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Wolters Kluwer

Drug-induced liver injury

AUTHOR: Anne M Larson, MD, FACP, FAASLD, AGAF
SECTION EDITOR: Keith D Lindor, MD
DEPUTY EDITOR: Kristen M Robson, MD, MBA, FACG

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Literature review current through: **Sep 2023.**
This topic last updated: **Apr 14, 2023.**

INTRODUCTION

Numerous drugs, both prescription and over-the-counter, herbal products, or toxins can cause hepatotoxicity through a variety of mechanisms. A high index of suspicion is often necessary to expeditiously establish the diagnosis.

This topic will review the epidemiology, clinical manifestations, diagnosis, and management of drug-induced liver injury (DILI). The metabolism of drugs by the liver, the mechanisms by which drugs might injure the liver, and the use of medications in patients with liver disease are discussed separately. (See "Drugs and the liver: Metabolism and mechanisms of injury" and "Overview of the management of chronic hepatitis C virus infection", section on 'Dose adjustments of medications' and "Cirrhosis in adults: Overview of complications, general management, and prognosis", section on 'Medication adjustments'.)

EPIDEMIOLOGY

Drug-induced liver injury (DILI) and herbal-induced liver injury (HILI) are well-recognized and symptomatically can mimic both acute and chronic liver diseases. It is reported that there are over 1000 prescription medications and over 100,000 herbal and dietary supplements available in the United States [1]. The probability of an individual drug causing liver injury ranges from 1 in 10,000 to 100,000, with some drugs reported as having an incidence of 100 in 100,000 (chlorpromazine, isoniazid) [2,3]. DILI has a worldwide estimated annual incidence between 14

to 19.1 per 100,000 persons exposed and 30 percent of cases will develop jaundice [2,4-15]. The prevalence and cause of DILI varies geographically [1,16]. DILI accounts for approximately 10 percent of all cases of acute hepatitis [17], is the cause of acute jaundice in 50 percent of patients who present with new jaundice, and accounts for up to one-half of the cases of acute liver failure in Western countries [4,8,13,18-22].

DILI is also the most frequently cited reason for withdrawal of medications from the marketplace (up to 32 percent of drug withdrawals) [18,23-27]. DILI may not be detected prior to drug approval, because most new drugs are tested in fewer than 3000 people prior to drug approval. As a result, cases of DILI with an incidence of 1 in 10,000 may be missed. It has been suggested that for every 10 cases of alanine aminotransferase (ALT) elevation (>10 times the upper limit of normal) in a clinical trial, there will be one case of more severe liver injury that develops once the drug is widely available [28,29]. Following publication of the US Food and Drug Administration (FDA) guidance statement for DILI in drug development, awareness of the issue increased, and drug withdrawal significantly decreased [2,24,27,30].

Risk factors — Several risk factors have been associated with the development of DILI, although their impact on DILI susceptibility has yet to be firmly established [1,31].

- Age – Adults appear to be at higher risk for DILI than children, with overall incidence increasing with patient age. Children are not without risk, however, as DILI has been reported with use of valproic acid, anticonvulsants, antimicrobials, propylthiouracil, and aspirin [14,32].

- Sex – Females are more susceptible to DILI associated with certain medications and develop more severe hepatotoxicity [2,9,33-36]. Males appear to develop DILI more often from azathioprine, anabolic steroids, and amoxicillin-clavulanate [1,35,37].

- Race and ethnicity – Given the small number of underrepresented groups in most studies, the impact of race on DILI remains uncertain. The predominant drug implicated in DILI in African Americans is trimethoprim-sulfamethoxazole, while in White Americans, it is amoxicillin-clavulanate [1,38,39]. African Americans also appear to have greater likelihood of adverse outcome and development of chronic DILI [38,39]. Asian Americans are more likely to die or require transplantation [1].

- Other Factors – Factors such as obesity, diabetes, and chronic viral hepatitis have been associated with worsening liver injury in the setting of some medications (tamoxifen, methotrexate) [1,40-42]. In the Drug-Induced Liver Injury Network (DILIN) registry, alcohol was not associated with clinical outcomes [43].

- Numerous genetic polymorphisms in the CYP isoenzymes, HLA alleles, and other drug-processing enzymes and transporters have been identified and associated with DILI. CYP polymorphisms have been shown to have five metabolic phenotypes: poor metabolizers, intermediate metabolizers, normal metabolizers, rapid metabolizers, and ultra-rapid metabolizers [44]. Drug-drug interactions can also lead to hepatotoxicity. Alcohol use disorder and malnutrition have been purported to predispose DILI in some cases, as is seen with acetaminophen toxicity. However, in a large cohort study, any alcohol use in the prior 12 months was a negative predictor of severe DILI [9,43]. (See "Acetaminophen (paracetamol) poisoning in adults: Pathophysiology, presentation, and evaluation", section on 'Clinical factors that may influence toxicity'.)

  A missense mutation in PTPN22, a protein involved in signaling control of T-cells, has been identified as a risk factor for all-cause DILI [45-47].

ASSOCIATED DRUGS

Over 1000 medications and 60 herbal products have been implicated in the development of DILI, and the list continues to grow [48,49]. The National Institutes of Health maintains a searchable database of drugs, herbal medications, and dietary supplements that have been associated with DILI. Herbal products associated with DILI are discussed separately [50]. (See "Hepatotoxicity due to herbal medications and dietary supplements".)

The most common drug implicated in DILI-associated acute liver failure in the United States is acetaminophen, followed by antibiotics [18,19,38,39,51,52]. Worldwide, amoxicillin-clavulanate is one of the most commonly reported causes of DILI [53,54]. Antibiotics and antiepileptics account for over 60 percent of DILI overall [2,33].

CLASSIFICATION

DILI can be classified in several ways (table 1), including by its [53]:

- Clinical presentation:
  - Hepatocellular (cytotoxic) injury
  - Cholestatic injury
  - Mixed injury
- Mechanism of hepatotoxicity:

    - Predictable
    - Idiosyncratic

- Histologic findings, such as:

    - Hepatitis
    - Cholestasis
    - Steatosis

DILI is initially categorized based on its clinical presentation. When a liver biopsy is performed to make the diagnosis or assess the degree of damage, DILI can then be further categorized based on its histologic findings [33]. (See 'Diagnosis' below.)

