Drug-induced liver injury

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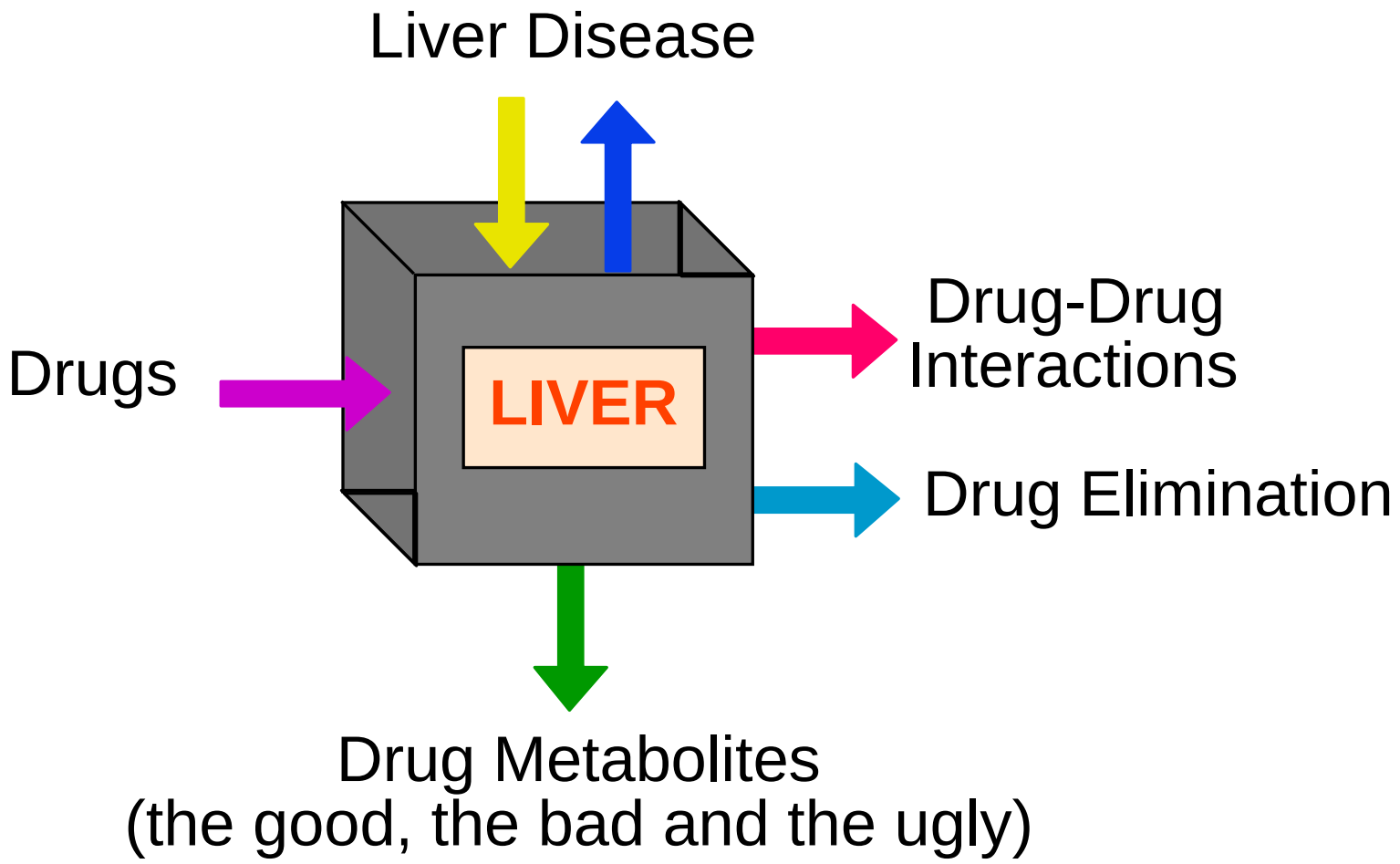
Drugs and the Liver



EPIDEMIOLOGY

- Drug-induced liver injury (DILI) has an estimated annual incidence between 10 and 15 per 10,000 to 100,000 persons exposed to prescription medications
- 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 .

