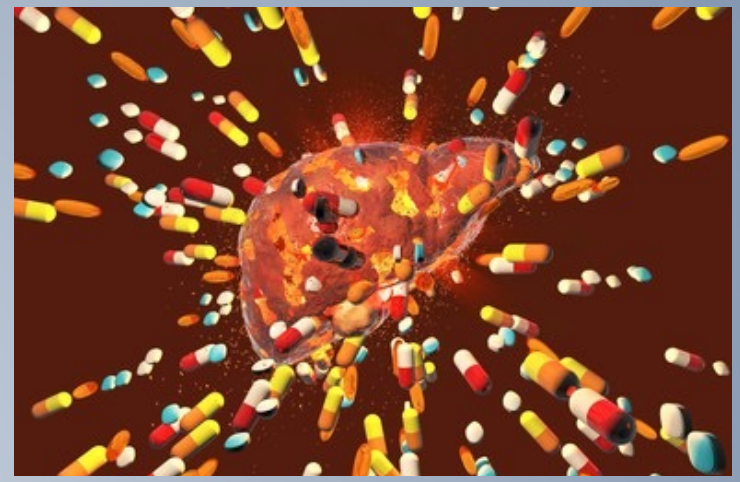
Drug, Herbal, and Dietary Supplement Induced Liver Injury (DILI)



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CME Procedures
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Objectives

- Define Drug-Induced Liver Injury (DILI) and differentiate between intrinsic vs idiosyncratic DILI
- Review DILI classification, epidemiology, causality assessment, and prognosis
- Explain the medical management of idiosyncratic patients with DILI and review monitoring strategies for commonly used medications

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Background

- In the United States, there are currently >1,000 prescription medications available and >100,000 over-the-counter herbal and dietary supplements (HDS) available for purchase at stores or online
- The average American receives >6 prescription medications per year
- DILI is the leading reason for regulatory actions for drugs still in development as well as those available in the market

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Drug-Induced Liver Injury (DILI)

- An adverse response by the liver to the administration of any medication or herbal or dietary supplement

- Diagnosis can be challenging since often patients are taking multiple medications or HDS that may cause liver injury
  - Need to exclude more common competing causes of liver injury
  - Requires the provider to understand biochemical patterns of injury associated with the causative agent
  - No validated diagnostic biomarker available for DILI

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DILI Classification

- Can be broadly broken into 3 categories:
  - Direct
    - Dose-dependent, intrinsic, and predictable
    - Reproducible in animal models
    - Injury seen in many patients exposed to the medication above a certain dose threshold and occurs within hours to days
  - Idiosyncratic
    - Generally dose-independent, individualized and unpredictable
      - Recent research suggests there may be a dose-dependent component
    - Observed in 1 in 2000 to 1 in 10,000 patient exposures
    - Onset can be anywhere from days to weeks
  - Indirect
    - Proposed 3rd category to account for an oversimplification of the classification system
    - Indirect agents cause hepatotoxicity by inducing a new liver condition or exacerbating an underlying disease
      - Often the biological action of the agent affects the host immune system, leading to a secondary form of liver injury
    - Toxicity caused by the pharmacodynamics of the medication and NOT its chemical structure
    - Generally dose-independent and can have an onset of weeks to months

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Proposed Classification of DILI

Mechanistic Classification	Direct Hepatotoxicity	Idiosyncratic Hepatotoxicity	Indirect Hepatotoxicity
Incidence	Common	Rare	Intermediate
Dose-related?	Yes	No	No
Predictable?	Yes	No (?)	Partially
Reproducible in animal models?	Yes	No	Not usually
Latency?	Rapid (days)	Variable (days to years)	Delayed (months)
Phenotypes of injury	Serum AST, ALT, ALP elevations. Hepatic necrosis, acute fatty liver, nodular regeneration	Mixed or cholestatic hepatitis, bland cholestasis, chronic hepatitis	Immune-mediated hepatitis, fatty liver, chronic hepatitis
Likely mechanism of injury	Intrinsic hepatotoxicity that is dose-dependent	Idiosyncratic host metabolic or immune reaction	Indirect effect on liver or host immunity

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Epidemiology

- The risk of DILI is difficult to quantify because:
  - it is a relatively new area of epidemiologic interest
  - difficulty in capturing/diagnosing outside of clinical trials where liver function tests are closely monitored
- Estimated annual incidence of idiosyncratic DILI in the general population of 14 – 19 events per 100,000 inhabitants or 60,000 cases per year in the USA
- Among hospitalized patients, reported rates of DILI are 0.7% - 1.4%, however this may be an underestimation
  - In patients with jaundice, DILI was the reported cause in 2% - 4% of patients
- HDS products surpass pharmaceuticals in China, Korea and Singapore, and therefore account for 27% - 62% of their DILI cases
  - HDS products represent only a minority of cases in Japan, USA, and Spain, however the incidence has increased in recent years

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Associated Medications

- Drugs are the most common cause of acute liver failure (ALF) in the USA, Europe and Japan
- Acetaminophen is the most well-known cause of intrinsic DILI
- Antimicrobials account for the top 10 agents associated with idiosyncratic DILI
  - Other common classes associated with idiosyncratic DILI include central nervous system agents, immunomodulatory agents, and antineoplastic agents

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Associated Medications – Direct/Intrinsic

- Acetaminophen
- Amiodarone
- Anabolic steroids
- Antimetabolites
- Cholestyramine
- Cyclosporine
- HAART
- Heparins
- Nicotinic Acid
- Statins
- Valproic acid

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Associated Medications – Idiosyncratic

- Allopurinol
- Amiodarone
- Amoxicillin/clavulanate
- Bosentan
- Dantrolene
- Diclofenac
- Disulfiram
- Felbamate
- Fenofibrate
- Flutamide
- Halothane
- Isoniazid
- Ketoconazole
- Lapatinib
- Leflunomide
- Lisinopril
- Methyldopa
- Minocycline
- Nitrofurantoin
- Pazopanib
- Phenytoin
- Propylthiouracil (PTU)
- Pyrazinamide
- Statins
- Sulfonamides
- Terbinafine
- Ticlopidine
- Tolcapone
- Tolvaptan

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Associated Medications by Drug Class

- Antimicrobials
- Antiepileptics
- Immunotherapies
- Herbal and Dietary Supplements (HDS)

ANTIMICROBIALS

- Amoxicillin/Clavulanate
- Isoniazid (INH)
- Nitrofurantoin
- Sulfamethoxazole/ Trimethoprim (SMX-TMP)
- Minocycline

Amoxicillin/Clavulanate

- Leading cause of idiosyncratic DILI in the western world
- A prospective study in Iceland identified 15 cases of amoxicillin/clavulanate-induced DILI among 35,000 treated patients over a 2-year period
  - If extrapolated to USA, this would suggest about 30,000 cases of DILI each year
- Proposed risk factors: higher dose, longer therapy duration, increasing age
  - None have been reliably observed in all studies
- In the Drug-Induced Liver Injury Network (DILIN), the amoxicillin/clavulanate group had the following characteristics compared to the overall DILIN:
  - Increased age (60 vs 47 years, $p<0.001$)
  - Higher incidence in men (62% vs 39%, $p<0.001$)

Amoxicillin/Clavulanate, cont.

