

Case Definition and Phenotype Standardization in Drug-Induced Liver Injury

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Drug-induced liver injury (DILI) is the most frequent reason cited for the withdrawal of approved drugs from the market and accounts for up to 15% of the cases of acute liver failure. Investigators around the globe have begun to identify and study patients with DILI; several large registries and tissue banks are being established. In order to gain the maximum scientific benefit from these efforts, the definitions and terminology related to the clinical phenotypes of DILI must be harmonized. For this purpose, an international DILI Expert Working Group of clinicians and scientists reviewed current DILI terminology and diagnostic criteria so as to develop more uniform criteria that would define and characterize the spectrum of clinical syndromes that constitute DILI. Consensus was established with respect to the threshold criteria for definition of a case as being DILI, the pattern of liver injury, causality assessment, severity, and chronicity. Consensus was also reached on approaches to characterizing DILI in the setting of chronic liver diseases, including autoimmune hepatitis (AIH).

Idiosyncratic drug-induced liver injury (DILI) is best described as an adverse hepatic reaction that is unexpected on the basis of the pharmacological action of the drug administered. It is therefore distinct and different from DILI secondary to drug overdose. DILI, excluding injury caused by acetaminophen overdose, accounts for 7–15% of the cases of acute liver failure in Europe and the United States^{1–4} and is the most frequent reason for the withdrawal of an approved drug from the market.⁵ Estimates of the rate of incidence of DILI leading to hospital referral vary from 2.4 per 100,000 person-years (in a retrospective population-based study of 1.64 million UK subjects⁶) to 13.9 per 100,000 inhabitants (in a prospective analysis in France).⁷ Complementary or alternative medicines are used by at least 20% of individuals in Western, Eastern, and African cultures,⁸ and reports of DILI have increased.⁹ Given its rarity, DILI may not be identified during clinical trials¹⁰ and may come to light only after the culprit drug has obtained market approval and large numbers of patients have been exposed. In addition, in

preregistration clinical trials, mild asymptomatic liver injuries, often characterized by asymptomatic elevations in liver enzymes, are commonly seen.¹⁰ However, drugs capable of inducing severe DILI as well as drugs that have a low potential for causing severe injury (e.g., aspirin and heparin) can generate similar patterns of liver injury.¹⁰ It is therefore necessary to develop an approach that can distinguish drugs that are likely to cause severe DILI from drugs that are unlikely to do so.

Furthermore, DILI is commonly misdiagnosed. An expert review of suspected DILI reports from primary and secondary care clinicians to the UK Committee on the Safety of Medicines revealed that approximately half of the cases were not DILI and that the misdiagnoses led to a delay in arriving at the correct diagnosis, possibly affecting patient care.¹¹ Inclusion of such cases in the characterization of the genetic architecture underlying DILI would introduce unnecessary misclassification and increase the likelihood of type II error. Therefore, clearly identified DILI criteria are needed to improve its accurate

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detection and assessment in genetic, clinical, and epidemiologic studies.

Advances in genetic research and molecular biology techniques have allowed researchers to begin to characterize the genetic components underlying some serious adverse drug reactions.¹² Genetic factors that increase susceptibility to clinically significant hepatotoxicity are increasingly being identified.^{13–19}

The identification and validation of these genetic markers will require a large and sufficiently diverse patient database as well as standardized phenotyping and genotyping. To meet this challenge, researchers around the world have begun to assemble cohorts of patients who have experienced DILI. Ongoing efforts to link comprehensive electronic medical records with archived biological material may accelerate the identification and recruitment of these rare patients.²⁰

To harmonize these international efforts, and to facilitate cross-study comparisons and collaborations, it is important that the phenotypes of DILI be standardized and accepted. With this goal in mind, we sought to standardize the definitions, the optimal phenotyping data, and the process for causality assessment.

