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Transaminase Elevations in the Treatment of Heart Failure

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Drug-Induced Liver Injury Conference XV

Wednesday, March 18, 2015



Disclosure Slide

I have nothing to disclose, and the opinions expressed here are my own.



Objectives

- **To review the effects of acute and chronic heart failure on acute and chronic liver injury, respectively.**
- **To discuss the challenges in assessing the potential for a drug product to cause drug-induced liver injury in the setting of heart failure.**



Hepato-Cardiac Diseases

- **Heart diseases affecting the liver**
- **Liver diseases affecting the heart**
- **Conditions affecting the heart and the liver at the same time**



Heart Failure

Acute heart failure



Acute ischemic hepatitis

(acute liver injury)

Chronic heart failure



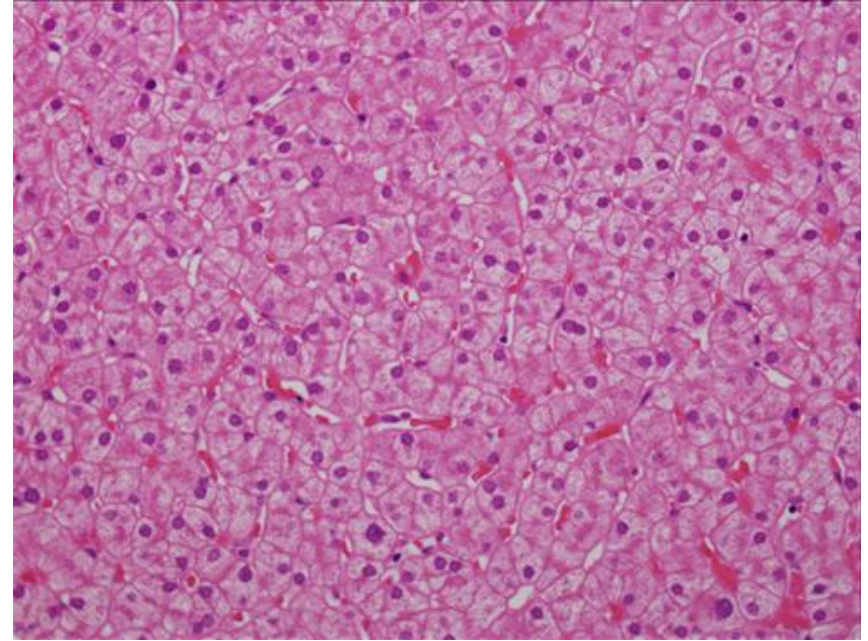
Chronic congestive hepatopathy

(“nutmeg liver”)

Goal is to treat the underlying heart disease



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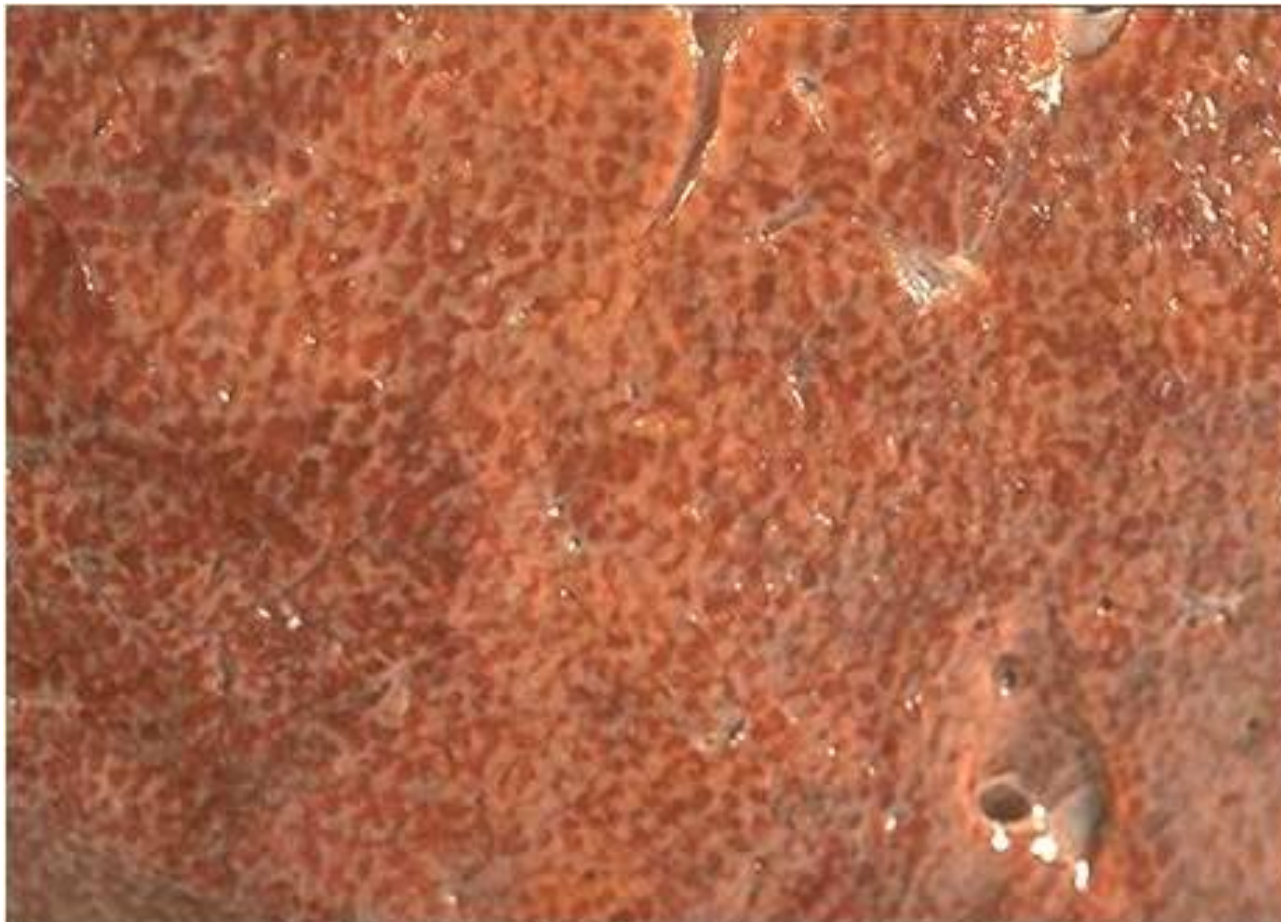