Clinical presentation — DILI is often clinically characterized by the type of hepatic injury: hepatocellular injury, cholestatic injury, or a mixed injury picture (which includes features of both hepatocellular injury and cholestatic injury) [55]. The type of injury is reflected by the pattern of liver test abnormalities (see "Approach to the patient with abnormal liver biochemical and function tests", section on 'Patterns of liver test abnormalities'):

- Hepatocellular injury (hepatitis):

    - Disproportionate elevation in the serum aminotransferases compared with the alkaline phosphatase
    - Serum bilirubin may be elevated
    - Tests of synthetic function may be abnormal

- Cholestatic injury (cholestasis):

    - Disproportionate elevation in the alkaline phosphatase compared with the serum aminotransferases
    - Serum bilirubin may be elevated, at times to very high levels
    - Tests of synthetic function may be abnormal

DILI is considered acute if the liver tests have been abnormal for less than three months and chronic if they have been abnormal for more than three months [56,57].

Mechanism of hepatotoxicity — Drugs associated with DILI may cause injury in a dose-dependent, predictable way (direct hepatotoxicity) or in an unpredictable (idiosyncratic) fashion. Idiosyncratic reactions may be immune-mediated or metabolic. The mechanisms of drug-induced hepatotoxicity are discussed in detail elsewhere. (See "Drugs and the liver: Metabolism and mechanisms of injury", section on 'Mechanisms of drug-induced hepatotoxicity'.)

Histology — DILI can be further classified based on the histologic findings. These findings may also provide clues to the possible etiology and determine the severity of the injury. Histologic findings in patients with DILI include (see 'Histologic findings' below):

- Acute or chronic hepatocellular injury
- Acute or chronic cholestasis
- Steatosis and steatohepatitis
- Granulomas
- Zonal necrosis
- Signs of hepatic venous outflow obstruction
- Sinusoidal obstruction syndrome (SOS)
- Nodular regenerative hyperplasia
- Phospholipidosis
- Peliosis hepatis

CLINICAL MANIFESTATIONS

Acute presentations of drug-induced liver injury (DILI) include asymptomatic mild liver test abnormalities, marked elevation in liver enzymes with clinical features of acute hepatitis, cholestasis with pruritus, an acute illness with jaundice that resembles viral hepatitis, and acute liver failure [4,51,53,54,58-62]. Chronic liver injury can resemble other causes of chronic liver disease, such as autoimmune hepatitis, primary biliary cholangitis, sclerosing cholangitis, or alcohol-associated liver disease. In some patients, chronic injury secondary to DILI progresses to cirrhosis.

Symptoms and examination findings — The most common type of injury is acute hepatitis (elevated liver enzymes). Many patients with DILI are asymptomatic, detected only because of laboratory testing. Patients with acute DILI who develop symptoms may report malaise, low-grade fever, anorexia, nausea, vomiting, right upper quadrant pain, jaundice, acholic stools, or dark urine. In addition, patients with cholestasis may have pruritus, which can be severe, leading to excoriations from scratching. Hepatomegaly may be present on physical examination. In severe cases, coagulopathy and hepatic encephalopathy may develop, indicating acute liver failure [31]. Patients with chronic DILI may go on to develop advanced fibrosis or cirrhosis and have signs and symptoms associated with cirrhosis or hepatic decompensation (eg, jaundice, palmar erythema, and ascites). (See "Acute liver failure in adults: Etiology, clinical manifestations, and diagnosis", section on 'Clinical manifestations' and "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis", section on 'Clinical manifestations' and "Pruritus associated with cholestasis".)

Patients with DILI may develop signs and symptoms of a hypersensitivity reaction, such as a fever and rash, Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS), a mononucleosis-like illness (pseudomononucleosis). In some cases, patients will have evidence of toxicity to other organs (eg, bone marrow, kidney, lung, skin, and blood vessels).

DIAGNOSIS

DILI remains a diagnosis of exclusion. Development of elevated liver enzymes and/or nonspecific symptoms (eg, nausea, anorexia, malaise, fatigue, right upper quadrant pain, or pruritus) after introduction of a drug may indicate drug toxicity and should prompt an evaluation for DILI. The diagnosis begins by obtaining a detailed history, including type of medications, drug dosing details (ie, dosing quantity, frequency and adjustments, in addition to duration of use), and timing of symptom onset. The history must also include use of complementary and herbal remedies as well as illicit drugs (eg, cocaine, methylenedioxymethamphetamine [MDMA]) [63]. DILI generally develops within six months of beginning a new medication, although onset of liver injury may occur greater than six months after exposure to some medications (methotrexate, nitrofurantoin) [12].

Patients with an autoimmune-like presentation (hypersensitivity) may present within 24 to 72 hours of exposure to the drug and may have serologic markers of autoimmunity (eg, an elevated antinuclear antibody). Patients with hypersensitivity reactions may have peripheral eosinophilia, whereas those with a mononucleosis-like illness may have lymphocytosis and atypical lymphocytes. If there is evidence of cholestasis, imaging to rule out biliary obstruction is also indicated. Imaging is also necessary to exclude venous outflow obstruction such as Budd-Chiari syndrome.

Patients with clinically significant DILI have at least one of the following [1]:

- Serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5 times upper limit of normal (ULN) or alkaline phosphatase (ALP) >2 times ULN (or the baseline value if baseline is elevated) on two separate occasions
- Total serum bilirubin >2.5 mg/dL with elevated AST, ALT or ALP
- International normalized ratio (INR) >1.5 with elevated AST, ALT or ALP

The pattern of liver injury, categorized by the *R* value at presentation, can be helpful in determining next steps. DILI with cholestatic injury is defined as an elevated ALP >2 times ULN

and/or an ALT to ALP ratio (*R*-value) of ≤2 (table 2) [64]. Injury is regarded as mixed if the *R* value is greater than 2 but less than 5. DILI with hepatocellular injury has disproportionate elevation of aminotransferases with an *R* value ≥5. In the case of acute hepatocellular injury, the elevation of the aminotransferases can be marked (≥25 times ULN). The presence of jaundice (serum bilirubin ≥2.5 mg/dL) with elevated serum aminotransferases (>3 times ULN) and alkaline phosphatase <2 times ULN has been associated with a worse prognosis (an observation noted by Hyman Zimmerman and known as "Hy's law") [60,65-67]. In this setting, the reported mortality was as high as 14 percent [9,54,64,68,69]. Serum bilirubin may be elevated both with hepatocellular and cholestatic injury. The serum albumin and INR are markers of disease severity. (See "Approach to the patient with abnormal liver biochemical and function tests".)

