

Toxic and Drug-Induced Hepatitis

Chapter 351 | Harrison's 22e

KEY CLINICAL POINTS

- 1 Drug-induced liver injury (DILI) is the most common cause of acute liver failure.
- 2 Chemical hepatotoxicity is categorized into two main types: Direct toxic and Idiosyncratic.
- 3 Direct toxic hepatitis is predictable, dose-dependent, and typically has a short latent period (hours), with clinical manifestations appearing within 24–48 hours.
- 4 Idiosyncratic reactions are unpredictable, occur in 1 in 10^3 – 10^5 patients, and have a longer latent period (typically 5 to 90 days).
- 5 Acetaminophen is the primary example of a direct hepatotoxin.
- 6 Hepatotoxicity often results from Phase I metabolic activation into toxic intermediates or glutathione depletion.
- 7 Mechanism of injury includes membrane damage, bile canaliculus disruption, covalent binding, immune-mediated attack, apoptosis, and mitochondrial dysfunction.
- 8 Idiosyncratic 'adaptation' refers to mild, transient transaminase elevations that resolve with continued drug use (e.g., isoniazid, valproate, phenytoin, HMG-CoA reductase inhibitors).
- 9 Morphological changes are characteristic of specific toxins; e.g., centrilobular zonal necrosis for acetaminophen and carbon tetrachloride.
- 10 DILI is a major cause of failure for new compounds to reach approval during clinical trials due to 'off-target' effects, especially in low-potency drugs requiring higher doses.

DEFINITION & CLASSIFICATION

- **Drug-Induced Liver Injury (DILI):** The most common cause of acute liver failure.
- **Classification of Chemical Hepatotoxicity:**
 - **Direct Toxic:**
 - Predictable and dose-dependent
 - Short latent period (often several hours; clinical manifestations may be delayed 24–48 h)
 - Results in morphologic abnormalities that are characteristic and reproducible for each toxin.
 - Examples: Carbon tetrachloride, trichloroethylene (centrilobular zonal necrosis), and Acetaminophen.
 - **Idiosyncratic:**
 - Infrequent occurrence (1 in 10^3 – 10^5 patients)
 - Unpredictable; not clearly dose-dependent
 - Latent period: Typically 5 to 90 days following initiation
 - **Adaptation:** Mild, transient serum aminotransferase elevations that resolve with continued drug use (e.g., isoniazid, valproate, phenytoin, and HMG-CoA reductase inhibitors).

ETIOLOGY & PATHOPHYSIOLOGY

- **Drug Metabolism:**

- Most drugs are water-insoluble → require conversion to a water-soluble form for renal or biliary excretion.
- Phase I: Oxidation or methylation (mediated by microsomal mixed function oxygenases).
- Phase II: Glucuronidation, sulfation, or inactivation by glutathione.
- **Mechanisms of Toxicity:**

→ Formation of a phase I toxic metabolite

→ Glutathione depletion → prevents inactivation of harmful compounds

→ Exposure to industrial toxins, pharmacologic agents, and complementary/alternative medicines (CAMs).

- **Mechanisms of Hepatocyte Injury (Figure 351-1):**

- **A. Membrane Damage:** Disruption of intracellular calcium homeostasis → disassembly of actin fibrils → membrane blebbing, rupture, and cell lysis.
- **B. Bile Canaliculus Injury:** Disruption of actin filaments near the canaliculus → loss of villous processes → failure of transport pumps (e.g., MRP3) → inability to excrete bilirubin and other organic compounds.
- **C. Covalent Binding:** Cytochrome P450 enzymes bind to drugs → formation of nonfunctioning adducts.
- **D. Immune-Mediated Attack:** Enzyme-drug adducts move to cell surface in vesicles → serve as target immunogens for cytolytic T cells (CTLs) → trigger cytokine response.
- **E. Apoptotic Pathway:** Activation of TNF- α receptor or Fas (death domain) → cascade of intercellular caspases → programmed cell death.
- **F. Mitochondrial Dysfunction:** Inhibition of β -oxidation and/or respiratory-chain enzymes → failure of free fatty acid metabolism → lack of aerobic respiration → accumulation of lactate and reactive oxygen species (ROS).