This article presents the consensus statements generated from the discussions and meetings of an international expert working group (see the related Commentary in this issue of *Clinical Pharmacology & Therapeutics*). We have used the levels of evidence recommended by the Oxford Centre for Evidence-based Medicine because they are suitable for critical appraisal of the diagnosis, symptom prevalence, and natural history studies.²¹

DESCRIPTION OF PHENOTYPE

Clinical threshold for DILI

Liver injury in the context of DILI has been defined as an elevation in the serum concentration of alanine aminotransferase (ALT), conjugated bilirubin, or alkaline phosphatase exceeding 2× the upper limit of normal (ULN).²² With the increasing incidence of nonalcoholic fatty liver disease, and the increased frequency with which liver tests are being performed as a part of routine investigations of nonspecific symptoms, modest ALT elevations are commonly detected.²³ Another relevant aspect is that small elevations in liver parameters, even if drug induced, may be transient in nature and may revert to baseline even when therapy is continued (as described with antituberculosis drug therapy and with statin therapy). These elevations may represent true mild liver injury with spontaneous resolution, or “adaptation,” but they do not represent clinically important liver injury. A low threshold for the definition of DILI may therefore lead to unnecessary investigations and, on some occasions, an inappropriate withdrawal of otherwise useful medications. Raising the cutoff level of ALT elevation to 5× ULN is more likely to exclude clinically unimportant and self-limited drug-related events as well as nonalcoholic steatohepatitis not related to DILI. This has been supported by an observational study involving patients with atrial fibrillation (in whom underlying liver disease was excluded) over a 2-year period. A transient ALT concentration of 2× ULN affected 6–8%, whereas ALT concentration of 5× ULN was observed in 1.4% of the patients, with an incidence of 0.4/100 patient-years.²⁴ In clinical trials of

more than 18,000 patients, predominantly female and without known liver disease at baseline, the prevalence of ALT concentration 5× ULN at baseline was 0.005%, and the incidence was 2.6/10,000 person-months (95% confidence interval 1.6–4.0).²⁵ An American Thoracic Society guidance recommends that subjects who have raised ALT levels between 2× ULN and 5× ULN but no symptoms should continue antituberculosis drug therapy, implying that elevations of ALT level below the recommended threshold (5× ULN) are unlikely to represent clinically significant DILI.²⁶ Therefore, it is the opinion of our Expert Working Group that an upper threshold of 5× ULN for ALT appears to better represent clinically important liver injury.

A majority of the hepatotoxicity networks have used alkaline phosphatase concentration 2× ULN as the threshold to identify the cholestatic pattern of liver injury;²² the cases as defined by this criterion are associated with 5–14.3% mortality.^{27,28} In addition, jaundiced patients with a hepatocellular pattern of liver injury are prone to acute liver failure (referred to as Hy’s Law) and have a death or transplantation rate of ~10% (ref. 27). Therefore, we defined the clinical chemistry criteria for DILI as summarized in **Box 1**.

Clinical notes for clinical threshold for DILI

- The phenotype is not exclusive for any single hypothetical mechanism that may be responsible for DILI (e.g., chemically active drug metabolites, hypersensitivity reaction, and autoimmunity).
- These recommended thresholds can be reached at any point of the clinical event that is being considered (i.e., determined by the highest levels).
- If the patient has had previous liver injury and hence abnormal liver biochemistry prior to starting treatment with the implicated drug, ULN is replaced by the mean baseline values obtained prior to the exposure to the suspect drug, and the changes should be proportionate to this modified baseline (i.e., 5× baseline for ALT, 2× baseline for alkaline phosphatase, and 2× baseline for bilirubin with associated 3× baseline elevation in ALT).
- Aspartate transaminase levels may be used instead of ALT levels only when the latter are unavailable and when there

Box 1 Clinical chemistry criteria for drug-induced liver injury (DILI)

Any one of the following:

- More than or equal to fivefold elevation above the upper limit of normal (ULN) for alanine aminotransferase (ALT)
- More than or equal to twofold elevation above the ULN for alkaline phosphatase (ALP) (particularly with accompanying elevations in concentrations of 5′-nucleotidase or γ-glutamyl transpeptidase in the absence of known bone pathology driving the rise in ALP level)
- More than or equal to threefold elevation in ALT concentration and simultaneous elevation of bilirubin concentration exceeding 2× ULN

Level of evidence: 2b (exploratory/retrospective cohort studies)

is no known muscle pathology driving the rise in aspartate transaminase.

