Drug-Induced Liver Injury

Nizar A. Mukhtar, MD
Swedish Organ Transplant & Liver Center

2017 Spring Hepatology Update

April 29, 2017

DILI - Outline

- Definition/Epidemiology
- Pathogenesis
- Risk Factors
- Clinical Features/Diagnosis
- Management
- Common Consultations
- Prevention
- Future Directions

DILI - Clinical Significance

- More than 600 drugs and chemicals associated with DILI
- The leading cause of ALF in the U.S (50%)
- 30% of acute hepatitis cases; 10% of hepatology consults; 1% of admits
- Severe DILI is a life-threatening illness and mild-to-moderate DILI may reduce availability of effective therapies
- A leading cause of drug withdrawal from the marketplace and most common cause for FDA regulatory action
- Represents significant liability risk for physicians and marked financial losses for pharma industry

"Actually, I was hoping for a more inspiring mission statement."

DILI – Definitions and Categories

Liver injury caused by drugs or other chemicals

Mechanism of Hepatotoxicity

Predictable/Intrinsic vs Unpredictable/idiosyncratic

Pattern of Liver Injury

Hepatocellular vs Cholestatic vs Mixed

Clinical Trials

ALT > 3x ULN
vs Alk Phos > 2x ULN
vs Tbili > 2x ULN +
ALT or alk phos elev

DILI - Epidemiology

- Growing list of culprit drugs; majority idiosyncratic
- Incidence: 1 in 10,000 – 1 in 100,000 patients
- Incidence likely higher: detection limited by underreporting and diagnostic challenges
- French study*: 14 per 100,000 persons (8000 cases annually); 12% hospitalized; 6% died (~500 deaths annually)
- Antibiotics (45%) and herbal/dietary supplements (16%) most often implicated
- Hepatotoxicity more frequently recognized after drug enters market (e.g., troglitazone for DM)

*Sgro et al. Hepatology 2002;36:451-5.

Hy's Law

- Derived from the observation of Hy Zimmerman that drug-induced hepatocellular jaundice is a serious clinical entity
- Aminotransferase elevation >3x ULN + bilirubin >2x ULN (+ alternative etiologies of liver disease excluded)
- Hepatocellular injury accompanied by jaundice implies impaired biliary excretion and globally impaired liver function
- Of 116 patients meeting these criteria, 76% required a liver transplant or died (10-50% mortality in subsequent studies)
- Term coined by Robert Temple who defined these criteria for use in clinical trials and FDA approval process

Zimmerman, Hyman. *Hepatotoxicity.* 1999.

Drug Development

- FDA established reporting guidelines for pharmaceutical companies:

ALT 3x ULN

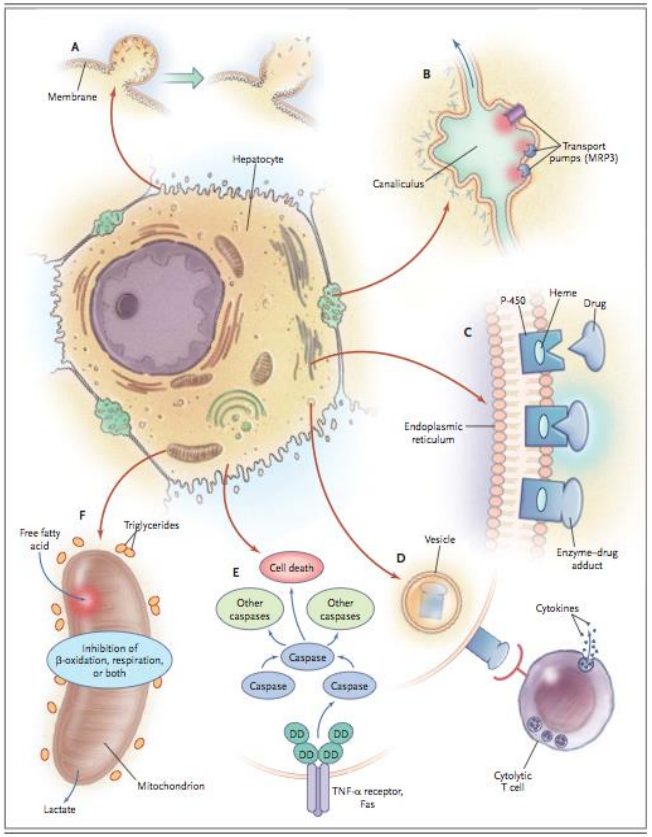
ALT 5x ULN

Hy's Law

ALF

Hy Zimmerman
1916-1999

DILI - Pathogenesis



- **Likely involves "Multihit" process**
- **Intracellular disruption, cell necrosis/lysis apoptosis, inhibition of bile transport, mitochondrial injury, immune response**

Adaptation

Liver Injury

- **At least six mechanisms of liver injury**

Lee WM. N Engl J Med. 2003;349:474-85.

DILI - Risk Factors

Table 1. Factors That Cause Predisposition to Idiosyncratic DILI

Nongenetic factors	Genetic variability
Age	Phase 1 enzymes
	CYP 2C8
Sex	CYP 2C9
	CYP 2C19
Daily dose	CYP 2D6
	CYP 2E1
Metabolism profile	Phase 2 and detoxifying enzymes
	NAT2
Drug interactions	GSTM1 and T1
	MnSOD
Alcohol	UGT2B7
Underlying comorbidities (pre-existing liver disease, HIV infection, diabetes)	Drug transporters
	BSEP (ABCB11)
	MRP2 (ABCC2)
	MDR3 (ABCB4)
	Immunologic
	HLA class antigen
	Cytokines (IL-10, IL-4, tumor necrosis factor-α)
	Mitochondrial DNA mutations (POLG)

GST, glutathione S-transferase.