EPIDEMIOLOGY

- Several risk factors have been associated with the development of DILI . In general, adults are at higher risk for DILI than children (with the notable exception of DILI from valproic acid, which is more common in children).
- Women may be more susceptible to DILI than men, which may in part be due to their generally smaller size . Alcohol abuse and malnutrition predispose to DILI in some cases, as is seen with acetaminophen toxicity.

EPIDEMIOLOGY

- The most common drug implicated in acute DILI in the United States is acetaminophen, followed by antibiotics. Worldwide, amoxicillin-clavulanate is one of the most commonly reported causes of DILI

Steps in Liver Biotransformation and Elimination of Drugs - I

- Transport of drugs/xenobiotics from blood
  - Liver has unique access to blood
  - Versatile transporters in liver membrane

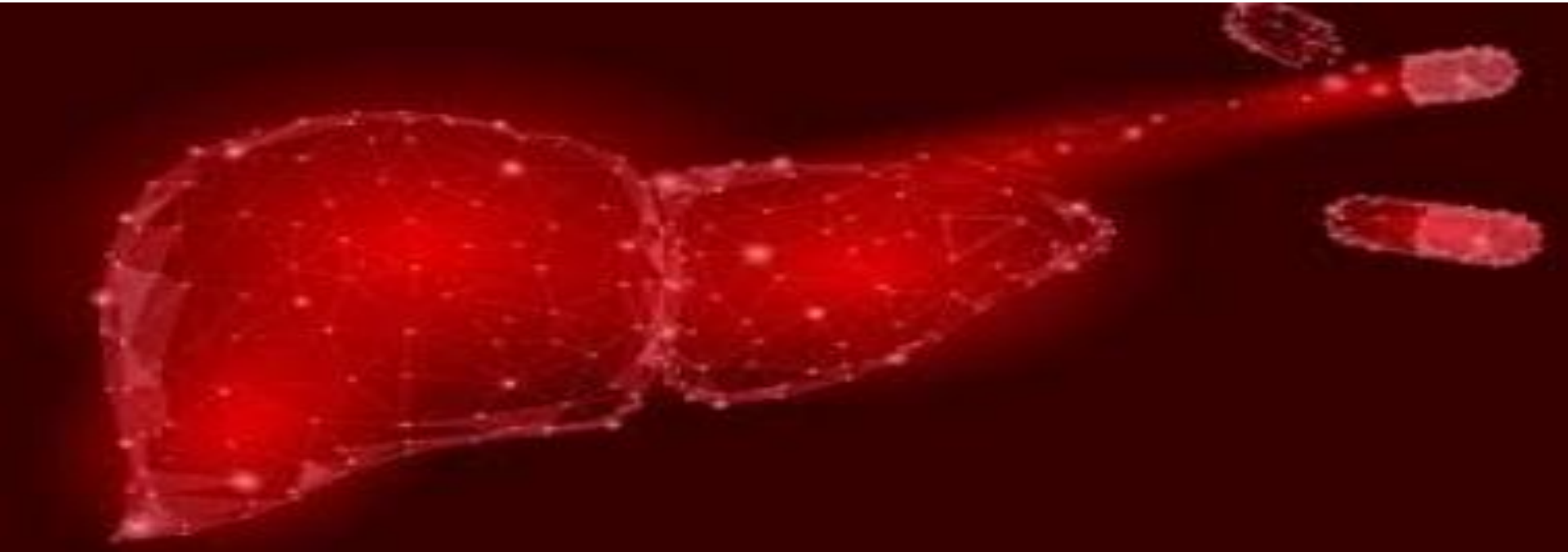
- Biotransformation in the liver
  - Phase I (cytochromes P450)
  - Phase II (conjugation)

