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Toxic and Drug-Induced Hepatitis Liver injury is a possible consequence of ingestion of any xenobiotic, including industrial toxins, pharmacologic agents, and complementary and alternative medications (CAMs). Among patients with acute liver failure, drug-induced liver injury (DILI) is the most common cause, and evidence for hepatotoxicity detected during clinical trials for drug development is the most common reason for failure of compounds to reach approval status. DILI requires careful history-taking to identify unrecognized exposure to chemicals used in work or at home, drugs taken by prescription or bought over the counter, and herbal or dietary supplement medicines. Hepatotoxic drugs can injure the hepatocyte directly, for example, via a free-radical or metabolic intermediate that causes peroxidation of membrane lipids and that results in liver cell injury. Alternatively, a drug or its metabolite may activate compo nents of the innate or adaptive immune system, stimulate apoptotic pathways, or initiate damage to bile excretory pathways (Fig. 351-1). Interference with bile canalicular pumps can allow endogenous bile acids, which can injure

the liver, to accumulate. Such secondary injury, in turn, may lead to necrosis of hepatocytes; injure bile ducts, produc ing cholestasis; or block pathways of lipid movement, inhibit protein synthesis, or impair mitochondrial oxidation of fatty acids, resulting in lactic acidosis and intracellular triglyceride accumulation (expressed histologically as microvesicular steatosis). In other instances, drug metabolites sensitize hepatocytes to toxic cytokines. The differences

observed between susceptible and nonsusceptible drug recipients may be attributable to human leukocyte antigen (HLA) haplotypes that determine binding of drug-related haptens on the cell surface as well as to polymorphisms in elaboration of competing, protective cytokines, as has been suggested for acetaminophen hepatotoxicity (see below). Immune mechanisms may include cytotoxic lymphocytes or antibodymediated cellular cytotoxicity. In addition, a role has been shown for activation of nuclear transporters, such as the constitutive androstane receptor (CAR) or, more recently, the pregnane X receptor (PXR), in the induction of drug hepatotoxicity.

■ ■DRUG METABOLISM Most drugs, which are water-insoluble, undergo a series of metabolic steps, culminating in a water-soluble form appropriate for renal or biliary excretion. This process begins with oxidation or methylation mediated initially by the microsomal mixed function oxygenases, cytochrome P450 (phase I reaction), followed by glucuronidation or sulfation (phase II reaction) or inactivation by glutathione. Most drug hepatotoxicity is the result of formation of a phase I toxic metabolite, but glutathione depletion, precluding inactivation of harmful com pounds by glutathione S-transferase, can contribute as well by ensuring that the toxic compound is not abrogated. ■ ■LIVER INJURY CAUSED BY DRUGS In general, two major types of chemical hepatotoxicity have been rec ognized: (1) direct toxic and (2) idiosyncratic. As shown in Table 351-1, direct toxic hepatitis occurs with predictable regularity in individuals exposed to the offending agent and is dose-dependent. The latent period between exposure and liver injury is usually short (often several hours), although clinical manifestations may be delayed for 24–48 h. Agents producing toxic hepatitis are generally systemic poisons or are converted in the liver to toxic metabolites. The direct hepatotoxins result in morphologic abnormalities that are reasonably characteristic and reproducible for each toxin. Examples of rare toxins currently include carbon tetrachloride and trichloroethylene that characteristi cally produce a centrilobular zonal necrosis. The hepatotoxic octapep tides of Amanita phalloides usually produce massive hepatic necrosis; the lethal dose of the toxin is ~10 mg, the amount found in a single deathcap mushroom. Acetaminophen, the prime example of a direct toxin, is discussed below. CHAPTER 351 Toxic and Drug-Induced Hepatitis In idiosyncratic drug reactions, the occurrence of liver injury is infrequent (1 in 103–105 patients) and unpredictable; the response is not as clearly dose-dependent as is injury associated with direct hepatotoxins, and liver injury may occur at any time after exposure to the drug but typically between 5 and 90 days following its initiation. Although regarded as not dose-related in the fashion of direct toxins, most agents causing idiosyncratic toxicity are given at relatively high daily doses, typically exceeding 100 mg, suggesting a role for dose— drugs with low potency must be given in higher doses that engender greater chances for “off-target” effects. Likewise, drugs given in mil ligram amounts are of high potency and rarely cause liver or other off-target effects. Adding to the difficulty of predicting or identifying idiosyncratic drug hepatotoxicity is the occurrence of mild, transient, nonprogressive serum aminotransferase elevations that resolve with continued drug use. Such “adaptation,” the mechanism of which is unknown, is well recognized for drugs such as isoniazid (INH), valpro ate, phenytoin, and HMG-CoA reductase inhibitors (statins). Extrahe patic manifestations of hypersensitivity, such as rash, arthralgias,

fever, leukocytosis, and eosinophilia, occur in a small fraction of patients with idiosyncratic hepatotoxic drug reactions but are characteristic for certain drugs (phenytoin, trimethoprim-sulfamethoxazole) and not others. Both primary immunologic injury and direct hepatotoxicity related to idiosyncratic differences in generation of toxic metabolites have been invoked to explain idiosyncratic drug reactions. The most current data implicate the adaptive immune system responding to the formation of immune stimulatory compounds resulting from phase I metabolic activation of the offending drug. Differences in host sus ceptibility may result from varying kinetics of toxic metabolite gen eration and genetic polymorphisms in downstream drug-metabolizing