- Injury may develop within a few days but may not be seen until months after completion
  - In a 2016 study, mean time to onset was 31 days and mean time to resolution was 55 days
    - 12 patients developed chronic DILI
    - 6 patients developed severe DILI (3 liver transplantation, 2 recovered, 1 chronic liver injury)
- Patients with underlying liver disease are more likely to have progression to chronic DILI, however preexisting liver disease is NOT a contraindication to amoxicillin/clavulanate
- Studies have shown that certain *HLA* class I and II single-nucleotide polymorphisms are associated with amoxicillin/clavulanate DILI
  - Routine testing before prescribing NOT recommended due to limited association with hepatotoxicity, lack of cost-effectiveness, and limited test availability
- **Overall latency and pattern:**
  - Short to moderate
  - Primarily cholestatic but can be hepatocellular

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Isoniazid (INH)

- INH is still a leading cause of DILI in the USA despite the relatively low prevalence of tuberculosis
  - ~20% of patients will experience a transient increase in AST/ALT
- Most cases resolve after the discontinuation of therapy
  - ~1% of cases of liver toxicity progress to liver failure
    - 10% of these cases are fatal
- Risk factors for INH-induced hepatotoxicity include age, alcohol use, preexisting liver disease, concurrent use of medications that induce CYP, prior INH intolerance, African American race, female sex
  - Patients >50 yo or with preexisting liver disease should have monthly LFT monitoring while on therapy
- **Overall latency and pattern:**
  - Moderate to long
  - Acute hepatocellular injury similar to viral hepatitis

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Nitrofurantoin

- Clinical presentation varies
  - Autoimmune-mediated hepatitis to chronic low-grade hepatitis
- Chronic injury more common than acute
- Risk factors include female patients, older age, and impaired kidney function
- A prospective study by DILIN noted that 82% of nitrofurantoin cases had features consistent with autoimmune hepatitis; more than 2/3 had some degree of antinuclear antibody (ANA) and anti-smooth muscle antibody (ASMA) elevation, and ½ had some immunoglobulin G (IgG) elevatopn
- Complete recovery can be up to 6 months; not recommended to rechallenge because recurrent injury is common
- **Overall latency and pattern:**
  - Acute form: Short; Chronic form: Moderate to long
  - Acute form: hepatocellular/resembles autoimmune hepatitis; Chronic form: hepatocellular

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SMX-TMP

- DILI predominantly related to a hypersensitivity-like reaction from the sulfa component of the drug
  - Trimethoprim can also damage the liver
- Symptoms generally begin with fever, rash, and eosinophilia and eventually progress to jaundice
- Most cases resolve within 2 months of drug discontinuation, but cases can progress to ALF or prolonged cholestasis even after discontinuation
  - Recovery from cholestasis and associated vanishing bile duct syndrome can take up to 2 years and may require treatment with ursodeoxycholic acid
- Rechallenge NOT recommended due to acute and severe presentation
- **Overall latency and pattern:**
  - Short to moderate
  - Primarily cholestatic but can be hepatocellular; immunoallergic features common

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Minocycline

- Usually presents as either acute severe hepatitis or chronic indolent hepatitis
  - With the acute form, patients usually present with a syndrome similar to viral hepatitis, including fevers, general malaise, and eosinophilia
  - Lymphocytosis and/or exfoliative dermatitis are occasionally seen
- Liver injury usually develops within 1 – 3 months of initiation and resolves 1 – 2 months after discontinuation
  - Most cases resolve following discontinuation, but fibrosis can develop, esp if medication not promptly discontinued
  - Persistently elevated ANA has been observed for several months after discontinuing minocycline
- Rechallenge is NOT recommended due to likelihood of recurrent DILI
- A DILIN prospective study showed that 73% of patients with minocycline-induced DILI had features similar to autoimmune hepatitis
- **Overall latency and pattern:**
  - Moderate to long
  - Hepatocellular; resembles autoimmune hepatitis

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ANTIEPILEPTICS

- Valproate
- Phenytoin
- Carbamazepine
- Lamotrigine

Valproate

- About 10% of patients will develop mild LFT elevations with chronic use
  - These elevations are usually self-limited and will resolve even with therapy continuation (intrinsic DILI)
- Idiosyncratic DILI can also occur and seems to be irrespective of serum valproate concentrations
  - Thought to be caused by mitochondrial damage
  - Usually presents ~3 months into therapy
- Can cause altered mental status (AMS) with elevated ammonia levels in the absence of LFT abnormalities or changes on liver biopsy
- Valproate should be discontinued when liver enzymes reach 3x the upper limit of normal (ULN)
- Risk factors fer severe injury include younger age and concurrent use of other antiepileptics
- Rechallenge NOT recommended
- **Overall latency and pattern:**
  - Hyperammonemia or hepatocellular: Moderate to long
  - Encephalopathy (hyperammonemia); hepatocellular

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Phenytoin

- Phenytoin is one of the leading causes of DILI
  - ~25% of patients will develop mild LFT elevations that do not require drug discontinuation
  - Usually occurring within 6 – 8 weeks of the start of therapy, most cases are thought to be mediated by a hypersensitivity reaction, manifesting as a viral-like syndrome
  - Mixed injury (hepatocellular and cholestatic) pattern most common
    - Cases of vanishing bile duct have been documented
  - Therapy should be help for ALT elevations >3x the ULN with jaundice
    - Mortality rate >10%
    - Rechallenge NOT recommended

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Immunotherapies

- Methotrexate
- TNF-α inhibitors
  - Adalimumab, Certolizumab Pegol, Etanercept, Golimumab, Infliximab
- Immune Checkpoint Inhibitors (ICIs)
  - Atezolizumab, Avelumab, Cemiplimab, Dostarlimab, Ipilimumab, Nivolumab, Pembrolizumab, Retifanlimab, Toripalimab, Tremelimumab