Steps in Liver Biotransformation and Elimination of Drugs - II

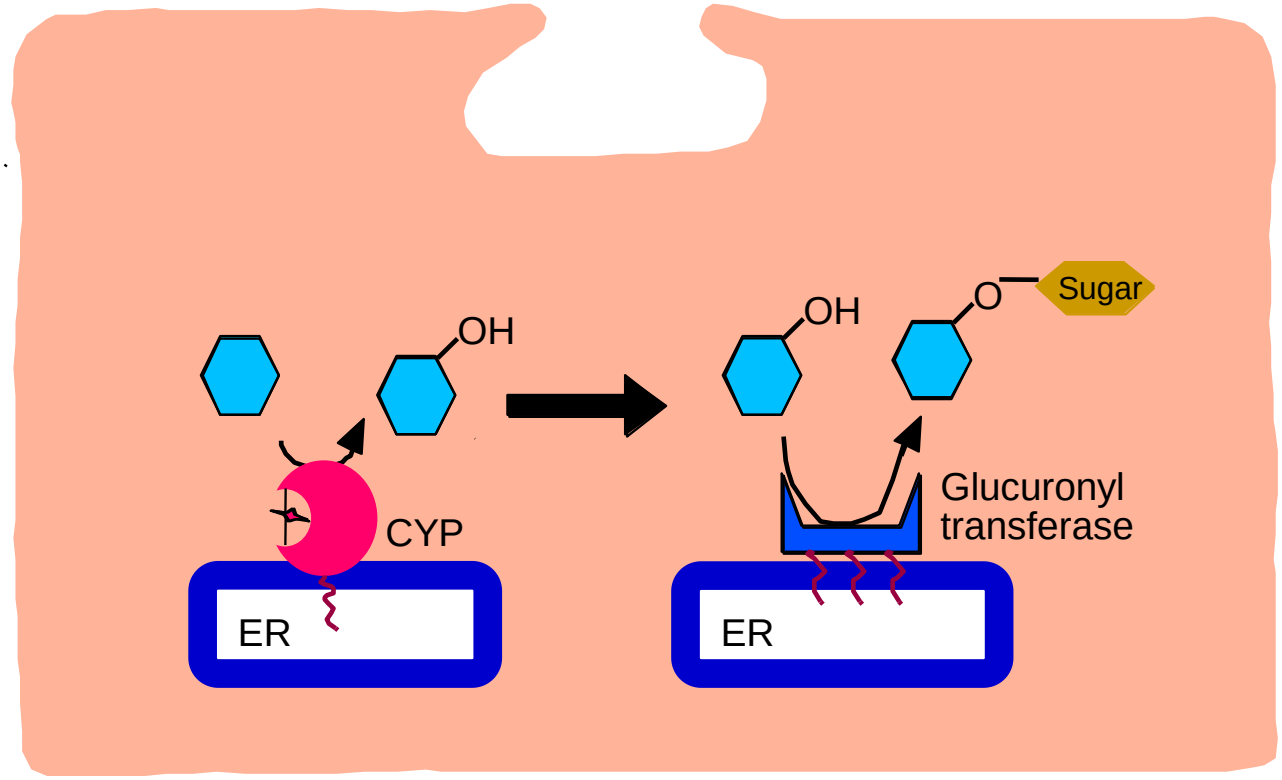
- Biliary excretion
- Efflux to blood for eventual renal excretion

Liver Biotransformation and Elimination of Drugs - III

- These processes exist for endogenous compounds, not just for drugs and xenobiotics



