Drug-induced liver injury

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MIDSTREAM MEDICLINIC

- (DILI) can develop following the use of many prescription and over-the-counter drugs through a variety of mechanisms
- A high index of suspicion is often necessary to establish the diagnosis.
- DILI accounts for approximately 10 percent of all cases of acute hepatitis
- Most common cause of acute liver failure in the United States
- DILI is also the most frequently cited reason for withdrawal of medications from the marketplace

- DILI may not be detected prior to drug approval, because most new drugs are tested in fewer than 3000 people prior to drug approval.
- Cases of DILI with an incidence of 1 in 10,000 may be missed
- Several risk factors have been associated with the development of DILI
- Adults are at higher risk for DILI than children
- Women may be more susceptible to DILI than men
- Alcohol use disorder and malnutrition

ASSOCIATED DRUGS

- Over 1000 medications and herbal products have been implicated in the development of DILI.
- The two most common drugs associated with DILI is acetaminophen and amoxicillin-clavulanate.

Flucloxacillin	***1.8-3.6 per 100,000 prescriptions Cholestatic***	**Can be early (1-9 weeks after starting) or delayed after treatment has stopped**	**Usually within 12 weeks of stopping. 30% have a protracted course**
Amoxicillin/ Clavulanic acid	*1-17 per 100,000 prescriptions Hepatocellular, cholestatic or mixed*	Within 4 weeks of starting but typically after stopping	Within 16 weeks of stopping therapy
Ceftriaxone	Up to 25% adults and 40% children develop *cholelithiasis*	After 9-11 days of treatment	Within 2-3 weeks of stopping

Erythromycin	***< 4 cases per 100,000 prescriptions Cholestatic***	**Within 10-20 days of starting**	**Within 8 weeks of stopping**
(Trimethoprim/ Sulfamethoxazole) Cotrimoxazole	*< 2 per 10,000 prescriptions Cholestatic or mixed*	Unknown	Within a few weeks of stopping
Doxycycline	*< 1 per 18 million daily doses Cholestatic*	Long latency of over 1 year	Variable. Most recover on stopping
Ciprofloxacin	*Isolated cases only Hepatocellular and cholestatic*	Unknown	Unknown

CLASSIFICATION

Clinical presentation:

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

Mechanism of hepatotoxicity:

- Predictable
- Idiosyncratic

Histologic findings, such as:

- Hepatitis
- Cholestasis
- Steatosis

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.

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Clinical presentation

- Hepatocellular injury (hepatitis)
- Cholestatic injury (cholestasis)
- Mixed picture

- 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

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

Mechanism of hepatotoxicity

- 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.

Histology

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

CLINICAL MANIFESTATIONS

- Wide spectrum of presentation, ranging form mild derangements of liver enzymes to fulminant liver failure.
- DILI cholestasis: alkaline phosphatase (ALP) >2 times the upper limit of normal and/or an alanine aminotransferase (ALT) to ALP ratio of less than 2.
- Mixed: ALT/ALP ratio is greater than 2 but less than 5
- Hepatocellular: ALT/ALP ratio is greater than 5.
- Hy's law: Serum bilirubin >2 times the upper limit of normal in association with an elevation in serum aminotransferases (>3 times the upper limit of normal. Mortality is as high as 14 percent

Symptoms and examination findings

- Many patients with DILI are asymptomatic.
- Symptomatic patient may report malaise, low-grade fever, anorexia, nausea, vomiting, right upper quadrant pain, jaundice, acholic stools, or dark urine.
- Patients with cholestasis may complain of pruritus.
- In severe cases, coagulopathy and hepatic encephalopathy may develop indicating acute liver failure.
- Hypersensitivity reaction, such as a fever and rash, or a mononucleosis-like illness (pseudomononucleosis).

Laboratory tests

- hepatocellular injury will have a disproportionate elevation of their aminotransferases
- Cholestatic injury will predominantly have an elevation of their ALP.
- Bilirubin may be elevated both with hepatocellular and cholestatic injury
- Autoimmune-like presentation may have serologic markers of autoimmunity.
- Hypersensitivity reactions may have peripheral eosinophilia
- Mononucleosis-like illness may have a lymphocytosis and atypical lymphocytes.

