UNIVERSITY OF MANITOBA: Thompson Community Based CPD Program 2021-2022

Liver Disease and Non-viral Hepatitis
a simplified approach

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Dec 10 2021

Rady Faculty of Health Sciences | University of Manitoba

Conflicts of Interest

- **Faculty:** Nathan Coleman

- **Relationships with commercial interests:**
  - Employee:
    - Northern Regional Health Authority
    - University of Manitoba
  - All of my income currently comes from serving and teaching in Northern Manitoba
  - No Grants, Honoraria or Consulting Fees form Commercial Sources

Acknowledgements

- Dr Jonathan Gabor- Department of Internal Medicine

Objectives

- Describe an approach to abnormalities in Liver Chemistries
- Review common non-viral liver disease and management principles
- Review Monitoring and Management of Cirrhosis
- Identify key implications for practice in Northern Manitoba

CFPC Core Topic Key Features

- Hepatitis symptoms and/or abnormal liver function tests:
  - Establishing the etiology (e.g., new drugs, alcohol, blood or body fluid exposure, viral hepatitis)
- Abnormal liver enzyme tests:
  - distinguish between obstructive and hepatocellular causes for hepatitis as the subsequent investigation differs.
- Obstructive pattern has been identified
  - Promptly arrange for imaging, and Refer for more definitive management in a timely manner.
- Positive for Hepatitis B and/or C,
  - Assess infectiousness, Determine HIV status.
  - Hepatitis C antibody positive determine if chronically infected with Hepatitis C, and refer for further assessment and treatment.
- In patients who are at risk for Hepatitis A+B and/or Hepatitis C exposure,
  - Hep B and C- Counsel about harm reduction strategies, risk of other blood borne diseases, Vaccinate accordingly
  - Offer post-exposure prophylaxis to patients who are exposed or possibly exposed to Hepatitis A or B..
- Periodically look for complications (e.g., cirrhosis, hepatocellular cancer) in patients with chronic viral hepatitis, especially hepatitis C infection.

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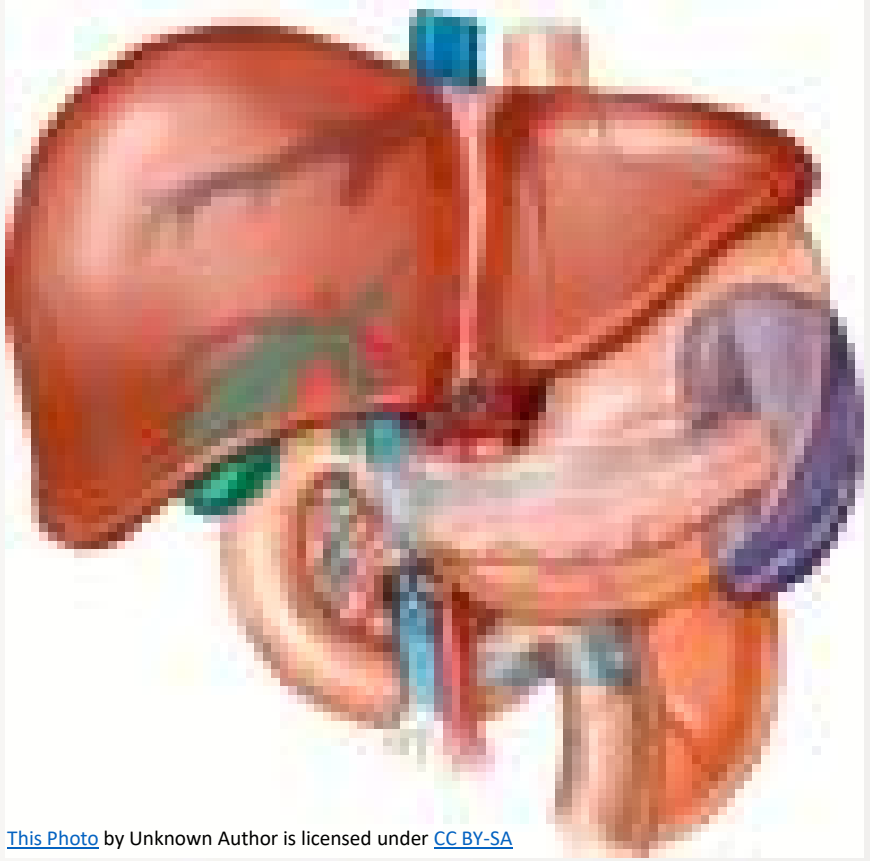
Frequently Forgotten, Commonly Confusing

Why?