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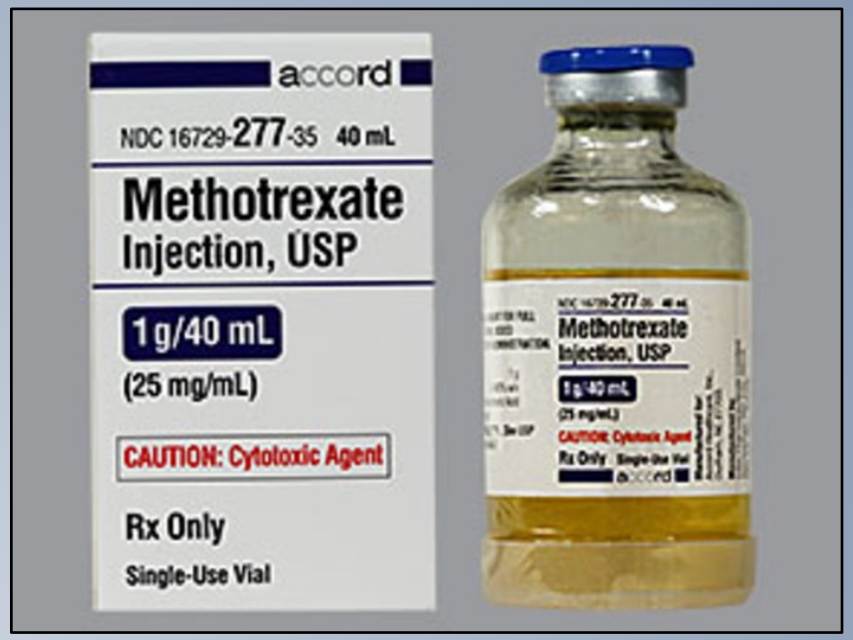
Methotrexate



- Dose-dependent
  - More common with high IV doses
- Typically, hepatocellular
  - Severe transaminase elevations typically resolve following methotrexate discontinuation
- Induces liver injury through several mechanisms
  - The metabolite, methotrexate polyglutamate signals proinflammatory signaling pathways, including tumor necrosis factor (TNF)-α, nuclear factor κB, and interleukin-6
    - Triggers hepatocyte oxidative stress, inflammation, steatosis, fibrosis, and apoptosis
    - Depletes hepatic folate concentrations and decreases RNA and DNA synthesis → death of hepatocytes

Guideline Recommendations for Monitoring of Methotrexate

- American College of Rheumatology
  - Baseline and every 2 – 4 weeks upon initiation
  - After 3 months of normal liver function, can decrease to every 8 – 12 weeks
  - After 6 months, can decrease to every 12 weeks
  - If liver dysfunction arises, reduce dose and increase frequency of monitoring
- National Psoriasis Foundation
  - Monitor every 4 – 12 weeks with lab draw at least 5 days after methotrexate administration
  - If liver dysfunction arises, reduce dose and increase frequency of monitoring
- Obtain liver biopsy if liver dysfunction persists (at least 6 LFT elevations in a 12-month period or decline in albumin) despite dose reduction and/or discontinuation

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Guideline Recommendations for Monitoring of Methotrexate, cont.

- Evaluate for fibrosis BEFORE therapy initiation in the following patient populations:
  - Alcoholic liver disease
  - Nonalcoholic steatohepatitis (NASH)
  - Viral hepatitis
- American Association for the Study of Liver Diseases (AASLD) and other guidelines recommend assessment of fibrosis (transient elastography or biopsy) after 3.5 – 4 gm cumulative dose exposure
  - No longer universally recommended across all guidelines because the risk of fibrosis is low in the absence of LFT abnormalities
- Recommend counseling patients on the importance of alcohol cessation while taking methotrexate

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TNF-α Inhibitors

- FDA issued a hepatotoxicity warning for infliximab in 2004
  - Estimated incidence is 1 case per every 16,500 patients treated
- Usually hepatocellular but can be cholestatic
  - Onset typically ~3 – 6 months after initiation
  - Later onset typically immune-mediated
    - Can see ANA, ASMA and anti-double-stranded DNA elevation
- TNF-α therapy considered moderate risk for Hepatitis B reactivation
  - HBsAg positive patients should receive antiviral prophylaxis
- Prognosis is encouraging after discontinuation
  - Corticosteroids can be initiated for immune-mediated hepatotoxicity
    - Continue steroids for 3 – 6 months after improvement in LFTs
- If patient develops hepatotoxicity on one agent, this does not preclude trying another medication in the class

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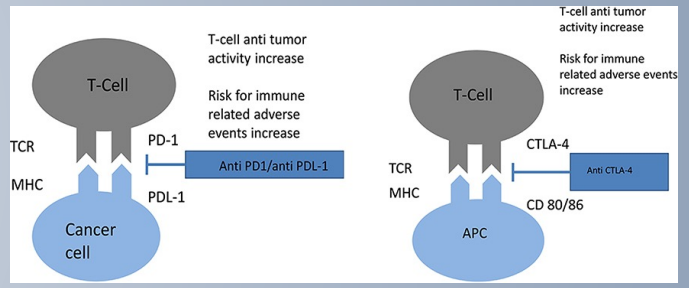
Immune Checkpoint Inhibitors (ICIs)

- ICIs have significantly improved prognosis in advanced cancers and have two primary targets and both can cause hepatotoxicity
  - Programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1)
    - Incidence of hepatotoxicity 37%
  - Cytotoxic T-lymphocyte antigen-4 (CTLA-4)
    - Incidence of hepatotoxicity 24%
  - Combination therapy can lead to hepatotoxicity in 73% of patients



- Hepatotoxicity appears to be dose-dependent
  - Usually hepatocellular but can be cholestatic or mixed
  - An increase in transaminases >50% over baseline persisting for 1 week should prompt discontinuation permanently

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Herbal and Dietary Supplements

Herbal and Dietary Supplements (HDS)

- Current estimates predict that ½ of the adult US population is taking some type of supplement, increasing over recent decades
- Incidence of DILI associated with HDS has increased from 7% in 2004/2005 to 20% in 2013/2014
  - Exact incidence hard to quantify because patients are often taking multiple supplements or supplements that contain multiple ingredients
- Less common than DILI of FDA approved medications but associated with more severe injury and worse outcomes (including survival and need for transplantation)
- Broadly divided into 3 categories
  - Body-building products, weight loss and energy enhancing supplements, and herbal products

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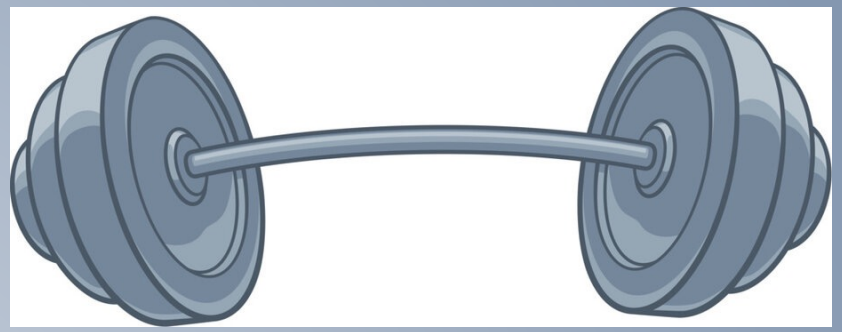
Anabolic Androgenic Steroids



