulanate, anabolic steroids, chlorpromazine, clopidogrel, erythromycin, estrogen, irbesartan, oral contraceptive
Mixed	Amoxicillin/clavulanate, anabolic steroids, azathioprine, carbamazepine, clindamycin, enalapril, erythromycin, nitrofurantoin, phenytoin, sulfonamides, trazodone, TMP-SMX, verapamil
Histologic Patterns	
Drug-induced autoimmune hepatitis	Atorvastatin, halothane, hydralazine, ipilimumab, methyldopa, minocycline, nitrofurantoin, TNF-alpha antagonists, vemurafenib
Steatohepatitis	Amiodarone, tamoxifen, valproic acid
Steatosis	Methotrexate, NRTIs, tetracycline, valproic acid
Granulomatous	Allopurinol, amiodarone, carbamazepine, diltiazem, hydralazine, penicillamine, procainamide, phenytoin, sulfonamides
Fibrosis	Methotrexate
Nodular regenerative hyperplasia	Azathioprine, bleomycin, cyclophosphamide, chlorambucil, doxorubicin, interleukin-2, trastuzumab

HAART = highly active antiretroviral therapy; NRTI = nucleoside reverse transcriptase inhibitor; NSAID = nonsteroidal anti-inflammatory drug; TMP-SMX = trimethoprim-sulfamethoxazole; TNF = tumor necrosis factor.

RISK FACTORS FOR DILI

Risk for DILI is complex and involves several interrelated factors. It has been suggested that DILI is more likely to occur in females, the elderly, and patients with chronic liver disease, HIV, and obesity. Many of these possibilities have come under scrutiny, and there is little empiric data available to support the validity of these factors.[15] With the exception of the Icelandic and French epidemiologic studies, the study of risk factors for DILI is an imperfect science because the population and the number of prescriptions are very difficult to enumerate.

Age has been cited as a risk factor for DILI, but the at-risk age groups differ according to specific drugs.[16] For instance, older age is a risk factor for DILI from isoniazid, whereas youth is a risk factor for DILI related to valproate and aspirin (Reyes syndrome). The increased risk or incidence of DILI in the elderly carries some biologic plausibility because the critical factors of absorption, distribution, metabolism, and elimination may be different in this subgroup.[17] Indeed, there were more patients older than 50 years in the French population study (n=23) vs younger than 50 years (n=11).[1] In the Icelandic population, there was a gradual increase in the age-standardized incidence of DILI in the 70- to 79-year-old age group (40 per 100,000) vs that in the 40- to 59-year-old age group (19 per 100,000).[5] However, there was an expected increase in the mean prescription rates in those 2 groups (9 vs 2, respectively), which confounds the relationship between DILI risk and age. In addition, elderly patients may receive more health care and laboratory monitoring, which may lead to an increase in the diagnosis of DILI in this population. A cholestatic liver enzyme pattern is also consistently more likely to be seen in older patients

It has been suggested that females have a higher risk of idiosyncratic DILI than do males. Many retrospective studies and a prospective study have reported a female preponderance in DILI.[1,3-5,7,18,19] The French prospective study demonstrated a crude annual incidence of DILI of 17 per 100,000 in females vs 10 per 100,000 in males, which was not a statistically significantly difference, while the Icelandic study showed a fairly even distribution of DILI in females (56%) vs males (44%). In the Icelandic and Spanish epidemiology studies (Table 1), females with DILI represented 55% and 53% of the studied population, respectively. Thus, if female gender is a risk factor for DILI, like age, it may be drug-specific. Females have been shown to have a higher risk of DILI from nitrofurantoin, erythromycin, flucloxacillin, minocycline, and isoniazid. It is possible that females may receive antibiotics more frequently than do males, but this is speculation. In addition, DILI is more often

hepatocellular in females and may be associated with a more severe course, which can result in the need for LTx, or death.[3,20,21]

Currently, there is a lack of robust data that alcohol use is a risk factor for idiosyncratic DILI. However, chronic alcohol use does increase the risk of nonidiosyncratic DILI from multiple supratherapeutic doses of acetaminophen, and increases the risk of fibrosis/cirrhosis from methotrexate.[22-25]

The contribution of an underlying liver disease to the risk of DILI is also contentious, but it seems to hold true for patients with hepatitis B and C receiving antituberculous and antiretroviral medications.[26,27] Nonalcoholic fatty liver disease (NAFLD) may be aggravated by drugs such as corticosteroids, methotrexate, tamoxifen, tetracycline, irinotecan, and nucleoside reverse transcriptase inhibitors.[28] However, NAFLD has not been proven to be a risk factor for DILI in general.

