

Drug-Induced Liver Injury: A Comprehensive Review of Mechanisms, Risk Factors, Diagnosis, and Management: A Narrative Review.

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Abstract

Drug-induced liver injury (DILI) is a clinically significant and increasingly recognized adverse event encompassing a broad spectrum of hepatic pathology, ranging from asymptomatic enzyme elevation to acute liver failure. It arises from exposure to prescription medications, over-the-counter drugs, herbal products, and dietary supplements, and remains a leading cause of acute liver failure and post-marketing drug withdrawal worldwide. This review synthesizes current knowledge on the epidemiology, hepatic physiology, and metabolic basis of DILI, along with its classification into intrinsic and idiosyncratic, and hepatocellular, cholestatic, and mixed subtypes. The molecular mechanisms underlying hepatotoxicity are examined in detail, including reactive metabolite formation, oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress, immune-mediated injury, inflammatory cytokine signaling, the gut-liver axis, and the convergent pathways of necrosis, apoptosis, and necroptosis. Key host and environmental risk factors, including age, sex, genetic susceptibility, alcohol use, obesity, polypharmacy, and herbal supplement use, are discussed alongside commonly implicated drug classes such as antimicrobials, anticonvulsants, and emerging oncology therapeutics including immune checkpoint inhibitors. Diagnostic strategies are reviewed, emphasizing the R-value, the Roussel Uclaf Causality Assessment Method (RUCAM), liver biopsy, and imaging, given the continued absence of a definitive diagnostic biomarker. Management principles, centered on prompt drug withdrawal, supportive care, and targeted interventions such as N-acetylcysteine and corticosteroids in select cases, are also outlined. Despite advances in mechanistic understanding, DILI remains a diagnosis of exclusion, underscoring the need for improved biomarkers, refined genetic risk stratification, and continued international registry collaboration to enable earlier recognition and more precise management.

Keywords

Drug-induced liver injury; Hepatotoxicity; Idiosyncratic liver injury; RUCAM; Liver enzymes; Cholestasis; Mitochondrial dysfunction; Immune-mediated hepatitis; Hepatocellular injury; Herbal and dietary supplements.

1.Introduction

Drug-induced liver injury (DILI) refers to hepatic damage caused by prescription medications, over-the-counter drugs, herbal products, or dietary supplements, in the absence of other identifiable causes of liver disease. It encompasses a broad clinicopathological spectrum ranging from asymptomatic elevations in liver enzymes to acute liver failure requiring transplantation. DILI is conventionally divided into intrinsic (dose-dependent and predictable) injury, exemplified by acetaminophen overdose, and idiosyncratic (dose-independent and unpredictable) injury, which accounts for the majority of clinically significant cases and is far more difficult to anticipate or prevent.

DILI holds major importance in clinical practice for several reasons. It is one of the leading causes of acute liver failure in Western countries, a frequent reason for drug non-approval or post-marketing withdrawal, and a diagnosis of exclusion that complicates routine hepatology and internal medicine practice. Because almost any drug can theoretically injure the liver, clinicians across nearly every specialty must maintain a high index of suspicion when unexplained liver test abnormalities arise in a patient taking any medication.

The global burden of DILI is substantial, though estimates vary widely depending on population, surveillance methods, and causality assessment tools used. Population-based studies have reported crude annual incidence rates ranging from roughly 14 to 19 cases per 100,000 persons in Western cohorts, while hospital-based and referral populations show considerably higher rates because of selection bias and greater medication exposure. Incidence also differs by region, with antituberculosis drugs being disproportionately implicated in Asian and African cohorts, and antibiotics, particularly amoxicillin-clavulanate, dominating case series from Europe and the United States. Emerging classes of therapeutics, including immune checkpoint inhibitors, targeted anticancer agents, and herbal and dietary supplements, are increasingly recognized contributors, reflecting evolving prescribing patterns and the growing use of complementary medicine worldwide.

Commonly implicated agents include antimicrobials (amoxicillin-clavulanate, isoniazid, nitrofurantoin, sulfonamides), nonsteroidal anti-inflammatory drugs, anticonvulsants (valproate, phenytoin, carbamazepine), statins, antiretrovirals, immune checkpoint inhibitors, and a wide range of herbal and dietary supplements. The relative contribution of each class varies with prescribing habits, regulatory oversight of supplements, and regional disease burden, such as the high use of antituberculosis therapy in endemic regions.

Diagnosing DILI remains one of the most persistent challenges in hepatology. There is no specific biomarker or diagnostic test that confirms the diagnosis; instead, clinicians must rely on a temporal association between drug exposure and liver injury, exclusion of competing causes such as viral hepatitis, biliary obstruction, autoimmune and metabolic liver disease, and structured causality assessment instruments such as the Roussel Uclaf Causality Assessment Method (RUCAM). This diagnostic uncertainty is compounded by polypharmacy, latency periods that can extend from days to several months after drug initiation or even after discontinuation, and the wide morphological overlap between DILI and other liver diseases on biopsy.

The purpose of this review is to provide a comprehensive and clinically oriented synthesis of current knowledge on DILI, encompassing normal liver physiology and drug metabolism, classification systems, molecular mechanisms of hepatotoxicity, risk factors, commonly implicated drugs, clinical presentation, diagnostic strategies, and management approaches. By integrating recent epidemiological and mechanistic literature, this review aims to support clinicians, researchers, and trainees in recognizing, diagnosing, and managing this important and evolving clinical entity.

1. Normal Liver Function and Drug Metabolism

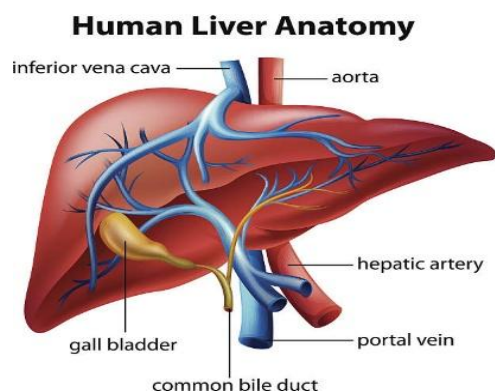


Figure 1.1: Liver Anatomy and Physiology

The liver is the largest solid organ in the body and the principal site of xenobiotic metabolism. It is organized into functional units called lobules, each centered on a central vein and bordered by portal triads containing branches of the hepatic artery, portal vein, and bile duct. Hepatocytes, which make up roughly 70-80% of liver mass, are arranged in a zonal fashion (periportal zone 1, midzonal zone 2, and pericentral zone 3), with each zone exhibiting distinct oxygen tension, enzyme expression, and metabolic capacity. Zone 3 hepatocytes, being relatively hypoxic and rich in cytochrome P450 enzymes, are particularly vulnerable to toxic and hypoxic insults, which explains the classic centrilobular necrosis seen with agents such as acetaminophen.