Testing to exclude other causes of hepatic injury are important. This includes evaluating for autoimmune hepatitis, Wilson disease, and acute viral hepatitis. Ischemic liver injury and Budd-Chiari syndrome must also be excluded. If testing for alternative causes of liver injury is negative and the patient has been exposed to a drug known to be associated with hepatic injury, we typically do not proceed with a liver biopsy. However, if the diagnosis remains uncertain (particularly in the setting of acute liver failure), if the severity of injury is uncertain, or if there is clinical evidence of chronic liver disease, a liver biopsy should be obtained [33,70]. Liver histology may confirm a specific histologic pattern associated with the suspected drug. A transjugular approach may be needed in patients with a coagulopathy. (See "Approach to liver biopsy" and "Transjugular liver biopsy".)

Assessing causality — Diagnosing DILI can be difficult. It depends on obtaining a careful drug use history and ruling out other potential causes of liver injury. There are no specific serum biomarkers or characteristic histologic features that reliably identify a drug as the cause of hepatic injury. The presence of serum acetaminophen-protein adducts has shown promise in identifying acetaminophen overdose, but testing is not clinically available [71,72]. The general approach to evaluating a patient with abnormal liver tests is discussed in detail elsewhere. (See "Approach to the patient with abnormal liver biochemical and function tests".)

The key elements for attributing liver injury to a drug include [66]:

- Drug exposure preceded the onset of liver injury (although the latent period is highly variable)
- Other causes of liver disease are excluded
- Drug discontinuation leads to improvement in the liver injury
- Rapid and severe recurrence occurs if there is repeated exposure to the drug (however, rechallenge is not advised)

Another factor that supports a diagnosis of DILI is hepatic injury occurring in the setting of exposure to a drug with a known history of causing DILI in other patients [31,50].

Identifying the offending drug may be difficult for several reasons. Obtaining a reliable drug history can be challenging. Reviewing a patient's pharmacy records may help confirm the use of prescription medications, although this is also not always reliable [73]. Patients may not disclose the use of herbal and dietary remedies or illicit drugs. Even when a reliable drug history is available, the relationship between exposure to the drug and hepatic toxicity is not always clear. Patients may be taking multiple medications, making identification of a single offending agent difficult. In addition, patients may have concomitant liver disease, which can produce similar clinical and laboratory features.

The Council for International Organizations of Medical Sciences (CIOMS) developed a series of standard designations of drug-induced liver disorders and a classification of injury [56]. The US Food and Drug Administration (FDA) Drug Hepatotoxicity Steering Committee proposed modifications to the CIOMS classification scheme for classifying hepatotoxicity in clinical trials [74,75].

A number of scales have been developed that attempt to codify causality of drug toxicity into objective criteria [76]. Examples include the CIOMS Roussel-Uclaf Causality Assessment Method (RUCAM) scale, the Maria & Victorino System, and the clinical and diagnostic scale (CDS) [56,77-81]. However, they do not address all risk factors in all patients. Among these scales, the RUCAM scale has been widely used [33,77]. The Drug-Induced Liver Injury Network (DILIN) developed the DILIN Causality Scoring System, a semiquantitative scale, to adjudicate the causality of DILI for patients enrolled in its prospective clinical trial [82]. This model relies on structured expert opinion and, when compared with the RUCAM, it produced higher agreement rates and likelihood scores. However, intraobserver variability remains significant in both scales [82]. The DILIN scale was not a clinically viable option for assessing causality because it relied on expert opinion. The DILIN group redesigned the RUCAM's criteria and developed an electronic causality assessment tool, the Revised Electronic Causality Assessment Method (RECAM). This tool has performed at least as well as the RUCAM [81,83]. Overall, these tools summarize the clinical and laboratory features that are used in addition to the history when evaluating patients for DILI [77,82,84].

Histologic findings — Liver biopsy is not generally required to establish the diagnosis of DILI. The histologic findings in patients with DILI differ based on the mechanism of injury (eg, hepatocellular injury or cholestatic injury) and may mimic other causes of liver disease [85]. While histologic findings are not diagnostic for a specific cause of DILI, the pattern of injury may

provide clues to the etiology of the liver injury and may help to exclude other causes of liver injury (eg, autoimmune hepatitis) [86].

- **Hepatocellular injury** – DILI leads to acute hepatocellular injury in up to 50 percent of cases of toxicity with necro-inflammatory injury with or without mild cholestasis [85]. Histologically, acute portal and parenchymal hepatocellular injury leads to hepatocellular necrosis or apoptosis, steatosis, and/or cellular degeneration. More severe injury leads to panlobular hepatitis. Most acute hepatocellular injury recovers without the development of significant fibrosis [87].

  - **Acute hepatitis** – Hepatocellular injury in an acute hepatitis pattern can show spotty necrosis, affecting single isolated hepatocytes with lobular inflammation and apoptosis with or without portal inflammation.

  - **Panlobular hepatitis** – This is a more involved hepatitis with spotty or focal necrosis. Dying hepatocytes (acidophil bodies) are seen scattered throughout the hepatic lobules. There may be degenerative changes in the hepatocytes and lytic necrosis. This type of injury can be seen with the immune checkpoint inhibitors. Although serum autoantibodies can be seen in this setting, histologically there is no evidence of an autoimmune-like injury. Hepatotoxicity from immune checkpoint inhibitor therapy is discussed separately. (See "Hepatic, pancreatic, and rare gastrointestinal complications of immune checkpoint inhibitor therapy", section on 'Hepatotoxicity'.)

  - **Confluent necrosis** – Confluent necrosis, the death of larger groups of hepatocytes, can be zonal or nonzonal, depending on the offending agent. If extensive, confluent necrosis leads to bridging, submassive, or massive necrosis and can result in acute liver failure. Severe confluent necrosis will show collapsed hepatic parenchyma intermingled with bile ductular reaction [85].

    Zonal necrosis is characteristic of compounds with predictable, dose-dependent, intrinsic toxicity, such as halothane (zone 3), carbon tetrachloride (zone 3), acetaminophen (zone 3), yellow phosphorus (zone 2), beryllium (zone 2), cocaine (zone 1), or iron sulfate (zone 1). Isolated necrosis in zones 1 and 2 is rare [88]. Centrilobular (zone 3) necrosis is the most common type of zonal necrosis seen [85]. There may be little or no inflammatory response; however, damaged cells may accumulate fat (triglycerides).