- Isolated hyperbilirubinemia is not DILI, even if it is associated with direct hyperbilirubinemia.
- Isolated elevation of γ -glutamyl transferase is insufficient to qualify as DILI.²⁹
- These thresholds are not applicable to some types of chronic drug-associated liver injury (e.g., methotrexate-associated liver fibrosis and nodular regenerative hyperplasia).
- Some forms of liver injury, especially mitochondrial toxicity (e.g., valproate or alpruridine hepatotoxicity), may not induce these threshold values but may nevertheless cause clinically significant liver injury. These cases should be judged on the basis of specific drug(s) and/or unique histological criteria, evaluated on an individual basis, and grouped separately as “other forms of DILI.”

Defining the pattern of DILI

The most common clinical presentations of DILI are hepatocellular, cholestatic, and mixed, which should be defined on the basis of biochemical criteria (Box 2). The earliest identified pattern of liver injury should be recorded because the pattern of liver injury can change over time. Liver biopsy can confirm the biochemical classification and detect additional useful information for assigning causality, such as the presence of zonal injury or microvesicular steatosis; however, DILI histology is often nonspecific and can mimic other acute and chronic liver diseases.^{8,30} Although liver biopsy is also useful in grading severity of injury, there is no standardized histological scoring system for DILI.^{8,30}

Clinical notes for clinical pattern of DILI

- These descriptions of clinical patterns may not be applicable to insidious forms of DILI (e.g., methotrexate-

associated liver fibrosis, tamoxifen-induced fatty liver disease, and nodular regenerative hyperplasia).

- Liver biopsy is not essential for the diagnosis of DILI but strengthens the diagnosis, particularly for cases in which an alternative diagnosis can be excluded only on the basis of findings from a liver biopsy.
- Liver biopsy can support the classification of a clinical pattern but does not replace classification based on biochemical criteria.

Grading the severity of DILI

The degree of elevation of enzyme levels alone may not reflect the severity of liver injury because these values do not accurately predict specific clinical outcomes. This is evident from the fact that none of the validated models of prognosis (such as Child–Pugh score, King’s College Criteria for transplantation in acute liver failure, MELD and its modifications, and UKELD) includes liver enzymes as components. DILI accompanied by jaundice is associated with a 9–12% mortality in large, global DILI registries.^{3,27} Without liver transplantation, such severe injury can progress to acute liver failure with likely mortality.^{1,31} The criteria for defining acute liver failure have been well described and accepted in clinical practice. In classifying the severity of DILI, we have taken into account the evidence base, current definitions of acute liver failure, and the US Food and Drug Administration’s Guidance for Industry on the premarketing assessment of DILI,³² and we have aimed to achieve homogeneity in these recommendations. Our recommended classification of the clinical severity of DILI involves use of the highest measured values for each

Box 2 Criteria for classifying the clinical pattern of drug-induced liver injury (DILI)

- Pattern of liver injury is based on earliest identified liver chemistry elevations that qualify as DILI (Box 1)
- Pattern of liver injury is defined using R value where $R = (ALT/ULN)/(ALP/ULN)$. This will require estimation of alanine aminotransferase (ALT) (aspartate transaminase is used when ALT is unavailable) and alkaline phosphatase (ALP) from the same serum sample
- $ALT\ activity = patient's\ ALT/upper\ limit\ of\ normal\ (ULN)$; $ALP\ activity = patient's\ ALP/ULN$; $R = ALT\ activity/ALP\ activity$
- Hepatocellular pattern of DILI = $R \geq 5$
- Mixed pattern of DILI = $R > 2$ and < 5
- Cholestatic pattern of DILI = $R \leq 2$
- Histological summary should be recorded separately (if liver biopsy has been performed). However, the liver biopsy interpretation will generally not replace the R value for purposes of classification

Level of evidence: 2b (retrospective cohort studies)

