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REVIEW

Diagnostic challenges in drug-induced liver injury

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INTRODUCTION

DILI remains a diagnosis of exclusion and one of the most difficult challenges in hepatology. DILI can mimic virtually any liver disease, and with few exceptions, there are no laboratory tests, imaging studies, or liver biopsy findings that definitively prove causality. The diagnosis is based upon a careful medical history with the timing of starting and stopping medications and the onset of liver test abnormalities, as well as supportive laboratory tests, serologic and virologic markers, and imaging of the liver and gallbladder. In this short review, we provide some general considerations, including important resources, but we focus largely on selected challenges in differential diagnosis and drug attribution.

GENERAL DIAGNOSTIC CONSIDERATIONS

A helpful starting point when considering the diagnosis of DILI is LiverTox,[1] the online website supported by the National Institutes of Health and the National Library of Medicine, which provides a concise description of critical information on liver injury due to more than 1400 prescription and over-the-counter medications, herbal products, and dietary supplements. Each chapter describes the mechanism of action, clinical indications, and major side effects as well as potential for causing liver injury. It describes the typical latency to liver injury onset, clinical characteristics (phenotype), course, mechanism of injury, and management, as well as a comprehensive and annotated bibliography. LiverTox also has overviews about DILI, including discussion of causality, likelihood scores for specific agents, and classical phenotypes of injury. Other helpful components include causality forms, a master list of all agents discussed, and a list of important elements to include in writing case reports.

The diagnosis of DILI rests upon 6 major elements or domains: (1) latency, the time from starting the implicated agent to onset of injury, (2) dechallenge, the change in the course of the injury upon stopping the agent, (3) exclusion of other major causes of liver injury, (4) the likelihood that the implicated agent causes liver injury, (5) supportive information, and (6) results of rechallenge, if performed. These elements are captured and scored in several well-described causality tools, including the Roussel Uclaf Causality Assessment Method[2] and, more recently, Revised Electronic Causality Assessment Method.[3] Both are reasonably accurate but assess DILI as a single diagnostic challenge and are not tailored to the specific agent or phenotype of injury. These tools cannot replace the clinical judgment used in expert opinion. Importantly, they provide a valuable checklist of the information needed for the diagnosis of DILI.

CHALLENGES IN DIFFERENTIAL DIAGNOSIS

DILI can mimic almost any liver disease, from viral hepatitis to fatty liver disease, genetic liver conditions, gallstone disease, metastatic cancer, and autoimmune liver diseases. Three diagnoses that are particularly

Abbreviations: AIH, autoimmune hepatitis; HDS, herbal and dietary supplements.

The opinions expressed in this article are solely the responsibility of the authors and do not necessarily reflect the views or recommendations of the Food and Drug Administration or the National Institutes of Health.

TABLE 1 The 24 most frequent drugs causing liver injury in the DILIN prospective study ranked highest to lowest frequency

#	Agent	Year of approval	Drug class	LiverTox likelihood category
1	Amoxicillin/Clavulanate	1984	Anti-infective	A
2	Trimethoprim/Sulfamethoxazole	1981	Anti-infective	A
3	Nitrofurantoin	1953	Anti-infective	A
4	Isoniazid	1953	Anti-infective	A
5	Minocycline	1971	Anti-infective	A
6	Atorvastatin	1996	Cholesterol lowering	A
7	Cefazolin	1973	Anti-infective	A
8	Azithromycin	1991	Anti-infective	A
9	Diclofenac	1988	Nonsteroidal anti-inflammatory	A
10	Ciprofloxacin	1987	anti-infective	A
11	Infliximab	1998	Immune modulator	A
12	Terbinafine	1996	Anti-infective	B
13	Amoxicillin	1974	Anti-infective	B
14	Azathioprine	1968	Immune modulator	A
15	Lamotrigine	1994	Antiepileptic	A
16	Levofloxacin	1996	Anti-infective	A
17	Phenytoin	1939	Antiepileptic	A
18	Mercaptopurine	1953	Immune modulator	A
19	Ipilimumab	2011	Immune modulator	A
20	Allopurinol	1966	Xanthine oxidase inhibitor	A
21	Carbamazepine	1968	Antiepileptic	A
22	Hydralazine	1953	Anti-hypertensive	A
23	Interferon beta	1993	Immune modulator	A
24	Methyldopa	1962	Anti-hypertensive	A

Note: The major class of drugs causing DILI are anti-infective agents. The most common causes are drugs that have been available for several decades.
Data from the US Drug-Induced Liver Injury Network (September 2021) with permission. LiverTox likelihood scores are updated periodically based on current DILI risk data.