SWEDISH

Chalasani N and Bjornsson E. Gastroenterology. 2010;138:2246-2259.

DILI – Risk Factors

- Age
  - Adults > children
  - Younger at risk for DILI from valproic acid, Reye syndrome
  - DILI phenotype: hepatocellular → younger
    cholestatic → elderly

- **Sex**
  - Women more susceptible?
  - Women more likely to have: autoimmune DILI
    hepatocellular DILI
    severe DILI

SWEDISH | 10

Lucena et al. Hepatology. 2009;49:2001-2009.

DILI – Risk Factors

- Dose

Table 2. Relationship Between Daily Doses of Oral Medications and Hepatic Adverse Events

Outcome	≤10 mg (n = 54)	10–50 mg (n = 83)	≥50 mg (n = 93)	*P* value
ALT > 3 × ULN, n (%)	10 (19)	22 (27)	29 (31)	.10
Jaundice, n (%)	18 (33)	33 (40)	42 (45)	.16
Liver failure, n (%)	9 (17)	10 (12)	30 (32)	.009
Death, n (%)	6 (11)	9 (11)	26 (28)	.004
Transplant, n (%)	0 (0)	2 (2)	12 (13)	<.001

ULN, upper limit of normal.
Reproduced from Lammert et al.[35]

- Metabolism: Liver metabolism associated with more
  - ALT >3xULN (34% vs 10%; *P* .007)
  - Liver failure (28% vs 9%; *P* .001)
  - Liver transplantation (9% vs 1%; *P* .045)
  - Fatal DILI (23% vs 4%; *P* .0003)

SWEDISH

Lammert et al. Hepatology. 2010;51:615-620.

DILI – Risk Factors

- Drug Interactions:
  - Enzyme induction → reactive metabolites → Liver
    inhibition → increased drug conc → Injury
  - e.g., Rifampin causes increased INH hepatotoxicity

- Alcohol Consumption:
  - Increased risk for DILI from methotrexate, isoniazid, halothane or acetaminophen
  - No significant association with severity or chronicity of DILI

SWEDISH | 12

*Andrade et al. Hepatology. 2006;44:1581-1588.

DILI – Risk Factors

- Underlying Disease States:
  - Chronic liver disease patients are at higher risk for complicated courses and adverse outcomes from DILI
  - Co-morbid illnesses such as HIV, HBV, HCV, diabetes, and fatty liver disease may increase risk, but evidence is weak

- Genetic factors:
  - CYP isoenzymes polymorphisms
  - HLA haplotypes; phase I and II enzyme variants
  - Immune response
  - Hepatobiliary transporters

DILI - Clinical Features

- Characterized by a broad range of clinical patterns → mimics virtually any form of liver disease
- Often asymptomatic or associated with vague symptoms: fatigue, anorexia, nausea, RUQ discomfort, and dark urine
- Labs: liver injury (enzyme elevations) or impaired liver function (elevated Tbili, albuminemia, coagulopathy)
- DILI usually resolves with discontinuation of the drug without significant morbidity or long-term consequences
- Liver tests may improve over time despite continued use of the drug → poorly understood process of adaptation
- Severe DILI can have serious consequences (Hy's Law)

SWEDISH | 14

Reuben A. Hepatology 2004;39(2):574-8.

DILI – Diagnosis

- DILI is a diagnosis of exclusion that relies on clinical judgment

- Six important features to consider to make the diagnosis:
  - Time to onset
  - Time to recovery
  - Clinical pattern: injury pattern and clinical phenotype
  - Exclusion of other causes of liver injury
  - Whether the drug is a known cause of liver injury
  - Response to re-exposure

DILI – Diagnosis

- Time to onset
  - Time from first day of therapy to onset of liver injury
  - Typically 5 days to 3 months
  - Short incubation period → hypersensitivity reactions (Ex: sulfonamide and macrolide antibiotics)
  - Long incubation period → 3 to 12 months (Ex: INH and flutamide), or after years (Ex: amiodarone, minocycline)
  - May be difficult to define
- Time to recovery
  - Time from stopping drug to full recovery from liver injury
  - Typically few days to weeks
  - Sometimes rapid (Ex: acetaminophen, niacin), or prolonged

DILI – Clinical Phenotypes

- Subclinical Liver Enzyme Elevations
- Acute liver injury
  - Acute hepatitis/necrosis
  - Cholestatic injury
  - Mixed pattern
  - Acute steatosis
- Chronic hepatocellular injury
  - Chronic hepatitis
  - Chronic steatosis/ Steatohepatitis
  - Fibrosis and Cirrhosis
- Chronic cholestatic injury
  - Chronic intrahepatic cholestasis
  - Vanishing bile duct syndrome
  - Biliary sclerosis
- Other
  - Vascular disease
  - Granulomatous hepatitis
  - Neoplasia

DILI – Clinical Phenotypes

- Subclinical enzyme elevations
  - Mild ALT or alk phos elevation without jaundice or Sx
  - Spontaneous improvement within weeks
  - Ex.: INH, HAART, MTX, ASA, acetaminophen

