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Regulation and Guideline

Guidelines for the Diagnosis and Management of Herb-Induced Liver Injury*

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ABSTRACT Herb-induced liver injury (HILI) is a type of adverse drug reactions related to using Chinese medicine (CM) or herbal medicine (HM), and is now a growing segment of drug-induced liver injury (DILI) worldwide. Owing to the complicated compositions and miscellaneous risk factors associated with the clinical usage of CM or HM, it is more challenging to diagnose and manage HILI than DILI. In the present guideline issued by the China Association of Chinese Medicine (CACM), the authors present an evidence chain-based workflow with 9 structured judgment criteria for diagnosing HILI. The 3 diagnostic ending points—suspected diagnosis, clinical diagnosis, and confirmed diagnosis—could be reached according to the length of the evidence chain acquired in the structured diagnostic workflow. Either identifying the species of CM or HM or excluding adulterations and toxin contaminants was strongly recommended to improve the level of evidence for a clinical diagnosis of HILI. In addition, the authors report that the improper use of CM, which violates the general law of CM theory, is one of the most important factors that contributes to HILI and should be avoided. By contrast, based on syndrome differentiation, some CM can also be used to treat HILI if used in accordance with the general law of CM theory. Therefore, 9 recommendations are put forward in this guideline.

KEYWORDS herb-induced liver injury, diagnosis, treatment, management, Chinese medicine, guideline

Preamble

The writing group was invited by the China Association of Chinese Medicine (CACM) and sponsored by the China Association of Science and Technology to develop clinical guidelines for the diagnosis and management of herb-induced liver injury (HILI). These clinical guidelines were developed based on the following resources: (1) a formal review and analysis of the published literature on the topic by China National Knowledge Infrastructure (CNKI) and MEDLINE search up to February 2016; (2) the American College of Gastroenterology's Clinical Guideline for the Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury; (3) the Chinese Medical Association's Guidelines for the Management of Drug-Induced Liver Injury; (4) regulation of the Standardization Administration of China, the Directives for Standardization – Part 1: Structure and Drafting of Standards (GB/T 1.1-2009); and (5) the experience of the independent expert reviewers and writing group authors with regard to HILI.

These guidelines and recommendations are intended for use by physicians, clinical pharmacists, medical supervisors, and other healthcare providers to achieve preferable approaches regarding the diagnosis, treatment, and management of HILI. They are formulaic for general applications in the diagnosis, treatment, and management of HILI and could be flexibly adjusted when applied to individual HILI cases. Recommendations are developed based on evidence wherever possible, and, when such evidence

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is unavailable, recommendations are made based on the consensus opinion of the writing group and the advisory experts committee, according to the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) evidence classification system.[1]

Introduction

Herb-induced liver injury (HILI) refers to liver damage associated with the use of Chinese medicine (CM), herbal medicine (HM) or their related products. Recently, HILI has been given more attention because of increasing reports of HILI with the extensive worldwide application of CM and HM as well as continuous improvements in monitoring adverse drug reactions.[2] Despite its low incidence among the general population, HILI can lead to jaundice, liver failure, or even death. Because of the wide range of presentations, culprit agents and a lack of objective diagnostic tests, the diagnosis and management of HILI and DILI remains one of the most challenging problems in clinical practice.

Diverse factors can result in HILI, including drug characteristics, improper drug use and individual differences.[3] Owing to the complicated composition and miscellaneous risk factors in the clinical usage of herbal products, it is more challenging to diagnose and manage HILI than DILI. The lack of diagnostic norms and guidelines that could reflect the complexity of CM and HM results in the current inaccurate clinical diagnosis of HILI. In addition, the lack of a unified classification of culprit agents also increases the ratio of HILI to DILI, resulting in an incorrect understanding of the safety of CM and HM.[4] Therefore, it is critical to establish HILI diagnosis and management guidelines that are especially applicable to CM and HM, to provide more accurate causality recognition between liver injury and either CM or HM use in an objective and direct manner. Appropriate guidelines can also provide a rationale for the use of CM or HM, reduce the occurrence of liver injury, and promote development of CM, in clinic.

The writing group recognized that many clinical problems needed to be solved in the field of HILI diagnosis, treatment, and management; hence, these guidelines require ongoing revisions and improvements as more evidence-based data are obtained in the future.

Epidemiology of HILI

Incidence Rate of HILI

The prevalence and incidence of DILI and HILI throughout the world are still unknown. Currently, there is only an estimated number of patients for an extended period in a specific region. Owing to non-commercial and non-prescription reasons, the incidence of HILI is still more difficult to estimate than that of DILI, and the overall incidence of HILI remains unknown.[5] We can merely calculate the constituent ratio of HILI within DILI.

