Drug, Herbal & Dietary Supplement-Induced Liver Injury

Mechanistic classification, diagnostic approach, causality assessment, natural history/treatment, acetaminophen hepatotoxicity, monitoring, and biomarkers.

2022 AASLD Practice Guidance
Drug, Herbal, and Dietary Supplement-Induced Liver Injury
Fontana et al. · Hepatology 2023;77:1036-1065

FORMAT *64 numbered guidance statements — narrative consensus format (not GRADE-rated); grouped by clinical theme.*

1 Mechanistic Classification & Epidemiology

GS	STATEMENT
1	Know the three main types of hepatotoxicity (direct, idiosyncratic, indirect) when evaluating suspected DILI
2	Direct hepatotoxins (e.g., APAP) injure nearly all exposed individuals once dose/duration threshold is exceeded
3	Idiosyncratic DILI: dose/duration-independent, low incidence, variable latency and clinical/histological features
4	Idiosyncratic DILI arises from an aberrant adaptive host immune response to the drug/metabolite
5	Indirect hepatotoxins: dose-independent, latency weeks–months, act via host immune system (e.g., ICI-induced immune hepatitis, HBV reactivation with rituximab)
6	Annual incidence 14–19/100,000 (general population); 33–40/100,000 in EMR exposure-based studies
7	Antimicrobials, CNS agents, and anti-inflammatories most commonly implicated; HDS increasingly implicated
8	Daily dose, lipophilicity, and extent of hepatic metabolism influence relative DILI risk
9	Age/sex/race not well-established risk factors; some drugs more common in older adults (amox-clav, isoniazid) or children (valproate, minocycline)
10	Obesity/diabetes increase incidence/severity with specific drugs; alcohol/tobacco/diet role unestablished
11	Pre-existing liver disease increases risk with select drugs (methotrexate, anti-TB) and risk of poor DILI outcomes
12	PTPN22 polymorphism = genetic risk factor across drugs/ethnicities; HLA alleles also implicated, clinical testing utility undetermined

2 Diagnostic Approach & Biochemical Patterns

GS	STATEMENT
13	Significant DILI: AST/ALT >5×ULN or ALP >2×ULN (2 occasions); OR bilirubin >2.5 mg/dL + elevated AST/ALT/ALP; OR INR >1.5 + elevated AST/ALT/ALP
14	Most injury occurs within first 6 months of use; obtain medication/HDS history covering prior 180 days
15	Categorize by R value (ALT/ULN ÷ ALP/ULN): hepatocellular R≥5, mixed 2<R<5, cholestatic R≤2
16	Exclude alternative causes in all cases: viral hepatitis, metabolic liver disease, AIH, pancreaticobiliary disease
17	Certain drugs show characteristic lab/histologic "signatures" useful for causality assessment
18	Use LiverTox website — literature synopsis for >1000 drugs and >60 HDS

3 Liver Biopsy

GS	STATEMENT
19	Not required for diagnosis; useful in severe/protracted or diagnostically uncertain cases, not mild/self-limited disease
20	Can identify hepatotoxic drug via histologic pattern; excludes concurrent liver disease
21	Broad range of histologic patterns reported; a single drug may show more than one pattern
22	Eosinophils/granulomas → more favorable outcome; necrosis/fibrosis → poorer outcome
23	May reveal injury mechanism (e.g., fialuridine → microvesicular steatosis/necrosis)

4 Causality Assessment

GS	STATEMENT
24	Three commonly used causality assessment methods, each with strengths/limitations
25	Structured instruments incorporate dose/duration/timing, concomitant drugs/HDS, labs/imaging/histology, exclusion of competing causes
26	DILIN semiquantitative expert-opinion scale widely used but requires specialized expertise
27	Updated RUCAM improved but retains age/alcohol/pregnancy factors of unclear value
28	RECAM: newer computerized instrument, potentially more reproducible; needs further validation
29	Intentional rechallenge rarely done but may aid causality assessment when available