Six Mechanisms of Liver Injury A Membrane Hepatocyte PART 10 Disorders of the Gastrointestinal System F Vesicle Triglycerides Free fatty acid D E Cell death Other caspases Inhibition of β-oxidation, respiration, or both Caspase Caspase Mitochondrion Lactate A. Rupture of cell membrane. B. Injury of bile canaliculus (disruption of transport pumps). C. P-450-drug covalent binding (drug adducts). FIGURE 351-1 Potential mechanisms of drug-induced liver injury. The normal hepatocyte may be affected adversely by drugs through (A) disruption of intracellular calcium homeostasis that leads to the disassembly of actin fibrils at the surface of the hepatocyte, resulting in blebbing of the cell membrane, rupture, and cell lysis; (B) disruption of actin filaments next to the canaliculus (the specialized portion of the cell responsible for bile excretion), leading to loss of villous processes and interruption of transport pumps such as multidrug resistance–associated protein 3 (MRP3), which, in turn, prevents the excretion of bilirubin and other organic compounds; (C) covalent binding of the heme-containing cytochrome P450 enzyme to the drug, thus creating nonfunctioning adducts; (D) migration of these enzyme-drug adducts to the cell surface in vesicles to serve as target immunogens for cytolytic attack by T cells, stimulating an immune response involving cytolytic T cells and cytokines; (E) activation of apoptotic pathways by tumor necrosis factor α (TNF-α) receptor or Fas (DD denotes death domain), triggering the cascade of intercellular caspases, resulting in programmed cell death; or (F) inhibition of mitochondrial function by a dual effect on both β-oxidation and the respiratory-chain enzymes, leading to failure of free fatty acid metabolism, a lack of aerobic respiration, and accumulation of lactate and reactive oxygen species (which may disrupt mitochondrial DNA). Toxic metabolites excreted in bile may damage bile-duct epithelium (not shown). CTLs, cytolytic T lymphocytes. (From WM Lee: Drug-induced hepatotoxicity. N Engl J Med 349:474, 2003. Copyright © 2003, Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

B Transport pumps (MRP3) Canaliculus P-450 Heme Drug C Endoplasmic reticulum Enzyme-drug adduct Other caspases Cytokines Caspase DD DD DD DD Cytolytic T cell TNF-α receptor, Fas D. Drug adducts targeted by CTLs/cytokines. E. Activation of apoptotic pathway by TNFα/Fas. F. Inhibition of mitochondrial function.

TABLE 351-1 Some Features of Toxic and Drug-Induced Hepatic Injury DIRECT TOXIC EFFECTa IDIOSYNCRATICa OTHERa CARBON TETRACHLORIDE ACETAMINOPHEN AMOXICILLINCLAVULANATE ISONIAZID CIPROFLOXACIN FEATURES Predictable and doserelated toxicity + +

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Latent period Short Short Delayed onset Variable May be short Variable Arthralgia, fever, rash, eosinophilia

Liver morphology Necrosis, fatty infiltration Centrilobular necrosis Mixed hepatocellular/ cholestatic aThe drugs listed are typical examples. pathways or cytokine activation; in addition, certain HLA haplotypes have been associated with hepatotoxicity of certain drugs such as amoxicillin-clavulanate and flucloxacillin. Occasionally, however, the clinical features of an allergic reaction (e.g., prominent tissue eosino philia, autoantibodies) are difficult to ignore and suggest activation of IgE pathways. A few instances of drug hepatotoxicity are observed to be associated with autoantibodies, including a class of antibodies to liver-kidney microsomes, anti-LKM2, directed against a cytochrome P450 enzyme. Four agents that specifically have a phenotype of auto immune hepatitis with a high likelihood of positive antinuclear anti bodies (ANAs) include nitrofurantoin, minocycline, hydralazine, and α-methyldopa. Idiosyncratic reactions lead to a morphologic pattern that is more variable than those produced by direct toxins; a single agent is often capable of causing a variety of lesions, although certain patterns tend to predominate. Depending on the agent involved, idiosyncratic hepatitis may result in a clinical and morphologic picture indistin guishable from that of viral hepatitis (e.g., INH or ciprofloxacin). So-called hepatocellular injury is the most common form, featuring spotty necrosis in the liver lobule with a predominantly lymphocytic infiltrate resembling that observed in acute hepatitis A, B, or C. Drug-induced cholestasis ranges from mild to increasingly severe: (1) bland cholestasis with limited hepatocellular injury (e.g., estro gens, 17,α-substituted androgens); (2) inflammatory cholestasis (e.g., amoxicillin-clavulanic acid [the most frequently implicated antibiotic among cases of DILI], oxacillin, erythromycin estolate); (3) sclerosing cholangitis (e.g., after intrahepatic infusion of the chemotherapeutic agent floxuridine for hepatic metastases from a primary colonic car cinoma); and (4) disappearance of bile ducts, “ductopenic” cholestasis or vanishing bile duct syndrome, similar to that observed in chronic rejection (Chap. 357) following liver transplantation (e.g., carbam azepine, levofloxacin). More recently, a picture resembling primary sclerosing cholangitis has been observed secondary to chemotherapy and after long-term ketamine use. Cholestasis may result from bind ing of drugs to canalicular membrane transporters, accumulation of toxic bile acids resulting from canalicular pump failure, or genetic defects in canalicular transporter proteins. Clinically, the distinction between a hepatocellular and a cholestatic reaction is indicated by the R value, the ratio of alanine aminotransferase (ALT) to alkaline phosphatase values, both expressed as multiples of the upper limit of normal. An R value of >5.0 is associated with hepatocellular injury, R <2.0 with cholestatic injury, and R between 2.0 and 5.0 with mixed hepatocellular-cholestatic injury. Morphologic alterations may also include hepatic granulomas (e.g., sulfonamides) or macrovesicular or microvesicular steatosis or steato hepatitis. Severe hepatotoxicity associated with steatohepatitis, most likely a result of mitochondrial toxicity, was recognized with certain antiretroviral therapies, although most of these drugs have been with drawn (Chap. 208). Another potential target for idiosyncratic drug hepatotoxicity is sinusoidal lining cells; when these are injured, such as by high-dose chemotherapeutic agents (e.g., cyclophosphamide, mel phalan, busulfan) administered prior to bone marrow transplantation, venoocclusive disease can result. Nodular regenerative hyperplasia, a subtle form of portal hypertension, may also result from vascular