- Body-building products are the most common cause of liver injury among those use HDS
- Oral derivatives of testosterone such as methyltestosterone, methandrostenolone, oxymetholone, oxandrolone, and stanozolol are resistant to inactivation by first-pass metabolism ➔ potentially hepatotoxic
- Can develop prolonged cholestasis within 1 – 4 months of initiation
  - Jaundice can last for up to 3 months but is usually nonfatal
- Rare but more serious – patients can develop benign or malignant hepatic neoplasms

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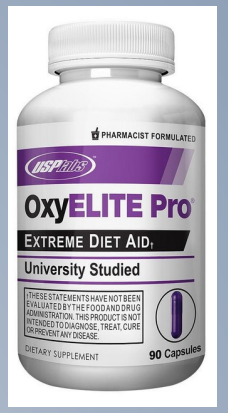
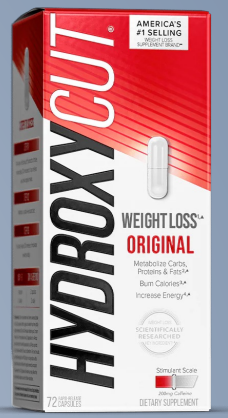
Weight-Loss Supplements





- Hepatocellular liver injury has been associated with Hydroxycut® and OxyELITE Pro®
  - Associated with significant morbidity requiring transplantation
  - Hydroxycut contains *G. cambogia*, containing hydroxycitric acid, used to alter adipogenesis and reduce visceral fat in mouse models
    - Laboratory studies have shown an association with *C. cambogia* and hepatic fibrosis, inflammation, and oxidative stress
- Both products contain multiple ingredients increasing the risk of interactions and mislabeling
- Green Tea Extract
  - Common herbal product used in weight-loss supplements due to epigallocatechin gallate (EGCG), its active ingredient that inhibits lipogenic enzymes
  - Can cause hepatocellular injury through mitochondrial damage and formation of oxygen free radicals

Additional Herbal Products

- Kratom
  - Used for its opioid, analgesic and stimulant properties
    - Used to mitigate symptoms of opioid withdrawal
    - "Drug of Concern" by the FDA
      - Also, banned in several stated and in 2016, the DEA attempted to make it a schedule 1 drug
    - Mechanism for hepatotoxicity is unknown but likely multifactorial
- Kava Kava
  - Anxiolytic properties
  - Hepatotoxicity can range from cholestatic hepatitis to fulminant liver failure
- Usnic Acid
  - Used for its antimicrobial, antiviral and anti-inflammatory properties
  - Can cause hepatotoxicity likely from oxidative stress and disruption of mitochondrial function
- Ephedra
  - *Ephedra sinica* contains alkaloid compounds with effects comparable to ephedrine and pseudoephedrine
  - Mechanism of hepatotoxicity unknown
    - Mitochondrial oxidative stress?

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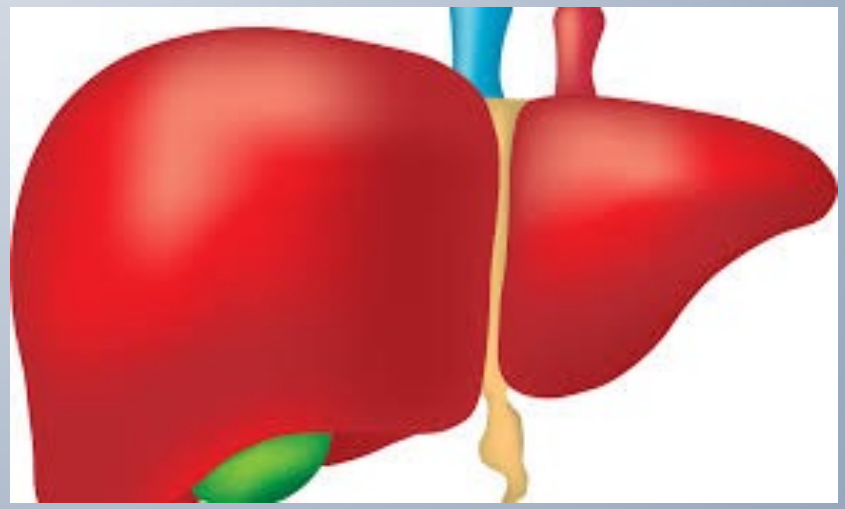
Pathophysiology and Clinical Presentation



Risk Factors

- Older Age
  - Proposed risk factor
  - May be drug specific
    - INH, nitrofurantoin, amoxicillin/clavulanate
  - Cholestatic injury more common
- Male and Female Sex
  - Relatively same risk of DILI
  - Females have higher risk with nitrofurantoin, minocycline, and diclofenac
    - These agents more commonly associated with drug-induced autoimmune hepatitis, which occurs almost exclusively in females
    - Females have more severe disease
- Race
  - DILI Network (DILIN) study in 2017 showed that DILI from SMX-TMP, methyldopa and phenytoin were more common in African-Americans; amoxicillin/clavulanate was more common in white patients
  - Severity was greater in African-Americans
    - More likely to have severe skin reactions, higher hospitalization rates, liver transplantation or liver-related death by 6 months, and chronic DILI
- Pregnancy
  - A risk factor for cholestatic or mixed DILI despite evidence to support
    - Only agent associated with an increased risk of DILI in pregnancy is tetracycline

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Risk Factors, cont.

- Alcohol
- Genetic Risk Factors
  - Missense variant in *PTPN22* often associated with autoimmune disorders appears to be a risk factor for all-cause DILI
- Dose
  - Intrinsic DILI is well-known to have a dose-dependent causation
  - Idiosyncratic DILI dose-independent?
- Hepatic metabolism
  - Reactive metabolites can form causing DILI
- Lipophilicity
  - Often associated with hepatic metabolism
- Concomitant agents
  - Usually able to determine the most likely causative agent but other agents should not be considered harmless due to possible alterations in metabolism by induction, inhibition, or substrate competition

Diagnosis

Mostly diagnosis of **exclusion** and relies on a detailed analysis of patient's medical history, medication use, pattern and course of liver biochemistries, and exclusion of other causes of liver disease

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Definitions of Clinically Significant DILI

- Serum AST or ALT >5x ULN *OR* ALP >2x ULN on two separate occasions at least 24 hours apart
- Total serum bilirubin >2.5 mg/dL + elevated serum AST, ALT, or ALP
- INR >1.5 + elevated serum AST, ALT, or ALP