Progress has been made in identifying the general characteristics of medications that pose a higher risk of DILI. Lammert et al[29] found an important association between the dose of oral medication and hepatoxicity in the United States and Sweden. Daily medication doses were categorized as 10 mg or less, between 10 and 49 mg, and 50 mg or more. A higher daily dose of oral medication was associated with liver failure (P=.009), LTx (P<.001), and death caused by DILI (P=.004) in the United States. Similarly, a substantial gradient was found among Swedish DILI cases with respect to the daily dose, with 9% of the DILI cases in the 10 mg or less, 14.2% in the 11 to 49 mg, and 77% in the 50 mg or more category. Higher daily dose was also associated with death or LTx, with 2%, 9.4%, and 13.2% of the cases among the 3 categories, respectively. It is interesting to note that in the Spanish DILI registry (Table 1), the same percentage (77%) of the drugs causing DILI were in the 50 mg or more daily dose category as witnessed in the Swedish study. The Lammert study authors acknowledged the possibility of an imbalance in the frequency of prescriptions among the 3 dose categories but suggested that future studies should be performed. Indeed, a recent study has confirmed the same findings, but it also found a very positive association between higher drug lipophilicity and DILI in drug doses of 100 mg or more.[30] Lipophilicity of drug affects the absorption, distribution, metabolism, excretion, and toxicity of drugs and can be defined by the octanol-water partition coefficient or logP value. For drugs with high lipophilicity (logP≥3) and daily dose of 100 mg, the odds ratio for hepatotoxicity vs no hepatotoxicity was 14.0 (96% vs 41%; P<.001) among 164 FDA-approved drugs and 3.89 (85% vs 59% P<.01) in an independent data set of 179 oral medications. Lipophilicity alone without high drug dose was not an independent predictor of DILI. Drug metabolism is also associated with the risk of DILI. In another study by Lammert et al, drugs with considerable hepatic metabolism (>50%) had a significantly elevated risk of ALT > 3× ULN (35% vs 11%, P=.001), liver failure (28% vs 9%, P=.004), and fatal DILI (23% vs 4%, P=.001). Daily drug dose of 50 mg or more was also an additive risk for DILI in those drugs with hepatic metabolism. Jaundice was also found to be significantly more common in drugs undergoing biliary excretion.[31]

Genetic variations have been explored as possible risk factors for DILI. An impressive number of amoxicillin/clavulanate DILI cases (n=201) were subjected to a genomewide associated study that demonstrated that human leukocyte antigen (HLA)-I and HLA-II genotypes conferred susceptibility.[32] By using the single nucleotide polymorphisms isolated from this study, the positive predictive value for amoxicillin/clavulanate DILI was found to be 0.1%. Additional exome-type analyses may improve the predictive ability of genetic testing in the future. A genetic basis for DILI from flucloxacillin is also well established, whereby the (HLA)-B*5701 allele conferred an 80-fold increase in the risk of developing DILI after exposure to flucloxacillin.[33] Variants of UGT2B7, CYP2C8, and ABCC2 have been shown to be associated with diclofenac hepatoxicity.[34] N-Acetyltransferase 2 polymorphisms appear to predispose to hepatoxicity from sulfonamides and isoniazid.[35,36] Mutations in bile salt export pump and multi—drug-resistant 3 transporter are associated with an increased risk of cholestasis from various drugs.[37]

DIAGNOSIS

A patient with suspected DILI should have a careful evaluation for other forms of liver