Beyond hepatocytes, the liver contains Kupffer cells (resident macrophages), hepatic stellate cells, liver sinusoidal endothelial cells, and cholangiocytes lining the biliary tree, all of which participate in metabolic, immune, and secretory functions.

The dual blood supply, receiving both oxygenated arterial blood and nutrient-rich portal venous blood draining the gut, positions the liver as a first-pass filter for ingested drugs and gut-derived antigens, a role central to both its physiological function and its vulnerability to toxic injury.

1.2 Drug Metabolism

Hepatic drug metabolism is classically divided into three phases that work together to convert lipophilic xenobiotics into water-soluble compounds suitable for excretion.

Phase I reactions

Phase I metabolism involves oxidation, reduction, and hydrolysis, predominantly mediated by the cytochrome P450 (CYP) superfamily of enzymes located in the smooth endoplasmic reticulum. These reactions introduce or expose polar functional groups (such as hydroxyl or amine groups) on the parent drug. While Phase I reactions are usually detoxifying, they can also generate reactive, electrophilic, or chemically unstable intermediates capable of covalently binding cellular macromolecules, a key initiating step in many cases of hepatotoxicity.

Phase II reactions

Phase II metabolism conjugates Phase I metabolites (or, in some cases, the parent drug directly) with endogenous molecules such as glucuronic acid, sulfate, glutathione, glycine, or acetyl groups. These conjugation reactions, catalyzed by enzymes such as UDP-glucuronosyltransferases, sulfotransferases, and glutathione S-transferases, generally increase water solubility and reduce reactivity, facilitating safe excretion. Glutathione conjugation is particularly important as a defense mechanism against reactive metabolites; depletion of hepatic glutathione stores, as occurs in acetaminophen overdose, removes this protective buffer and allows reactive intermediates to bind cellular proteins.

Phase III transporters

Phase III involves the active transport of metabolites and conjugates across the hepatocyte membrane into bile or blood, mediated by ATP-binding cassette transporters such as P-glycoprotein (P-gp), multidrug resistance-associated proteins (MRP2, MRP3, MRP4), the bile salt export pump (BSEP), and uptake transporters such as organic anion-transporting polypeptides (OATPs). Genetic polymorphisms or drug-mediated inhibition of these transporters, particularly BSEP, can cause intracellular accumulation of bile acids and toxic metabolites, contributing to cholestatic patterns of liver injury.

Figure 1. Drug Metabolism Pathway in the Liver

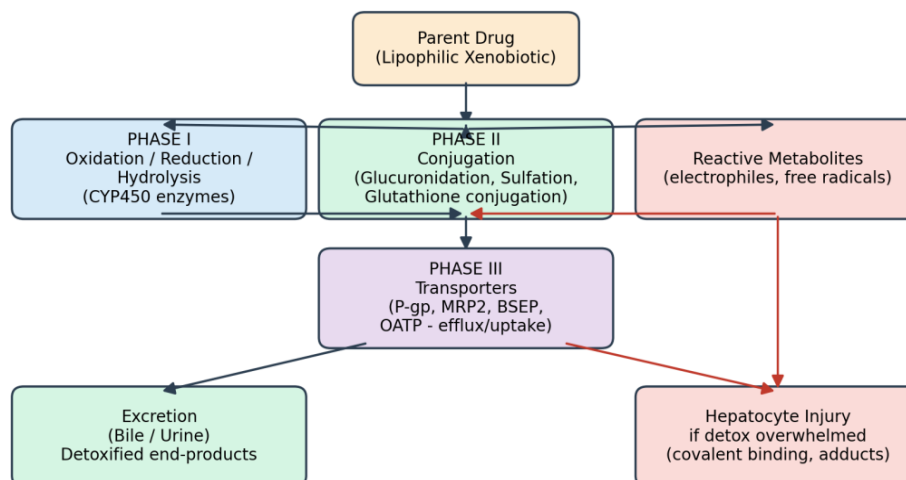


Figure 1.2: Drug metabolism pathway in the liver, illustrating sequential Phase I, Phase II, and Phase III processing and the branch point toward reactive metabolite formation and hepatocyte injury.

1.3 Why the Liver Is Susceptible to Toxicity

Several features render the liver uniquely vulnerable to drug-induced injury. Its position as the primary site of xenobiotic biotransformation exposes it to high local concentrations of parent drugs and their metabolites. The rich content of CYP450 enzymes generates reactive intermediates capable of forming protein and DNA adducts. Zonal heterogeneity in oxygen tension and enzyme expression creates pockets of particular vulnerability, especially in the relatively hypoxic pericentral zone. Furthermore, the liver's immunological environment, containing large numbers of resident and recruited immune cells, means that drug-protein adducts (haptens) can trigger adaptive immune responses in genetically susceptible individuals, converting a metabolic insult into an immune-mediated injury.

2. Epidemiology of Drug-Induced Liver Injury

Drug-induced liver injury (DILI) is a globally significant cause of acute liver injury, hospitalization, and liver failure. Population-based studies estimate an annual incidence of roughly 13.9–19.1 cases per 100,000 people in Western countries, with the Icelandic cohort—the only true population-based prospective study—reporting a similar rate. In mainland China, a large multicentre registry of nearly 26,000 DILI cases found a substantially higher incidence, exceeding 23 per 100,000 per year, a difference attributed in part to the widespread use of traditional Chinese medicines and herbal and dietary supplements (HDS). In Japan, the estimated incidence is 14–19 per 100,000, with roughly 30% of cases presenting with jaundice.

Regional differences in etiology are pronounced. Acetaminophen remains the leading cause of acute liver failure in North America and the United Kingdom, whereas DILI from acetaminophen is comparatively rare in Asia. In Africa and South and Southeast Asia, anti-tuberculosis therapy and antiretroviral drugs predominate, reflecting the high regional burden of tuberculosis and HIV. In India, a prospective cohort of 1,288 patients found that 46.4% of DILI cases were linked to anti-tuberculosis medications and 13.9% to complementary and alternative therapies; nearly one-third of cases were severe, and 68% presented with jaundice requiring hospitalization.