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PROPOSED DIAGNOSTIC ALGORITHM FOR PATIENTS WITH SUSPECTED DILI

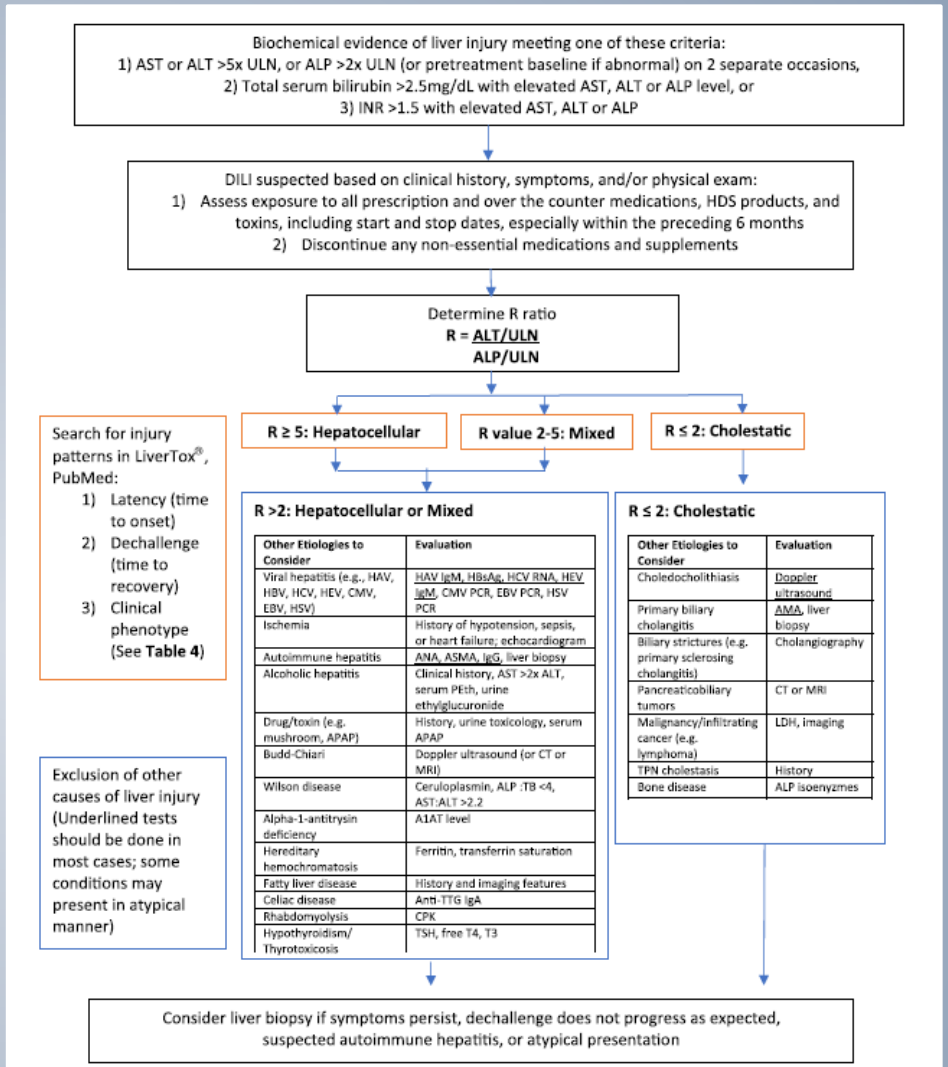

FIGURE 1 Proposed diagnostic algorithm for patients with suspected DILI. A diagnosis of DILI relies on careful elicitation of clinical history and drug exposures along with exclusion of other more common causes of liver injury. Abbreviations: A1AT, alpha-1-antitrypsin; ALP, alkaline phosphatase; ALT alanine aminotransferase; AMA, anti-mitochondrial antibody; ANA, antinuclear antibody; APAP, acetaminophen; ASMA, anti-smooth muscle antibody; AST, aspartate aminotransferase; CK, creatine kinase; CMV, cytomegalovirus; EBV, Epstein–Barr virus; HDS, herbal and dietary supplement; HSV, herpes simplex virus; INR, international normalized ratio; LDH, lactate dehydrogenase; T3, triiodothyronine; T4, thyroxine; TB, total bilirubin; TSH, thyroid stimulating hormone; TTG, tissue transglutaminase; ULN, upper limit of normal.

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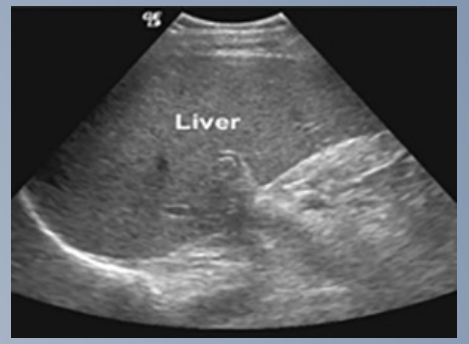
Liver Imaging and Biopsy



- All patients should undergo some type of imaging
  - Ultrasound most common initial imaging to identify cirrhosis, biliary obstruction, or other focal changes
  - CT or magnetic resonance cholangiography may be ordered to assess vascular abnormalities or pancreaticobiliary disease

- Liver biopsy not a requirement for diagnosis
  - May be ordered to rule out other causes of liver injury
  - Also used when drug discontinuation does not lead to symptom improvement or decrease in lab values

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HISTOLOGIC PHENOTYPES OF IDIOSYNCRATIC DILI

Table 4. Clinical and Histologic Phenotypes of Idiosyncratic DILI

Clinical Phenotype	Histologic Pattern	Associated Drugs
Hepatocellular	Acute hepatitis	Phenytoin, dapsone, isoniazid, sulfonamides
	Panlobular hepatitis	Immune checkpoint inhibitors
	Zonal or nonzonal necrosis	Acetaminophen, halothane, cocaine, ferrous sulfate
	Granulomatous hepatitis	Sulfonamides, sulfonylureas, phenytoin, carbamazepine, quinidine, hydralazine, interferon-α, etanercept, ipilimumab
	Chronic hepatitis	Atorvastatin, HDS, methotrexate
	Autoimmune hepatitis	Nitrofurantoin, diclofenac, methyldopa, hydralazine, minocycline, statins, TNF-α inhibitors
Cholestatic	Acute cholestasis	Anabolic steroids, oral contraceptives
	Chronic cholestasis	Amoxicillin/clavulanate, enalapril, terbinafine
	Mixed hepatocellular/cholestatic injury	Amoxicillin/clavulanate, ACE inhibitors, phenothiazines
	Sclerosing cholangitis	Nivolumab
Steatosis and steatohepatitis	Microvesicular	Aspirin, valproic acid, NSAIDs, tetracycline, cocaine
	Macrovesicular	Glucocorticoids, methotrexate, NSAIDs, metoprolol, fluorouracil, cisplatin, irinotecan, tamoxifen
	Mixed micro- and macrovesicular	Amiodarone, valproic acid, methotrexate
	Steatohepatitis	Amiodarone, methotrexate, fluorouracil, cisplatin, irinotecan, tamoxifen
Vascular	Sinusoidal obstruction syndrome	Busulfan, cyclophosphamide
	Nodular regenerative hyperplasia and obliterative portal venopathy	Arsenic, copper sulfate, azathioprine, methotrexate, mercaptopurine, oxaliplatin, didanosine, stavudine
	Peliosis hepatis	Androgens, oral contraceptives
Chronic DILI	Fibrosis and cirrhosis	Methotrexate, valproic acid, HDS, oral contraceptives, isoniazid, sulfamethoxazole/trimethoprim, nitrofurantoin, methotrexate, diclofenac, fenofibrate, amoxicillin/clavulanate
Miscellaneous	Ground-glass cytoplasm	Barbiturates, phenytoin, immunosuppressive agents, antibiotics
	Phospholipidosis	Antibiotics, antipsychotics, antidepressants, antiarrhythmics, amiodarone
	Pigment deposition	Mercaptopurine, phenothiazines
Neoplastic	Hepatocellular adenoma	Oral contraceptives, anabolic steroids, danazol

ACE = angiotensin-converting enzyme; DILI = drug-induced liver injury; HDS = herbal and dietary supplements; TNF-α = tumor necrosis factor-α.