    Nonzonal necrosis appears in a viral hepatitis-like pattern. It is more often seen with compounds that produce unpredictable idiosyncratic injury (eg, phenytoin, methyldopa, isoniazid, and diclofenac). Certain medications, such as aspirin, produce a

nonspecific pattern of injury, which is typically reversible but rarely is associated with progressive hepatic failure [89].

- **Granulomatous hepatitis** – In patients with drug-induced hepatic granulomas, the granulomas are usually noncaseating and located in the periportal and portal areas; however, they can be seen within the parenchyma as well (picture 1). Drug-induced granulomas are generally non-necrotizing, are not associated with the bile ducts, and are associated with significant inflammation. (See "Evaluation of the adult patient with hepatic granuloma".)

- **Chronic injury** – Acute hepatocellular injury progresses to chronic injury in 5 to 10 percent of cases of DILI [90]. Chronic hepatocellular injury can histologically resemble other causes of chronic liver disease, such as autoimmune hepatitis, viral hepatitis, or alcohol-associated liver disease. (See "Alcoholic hepatitis: Clinical manifestations and diagnosis", section on 'Pathologic criteria for alcoholic hepatitis' and "Histologic scoring systems for chronic liver disease", section on 'Chronic hepatitis' and "Overview of autoimmune hepatitis", section on 'Histology'.)

  Some of the agents most commonly associated with chronic DILI include amoxicillin-clavulanic acid, bentazepam, atorvastatin, methotrexate, hypervitaminosis A, vinyl chloride, heroin, herbal products, and dietary supplements [85,87,91]. Drugs that can lead to cirrhosis include methotrexate, isoniazid, ticrynafen, amiodarone, enalapril, and valproic acid [85].

- **Drug-induced autoimmune hepatitis** – There are also several drugs that can present clinically, serologically, and histologically like autoimmune hepatitis (AIH) [92,93]. This presents a challenge diagnostically. The most common drugs associated with this presentation include clometacin, infliximab, and other tumor necrosis factor-alpha blocking agents, methyldopa, minocycline, and nitrofurantoin. The classic findings seen in idiopathic AIH (ie, interface hepatitis, rosette formation and emperipolesis) are seen in 89, 40, and 34 percent, respectively, of patients with drug-induced AIH. Some reports suggested that a prominent eosinophilic infiltrate was helpful in distinguishing DILI from autoimmune hepatitis; however, others have not seen this [88,94,95]. It has also been suggested that drug-induced AIH may show more portal neutrophils and cholestasis [94].

- **Acute cholestatic injury** – Findings in patients with acute cholestasis include [96-100]:

  - Pure (canalicular, bland, or noninflammatory) cholestasis, which is characterized by prominent hepatocellular and/or canalicular cholestasis with very little hepatocellular injury or inflammation. Bile plugging is frequently seen, predominantly in zone 3

hepatocytes or canaliculi. This type of injury is often seen with the use of anabolic steroids or oral contraceptives. Drugs causing this type of injury interfere with hepatocyte secretion of bile constituents and other pigment and dye substances via the bile salt excretory protein (BSEP) [98]. The degree of cholestasis is characteristic for each drug.

- Cholestatic hepatitis (hepatocanalicular, cholangiolitic, or inflammatory) is characterized by portal inflammation, prominent cholestasis, and hepatocellular injury with prominent lobular inflammation. Bile duct proliferation may be seen. Hepatocyte injury is usually localized to the zones of cholestasis. Some of the drugs associated with this type of injury include erythromycin, amoxicillin-clavulanate, herbal products, and angiotensin-converting enzyme (ACE) inhibitors [101-105].

- **Chronic cholestatic injury** – Chronic cholestatic injury develops when the acute liver injury does not resolve. Drug-induced chronic cholestasis histologically resembles other causes of chronic cholestasis, such as primary biliary cholangitis, biliary obstruction, or primary sclerosing cholangitis [88,96,99]. (See "Primary sclerosing cholangitis in adults: Clinical manifestations and diagnosis", section on 'Liver biopsy' and "Clinical manifestations, diagnosis, and prognosis of primary biliary cholangitis", section on 'Liver biopsy'.)

  Histologic features include bile in dilated canaliculi, bile within the hepatocyte cytoplasm, bile duct loss and/or the presence of cholate stasis (a rim of pale hepatocytes adjacent to the portal tracts) [85]. Some patients develop prolonged damage leading to loss of the bile ducts and overt ductopenia that may progress to vanishing bile duct syndrome [106-109]. Antibiotics have been most often implicated in this setting. In rare cases, there is progression to cirrhosis and ultimately liver failure. Drugs that have been associated with ductopenia include amoxicillin-clavulanate, flucloxacillin, ACE inhibitors, and terbinafine [88,110]. (See "Hepatic ductopenia and vanishing bile duct syndrome in adults", section on 'Liver biopsy'.)

- **Steatosis** – Histologically, acute steatosis is typically microvesicular and composed predominantly of triglycerides. Drugs that disrupt mitochondrial beta-oxidation of lipids and oxidative energy production lead to steatosis [111]. This is especially true of steatohepatitis related to high-dose intravenous tetracycline, valproic acid, acetylsalicylic acid (Reye syndrome), and amiodarone [88,95,112-117].

  In contrast with the microvesicular steatosis usually seen in acute steatosis, drug-induced chronic steatosis is predominantly macrovesicular. The distribution of fat within the

hepatocyte may be in one of two forms: large droplet (at least one-half of the cytoplasm is occupied by a single lipid droplet) or small-to-medium droplet (multiple lipid vacuoles are seen) [88].

Drug-induced macrovesicular steatosis may either be bland or associated with inflammation (steatohepatitis). The histologic features of steatohepatitis include variable steatosis, lobular inflammation (predominantly neutrophilic), and hepatocellular injury (ballooning) [88]. Acidophil bodies, Mallory hyaline, and pericellular fibrosis may also be present. Macrovesicular steatosis has been associated with amiodarone, glucocorticoids, methotrexate, metoprolol, nonsteroidal anti-inflammatory drugs (NSAIDs), tamoxifen, and total parenteral nutrition [85].

- **Hepatic venous outflow obstruction (Budd-Chiari syndrome)** – Budd-Chiari syndrome may arise from drug-induced thrombosis of the hepatic veins or inferior vena cava. Histologic findings in Budd-Chiari syndrome include centrizonal congestion, hepatocellular necrosis, and hemorrhage. Large regenerative nodules and obstructive portal venopathy may also be present. Cirrhosis may develop in the chronic form of the disease. (See "Budd-Chiari syndrome: Epidemiology, clinical manifestations, and diagnosis", section on 'Liver biopsy'.)