Phase 1 and Phase 2 Biotransformation in Liver



Phase 1

Oxidative reactions
CYP-mediated

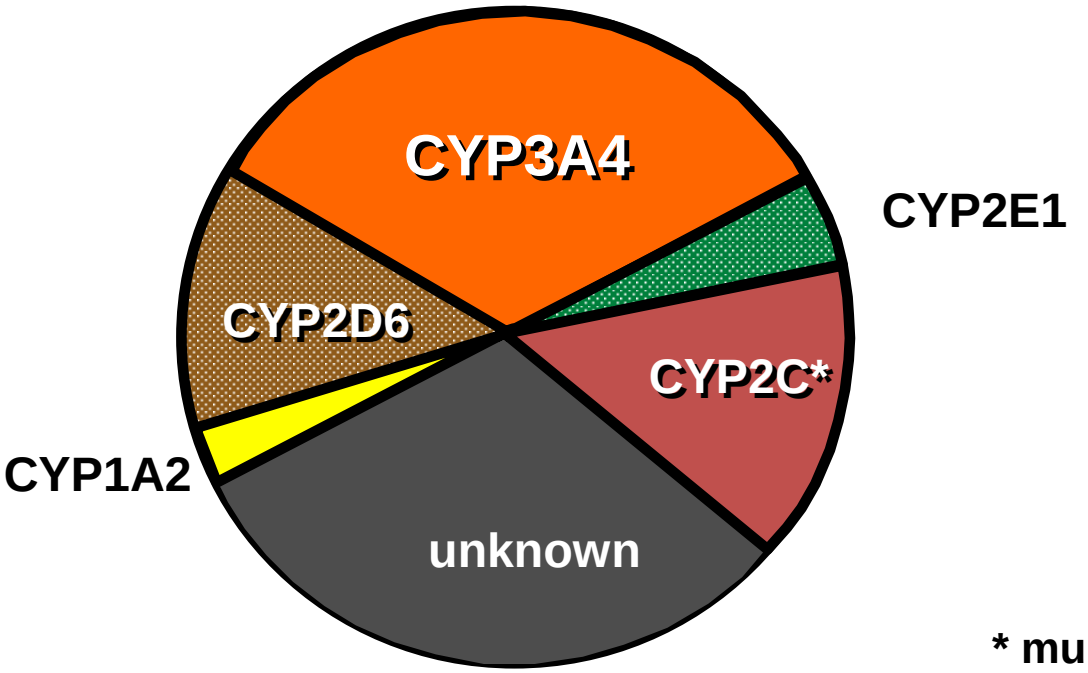
Phase 2

Conjugation to polar ligand
Glucuronyl transferases
Sulfotransferases
Glutathione-S-transferases

Phase 1: Biotransformation

- Direct modification of primary structure
- Cytochromes P450
  - Oxidative reactions
  - Add reactive/hydrophilic groups (-OH)
- Often rate-limiting, located in ER
- May eliminate or generate toxic molecules
- Account for many drug-drug interactions
- HIGHLY VARIABLE (genetic polymorphisms, inhibitable, inducible)

Contributions of Specific P450s to Drug Metabolism



*** multiple subfamily members exist**

CLASSIFICATION

Drug-induced liver injury (DILI) can be classified in several ways , including by its :

- Clinical presentation
- Mechanism of hepatotoxicity
- Histologic findings

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

CLASSIFICATION

Clinical presentation:

- Hepatocellular (cytotoxic) injury
- Cholestatic injury
- Mixed injury

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
- •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

CLASSIFICATION

Mechanism of hepatotoxicity:

- Predictable
- Idiosyncratic

Drugs associated with DILI may cause injury in a dose-dependent, predictable way (eg, acetaminophen) or in an unpredictable (idiosyncratic) fashion. Idiosyncratic reactions may be immune-mediated or metabolic.

CLASSIFICATION

Histologic findings, such as:

- Hepatitis
- Cholestasis
- Steatosis

Typically, DILI is initially categorized based on its clinical presentation. If a liver biopsy is required to make the diagnosis or assess the degree of damage, DILI can then be further categorized based on its histologic findings.

Histology

DILI can be classified based on the histologic findings. These findings may also provide clues to the possible etiology. Histologic findings include:

- Acute and chronic hepatocellular injury
- Acute and chronic cholestasis
- Steatosis and steatohepatitis
- Granulomas
- Zonal necrosis
- Signs of hepatic venous outflow obstruction
- Sinusoidal obstruction syndrome
- Phospholipidosis
- Peliosis hepatis

CLINICAL MANIFESTATIONS

- Acute presentations of drug-induced liver injury (DILI) include mild asymptomatic liver test abnormalities, cholestasis with pruritus, an acute illness with jaundice that resembles viral hepatitis, and acute liver failure .
- Chronic liver injury can resemble other causes of chronic liver disease, such as autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, or alcoholic liver disease.
- In some patients, chronic injury secondary to DILI progresses to cirrhosis.

CLINICAL MANIFESTATIONS

- DILI cholestasis is defined as an elevated alkaline phosphatase (ALP) >2 times the upper limit of normal and/or an alanine aminotransferase (ALT) to ALP ratio of less than 2 (table 2).
- Injury is considered to be mixed if the ALT/ALP ratio is greater than 2 but less than 5 and hepatocellular if this ratio is >5.
- The presence of jaundice (serum bilirubin >2 times the upper limit of normal) in association with an elevation in serum aminotransferases (>3 times the upper limit of normal) is associated with a worse prognosis (an observation noted by Hyman Zimmerman and known as "Hy's law"). In this setting, the mortality is as high as 14 percent.

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.

Symptoms and examination findings

- 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**.
- 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 .