Frequently Forgotten, Commonly Confusing

An Approach to Liver Badness

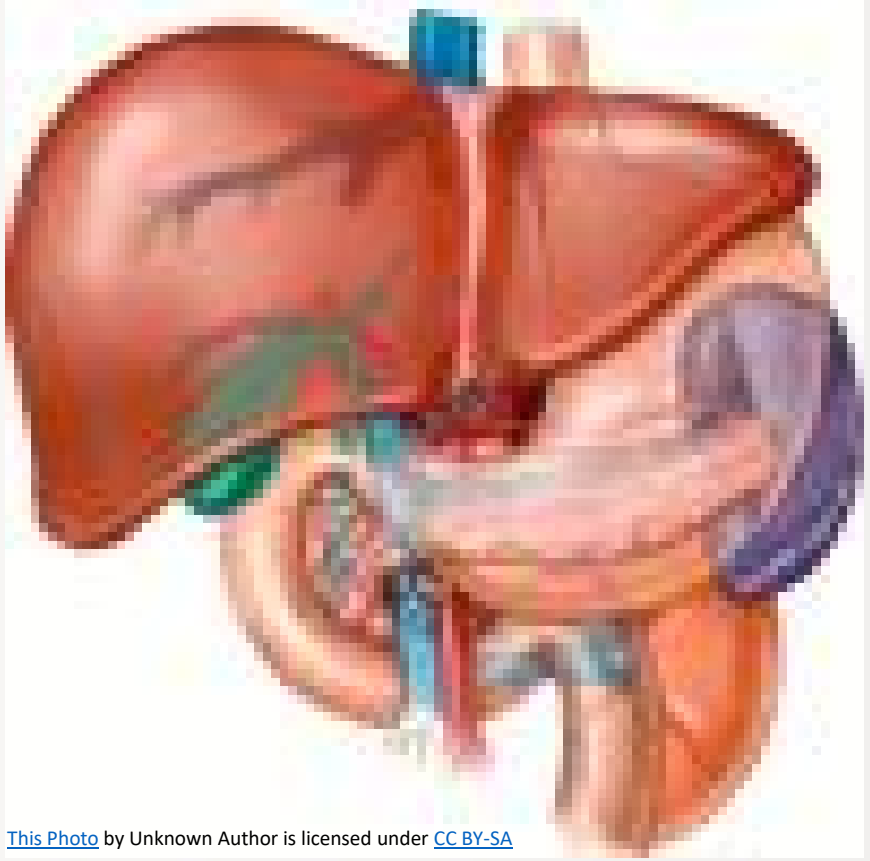
4 questions:

Is the patient sick? Clinical context

Is it failing? Function

Is damage occurring?
Severity/Why

Is help needed? Referral



Is the patient Sick?

- If patient has clinical disease you NEED to know why.
- Signs and Symptoms=Liver Badness:
  - Jaundice, Ascites, Variceal or non variceal hemorrhage, hepatic encephalopathy, low platelets, low albumin.
- Moderate to severe elevations in Liver enzymes
- Evidence of cirrhosis on imaging or its sequalae (example: Varices)
- Sick but NOT the Liver? (Heart failure, Celiac Disease, Hypothyroidism, Rhabdomyolysis, Sepsis)

Is the patient Sick?

NOTE: Liver injury secondary to other illness is generally a poor prognostic sign and frequently indicates increased severity and risk.