- **Hepatic sinusoidal obstruction syndrome (formerly veno-occlusive disease)** – Clinically, sinusoidal obstruction syndrome (SOS) resembles Budd-Chiari syndrome or congestive hepatopathy secondary to heart failure. The hepatic venous outflow obstruction in SOS, however, is due to occlusion at the level of the terminal hepatic venules and hepatic sinusoids, rather than the hepatic veins and inferior vena cava. Endothelial cell injury results in sinusoidal endothelial injury with swelling and ultimately endothelial denudation. There is edematous thickening in the subintimal zone of the central and sublobular venules. This leads to concentric luminal narrowing (non-thrombotic obstruction) with subsequent increased resistance to blood flow, resulting in hepatic congestion, sinusoidal dilation, and portal hypertension [118]. Obstruction then leads to sinusoidal dilation and congestion and hepatocellular necrosis, which can, in some cases, result in fibrosis (picture 2 and picture 3) [88]. The most common drug-related cause of SOS is myeloablative-conditioning therapy in hematopoietic stem cell transplant. It can also be seen with immunosuppressive drugs (eg, azathioprine) or toxic pyrrolizidine alkaloids [119,120]. (See "Hepatic sinusoidal obstruction syndrome (veno-occlusive disease) in adults".)

- **Nodular regenerative hyperplasia** – Nodular regenerative hyperplasia has been linked to chemotherapeutic agents and first-generation nucleoside antiretroviral agents. Its

pathogenesis is poorly understood, but it may be linked to chronic injury involving the hepatic microvasculature [121].

- **Phospholipidosis** – The lesions in phospholipidosis consist of lysosomes that are engorged with phospholipid, resulting in foamy hepatocytes [116,122-124]. It is believed that an interaction between the phospholipid and the offending drug leads to the formation of a complex that prevents degradation of the phospholipid molecules [99]. These characteristically abnormal, lamellated lysosomes are visible on electron microscopy. There appears to be a high incidence of cirrhosis associated with this lesion, although the exact mechanism is not clear. Phospholipidosis may develop acutely but is more commonly seen after prolonged administration of the offending agent.

- **Peliosis hepatis** – Peliosis hepatis is rare and is characterized by multiple small, dilated, blood-filled cavities in the hepatic parenchyma (picture 4 and picture 5). Drugs that can lead to peliosis hepatis include androgens, contraceptive steroids, and chemotherapeutic medications. (See "Peliosis hepatis", section on 'Liver biopsy'.)

DIFFERENTIAL DIAGNOSIS

Drug-induced liver injury (DILI) is one of numerous causes of hepatic injury. The differential diagnosis depends on the pattern of liver test abnormalities and, if a biopsy is obtained, histologic findings. (See "Approach to the patient with abnormal liver biochemical and function tests".)

- Hepatitis – The differential diagnosis for acute and chronic hepatitis is broad and includes viral infection, alcohol-associated liver disease, nonalcoholic fatty liver disease (NAFLD), autoimmune hepatitis, Budd-Chiari and Wilson disease. (See "Approach to the patient with abnormal liver biochemical and function tests", section on 'Elevated serum aminotransferases'.)

  Distinguishing autoimmune hepatitis from autoimmune-like DILI can be difficult and liver biopsy may be helpful in this setting. Rarely, presentations of acute Wilson disease and Budd-Chiari can mimic DILI.

- Cholestasis – Causes of cholestasis include biliary obstruction, primary biliary cholangitis, primary sclerosing cholangitis, and intrahepatic cholestasis of pregnancy. (See "Approach to the patient with abnormal liver biochemical and function tests", section on 'Elevated alkaline phosphatase'.)

- Steatosis – Several disorders may result in hepatic steatosis. It can be challenging to differentiate drug-induced steatosis (eg, tamoxifen) from that associated with disorders such as nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), alcohol-associated steatosis/steatohepatitis, and acute fatty liver of pregnancy [96,99,125]. (See "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults", section on 'Alternative causes of hepatic steatosis' and "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults", section on 'Diagnosis' and "Clinical manifestations and diagnosis of alcohol-associated fatty liver disease and cirrhosis", section on 'Diagnosis'.)

- Granulomatous hepatitis – Granulomas in the liver are most commonly seen in the setting of infection, sarcoidosis, and primary biliary cirrhosis. Granulomas can be seen incidentally; however, in up to 15 percent of all liver biopsy specimens [85]. (See "Evaluation of the adult patient with hepatic granuloma", section on 'Causes'.)

- Peliosis hepatis – While drugs may rarely cause peliosis hepatis, it is also associated with infections, hematologic disorders, malignancies, and organ transplantation (table 3). (See "Peliosis hepatis", section on 'Etiology'.)

MANAGEMENT

The primary treatment for drug-induced liver injury (DILI) is withdrawal of the offending drug. Early recognition of drug toxicity is important to permit assessment of severity and monitoring for acute liver failure. Few specific therapies have been shown to be beneficial in clinical trials. Two noted exceptions are the use of N-acetylcysteine for acetaminophen toxicity and L-carnitine supplementation for cases of valproic acid overdose [126,127]. (See "Acetaminophen (paracetamol) poisoning in adults: Treatment", section on 'Antidote: acetylcysteine' and "Valproic acid poisoning", section on 'Carnitine supplementation'.)

Glucocorticoids are of unproven benefit for most forms of drug hepatotoxicity, although they may have a role for treating patients with hypersensitivity reactions [33,128]. Our practice is to give glucocorticoids to patients with hypersensitivity reactions who have progressive cholestasis despite drug withdrawal or who have biopsy features that resemble those seen in autoimmune hepatitis. In addition, we give glucocorticoids to patients with extrahepatic manifestations of a hypersensitivity reaction that warrant glucocorticoid treatment (eg, severe pulmonary involvement in patients with DRESS [drug reaction with eosinophilia and systemic symptoms]). (See "Drug reaction with eosinophilia and systemic symptoms (DRESS)" and "Drug reaction with eosinophilia and systemic symptoms (DRESS)", section on 'Organ involvement'.)

In patients with cholestatic liver disease and pruritus, treatment with a bile acid sequestrant may relieve the pruritus. Use of bile acid sequestrants and other treatments for pruritus (eg, antihistamines, ursodeoxycholic acid) are discussed separately [9]. (See "Pruritus associated with cholestasis".)