5 Herbal & Dietary Supplements

GS	STATEMENT
30	HDS widely used; permissive safety standards raise risk of mislabeling, adulteration, contamination
31	Supplements can cause severe hepatotoxicity with variable clinical/lab/histologic phenotypes
32	HLA polymorphisms and consumption conditions influence individual HDS hepatotoxicity risk
33	HLA-B*35:01 linked to green tea extract hepatotoxicity (White populations) and *P. multiflorum* hepatotoxicity (Asian populations)

6 Natural History, Prognosis & Treatment

GS	STATEMENT
34	Most present with acute liver injury (may be asymptomatic); resolves <6 months without sequelae in 80%
35	10% of registry patients have adverse hepatic outcomes (ALF, transplant, death) within 6 months
36	Spontaneous survival in DILI-ALF only ~25% — early transfer to transplant center recommended
37	Chronic injury (>6–12 months) in 10–20%, more common with cholestatic DILI
38	Adverse-outcome risk factors: ↑bilirubin/INR, ↓albumin at presentation; severe necrosis/fibrosis on biopsy; comorbidities/pre-existing liver disease
39	Mainstay: discontinue suspect drug plus supportive care (antiemetics, antipruritics, hydration)
40	Short IV NAC course may benefit hospitalized adults with DILI-ALF; not recommended in children
41	Corticosteroids ×1–3 months may benefit selected patients (severe hypersensitivity, DRESS, autoimmune features on biopsy) — optimal dose/duration unknown
42	UDCA not an established therapy but presumed safe
43	Defibrotide approved for HCT-associated moderate–severe SOS
44	Avoid rechallenge unless anticipated benefit is high for a severe/life-threatening condition

7 Acetaminophen (APAP) Hepatotoxicity

GS	STATEMENT
45	Dose-dependent, pericentral injury with >4 g/24h or excessive doses over several days
46	Leading cause of ALF among US adults
47	Diagnosis: history of excessive ingestion + elevated serum level (single time-point) + exclusion of competing causes
48	Gastric lavage + activated charcoal for presentation within 4h of a single-time-point overdose
49	IV/oral NAC nearly fully prevents injury if given within 12h; still recommended if later
50	Prognosis relates to degree of encephalopathy, coagulopathy, and acidosis

8 Early Detection & Monitoring

GS	STATEMENT
51	Educate patients to report symptoms; prospective monitoring with high-risk drugs (ICIs, isoniazid, methotrexate)
52	Voluntarily report suspected DILI to FDA MedWatch
53	Transient enzyme elevations (e.g., isoniazid) can be self-limited despite continued dosing (metabolic/immune adaptation)
54	FDA/LiverTox are rich resources for hepatotoxicity surveillance info, labeling, package inserts
55	Monitoring recommendations vary — apply common sense/expert consultation
56	Isoniazid: symptom-reporting education; routine monthly labs not proven to reduce significant injury (may cause premature discontinuation), though many societies still advise baseline/on-treatment labs in high-risk patients
57	Annual elastography for silent-fibrosis drugs like methotrexate; not broadly applicable to other DILI
58	Predosing LFTs for all statin initiators; routine on-treatment monitoring not recommended (low hepatotoxicity risk)
59	Compensated CLD/cirrhosis: statins indicated as appropriate; decompensated cirrhosis — individualize risk/benefit
60	ICI oncology patients: predosing + on-treatment monitoring is standard of care, with stepwise hold/monitor/corticosteroid algorithm by severity

9 Biomarkers & Research

GS	STATEMENT
61	Current serum markers (AST/ALT/ALP) are not sensitive/specific enough for early DILI detection
62	Research hampered by lack of an objective test to confirm the causative drug
63	Emerging biomarkers aim to improve diagnosis, prognosis, and mechanistic insight
64	DILI registries should use standardized methods/protocols for epidemiology, outcomes, and treatment research

Fontana RJ, Liou I, Reuben A, et al. AASLD 2022 Practice Guidance on Drug, Herbal, and Dietary Supplement-Induced Liver Injury. *Hepatology*. 2023;77(3):1036-1065.