DILI carries substantial mortality: overall case-fatality (or need for liver transplantation) is estimated at 5–10%, rising to 10–50% once acute liver failure develops, and reaching 35–50% in DILI-related acute-on-chronic liver failure. Underlying chronic liver disease independently worsens outcomes, with registry data showing three- to four-fold higher mortality among DILI patients with pre-existing liver disease. Beyond direct mortality, DILI imposes a major economic burden through prolonged hospitalization, intensive monitoring, immunosuppressive or supportive therapy, post-marketing drug withdrawals, and liver transplantation; pharmacist-led medication review and monitoring programs have been shown to reduce these downstream healthcare costs.

Table 1: Global incidence of DILI

Region / Country	Estimated Incidence	Study / Registry	Notes
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Region / Country	Estimated Incidence	Study / Registry	Notes
Iceland (general population)	~19.1 per 100,000/year	Icelandic DILI cohort	Population-based, prospective ascertainment
Western countries (overall)	13.9–19.1 per 100,000/year	Multiple Western cohorts	Most-cited range in Western literature
Mainland China	>23 per 100,000/year	National mainland China cohort (25,927 DILI cases)	Higher burden partly attributed to traditional/herbal medicine use
Japan	~14–19 per 100,000/year	27-institution Japanese survey	~30% of cases present with jaundice
United States / Europe	~15% of acute liver failure cases	DILIN and European cohorts	Acetaminophen remains leading intrinsic cause
Africa	Not precisely defined; high burden	TB/HIV-focused cohorts	Anti-tuberculosis and antiretroviral drugs predominate
India	46.4% of DILI linked to anti-TB drugs	Prospective Indian cohort (1,288 patients, 2013–2018)	32.4% severe; 68% presented with jaundice requiring hospitalization

3. Classification of Drug-Induced Liver Injury

3.1 Intrinsic DILI

Intrinsic DILI is dose-dependent, predictable, and reproducible in experimental animal models. It typically has a short and consistent latency period and affects most or all individuals exposed to a sufficiently high dose. The prototypical example is acetaminophen hepatotoxicity, in which supratherapeutic dosing overwhelms Phase II glutathione conjugation, allowing the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI) to accumulate and cause centrilobular necrosis.

3.2 Idiosyncratic DILI

Idiosyncratic DILI is dose-independent (within therapeutic ranges), unpredictable, and occurs in only a small minority of exposed individuals, often after a variable latency of days to months. It is thought to result from a combination of metabolic, immunological, and genetic factors, and is the form most commonly implicated in clinically significant, unexpected liver injury reported to regulatory agencies and DILI registries.

3.3 Hepatocellular Injury

Hepatocellular injury is characterized by a disproportionate elevation in alanine aminotransferase (ALT) relative to alkaline phosphatase (ALP), typically defined by an R-value of 5 or greater. It reflects direct hepatocyte damage and carries the highest risk of progression to acute liver failure, particularly when accompanied by jaundice (Hy's Law).

3.5 Cholestatic Injury

Cholestatic injury is defined by a predominant rise in ALP with an R-value of 2 or less, and reflects impaired bile formation or flow, often due to injury to bile canaliculi, cholangiocytes, or bile transporters such as BSEP. Clinically, it presents with pruritus, jaundice, and a more indolent course, though it carries risk of chronic cholestasis and vanishing bile duct syndrome in severe cases.

3.6 Mixed Injury

Mixed injury shows intermediate elevations of both ALT and ALP, with an R-value between 2 and 5, and combines features of hepatocellular and cholestatic damage. Many drugs, including amoxicillin-clavulanate, can produce any of the three patterns depending on the individual case.

3.7 Acute and Chronic DILI

Most DILI episodes are acute, resolving within weeks to a few months of drug withdrawal. However, a clinically important subset, estimated at roughly 15-20% of cases in some registries, progresses to chronic DILI, defined as persistent biochemical or histological abnormalities beyond 6-12 months from onset. Chronic DILI is more frequently observed with cholestatic and mixed injury patterns and can progress to fibrosis, cirrhosis, or vanishing bile duct syndrome.

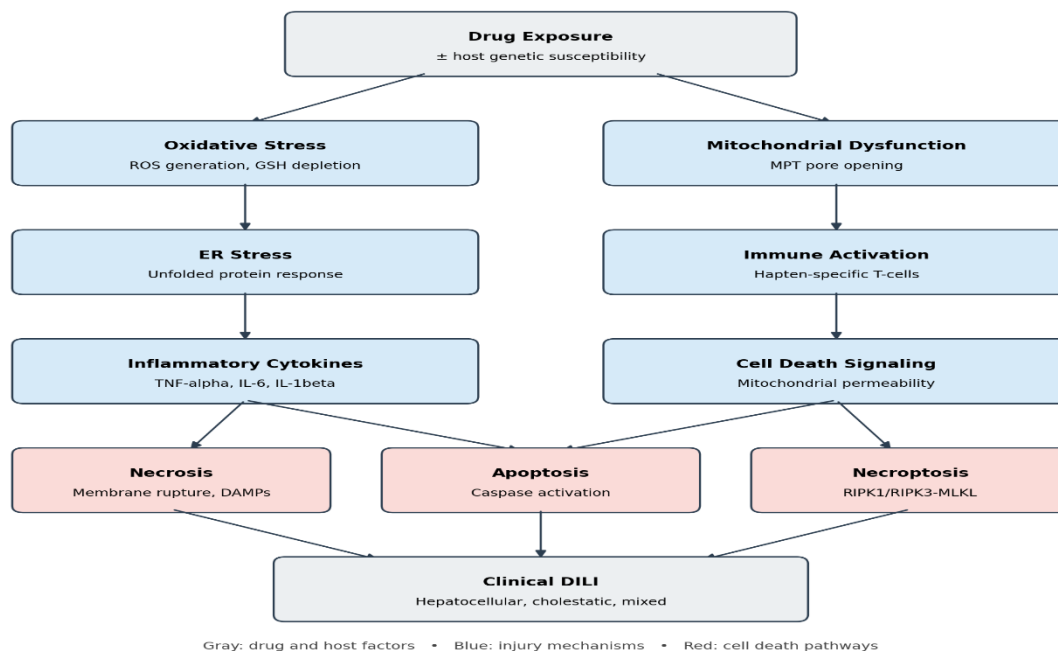
Table 2: Classification of drug-induced liver injury.