Intravenous *N*-acetylcysteine may improve survival in early acute liver failure not due to acetaminophen in some settings [129,130]. (See "Acute liver failure in adults: Management and prognosis", section on 'N-acetylcysteine'.)

Patients should be followed by serial biochemical measurements until the liver tests return to normal. Hepatology consultation should be considered if there is concern that the patient may be developing acute liver failure (eg, if the patient shows signs of hepatic encephalopathy or coagulopathy), if there are signs of chronic liver disease, or if the diagnosis remains uncertain after an initial evaluation. In addition, patients with evidence of acute liver failure should be transferred to a transplant center early in the course of the illness [126]. The development of jaundice (bilirubin greater than two times the upper limit of normal) in the setting of an alanine aminotransferase (ALT) >3 times the upper limit of normal following introduction of a drug potentially portends a poor prognosis and should also prompt immediate referral to a center with expertise in hepatology [60,67]. (See "Acute liver failure in children: Management, complications, and outcomes", section on 'General management principles'.)

PROGNOSIS

Prognosis is generally dependent on the type of drug-induced liver injury (DILI). Most patients with DILI will experience complete recovery once the offending medication is discontinued or the dosage is decreased. Alternatively, adaptation can develop in which the injury resolves spontaneously despite continuation of the medication [121]. In the setting of cholestatic injury, jaundice can take weeks to months to resolve. Severe cases will worsen despite drug discontinuation. This progression leads to acute liver failure, often necessitating liver transplantation [19,20].

Factors associated with a poorer prognosis include:

- The development of jaundice (defined as a bilirubin >2 times the upper limit of normal) in the setting of an alanine aminotransferase (ALT) >3 times the upper limit of normal [54,60,67]. The mortality rate in this setting can be as high as 14 percent [68] (80 percent if acute liver failure develops and the patient does not undergo liver transplantation) [18,131,132]. However, patients who recover from acute DILI with jaundice generally have

a favorable prognosis, although some will go on to develop progressive chronic liver disease [133].

- Acute liver failure due to antiepileptics in children [134].
- Acute liver failure due to acetaminophen requiring hemodialysis [134].
- An elevated serum creatinine [134].
- Presence of pre-existing liver disease [12].
- Some data suggested that African Americans were at higher risk for severe acute liver injury, chronic liver injury, liver transplantation, or mortality [38,39]. Studies also suggested that Asian populations were at higher risk for transplantation or mortality [1].

The overall prognosis for purely cholestatic injury (ie, no significant elevation in aminotransferases), tends to be better than that for hepatocellular injury.

Cholestatic DILI is more likely to develop into chronic injury. Chronic injury generally resolves upon discontinuation of the offending drug, but this pattern of injury may progress to cirrhosis and ultimately liver failure. Cholestasis can be prolonged, requiring months (>3 months) to resolve [65,107]. Progression to chronic disease is reported to occur in approximately 5 to 10 percent of adverse drug reactions and is more common among the cholestatic/mixed types of injury [90].

Gradual progression to cirrhosis can be seen without any manifestation of clinical illness (as with amiodarone, methotrexate, or methyldopa) [131,135,136]. Once cirrhosis is established, the clinical manifestations are typical of those seen with cirrhosis from other causes. (See "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis", section on 'Clinical manifestations' and "Cirrhosis in adults: Overview of complications, general management, and prognosis".)

Some patients with chronic cholestasis develop vanishing bile duct syndrome [106-108]. In this setting, prolonged damage leads to the loss of bile ducts and overt ductopenia. In rare cases, a progression to cirrhosis and ultimately liver failure results.

Drug-induced acute steatosis (fatty degeneration) is uncommon and occurs less often than chronic steatosis. Jaundice is usually mild, and serum aminotransferases are lower than they are in cytotoxic injury. Although the biochemical features generally do not appear to be as severe as those seen in hepatocellular disease, the illness can be severe with high mortality [125,137].

A Model for End-stage Liver Disease (MELD) score of greater than 19 has been shown to predict liver-related death in patients with DILI. A modification to Hy's law (ie, new-R ratio [nR] Hy's Law) has been developed (table 2) [138]. The nR Hy's law criteria are bilirubin ≥2.5 mg/dL and [(ALT/ULN) ÷ (ALP/ULN)] >5, and these modified criteria had a higher positive predictive value for risk of overall mortality within 26 weeks compared to the original Hy's law (see 'Diagnosis' above). Additionally, a model to predict risk of DILI-related mortality has been developed and validated [139].

PREVENTION

Preventing drug-induced liver injury (DILI) includes educating patients taking hepatotoxic drugs (eg, acetaminophen) on their safe use, including appropriate dosing and potential interactions with other drugs or alcohol. Patients should also be warned about signs and symptoms associated with hepatic injury. Whether to monitor for DILI by checking alanine aminotransferase (ALT) levels during treatment with a known hepatotoxin remains controversial. In some cases, acute liver failure has developed in patients who were undergoing screening, and the significance of mild ALT elevations is not always clear and may lead to inappropriate discontinuation of a needed medication [140]. Our approach is to monitor the ALT level in patients taking medications associated with relatively high incidences of severe liver injury, such as isoniazid and methotrexate. (See "Isoniazid hepatotoxicity" and "Hepatotoxicity associated with chronic low-dose methotrexate for nonmalignant disease".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Drug-induced liver injury".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading

level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Drug-induced hepatitis (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Drugs associated with liver injury** – Liver injury can develop following the use of many drugs. A searchable database of drugs, herbal medications, and dietary supplements associated with drug-induced liver injury (DILI) has been developed by the National Institutes of Health. (See 'Associated drugs' above.)

- **Classification** – DILI can be classified in several ways, including by its clinical presentation (hepatocellular injury, cholestatic injury, or mixed injury), the mechanism of hepatotoxicity (predictable or idiosyncratic), and the histologic findings (eg, hepatitis, cholestasis, and steatosis) (table 1). (See 'Classification' above.)

- **Clinical manifestations** – Many patients with DILI are asymptomatic and are only detected because of laboratory testing. Patients with acute DILI who are symptomatic may report malaise, low-grade fever, anorexia, nausea, vomiting, right upper quadrant pain, jaundice, acholic stools, or dark urine. In addition, patients with cholestasis may have pruritus. In severe cases, hepatic encephalopathy may develop, indicating acute liver failure. Patients with chronic DILI may go on to develop significant fibrosis or cirrhosis and have signs and symptoms associated with cirrhosis or hepatic decompensation (eg, jaundice, ascites). (See 'Clinical manifestations' above.)