Proportion of HILI in DILI

Some small-scale surveys from different countries and regions showed discrepant data with regard to the proportion of HILI in DILI, ranging from 0.5%–24.2%.[6,7] A multicenter retrospective cohort study showed that the proportion of HILI in DILI was 21% in China.[8] The retrospective and prospective data from the DILI Network indicated that 18% and 16% of DILI cases were attributed to herbal and dietary supplements (HDS) in the United States, respectively.[9,10] However, it should be noted that most but not all of the natural medicines, health products, and dietary supplements contained herbal products. Overall, based on current data, the proportion of HILI in DILI was approximately 20%; and the other 80% of DILI cases were associated with Western medicines (mostly synthetic drugs).

It should be noted that CM could be divided into 21 categories of activities, such as diaphoretic and antipyretic, while synthetic drugs can be classified into 11 subcategories such as anti-tuberculosis drugs and anti-tumor drugs.[4] Hence, it is not reasonable to compare the entire CM encyclopedia with a category of synthetic drugs (such as anti-tuberculosis) or a specific synthetic drug (such as acetaminophen). The incidence of liver injury caused by CM was relatively lower than that of synthetic drugs if CM and synthetic medicine were considered 2 groups. Therefore, to avoid an incorrect understanding of the safety of CM or HM, canonical classification and comparisons of culprit drugs are recommended by 3 levels in Recommendation 1.

Clinical Characteristics of HILI

Despite some reports showing several different characteristics of HILI versus DILI, the overall clinical features of HILI were similar to DILI. A DILI Network study showed that there were more females than males who developed HILI,[9] while 2 Chinese studies showed contradictory results.[11,12] HILI patients might have neither age-related susceptibility nor specific relevance to age, although some studies reported that patients over 40 years old composed the majority.[13,14]

The reason for this phenomenon might be related to the frequency of drug use and the age-related changes in the cytochrome P450 isoenzymes.[15]

Recommendation 1

Canonical classification and comparisons of the culprit drugs are recommended using 3 levels (strong recommendation, high level of evidence)

(1) The first level of classification of culprit drugs can be divided into CM/HM, synthetic drugs, and biological preparations.

(2) The second level of classification of CM and synthetic drugs can be divided into categories according to their therapeutic purpose.

(3) The third level of classification and comparisons can be performed based on a direct comparison of a specific CM with a particular synthetic drug.

Risk Factors of HILI

CM Species and Quality

Although CM and HM are quite safe from a general perspective, some species have been recognized as having intrinsic hepatotoxicity when used at excessive doses, such as *Tripterygium wilfordii* Hook. f. and *Dioscorea bulbifera* L.[16] Beyond those limited species, most types of CMs and HMs are associated with HILI exert idiosyncratic hepatotoxicity.

It has been well recognized that either misuse of a CM species or the inferior quality of herbal products are important risk factors for HILI. First, CM and HM are susceptible to variability depending upon the harvesting location, methods of manufacture, and preservation procedure, all of which can lead to variability of the chemical composition from batch to batch.[17] The variability of the quality may be an important risk factor for HILI.[2] Second, some toxic plants were occasionally misused as substitutes for genuine species and thus caused HILI. For example, *Radix Gynurae* Segeti. (Tu Sanqi in Chinese) is sometimes misused as *Panax notoginseng* (Burk.) F. H. Chen (Sanqi in Chinese). *Panax notoginseng* (Burk.) F. H. Chen contains ginsenosides and is a safe herb in CM; however, *Radix Gynurae* Segeti (meaning substitutive for Sanqi) contains pyrrolizidine alkaloids (PAs) and has been proven to induce hepatic sinusoidal obstruction syndrome/veno-occlusive disease (HSOS/VOD).[18,19] Third, improper processing of CM might increase the risk of liver injury. It has been well documented that unprocessed or insufficiently processed *Polygonum multiflorum* Thunb. (Heshouwu in Chinese) results in a higher risk of idiosyncratic liver injury than completely processed *Polygonum multiflorum* Thunb. (Zhi Shouwu in Chinese).[20] Finally, herbal products contaminated by excessive exogenous harmful substances, e.g., pesticides, heavy metals, and mycotoxins, during the process of cultivation, processing, storage, and transport could lead to further liver injury.

Improper Use of CM

The use of CM should follow the CM theory, which guides herb combinations, formula prescriptions, and decoction based on CM syndrome differentiation. The proper use of CM formulae (dose, period of treatment, and formula compatibility) has been practically recognized for treating suitable syndromes or diseases and can assure the safety of the treatment, while improper or inappropriate use of formulae against the CM theory could raise the risk of liver injury.[21] This point requires specific attention when CM is used outside the guidance of a qualified CM practitioner, such as folk medicine use, patient self-use, and administration from Western healthcare providers.