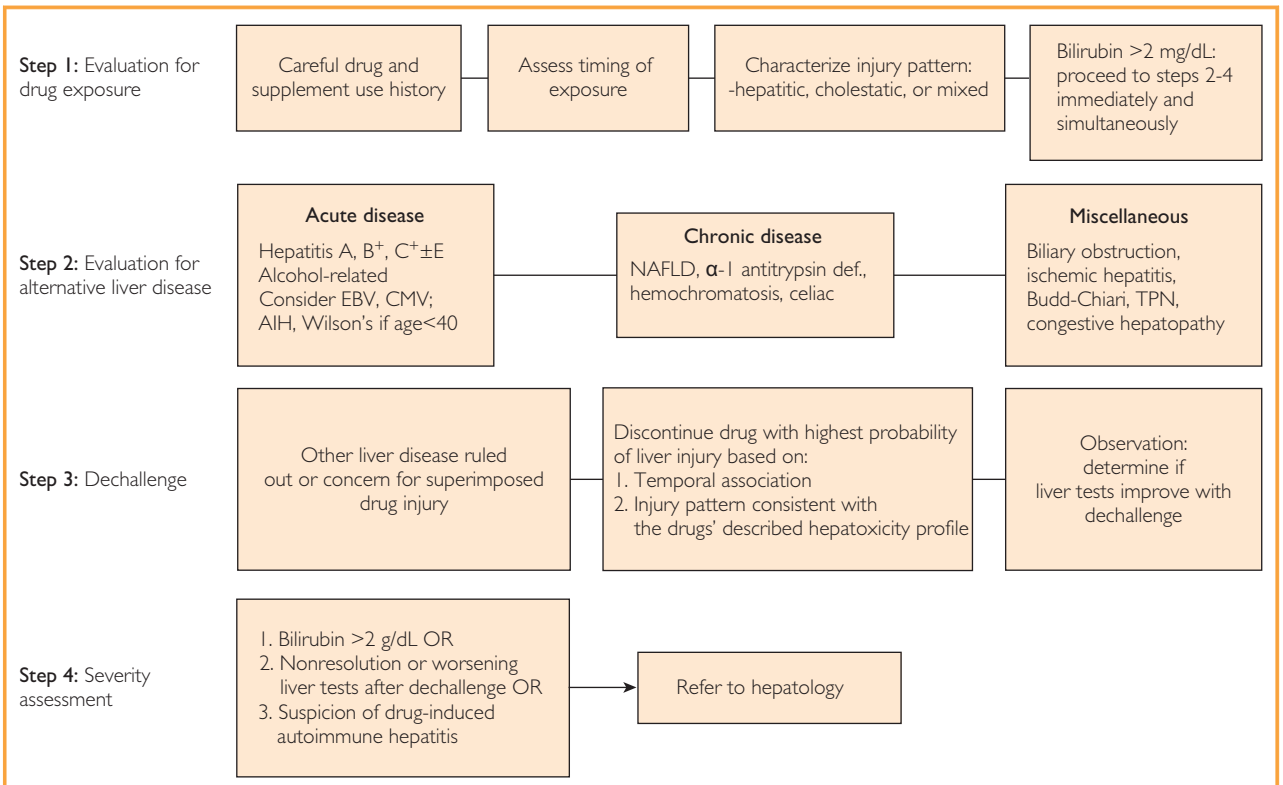

FIGURE. Evaluation of potential drug-induced liver injury. Testing for diseases in step 2 is as follows (see text for discussion of diagnostic pitfalls): Acute: hepatitis A, hepatitis A IgM; hepatitis B, hepatitis B surface antigen and hepatitis B core antibody IgM; hepatitis C, hepatitis C antibody test followed by HCV RNA if antibody is positive; hepatitis E, hepatitis E IgM; CMV, CMV IgM and/or PCR; EBV, EBV heterophile antibody test or EBV-specific antibody tests; AIH, anti—smooth muscle antibody, antinuclear antibody, or serum IgG (no singular test for diagnosis); Wilson's disease, ceruloplasmin; also consider ophthalmologic examination and 24-hour urine copper (no singular test for diagnosis). Chronic: NAFLD, combination of historic and imaging features ± histology (no singular test for diagnosis); alpha 1 antitrypsin deficiency, alpha 1 antitrypsin phenotype; hemochromatosis, transferrin saturation and ferritin; Celiac disease, tissue transglutaminase IgA. Miscellaneous: Biliary obstruction, ultrasound or MRCP; ischemic hepatitis (clinical diagnosis); Budd-Chiari syndrome, ultrasound with Doppler studies of hepatic veins; TPN, clinical diagnosis ± histology; congestive hepatopathy, transthoracic echocardiogram. AIH = autoimmune hepatitis; EBV = Epstein-Barr virus; CMV = cytomegalovirus; def. = deficiency; HCV, hepatitis C virus; MRCP = magnetic resonance cholangiopancreatography; NAFLD = nonalcoholic fatty liver disease; PCR, polymerase chain reaction; TPN = total parenteral nutrition.