Box 3 DILI severity index

Category	Severity	Description
1	Mild	Elevated alanine aminotransferase/alkaline phosphatase (ALT/ALP) concentration reaching criteria for DILI* but bilirubin concentration $< 2 \times$ upper limit of normal (ULN)
2	Moderate	Elevated ALT/ALP concentration reaching criteria for DILI* and bilirubin concentration $\geq 2 \times$ ULN, or symptomatic hepatitis
3	Severe	Elevated ALT/ALP concentration reaching criteria for DILI*, bilirubin concentration $\geq 2 \times$ ULN, and one of the following: <ul style="list-style-type: none"> • International normalized ratio ≥ 1.5 • Ascites⁷³ and/or encephalopathy, disease duration < 26 weeks, and absence of underlying cirrhosis³¹ • Other organ failure considered to be due to DILI
4	Fatal or transplantation	Death or transplantation due to DILI

*Criteria for DILI are defined in Box 1

Level of evidence: 1b (inception cohort studies)

Modified from ref. 70.

of the biochemical parameters during the course of DILI (**Box 3**).

In addition to the criteria in **Box 3**, hospitalization or prolongation of ongoing hospitalization should be noted because these would have socioeconomic consequences. However, hospitalization was not chosen as a distinct criterion for severity because indications for hospitalization vary substantially across the globe.

Clinical notes for severity of DILI

- **Symptomatic hepatitis:** symptoms attributed to hepatitis include fatigue, nausea, vomiting, right upper quadrant pain, itching, skin rash, jaundice, weakness, anorexia, and weight loss. Any of these symptoms, if attributed to DILI by the clinician responsible for the care of the patient, would qualify to be included under the severity assessment because these have been shown to be associated with a poorer clinical outcome.^{33,34}
- **Isolated coagulopathy** in the absence of hyperbilirubinemia or encephalopathy is rare but theoretically possible. However, the clinical significance and impact of this on prognosis are unknown.

Causality assessment

Because there are no specific tests to confirm the diagnosis of DILI, causality assessment must be employed to establish a definitive link between drug intake and liver injury. The usual assessment tools for determining the causes of adverse events during drug therapy, as are used in many DILI cases reported to pharmacovigilance agencies, are inadequate in the evaluation of DILI. Although consensus opinion among hepatologists with expertise in DILI adjudication remains a “gold standard,” this is impractical for widespread and international use. In contrast, the Roussel Uclaf Causality Assessment Method (RUCAM), endorsed by the Council of International Organizations of Medical Sciences,³⁵ and the DILI diagnostic scale³⁶ can be used by nonexperts and are clear improvements over instruments that are not specific to liver-related adverse events. When compared with the DILI diagnostic scale, the RUCAM scale was generally more reliable and correlated better with expert reviews.^{37–39} The RUCAM data elements for hepatocellular or cholestatic/mixed liver injury are described in **Supplementary Tables S1 and S2** online. However, the RUCAM has limitations when there are no data on drug re-challenge or de-challenge, when there is concomitant exposure to other drugs that are potentially hepatotoxic, when there are risk factors for DILI other than those listed in the algorithm, and when a drug typically produces delayed DILI (e.g., amoxicillin–clavulanate); also, the method does not fully eliminate subjectivity in the interpretation of data. Nonetheless, the RUCAM is the most commonly used diagnostic tool for DILI, and its formal and practical approach increases consistency and objectivity in causality assessment. Moreover, improved diagnostic instruments will most likely be based on modifications of the RUCAM; therefore, collecting causality assessment scores using the RUCAM may aid research in improving causality assessment. **Box 4** summarizes the recommended approach to causality assessment with respect to DILI. In the specific context of development

Box 4 DILI causality assessment

- The Roussel Uclaf Causality Assessment Method (RUCAM) scale should be used for causality assessment (**Supplementary Tables S1 and S2** online)
- If more than one drug is suspected to be causing DILI, the RUCAM scale should be applied to each drug separately. If such assessments are not practical (e.g., antituberculosis medications), all the drugs involved may be implicated as a single entity
- If more than one drug is rated “possible” or higher by RUCAM, evaluation should be sought by a specialist to rank the drugs by order of likelihood of causing DILI. This may be done on the basis of the signature pattern of DILI and a review of the literature^{74,75}

Level of evidence: 1b (validating cohort studies)

and validation of a new tool of causality assessment (or a modified version of a current causality assessment method), it may be necessary to evaluate the performance of the new tool against the gold standard of the “expert assessment.” The relative performance of the tool can be assessed in terms of sensitivity, specificity, and positive and negative predictive values.