Host Factors

Host-related risk factors for HILI, including genetic and nongenetic risk factors, can be pivotal in causing HILI; these factors can be herb- or compound-specific in nature.[2] The current understanding of the genetic risk factors for HILI or DILI is still in its preliminary stage. However, human leukocyte antigen (HLA) risk alleles have been found to be associated with the susceptibility of developing idiosyncratic DILI.[22] Beyond genetic risk factors, age, gender, pregnancy, malnutrition, obesity, diabetes mellitus, co-morbidities (especially including underlying liver disease), and habitus under the CM theory all may confer susceptibility to HILI in a drug-specific manner.[2,23] However, such risk factors still need solid evidence to show a direct correlation to a specific herb. Alternatively, a predictive risk model might be useful to guide the physicians' usage of CM to avoid the development of HILI.

Combined Medications between CM and Synthetic Drugs

Polypharmacy and herb-drug interactions are often considered risk factors for HILI, although there is limited evidence showing a specific example. However, much more consideration should be made regarding

the herb-drug combinations in diagnosing HILI. A complete medication history is important to avoid a misdiagnosis of HILI.[24] For instance, patients might take an anti-flu CM along with acetaminophen, which is the most popular over the counter (OTC) drug to relieve flu symptoms but has well established hepatotoxicity; thus, incomplete inquiry of the patient's medication history might implicate the wrong culprit agent.[24] Moreover, it should be especially concerning that some CM-related patent drugs that contain synthetic drugs as well as herbal components might be misrepresentative, because their trade names deceptively suggest that they are pure herbal preparations. If these preparations contain a known hepatotoxic agent (commonly acetaminophen), such liver injuries may not be strictly diagnosed as HILI. Similarly, CM-related products with modifications should be verified by pharmaceutical analysis before diagnosing a patient with HILI.

Characteristics of HILI

Despite the wide spectrum of CMs and HMs related to HILI, there is little knowledge of the specific clinical symptoms of HILI, and there are no known features to distinguish HILI from DILI. The median time from starting CM or HM use to the onset of HILI is 1 to 3 months, but it should be noted that the latency of HILI might be longer than that of DILI.[4] HILI might present as acute, subacute or chronic liver injuries that were already established.[13] The clinical symptoms of acute and subacute HILI vary greatly. Some HILI patients may be asymptomatic with biochemical liver abnormalities; others may experience fatigue, loss of appetite, nausea, disgust towards greasy foods, epigastric discomfort, hepatalgia, and flatulence. Patients with cholestasis may have jaundice with yellowish pigmentation of the skin or sclera, itchiness, pale feces, and dark urine. A small number of patients may present extrahepatic allergy symptoms, such as rash and abnormal elevation of eosinophilia in peripheral blood,[14] and a limited number of severe cases can develop into liver failure or even death. Chronic HILI can manifest as various forms of chronic liver disease, including chronic hepatitis, cirrhosis, chronic intrahepatic cholestasis, sclerosing cholangitis, fatty liver, liver phospholipidosis, HSOS/VOD, liver neoplasms, and idiopathic portal hypertension.[25]

The histopathological characteristics of HILI liver tissues include some nonspecific pathological changes such as hepatic cell injury, inflammatory cell infiltration, hyperplasia of tissue fibers, bile duct injury and vasculopathy. Compared to liver injuries caused by synthetic drugs, HILI is more likely to induce confluent necrosis, a fibrous septum, and lymphocyte or plasmocyte infiltration in the portal area.[26]

Clinical Classification of HILI

Similar to DILI, HILI can be separated into intrinsic or idiosyncratic types. Intrinsic HILI is usually dose- or time-dependent and predictable with relatively short latency and little individual differences. However, idiosyncratic HILI is unpredictable, affects only susceptible individuals, is less dose-dependent, and has variable latency, presentation, and course. Some CMs or HMs can cause either intrinsic or idiosyncratic types of HILI.[2,27]

HILI can also be separated into acute or chronic subtypes; the latter can be practically defined as the failure of return either liver enzymes or bilirubin to pre-HILI levels, and/or other signs or symptoms of ongoing liver disease 6 months after HILI onset.[2,25] An important consideration in managing HILI is the possibility that the percentage of individuals with chronic HILI may be higher than that of DILI.[4]

The most common and useful classification of HILI is the stratification into 4 subtypes according to pattern or target cells of liver injury at presentation: hepatocellular, cholestatic, mixed, or hepatic vascular endothelium injury. The first three types can be separated using an R-value, which is defined as fold upper limit of normal (ULN) of serum alanine aminotransferase divided by the fold ULN of serum alkaline phosphatase. $R \geqslant 5$ is conventionally defined as hepatocellular HILI, $R < 2$ is defined as cholestatic HILI, and $2 < R < 5$ is defined as "mixed" HILI. The fourth type, hepatic vascular endothelium-injured HILI, is selectively found in patients with HSOS/VOD, which is caused by herbs containing pyrrolizidine alkaloids (e.g., Tu Sanqi).