CLINICAL FEATURES

- **Direct Toxic Agents:**

- **Carbon tetrachloride & trichloroethylene:** Characteristically produce centrilobular zonal necrosis.
- **Amanita phalloides (Deathcap mushroom):** Produces massive hepatic necrosis; lethal dose $\approx$ 10 mg.
- **Acetaminophen:** The primary example of a direct toxin.

- **Idiosyncratic Reactions:**

- **Clinical Presentation:** May include hypersensitivity features such as rash, arthralgias, fever, leukocytosis, and eosinophilia (characteristic for phenytoin and trimethoprim-sulfamethoxazole).
- **Adaptation:** Recognized in drugs like isoniazid, valproate, phenytoin, and HMG-CoA reductase inhibitors.

DIAGNOSTIC APPROACH

1. Comprehensive History-Taking:

- Identify exposure to industrial chemicals, pharmaceuticals (prescription or over-the-counter), and herbal/dietary supplements (CAMs).

2. Determine Toxicity Type via Clinical Markers:

- **Predictability & Dose Relationship:**

→ Predictable/Dose-dependent → Suggests Direct Toxic (e.g., Acetaminophen, Carbon tetrachloride).

→ Unpredictable/Not dose-related → Suggests Idiosyncratic (e.g., Isoniazid, Ciprofloxacin).

- **Latent Period:**

→ Short period (hours to 48h) → Direct Toxic.

→ Delayed onset (5 to 90 days) → Idiosyncratic.

3. Evaluate Morphologic Patterns (Table 351-2):

– **Cholestasis:** Associated with steroids, antibiotics (Erythromycin, Nitrofurantoin, Rifampin, Amox-Clav, Oxacillin), and anticonvulsants (Carbamazepine).

– **Hepatitis:** Associated with anesthetics (Halothane, Flutothane), antiandrogens (Flutamide), antibiotics (Isoniazid, Rifampicin, Nitrofurantoin, Telithromycin, Minocycline, Pyrazinamide, Trovafloxacin), and anticonvulsants (Phenytoin, Carbamazepine, Valproic acid, Phenobarbital).

– **Toxic (Necrosis):** Acetaminophen, Carbon tetrachloride, Yellow phosphorus, Amanita phalloides, Dimethylformamide.

– **Vascular Injury:** Oxaliplatin, Melphalan.

KEY PEARLS & HIGH-YIELD POINTS

• DILI as a Barrier to Drug Approval:

- DILI is the most common reason for compounds failing to reach approval during development.
- High potency drugs (mg amounts) rarely cause off-target effects.
- Low potency drugs require higher doses → increased risk of "off-target" effects and toxicity.

• Table 351-1 Summary:

- **Direct Toxic:** Predictable (+), Short latent period, Necrosis/fatty infiltration.
- **Acetaminophen:** Predictable (+), Short latent period, Centrilobular necrosis.
- **Idiosyncratic (Amox-Clav, Isoniazid, Cipro):** Not predictable (0), Delayed onset, Mixed or viral-like morphology.
- **Other (Estrogens/Androgens):** Predictable (+), Variable/Short period.

• Table 351-2 Summary (Morphology by Class):

- **Cholestasis:** Steroids, Antibiotics (Erythromycin, Nitrofurantoin, Rifampin, Amox-Clav, Oxacillin), Anticonvulsants (Carbamazepine).
- **Hepatitis:** Anesthetics (Halothane, Flutothane), Antiandrogens (Flutamide), Antibiotics (Isoniazid, Rifampicin, Nitrofurantoin, Telithromycin, Minocycline, Pyrazinamide, Trovafloxacin), Anticonvulsants (Phenytoin, Carbamazepine, Valproic acid, Phenobarbital).
- **Toxic (Necrosis):** Acetaminophen, Carbon tetrachloride, Yellow phosphorus, Amanita phalloides, Dimethylformamide.
- **Vascular Injury:** Oxaliplatin, Melphalan.