disease, especially viral hepatitides. Other forms of acute and chronic liver disease can be evaluated as outlined in the Figure. In most cases, the diagnostic steps are carried concurrently, especially if the suspected DILI is deemed to be severe. There are some important potential diagnostic pitfalls to consider when evaluating for other liver diseases. Nonalcoholic fatty liver disease is the most common liver disease in the United States (10%-46%), and the index of suspicion for this disease should be very high. Some patients may have background NAFLD with superimposed DILI. Aminotransferase levels in NAFLD are usually elevated 2 to 5 times the upper limit of normal, and alkaline phosphatase values are 2 to 3 times the upper limit of normal. Values above these thresholds should suggest a different or superimposed liver process including DILI. The antinuclear antibody and anti—smooth muscle antibody numbers may also be elevated in about 20% of the patients with NAFLD. It is also important to note that ferritin is an acute-phase reactant and values may be moderately elevated as a result of liver inflammation from DILI, rather than due to hemochromatosis. Ferritin values may also be evaluated in NAFLD and hepatitis C.

Emerging data suggest that acute hepatitis E virus (HEV) infection may be a cause of acute liver injury in the United States. Data

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from the National Health and Nutrition Examination Survey registry demonstrate a seroprevalence rate of 21% in the 18,695 noninstitutionalized US citizens tested for exposure to HEV infection.[38] In the US DILIN prospective study, 50 of the 318 (16%) patients with suspected DILI tested positive for HEV IgG and 9 tested positive for HEV IgM (3%).[39] In the United Kingdom, 6 of 47 (13%) suspected cases of DILI had evidence of acute HEV infection. Travel to endemic areas, consumption of pork or liver meats, blood transfusions, and pet ownership may be risk factors for HEV infection and should be queried during the initial evaluation.[40]

Drug exposure is a necessary component to the diagnosis of DILI. Idiosyncratic DILI usually occurs within 6 months of a drug exposure, but it can occur within days or up to 1 year later. The interval between time of drug exposure and time of diagnosis of DILI is known as latency. After exclusion of other diagnoses and a thorough history of drug exposure is obtained, one must determine whether a certain drug or group of drugs may be the culprit. It is important to be able to identify which drugs may be associated with a higher incidence of DILI and whether the clinical, laboratory (R ratio), and histologic (when available) features are compatible with that agent. In addition, the drug injury should improve with dechallenge, or removal of the potential offending agent, in the majority of the cases. In the report on the first 300 patients enrolled in the DILIN study, the mean time to resolution of jaundice was 38 days for those with mixed or cholestatic liver injury as compared with 30 days for those with a hepatocellular injury pattern (P=.06).[3]