Category	Defining Features
Intrinsic DILI	Dose-dependent, predictable, short latency (e.g., acetaminophen)
Idiosyncratic DILI	Dose-independent, unpredictable, variable latency (days-months)
Hepatocellular	$R \geq 5$; ALT-predominant; higher risk of acute liver failure
Cholestatic	$R \leq 2$; ALP-predominant; pruritus, jaundice, indolent course
Mixed	$2 < R < 5$; combined hepatocellular and cholestatic features
Acute DILI	Resolution of liver injury within 6 months of onset
Chronic DILI	Persistent biochemical/histological abnormality beyond 6-12 months

4. Pathophysiology and Molecular Mechanisms

4.1 Reactive Metabolite Formation

Many hepatotoxic drugs undergo bioactivation via CYP450-mediated Phase I metabolism into chemically reactive electrophilic intermediates. These reactive metabolites can covalently bind cellular proteins, lipids, and nucleic acids, forming drug-protein adducts. Such adducts may directly impair protein function (for example, mitochondrial enzymes) or act as neoantigens capable of triggering an adaptive immune response, linking the metabolic and immunological arms of DILI pathogenesis.

Figure 2. Pathophysiology and Molecular Mechanisms of Drug-Induced Liver Injury**Figure 4.1: Mechanisms of drug-induced liver injury, integrating reactive metabolite formation, oxidative and organellar stress, immune activation, and convergent cell death pathways.**

4.2 Oxidative Stress

Reactive metabolites and their downstream effects generate excess reactive oxygen species (ROS), overwhelming the hepatocyte's antioxidant defenses, particularly glutathione. Depletion of glutathione impairs the cell's capacity to neutralize electrophiles and ROS, promoting lipid peroxidation, protein oxidation, and DNA damage. Oxidative stress is both a cause and consequence of mitochondrial dysfunction, creating a self-amplifying cycle of cellular injury.

4.3 Mitochondrial Dysfunction

Mitochondria are a convergent target for many hepatotoxic drugs and their metabolites. Injury mechanisms include direct inhibition of the electron transport chain, impaired fatty acid beta-oxidation, mitochondrial DNA damage, and opening of the mitochondrial permeability transition (MPT) pore. MPT pore opening collapses the mitochondrial membrane potential, halts ATP synthesis, and releases pro-apoptotic factors such as cytochrome c into the cytosol, activating caspase cascades. Depending on the severity and speed of ATP depletion, mitochondrial injury can tip the cell toward either apoptosis (if ATP is preserved) or necrosis (if ATP is rapidly depleted).

4.4 Endoplasmic Reticulum Stress

Accumulation of misfolded proteins or reactive metabolite adducts within the endoplasmic reticulum (ER) triggers the unfolded protein response (UPR), mediated by sensors such as PERK, IRE1, and ATF6. While the UPR initially serves an adaptive, protective function by reducing protein synthesis and enhancing folding capacity, prolonged or severe ER stress activates pro-apoptotic transcription factors such as CHOP and can trigger calcium release into the cytosol, activating calpain and caspase-12-mediated cell death pathways. ER stress and mitochondrial stress pathways are increasingly recognized as interconnected contributors to DILI.

4.5 Immune-Mediated Liver Injury

In idiosyncratic DILI, drug-protein adducts can function as haptens that, when presented on major histocompatibility complex (MHC) molecules, activate drug-specific T-cell responses. This process is strongly influenced by human leukocyte antigen (HLA) genotype, explaining the strong genetic associations observed for specific drug-DILI pairs (for example, HLA-B*57:01 with flucloxacillin, and HLA-DRB1 alleles with amoxicillin-clavulanate). Innate immune activation, including danger-associated molecular pattern (DAMP) release from injured hepatocytes and subsequent Kupffer cell and dendritic cell activation, amplifies and sustains the adaptive immune response, contributing to the heterogeneous and sometimes delayed presentation of idiosyncratic DILI.

4.6 Inflammatory Cytokines

Activated Kupffer cells, recruited monocytes, and T-cells release pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), and interleukin-1 beta (IL-1beta). These cytokines amplify hepatocyte stress, promote further mitochondrial dysfunction, and can directly engage death receptor pathways (such as Fas and TNF receptor 1) on hepatocyte membranes, linking the inflammatory and cell death components of liver injury.

4.7 Cell Death

4.7.1 Necrosis

Necrosis is an unregulated, ATP-depletion-associated form of cell death characterized by cell swelling, membrane rupture, and release of intracellular contents and DAMPs, which incite local inflammation. It is the dominant pattern in severe intrinsic DILI, such as acetaminophen-induced centrilobular necrosis.

4.7.2 Apoptosis

Apoptosis is a regulated, ATP-dependent form of cell death involving caspase activation, chromatin condensation, and formation of apoptotic bodies that are cleared without significant local inflammation. It predominates when mitochondrial injury is less severe and cellular energy stores are preserved.

4.7.3 Necroptosis

Necroptosis is a form of programmed necrosis mediated by receptor-interacting protein kinases RIPK1 and RIPK3 and their downstream effector, mixed lineage kinase domain-like protein (MLKL). It

combines features of both apoptosis (a defined signaling cascade) and necrosis (membrane rupture and DAMP release), and is increasingly recognized as a contributor to inflammatory amplification in DILI.

4.8 Gut-Liver Axis

Emerging evidence implicates gut microbiota dysbiosis in DILI pathogenesis. Alterations in the intestinal microbiome can increase gut permeability, allowing translocation of bacterial products such as lipopolysaccharide (LPS) into the portal circulation. These microbial products activate Kupffer cells via toll-like receptors, amplifying hepatic inflammation and modulating individual susceptibility to drug hepatotoxicity. This gut-liver axis is an active area of research with potential implications for biomarker development and adjunctive therapeutic strategies.

4.9 Genetic Susceptibility

Genetic factors, particularly HLA polymorphisms, strongly influence individual susceptibility to idiosyncratic DILI for specific drugs. Non-HLA genetic variants, including polymorphisms in drug-metabolizing enzymes (such as NAT2 slow acetylator status for isoniazid) and transporter genes (such as ABCB11/BSEP variants), also modulate risk. Genome-wide association studies continue to identify novel loci, supporting the long-term goal of pre-treatment genetic risk stratification for high-risk drugs.