- Acute Liver Injury

Hepatocellular (Elevated ALT)	Mixed (Elevated ALP + Elevated ALT)	Cholestatic (Elevated ALP + TBL)
Acarbose	Amitriptyline	Amoxicillin–clavulanic acid
Acetaminophen	Azathioprine	Anabolic steroids
Allopurinol	Captopril	Chlorpromazine
Amiodarone	Carbamazepine	Clopidogrel
Baclofen	Clindamycin	Oral contraceptives
Buproprion	Cyproheptadine	Erythromycins
Fluoxetine	Enalapril	Estrogens
HAART drugs	Flutamide	Irbesartan
Herbals: kava kava and germander	Nitrofurantoin	Mirtazapine
Isoniazid	Phenobarbital	Phenothiazines
Ketoconazole	Phenytoin	Terbinafine
Lisinopril	Sulfonamides	Tricyclics
Losartan	Trazodone	
Methotrexate	Trimethoprim–sulfamethoxazole	
NSAIDs	Verapamil	
Omeprazole		
Paroxetine		
Pyrazinamide		
Rifampin		
Risperidone		
Sertraline		
Statins		
Tetracyclines		
Trazodone		
Trovafloxacin		
Valproic acid		

SWEDISH

*Navarro, V and Senior, J. N Engl J Med. 2006. 354;7:731-9.

DILI – Clinical Phenotypes

- Acute hepatitis
  - Resembles acute viral hepatitis; marked ALT elevation
  - Sx: prodromal period of fatigue, nausea, anorexia → abdominal discomfort, dark urine and jaundice
  - Liver bx: resembles viral hepatitis
  - Ex: INH, ketoconazole, flutamide
- Acute hepatic necrosis
  - Resembles acute ischemic or toxic injury
  - Rapid onset of injury and rapid resolution
  - Hepatic dysfunction occurs early, preceding jaundice
  - Sx: nausea, vomiting, abd pain →AMS, somnolence, coma
  - Liver bx: centrolobular necrosis
  - Ex: acetaminophen, ASA, amiodarone

SWEDISH

*

DILI – Clinical Phenotypes

- Pure or bland cholestasis
  - Cholestasis; Alk phos and GGT elevation
  - Sx: Itching, jaundice, dark urine, but otherwise well
  - Liver bx: intrahepatic cholestasis
  - Ex: anabolic steroids, estrogen, azathioprine, mercaptopurine
- Cholestatic and mixed hepatitis
  - Most common phenotype; elevated alk phos + ALT elev
  - Arises 2 to 12 weeks after starting medication; can be mild and short lived or severe and prolonged
  - Sx: fatigue, nausea, dark urine, itching, jaundice
  - Liver bx: intrahepatic cholestasis, inflammation, necrosis
  - Ex: amoxicillin/clavuanate, sulfonylureas, macrolide abx, phenytoin

*

DILI – Clinical Phenotypes

- Acute steatosis
  - Rare and often severe form of DILI
  - Caused by inhibition of mitochondrial function and alterations of fat metabolism
  - Sx: nonspecific prodromal sx → acute liver failure (coagulopathy, hyperammonemia and lactic acidosis)
  - Liver bx: microvesicular fat → macrovesicular fat and liver cell injury
  - Ex.: antiviral drugs, tetracycline, linezolid

DILI – Clinical Phenotypes

- Chronic hepatitis
  - Liver injury >6 months
  - 5-10% of cases of DILI will not resolve within a few weeks to months
  - May be due to slow resolution of severe acute injury vs triggering of chronic liver disease such as AIH or PBC
  - Ex: INH, nitrofurantoin, statins, methyldopa
- Autoimmune hepatitis
  - Hepatocellular injury pattern accompanied by presence of high titers of ANA, ASMA and IgG
  - Long latency periods (months or years); symptoms and lab abnormalities resolve once medication is stopped
  - Ex: methyldopa, nitrofurantoin, minocycline, hydralazine, fenofibrate

DILI – Clinical Phenotypes

- Chronic steatosis/ Steatohepatitis
  - Uncommon and often difficult to distinguish from spontaneous NAFLD
  - Insidious onset without signs or symptoms of liver disease; arises months to years after initiation of therapy
  - Mild AST/ALT elevations; imaging suggestive of steatosis
  - Liver bx: steatosis +/- lobular inflammation and ballooning degeneration
  - Ex: chemotherapeutic agents (5-fluorouracil, cisplatin, tamoxifen), griseofulvin, methotrexate
- Cirrhosis
  - DILI is a rare cause of cirrhosis; likely due to unrecognized liver injury
  - Ex: methyldopa, amiodarone, methotrexate, valproate