ESTROGENS/ ANDROGENIC STEROIDS Hepatocellular injury resembling viral hepatitis Hepatocellular injury resembling viral hepatitis Cholestasis without portal inflammation injury to portal or hepatic venous endothelium following systemic chemotherapy, such as with oxaliplatin, as part of adjuvant treatment for colon cancer. Not all adverse hepatic drug reactions can be classified as either toxic or idiosyncratic. For example, oral contraceptives, which combine estro

genic and progestational compounds, may result in impairment of liver tests and, occasionally, jaundice; however, they do not produce necrosis or fatty change, manifestations of hypersensitivity are generally absent, and susceptibility to the development of oral contraceptive–induced cholestasis appears to be genetically determined. Such estrogen-induced cholestasis is more common in women with cholestasis of pregnancy, a disorder linked to genetic defects in multidrug resistance–associated canalicular transporter proteins. CHAPTER 351 Any idiosyncratic reaction that occurs in <1:10,000 recipients will go unrecognized in most clinical trials, which involve at most several thousand subjects. The U.S. Food and Drug Administration (FDA) and pharmaceutical companies have learned to look for even subtle indications of serious toxicity and monitor regularly the number of trial subjects in whom any aminotransferase elevations develop, as a possible surrogate for more serious toxicity. Even more valid as a predictor of severe hepatotoxicity is the occurrence of jaundice in patients enrolled in a clinical drug trial, so-called “Hy’s Law,” named after Dr. Hyman Zimmerman, one of the pioneers of the field of drug hepatotoxicity. He recognized that, if jaundice occurred dur ing a phase 3 trial, more serious liver injury was likely, with a 10:1 ratio between cases of jaundice and liver failure (i.e., 10 patients with jaundice would result in 1 patient with acute liver failure). Thus, the finding of such Hy’s Law (jaundiced) cases during drug development often portends failure of approval, particularly if any of the subjects sustains a bad outcome. Troglitazone, a peroxisome proliferator–activated receptor γ agonist, was the first in its class of thiazolidinedione insulin-sensitizing agents. Although in retrospect, Hy’s Law cases of jaundice had occurred during phase 3 trials, no instances of liver fail ure were recognized until well after the drug was introduced, empha sizing the importance of postmarketing surveillance in identifying toxic drugs and in leading to their withdrawal from use. Fortunately, such hepatotoxicity is not characteristic of the second-generation thiazolidinediones rosiglitazone and pioglitazone; in clinical trials, the frequency of aminotransferase elevations in patients treated with these medications did not differ from that in placebo recipients, and isolated reports of liver injury among recipients are extremely rare. Since troglitazone was withdrawn from the market in 2001, no fully approved drugs have had to be withdrawn from the market by the FDA. Several agents have received black box warnings indicating that caution is needed; overall, the industry and FDA in concert have been able to avert severe toxicity in approved agents over the past 25 years. Toxic and Drug-Induced Hepatitis Proving that an episode of liver injury is caused by a drug (causality) is difficult in many cases. DILI is nearly always a presumptive diagnosis, and many other disorders produce a similar clinicopathologic picture. Thus, causality may be difficult to establish and requires several sepa rate supportive assessment variables to lead to a high level of certainty, including temporal association (time of onset, time to resolution), clin ical-biochemical features, type of injury (hepatocellular vs cholestatic), extrahepatic features, likelihood that a given agent is to blame based on

its past record, and exclusion of other potential causes. Scoring systems such as the Roussel-Uclaf Causality Assessment Method (RUCAM) yield residual uncertainty and have not been adopted widely. Cur rently, the U.S. Drug-Induced Liver Injury Network (DILIN) relies on a structured expert opinion process requiring detailed data on each case and a comprehensive review by three experts who arrive at a consensus on a five-degree scale of likelihood (definite, highly likely, probable, possible, unlikely); however, this approach is not practical for routine clinical application. A new Revised Electronic Causality Assessment Method (RECAM) has now been developed to improve on the other two methods but, to date, is not yet in widespread use. The RECAM website can be accessed via the link dilirecam.com.

Generally, drug hepatotoxicity is not more frequent in persons with underlying chronic liver disease, although the severity of the outcome may be amplified. Reported exceptions include hepatotoxicity of aspi rin, methotrexate, INH (only in certain experiences), antiretroviral therapy for HIV infection, and certain drugs such as conditioning regi mens for bone marrow transplantation in the presence of hepatitis C. TREATMENT Toxic and Drug-Induced Hepatic Disease Treatment is largely supportive, except in acetaminophen hepato toxicity (for which N-acetylcysteine is effective, see below). Acute liver failure develops in 10% of patients with DILI; spontaneous recovery, once that threshold is reached, occurs in <30%, and liver transplantation is performed in >40% of those who reach the level of severity of acute liver failure (coagulopathy and hepatic encephalopathy) (Chap. 356). Withdrawal of the suspected agent is indicated at the first sign of an adverse reaction or when ami notransferase levels reach five times the upper limit of normal. A number of studies have suggested that lethal outcomes follow continued use of an agent in the face of symptoms and signs of liver injury. In the case of the direct toxins, liver involvement should not divert attention from renal or other organ involvement, which may also threaten survival. Agents used occasionally but of question able value include glucocorticoids for DILI with allergic features, silibinin for mushroom poisoning, and ursodeoxycholic acid for cholestatic drug hepatotoxicity. While these medications have been shown to be effective and to have reasonable safety profiles, they are of uncertain value. A double-blind, randomized controlled trial of the use of N-acetylcysteine for nonacetaminophen acute liver failure, including cases of DILI, demonstrated benefit, particularly for patients with early-stage hepatic encephalopathy; however, the drug has not been approved by the FDA for this indication, pending “further studies,” which, however, are unlikely to be undertaken. PART 10 Disorders of the Gastrointestinal System In Table 351-2, several classes of chemical agents are listed together with examples of the pattern of liver injury they produce. Certain drugs appear to be responsible for the development of chronic as well as acute hepatic injury. For example, nitrofurantoin, minocycline, hydralazine, and methyldopa have been associated with moderate to severe chronic hepatitis with autoimmune features; corticosteroids may be used and can virtually always be discontinued after 6 months of therapy. Metho trexate, tamoxifen, and amiodarone have been implicated in the devel opment of cirrhosis. Portal hypertension in the absence of cirrhosis, termed nodular regenerative hyperplasia, may result from alterations in hepatic architecture produced by excessive intake of vitamin A or fol lowing chemotherapy with oxaliplatin. Oral contraceptives have been implicated in the development of focal nodular hyperplasia or hepatic adenoma (both benign lesions) and, rarely, hepatocellular carcinoma and hepatic vein occlusion (Budd-Chiari syndrome). Another unusual lesion, peliosis hepatis (blood cysts of the liver), has been observed in some patients treated with anabolic or contraceptive steroids. The exis tence of these hepatic disorders expands the spectrum of liver injury induced by chemical agents and emphasizes the need for a thorough drug history in all patients with liver dysfunction. The comprehensive,