Clinical notes for causality assessment

- A temporal relationship needs to be established with respect to medication exposure, laboratory data, and relevant clinical signs and symptoms which may need to be extracted from free-text documents.⁴⁰
- The “time of DILI onset” is the time of the first qualifying laboratory tests (see **Box 1**) except in cases in which symptoms directly related to DILI have clearly preceded the laboratory test that was performed.
- Under the category “course of the reaction,” “decrease” in levels of liver enzymes is to be interpreted as a fall by at least 50% from the peak value above the ULN (one can thereafter evaluate time to decrease >50%).
- **Risk factors:** alcohol intake of >2 drinks per day (>14 units/week) in women and >3 drinks per day (>21 units/week) in men is considered the upper threshold for alcohol intake to be considered a risk factor.
- The dose (defined daily dose or cumulative dose) of a drug may be important to consider when assessing causality,⁴¹ especially when considering the potential roles of more than one drug in a clinical episode. Although this does not appear in the RUCAM scale, information regarding the dose of the drug should be collected whenever possible because it may be used in the future with an improved diagnostic instrument. The possibility of a drug–drug interaction that modifies the drug concentration should also be taken into account: established drug–drug interactions should be highlighted, and possible drug–drug interactions (e.g., those with similar drug clearance pathways) can be noted.
- It should be specifically recorded whether the patient continued on the drug after the liver injury was identified and, if so, for what duration.

- Information regarding potential risk factors such as diabetes, metabolic syndrome,^{42,43} sex, ethnicity, and body mass index should be collected whenever possible, although these are not currently considered in the RUCAM scale.
- Exclusions to reduce potential misclassification: information regarding hepatitis A, B, and C, cytomegalovirus, and Epstein–Barr virus serology⁴⁴ should be sought whenever possible. In addition, biliary obstruction, hypoxic injury, and other alternative causes of acute liver injury should be considered. There have been reports suggesting that infection with hepatitis E virus (HEV) may be misdiagnosed as DILI;⁴⁴ therefore, HEV testing should be carried out if available. Considering the high rate of false-positive tests of HEV immunoglobulin M antibody, HEV RNA should be considered the gold-standard test for acute HEV infection if the patient is in the icteric stage. However, detectability of HEV RNA appears to vary; it is detectable from 1 week before the icteric stage to 2 weeks during acute hepatitis, but in one study it was detectable in only 20% (4/22) of patients from 3 weeks to 3 months,⁴⁵ although detection of HEV RNA has been reported even up to 6 months.⁴⁶ HEV immunoglobulin M antibody is a useful assay because it is detectable for a period of a few months.⁴⁷ Additionally, the greater utility of HEV immunoglobulin M antibody screening as compared with HEV RNA screening was established in a large series of Japanese blood donors with elevated ALT levels⁴⁸ and in severe hepatitis in pregnant women in India.⁴⁹
- In appropriate clinical settings, herpes simplex viral infection must be considered and excluded as a cause of prolonged cholestasis.
- When missing data limit causality assessment, expert assessment may be the only appropriate method to evaluate cases, and these should be grouped separately.

Chronicity

It has long been recognized that DILI can be associated with the development of progressive liver fibrosis and cirrhosis if treatment with the implicated drug is not discontinued.⁵⁰ More recently, persistence of DILI has been described after an acute episode of DILI, long after discontinuation of the implicated drug.^{28,51–53} It is a challenge to distinguish persistence, which may simply reflect slow resolution of the initial injury, from a self-sustained and potentially progressive chronic liver injury.