Examples: Sepsis with Multi-Organ Dysfunction (MODS), CHF with hepatic congestion, Disseminated Intravascular Coagulation

IS IT FAILING? Liver Function Tests

"The Liver's Creatinine"

- Bilirubin- Direct and Indirect
- INR/PT
- Albumin
- Platelets

Typically indicates >80-90% loss of function!

- Acute
  - Toxins
  - Ischemia
  - Viral
  - Alcoholic Hepatitis
  - Obstructive Jaundice
- Chronic
  - Cirrhosis

Acute or Acute on Chronic Conjugated Hyperbilirubinemia?

1) Rule out obstruction

- Ascending Cholangitis is Emergent- (Abx, Imaging, ERCP)
- Others require Urgent workup, CBD stone, Cancer, etc.

- 2) Identify etiologies responsive to treatment and intervene
- Acute Viral
- Acute Alcoholic Hepatitis
- Toxins (Acetaminophen)
- Thrombosis

IS DAMAGE OCCURRING? Liver Enzymes

"A slow troponin"

- **Severity? How fast?**
  - Mild <5X ULN
  - Moderate 5-10X ULN
  - Severe> 10XULN
- **Etiology?**
  - **Pattern**
    - **Cholestatic (Obstructive)**
    - **Hepatocellular**
    - **Mixed**

Severity

Severe elevations >5-10XULN

- Ischemia
- Toxins (e.g. Tylenol)
- Acute Viral Hepatitis
- Acute Alcoholic hepatitis (can be less even with ++ elevations in Billi/INR)
- Acute Biliary Obstruction

ALWAYS BAD

Mildly elevated <5 X times

- Common- 10% population
- Opportunity for intervention

Etiology- First Questions

Is it Medications?

- Resource: LiverTox

Is it NOT the Liver?

- Heart failure
- Celiac Disease
- Hypothyroidism, Rhabdomyolysis…

Table 4. Selected Medications Commonly Associated with Elevated Liver Transaminase Levels

Antihypertensive
Lisinopril
Losartan (Cozaar)

Antimicrobial
Ciprofloxacin
Isoniazid
Ketoconazole
Pyrazinamide
Rifampin
Tetracycline

Chemotherapeutics
Imatinib (Gleevec)
Methotrexate

Pain relievers/anti-inflammatory
Acetaminophen
Allopurinol
Aspirin
Nonsteroidal anti-inflammatory drugs

Psychiatric
Bupropion (Wellbutrin)
Risperidone (Risperdal)
Selective serotonin reuptake inhibitors
Trazodone
Valproic acid (Depakene)

Other
Acarbose (Precose)
Amiodarone
Baclofen
Herbal and dietary supplements
Highly active antiretroviral therapy
Omeprazole (Prilosec)

Etiology- Pattern

Cholestatic /Obstructive

ALP +/- GGT

- Primary Biliary Cholangitis
- Primary Sclerosing Cholangitis
- Obstructive disease (CBD Stone, Cancer)
- Viral

Hepatocellular

ALT/AST

Common

- NAFLD
- Alcoholic Liver Disease

Uncommon

- Viral
- Drug Induced
- Hereditary Hemochromatosis
- Autoimmune

Rare- Alpha 1 Antitrypsin, Wilsons disease

Diagnostic Clues and Investigation

Etiology	Clue/Investigation
Alcoholic Hepatitis	AST:ALT>2, (GGT but so can NASH)
Non Alcoholic	ALT>AST, lipids/A1c, U/S
Viral	Hx, Serology
Autoimmune	Fam Hx, Autoimmune work up (AMA,ASMA, LKM, HEP2)
Hereditary Hemochromatosis	Fam Hx, Iron Sat >, ferritin*

Etiology	Clue/Investigation
Primary Sclerosing Cholangitis	IBD Hx, Autoimmune workup (AMA), MRCP
Primary Biliary Cholangitis	
Biliary Obstruction	Imaging, ERCP/MRCP

Note: Ferritin frequently elevated in liver disease, alcohol use, NAFLD and chronic inflammatory diseases including metabolic syndrome.