In addition, HILI can be divided into syndrome-based subtypes according to the CM theory. The common syndrome types include "dampness-heat jaundice", "Gan (Liver) depression and Pi (Spleen) deficiency", "internal obstruction of cold-dampness", "qi stagnation and blood stasis", and "Gan (Liver)-Shen (Kidney) yin deficiency", all of which are defined in the International Standard Chinese-English Basic Nomenclature of Chinese Medicine.[28] CM physicians usually treat HILI patients with a specific CM formula corresponding to syndrome-based subtypes.

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Severity Grading in HILI

It has been well-recognized that the severity of either DILI or HILI cases can vary greatly, from asymptomatic elevations in serum enzyme levels to acute liver failure and even death. Using the variability in the manifestation of DILI or HILI, a well-organized 5-point scale (Appendix 1) proposed by the DILI Network can provide an objective manner to categorize the severity of DILI and HILI and give a rough prognostic view for physicians to manage those patients. Along with this DILI network scale, there are different grading systems developed by other associations or organizations, such as the Acquired Immune Deficiency Syndrome (AIDS) Clinical Trials Group (CTG) and the Cancer Therapy Evaluation Program of the National Cancer Institute (NCI) at the National Institutes of Health. The latter scale is also referred to as the Common Terminology Criteria for Adverse Events, Version 4.0 (CTCAE V4). These 2 grading systems are similar but have some limitations in clinical practice. For instance, the CTCAE V4 defines "grade 3-severe" as ALT levels of 5 to 20 times greater than ULN (about 200 to 800 U/L), but an elevation of serum enzymes without symptoms or jaundice is not considered severe liver injury. In addition, the grading of liver biochemistry elevations by calculating multiples of the ULN in CTCAE V4 is sometimes inappropriate and should be adjusted to the baseline values in those patients with underlying chronic liver disease. In the management of HILI, this aspect should receive additional attention since HILI may be more frequently the result of long-term administration of CM or HM used for treating underlying chronic liver diseases. Therefore, the U.S. DILI Network 5-point grading system is recommended to categorize the severity of HILI.

Recommendation 2

HILI can be classified using the following criteria:

(1) Intrinsic or idiosyncratic subtypes (strong recommendation, high level of evidence).

(2) Acute or chronic subtypes (strong recommendation, high level of evidence).

(3) Hepatocellular, cholestatic, mixed, or hepatic vascular endothelium-injured subtypes (strong recommendation, high level of evidence).

(4) "Dampness-heat jaundice", "Gan (Liver) depression and Pi (Spleen) deficiency", "syndrome of internal obstruction of cold-dampness", "syndrome of qi stagnation and blood stasis", and "Gan (Liver)-Shen (Kidney) yin deficiency" (conditional recommendation, low level of evidence).

Recommendation 3

The severity of HILI can be graded into 5 levels: mild (level 1), moderate (level 2), moderate to severe (level 3), severe (level 4), and fatal (level 5), strong recommendation, high level of evidence.

Differential Diagnosis for HILI

Diagnosing HILI is challenging since the clinical presentation and liver histopathological features of HILI can mimic nearly all known forms of acute or chronic liver injury, and there are no features of HILI distinct from those of DILI to date. Hitherto, HILI is still an exclusionary diagnosis based on, for example, the patients' medical history, physical examination, laboratory tests and imaging examinations. Examining the liver histopathology might be helpful but is not mandatory in the diagnosis of HILI.[2,25] It should be noted that some types of preexisting chronic liver diseases, e.g., alcoholic hepatitis, autoimmune hepatitis, and chronic hepatitis B virus (HBV), can present with an icteric flare that may be mistaken as DILI or HILI.[2] These major diseases are summarized below.

Viral Hepatitis

Viral hepatitis (A, B, C, and E) or virus infection-related liver dysfunction (*Epstein-Barr* virus, cytomegalovirus, and herpes simplex virus infection) should be excluded in patients with suspected hepatocellular or mixed HILI by using standard serology tests, including anti-HAV IgM, anti-HBsAg, anti-HCV antibodies; quantification of HCV RNA, anti-HEV IgM, anti-EBV IgM, anti-CMV IgM, anti-HSV IgM antibodies, and a thorough inquiry of the patients' epidemiological history.

