

# Liver 102: Injury and Healing

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# Liver 102 Outline

- Biochemical patterns of hepatic injury
- Inflammation/fibrosis scoring
- Regenerative/healing processes

# Term Clarification

- Liver enzymes
  - Refers to AST and ALT, may also refer to GGT
- Liver chemistries
  - Often means chemistry panel which includes bilirubin, alkaline phosphatase, AST, ALT and albumin
- Liver function tests
  - Correctly refers to bilirubin, albumin and PT or INR
  - Incorrectly used to cover all enzymes

# Biochemical Patterns of Hepatic Injury

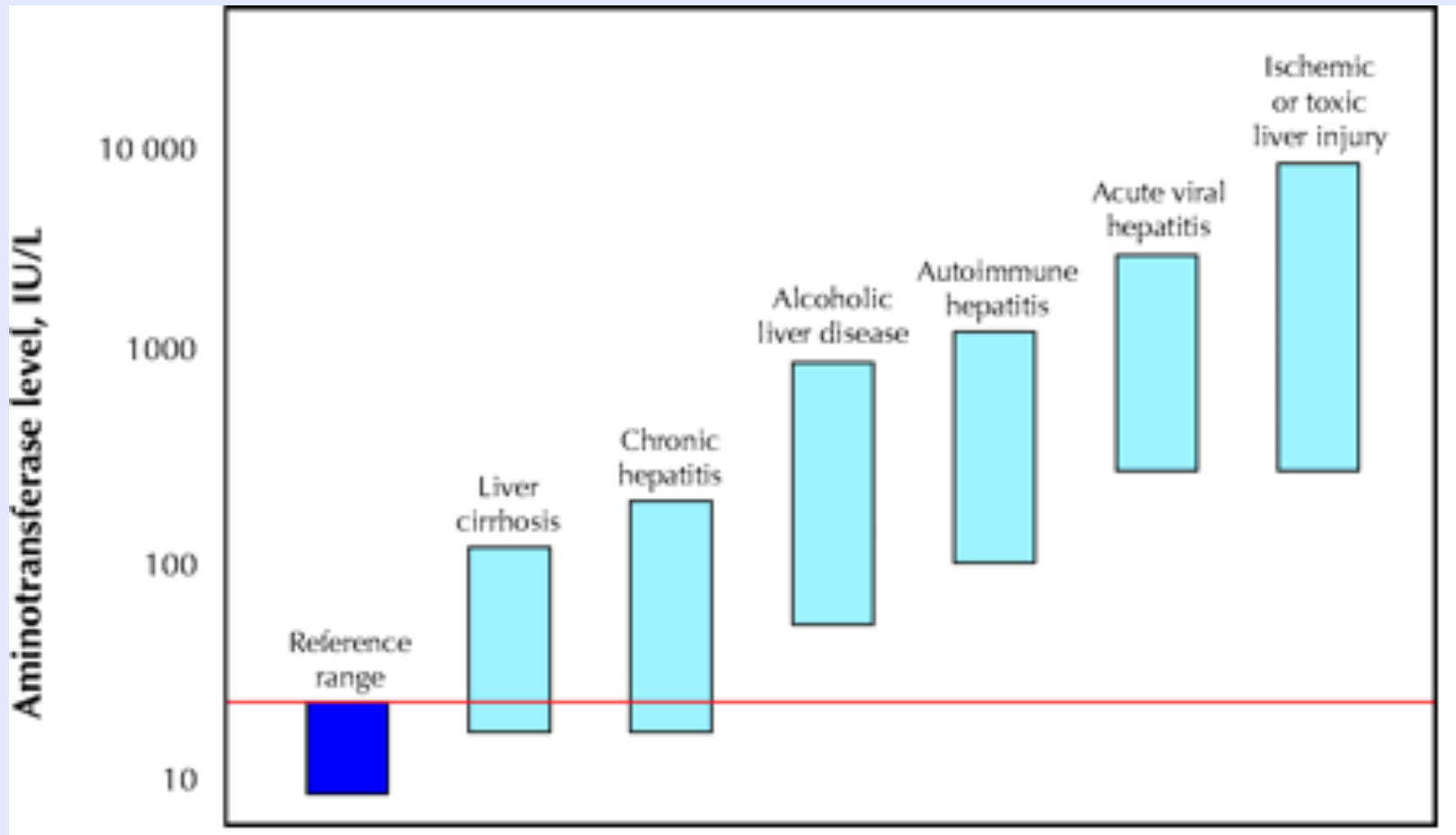
## Key biochemical markers in hepatic systems and function