DIAGNOSIS

- Diagnosing DILI can be difficult. It depends on obtaining a careful drug use history and ruling out other potential causes of liver injury.
- 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)

- Identifying the offending drug may be difficult for several reasons
- Obtaining a reliable drug history can be challenging
- relationship between exposure to the drug and hepatic toxicity is not always clear
- Patients may be taking multiple medications
- Patients may have concomitant liver disease

Role of a liver biopsy

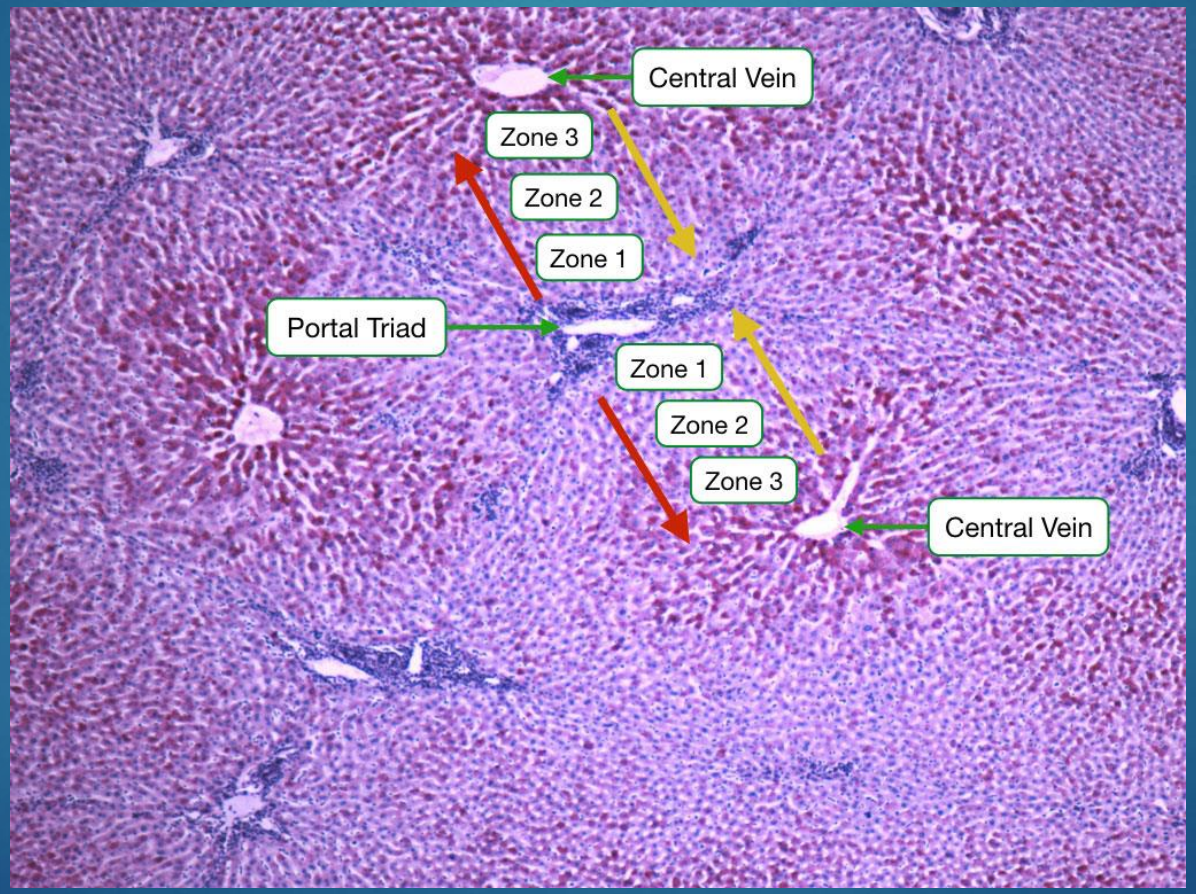
- Not routinely needed to make the diagnosis.
- In case of diagnostic uncertainty.
- Clinical evidence of chronic liver disease
- If fulminant disease is present.

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.
- Histologic findings are not diagnostic for a specific cause of DILI.
- 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

- Can be described histologically as Zonal and non-zonal.
- Histologically divided into three zones.
- Zone 1 adjacent to the portal triad.
- Zone 2 between zone 1 and 3.
- Zone 3 adjacent to the central vein
- Non-zonal necrosis appears in a viral hepatitis-like pattern.