Biomarkers for DILI have shown some promise and ultimately one day may take the place of causality assessment systems. Two liver-enriched micro RNAs (miRs) were examined, miR-192 and miR-122, in multiple scenarios including patients with acute liver injury due to acetaminophen, acetaminophen overdose without acute liver injury (ALT<3× ULN), and nonacetaminophen acute liver injury (ALT>3×ULN), healthy controls, and patients with chronic kidney disease.[41] The miR-122 level was substantially elevated in patients with acetaminophen-induced liver injury at 1265 (491, 4270) as well as nonacetaminophen acute liver injury at 279.2 (194.7, 922.9) compared with healthy controls at 12.1 (7.0, 26.9) (P<.0001 for both comparisons). The difference between acetaminophen and nonacetaminophen miR-122 levels was also significant at P<.05. The miR-192 level was also elevated in acetaminophen-induced liver injury at 6.9 (1.96, 29.16) vs 0.4 (0.30, 0.69) for healthy controls (P<.0001), but the nonacetaminophen liver injury group was not different as compared with healthy controls. Chronic kidney disease did not affect the results. Day 1 miR-122 level also correlated with the peak ALT level for acetaminophen-related DILI and was 2-fold higher in those who ultimately met Kings College Criteria for need for LTx. Therefore, miR-122 is an exciting candidate biomarker that may aid in detection and prognostication for acetaminophen-induced DILI and should be studied in idiosyncratic DILI. It is of interest to note that miR-122 is integral to the replication of the hepatitis C virus, and miR-122 antagonists in a phase 2 study in humans were well tolerated and reduced hepatitis C viral load.[42] Therefore, miRNAs may be a diagnostic marker as well as a therapeutic target in patients with DILI in the future.

The proteome has been analyzed in patients with DILI and compared with that in healthy controls.[43] Apoprotein E expression was the best at differentiating DILI from controls, correctly classifying 89% of the patients with an area under the receiver-operating characteristic curve of 0.97. The addition of gelsolin, complement component C7, serum amyloid P, and age improved the discrimination to 96%, with an area under the receiver-operating characteristic curve of 0.99. A limitation of this study is the lack of a positive control group with acute liver injury from a nondrug source. These fascinating results will require application to larger numbers of patients including those with nondrug liver injury and chronic liver diseases.

Protein adducts have been investigated as a diagnostic marker for acetaminophen-induced liver injury and found to be helpful. More recently, the Acute Liver Failure Study Group has measured acetaminophen-cysteine adducts in the serum of 110 patients with indeterminate ALF and compared the results with 199 known cases of acetaminophen-related ALF. Approximately 18% of the indeterminate cases had substantial levels of the acetaminophen-cysteine

adducts, whereas 95% of the acetaminophen ALF cases were positive.[44] This marker could be clinically relevant given that there is treatment available for acetaminophen-related ALF.

Polypharmacy and inappropriate drug use are common in the elderly population.[45,46] From a practical standpoint, it may be helpful to obtain a pharmacy consultation early in the diagnostic evaluation, especially in patients taking multiple medications and supplements.

NEW DATA ON INDIVIDUAL AGENTS AND SPECIFIC FORMULATIONS

In this section, we provide an update on individual agents that cause DILI. We would also like to direct the reader to a new website called LiverTox (www.livertox.nih.gov), which is sponsored by the National Institutes of Health and serves as a repository of information on drugs known to cause DILI. This database is searchable and is helpful when it is unclear as to whether an agent may be responsible for DILI or not. Other common drugs that can lead to DILI are listed in Table 2 with their associated biochemical and/or histologic features.

Tumor Necrosis Factor Alpha (α) Inhibitors

A recent report has compiled data on cases of DILI secondary to TNF-α inhibitors from the DILIN study (n=6) and 28 additional cases from the literature.[13] All reported cases occurred in those taking infliximab (n=26), adalimumab (n=4), and etanercept (n=4), with no cases reported for golimumab, certolizumab, or natalizumab. There were no fatalities, but 1 liver transplant was required for a patient with preexisting cirrhosis. Indications for treatment from most common to least common were psoriasis, inflammatory bowel disease, and ankylosing spondylitis. About one third of the patients taking infliximab were concurrently treated with immunomodulators, most commonly methotrexate. Autoimmune serologies were positive in 22 of the 33 subjects (67%), with 15 of the 17 who underwent a liver biopsy demonstrating histological findings consistent with autoimmune hepatitis. Those with autoimmune features had longer latency (16 vs 10 weeks, P=.17) and higher transaminase levels (784 vs 528, P =.01). The severity of DILI for the entire population was most often mild to moderate with a hepatocellular pattern. Twelve patients were treated with steroids and removal of the offending drug, and the remainder were treated only by removal of the offending drug. All but 1 patient improved. Several of the patients who had developed DILI because of infliximab or adalimumab did not develop recurrence when treated with etanercept.