System or function	Marker	Site or significance	Function
Hepatocyte integrity	Aspartate aminotransferase	Liver, heart skeletal muscle, kidney, brain, red blood cell	Catabolizes amino acids, permitting them to enter the citric acid cycle.
Cholestasis	Alanine aminotransferase	Liver	
	Alkaline phosphatase	Bone, intestine, liver, placenta	Canicular enzyme that plays a role in bile production.
	$\gamma$ -Glutamyl-transpeptidase	Correlated levels with alkaline phosphatase indicate hepatobiliary origin	Catalyzes transfer of $\gamma$ -glutamyl group from peptides to other amino acids.
	Bilirubin	Elevations may indicate hepatic or extrahepatic disorder	Breakdown product of hemolysis taken up by liver cells and conjugated to water-soluble product excreted in bile.
Liver function mass	Serum albumin	Diet or liver	Liver synthesizes albumin
	Prothrombin time	Liver synthesizes vitamin K-dependent clotting factors	Bile salts are synthesized in the liver and necessary for vitamin K absorption

Adapted from Giannini et. al. CMAJ. 2005 Feb 1; 172(3): 367–379.

# Biochemical Patterns of Hepatic Injury

- Common liver diseases/injuries have typical elevations in the ALT and AST
- The extent of elevation can be used to narrow list of differential diagnoses



# Biochemical Patterns of Hepatic Injury

Test	Liver Disease Category		
	Hepatocellular	Cholestatic	Infiltrative
AST, ALT higher than alkaline phosphatase level	Typical	—	—
Alkaline phosphatase higher than AST, ALT levels	—	Typical	—
Elevation of alkaline phosphatase with near-normal AST, ALT levels	—	Typical	Typical

# Caveat...

- Some patients with chronic, advanced liver disease and cirrhosis may have:
  - Normal AST, ALT, and/or Alk Phos
  - And/or a “normal” ultrasound/CT/MRI
- Important to know how to look for other signs of cirrhosis in a biochemical assessment – they may be your only clues to a significant problem.

# Inflammation/Fibrosis

- In chronic liver disease, ongoing injury leads to:
  - Prolonged inflammation of liver tissue
  - Fibrotic liver tissue changes
- Inflammation can wax and wane depending upon a variety of factors, but fibrotic changes generally progress, with increasingly less likelihood of regression (healing) in advanced stages



# What is Fibrosis?

- A wound healing response in which damaged regions are encapsulated by an extracellular matrix or scar
- Develops in almost all patients with chronic liver injury
- Liver scarring and healing similar to processes in other tissue (skin, lung, and kidney) due to similar cell types and mediators (collagen)

# Which Patients Progress More Rapidly to Advanced Fibrosis?

Particularly at risk:

- HIV/HCV co-infection
- Multiple concomitant liver diseases (ex. the patient with chronic HCV, chronic HBV, and NASH)
- ETOH consumption + chronic liver disease

Retrospective study 4852 patients demonstrated

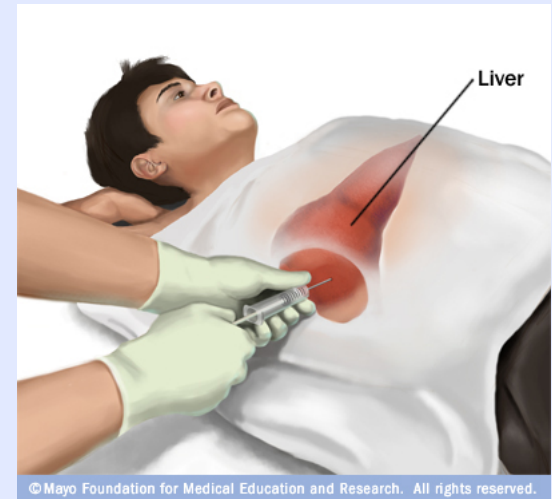
- Highly significant differences in the rates of fibrosis progression - most rapid: HIV-HCV (50% w/cirrhosis at age 52), slowest - PBC (50% w/cirrhosis at age 81 ).
- Acceleration of fibrosis progression with aging.
- Fibrosis progression slower in females for HCV, HBV, GH, and PBC; slower in males for ALD.

# Why important to know a liver patient's inflammation and fibrosis status?

- Gives an impression of the activity of a disease process and extent of liver damage.
- Provides significant information about how to direct care plan and anticipate clinical needs.
- If comparative values are available over time, can give indication of healing progress or, conversely, deterioration in liver condition.

# Liver Biopsy

- The **most reliable approach** to identify the presence of inflammation, steatohepatitis and fibrosis and remains the ‘gold standard’.