REFERENCE TABLES

TABLE 351-1

Some Features of Toxic and Drug-Induced Hepatic Injury FEATURES Predictable and dose- + related toxicity Latent period...

FEATURES	DIRECT TOXIC EFFECT ^a		IDIOSYNCRATIC ^a			OTHER ^a
	CARBON TETRACHLORIDE	ACETAMINOPHEN	AMOXICILLIN-CLAVULANATE	ISONIAZID	CIPROFLOXACIN	ESTROGENS/ANDROGENIC STEROIDS
Predictable and dose-related toxicity	+	+	0	0	0	+
	Short	Short	Delayed onset	Variable	May be short	
Arthralgia, fever, rash, eosinophilia	0	0	0	0	0	0
	Necrosis, fatty infiltration	Centrilobular necrosis	Mixed hepatocellular/cholestatic	Hepatocellular injury resembling viral hepatitis	Hepatocellular injury resembling viral hepatitis	

TABLE 351-2

Principal Alterations of Hepatic Morphology Produced by Some Commonly Used Drugs and Chemicals ^a

PRINCIPAL MORPHOLOGIC CHANGE	CLASS OF AGENT	EXAMPLE
Cholestasis	Anabolic steroid Antibiotic Anticonvulsant Antidepressant Anti-inflammatory Antiplatelet Antihypertensive Antithyroid Calcium channel blocker Immunosuppressive Lipid-lowering Oncotherapeutic Oral contraceptive Oral hypoglycemic Tranquilizer	Methyl testosterone, many other body-building supplements Erythromycin estolate, nitrofurantoin, rifampin, amoxicillin-clavulanic acid, oxacillin Carbamazepine Duloxetine, mirtazapine, tricyclic antidepressants Sulindac Clopidogrel Irbesartan, fosinopril Methimazole Nifedipine, verapamil Cyclosporine Ezetimibe Anabolic steroids, busulfan, tamoxifen, irinotecan, cytarabine, temozolomide Norethynodrel with mestranol Chlorpropamide Chlorpromazine

PRINCIPAL MORPHOLOGIC CHANGE	CLASS OF AGENT	EXAMPLE
	Antiarrhythmic Antibiotic Anticonvulsant Antiviral Oncotherapeutic	
Hepatitis	Anesthetic Antiandrogen Antibiotic Anticonvulsant Antidepressant Antifungal Antihypertensive Anti-inflammatory Antipsychotic Antiviral Calcium channel blocker Cholinesterase inhibitor Diuretic Laxative Norepinephrine reuptake inhibitor Oral hypoglycemic Immune checkpoint inhibitor	Halothane, fluothane Flutamide Isoniazid,c rifampicin, nitrofurantoin, telithromycin, minocycline,d pyrazinamide, trovafloxacin Phenytoin, carbamazepine, valproic acid, phenobarbital Iproniazid, amitriptyline, trazodone, venlafaxine, fluoxetine, paroxetine, duloxetine, sertraline, nefazodone Ketoconazole, fluconazole, itraconazole Methyldopa,c captopril, enalapril, lisinopril, losartan Ibuprofen, indomethacin, diclofenac, sulindac, bromfenac Risperidone Zidovudine, didanosine, stavudine, nevirapine, ritonavir, indinavir, tipranavir, zalcitabine Nifedipine, verapamil, diltiazem Tacrine Chlorothiazide Oxyphenisatin,c,e Atomoxetine Troglitazone,e acarbose Ipilimumab, pembrolizumab, nivolumab
	Antibiotic Antibacterial Antifungal Antihistamine Immunosuppressive Lipid-lowering	
Toxic (necrosis)	Analgesic Hydrocarbon Metal Mushroom Solvent	Acetaminophen Carbon tetrachloride Yellow phosphorus Amanita phalloides Dimethylformamide
	Antiarrhythmic Antibiotic Anticonvulsant Anti-inflammatory Xanthine oxidase inhibitor	
Vascular injury	Chemotherapeutic	Oxaliplatin, melphalan