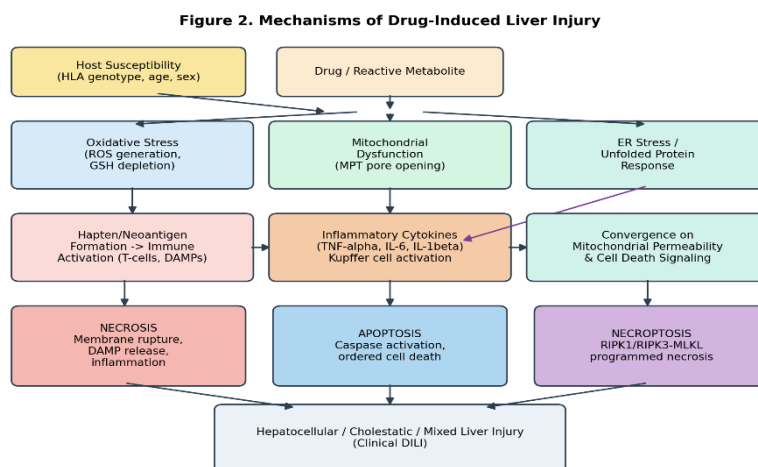


Figure 4.1: Mechanisms of drug-induced liver injury, integrating reactive metabolite formation, oxidative and organellar stress, immune activation, and convergent cell death pathways.

5. Risk Factors

- i. **Age:** Older adults are more susceptible to cholestatic and chronic DILI due to reduced hepatic reserve, polypharmacy, and altered drug clearance, whereas children are more susceptible to certain intrinsic toxicities such as valproate-associated hepatotoxicity.
- ii. **Sex:** Women appear to be at higher risk of idiosyncratic and autoimmune-like DILI and of developing acute liver failure from certain agents, though men predominate in some drug-specific cohorts (e.g., amoxicillin-clavulanate).

- iii. **Genetics:** HLA polymorphisms and variants in drug-metabolizing enzymes and transporters substantially modify individual susceptibility to specific drug-DILI pairs.
- iv. **Alcohol use:** Chronic alcohol consumption induces CYP2E1 and depletes glutathione stores, increasing susceptibility to reactive metabolite-mediated injury, notably with acetaminophen.
- v. **Obesity:** Obesity and underlying nonalcoholic fatty liver disease may alter drug metabolism and increase baseline hepatic vulnerability, although evidence is mixed and drug-specific.
- vi. **Diabetes mellitus:** Diabetes is associated with altered hepatic microcirculation and metabolic stress that may compound drug-induced hepatotoxicity.
- vii. **Polypharmacy:** Concurrent use of multiple medications increases the likelihood of drug-drug interactions that alter hepatic metabolism and elevate hepatotoxic potential.
- viii. **Herbal and dietary supplements:** Widespread and often unregulated use of herbal and dietary supplements is an increasingly recognized and growing cause of DILI worldwide, complicated by inconsistent product labeling and contamination.
- ix. **Pregnancy:** Certain conditions and drug exposures during pregnancy (e.g., antiretroviral therapy) carry distinct hepatotoxicity risks and require special monitoring.
- x. **Drug-drug interactions:** Concomitant use of enzyme-inducing or enzyme-inhibiting agents can increase the formation or accumulation of reactive metabolites, heightening hepatotoxic risk.

6. Drugs Commonly Associated with DILI

Table 4: Drugs commonly associated with drug-induced liver injury.

Drug Class	Example Agents	Typical Pattern Injury	Key Mechanism
Antibiotics	Amoxicillin-clavulanate, nitrofurantoin, sulfonamides	Cholestatic / mixed	Immune-mediated, hapten formation; delayed onset
Antituberculosis drugs	Isoniazid, rifampicin, pyrazinamide	Hepatocellular	Reactive metabolites (e.g., hydrazine via CYP2E1); NAT2 acetylator status
Analgesics	Acetaminophen (paracetamol)	Hepatocellular (centrilobular necrosis)	NAPQI accumulation after glutathione depletion (intrinsic, dose-dependent)
NSAIDs	Diclofenac, ibuprofen	Hepatocellular	Reactive acyl glucuronide metabolites, idiosyncratic
Anticonvulsants	Valproate, phenytoin, carbamazepine	Hepatocellular / mixed	Mitochondrial fatty-acid oxidation impairment;

Drug Class	Example Agents	Typical Pattern Injury	Key Mechanism
			reactive arene oxide metabolites
Statins	Atorvastatin, simvastatin	Hepatocellular (usually mild, self-limited)	Direct hepatocyte stress; rarely progresses to significant injury
Antiretrovirals	Nevirapine, older HIV regimens	Hepatocellular	Immune-mediated hypersensitivity, mitochondrial toxicity
Immune checkpoint inhibitors	Nivolumab, pembrolizumab, ipilimumab	Hepatocellular (immune hepatitis)	CD8+ T-cell-mediated hepatitis; immune tolerance breakdown
Targeted anticancer agents	Sorafenib, lenvatinib (TKIs)	Mixed	Mitochondrial and oxidative injury via CYP450 bioactivation
Antifungals	Terbinafine, ketoconazole, itraconazole	Cholestatic / hepatocellular	Reactive metabolite formation, transporter inhibition
Herbal / dietary supplements	Green tea extract, anabolic/bodybuilding supplements, kava, weight-loss products	Hepatocellular / cholestatic	Variable; unregulated content, contamination, idiosyncratic

7. Clinical Manifestations

The clinical presentation of DILI is highly variable and often nonspecific, ranging from asymptomatic liver enzyme elevations detected incidentally on routine bloodwork to fulminant acute liver failure. Common symptoms, when present, include **fatigue, malaise, anorexia, nausea, right upper quadrant abdominal discomfort, and low-grade fever**. Hepatocellular injury may present with jaundice, dark urine, and pale stools when severe, while cholestatic injury more typically presents with pruritus and jaundice with relatively preserved synthetic function. **Hypersensitivity features such as rash, fever, and eosinophilia may accompany immune-mediated idiosyncratic reactions, particularly with certain antimicrobials and anticonvulsants** (drug reaction with eosinophilia and systemic symptoms, or DRESS syndrome). Severe cases can progress to coagulopathy, hepatic encephalopathy, and multiorgan failure, particularly when Hy's Law criteria (ALT or AST greater than 3 times the upper limit of normal with total bilirubin greater than 2 times the upper limit of normal, in the absence of cholestasis or alternative explanation) are met, which historically predicts a mortality or transplantation risk of approximately 10% or higher.

8. Diagnosis

The diagnosis of DILI is one of exclusion, requiring careful integration of clinical history, biochemical patterns, and, where necessary, histological and imaging data, since no single laboratory test can confirm the diagnosis with certainty.