Symptoms and examination findings

- 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**, **palmar erythema**, and **ascites**).
- Patients with DILI may also have signs and symptoms of a hypersensitivity reaction, such as a fever and rash, or 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).

Laboratory tests

- Patients with hepatocellular injury will have a disproportionate elevation of their aminotransferases, whereas patients with cholestatic injury will predominantly have an elevation of their alkaline phosphatase .
- In the case of acute hepatocellular injury, the elevation of the aminotransferases can be marked (>25 times the upper limit of normal). Serum bilirubin may be elevated both with hepatocellular and cholestatic injury.

Laboratory tests

- Patients with an autoimmune-like presentation 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 a lymphocytosis and atypical lymphocytes.

DIAGNOSIS

- Nonspecific symptoms developing after introduction of a drug (such as nausea, anorexia, malaise, fatigue, right upper quadrant pain, or pruritus) may indicate drug toxicity and should prompt an evaluation for drug-induced liver injury (DILI).
- The diagnosis includes obtaining a thorough history and performing blood tests to look for other causes of hepatic injury.

If there is evidence of cholestasis, imaging to rule out biliary obstruction is also indicated.

DIAGNOSIS

- 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.

If the diagnosis remains uncertain (particularly in the setting of acute liver failure) or if there is clinical evidence of chronic liver disease, a liver biopsy should be obtained.

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.

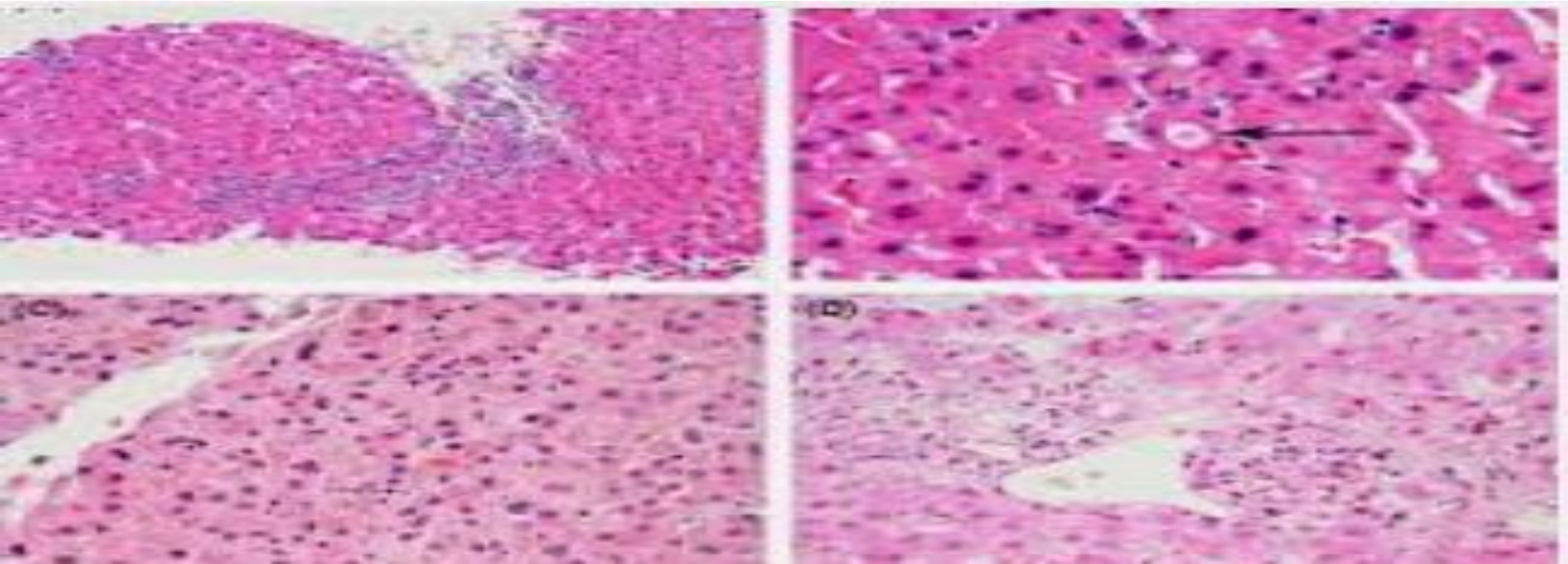
Assessing causality

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

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

Histologic findings

- Histologic findings in patients with DILI differ based on the mechanism of injury (eg, hepatocellular injury or cholestatic injury) and often mimic other causes of liver disease .
- 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 rule out other causes of liver injury (eg, Wilson disease and hemochromatosis)



Acute hepatocellular injury

- DILI leads to acute hepatocellular injury in about 90 percent of cases of toxicity .
- 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 . Centrilobular (zone 3) necrosis is the most common type of zonal necrosis seen . There may be little or no inflammatory response; however, damaged cells may accumulate fat (triglycerides).