Etiology- Simplified Workup- Mild asymptomatic

History- alcohol, metabolic risk, drug exposures, Fam Hx, Travel/STBBI

Tests- lipid levels, HbA1C, Viral serologies, Iron Studies: (Iron, Iron Sat, TIBC, ferritin level), albumin level, complete blood count with platelets, bilirubin T/D

Autoimmune panel if indicated

Consider Ultrasound

(can usually leave AAT, Ceruloplasmin, biopsy for specialists)

Is Help Needed?
When to refer IM/GI/Hepatology

- Acute presentations as indicated
- Persistent elevation NYD (i.e. not NAFLD)
- Clinical disease NYD
- Chronic Viral Hepatitis
- NAFLD with risk of progression (see below),
- Cirrhosis- MELD Score >14, complications (ascites, hepatic encephalopathy, variceal hemorrhage)

SPECIFIC ETIOLOGIES- Acute Alcoholic Hepatitis

Presentation: Jaundice/elevated Billi and elevated INR from baseline.

Note: Can occur with or without underlying cirrhosis, after severe episode are at high risk for cirrhosis

First Determine Severity:

Maddrey's Discriminant Function >32 or MELD >11

= SEVERE (Almost 50% 30 d mortality)- admission

Treatment

- avoid all alcohol/manage AUD, manage withdrawal,
- nutritional support- thiamine, multivit, Mg and K, protein
- Monitoring and early treatment of infection/sepsis
- Ulcer prophylaxis, AVOID AKI- (stop diuretics and BB)
- If SEVERE- Glucocorticoids (infection risk and requires tapering) or Pentoxifylline

SPECIFIC ETIOLOGIES-Acetaminophen Overdose

- Suspect in all cases of suspected Overdose or liver injury NYD
- N-acetylcysteine indications:
  - >4hr level above nomogram (for 1 time immediate release ingestion)
  - Suspected ingestion >7.5g
  - Unknown ingestion time level>66micromol/L
  - Acetaminophen and ANY evidence of liver injury
- Within 8 hours

SPECIFIC ETIOLOGIES- NAFLD

- AST>ALT + metabolic risk
- Ultrasound- fatty liver without EtOH
- Advise lifestyle measures and follow up
- NAFLD Fibrosis score
- https://nafldscore.com/

(Age, ALT, AST, body mass index, diabetes mellitus or glucose intolerance, platelets, serum albumin) Predicts Fibrosis