Nutmeg

Liver



Nutmeg Liver





Liver Injury

- **Acute (ischemic hepatitis)**
- **Chronic**



Acute Liver Injury

- **Occurs when hepatic blood flow is decreased and the liver can no longer protect itself from hypoxic damage → get hepatocellular injury**

Acute Liver Injury

- **Hypotension**
- **Hypoxemia**
- **Increased metabolic demand**



Hypotension

- **Acute myocardial infarction (AMI)**
- **Heart failure (HF)**
 - **Accounts for most cases of acute liver injury**
- **Pulmonary embolus**
- **Sustained arrhythmia (afib/flutter with RVR)**



Hypoxemia

- **Respiratory failure**
- **Obstructive sleep apnea**



Increased Metabolic Demand

- **Toxic/Septic Shock**



Acute Liver Injury: Symptoms

- **Asymptomatic; or**
- **Nonspecific Symptoms**
 - Nausea/vomiting
 - Anorexia
 - Malaise
 - Right-upper quadrant pain
 - Jaundice
 - Oliguria
 - Flapping tremors



Acute Liver Injury: Laboratory Evaluation

- **Sharp increases in ALT, AST, TB, ALP, LDH, PT, occasionally accompanied by renal impairment**
 - **Peak 1-3 days after the onset of the insult**
 - **Normalize within 5 to 10 days**
- **ALT/LDH ratio < 1.5**