authoritative LiverTox website, which contains up-to-date information on DILI, is available as a valuable reference through the National Insti tutes of Health and the National Library of Medicine (livertox.nih.gov). The following are patterns of adverse hepatic reactions for some prototypic agents. ■ ■ACETAMINOPHEN HEPATOTOXICITY

(DIRECT TOXIN) Acetaminophen represents the most prevalent cause of acute liver failure in the Western world; up to 72% of patients with acetaminophen hepa totoxicity in Scandinavia—somewhat lower frequencies in the United Kingdom and the United States—progress

to encephalopathy and coagulopathy. Acetaminophen causes dose-related centrilobular hepatic necrosis after single-time-point ingestions, as intentional self-harm, or over extended periods, as unintentional overdoses, when multiple drug preparations or inappropriate drug amounts are used daily for several days, for example, for relief of pain or fever. In these instances, 8 g/d, twice the daily recommended maximum dose, over several days can readily lead to liver failure. Use of opioid-acetaminophen combinations appears to be particularly harmful, because habituation to the opioid may occur with a gradual increase in opioid-acetaminophen combina tion dosing over days or weeks. A single dose of 10–15 g, occasionally less, may produce clinical evidence of liver injury. Fatal fulminant disease is usually (although not invariably) associated with ingestion of ≥25 g. Blood levels of acetaminophen correlate with severity of hepatic injury (levels >300 μg/mL 4 h after ingestion are predictive of the devel opment of severe damage; levels <150 μg/mL suggest that hepatic injury is highly unlikely). Nausea, vomiting, diarrhea, abdominal pain, and shock are early manifestations occurring 4–12 h after ingestion. Then 24–48 h later, when these features are abating, hepatic injury becomes apparent. Maximal abnormalities and hepatic failure are evident 3–5 days after ingestion, and aminotransferase levels exceeding 10,000 IU/L are not uncommon (i.e., levels far exceeding those in patients with viral hepatitis). Renal failure and myocardial injury may be present. Whether or not a clear history of overdose can be elicited, clinical suspicion of acetaminophen hepatotoxicity should be raised by the presence of the extremely high aminotransferase levels in association with low bilirubin levels that are characteristic of this hyperacute injury. This biochemical signature should trigger further questioning of the subject if possible; however, outright denial (or denial of high doses) or altered mentation may confound diagnostic efforts. In this setting, a presumptive diagno sis is reasonable, and the proven antidote, N-acetylcysteine, is both safe and will be effective if given early (within 12 h) but is also used even when injury has evolved. Acetaminophen is metabolized predominantly by a phase II reaction to innocuous sulfate and glucuronide metabolites; however, a small proportion is metabolized by a phase I reaction to a hepatotoxic metab olite formed from the parent compound by cytochrome P450 CYP2E1. This metabolite, N-acetyl-p-benzoquinone-imine (NAPQI), is detoxi fied by binding to “hepatoprotective” glutathione to become harmless, water-soluble mercapturic acid, which undergoes renal excretion. When excessive amounts of NAPQI are formed, or when glutathione levels are low, glutathione levels are depleted and overwhelmed, per mitting covalent binding to nucleophilic hepatocyte macromolecules forming acetaminophen-protein “adducts.” These adducts, which can be measured in serum by high-performance liquid chromatography, hold promise as diagnostic markers of acetaminophen hepatotoxicity, and a point-of-care assay for acetaminophen-Cys adducts is under development. The binding of acetaminophen to hepatocyte macromol ecules is believed to lead to hepatocyte necrosis; the precise sequence and mechanism are unknown. Hepatic injury may be potentiated by prior administration of alcohol, phenobarbital, INH, or other drugs; by conditions that stimulate the mixed-function oxidase system; or by conditions such as starvation (including inability to maintain oral intake during severe febrile illnesses) that reduce hepatic glutathione levels. Alcohol induces cytochrome P450 CYP2E1; consequently, increased levels of the toxic metabolite NAPQI may be produced in chronic alcoholics after acetaminophen ingestion, but the role of alco hol in potentiating acute acetaminophen injury is still debated. Alcohol

TABLE 351-2 Principal Alterations of Hepatic Morphology Produced by Some Commonly Used Drugs and Chemicalsa 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 Fatty liver 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 Mixed hepatitis/cholestatic Antibiotic Antibacterial Antifungal Antihistamine Immunosuppressive Lipid-lowering Toxic (necrosis) Analgesic Hydrocarbon Metal Mushroom Solvent Granulomas Antiarrhythmic Antibiotic Anticonvulsant Anti-inflammatory Xanthine oxidase inhibitor Vascular injury Chemotherapeutic Oxaliplatin, melphalan aSeveral agents cause more than one type of liver lesion and appear under more than one category. bRarely associated with primary biliary cholangitis-like lesion. cOccasionally associated with chronic hepatitis or bridging hepatic necrosis or cirrhosis. dAssociated with an autoimmune hepatitis-like syndrome. eWithdrawn from use because of severe hepatotoxicity.