8.1 Liver function tests

Serum ALT, aspartate aminotransferase (AST), ALP, gamma-glutamyl transferase (GGT), and total and direct bilirubin form the initial biochemical assessment. Serial measurements help establish the pattern and trajectory of injury and are essential for monitoring resolution after drug withdrawal.

8.2 R-value

The R-value, calculated as (ALT / upper limit of normal) divided by (ALP / upper limit of normal), classifies the pattern of injury as hepatocellular ($R \geq 5$), cholestatic ($R \leq 2$), or mixed ($2 < R < 5$), guiding the differential diagnosis and subsequent workup.

8.3 RUCAM score

The Roussel Uclaf Causality Assessment Method (RUCAM), first published in 1993 and updated in 2016, is the most widely used structured causality assessment instrument for suspected DILI, having been applied in tens of thousands of published cases worldwide. It assigns points across domains including time to onset, course after drug discontinuation, risk factors, concomitant medications, exclusion of alternative causes, prior information on drug hepatotoxicity, and response to rechallenge, yielding a total score that categorizes causality as excluded, unlikely, possible, probable, or highly probable.

8.4 Liver biopsy

Liver biopsy is not required in most cases but is valuable when the diagnosis remains unclear, when autoimmune hepatitis is a competing possibility, when there is no improvement after drug withdrawal, or when chronic liver disease is suspected. Histological findings in DILI are diverse and can mimic almost any pattern of liver disease, including acute hepatitis, cholestasis, granulomatous inflammation, steatohepatitis, and vascular injury, so biopsy findings must always be interpreted in clinical context.

8.5 Imaging

Abdominal ultrasound, and occasionally cross-sectional imaging or magnetic resonance cholangiopancreatography, are used to exclude biliary obstruction, malignancy, and vascular causes of liver test abnormalities, particularly in patients presenting with a cholestatic biochemical pattern.

8.6 Differential diagnosis

Alternative causes that must be systematically excluded include viral hepatitis (A, B, C, E, and, in the appropriate context, cytomegalovirus and Epstein-Barr virus), autoimmune hepatitis, primary biliary

cholangitis and primary sclerosing cholangitis, alcohol-associated liver disease, ischemic hepatitis, Wilson disease, and biliary tract obstruction. A detailed medication and supplement history, including over-the-counter and herbal products, alongside a precise timeline of exposure and symptom onset, remains the single most important diagnostic tool.

Figure 3. Diagnostic Algorithm for Suspected DILI

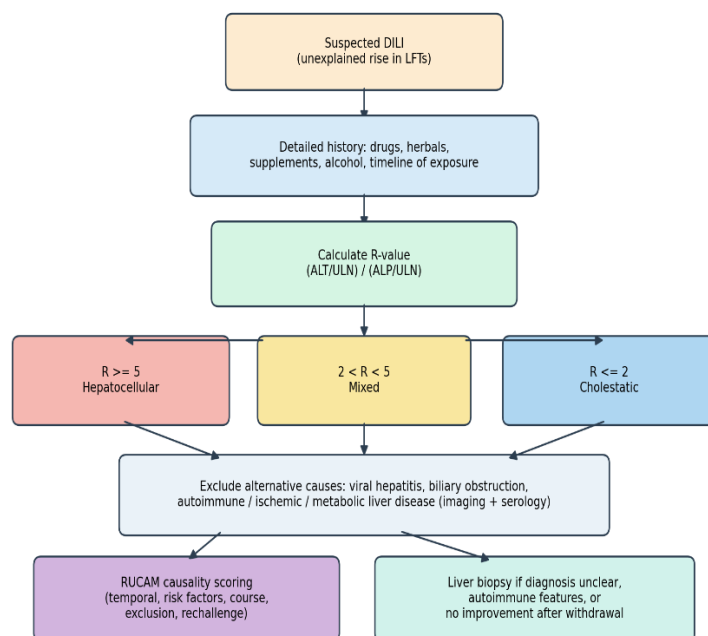


Figure 8.1: Diagnostic algorithm for suspected drug-induced liver injury, from initial biochemical pattern recognition through causality assessment.

9. Biomarkers of DILI

Accurate biomarkers are central to diagnosing DILI, distinguishing its clinical subtype, and predicting outcome, since diagnosis still relies heavily on exclusion of other causes and standardized causality tools such as RUCAM.

9.1 Traditional biomarkers

- Alanine aminotransferase (ALT): the most sensitive and widely used marker of hepatocellular injury; a value greater than five times the upper limit of normal (ULN) is a diagnostic threshold for acute hepatocellular DILI.
- Aspartate aminotransferase (AST): less liver-specific than ALT but useful in combination; an AST/ALT ratio above 2 suggests alcohol-associated liver disease or cirrhosis, while a ratio below 1 is typical of acute hepatocellular injury.
- Alkaline phosphatase (ALP): the principal marker of cholestatic or obstructive injury; a value more than twice the ULN, especially with concurrent bilirubin elevation, defines cholestatic DILI.
- Bilirubin: reflects the liver's excretory capacity and is a key component of Hy's Law and the newer R-ratio, both of which help predict progression to acute liver failure or the need for transplantation.

9.2 Emerging biomarkers

- Glutamate dehydrogenase (GLDH) and mitochondrial DNA (mtDNA): mitochondrial-matrix constituents released when severe mitochondrial injury ruptures hepatocyte membranes, offering greater mechanistic specificity than transaminases alone.
- microRNA-122 (miR-122): a liver-enriched microRNA that rises early after hepatocyte injury and shows promise as a sensitive, liver-specific complement to ALT.
- High mobility group box-1 protein (HMGB1), including its acetylated form: a damage-associated molecular pattern that can help distinguish necrotic from apoptotic cell death and signals innate immune activation in DILI.
- Keratin-18 (K18): full-length K18 reflects necrosis while caspase-cleaved K18 reflects apoptosis, allowing biomarker-based discrimination of the dominant mode of hepatocyte death.
- Additional candidate microRNAs (mir-192, mir-6, mir-320-3p, mir-1-3p, mir-877-5p), sorbitol dehydrogenase, glutathione-S-transferase alpha, osteopontin, and anti-CYP450 antibodies, alongside pharmacogenomic markers such as HLA-B*57:01, DRB1*07/DQA1*02, and GSTM1/GSTT1/GSTP1 variants, are under active investigation to refine risk prediction and mechanistic subtyping.