Autoimmune Liver Diseases

Autoimmune liver diseases include autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and IgG4-related hepatopathy. In individuals with suspected hepatocellular or mixed HILI, AIH should be excluded by using serological tests for antinuclear antibodies, anti-smooth muscle antibodies, anti-kidney microsomal antibodies, anti-soluble liver antigen antibodies. In individuals with suspected cholestatic HILI, PBC and PSC should be especially excluded for patients with evidence of obvious biliary tract pathology on abdominal imaging. Anti-mitochondrial antibodies, especially its subtype M2

antibody, are recommended for a PBC diagnosis. Liver nuclear magnetic resonance imaging examination is recommended for diagnosing PSC.

An important consideration in diagnosing HILI is the possibility that some HILI cases might present either similar clinical characteristics with AIH or serological autoantibodies. Such situations should be noted with special attention to discriminate HILI from AIH: (1) relapse of AIH – not associated to HILI; (2) AIH induced by CM/HM; and (3) AIH-like HILI. A liver biopsy should be considered if AIH remains a competing etiology to HILI. In addition, prudent use of corticosteroids to observe the therapeutic response and potential recurrence after withdrawal of corticosteroids is a preferable approach to distinguish AIH and HILI during the course of treatment.

Alcoholic Liver Disease

In individuals with suspected HILI, the amount of alcohol consumption should be below the diagnostic standard of alcoholic liver disease (ALD), which is defined as either alcohol intake ⩾ 40 g per day in men or ⩾ 20 g per day in women for more than 5 years or instances of heavy drinking within the previous 2 weeks with alcohol intake ⩾ 80 g/d. It should be noted that individuals with alcoholic hepatitis presenting an icteric flare may be mistakenly diagnosed with HILI.

Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of preexisting chronic liver disease among the general population. Although patients with NAFLD and obesity might not always have an increased risk of developing DILI/HILI, NAFLD should be excluded by routine examination of the body mass index and blood lipid levels as well as abdominal ultrasonography or computerized tomography when necessary.

Inherited Metabolic Liver Disease

Although rare, inherited liver diseases such as Wilson's disease (hepatolenticular degeneration), α 1-antitrypsin deficiency, and hereditary hemochromatosis should be excluded when diagnosing HILI via serological examinations of ceruloplasmin, α-antitrypsin, serum ferritin, and transferrin, among others.

Biliary Disease

In individuals with suspected cholestatic HILI, abdominal imaging by ultrasound, computerized tomography, or magnetic resonance scan should be performed to exclude biliary tract etiology, including intrahepatic and extrahepatic biliary obstruction (calculus) and tumors. Endoscopic retrograde cholangiopancreatography (ERCP) may be used if necessary.

Vascular Disease

Vascular diseases such as Budd-Chiari syndrome and sinusoidal obstruction syndrome should be considered when clinically appropriate by using ultrasonography, computerized tomography, and magnetic resonance imaging.

Other Diseases

In some cases, industrial and environmental toxins as well as ingestion of poisonous foods might be mistaken for HILI, which warrants additional exclusion by investigating the patients' personal history as well as serological examination of lead, mercury or other poisons. Moreover, local liver infection, systemic infection (sepsis), heart failure, hypotension, and shock-induced hepatic injury should be excluded when clinically appropriate.

Recommendation 4

A clinical diagnosis of HILI should be based on a medication history, physical examination, laboratory tests, imaging tests, and liver histopathology (when necessary) to exclude non-drug-related etiologies of liver injury, including viral, autoimmune, alcoholic, inherited/metabolic, biliary, vascular-related, and other systemic dysfunctions (strong recommendation, low level of evidence).

Strategy and Method for HILI Diagnosis

HILI falls under the umbrella of DILI and therefore can be diagnosed according to the Guidelines for the Management of DILI released by the American College of Gastroenterology.[2] However, making a diagnostic connection between CM or HM and liver injury is especially challenging compared to synthetic drugs because of the complicated composition, variety of quality, and combinational usage of herbal products[4,5] For instance, there are either adulterated or unintentional combinations of synthetic drugs with CMs or HMs, which might result in a mistaken attribution for suspected agents. In a Taiwanese report, 24% of Chinese patent drugs were adulterated with synthetic drugs without

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physicians' knowledge;[29] thus, these adulterated drugs will result in an incorrect attribution regarding the cause of liver injury. In addition, some government-authorized CM patent drugs are legally combined with synthetic drugs such as acetaminophen, but they are seldom recognized for their CM-like trade names. Third, improper substitutes of CMs, variations in quality (including fake CM), and contamination with exogenous toxins might cause a mistaken causality attribution of HILI.