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 Chlorpromazineb Amiodarone Tetracycline (high-dose, IV) Valproic acid Dideoxynucleosides (e.g., zidovudine), protease inhibitors (e.g., indinavir, ritonavir) Asparaginase, methotrexate, tamoxifen Halothane, fluothane Flutamide Isoniazid,c rifampicin, nitrofurantoin, telithromycin, minocycline,d pyrazinamide, trovafloxacine CHAPTER 351 Phenytoin, carbamazepine, valproic acid, phenobarbital Iproniazid, amitriptyline, trazodone, venlafaxine, fluoxetine, paroxetine, duloxetine, sertraline, nefazodonee 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 Oxyphenisatinc,e Toxic and Drug-Induced Hepatitis Atomoxetine Troglitazone,e acarbose Ipilimumab, pembrolizumab, nivolumab Amoxicillin-clavulanic acid, trimethoprim-sulfamethoxazole Clindamycin Terbinafine Cyproheptadine Azathioprine Nicotinic acid, lovastatin, ezetimibe Acetaminophen Carbon tetrachloride Yellow phosphorus Amanita phalloides Dimethylformamide Quinidine, diltiazem Sulfonamides Carbamazepine Phenylbutazone Allopurinol

also suppresses hepatic glutathione production. Therefore, in chronic alcoholics, the toxic dose of acetaminophen may be as low as 2 g, and alcoholic patients should be warned specifically about the dangers of even standard doses of this commonly used drug. In a 2006 study, ami notransferase elevations were identified in 31–44% of normal subjects treated for 14 days with the maximal recommended dose of acetamino phen, 4 g daily (administered alone or as part of an acetaminophenopioid combination); because these changes were transient and never associated with bilirubin elevation, the clinical relevance of these find ings remains to be determined. Although underlying hepatitis C virus (HCV) infection was found to be associated with an increased risk of acute liver injury in patients hospitalized for acetaminophen overdose, generally, in patients with nonalcoholic liver disease, acetaminophen taken in recommended doses is well tolerated. Acetaminophen use in cirrhotic patients has not been associated with hepatic decompensa tion. On the other hand, because of the link between acetaminophen use and liver injury and because of

the limited safety margin between safe and toxic doses, the FDA has recommended that the daily dose of acetaminophen be reduced from 4 g to 3 g (even lower for persons with chronic alcohol use), that all acetaminophen-containing products be labeled prominently as containing acetaminophen, and that the poten tial for liver injury be prominent in the packaging of acetaminophen and acetaminophen-containing products. Within opioid combina tion products, the limit for the acetaminophen component has been lowered to 325 mg per tablet. Adoption of this limit appears to have had a salutary effect in decreasing the number of hospital admissions and instances of liver failure associated with acetaminophen-opioid combinations.

PART 10 Disorders of the Gastrointestinal System TREATMENT Acetaminophen Overdosage Treatment includes gastric lavage, supportive measures, and oral administration of activated charcoal or cholestyramine to prevent absorption of residual drug. Neither charcoal nor cholestyramine appears to be effective if given >30 min after acetaminophen inges tion; if they are used, the stomach lavage should be done before other agents are administered orally. The chances of possible, prob able, and high-risk hepatotoxicity can be derived from a nomogram plot, readily available in emergency departments, as a function of measuring acetaminophen plasma levels 4–8 h after ingestion. In patients with high acetaminophen blood levels (>200 μg/mL mea sured at 4 h or >100 μg/mL at 8 h after ingestion), the administra tion of N-acetylcysteine reduces markedly the severity of hepatic necrosis. This agent provides sulfhydryl donor groups to replete glutathione, which is required to render harmless toxic metabolites that would otherwise bind covalently via sulfhydryl linkages to cell proteins, resulting in the formation of drug metabolite-protein adducts. Therapy should be begun within 8 h of ingestion but may be at least partially effective when given as late as 24–36 h after overdose. Routine use of N-acetylcysteine has substantially reduced the occurrence of fatal acetaminophen hepatotoxicity. N-acetylcysteine may be given orally but is more commonly used as an IV solution, with a loading dose of 140 mg/kg over 1 h, fol lowed by 70 mg/kg every 4 h for 15–20 doses. Whenever a patient with potential acetaminophen hepatotoxicity is encountered, a local poison control center should be contacted. Treatment can be stopped when plasma acetaminophen levels indicate that the risk of liver damage is low. If signs of hepatic failure (e.g., progressive jaundice, coagulopathy, confusion) occur despite N-acetylcysteine therapy for acetaminophen hepatotoxicity, liver transplantation may be the only option. Early arterial blood lactate levels among such patients with acute liver failure may distinguish patients highly likely to require liver transplantation (lactate levels >3.5 mmol/L) from those likely to survive without liver replacement. Acute renal injury occurs in nearly 75% of patients with severe acetaminophen injury but is virtually always self-limited.