Information from: Fontana RJ, Liou I, Reuben A, et al. AASLD practice guidance on drug, herbal, and dietary supplement-induced liver injury. Hepatology 2023;77:1036-65.

Models of Causality Assessment

- Although expert opinion remains the gold standard, several assessment tools can be used to guide DILI diagnosis

- Example tools:
  - Roussel Uclaf Causality Assessment Method (RUCAM)
  - Revised Electronic Causality Assessment Method (RECAM)
  - Maria and Victorino Scale
    - AKA Clinical Diagnostic Scale (CDS)
  - Digestive Disease Week-Japan Scale
  - Drug-Induced Liver Injury Network (DILIN)
  - Naranjo Adverse Drug Reaction Probability Scale
    - Assessment of causality for all adverse drug reactions; not specific to DILI

Guidance statements

24. Currently there are three commonly used causality assessment methods, and each has its own strengths and limitations.
25. Structured causality assessment instruments incorporate the dose, duration, and timing of suspect drug and other concomitant drug or HDS product use; an assessment of the laboratory, radiological, and histological features at presentation; and exclusion of competing causes of liver injury.
26. The semiquantitative expert opinion causality assessment scale developed by the DILIN is frequently used in clinical practice and in prospective research studies, but the need for specialized expertise limits its generalizability.
27. The updated RUCAM has improved user instructions and more complete diagnostic evaluation compared with the original RUCAM but retains risk factors of age, alcohol, and pregnancy that are of unclear value.
28. The RECAM is a newly developed, computerized causality assessment instrument that may prove more reproducible and reliable than RUCAM but further validation studies are needed.
29. Intentional suspect drug rechallenge is rarely undertaken in clinical practice, but when available, may prove useful in causality assessment.

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TABLE 5 Data fields in the RUCAM, CDS, and RECAM causality assessment instruments

Data field	Updated RUCAM[108] score	CDS[109] score	RECAM[113] score
1. Chronology (latency)			
1a. Drug start to liver injury onset[a]	+1 to +2	+1 to +3	−6 to +4
1b. Drug discontinuation to liver injury onset[a]	+1	−3 to +3	−6 to 0
2. Dechallenge[b]	−2 to +3 hepatocellular; 0 to +2 cholestatic/mixed	0 to +3	−6 to +4
3. Competing causes of liver injury	−3 to +2	−3 to +3	−6 to 0
4. Rechallenge	0 to +3	+3	0 or + 6
5. Track record of drug/HDS hepatotoxicity	0 to +2	−3 to +2	0 to +3
Risk factors	0 to +1	N/A	N/A[c]
6. Concomitant medication	−3 to 0	N/A	N/A[d]
7. Extrahepatic manifestations	–	0 to +3	–
Range of scores	−9 to +14	−6 to 17	−6 to +20
DILI likelihood categories			
Definite	≥ 9	> 17	Highly likely/high probable ≥ 8
Probable	6–8	14–17	4–7
Possible	3–5	10–13	−3 to +3
Unlikely	1–2	6–9	Unlikely/excluded, < −4
Excluded	≤ 0	≤ 6	

Note: Only scores from the updated RUCAM are shown and are composites derived from hepatocellular and mixed/cholestatic categories.[110]
Abbreviations: CDS, clinical diagnostic scale; NA, not applicable; RECAM, Revised Electronic Causality Assessment Method; RUCAM, Roussel-Uclaf Causality Assessment Method.
[a]Only 1 of those 2 (i.e., only 1a or 1b) is counted.
[b]Stratified by hepatocellular versus mixed/cholestatic in early version.
[c]In RECAM, risk factors were not assigned scores.
[d]RECAM was developed only for single drug cases and does not account for concomitant medications.

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Management of Acute DILI

Nonpharmacologic Therapy
Supportive Care
Targeted Pharmacologic Agents

Drug Discontinuation

- Core principle of DILI management
- Many cases of DILI do **NOT** require hospitalization and are often self-limiting
- In patients progressing to acute liver failure (ALF), hospitalization is needed, and consideration of liver transplant should urgently be pursued
  - Stopping the offending agent not only limits progression of liver injury but is also an important component in confirming the diagnosis
  - Rechallenge NOT recommended

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Supportive Care

- Can consider gastric decontamination with activated charcoal in an acute ingestion
  - Give 1 gm/kg enterally in patients with a patent or secure airway optimally within 4 hours of digestions (the sooner the better)
  - Gastric lavage?

- General supportive care can be implemented according to symptomology and illness severity
  - Antiemetics, analgesics, parenteral hydration, and ursodeoxycholic acid (aka ursodiol)
    - APAP generally safe in DILI but restrict dose to 2000 mg per day
    - Ursodeoxycholic acid is recommended in patients with severe pruritis at 10 – 15 mg/kg/day in divided doses
      - Minimal prospective data available for use; well-tolerated and likely safe

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TARGETED THERAPIES/ ANTIDOTES

Table 5. Management of DILI

	Treatment	Indication(s)	Dose	Notes
Supportive care	Acetaminophen analgesics	Mild to moderate pain	2 g max enterally per day in divided doses	Escalation to other agents, including opioid-based therapies, may be required
	Antiemetics	Moderate nausea/vomiting	Per package insert(s)	—
	Activated charcoal	Ingestion within 4 hr	1 g/kg enterally	Patent and protected airway required
	Ursodeoxycholic acid	Severe pruritus	10–15 mg/kg/day enterally in divided doses	Prospective efficacy data lacking; likely safe
Targeted therapies (antidotes)	Cholestyramine	Leflunomide cases with persistent cholestasis and terbinafine cases (in combination with antihistamines)	4 g enterally every 6 hr for 2 wk	Thought to increase drug clearance
	Corticosteroids	ICI hypersensitivity with AIH-like features	Methylprednisolone 1 mg/kg/day intravenously for 1–3 mo followed by rapid tapering	Possible role when autoimmune features are present on biopsy or ICI/TKI are involved
	Levocarnitine	Valproic acid cases with hyperammonemia	100 mg/kg (max 6 g) intravenously/enterally over 30–60 min followed by 15–25 mg/kg intravenously/enterally every 4–6 hr until clinical improvement noted	Increases valproic acid metabolism and reduces serum ammonia concentrations
	Acetylcysteine	Acetaminophen cases • Nonmassive acute ingestion • Massive acute ingestion • Modified-release formulations Non-acetaminophen cases	Dose per indication: • Three-bag intravenous 21-hr regimen • Consider double-dose of third bag • May require extended course 72-hr intravenous regimen	Coordination with the poison control center should be pursued for massive and modified-release formulation ingestions
	Penicillin G Silibinin	*Amanita* mushroom toxicity	Penicillin G 500,000 to 1 million units/kg/day intravenously Silibinin 5-mg/kg intravenous loading dose followed by 20 mg/kg/day as a continuous infusion	Silibinin requires FDA expanded access request for acquisition
Nontargeted and advanced therapies	Artificial extracorporeal devices (e.g., MARS)	Bridge to transplantation or recovery	3–10 sessions	—
	Bioartificial devices	Bridge to transplantation or recovery	N/A	Currently in development
	Liver transplantation	DILI-ALF (and appropriate candidate)	N/A	All patients with DILI-ALF should promptly be transferred to a transplant center