Although the Roussel Uclaf Causality Assessment Method (RUCAM)[30] has been widely documented in the literature for DILI, it is rarely used in general clinical practice because of its ambiguities on how to score certain sections[31] and its high variability among different practitioners.[32] In diagnosing HILI, it has been noted that RUCAM is more limited in assessing the causality of herbal and dietary supplements (HDS) owing to fewer warning labels and published reports regarding the hepatotoxicity and frequent polypharmacy of these supplements.[2] Moreover, the quality variation, adulteration, and toxin contaminants of CMs and HMs are not included in the RUCAM system. A DILI Network study illustrated that, compared to the DILI Network structured expert opinion process (SEOP) system, a lower percentage of highly probable causality was reached using RUCAM system; and some cases given a high RUCAM score (> 8 points) were judged as "unlikely".[32] These results suggest that the RUCAM system could be a basal assessment for HILI diagnosis, but not always be the final adjudication.

The SEOP system is a newly proposed and powerful causality assessment strategy for DILI based on a consensus of expert opinions,[32] but this system is usually limited in general clinical practice because of a lack of sufficiently qualified experts. In addition, according to the SEOP process, a non-consensus of the experts' opinions will result in additional independent reviews and the requirement of more time to complete the diagnosis. Its voting process also introduces non-objective factors into the diagnostic progress.

Recently, a new causality identification strategy especially designed for HILI diagnosis has been proposed: the integrated evidence-chain method (iEC),[33] which addresses the abovementioned challenges. The iEC method uses a structured flowchart (Appendix 2) to organize all the diagnostic data into an evidence chain and a tri-grade diagnosis system. Distinct from the 5 likelihood level-based categories in RUCAM or SEOP, a diagnosis based on the iEC method was divided into 3 levels—suspected diagnosis, clinical diagnosis, and confirmed diagnosis. The arrival to a level of diagnosis relies only on the length of evidence chain acquired using the iEC flowchart.[34] With the iEC flowchart, the RUCAM score is included only as a basal causality assessment criterion and 9 total judgment criteria compose an evidence chain for diagnosing a case of HILI.

Diagnostic Criteria of HILI

When a suspected HILI case enters the structured flowchart of the iEC method, there are 3 diagnostic ending points suspected–diagnosis, clinical diagnosis, and confirmed diagnosis–that might be reached according to the length of the evidence chain acquired. The 9 judgement criteria are listed as follows.

Ⅰ In Accordance with Liver Biochemistry Standards of DILI and Medication History of CM/HM or Related Products Prior to Onset of Abnormal Liver Biochemistries

The liver biochemistry criteria for diagnosing HILI is based on the diagnostic biochemical criteria for DILI as recommended by the International Serious Adverse Event Consortium (iSAEC) in 2011:[35] (1) ALT $\geqslant 5\times$ ULN; or (b) ALP $\geqslant 2\times$ ULN, particularly with a rise of both 5'-nucleotidase or γ-glutamyl transpeptidase and the exclusion of bone disease-induced ALP elevation; or (2) ALT $\geqslant 3\times$ ULN and TBiL $\geqslant 2\times$ ULN. For patients with previous liver injury, the ULN should be replaced by the mean baseline values obtained prior to exposure to the implicated drug. Although such biochemical criteria are the international consensus for the clinical threshold for DILI, it should be noted that some drugs, especially those with mitochondrial toxicity (e.g., valproate or fialuridine hepatotoxicity), may not induce these threshold values.[35] The time from medication start to onset of abnormal liver biochemistries should be less than 6 months.

Ⅱ Exclusion of Non-Drug Etiologies of Liver Injury

In diagnosing HILI, non-drug etiologies of liver injury, including viral, autoimmune, alcoholic, inherited metabolic, biliary, vascular-related, and other systemic dysfunction, should be reasonably excluded using physical examination, laboratory tests and imaging techniques, among others. Liver biopsy is not mandatory and should be selectively performed in situations with

suspected yet unclear etiology. Moreover, special attention should be paid to discriminate HILI cases among individuals with a preexisting chronic liver disease from an acute exacerbation of said chronic liver disease, e.g., chronic hepatitis B.

Ⅲ RUCAM Score ⩾ 3 Points

In the flowchart of the iEC method, a RUCAM score equal to or exceeding 3 points (defined as "possible"[30]) is one of the 9 obligatory criteria to diagnose a case of HILI (Appendix 3). Because of the limitations of the RUCAM method in attributing the causality to CM or HM, it is not recommended to assess the causality of HILI solely according to the RUCAM score. A high RUCAM score does not always confer a high likelihood with a specific CM or HM, especially if the species, quality, adulterations, and toxin contaminants are not examined.