Central Vein
Zone 3
Zone 2
Zone 1
Portal Triad
Zone 1
Zone 2
Zone 3
Central Vein

- Zonal necrosis is characteristic of compounds with predictable, dose-dependent, intrinsic toxicity.
- halothane (zone 3),
- acetaminophen (zone 3),
- beryllium (zone 2),
- cocaine (zone 1),
- iron sulfate (zone 1)

- Centrilobular (zone 3) necrosis is the most common type of zonal necrosis seen.
- Zone III cells are more important for glycolysis, lipogenesis and cytochrome P-450-based drug detoxification. This specialization is reflected histologically; the detoxifying zone III cells have **the highest concentration of CYP2E1** and thus are most sensitive to NAPQI production in acetaminophen toxicity.
- Non-zonal necrosis is caused by compounds that produce unpredictable idiosyncratic injury.
- Examples include phenytoin, methyldopa, isoniazid, and diclofenac.

Chronic hepatocellular injury

- Acute hepatocellular injury can progress to chronic injury in 5 to 10 percent of cases of DILI.
- Chronic hepatocellular injury can histologically resemble other causes of chronic liver disease, such as autoimmune hepatitis, viral hepatitis, or alcoholic liver disease.
- Chronic DILI include amoxicillin-clavulanic acid, atorvastatin, methotrexate, hypervitaminosis A, vinyl chloride, heroin, herbal products, and dietary supplements.
- Drugs that can lead to cirrhosis include methotrexate, isoniazid, Amiodarone, Enalapril, and Valproic acid.

- Certain drugs can present clinically, serologically, and histologically like autoimmune hepatitis.
- Examples include
- Infliximab and other tumor necrosis factor-alpha blocking agents, methyldopa, minocycline, and nitrofurantoin.

Acute cholestatic injury

- Described as Pure or bland cholestasis, characterized by prominent hepatocellular and/or canalicular cholestasis with very little hepatocellular injury or inflammation. This type of injury is often seen with the use of anabolic steroids or oral contraceptives.
- Or cholestatic hepatitis, characterized by portal inflammation, prominent cholestasis, and hepatocellular injury. Some of the drugs associated with this type of injury include erythromycin, amoxicillin-clavulanate, herbal products, and angiotensin-converting enzyme (ACE) inhibitors.

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
- Some patients with chronic cholestasis go on to develop vanishing bile duct syndrome.
- Drugs that have been associated with ductopenia include amoxicillin-clavulanate, flucloxacillin, ACE inhibitors, and terbinafine.

Steatosis

- Acute steatosis is usually microvesicular histologically and caused by high-dose intravenous tetracycline, Valproic acid, acetylsalicylic acid (Reye syndrome), and Amiodarone.
- Chronic steatosis is usually macrovesicular histologically. Causes include Amiodarone, glucocorticoids, methotrexate, metoprolol, nonsteroidal anti-inflammatory drugs (NSAIDs), Tamoxifen, and total parenteral nutrition.

DIFFERENTIAL DIAGNOSIS

- Hepatitis (viral infection, alcohol-associated liver disease, nonalcoholic fatty liver disease (NAFLD), autoimmune hepatitis, and Wilson disease)
- Cholestasis (biliary obstruction, primary biliary cirrhosis, primary sclerosing cholangitis, and intrahepatic cholestasis of pregnancy)
- Steatosis (NAFLD, nonalcoholic steatohepatitis (NASH), alcoholic liver disease, and acute fatty liver of pregnancy)
- Granulomatous hepatitis (infection, sarcoidosis, and primary biliary cirrhosis)

MANAGEMENT

- Primary treatment for 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.
- Glucocorticoids are of unproven benefit for most forms of drug hepatotoxicity.
- Autoimmune hepatitis and extrahepatic manifestations of DRESS

- cholestatic liver disease and pruritus can be treated with bile acid sequestrants.
- When to consult with a hepatologists?
- 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.
- Remember Hy's law.

PROGNOSIS

- **Acute liver injury**
- The majority of patients with 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.

- Factors associated with a poorer prognosis in patients with hepatocellular injury include
- The development of jaundice (bilirubin >2 times the upper limit of normal) in the setting of an alanine aminotransferase (ALT) >3 times the upper limit of normal
- 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

Any questions?

- Thank you.