3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors ("statins") have been the subject of much controversy since their introduction. While their cardiovascular benefits are not in question, the idea of statin-induced DILI has been suggested to be a myth.[47] Initially, it was recommended that liver tests should be monitored periodically while taking a statin. It is important to note that the FDA changed the labeling for statin drugs in 2012. Baseline liver tests are appropriate before starting a statin, but routine monitoring of liver tests while on therapy is not recommended by the FDA. However, liver tests should be done in patients with new signs or symptoms of liver disease after initiating statin therapy. Periodic liver test monitoring is reasonable in patients with chronic liver disease. Evidence suggests that statins are safe in well-compensated liver disease, particularly, NAFLD and hepatitis C.[48]

DILI secondary to statins was recently investigated in Sweden by Bjornsson et al.[49] They used the Swedish Adverse Reactions Advisory Committee to capture all spontaneously reported adverse reactions thought to be related to statins (1988-2010). Case definitions for DILI were aminotransferases >5×ULN, and/or alkaline phosphatase >2×ULN or bilirubin >2×ULN. Of 217 cases of all types of adverse events for statins, 73 patients were identified with possible DILI. Seventy-one percent of liver injury cases were considered possibly related to statins, 19% were probable, and 10% highly probable. Median latency was 3 months. One patient required a liver transplant (highly probable), and 2 patients died (1 highly probable, 1 possible). Three patients received a rechallenge with the same statin, all accompanied by a repeat reaction of a similar type. Atorvastatin (n=30) and simvastatin (n=28) were the most common offenders, with atorvastatin more likely to exhibit a cholestatic/mixed profile (57%) vs simvastatin

(25%) (P=.02). Fluvastatin represented a minority of cases (n=11), but based on prescribing information, had the highest incidence among the class at 17×10^{-4} person-years compared with 2.9×10^{-4} person-years for atorvastatin and 1.6×10^{-4} person-years averaged across all cases. Other series have demonstrated that statins were responsible for 4.5% of the cases of ALF in the ALF Study Group series and 7.4% of the patients who died or were transplanted in the DILIN series. Thus, statins can cause serious, idiosyncratic drug reactions, but this remains an extremely rare phenomenon estimated to be 1.6 cases per 100,000 person-years of use.

Fluoroquinolones

Among 679 cases enrolled in the DILIN study by February 2010, information on 12 cases of fluoroquinolone DILI was collected and recently described.[12] The specific quinolones responsible were ciprofloxacin (n=4), moxifloxacin (n=4), levofloxacin (n=1), and gatifloxacin (n=1). Latency was very short, with the median onset to symptoms or abnormal liver tests of 2.5 days. In fact, 75% of the patients were still taking the drug when symptoms emerged. The biochemical signatures were evenly distributed, with 4 cases each in the hepatitic, cholestatic, and mixed groups. The outcomes were serious in some, with 3 developing hepatic or other organ failure, 1 dying from ALF, and 1 patient requiring LTx for vanishing bile duct syndrome. Of note, 7 of the 12 cases had features of hypersensitivity with fever, rash, or eosinophilia. Peripheral eosinophilia was rare, but increased numbers of eosinophils were seen in all 4 cases in which liver histology was available.

Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitors are an ever-expanding class of medications that now include 18 FDA-approved medications. Examples include imatinib, erlotinib, sorafenib, and sunitinib. Of these, 13 require liver test monitoring during use. Low-grade increases in aminotransferase levels occur in approximately 25% to 35% of the patients with high-grade elevations happening in approximately 2%.[50] Fatalities due to DILI have been reported for crizotinib, imatinib, lapatinib, pazopanib, ponatinib, regorafenib, and sunitinib. A hepatitic biochemical signature appears most commonly, accompanied by hepatic necrosis, in cases in which histology is available. We encourage the reader to visit the FDA website for instructions on liver monitoring during the use of individual agents.