Acute hepatocellular injury

- 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 .

Chronic cholestatic injury

- Drug-induced chronic cholestasis histologically resembles other causes of chronic cholestasis, such as primary biliary cirrhosis, biliary obstruction, or primary sclerosing cholangitis .
- Histologic features include bile duct loss and/or the presence of cholate stasis (a rim of pale hepatocytes adjacent to the portal tracts). Some patients with chronic cholestasis go on to develop vanishing bile duct syndrome.
- In this setting, prolonged damage leads to the loss of bile ducts and overt ductopenia. 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***

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 [70]. This is especially true of steatohepatitis related to ***high-dose intravenous tetracycline, valproic acid, acetylsalicylic acid (Reye syndrome), and amiodarone.***
- In contrast with the microvesicular steatosis usually seen in acute steatosis, drug-induced chronic steatosis is predominantly macrovesicular.
- Macrovesicular steatosis has been associated with ***amiodarone, glucocorticoids, methotrexate, metoprolol, nonsteroidal antiinflammatory drugs (NSAIDs), tamoxifen, and total parenteral nutrition.***

Granulomas

- In patients with drug-induced hepatic granulomas, the granulomas are usually located in the periportal and portal areas; however, they can be seen within the parenchyma as well .
- Drug-induced granulomas are generally non-necrotizing and are not associated with the bile ducts.

Granulomas

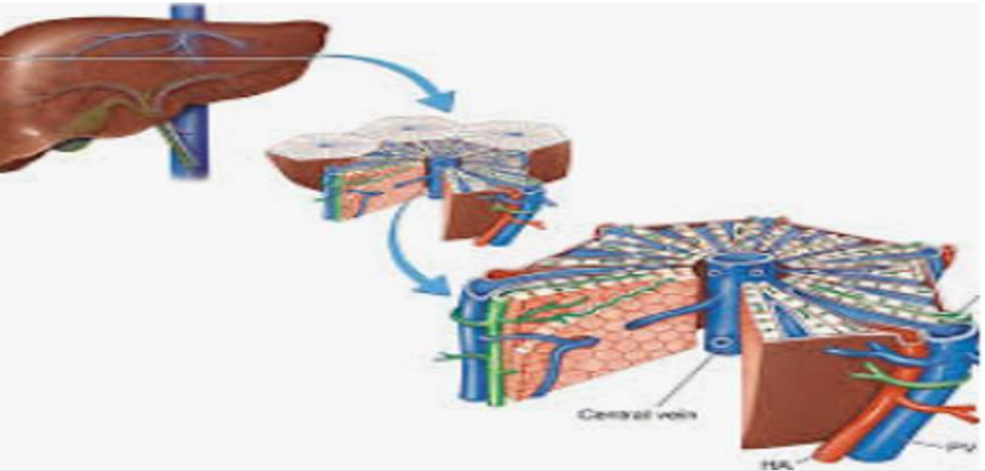
Allopurinol
Amiodarone
Carbamazepine
Cephalexin
Dapsone
Diazepam
Diclofenac
Diltiazem
Gold
Hydralazine
Interferon
Isoniazid
Mesalamine
Methyldopa
Nitrofurantoin
Penicillamine