AIH = autoimmune hepatitis; ALF = acute liver failure; DILI = drug-induced liver injury; HSCT = hematopoietic stem cell transplantation; ICI = immune checkpoint inhibitor; MARS = molecular adsorbent recirculating system; N/A = not applicable; TKI = tyrosine kinase inhibitor.

Information from: Fontana RJ, Liou I, Reuben A, et al. AASLD practice guidance on drug, herbal, and dietary supplement-induced liver injury. Hepatology 2023;77:1036-65. European Association for the Study of the Liver (EASL). EASL clinical practice guidelines: drug-induced liver injury. J Hepatol 2019;70:1222-61.

Cholestyramine

- Used in leflunomide hepatotoxicity
  - Leflunomide carries a Black Box Warning
- Leflunomide is a prodrug with a very long half-life due to an active metabolite, teriflunomide, which undergoes enterohepatic recycling
- Cholestyramine washouts are recommended to rapidly reduce serum concentrations of leflunomide
- Manufacturer recommendations:
  - Cholestyramine 8 gm orally TID for 11 days
- AASLD recommendations:
  - Cholestyramine 4 gm every 6 hours for 2 weeks
- Should serially monitor teriflunomide concentrations at least twice, 14 days apart
  - If level >0.02 mg/L, the cholestyramine regimen should be repeated

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Corticosteroids

- With immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors becoming more prevalent, corticosteroids are being more utilized in DILI management
  - Can also be considered in idiosyncratic DILI when hypersensitivity or autoimmune features are present

- Dosing and Duration
  - Methylprednisolone 1 mg/kg/day for ICI cases
  - Prednisone 40 – 60 mg daily for other indications
  - Continue for 1 – 3 months and then rapidly taper
    - Note: Optimal dose and duration not established

- For steroid-refractory disease, mycophenolate mofetil or azathioprine can be considered

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Levocarnitine

- Used in valproic acid cases of hyperammonemia
  - Carnitine is an essential cofactor in the β-oxidative mitochondrial metabolism of valproic acid to nontoxic metabolites
  - Valproic acid inhibits the endogenous synthesis of carnitine, shunting further valproic acid metabolism through mitochondrial processes responsible for producing toxic metabolites
    - These toxic metabolites can cause cerebral edema and hepatotoxicity

- Administer levocarnitine to replenish carnitine stores and reduce the formation of toxic metabolites
  - Adverse events
    - Generally well tolerated
    - Most common – n/v
    - More serious – hemodynamic changes, hypercalcemia and seizures
  - Dosing
    - 100 mg/kg (max 6 gm) IV/enteral loading dose followed by 50 mg/kg (max 3 gm) IV/enteral every 8 hours

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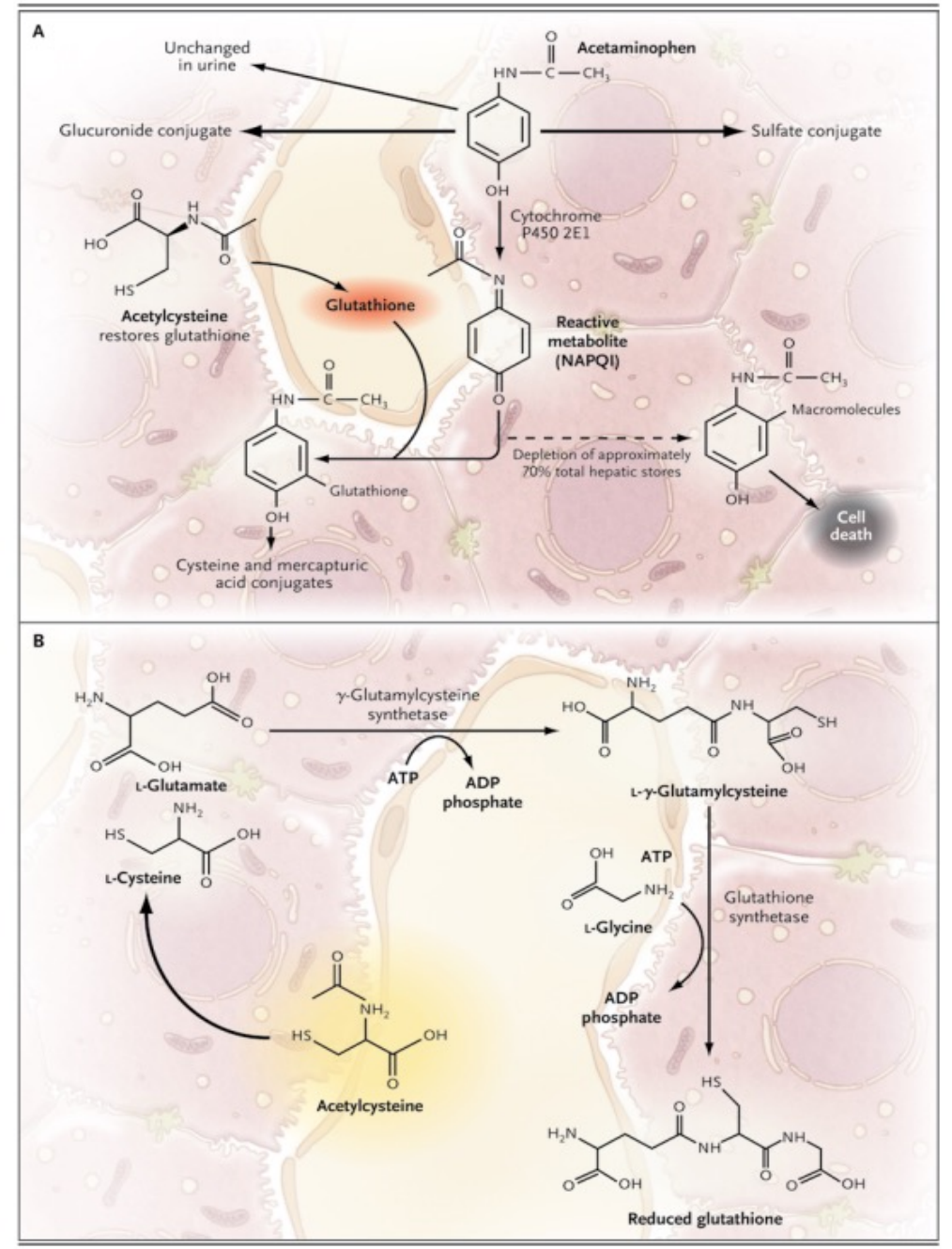
Acetylcysteine