SWEDISH

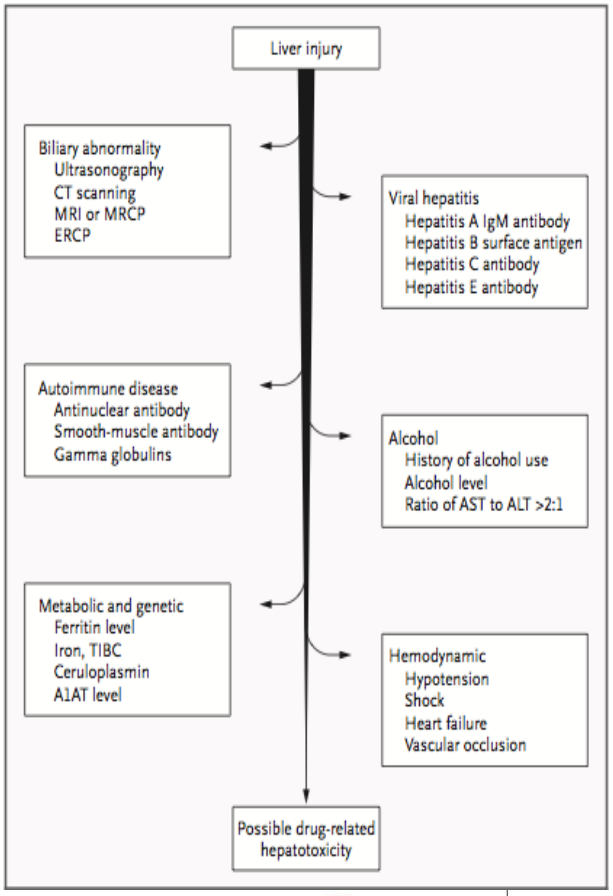
DILI – Clinical Phenotypes

- Vanishing bile duct syndrome
  - Acute cholestatic liver injury → bile duct injury and ductopenia
  - Transient or progresses to biliary cirrhosis, hepatic failure or death
  - Ex: augmentin, NSAIDs, sulfonamides
- Sinusoidal obstruction syndrome (busulfan, phytotoxins)
  - Endothelial cell injury → veno-occlusive disease
  - Rare; can lead to ALF
  - Ex: busulfan, phytotoxins
- Nodular regenerative hyperplasia
  - Endothelial cell injury → regenerative nodules; no fibrosis
  - Can cause portal HTN and liver dysfunction
  - Ex: azathioprine, oxaliplatin
- Liver tumors and cancer
  - Chronic hepatic injury or growth stimulation → adenoma, HCC
  - Ex: estrogen, androgenic steroids

DILI – Diagnosis

Exclusion of Other Diagnoses

- Perform careful history:
  - Risk factors for viral hepatitis
  - Alcohol use
  - Weight gain
  - Hx of autoimmune disease
  - Hx of cardiac failure, shock
  - Hx of drug use, including Rx and non-Rx drugs and herbals
- Labs/studies:
  - Viral hepatitis workup
  - AIH workup
  - Imaging for evaluation of biliary system, to r/o vascular insult
  - Assess for features of fatty liver disease



SWEDISH

Navarro, V and Senior, J. N Engl J Med. 2006. 354;7:731-9.

DILI – Diagnosis

- Response to re-exposure
  - Reappearance of liver injury following re-exposure offers convincing evidence in support of DILI
  - Re-challenge is usually not advisable; can lead to rapid recurrence of DILI or greater severity of injury
  - Re-challenge may be warranted if medication is considered life-sustaining and initial injury was mild, rapidly reversed, and/or atypical for the agent

- Known association with DILI (google: “NIH Livertox”)

DILI – Diagnosis

- Various causality instruments have been developed with the goal of enhancing the reliability of causality assessment
- One of the most popular is the Roussel-Uclaf Causality Assessment Method (RUCAM)
  - numerical weighting of key features in 7 domains: temporal relationship (latency and recovery), risk factors, concomitant drug use, exclusion of other etiology, prior information about liver injury and the drug, and the response to re-challenge
  - Now available as an online calculator that generates an overall numerical score intended to reflect the probability of causality
- The gold standard for diagnosis of DILI remains expert opinion

SWEDISH | 27

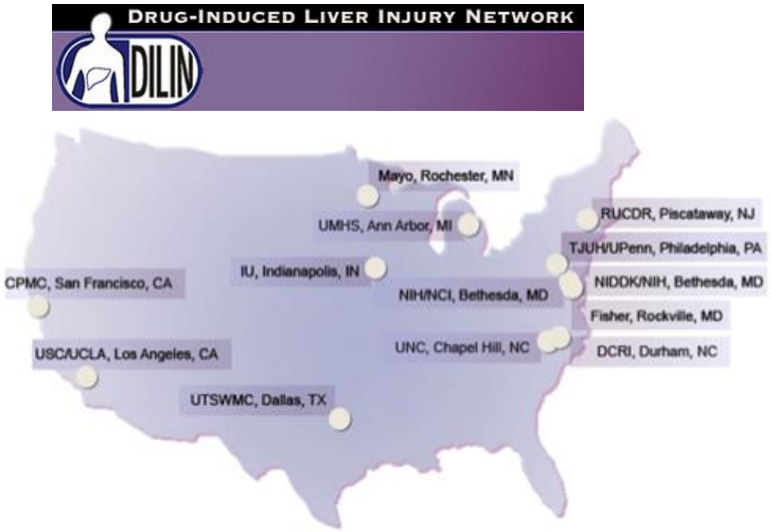
Benichou C. J Hepatol. 1990;11(2):272-6.

DILI - Management

- Mainstay of therapy is drug discontinuation
- Avoid re-exposure to the implicated drug
- Specific therapies available:
  - NAC for acetaminophen
  - L-carnitine for valproate
  - Cholestyramine for leflunomide
  - Ursodeoxycholic acid for cholestatic DILI
  - Steroids for hypersensitivity reactions
- Patients with severe DILI should be referred to a liver transplant center (Remember “Hy’s Law”)
- Report cases of DILI to “MedWatch”

DILI – Future Directions

- "Holy Grail": developing robust and accurate tests to detect the specific genetic or environmental traits that increase risk for DILI
- Pharmacogenomics: identificiation of gene polymorphisms or RNA-expression profiles before a patient uses a drug



Thanks for your attention!