Given that fibrosis can develop as soon as 3 months after acute DILI,⁵⁰ it has been suggested that liver injury can be considered chronic if it has persisted longer than 3 months.^{54,55} In addition, natural history studies in large cohorts of subjects with acute liver injury of all etiologies indicate that liver failure develops within a 3-month period, which is associated with mortality.⁵⁶ A previous international consensus meeting recommended that a hepatocellular pattern of liver injury persisting >3 months after onset should be considered chronic liver injury.²² Noting that cholestatic liver injury typically resolves more slowly than hepatocellular injury, it was proposed that >6 months be the criterion for defining cholestatic

DILI. However, a recent prospective multicenter study of the natural history of DILI suggested that ~42% of those with an acute DILI episode had persistent elevation of liver enzymes at the 3-month follow-up, and 17% had persistent elevation at the 1-year follow-up.⁵⁷ Moreover, regardless of whether the injury was hepatocellular or cholestatic, the rate of resolution fell notably at 1 year, suggesting that this may be the best cutpoint to define chronicity.⁵⁷ We therefore propose that persistent DILI be defined as evidence of continued liver injury >3 months after hepatocellular or mixed liver injury, and >6 months after cholestatic liver injury, and that the term “chronic DILI” be reserved for cases in which there is evidence of persistent liver injury at >1 year after the onset of DILI (**Box 5**).

Clinical notes for chronicity of DILI

- Levels of liver enzyme elevations do not always reflect the degree of liver injury or its progression, and liver biopsy is clearly superior in this regard. But, in the context of assessing persistence or chronicity, measurement of liver enzymes may be the only practical method for identifying continued liver injury.
- The diagnosis of chronic DILI does not necessarily imply progressive liver injury because it appears that, in some patients, DILI will resolve after 1 year. This aspect requires further study. Progression of liver injury, in contrast to persistence of liver injury, can be established only if validated methods are used to demonstrate progression, such as clinical evidence of development or progression of cirrhosis, evidence of development or progression as shown by liver biopsy or other emerging tools such as ultrasound elastography, and serum markers of fibrosis.

Acute DILI occurring in patients with chronic liver disease. Patients with chronic liver disease such as chronic viral hepatitis can have acute episodes of DILI that may be difficult to distinguish

Box 5 Characteristics of persistent and chronic drug-induced liver injury (DILI)

- Initial clinical episode met the criteria to qualify as acute DILI (**Box 1**)
 - Initial episode on causality assessment has been considered possible, probable, or highly probable DILI on the basis of Roussel Uclaf Causality Assessment Method scoring criteria. Persistent DILI is defined as evidence of continued liver injury after withdrawal of the causative agent, beyond 3 months of follow-up for hepatocellular and mixed DILI, and beyond 6 months for cholestatic DILI
 - Chronic DILI is defined as evidence of continued liver injury after withdrawal of the causative agent beyond 12 months of follow-up, regardless of the classification of DILI
 - There is no new risk factor other than exposure to the suspect drug that would explain the persistence of liver injury, and other causes of chronic liver diseases have been excluded
- Level of evidence: 4 (prognostic cohort studies of modest quality)

from the natural history of their underlying disease. In these cases, standard causality assessment procedures can usually be applied, but additional phenotypic information, such as viral titers in patients with chronic viral hepatitis or CD4 counts in patients with AIDS, may be important.

Drug-associated chronic liver diseases. In contrast to acute DILI, treatment with some drugs has been associated with a variety of chronic liver diseases, including fatty liver disease, fibrosis, cirrhosis, nodular regenerative hyperplasia, and vascular diseases. Some drugs may aggravate or even initiate these conditions. For example, tamoxifen has been shown to be associated with fatty liver disease in those who have preexisting metabolic syndrome.⁴³ Standard causality assessment methods do not work well in these conditions, given the prolonged induction time to the recognition of chronic liver disease and other risk factors acting in conjunction with the drug as component causes.^{42,43} Patients with suspected chronic liver disease due to, or aggravated by, a drug will be classified according to whether chronic liver disease was present before starting the implicated drug (**Box 6**). A liver biopsy can provide critical information in chronic hepatitis with respect to the assessment of disease etiology, inflammation, and fibrosis or cirrhosis.⁵⁸