Survivors of acute acetaminophen overdose rarely, if ever, have ongoing liver injury or sequela but may be subject to repeat overdosing. ■ ■ISONIAZID HEPATOTOXICITY

(IDIOSYNCRATIC REACTION) INH remains central to most antituberculous prophylactic and therapeutic regimens, despite its long-standing recognition as a hepatotoxin. In 10% of patients treated with INH, elevated serum aminotransferase levels develop during the first few weeks of ther apy; however, these elevations in most cases are self-limited, are mild (values for ALT <200 IU/L), and resolve despite continued drug use. This adaptive response allows continuation of the agent if symptoms and progressive enzyme elevations do not follow the initial eleva tions. Acute hepatocellular DILI secondary to INH is evident with a variable latency period up to 6 months and is more frequent in alcoholics and patients taking certain other medications, such as barbiturates,

rifampin, and pyrazinamide. If the clinical threshold of encephalopathy is reached, severe hepatic injury is likely to be fatal or to require liver transplantation. Liver biopsy reveals morpho logic changes similar to those of viral hepatitis or bridging hepatic necrosis. Substantial liver injury appears to be age-related, increas ing substantially after age 35; the highest frequency is in patients over age 50, and the lowest is in patients under the age of 20. Even for patients >50 years of age monitored carefully during therapy, hepatotoxicity occurs in only ~2%, well below the risk estimate derived from earlier experiences. Fever, rash, eosinophilia, and other manifestations of drug allergy are distinctly unusual. Antibodies to INH have been detected in INH recipients, but a link to causality of liver injury remains unclear. A clinical picture resembling chronic hepatitis has been observed in a few patients. Many public health programs that require INH prophylaxis for a positive tuberculin skin test or blood test (Quantiferon or T-Spot) include monthly monitor ing of aminotransferase levels, although this practice has been called into question. Even more effective in limiting serious outcomes may be encouraging patients to be alert for symptoms such as nausea, fatigue, or jaundice, because most fatalities occur in the setting of continued INH use despite clinically apparent illness. The incidence of severe INH toxicity may be declining as a result of less frequent use and/or better management. ■ ■SODIUM VALPROATE HEPATOTOXICITY

(TOXIC AND IDIOSYNCRATIC REACTION) Sodium valproate, an anticonvulsant useful in the treatment of petit mal and other seizure disorders, has been associated with the devel opment of severe hepatic toxicity and, rarely, fatalities, predominantly in children but also in adults. Among children listed as candidates for liver transplantation, valproate is the most common antiepileptic drug implicated. Asymptomatic elevations of serum aminotransferase levels have been recognized in as many as 45% of treated patients. These “adaptive” changes, however, appear to have no clinical impor tance, because major hepatotoxicity is not seen in the majority of patients despite continuation of drug therapy. In the rare patients in whom jaundice, encephalopathy, and evidence of hepatic failure are found, examination of liver tissue reveals microvesicular fat and bridging hepatic necrosis, predominantly in the centrilobular zone. Bile duct injury may also be apparent. Most likely, sodium valproate is not directly hepatotoxic, but its metabolite, 4-pentenoic acid, may be responsible for hepatic injury. Valproate hepatotoxicity is more common in persons with mitochondrial enzyme deficiencies and may be ameliorated by IV administration of carnitine, which valproate therapy can deplete. Valproate toxicity has been linked to HLA hap lotypes (DR4 and B∗1502) and to mutations in mitochondrial DNA polymerase gamma 1. ■ ■NITROFURANTOIN HEPATOTOXICITY (IDIOSYNCRATIC REACTION) This commonly used antibiotic for urinary tract infections may cause an acute hepatitis leading to fatal outcome or, more frequently, chronic hepatitis of varying severity but indistinguishable from autoimmune

hepatitis. These two scenarios may reflect the frequent use and reuse of the drug for treatment of recurrent cystitis in women. Although most toxic agents manifest injury within 6 months of first ingestion, nitro furantoin may have a longer latency period, in part perhaps because of its intermittent, recurrent use. Autoantibodies to nuclear components, smooth muscle, and mitochondria are seen and may subside after reso lution of injury; however, glucocorticoid or other immunosuppressive medication may be necessary to resolve the autoimmune injury, and cirrhosis may be seen in cases that are not recognized quickly. Intersti tial pulmonary fibrosis presenting as chronic cough and dyspnea may be present and resolve slowly with medication withdrawal. Histologic findings are identical to those of autoimmune hepatitis. A similar dis ease pattern can be observed with minocycline, which is used repeat edly for the treatment of acne in teenagers, as

well as with hydralazine and α-methyldopa. ■ ■AMOXICILLIN-CLAVULANATE HEPATOTOXICITY (IDIOSYNCRATIC MIXED REACTION) Currently, the most common agent implicated as causing DILI in the United States and in Europe is amoxicillin-clavulanate (most frequent brand name: Augmentin). This medication causes a very specific syn drome of mixed or primarily cholestatic injury. Because hepatotoxic ity may follow amoxicillin-clavulanate therapy after a relatively long latency period, the liver injury may begin to manifest after the drug has been withdrawn. The high prevalence of hepatotoxicity reflects in part the very frequent use of this drug for respiratory tract infec tions, including community-acquired pneumonia. The mechanism of hepatotoxicity is unclear, but the liver injury is thought to be caused by amoxicillin toxicity that is potentiated in some way by clavulanate, which itself appears not to be toxic. Symptoms include nausea, anorexia, fatigue, and jaundice—which may be prolonged—with pruritus. Rash is quite uncommon. On occasion, amoxicillin-clavulanate, like other cholestatic hepatotoxic drugs, causes permanent injury to small bile ducts, leading to the so-called “vanishing bile duct syndrome.” In van ishing bile duct syndrome, initially, liver injury is minimal except for severe cholestasis; however, over time, histologic evidence of bile duct abnormalities is replaced by a paucity and eventual absence of discern ible ducts on subsequent biopsies. ■ ■AMIODARONE HEPATOTOXICITY