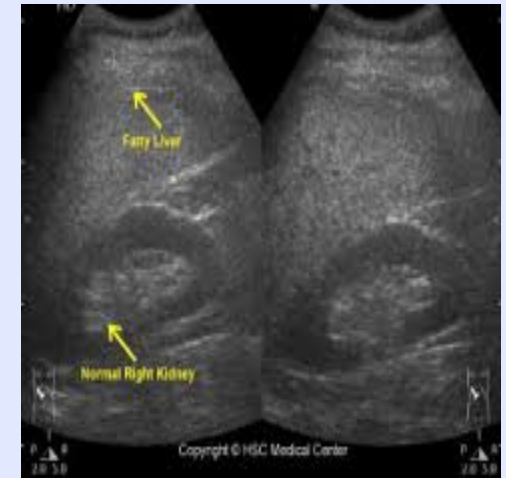


# Imaging Modalities to Assess Fibrosis

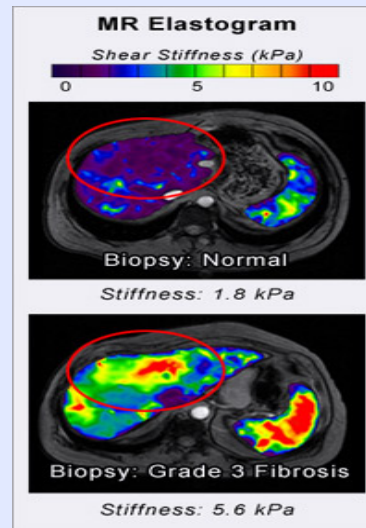
- Lacks sensitivity for minor amounts of steatosis (i.e. less than 30%)
- US
  - Sensitivity 83%
  - Specificity 100%
- CT
  - Sensitivity 54%
  - Specificity 95%
- Shear Wave or MR Elastography
  - Sensitivity 85%
  - Specificity 88%



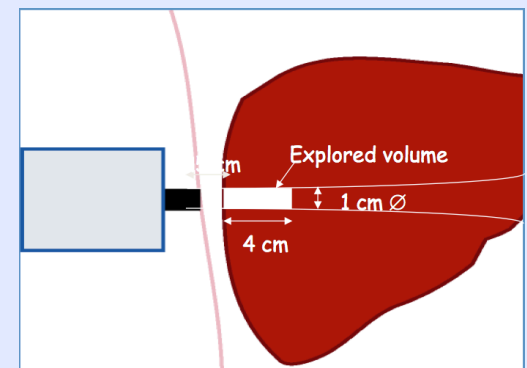
CT



US



MRE



Elastography

# Non-invasive Markers of Fibrosis

<ul style="list-style-type: none"> <li>• FibroTest /FibroSure</li> <li>• FibroSpect</li> <li>• ELF (Bayer)</li> <li>• HepaScore</li> </ul>	<ul style="list-style-type: none"> <li>• Bili, gGT, g-globulin, haptoglobin, a2 M, apolipoprotein A</li> <li>• Hyaluronic acid, TIMP-1, a2 M</li> <li>• HA, Procollagen III amino terminal peptide (PIIINP), TIMP1</li> <li>• Hyaluronic acid, gGT, a2 M</li> </ul>	<p><b>Commercial</b></p>
<ul style="list-style-type: none"> <li>• Forns</li> <li>• APRI</li> <li>• SHASTA; (HIV/HCV)</li> <li>• FIB-4</li> </ul>	<ul style="list-style-type: none"> <li>• gGT, cholesterol, platelets, age</li> <li>• AST /ULN X 100 / platelets (<math>10^9</math>/ L)</li> <li>• AST, HA, albumin</li> <li>• AST, ALT, platelets, age</li> </ul>	<p><b>Available</b></p>

**None Are Accurate In The Middle Fibrosis Ranges**

# Regenerative/Healing Processes

We used to believe that once it developed in the setting of chronic liver diseases, fibrosis was there to stay – basically irreversible.

There is now mounting evidence that fibrosis regression is possible - sometimes significantly so - depending upon several factors, including the underlying causative condition, host factors, and the severity of fibrosis.

# Regenerative/Healing Processes

- New research in this area, as well as emerging drug therapies to promote regression
- Treat underlying condition(s)
- Stop ETOH!
- Therapeutic lifestyle modifications to ameliorate risk factors for progression



# How long does it take, and how much benefit?

- As with developing fibrosis, timetable to regression varies – months to years
- Evidence that even early cirrhosis can be reversed with treatment of underlying conditions and management of contributing comorbidities
- Even if complete resolution of fibrosis is not yet possible, every attempt to maximize healing should be attempted

# Summary

- Laboratory tests and imaging studies important for early identification of damage in many cases.
- Liver biopsy remains gold standard for assessing the extent of liver damage.
- Regression is possible.