Table 5: Biomarkers used in DILI

Biomarker	Category	Clinical Utility
ALT	Traditional	Sensitive marker of hepatocellular injury; central to RUCAM classification and ACG/DILIN diagnostic thresholds
AST	Traditional	Reflects hepatocellular necrosis; AST/ALT ratio >2 suggests alcohol-associated or cirrhotic injury
ALP	Traditional	Marker of cholestatic/biliary injury; elevated with concurrent bilirubin rise in obstructive patterns
Bilirubin	Traditional	Reflects excretory liver function; core component of Hy's Law and the new R-ratio for predicting severe outcomes
GLDH / mitochondrial DNA	Emerging	Mitochondrial-matrix enzymes released with severe mitochondrial damage; may improve specificity for hepatocellular necrosis
miR-122	Emerging	Liver-enriched microRNA released early in hepatocyte injury; complements ALT as a safety biomarker
HMGB1 (incl. acetylated form)	Emerging	Damage-associated molecular pattern distinguishing necrosis from apoptosis; implicated in innate immune activation
Keratin-18 (K18, full-length and caspase-cleaved)	Emerging	Differentiates apoptotic from necrotic cell death; used as an exploratory DILI safety biomarker in cohort studies
Additional microRNAs (mir-	Emerging	Panel-based candidates under investigation for earlier or more specific detection of liver injury

Biomarker	Category	Clinical Utility
192, mir-6, mir-320-3p, mir-1-3p, mir-877-5p)		

10. Management

The cornerstone of DILI management is prompt identification and discontinuation of the suspected causative agent, which alone leads to clinical and biochemical improvement in the majority of cases. Ongoing monitoring of liver function tests, typically at intervals of days to weeks depending on severity, is required to confirm resolution and detect any progression. For acetaminophen-induced intrinsic DILI, N-acetylcysteine is a specific antidote that replenishes hepatic glutathione stores and is highly effective when administered early after overdose, and it may also confer benefit in early-stage non-acetaminophen acute liver failure. For most idiosyncratic DILI cases, however, management is largely supportive, as no universally effective antidote exists.

Ursodeoxycholic acid is sometimes used in cholestatic DILI to promote bile flow, although high-quality evidence for its efficacy is limited. Corticosteroids may have a role in cases with pronounced hypersensitivity features, autoimmune-like histology, or immune checkpoint inhibitor-induced hepatitis, where immune-mediated mechanisms predominate; in the latter setting, drug discontinuation combined with corticosteroids, and occasionally additional immunosuppression, follows recently updated consensus and oncology guidelines.

Patients meeting Hy's Law criteria, or those with evidence of synthetic dysfunction (coagulopathy, encephalopathy), require urgent referral to a liver transplant center, as clinical deterioration can be rapid. Supportive intensive care, correction of coagulopathy, and management of complications such as hepatic encephalopathy and infection are essential in severe cases. Rechallenge with the suspected drug is generally avoided given the risk of more severe recurrent injury, except in exceptional circumstances where no therapeutic alternative exists and the potential benefit outweighs the risk, with rechallenge decisions made cautiously and with close monitoring.

Preventive strategies include careful medication reconciliation, avoidance of unnecessary polypharmacy, judicious use of hepatotoxic agents in high-risk populations (elderly patients, those with underlying liver disease, or heavy alcohol use), and patient education regarding the hepatotoxic potential of herbal and dietary supplements.

Pre-treatment genetic screening (for example, HLA-B*57:01 testing prior to certain drug exposures in specific contexts) represents an emerging strategy for reducing preventable idiosyncratic DILI, though this remains limited to specific drug-gene pairs with established clinical utility.

11.Prevention And Pharmacovigilance

Drug-induced liver injury (DILI) remains one of the major causes of acute liver failure and drug withdrawal from the market. Effective prevention relies on rational prescribing, careful patient monitoring, robust pharmacovigilance systems, patient education, and risk prediction strategies.

11.1 Rational Prescribing

Rational prescribing is the first step in preventing DILI. Healthcare professionals should prescribe drugs only when clearly indicated, use the lowest effective dose for the shortest possible duration, and avoid unnecessary polypharmacy. Before initiating potentially hepatotoxic medications, clinicians should assess patient-related risk factors such as age, sex, alcohol consumption, obesity, pre-existing liver disease, pregnancy, and concomitant medications. Drug interactions involving cytochrome P450 enzymes should also be considered because they may increase hepatotoxicity.

11.2 Monitoring Liver Enzymes

Routine monitoring of liver function tests (LFTs), including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), bilirubin, and gamma-glutamyl transferase (GGT), helps identify liver injury before severe damage occurs. High-risk drugs such as isoniazid, methotrexate, valproic acid, amiodarone, and immune checkpoint inhibitors require regular biochemical monitoring. Prompt discontinuation of the offending drug following significant liver enzyme elevation improves patient outcomes.

11.3 Pharmacovigilance

National and international pharmacovigilance programs play a critical role in detecting rare or delayed hepatotoxic reactions. Spontaneous adverse drug reaction (ADR) reporting systems such as the WHO Programme for International Drug Monitoring, Surveillance, and the FDA Adverse Event Reporting System (FAERS) facilitate early identification of hepatotoxic drugs. Causality assessment tools, including the Roussel Uclaf Causality Assessment Method (RUCAM), improve diagnostic accuracy and standardize DILI reporting.

11.4 Patient Education

Patients should receive clear instructions regarding early symptoms of liver injury, including jaundice, fatigue, nausea, anorexia, dark urine, pale stools, itching, and right upper quadrant pain. They should avoid alcohol, self-medication, and herbal supplements unless approved by healthcare providers. Immediate medical consultation is recommended when symptoms develop.

11.5 Risk Prediction

Risk prediction combines clinical characteristics, genetic susceptibility, laboratory biomarkers, and computational algorithms to identify high-risk individuals before drug initiation. Integration of pharmacogenomics, electronic health records, and artificial intelligence may significantly improve individualized risk assessment and prevention of DILI.

12.Recent Advances in drug induced Liver Injury

Recent technological advances have transformed the understanding, prediction, diagnosis, and management of DILI by integrating computational biology, advanced cell culture systems, genomics, and systems medicine.

12.1 Artificial Intelligence (AI)

Artificial intelligence has become an important tool for DILI prediction. AI algorithms analyse electronic health records, laboratory parameters, medication histories, and imaging data to identify patients at

increased risk. Deep learning models can detect complex relationships among multiple variables that traditional statistical methods may overlook, allowing earlier diagnosis and improved clinical decision-making.