SWEDISH

DILI – Case 1

A 66 year old Hispanic man was in good health except for hypertension for which he had been taking enalapril for more than a decade. Because of a positive purified protein derivative (PPD) tuberculin skin test, he was started on a 6 month course of isoniazid [300 mg daily with pyridoxine]. Laboratory tests taken before starting therapy were normal. He remained asymptomatic until onset of nausea and indigestion during week 6 of therapy. He denied fever or rash. He had not taken any over-the-counter medications, herbals or acetaminophen. He had a history of heavy drinking but had stopped 4 years previously. Physical examination showed jaundice but no signs of chronic liver disease. Laboratory tests showed a total bilirubin of 6.3 mg/dL, ALT 2326, and alk phos 114. Tests for hepatitis A, B and C were negative. Serum ANA was strongly positive (1:20,480), but smooth muscle antibody was negative, and immunoglobulin levels were normal. Liver imaging showed no evidence of biliary obstruction. Isoniazid was stopped promptly and he began to improve within days. Enalapril was restarted but therapy for latent tuberculosis was not pursued. One month later, he was asymptomatic and liver tests had returned to baseline.

DILI – Isoniazid

- Mainstay of TB therapy; inhibits mycobacterial cell wall synthesis
- One of the most common causes of serious, idiosyncratic liver injury in the United States; 14% of transplants for DILI
  - Transient aminotransferase elevations in 10 to 20%
  - Aminotransferase elevation > 5x ULN in 3-5%
- Causes two syndromes of hepatotoxicity:
  Mild INH hepatotoxicity and INH hepatitis
- Mild INH hepatotoxicity
  - Mildly elevated aminotransferases (<100 IU/L)
  - Liver bx: minor, focal hepatocellular damage
  - Adults > children; men = women
  - Excellent prognosis; overall mortality rate of 0.001%
  - Management: INH can be continued with careful monitoring

DILI – Isoniazid

- INH Hepatitis:
  - Less common, but more serious liver injury syndrome
  - Features indistinguishable from viral hepatitis
  - Cumulative rate in combination 0.6%; monotherapy 0.1-0.3%
  - Risk increases with age:

    20 to 34 years — 0.3 percent

    35 to 49 years — 1.2 percent

    50 to 64 years — 2.3 percent

    Over age 65 years — 4.6 percent
  - Additional risk factors: regular alcohol use, concurrent liver disease including viral hepatitis, cirrhosis, HIV, concurrent rifampin or pyrazinamide, female gender, AA or Asian race, genetic factors (slow acetylator status, cytochrome polymorphisms)

SWEDISH

Kopanoff et al. Am Rev Respir Dis. 1978; 117:991.

DILI – Isoniazid

- INH Hepatitis:
  - occurs within 2-3 months
  - Sx: fatigue, malaise, anorexia, nausea, vomiting, flu-like sx, RUQ pain → occur days to weeks prior to onset of jaundice
  - Labs: elevated aminotransferases with variable elevations of alk phos, bilirubin, and INR; autoantibodies can also be detected
  - May be self-limited, but may progress to severe liver failure with massive hepatocellular necrosis in up to 10% of cases
  - Liver bx: ranges from focal to diffuse necrosis to multilobular, bridging fibrosis and massive necrosis
  - Mechanism of hepatotoxicity:
    - Accumulation of toxic intermediate of metabolism
    - Rates of injury higher among slow acetylators of INH metabolites; CYP 2E1 abnormalities also implicated
    - Rapid recurrence of injury with re-challenge suggests a component of immune-mediated injury

SWEDISH

*Kopanoff et al. Am Rev Respir Dis. 1978; 117:991.

DILI – Management of INH Hepatitis

- Normal baseline liver function: discontinue INH if AST >5x ULN if asymptomatic and >3x ULN if symptomatic
- Abnormal baseline liver function (aminotransferases >3x ULN at baseline): discontinue if increased 2-3 x above baseline or if jaundice, AMS
- Rule-out viral hepatitis; screen for alcohol use, other hepatotoxins
- Weigh risk vs benefits: If AST decreases to <2x ULN, injury was mild, and INH considered essential, may reinitiate with lower dosing and close monitoring of LFTs (up to 80% of persons tolerate further treatment)
- Patients should receive detailed information about signs and symptoms of hepatitis and instructed to stop INH immediately upon onset of symptoms
- Baseline and monthly clinical and biochemical monitoring indicated for patients with preexisting liver disease or age >50

DILI – Case 1 INH Hepatitis

A 66 year old Hispanic man developed nausea followed by dark urine and jaundice 6 weeks after starting isoniazid for latent tuberculosis.

Key Points:

•An acute viral hepatitis-like syndrome arising 6 weeks after starting therapy is typical of isoniazid hepatitis

•Symptoms and signs may worsen for a few days after stopping isoniazid, but then usually improve rapidly

•Pattern of injury is hepatocellular; ANA reactivity can be seen, but with absence of other features that would suggest autoimmune hepatitis

•Age > 35 years is the single major risk factor for isoniazid hepatitis and treatment of latent TB should be done with caution; alcohol use may also be a risk factor

•Patients should be informed of the risk of liver injury and warned of the signs and symptoms of liver injury

•Routine biochemical monitoring is prudent if there is pre-existing liver disease or perceived increased risk for liver injury. The mortality rate of isoniazid hepatitis with jaundice is at least 10%

DILI – Case 2

A 51 year old man with active rheumatoid arthritis was treated with methotrexate at an initial dose of 7.5 mg weekly, increasing to 15 mg weekly with daily folic acid and low doses of prednisone (5 mg daily) for four years. He had significant improvement and continued on both drugs for a total of 3.5 years. During the first year of therapy, he had minor and transient serum ALT elevations, but none were more than 3 times the upper limit of normal (ULN). Recently, his platelet count began to fall, and it remained low despite a decrease in the dose of methotrexate to 5 mg weekly. An abdominal ultrasound showed mild hepatomegaly, splenomegaly with increased echogenicity of the liver suggestive of fatty infiltration. He denied alcohol use and any history or risk factors for liver disease. Tests for hepatitis A, B and C were negative as were routine autoantibody tests. Liver tests including serum aminotransferase levels, alkaline phosphatase, bilirubin and albumin were normal and prothrombin time was not increased. A percutaneous liver biopsy showed marked fibrosis, early cirrhosis, mild steatosis and nuclear variability without inflammation or obvious necrosis.