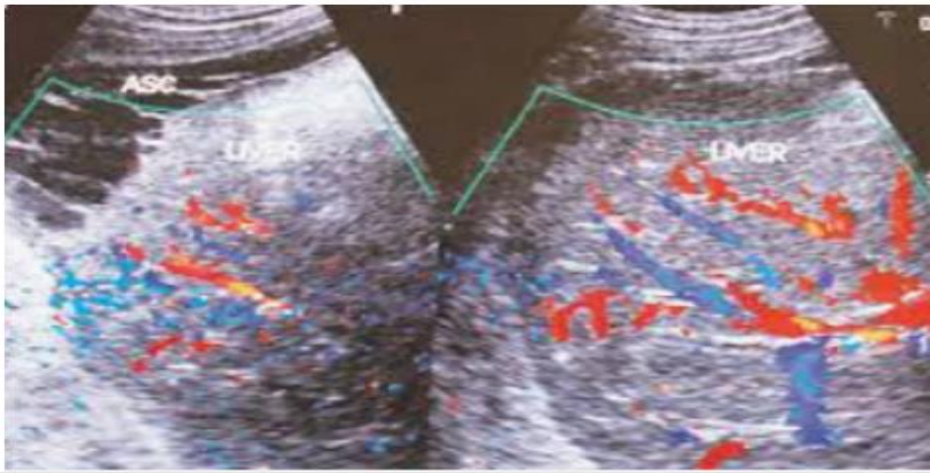
Penicillin
Phenytoin
Procainamide
Quinidine
Rosiglitazone
Sulfonamides
Sulfonylureas

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.

- Oral contraceptives





Hepatic sinusoidal obstruction syndrome (formerly known as veno-occlusive disease)

- sinusoidal obstruction syndrome (SOS) resembles Budd-Chiari syndrome or congestive hepatopathy secondary to heart failure.
- The hepatic venous outflow obstruction in SOS 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 with subsequent increased resistance to blood flow, resulting in hepatic congestion, sinusoidal dilation, and portal hypertension.
- Obstruction then leads to sinusoidal dilation and congestion and hepatocellular necrosis, which can, in some cases, result in fibrosis.

Phospholipidosis

- The lesions in phospholipidosis consist of lysosomes that are engorged with phospholipid, resulting in foamy hepatocytes.
- 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.
- 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.
- Drugs that can lead to peliosis hepatis include androgens, contraceptive steroids, and chemotherapeutic medications

Anabolic steroids
Arsenic
Azathioprine
Danazol
Diethylstilbestrol
Hydroxyurea
Mercaptopurine
Oral contraceptives
Tamoxifen
Vinyl chloride
Vitamin A

MANAGEMENT

- The primary treatment for drug-induced liver injury (DILI) is withdrawal of the offending drug.
- Few specific therapies have been shown to be beneficial in clinical trials. Two exceptions are the use of N-acetylcysteine for acetaminophen toxicity and L-carnitine for cases of valproic acid overdose.

MANAGEMENT

- Glucocorticoids are of unproven benefit for most forms of drug hepatotoxicity, although they may have a role for treating patients with hypersensitivity reactions .
- In patients with cholestatic liver disease and pruritus, treatment with a bile acid sequestrant may relieve the pruritus.

MANAGEMENT

- 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.
- The development of jaundice (bilirubin greater than two times the upper limit of normal) in the setting of an alanine aminotransferase greater than three 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 .

PROGNOSIS

- ***Acute liver injury*** — The majority of patients with drug-induced liver injury (DILI) will experience complete recovery once the offending medication is stopped. In the setting of cholestatic injury, jaundice can take weeks to months to resolve.
- The overall prognosis for purely cholestatic injury is better than that for hepatocellular injury, although fatalities have been reported in the former.

Factors associated with a poorer prognosis in patients with hepatocellular injury include:

- The development of jaundice (bilirubin greater than two times the upper limit of normal) in the setting of an alanine aminotransferase greater than three times the upper limit of normal, "Hy's law" The mortality rate in this setting can be as high as 14 percent (80 percent if acute liver failure develops and the patient does not undergo liver transplantation) . However, patients who recover from acute DILI with jaundice generally have a favorable prognosis, although some go on to develop progressive chronic liver disease .
- Acute liver failure due to antiepileptics in children .
- Acute liver failure due to acetaminophen requiring hemodialysis .
- An elevated serum creatinine .
- Presence of pre-existing liver disease.

Chronic liver injury

- Chronic injury generally resolves upon discontinuation of the offending drug, but this pattern of liver injury may progress to cirrhosis and liver failure. Cholestasis can be prolonged, requiring several months (>3 months) to resolve .
- A 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.
- Gradual progression to cirrhosis can be seen without any manifestation of clinical illness (as with amiodarone, methotrexate, or methyldopa)

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 is controversial.

THANKS