  Patients with DILI-associated hepatocellular injury have a disproportionate elevation of their aminotransferases, whereas patients with cholestatic injury predominantly have an elevation of their alkaline phosphatase (ALP). Serum bilirubin may be elevated both with hepatocellular and cholestatic injury.

  Patients with clinically significant DILI have at least one of the following:

  - Serum AST or ALT >5 times upper limit of normal (ULN) or ALP >2 times ULN (or the baseline value if baseline is elevated) on two separate occasions

- Total serum bilirubin >2.5 mg/dL with elevated AST, ALT or ALP
- International normalized ratio (INR) >1.5 with elevated AST, ALT or ALP

- **Diagnosis** – Nonspecific symptoms (such as nausea, anorexia, malaise, fatigue, right upper quadrant pain, or pruritus) that develop after initiating a drug may indicate drug toxicity and should prompt an evaluation for DILI. Making a diagnosis of DILI can be difficult. It depends on obtaining a careful drug use history and excluding other causes of liver injury. (See 'Diagnosis' above.)
- **Management** – The primary treatment for DILI is withdrawal of the offending drug and monitoring to ensure the liver tests normalize. (See 'Management' above.)
- **Prognosis** – Recovery will occur in the majority of patients with DILI once the offending medication is stopped. (See 'Prognosis' above.)

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Topic 3571 Version 37.0

GRAPHICS

Classifications of drug-induced liver injury

Type of classification	Examples
Clinical laboratory	Hepatocellular
	Cholestatic
	Mixed hepatocellular/cholestatic
Mechanism of hepatotoxicity	Direct hepatotoxicity
	Idiosyncratic
	Immune-mediated
	Metabolic
Histologic findings	Cellular necrosis or apoptosis
	Cholestasis
	Steatosis
	Fibrosis
	Phospholipidosis
	Granulomatous
	Sinusoidal obstruction syndrome

Graphic 74021 Version 2.0

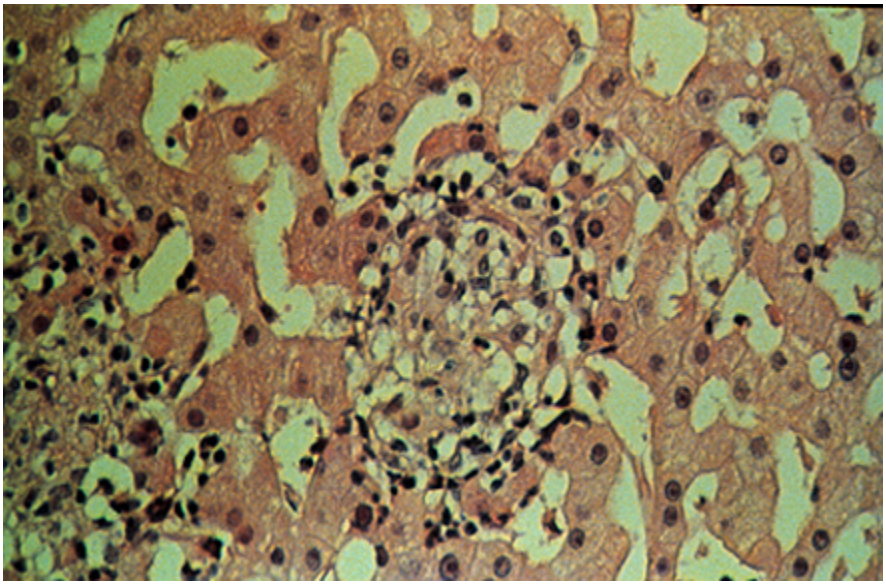
Classification of liver test abnormalities

Hepatitis (hepatocellular)	ALT ≥3 x ULN	R ≥5
Cholestasis	ALP ≥2 x ULN	R ≤2
Mixed	ALT ≥3 x ULN ALP ≥2 x ULN	R >2 to <5

ALT: alanine aminotransferase; ALP: alkaline phosphatase; ULN: upper limit normal; R: ALT/ULN divided by ALP/ULN.

Graphic 76892 Version 2.0

Granulomatous hepatitis

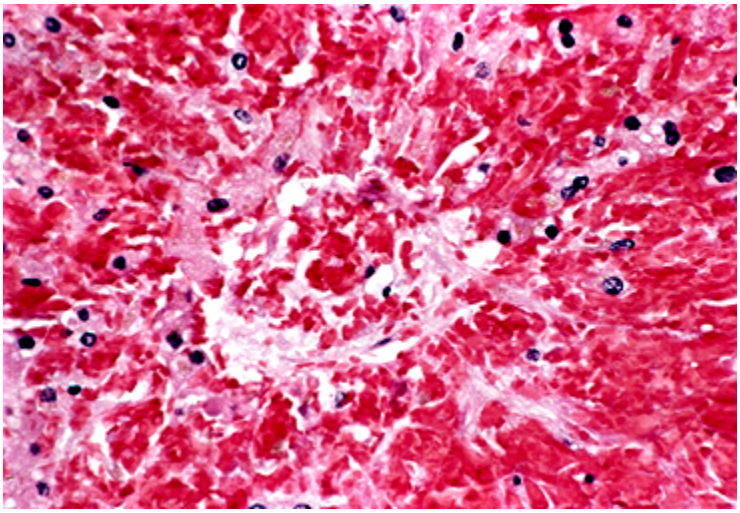


High power view of a liver biopsy shows a noncaseating granuloma and perigranulomatous mononuclear cell inflammation with hepatic necrosis.

Courtesy of Robert Odze, MD.

Graphic 64126 Version 1.0

Sinusoidal obstruction syndrome



Light micrograph of sinusoidal obstruction syndrome in which venular occlusion has led to widespread zonal liver disruption and centrilobular hemorrhagic necrosis.

Reproduced by permission from: Negrin RS, Blume KG. Bone marrow and peripheral blood progenitor cell transplantation. In: Leukemia, 6th ed, Henderson ES, Lister TA, Greaves ME (Eds), WB Saunders, Philadelphia, 1996. p.389.