DILI – Methotrexate

- Antineoplastic and immunosuppressive agent widely used in the therapy of leukemia, lymphoma, solid tumors, psoriasis and rheumatoid arthritis
- Acts by inhibition of folate metabolism, blocking dihydrofolic acid reductase, thereby inhibiting synthesis of purines and pyrimidines and decreasing DNA and RNA synthesis
- 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, as well as development of chronic liver injury, progressive fibrosis, cirrhosis and portal hypertension.
- High dose IV methotrexate → serum ALT levels can rise to 10 to 20 times the upper limit of normal (ULN) within 12 to 48 hours, but levels then fall rapidly to normal with only rare instances of jaundice or symptoms of liver injury
- With long-term, low-to-moderate dose methotrexate therapy, elevations in serum ALT or AST values occur in 15 to 50% of patients but are usually mild and self-limiting

*

DILI – Methotrexate

- Induces a variety of histologic changes including steatosis, stellate cell hypertrophy, anisonucleosis (nuclei of varying sizes), and hepatic fibrosis
- Mechanism of liver injury thought to be direct toxicity through inhibition of RNA and DNA synthesis in the liver resulting in cellular arrest
- 30% of patients develop mild-to-moderate histological abnormalities (fat, cellular unrest, mild inflammation, nuclear atypia) and 2-20% of patients develop some degree of hepatic fibrosis
- Hepatic fibrosis and cirrhosis typically arise in 2-10 years; often associated with other factors for fatty liver disease (alcohol use, obesity, diabetes), use of other potentially hepatotoxic agents
- Prior use of high doses and daily methotrexate dosing was associated with development of hepatic fibrosis and rates of cirrhosis of greater than 20% after 5 to 10 years of treatment; with more modern dose regimens with folate supplementation, fibrosis and clinically apparent liver disease are rare

DILI – Methotrexate

- Elevations of AST into the abnormal range are predictive of abnormal or worsening histological grade on liver biopsy
- Minimal deterioration was noted on serial liver biopsies when the MTX dose was adjusted for abnormalities in serum AST and albumin
- Noninvasive markers of hepatic fibrosis, such as serial platelet counts, serum procollagen III aminoterminal peptide (PIIIP), serum bile acids, hepatic ultrasound, advanced imaging techniques and transient elastography may help detect fibrosis in patients on long-term methotrexate
- Low dose, long-term methotrexate therapy has also been implicated in rare instances of reactivation of hepatitis B; all patients must be screened with HBsAg before starting tx
- There does not appear to be cross-reactivity in hepatic side effects between methotrexate and other disease modifying antirheumatic drugs (DMARDs) such as leflunomide, hydroxychloroquine, azathioprine, etanercept, or infliximab

DILI – Methotrexate

- Initiation of therapy:
  - careful history (alcohol use, viral hepatitis risk factors, family hx of liver disease) and physical examination
  - Baseline liver tests, viral hepatitis serology
  - Liver biopsy for patients with a history of excessive alcohol consumption, persistently abnormal AST or ALT values, or chronic hepatitis B or C infection
  - Patients must be counseled about strict avoidance of alcohol and this conversation is documented on the clinic chart

- Monitoring based on RA guidelines:
  - Monitoring of liver tests every 4-8 weeks → every 8-12 weeks after 3 months on stable dose → every 12 weeks after 6 months
  - Liver biopsy should be performed if 6 of 12 tests are abnormal in any year (or 5 of 9 if testing is performed at six-week instead of monthly intervals)

Saag et al. Arthritis Rheum 2008; 59:762.

DILI – Methotrexate

A 51 year old man with rheumatoid arthritis developed thrombocytopenia after 7.5 years of methotrexate therapy and was found to have cirrhosis.

Key Points:

- Significant hepatic fibrosis and portal hypertension can arise during methotrexate therapy without accompanying symptoms or significant elevations in serum aminotransferase levels; typically arises after 2 to 10 years of therapy
- A possible non-invasive marker for the development of significant fibrosis in this case was the decrease in platelet count
- Risk factors for developing methotrexate-related fibrosis include excessive alcohol use, underlying viral hepatitis
- Noninvasive tests such as PIIIP, hepatic imaging or elastography may have been helpful for identification of fibrosis in this patient who does not meet criteria for surveillance liver biopsies
- When cirrhosis develops, it is often non-progressive in nature despite continuation of methotrexate; however, therapy should be discontinued if advanced fibrosis or cirrhosis are detected

DILI – Case 3

A 28 year old woman with HIV/AIDS developed serum ALT elevation to 133 U/L five weeks after starting an antiretroviral regimen of ritonavir, stavudine and lamivudine. She did not drink alcohol and tests for hepatitis A, B and C were negative. Despite the ALT elevations, she was asymptomatic and the abnormalities rapidly resolved with stopping antiretroviral therapy. Five weeks after restarting this regimen, however, she developed abdominal pain, nausea and jaundice. She was found to have weight loss, an enlarged and tender liver, and ascites. Serum ALT was 327 U/L, bilirubin 18.0 mg/dL and prothrombin index was 22%. She developed lactic acidosis and encephalopathy. A liver biopsy showed microvesicular steatosis, cholestasis and fibrosis with minimal inflammation. The antiretroviral agents were stopped, and she improved slowly; liver tests being normal 8 weeks later. Lamivudine and stavudine without ritonavir were re-introduced and she remained without evidence of recurrence of liver injury over the next 9 months.