Ⅳ Exclusion of Combinational Use with Synthetic Drugs of Known Hepatotoxicity

Since CM or HM are almost always used with synthetic drugs, the causality should be carefully assessed. However, physicians must be aware that patients may not always be forthcoming with their history of CM or HM use.[36] A newly compiled questionnaire for drug, CM, or HM usage (Appendix 4) is recommended to obtain a thorough medication history. Since CMs and HMs are extensively used in China, a comprehensive literature review should be performed by using not only the LiverTox and PubMed databases but also the CNKI. To facilitate the acquisition of this Chinese literature and knowledge for non-Chinese physicians and researchers, we have launched an online HILI database embedded with an expert-reviewed DILI/HILI agent referential dictionary (www.HILIConsortium.org).

Ⅴ Verification of CM/HM or Related Products, Including the Remaining Drug Materials, Official License Number, Formula Composition, and Usage

An important consideration in assessing the causality is the possibility that CM- or HM-related products may comprise misused substitutes or be of inferior quality. It is strongly recommended to obtain and verify the CM or HM products whenever possible.

Ⅵ Identification of the Species of CM or HM, and Exclusion of Adulterations and Toxin Contaminants

If the CM or HM products could not be obtained and verified using general approaches, the remaining drug materials in question should be identified to ascertain the true species and exclude adulterations. For those CMs or HMs in the form of powders, extracts, or raw materials, identification is strongly recommended using appropriate methods, including DNA barcoding, macroscopic or microscopic character identification, and chemical determination (e.g., a combination of chromatography and mass spectrometry). It is also recommended to determine and then exclude any exogenous toxin contaminants in CM and HM products, especially those purchased using informal methods. The presence of pesticides, heavy metals, and mycotoxins could be determined at qualified institutions or laboratories based on the Chinese Pharmacopoeia (2015 edition).

Ⅶ Detection of the Characteristic *In Vivo* Metabolites Of CMs and HMs

For situations in which the remaining drug materials cannot be obtained, it would be helpful if the characteristic metabolites of the suspected CM/HM in collectable specimens (e.g., blood, urine, or feces) from patients can be detected.

Ⅷ Re-challenge Event of Suspected CM or HM

A re-challenge event can provide strong evidence to confirm a causal relationship with the suspected agent. Nevertheless, re-administration of a drug (including CM or HM) thought to have likely caused hepatotoxicity in a patient is strongly discouraged unless the re-challenge event occurred accidentally. However, negative re-challenge does not exclude HILI.

Ⅸ Detection of Characteristic *In Vivo* Biomarkers Associated with CM- or HM-Induced Liver Injury

If the *in vivo* characteristic biomarkers associated with CM or HM-induced liver injury can be detected, it would be helpful to confirm the causality of HILI. For instance, detection of PAs-protein adducts can provide direct evidence to make a diagnosis of PAs-induced HSOS based on clinically manifested evidence.[18]

According to the abovementioned judgement criteria, the requirements for the three levels of diagnosis are listed as below: for suspected diagnosis: (Ⅰ) + (Ⅱ) + (Ⅲ); for clinical diagnosis: suspected diagnosis + (Ⅳ) + [(Ⅴ) or (Ⅵ) or (Ⅶ)] for confirmed diagnosis: suspected diagnosis + (Ⅷ); or clinical diagnosis + (Ⅷ) or (Ⅸ).

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Recommendation 5

Based on the exclusive diagnosis of DILI, the diagnostic standard of HILI is especially strengthened upon completing the evidence chain. Relying on the length of the evidence chain acquired, a diagnosis of HILI is divided into 3 grades-suspected diagnosis, clinical diagnosis, and confirmed diagnosis. Acquisition and identification of the species of suspected CM or HM, exclusions of adulteration and toxin contaminant products, and determination of the characteristic *in vivo* metabolites or biomarkers can extend the length of the evidence chain (strong recommendation, high level of evidence).

Recommendation 6

A questionnaire recording drug, CM, or HM usage (Appendix 4) is recommended to obtain a thorough inquiry of medication history. Acquisition and verification of the CM or HM products, including the remaining drug materials, official license number, formula composition, and usage, are strongly recommended (strong recommendation, moderate level of evidence).

Recommendation 7

Identification of the species of the remaining drug materials of the suspected CM or HM as well as exclusions of adulterations and toxin contaminants are strongly recommended in diagnosing HILI. For situations in which the remaining drug materials cannot be acquired, it would be helpful if either the characteristic metabolites of the suspected CM or HM or the characteristic biomarkers associated with CM- and HM-induced liver injury can be detected in patient specimens (e.g., blood, urine, or feces) (strong recommendation, high level of evidence).

Recommendation 8

A re-challenge event can provide strong evidence to confirm a causal relationship with the suspected agent, but re-administration of the suspected CM or HM is strongly discouraged (strong recommendation, high level of evidence).