12.2 Machine Learning (ML)

Machine learning models use chemical structure information, pharmacological properties, transcriptomics, and clinical datasets to predict hepatotoxicity during drug development. Random forest, support vector machine, and neural network models have shown high predictive accuracy in identifying hepatotoxic compounds before clinical trials, thereby reducing drug attrition and improving patient safety.

12.3 Liver Organoids

Human liver organoids are three-dimensional mini organs derived from stem cells that closely resemble native liver tissue. These organoids preserve hepatocyte function, bile duct formation, and metabolic activity, making them valuable tools for studying DILI mechanisms, evaluating drug safety, and investigating patient-specific responses. Compared with conventional cell lines, liver organoids provide greater physiological relevance.

12.4 Three-Dimensional (3D) Liver Models

Three-dimensional liver spheroids, liver-on-a-chip systems, and micro physiological models recreate the structural and functional complexity of the human liver. These models improve long-term hepatocyte survival, maintain metabolic enzyme expression, and better predict chronic hepatotoxicity than traditional two-dimensional cultures. They are increasingly used in preclinical drug screening.

12.5 Multi-Omics Technologies

Multi-omics integrates genomics, transcriptomics, proteomics, metabolomics, lipidomic, and epigenomics to understand molecular mechanisms underlying DILI. These approaches identify novel biomarkers associated with oxidative stress, mitochondrial dysfunction, immune activation, and bile acid dysregulation. Multi-omics facilitates personalized risk assessment and improves mechanistic understanding of hepatotoxicity.

12.6 Gut Microbiome

Growing evidence indicates that the gut microbiome influences drug metabolism, immune regulation, and susceptibility to DILI through the gut-liver axis. Alterations in microbial composition may modify drug bioavailability and inflammatory responses, thereby affecting liver injury severity. Modulation of the microbiome through probiotics, prebiotics, or faecal microbiota transplantation is being investigated as a potential therapeutic strategy.

12.7 Precision Medicine

Precision medicine integrates genetic polymorphisms, clinical characteristics, environmental exposures, and biomarker profiles to individualize treatment decisions. Genetic markers such as HLA alleles have been associated with susceptibility to DILI caused by flucloxacillin, amoxicillin-clavulanate, and other drugs. Personalized medicine enables safer prescribing, improved monitoring strategies, and reduced incidence of severe hepatotoxicity.

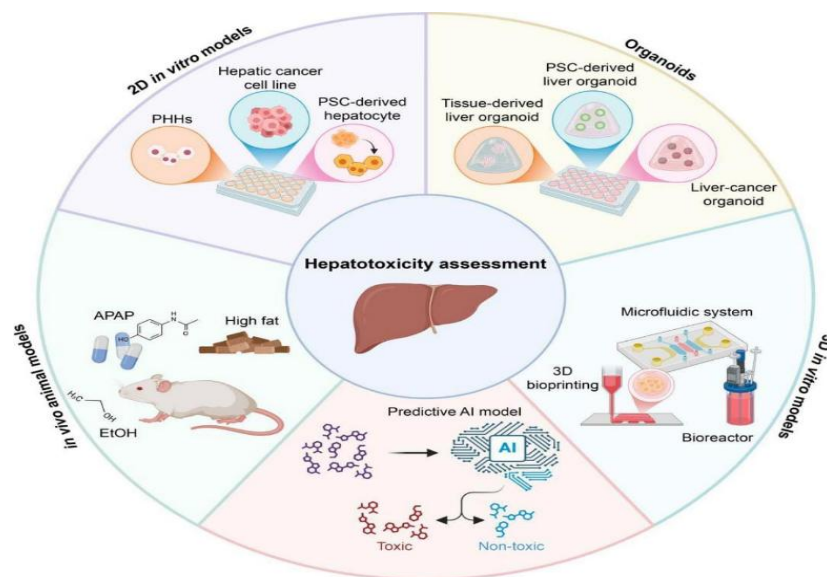


Figure 12.1: Emerging technologies for DILI prediction

Artificial intelligence, machine learning, pharmacogenomics, liver organoids, liver-on-a-chip platforms, 3D liver models, multi-omics technologies, gut microbiome analysis, wearable biosensors, and precision medicine approaches.

13. Future Perspectives.

Future research in DILI will focus on **personalized medicine, novel biomarkers, artificial intelligence (AI), and advanced preclinical models** to improve early detection and prevention. Biomarkers such as **miR-122, K18, GLDH, and HMGB1** may provide earlier and more accurate diagnosis than conventional liver enzymes. AI can enhance risk prediction and pharmacovigilance by integrating clinical and genomic data. Advanced models like **liver organoids, liver-on-a-chip, and iPSC-derived hepatocytes** may improve drug safety testing. Future clinical trials should include **pharmacogenomic stratification, biomarker-guided approaches, and long-term safety monitoring**, supported by international collaboration and stronger global pharmacovigilance systems.

14. Conclusion

Drug-induced liver injury remains a clinically significant and diagnostically challenging condition that spans nearly every field of medicine, given the sheer diversity of pharmaceutical, herbal, and dietary agents capable of causing hepatotoxicity. Its clinical importance is underscored by its role as a leading cause of acute liver failure, a major reason for drug withdrawal from the market, and a persistent diagnostic dilemma in everyday clinical practice.

Current challenges include the absence of specific, validated biomarkers for idiosyncratic DILI, the continued reliance on exclusionary and probabilistic diagnostic frameworks such as RUCAM, and the difficulty of predicting individual susceptibility despite growing understanding of genetic and

immunological risk factors. The rising use of complex oncology therapeutics, including immune checkpoint inhibitors and targeted agents, alongside the widespread and often unregulated use of herbal and dietary supplements, continues to reshape the epidemiological landscape of DILI.

Early diagnosis remains essential to prevent progression to irreversible liver injury, and requires a high index of clinical suspicion, thorough medication histories, and timely application of causality assessment tools. Future directions include the development and validation of specific circulating biomarkers (such as microRNAs and mitochondrial DNA), refinement of genetic risk-stratification strategies, greater integration of gut-liver axis research into risk prediction, and continued international collaboration through DILI registries to improve the granularity and generalizability of epidemiological and mechanistic data. Collectively, these advances hold promise for transforming DILI from a diagnosis of exclusion into one that can be anticipated, prevented, and managed with greater precision.

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