Intravenous Medications

A recent DILIN study focused on intravenous (IV) medication as a source of DILI.[51] Thirty-two cases were identified, and the most common drug categories were antimicrobial (63%), antineoplastic (16%), and CNS drugs (9%). Cephalosporins were responsible for 9 cases, while fluoroquinolones caused 7 cases. All 3 CNS drug cases were due to phenytoin. About 40% of the patients presented within the first month, and most had symptoms of nausea, fever, jaundice, or pruritus. The distribution of cases among hepatitic, cholestatic, and mixed patterns was nearly equal. Patients receiving daily IV medications rather than intermittent IV therapy had decreased mean latency (15 vs 47 days), which was not statistically significant (P=.12). Clinicians should maintain a high index of suspicion for DILI in patients receiving IV cephalosporins, fluoroquinolones, or phenytoin who develop new elevations in liver tests, especially within the first month after exposure.

Herbal and Dietary Supplements Causing DILI

Herbal and dietary supplements (HDS) are emerging as a major cause of DILI worldwide. This is underscored by the recent 56 cases of acute liver failure or acute hepatitis linked to the fat burner, OxyElite Pro. The incidence of DILI from HDS varies by geography and patterns of HDS use. It accounts for approximately 9% of the cases of DILI in the United States and up to 19% to 63% of the cases of DILI in Asian countries.[3,4,6] A full description of DILI related to herbal medications is beyond the scope of this review. Table 3 lists the most frequently implicated supplements. Please refer to a recent review by Reddy et al[52] for more information on this topic.

TREATMENT

Treatment for most forms of DILI is focused on supportive care and requires longitudinal monitoring of the patient and laboratory work. Discontinuation of the offending agent is the first step. Rechallenge is not recommended except

TABLE 3. Selected Herbals and Dietary Supplements Causing Hepatoxicity

Aloe vera	Ma huang (*Ephedra sinica*)	Mistletoe (*Viscus album*)
Atractylis gummifera	Dai-saiko-to (Sho-saiko-to, TJ-19, D-chai-hu-tang, Xiao-chia-hu-tang)	Noni juice (*Morinda citrifolia*)
Black cohosh	Geniposide (*Gardenia jasminoides*)	Pennyroyal (squawmint oil)
Callilepsis laureola (Impila)	Germander (*Teucrium chamaedrys*) and other Teucrium varieties	Pyrrolizidine alkaloids (Crotalaria, Heliotropium, Senecio, Symphytium [Comfrey])
Cascara (*Cascara sagrada*)	Greater Celendine (*Chelidonium majus*)	Saw Palmetto (*Serrenoa repens*)
Camphor oil	Green tea (*Camellia sinensis*)	Senna (*Cassia angustifolia* and *C acutifolia*)
Centella asciatica (Gotu kola)	Herbalife	Skull cap (Scutellaria)
Chaparral (*Larrea tridentate*)	Hydroxycut (first-generation formulation; production halted 2009)	Valerian (*Valeriana officinalis*)
Jin Bu Huan (*Lypocodium serratum*)	Kava (*Piper methysticum*)	OxyElite Pro

under very rare scenarios with the input of a hepatologist. Once DILI has been diagnosed, it is important to list that drug as an "allergy" and to counsel the patient on the importance of avoiding that particular drug, and when appropriate, other drugs in its class. The hypersensitivity or immunoallergic phenotype may respond to steroids, but there is not robust data for that practice. Drug-induced AIH generally responds to prednisone and may be given for shorter durations when compared with de novo or idiopathic AIH. Patients with suspected DI-AIH should be referred to a hepatologist. The authors use 20 to 40 mg of prednisone for initial treatment followed by a slow taper of prednisone over approximately 6 months if liver tests normalize. Some patients with DI-AIH may evolve toward an idiopathic form and thus require longer treatment and perhaps maintenance therapy to prevent relapse. Ursodeoxycholic acid has been used in patients with symptoms related to significant cholestasis secondary to DILI, but data supporting actual therapeutic efficacy from this agent remain limited. Drug-induced liver injury caused by certain medications does have specific treatments. For instance, DILI caused by valproate should be treated with carnitine.[53] N-Acetylcysteine (NAC) is the mainstay of treatment for patients presenting early in their course of acetaminophen toxicity. Recent data suggest that NAC improves mortality in patients with ALF and grade I to II hepatic encephalopathy (including some patients with idiosyncratic DILI) and NAC should be considered in this setting.[54] For patients who develop ALF and meet King's College criteria, LTx is necessary. In the future, stem cell therapy may be an acceptable and beneficial treatment modality for severe DILI.