Clinical notes for drug-associated chronic liver disease

- The usual causality assessment methods, including the RUCAM scale, are not suitable for use in the context of drug-associated chronic liver diseases. In the latter, causality can be determined by adopting an accepted method of ranking levels of evidence and carrying out a critical, formal appraisal of the likelihood of a particular drug being a potential risk factor for the relevant form of chronic liver disease.
- Validated markers of chronic liver disease may include emerging tools such as ultrasound elastography and serum markers of fibrosis, in the appropriate context.^{59,60} This information should be included if available.

Drug-induced autoimmune hepatitis. DILI caused by certain drugs, including minocycline, L-dopa, nitrofurantoin, indomethacin, and diclofenac, can mimic idiopathic true autoimmune hepatitis (AIH).^{61,62} In addition, given that AIH is believed to have environmental triggers, it is at least theoretically possible that a drug could initiate *de novo* AIH. Furthermore, medications such as tumor necrosis factor-inhibitors may unmask or aggravate preexisting AIH.^{63,64} This situation is further confounded because patients genetically predisposed to DILI associated with the use of certain drugs may also be predisposed to develop AIH.¹⁶ It can be challenging to distinguish between drug-induced autoimmune features, *de novo* AIH initiated or unmasked by a drug, and a flare-up of AIH unrelated to drug therapy. A recently developed abbreviated scoring system for the diagnosis of AIH⁶⁵ has been validated in independent cohorts and should be used to support the diagnosis of all three conditions; however, it does not distinguish among them. This scoring system requires assessment of multiple autoantibodies (antinuclear antibody, smooth muscle cell antibody, liver–kidney microsomal antibodies, and soluble liver/liver–pancreas antibodies); quantitative serum α -globulins; exclusion of viral hepatitis; and, ideally, histological evaluation of the liver.^{66,67} In >80% of patients with idiopathic AIH, there is a relapse within 1 year in the absence of adequate immunosuppression, whereas in patients with drug-induced AIH, there is no relapse.^{61,68,69} This feature is probably the most reliable one to use in identifying drug-induced AIH (**Box 7**);⁶¹ however, the appropriate duration of therapy with immunosuppressant agents in this setting is still unknown.

Algorithm for consideration, diagnosis, and classification of DILI

Figure 1 presents an algorithm that was generated on the basis of the recommendations for the diagnosis and classification of DILI.

Algorithm for consideration, diagnosis, and classification of DILI

Figure 1 presents an algorithm that was generated on the basis of the recommendations for the diagnosis and classification of DILI.

Optimal data to be collected

For genetic studies, DILI cases may be derived from a variety of sources. We recommend the collection of the patient history data described in **Table 1**.

Box 6 Characteristics of drug-associated chronic liver disease

- Evidence of chronic liver disease is established on the basis of validated methods such as clinical evidence of cirrhosis, histological evidence of chronic liver disease, and imaging in cases of vascular disorder and tumors, as appropriate
- Evidence of drug intake for an appropriate duration preceding the appearance of symptoms, signs, or test results suggestive of chronic liver disease
- Exclusion of other etiologies of chronic disease (outlined in **Supplementary Table S3** online)

Level of evidence: 1b (prospective/validating cohort studies with good follow-up)

Box 7 Characteristics of drug-induced autoimmune hepatitis (AIH)

- The score is ≥ 6 points on simplified diagnostic criteria for AIH (scores >6 points with the simplified criteria can be obtained if liver biopsy is performed. Hennes *et al.*⁶⁵ consider a probable diagnostic score to be ≥ 6)
- Injury resolves on withdrawal of medication that triggered the AIH, with or without immunosuppressive therapy to induce remission
- No relapse within a period of 1 year after withdrawal of all immunosuppressants. This criterion needs further confirmation and cannot be considered pathognomonic because it is quite variable depending on the cohorts analyzed

Level of evidence: 2b (exploratory cohort study)