challenging and most likely missed are choledocholithiasis, metastatic cancer, and autoimmune hepatitis (AIH). Special testing and monitored follow-up are often needed to demonstrate whether these conditions account for the liver injury. Choledocholithiasis, for instance, can present like acute hepatitis with marked elevations in serum alanine aminotransferase and only modest alkaline phosphatase levels, which increase later.[4] Imaging may show little or no evidence of obstruction after the gallstone is passed. Hepatic metastasis can also cause mixed liver enzyme patterns suggestive of DILI, which increases as tumors progress or undergo lysis. Even MRI or computerized tomography with contrast will not always discern tumor progression and lysis accurately. Most challenging, however, is AIH in DILI cases with autoimmune features (autoantibodies, IgG elevations). Agents commonly causing autoimmune-like DILI include minocycline, nitrofurantoin, statins,[5,6] and, more recently, checkpoint inhibitors[7] and the RNA-based COVID vaccines.[8] Even liver biopsy may not reliably differentiate AIH from DILI. Both usually respond to corticosteroid therapy, which is typically required long-term for AIH, but can be safely discontinued in DILI. Thus, the diagnosis of DILI with autoimmune features will often require following patients for the 4–12 weeks of immunosuppressive therapy and then another 3 to 6 months of follow-up to ensure a lack of relapse.[5,6]

ATTRIBUTION TO A PARTICULAR AGENT

Assigning causality to a specific agent can be as difficult as navigating the differential diagnosis. The 24 most common causes of DILI from the US Drug-Induced Liver Injury Network are shown in Table 1 (data as of September 2021). One difficulty is that most patients with DILI are taking more than one drug, and they may be taking 2 or more that are known causes of liver injury. Furthermore, patients may not be able to provide start and stop dates, dosing, drug names, or why they were prescribed. Polypharmacy is a major stumbling block in causality assignment. A common example is

"intensive care unit jaundice" with or without serum enzyme elevations. Besides the long list of medications taken, several of which are well-known hepatotoxins, there can be an equally long list of competing causes, including sepsis, shock, anoxia, parenteral nutrition, and the underlying disease (eg, metastatic cancer). Stopping the obvious hepatotoxins with suggestive timing for the injury is often the only option.

Sometimes, 2 or more drugs are started and stopped at or around the same time. Anti-infectives are often combined in the same pill (eg, amoxicillin/clavulanate), and others are usually given in combination (eg, tuberculosis regimens). A simple approach is to assign causality to the combination if all can be stopped, but this may not always be possible, as with agents for tuberculosis. Injury phenotypes can help, but even characteristic phenotypes are not always reliable indicators. Many agents that are used together have similar phenotypes, such as isoniazid and pyrazinamide. Comparing DILI incidences would be useful, but such data are rarely available. While not incidence based, the likelihood scores provided in LiverTox offer useable estimates of liver injury likelihood ranging from E (no cases) to A (more than 50 cases) based on the numbers of cases reported in the literature and includes agents that do, as well as those that do not, cause liver injury (Table 2).

Choosing one drug over others helps to decide about continuing needed drugs or rechallenging with those already held. When withholding all suspect agents is not clinically feasible, stopping only the most likely or restarting the least likely agents, one at a time, is the safest approach. Continuance of a drug or rechallenge must be done with close monitoring afterward. Recurrence can be abrupt and severe, particularly with immune allergic forms of DILI. Rechallenge is increasingly encountered with checkpoint inhibitors, particularly a cytotoxic T-lymphocyte–associated protein 4 inhibitor, given with a programmed cell death protein 1 or programmed death ligand 1 inhibitor. DILI recurrence on rechallenge is as low as 35%,[9] but it is best to change from one to another checkpoint inhibitor, particularly changing the death protein 1 or programmed death ligand 1.

Causality is particularly challenging when the patient denies or fails to mention taking a known hepatotoxic agent. This occurs frequently with anabolic steroids, which are used illicitly without prescription for bodybuilding. The patient often mentions other, largely benign bodybuilding agents (proteins, amino acids, and vitamins) but not anabolic steroids. Yet, the pattern of liver injury is unmistakable, arising in men presenting with marked itching and jaundice with minimal alkaline phosphatase and mild to moderate alanine aminotransferase elevations.[10] A liver biopsy is rarely necessary but will show marked canalicular cholestasis with minimal inflammation. The syndrome can be prolonged, and renal failure from cholemic nephropathy can occur, but eventually, the injury resolves and is rarely fatal.

TABLE 2 LiverTox likelihood categories

Category	No. convincing cases of DILI published	Description of likelihood
A	≥ 50	Well-known cause
B	12–49	Likely cause
C	4–11	Probable cause
D	1–3	Possible cause
E	0 (or unconvincing reports)	Unlikely cause
E*	0	Unproven but suspected cause

Finally, herbal and dietary supplements (HDS) can contain multiple ingredients, and patients often take more than one HDS. In the United States, the most common HDS ingredients causing liver injury are green tea extract, turmeric, and garcinia, which typically cause hepatocellular injury within 1 to 4 months.[1] Also common are kratom and ashwagandha, which more frequently cause cholestatic or mixed hepatitis with a shorter latency. HDS labels are not always reliable and rarely provide the concentration and dose. HDS products also can have contaminants, including medications such as diclofenac, statins, or estrogens.

DILI remains the single most challenging diagnosis in hepatology. The broad differential diagnosis and polypharmacy are particularly daunting. While follow-up can clarify the diagnosis, it is critical to discontinue the most likely offending agent(s) promptly.

CONFLICTS OF INTEREST

The authors have no conflicts to report.

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