(TOXIC AND IDIOSYNCRATIC REACTION) Therapy with this potent antiarrhythmic drug is accompanied in 15–50% of patients by modest elevations of serum aminotransferase levels that may remain stable or diminish despite continuation of the drug. Such abnormalities may appear days to many months after begin ning therapy. A proportion of those with elevated aminotransferase levels have detectable hepatomegaly, and clinically important liver dis ease develops in <5% of patients. Features that represent a direct effect of the drug on the liver and that are common to the majority of longterm recipients are ultrastructural phospholipidosis, unaccompanied by clinical liver disease, and interference with hepatic mixed-function oxidase metabolism of other drugs. The cationic amphiphilic drug and its major metabolite desethylamiodarone accumulate in hepatocyte lysosomes and mitochondria and in bile duct epithelium. The relatively common elevations in aminotransferase levels are also considered a predictable, dose-dependent, direct hepatotoxic effect. On the other hand, in the rare patient with clinically apparent, symptomatic liver disease, liver injury resembling that seen in alcoholic liver disease is observed. The so-called pseudoalcoholic liver injury can range from steatosis, to alcoholic hepatitis–like neutrophilic infiltration and Mal lory’s hyaline, to cirrhosis. Electron-microscopic demonstration of phospholipid-laden lysosomal lamellar bodies can help to distinguish amiodarone hepatotoxicity from typical alcoholic hepatitis. This cat egory of liver injury appears to be a metabolic idiosyncrasy that allows hepatotoxic metabolites to be generated. Rarely, an acute idiosyncratic hepatocellular injury resembling viral hepatitis or cholestatic hepatitis occurs. Hepatic granulomas have occasionally been observed. Because amiodarone has a long half-life, liver injury may persist for months after the drug is stopped.

■ ■ANABOLIC STEROIDS (CHOLESTATIC REACTION) The most common form of liver injury caused by CAMs is the profound cholestasis associated with anabolic steroids used by body builders. Unregulated agents sold in gyms and health food stores as diet supple ments, which are taken by athletes to improve their performance, may contain anabolic steroids. In a young male, jaundice that is accompanied by a cholestatic, rather than a hepatitic, laboratory profile almost invari ably will turn out to be caused by the use of one of a variety of androgen congeners. Such agents have the potential to injure bile transport pumps and to cause intense cholestasis; the time to onset is

variable, and reso lution, which is the rule, may require many weeks to months. Initially, anorexia, nausea, and malaise may occur, followed by pruritus in some but not all patients. Serum aminotransferase levels are usually <100 IU/L, and serum alkaline phosphatase levels are generally moderately elevated with bilirubin levels frequently exceeding 342 µmol/L (20 mg/dL). Exami nation of liver tissue reveals cholestasis without substantial inflammation or necrosis. Anabolic steroids have also been used by prescription to treat bone marrow failure. In this setting, hepatic centrizonal sinusoidal dilatation and peliosis hepatis have been reported in rare patients, as have hepatic adenomas and hepatocellular carcinoma. Recently, a large series of cases with a uniform phenotype has been described. Unfor tunately, no genomic signature has become evident despite the unique features of the injury. No permanent sequelae are evident besides pro longed jaundice, lasting frequently 10 weeks or more.

■ ■TRIMETHOPRIM-SULFAMETHOXAZOLE HEPATOTOXICITY (IDIOSYNCRATIC REACTION) This antibiotic combination is used routinely for urinary tract infec tions in immunocompetent persons and for prophylaxis against and therapy of Pneumocystis jirovecii pneumonia in immunosuppressed persons (transplant recipients, patients with AIDS). With its increas ing use, its occasional hepatotoxicity is being recognized with grow ing frequency. Its likelihood is unpredictable, but when it occurs, trimethoprim-sulfamethoxazole hepatotoxicity follows a relatively uniform latency period of several weeks and is often accompanied by eosinophilia, rash, and other features of a hypersensitivity reaction, including the drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. Biochemically and histologically, acute hepatocel lular necrosis predominates, but cholestatic features are quite frequent. Occasionally, cholestasis without necrosis occurs, and very rarely, a severe cholangiolytic pattern of liver injury is observed. In most cases, liver injury is self-limited, but rare fatalities have been recorded. The hepatotoxicity is attributable to the sulfamethoxazole component of the drug and is similar in features to that seen with other sulfonamides; tissue eosinophilia and granulomas may be seen. The risk of trime thoprim-sulfamethoxazole hepatotoxicity is increased in persons with HIV infection. In a recent study, unique HLA associations in European Americans and in African Americans have been identified. CHAPTER 351 Toxic and Drug-Induced Hepatitis ■ ■HMG-COA REDUCTASE INHIBITORS (STATINS) (IDIOSYNCRATIC MIXED HEPATOCELLULAR AND CHOLESTATIC REACTION) Between 1 and 2% of patients taking lovastatin, simvastatin, pravas tatin, fluvastatin, or one of the newer statin drugs for the treatment of hypercholesterolemia experience asymptomatic, reversible elevations (greater than threefold) of aminotransferase activity. Acute hepatitislike histologic changes, centrilobular necrosis, and centrilobular cho lestasis have been described in a very small number of cases. In a larger proportion, minor aminotransferase elevations appear during the first several weeks of therapy. Careful laboratory monitoring can distinguish between patients with minor, transitory changes, who may continue therapy, and those with more profound and sustained abnormalities, who should discontinue therapy. Because clinically meaningful aminotransferase elevations are so rare after statin use and do not differ in meta-analyses from the frequency of such laboratory abnormalities in placebo recipients, a panel of liver experts recom mended to the National Lipid Association’s Safety Task Force that liver test monitoring was not necessary in patients treated with statins and that statin therapy need not be discontinued in patients found to have

asymptomatic isolated aminotransferase elevations during therapy. Statin hepatotoxicity is not increased in patients with chronic hepatitis C, hepatic steatosis, or other underlying liver diseases, and statins can be used safely in these patients.