Treatment

Withdrawing Drugs

It is well recognized that withdrawal of the offending CM or HM is the basic and most common approach in the treatment of HILI. Most HILI patients have a good prognosis after promptly discontinuing suspected medication.[4] For those patients who cannot discontinue CM or HM for therapeutic purposes, a dose reduction is recommended.

Treatment with Liver-Protective Drugs

Liver-protective drugs can reduce the extent of liver injury via anti-inflammatory, anti-oxidative, or biliary excretory activities. The most commonly used liver-protective drugs include the following: the anti-inflammatory drugs glycyrrhizin, silymarin, and bicyclol; the anti-oxidative drugs N-acetyl cysteine, glutathione, and tiopronin; and biliary excretion drugs ursodeoxycholic acid and adenosine methionine. Although several clinical trials have demonstrated the effectiveness of these drugs for HILI, there is still a lack of quality evidence.[2,25]

Treatment with CM Based on Syndrome Differentiation

Apart from the possibility of inducing liver injury, CM has also been used to treat HILI. Based on the syndrome differentiation theory, CM physicians can use specific CM formulae to regulate the "bias" of HILI patients with the corresponding syndrome-based type. For instance, the syndrome of dampness-heat jaundice can be treated with a formula that clears heat and removes dampness; the syndrome of internal obstruction of cold-dampness can be treated with a warming cold-dampness and removing blood stasis formula; the syndrome of qi stagnation and blood stasis can be treated with a formula that relieves Liver qi and removes blood stasis; and the syndrome of "Gan (Liver)-Shen (Kidney) yin deficiency can be treated with a nourishing Gan and Shen formula. Although some literature supports the effectiveness of syndrome differentiation-based CM therapy,[37] more quality evidence is still needed.

Treatment with Corticosteroids

Owing to a lack of quality evidence, corticosteroid therapy should be limited and might be selectively used in HILI patients with hypersensitivity or evident autoimmune-like symptoms to carefully balance the benefits and adverse reactions. Considering that chronic recurrent DILI/HILI frequently accompanies autoimmune-like symptoms, some researchers have proposed to use the corticosteroid therapy traditionally used for AIH in treating chronic DILI/HILI with a relapse history.[38]

Other Treatments

Artificial liver support can be used in patients with liver failure, but quality evidence supporting this notion is still required. For acute or sub-acute liver failure patients liver transplantation should be considered.

Recommendation 9

Treatment of HILI is similar to that of DILI, which includes the basic approach–i.e., withdrawal of the offending CM or HM (strong recommendation, high level of evidence)–as well as treatment with liver-protective drugs (conditional recommendation, moderate level of evidence), artificial liver support for patients with liver failure (conditional recommendation, moderate level of evidence), and liver transplantation, if necessary (strong recommendation, moderate level of evidence).

Prevention of HILI

Having a high level of vigilance with respect to CM or HM hepatotoxicity may be the best management approach to prevent the occurrence of HILI. Some online sources of liver injury potential knowledges of CM or HM could be found at www.livertox.nih.gov and www.HILIConsortium.org. Herbs reported as exerting hepatotoxicity should be used with caution regarding the dose and duration. HILI patients should avoid re-exposure to those herbs (or herbs containing same hepatotoxic chemical structures) that have previously caused liver injury. Despite no confirmable data to show that underlying chronic liver disease is an important risk factor for HILI, it cannot be excluded that patients with chronic hepatitis B, C or nonalcoholic fatty liver disease may be more prone to liver injury due to specific CM or HM.

Although CM and HM are shielded under the notion of "natural and safe" alternative treatments, their hepatotoxicity potential has often been ignored by people and health care providers. It was reported that a large percentage of HILI cases were caused by or associated with the unreasonable use of CM or HM products without the guidance of CM physicians[4]. Names and categories of common used CMs are presented in Appendix 5. Under CM theory, CM formula with special herb combinations is prescribed intentionally to certain subcategory of patients fitting CM theory-defined syndrome, but not to whole population of a disease defined by modern medicine. The matchup between formula and syndrome is considered to be either effective or little side effects in clinical practice; while the mismatching is considered to be both less effective and high risk of safety concerns. For instance, *Polygonum multiflorum* Thunb. is supposed to use in those patients fitting such CM theory-defined syndrome–deficiency of Gan-yin and Shen-yin (but without excess of yang); however, prescription of the herb to the patients belonging to syndrom of excessive blood heat (yang) causing deficiency of yin or yin deficiency and yang excess is considered to be more susceptible to exert liver injury.[14,34] Recent experimental studies showed that *Polygonum multiflorum* Thunb. is more susceptible to induce liver injury in inflammatory stress rats model compared to normal rats.[39] Inflammatory stress is considered as a kind of characteristics of CM theory-defined yang excess. Thus rational use of CM accordance to CM theory is useful and practical to prevent occurrence of HILI.

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