- AKA NAC
- Most studied and widely used agents for DILI
- Known antidote for APAP-induced hepatotoxicity but also recommended in non-APAP DILI
- MOA in APAP-induced DILI: replaces glutathione stores, which allows breakdown of the highly reactive/ hepatotoxic oxidative metabolite, NAPQI



Hepatology. 2023; 77: 1036-1065.
NEJM. 2008; 359:285-92.
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Acetylcysteine

- Administration can be either enteral or IV
  - In general, no preference is given unless the patient has an ileus, is intolerant to oral intake, or pregnant, where IV would be preferred
- Multiple IV regimens available
  - Two most common are a 3-bag regimen and a 2-bag regimen
    - Some institutions have moved to a 1-bag regimen
  - The 3-bag regimen is what was originally studied and FDA approved; AASLD guideline recommended
  - The 2-bag method may have some benefits, including simplified prescribing, prevention of treatment delays, and lower rates of adverse reactions
  - ***Reach out to your local poison center or use your institution-specific guidelines for ordering in your patients***

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Table 6. Acetylcysteine Regimens Summary

Regimen	Doses
Oral	140 mg/kg administered as a loading dose followed by 70 mg/kg every 4 hr for 17 doses
Three-bag	150 mg/kg over 15–60 min followed by 50 mg/kg over 4 hr followed by 100 mg/kg over 16 hr
Two-bag	200 mg/kg over 4 hr followed by 100 mg/kg over 16 hr
Double-dose	150 mg/kg over 15–60 min followed by 50 mg/kg over 4 hr followed by 200 mg/kg over 16 hr
Extended treatment	150 mg/kg over 15–60 min followed by 50 mg/kg over 4 hr followed by 100 mg/kg over 16 hr until symptom resolution or death
72-hr	150 mg/kg over 1 hr, followed by 50 mg/kg over 4 hr, followed by a continuous infusion of 6.25 mg/kg/hr for 67 hr

Acetylcysteine

MONITORING

- AASLD guidelines recommend telemetry monitoring with IV acetylcysteine
  - Rates of dysrhythmias in the literature <5%

ADVERSE EFFECTS

- Dysrhythmias
- Nonallergic Anaphylactoid Reactions (NAARs)
  - ~5 – 10% of patients
  - Can be cutaneous but can also affect the respiratory, CV, and GI systems
  - Caused by a dose-dependent histamine release
    - Associated with faster rates of loading dose administration
  - Treated with histamine$_1$ antagonists (ie. diphenhydramine) and corticosteroids

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Acetylcysteine

- In addition to replacing glutathione stores to prevent hepatoxicity, there is also benefit of NAC seen after initial liver injury occurs
  - In fulminant liver failure, covert tissue hypoxia is thought to lead to multiorgan failure due to concerns with oxygen extraction
  - NAC has shown favorable effects on microcirculatory impairments as well as improvement in hemodynamics through vascular smooth muscle relaxation and restoring nitrate sensitivity in the vasculature
  - *Is this why we see benefit in non-APAP DILI??*

Non-Acetaminophen DILI

- **The AASLD guidelines recommend a 3-day course of acetylcysteine**

- A prospective, randomized, placebo-controlled study in 2009 for non-APAP ALF showed similar survival at 21 days (70% vs. 66%, p=0.28)
  - Transplant-free survival was improved in the aceytlcystine arm (40% vs. 27%, p=0.04)
  - The DILI subgroup showed similar results
    - 21-day survival (79% vs. 63%, p=0.33)
    - Transplant-free survival (58% vs. 27%, p=0.04)

- A more recent systematic review in 2021 showed an improvement in overall survival (OR 1.77 [95% CI 1.3-2.41]) as well as improved transplant-free and posttransplant
  - Hospital LOS was also significantly shorter

Ann Gastroenterol. 2021; 34:235-40.
Gastroenterology. 2009; 137:856-864.
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DILI Drug Information Resources

Table 3. DILI Drug Information Resources

Resource	Information Provided
FDA Guidance for Industry	• Background information on DILI epidemiology and clinical presentation • Guidance for clinical trial investigators on how to evaluate for DILI and identify signals within studies
LiverTox	• Provides information on epidemiology, clinical presentation, diagnosis, and management of drug-induced hepatotoxicity • Includes information on prescription and nonprescription drugs and some herbal or dietary supplements • Likelihood scale summarizes the number of reports of confirmed DILI attributed to a given drug
Drug-Induced Liver Injury Network	• Information about clinical research and ongoing studies • List of DILI-related publications

DILI = drug-induced liver injury.

LiverTox

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LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet].

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Methotrexate

Last Update: February 19, 2020.

OVERVIEW

Introduction

Methotrexate is an antineoplastic and immunosuppressive agent widely used in the therapy of leukemia, lymphoma, solid tumors, psoriasis and rheumatoid arthritis. When given in high intravenous doses, **methotrexate** can cause acute elevations in serum enzymes, and long term **methotrexate** therapy has been associated with frequent but mild elevations in serum liver enzymes and, more importantly, with development of chronic liver injury, progressive fibrosis, cirrhosis and portal hypertension.

Background

Methotrexate (meth" oh trex' ate) is an antifolate and antimetabolite that is used extensively in the therapy of leukemia, lymphoma and several solid organ tumors. It also has potent immunomodulatory activity against psoriasis, inflammatory bowel disease and the inflammatory arthritidies. **Methotrexate** is considered a disease modifying antirheumatic drug (DMARD) and used widely in rheumatoid arthritis and other autoimmune diseases. **Methotrexate** acts by inhibition of folate metabolism, blocking dihydrofolic acid reductase, thereby inhibiting synthesis of purines and pyrimidines and decreasing DNA and RNA synthesis. Recent results suggest that **methotrexate** also leads to increase and release of adenosine, which may mediate its immunosuppressive activity. Folic acid antagonists (aminopterin) were developed in the late 1940s and introduced into clinical medicine shortly thereafter. Aminopterin was later replaced by **methotrexate** because of its better tolerance and lower rate of toxicity. **Methotrexate** was approved for use in cancer in the United States in 1955, for psoriasis in 1972 and rheumatoid arthritis in 1988 and is

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Likelihood Scale
Phenotypes
Severity Grading

Questions?

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