DILI – HAART

- HAART has resulted in prolonged life expectancy for HIV patients, but an increase in mortality from liver disease has been reported
- ARV therapy associated with fatty liver, steatohepatitis, liver failure, nonspecific hepatitis, advanced fibrosis, ESLD and nodular regenerative hyperplasia
- Documentation of hepatotoxicity difficult owing to concomitant use of multiple hepatotoxic drugs and underyling risk factors for liver disease among patients with HIV, including viral hepatitis
- All antiretroviral agents can cause hepatotoxicity
  - NRTIs: stavudine and didanosine
  - NNRTIs: nevirapine, efavirenz
  - PIs: ritonavir
- Time of onset usually months to years after initiation; 24-48 mo
- Fluctuating LFTs often noted and do not necessarily correlate with histopathologic findings

SWEDISH | 44

Bader. Am J Gastroenterol. 2010;105:978-980.

DILI – HAART

- NRTIs:
  - Resemble naturally occurring nucleosides and act by competitively inhibiting viral polyperase and terminating DNA synthesis
  - Stavudine and didanosine most likely to cause hepatotoxicity
  - Cause dose-dependent hepatotoxicity; rarely idiosyncratic hepatotoxicity
  - Mechanism: cause hepatic mitochondrial injury by blocking mitochondrial DNA synthesis → lactic acidosis, microvesicular steatosis and hepatic synthetic failure
  - Clinical manifestations: hepatocellular injury pattern with mild aminotransferase elevations; jaundice arises late

DILI – HAART

- NNRTIs:
  - Inhibit HIV polymerase
  - Nevirapine most common cause of serious DILI among all antiretroviral agents
  - Often see cholestatic features, but initially hepatocellular injury pattern
  - Mechanism: immunoallergic; supported by increased rates among women and patients with higher CD4 T cell counts; production of toxic intermediates also implicated
  - Clinical manifestations: usually transient ALT elevation; ALT elevation >5x ULN in 4-20%; symptomatic liver injury in 1-5% with potential to cause severe or fatal liver injury; abdominal pain, fatigue, fever, rash, jaundice often seen; can also present with features of immunoallergic hepatitis (rash, fever, eosinophilia)

DILI – HAART

- PIs:
  - Inhibit HIV-1 protease activity needed for viral replication
  - Ritonavir most frequent cause of PI-related hepatotoxicity
  - Risk of severe hepatotoxicity is 5-fold higher among patients taking ritonavir
  - Time to onset 1 to 8 weeks; variable patterns of liver injury, ranging from hepatocellular to cholestatic
  - Mechanism: unknown; metabolized by and inhibits CYP 3A4, which may lead to production of toxic intermediates; may cause flares of HCV or HBV in co-infected patients due to immune reconstitution
  - Clinical manifestations: usually transient and asymptomatic ALT elevation when used at low “booster” doses; moderate-to-severe elevations in aminotransferase levels >5x ULN in 15% treated with full doses; more common in HIV-HCV co-infection; rarely leads to clinically apparent ALI; re-challenge leads to recurrent liver injury

SWEDISH

Sulkowski et al. JAMA. 2000. 283;1:74-80.

DILI – HAART

- Histopathologic findings include portal and lobular inflammation, micro- and macrosteatosis, NASH, mild-to-severe fibrosis, cirrhosis
- 5/6 patients with ARV-induced hepatoxicity had liver biopsy findings consistent with NASH (3 PI, 2 NRTIs, and 1 NNRTIs)

Case	Portal inflammation	Lobular inflammation	Steatosis	Fibrosis	Other
(d) Liver biopsy results					
1	Mild	Focal area of lobular inflammation with apoptosis	50% macrosteatosis and microsteatosis	Pericellular fibrosis	
2	None	Focal lobular apoptosis of more than 4 foci per 10X field (cluster of neutrophils)	10–15% macrosteatosis	None	
3	None	Mild lobular inflammation with apoptosis	5% microsteatosis and macrosteatosis	None	Minimal lobular cholestasis
4	Mild with neutrophils, lymphocytes and histiocytes	Scattered hepatocellular drop out with neutrophils and lymphocytes	15% macro steatosis and micro steatosis	None	
5	Mild	Focal area of lobular inflammation with apoptosis	5% macrosteatosis	Mild pericellular fibrosis	Mild, piecemeal necrosis
6	None	None	None	None	Focal hepatocellular drop out with sinusoidal dilation, hemorrhage and trabecular atrophy

SWEDISH

Akhtar et al. Eur J Gastroenterol Hepatol. 2008. 20(12):1194-204.

DILI – HAART

A 28 year old woman with HIV/AIDS developed symptomatic liver injury with HAART therapy including stavudine and ritonavir.

Key Points:

- Hepatic failure, lactic acidosis and hepatic microvesicular steatosis are typical of the mitochondrial liver injury that occurs with the stavudine (NRTI) therapy
- Often difficult to attribute the injury to a specific agent and the pathogenesis of HAART-related hepatotoxicity may relate to drug-drug interactions among the antiretroviral agents
- Liver injury tends to regress when therapy is held; re-challenge with ritonavir is not recommended as it can lead to severe liver injury
- ALT levels often do not correlate with severity of liver injury, and a lower threshold for liver biopsy in HIV patients is warranted

DILI – Case 4

A 47 year old man with familial hypercholesterolemia is referred to your office. He recently suffered a myocardial infarction, and his and his low-density lipoprotein (LDL) was 450 mg/dl (11.6 IU). The only therapy that lowered this patient's LDL below 200 mg/dl (5.18 IU) was statin treatment. Yet the cardiologist was adamant that the statin be stopped for fear of hepatotoxicity because the ALT was minimally out of range at 61 IU/l.