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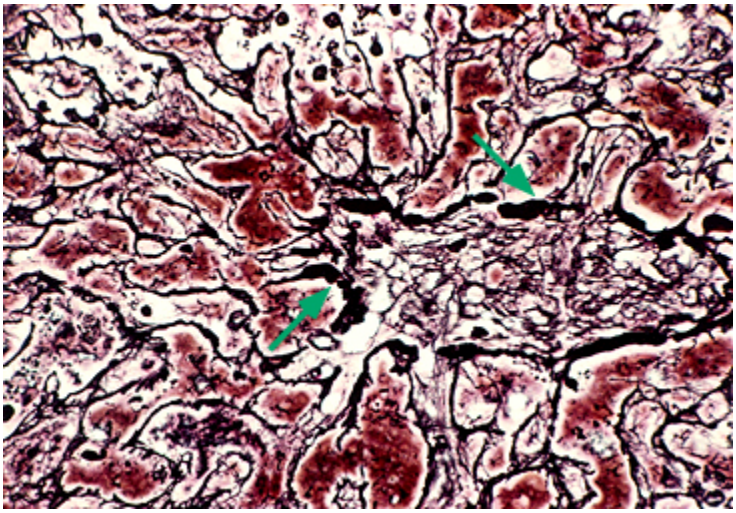
Sinusoidal obstruction syndrome



High power view of a reticulin stain of a liver biopsy from a patient with sinusoidal obstruction syndrome. There is prominent perivenular fibrosis (stained in black, arrows).

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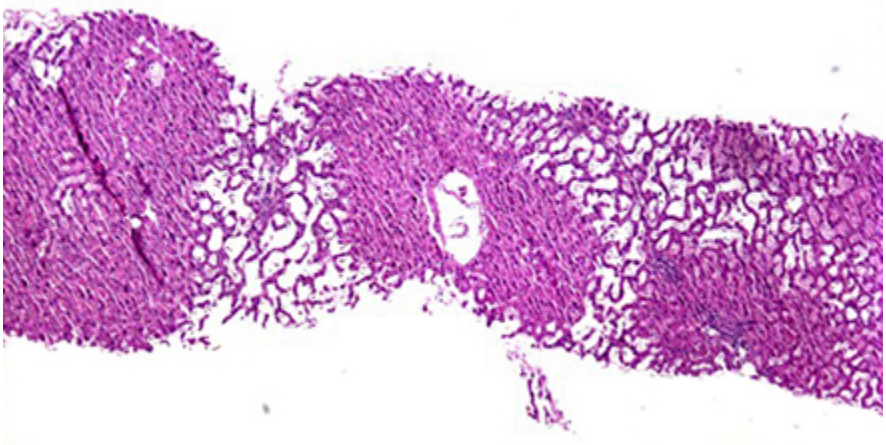
Peliosis hepatis

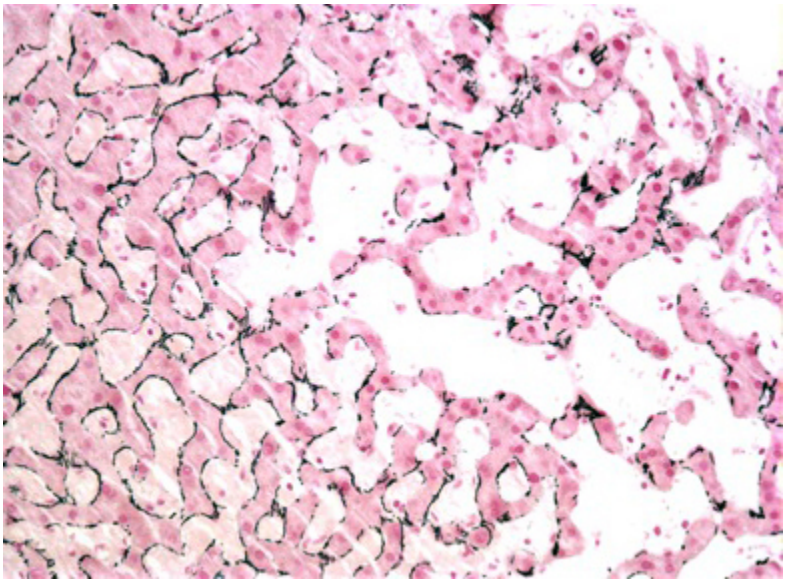


This low power (4x) view of a liver biopsy with H&E stain shows patches of sinusoidal dilatation and small cyst formation between areas of grossly normal liver parenchyma.

Courtesy of Tracy Challies, MD, Department of Pathology, Beth Israel Deaconess Medical Center, Boston, MA.

Graphic 74012 Version 1.0

Peliosis hepatis



High power (40x) view of reticulin stain showing dilated sinusoids with cyst formation and reticulin frame drop-off.

Courtesy of Tracy Challies, MD, Department of Pathology, Beth Israel Deaconess Medical Center, Boston, MA.

Graphic 59203 Version 1.0

Conditions associated with peliosis hepatis

Drugs and chemicals
2-Chloro-3'-deoxyadenosine
6-mercaptopurine
6-thioguanine
Androgenic-anabolic steroids
Arsenic
Azathioprine
Cadmium
Contraceptive steroids
Danazol
Glucocorticoids
Tamoxifen
Thorium dioxide
Urethane
Vinyl chloride
Vitamin A toxicity
Infections
Bacterial endocarditis
Bartonella henselae and Bartonella quintana
Human immunodeficiency virus infection
Leprosy
Pyelonephritis
Syphilis
Tuberculosis
Hematologic
Agnogenic myeloid metaplasia
Anaplastic anemia
Castelman's disease
Fanconi disease

Hodgkin disease
Lymphoma
Malignant histiocytosis
Multiple myeloma
Waldenström macroglobulinemia
Malignancies
Colorectal adenocarcinoma
Gastric adenocarcinoma
Hepatocellular carcinoma
Pancreatic cancer
Prostate cancer
Renal cell carcinoma
Seminoma
Other conditions
Cardiac transplantation
Chronic hemodialysis
Crohn's disease
Diabetes mellitus
Idiopathic restrictive cardiomyopathy
Liver transplant
Marasmus
Pregnancy
Renal transplantation
Rheumatoid arthritis
Systemic lupus erythematosus

Graphic 66092 Version 1.0

Contributor Disclosures

Anne M Larson, MD, FACP, FAASLD, AGAF No relevant financial relationship(s) with ineligible companies to disclose. **Keith D Lindor, MD** Consultant/Advisory Boards: Pliant [DSMB member]. All of the relevant financial relationships listed have been mitigated. **Kristen M Robson, MD, MBA, FACG** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

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