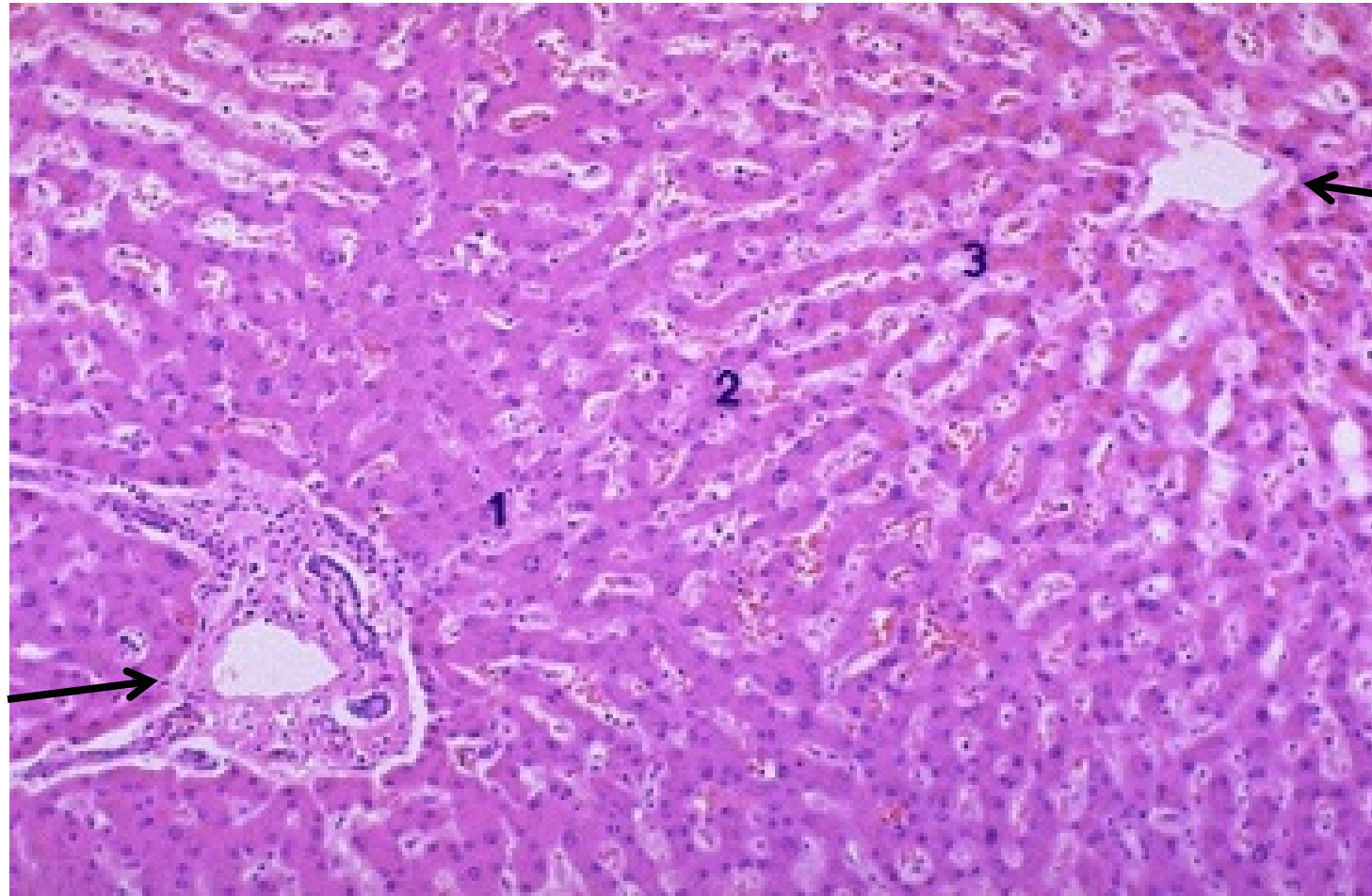


Acute Liver Injury: Pathophysiology

- **Characterized by centrilobular necrosis of zone 3 hepatocytes**



Histology



central vein

portal triad



Liver Injury

- **Acute (ischemic hepatitis)**
- **Chronic**



Chronic Heart Failure and Hepatic Dysfunction

- **Ischemic/nonischemic cardiomyopathies**
- **Pulmonary arterial hypertension**
- **Valvular heart disease**
 - **Mitral stenosis**
 - **Tricuspid regurgitation**
- **Constrictive pericarditis**
- **Fontan Procedure (postoperative consequences)**



Chronic Liver Injury: Symptoms

- **Mild, dull right upper quadrant pain**
- **Hepatomegaly**
- **Peripheral Edema**
- **Ascites**
- **Jaundice (uncommon)**



Chronic Liver Injury: Laboratory Evaluation

- **AST, ALT, LDH, GGT, and ALP 2-3x ULN**
- **Increased TB (direct and indirect)**
 - Rarely exceeds 3 mg/dL
- **Hypoalbuminemia**



Chronic Liver Injury: Pathophysiology

- **Hepatocyte atrophy**
- **Perisinusoidal edema**
- **Enhanced hepatic lymph formation**
- **Thrombosis within sinusoids, hepatic venules, and portal tracts (from stagnant flow)**
- **Zone 3 – alternating pattern of hemorrhage and necrosis**
- **Zones 1 and 2 – normal or slightly steatotic areas**



	ACUTE LIVER INJURY	CHRONIC LIVER INJURY
Etiology	Acute heart failure	Chronic heart failure
Laboratory Data		
TB	Marked Increase (15-20 mg/dL)	Mild Increase (rarely > 3 mg/dL)
ALT and AST	> 10x	Normal/Mild Increase (2-3 x ULN)
LDH	Marked Increase	Normal/Mild Increase (2-3 x ULN)
ALP	Increased	Normal/Mild Elevation (2-3 x ULN)
Prothrombin time	Normal or Prolonged	Prolonged
Albumin	Normal	Decreased
Prognosis	Benign and usually self-limited	Slowly progressive course



Severe Drug-Induced Liver Injury

- **Hepatocellular injury**
- **Aminotransferase (AT) elevations (ALT, AST) > 3x ULN and TB > 2x ULN**
- **Normal ALP**
- **No other reasons to explain the combination of increased AT and TB (e.g., hepatitis, preexisting or acute liver disease, another drug capable of causing the observed injury, PK interactions)**
- **May not be dose-related or evident nonclinically (exception: acetaminophen)**
- **Idiosyncratic hepatotoxicity (e.g., bromfenac, troglitazone, ximelagatran)**



Summary

- **There is a mutual relationship between the heart and the liver.**
- **Acute heart failure can lead to acute liver injury (acute ischemic hepatitis).**
- **Chronic heart failure can lead to chronic liver injury (chronic congestive hepatopathy).**
- **Treat the underlying heart failure.**
- **In the setting of heart failure, it can be challenging to assess whether a drug product can cause drug-induced liver injury.**



Back-Up Slides



Acute Liver Injury

- **Hypotension**
 - Acute myocardial infarction (AMI)
 - Heart Failure (HF)
 - Accounts for most cases of acute liver injury
 - Pulmonary embolus
 - Sustained arrhythmia (afib/flutter with RVR)
- **Hypoxemia**
 - Respiratory failure
 - Obstructive sleep apnea
- **Increased metabolic demand**
 - Toxic/septic shock