ALTERNATIVE AND COMPLEMENTARY MEDICINES (IDIOSYNCRATIC

HEPATITIS, STEATOSIS) Herbal medications that are of scientifically unproven efficacy and that lack prospective safety oversight by regulatory agencies account cur rently for >20% of DILI in the United States. Besides anabolic steroids, the most common category of dietary or herbal products is weight loss agents. Included among the herbal remedies associated with toxic hepatitis are Jin Bu Huan, xiao-chai-hu-tang, germander, chaparral, senna, mistletoe, skullcap, gentian, comfrey (containing pyrrolizidine alkaloids), ma huang, bee pollen, valerian root, pennyroyal oil, kava, celandine, Impila (Callilepis laureola), LipoKinetix, Hydroxycut, Oxy Elite Pro, Herbalife, herbal nutritional supplements, and herbal teas containing Camellia sinensis (green tea extract). Well characterized are the acute hepatitis-like histologic lesions following Jin Bu Huan use: focal hepatocellular necrosis, mixed mononuclear portal tract infiltra tion, coagulative necrosis, apoptotic hepatocyte degeneration, tissue eosinophilia, and microvesicular steatosis. Megadoses of vitamin A can injure the liver, as can pyrrolizidine alkaloids, which often contaminate Chinese herbal preparations and can cause a venoocclusive injury lead ing to sinusoidal hepatic vein obstruction. Because some alternative medicines induce toxicity via active metabolites, alcohol and drugs that stimulate cytochrome P450 enzymes may enhance the toxicity of some of these products. Conversely, some alternative medicines also stimulate cytochrome P450 and may result in or amplify the toxic ity of recognized drug hepatotoxins. In many instances, herbal and dietary supplements actually contain chemicals rather than only leaves, roots, and bark. Antirheumatic “herbs” have been found to contain a nonsteroidal anti-inflammatory drug (NSAID) such as diclofenac, for example. Given the widespread use of such poorly defined herbal preparations, hepatotoxicity is likely to be encountered with increasing frequency; therefore, a drug history in patients with acute and chronic liver disease should include use of “alternative medicines” and other nonprescription preparations sold in so-called health food stores. PART 10 Disorders of the Gastrointestinal System ■ ■CHECKPOINT INHIBITOR AND OTHER IMMUNOTHERAPIES FOR CANCER The introduction of a new class of immunotherapeutic agents for melanoma and other cancers has ushered in a new kind of hepato toxicity, that associated with activation of the immune response. The three classes of immune-active molecules are cytotoxic T-lymphocyteassociated antigen-4 (CTLA-4), programmed cell death receptor 1 (PD-1), and programmed cell death receptor ligand 1 (PD-L1). Within weeks of beginning treatment with any one of several agents, including ipilimumab (CTLA-4), pembrolizumab (PD-1), or nivolumab (PD-1), an active hepatitis evolves that is associated with positive ANAs and appears to respond to glucocorticoid therapy. Liver histology may share some of the features of, but does not resemble the chronic changes observed in, autoimmune hepatitis. Instead, histologic findings are compatible with a nonspecific acute hepatic injury, assumed to result from the release of host modulation of anti-self-immune responses and mediated predominantly by CD8+ lymphocytes. Immune-mediated injury to thyroid, muscle, and colon may be seen as well. Few deaths have been reported related to these immunotherapies; while these novel agents may need to be halted temporarily, in many cases, they can be restarted (and are tolerated better on retreatment) if patients are showing a favorable antitumor response. ■ ■HIGHLY ACTIVE ANTIRETROVIRAL THERAPY FOR HIV INFECTION (MITOCHONDRIAL TOXIC, IDIOSYNCRATIC, STEATOSIS; HEPATOCELLULAR, CHOLESTATIC, AND MIXED) The recognition of drug hepatotoxicity in persons with HIV infec tion is complicated in this population by the many alternative causes

of liver injury (chronic viral hepatitis, fatty infiltration, infiltrative disorders, mycobacterial infection, etc.), but drug hepatotoxicity associated with highly active antiretroviral therapy (HAART) was a common type of liver injury in HIV-infected persons in the early days of HIV therapy; however, it is less frequent now (Chap. 208). Impli cated most frequently are combinations including the nucleoside analogue reverse transcriptase inhibitors zidovudine, didanosine, and, to a lesser extent, stavudine; the protease inhibitors ritonavir and indinavir (and amprenavir when used together with ritonavir), as well as tipranavir; and the nonnucleoside reverse transcriptase inhibitors nevirapine and, to a lesser extent, efavirenz. Distinguish ing the impact of HAART hepatotoxicity in patients with HIV and hepatitis virus co-infection is made challenging by the following: (1) both chronic hepatitis B and hepatitis C can affect the natural history of HIV infection and the response to HAART, and (2) HAART can have an impact on chronic viral hepatitis. For example, immunologic reconstitution with HAART can result in immunologically mediated liver-cell injury in patients with chronic hepatitis B co-infection if treatment with an antiviral agent for hepatitis B (e.g., nucleoside ana logues such as tenofovir) is withdrawn. Infection with HIV, especially with low CD4+ T-cell counts, has been reported to increase the rate of hepatic fibrosis associated with chronic hepatitis C, and HAART therapy can increase levels of serum aminotransferases and HCV RNA in patients with hepatitis C co-infection. Didanosine or stavu dine should not be used with ribavirin in patients with HIV/HCV co-infection because of an increased risk of severe mitochondrial toxicity and lactic acidosis. ■ ■FURTHER READING Ahmad J et al: Sclerosing cholangitis-like changes on magnetic resonance cholangiography in patients with drug-induced liver injury. Clin Gastroenterol Hepatol 17:789, 2019. Björnsson ES, Hoofnagle JL: Categorization of drugs implicated in causing liver injury: Critical assessment based upon published case reports. Hepatology 63:590, 2016. Chalasani NP et al: ACG clinical guideline: Diagnosis and manage ment of idiosyncratic drug-induced liver injury. Am J Gastroenterol 116:878, 2021. Chalasani N et al: Drug Induced Liver Injury Network. Clinical features, outcomes, and HLA risk factors associated with nitrofurantoininduced liver injury. J Hepatol 78:293, 2023. Cirulli ET et al: A missense variant in PTPN22 is a risk factor for drug-induced liver injury. Gastroenterology 156:1707, 2019. de Boer YS et al: Features of autoimmune hepatitis in patients with drug-induced liver injury. Clin Gastroenterol Hepatol 15:103,

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