PROGNOSIS

For the vast majority of patients with DILI, full recovery is expected during the dechallenge. For patients with jaundice, this may take up to 30 to 40 days, and occasionally up to a year in those with severe cholestasis. In general, the hepatocellular injury phenotype carries a worse prognosis than do the cholestatic or mixed presentations. One of the oldest tools used for prognosis in DILI was developed by the famous hepatologist Hyman Zimmerman. His simple rule stated that a bilirubin level of 3 or more times the ULN in the context of hepatocellular-type DILI indicated a risk of death that is approximately 10% (range, 5%-50%).[55] Elevated bilirubin level in hepatocellular-type DILI is a reflection of the severity of injury, cell death, and hepatocellular dysfunction. This rule has been adopted in a modified form (bilirubin level of $>2\times$ULN) by the FDA and used to judge the severity of DILI in clinical trials. Hy's law has been validated in several DILI registries as well.[2,3,56] Cases of DILI with a bilirubin level of more than 2 g/dL should be referred to a hepatologist. ALF from acetaminophen carries a better prognosis than does ALF secondary to idiosyncratic DILI.

DILI may also evolve into a chronic form of liver disease. In the epidemiologic studies, DILI chronicity has varied from 0% in the French series and 1% in the Korean series to 14% in the US series. Time to follow-up can also result in varying results for the frequency of chronic DILI. Death from idiosyncratic DILI in the major series ranges from 1% to 8%, with 1% to 2% requiring LTx. These registry studies are likely enriched with

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more severe cases and thus, these numbers may be inflated.

Advances have been made to predict outcome in nonidiosyncratic acetaminophen DILI. Traditionally, the Rumack-Matthew nomogram is used to help predict the course of acetaminophen toxicity.[57] This nomogram uses acetaminophen plotted versus time elapsed from ingestion to predict the clinical course and need for NAC. As previously mentioned, miR-122 was found to be an early marker of acetaminophen-induced DILI and correlated with peak ALT, which could aid in early treatment decisions. White patients with keratin 8 and keratin 18 variants were also found to be less like to survive ALF, of which 49% of the cases were acetaminophen-related ALF.[58] Investigators at the University of Utah have developed the Model for Acetaminophen-induced Liver Damage.[59] Using the ALT, aspartate aminotransferase, international normalized ratio, and creatinine, this model was applied to 53 patients and predicted mortality with 100% sensitivity and 91% specificity, with a positive predictive value of 67% and a negative predictive value of 100%. While these advances are not yet prime for clinical use, they are a source of optimism.

CONCLUSION

The epidemiology of idiosyncratic DILI has become clearer with the addition of the Iceland study, demonstrating a crude annual incidence of 19 per 100,000 inhabitants. Idiosyncratic DILI is a serious problem, accounting for approximately 10% of the ALF cases in the United States. There is now a better understanding of drug-specific properties that result in the risk of DILI such as the interaction of drug dose and lipophilicity as well as the extent of hepatic metabolism. Specific host genetic factors also play a role in the risk of DILI and are specific to each drug. miRNA and proteomic studies in DILI provide optimism that a biomarker of DILI could become available in the future but is not currently ready for prime time. Removing the offending agent and supportive care remain the cornerstone of treatment, though patients with drug-induced AIH benefit from corticosteroids, and those meeting Hy's law have a higher risk of death and may ultimately require LTx.

Abbreviations and Acronyms: **AIH** = autoimmunelike hepatitis; **ALF** = acute liver failure; **ALT** = alanine aminotransferase; **CNS** = central nervous system; **DI-AIH** = drug-induced autoimmunelike hepatitis; **DILI** = drug-induced liver injury; **DILIN** = Drug Induced Liver Injury Network; **FDA** = Food and Drug Administration; **HDS** = herbal and dietary supplement; **HEV** = hepatitis E virus; **HLA** = human leukocyte antigen; **IV** = intravenous; **LTx** = liver transplantation; **miRNA** = micro RNA; **NAC** = N-Acetylcysteine; **NAFLD** = nonalcoholic fatty liver disease; **TNF** = tumor necrosis factor; **ULN** = upper limit of normal

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