DILI – Statins

- The most potent, best tolerated and most widely used cholesterol lowering agents
- Inhibit HMG-CoA reductase, the rate-limiting step in cholesterol synthesis → decrease in total and LDL cholesterol
- Among most commonly prescribed drug in developed countries: 10-20% of adults
- Statins prevent about 33% of major cardiovascular events when compared to placebo; NNT is 3
- Cause ALT elevation in up 10% of patients without liver disease; >3x ULN in 1% of patients
- Are statins hepatotoxic?
  - 6500 subjects randomized to lovastatin vs. placebo: no difference
  - 19,000 subjects randomized to pravastatin vs placebo: no difference
  - 20,000 subjects randomized to simvastatin vs. placebo: no hepatitis
  - Among 10,000 subjects receiving rosuvastatin: no hepatitis

SWEDISH | 51

Bader. Am J Gastroenterol. 2010;105:978-980.

DILI – Statins

- Statins may confer benefit in certain liver diseases:
  - NASH → histological and liver test improvements
  - HCV → decreased ALT levels and increased SVR rates
- Despite a lack of supporting evidence, package inserts continue to contain warnings regarding the potential for hepatotoxicity
- Estimated to cost $3 billion a year, routine ALT monitoring is not recommended; 1-10% of patients taking statins may be denied ongoing benefit

Table 1. Summary of changes in liver-test recommendations on US Food and Drug Administration package inserts

Statin	Older package insert	Current package insert
Lovastatin	(2001) LFTs before and at 6 and 12 weeks after start or elevation of dose and semiannually	(2009) LFTs before initiation of therapy in those with a history of liver disease or when otherwise clinically indicated
Simvastatin	(2000) LFTs before treatment and semiannually for first year or until 1 year after last elevation	(2008) LFTs before treatment and then when clinically indicated
Pravastatin	(2001) LFTs before initiation of therapy, before elevation of dose, and when otherwise clinically indicated	(2007) LFTs before initiation of therapy and when otherwise clinically indicated
Fluvastatin	(2001) LFTs before and at 12 weeks after the initiation of therapy and any elevation of dose	(2009) No change
Atorvastatin	(2001) LFTs before initiation of therapy, after elevation of dose, and semiannually	(2009) No change
Rosuvastatin	(2003) LFTs before and at 12 weeks after the initiation of therapy and any elevation of dose and periodically (e.g., semiannually) thereafter	(2009) No change

SWEDISH

Bader. Am J Gastroenterol. 2010;105:978-980.

DILI – Statins

- Rare cases of statin-induced DILI have been reported; rate of 1/100,000 to 1/1,000,000; number needed to harm of 1 million
- Until recently, only 40 cases of statin-induced DILI were reported in the literature; recent Swedish study* reported an additional 73 cases occurring over a period of 22 years
- Of seven statins on the market, DILI is most often seen with atorvastatin and simvastatin (most commonly prescribed)
- Significant statin-induced DILI is idiosyncratic, often occurs within 3-4 months and can be associated with hepatocellular (simvastatin) > cholestatic (atorvastatin) > or mixed injury pattern
- Mechanism of hepatotoxicity is unknown; mild self-limited ALT elevations likely due to toxic intermediate of drug metabolism; severe injury may be immune-mediated or due to failure of adaptation

DILI – Statins

- Outcome
  - Liver injury is usually self-limited and recovery is complete within 1 to 4 months
  - Some reports of triggering autoimmune chronic hepatitis
  - Rare instances of acute liver failure (0.2 cases per million); difficult to distinguish from idiopathic ALF
- Management
  - mild ALT elevations are self-limited and do not require dose modification
  - Should be discontinued if ALT > 10xULN or persists > 5xULN
  - Universal monitoring of ALT not recommended; measure liver tests in patients with newly developed symptoms (nausea, lethargy, abdominal pain)
  - Recurrence of injury with rechallenge has been reported and should be avoided
  - Switching to another statin appears safe, but monitoring required

DILI – Statins

A 47 year old man with CAD s/p MI referred for evaluation of ALT 2x ULN in the setting of statin use.

Key Points:

- Statins frequently cause mild ALT elevations, but this does not necessarily indicate significant liver injury
- Rare idiosyncratic DILI due to statins has been reported and can present with a hepatocellular > cholestatic > mixed injury pattern
- Routine ALT measurement is not indicated; patients who are symptomatic should undergo liver testing
- Statins should be held in patients with ALT >10x ULN or persistent elevations >5x ULN
- Re-challenge is not recommended
- There is no clear evidence of a class effect; a switch to an alternative statin may be attempted with close monitoring

*

DILI – Prevention

- Patient Education
  - Warn patients about sx of severe liver injury and instruct to discontinue and contact their MD/provider
  - Counsel regarding interaction with drugs and alcohol
  - Counsel to avoid re-exposure; document in chart
- Liver Test Screening
  - Periodic screening recommended for many drugs
  - Unclear benefit; marked elevations cannot be overlooked
- Legislation
  - Restriction or elimination of potentially toxic drugs from the marketplace
  - e.g., use of combined acetaminophen-opiate drugs and acetaminophen-containing cold/flu medications