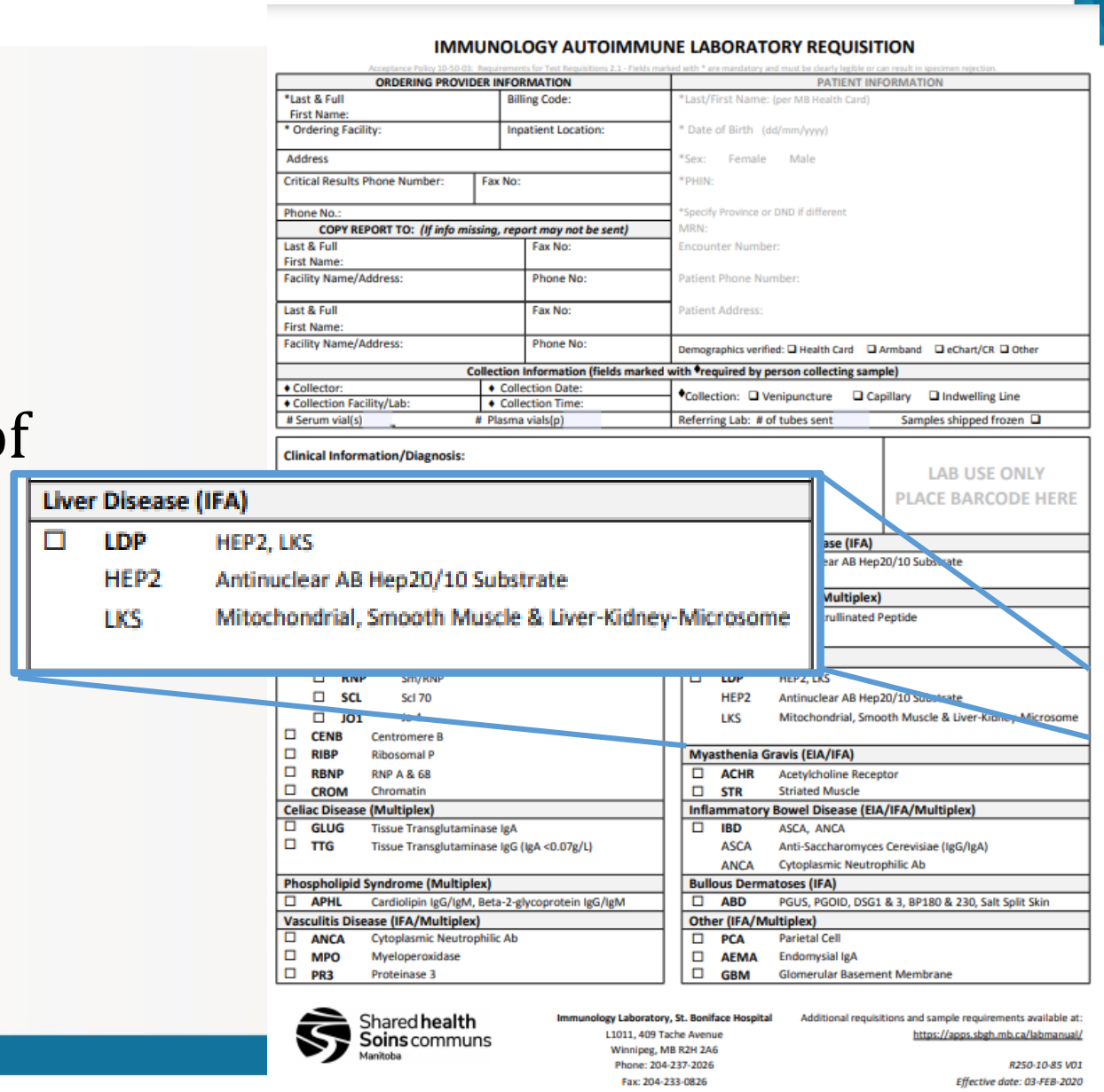
Lifestyle Measures

- Weight loss: aim to lose 7% to 10% body weight if overweight/obese
- General nutrition: low-fat to moderate-fat, low-carbohydrate, or Mediterranean diet
- Fructose intake: avoid fructose-containing beverages and foods
- Physical activity: 150 to 200 minutes per week of moderate to vigorous exercise*
- Alcohol intake: daily intake <30 g for men and <20 g for women
- Coffee drinking: no liver-related limitations

SPECIFIC ETIOLOGIES- Autoimmune Liver Disease

- FN increased risk
- Manitoba- 17% of cases 10% of referral population
- More likely to have elevations in Bilirubin at time of Diagnosis

(Minuk et Al)



IMMUNOLOGY AUTOIMMUNE LABORATORY REQUISITION

Acceptance Policy 10-50-03: Requirements for Test Requisitions 2.1 - Fields marked with * are mandatory and must be clearly legible or can result in specimen rejection.

ORDERING PROVIDER INFORMATION		PATIENT INFORMATION
*Last & Full First Name:	Billing Code:	*Last/First Name: (per MB Health Card)
* Ordering Facility:	Inpatient Location:	* Date of Birth (dd/mm/yyyy)
Address		*Sex: Female Male
Critical Results Phone Number:	Fax No:	*PHIN:
Phone No.:		*Specify Province or DND if different
COPY REPORT TO: *(If info missing, report may not be sent)*		MRN:
Last & Full First Name:	Fax No:	Encounter Number:
Facility Name/Address:	Phone No:	Patient Phone Number:
Last & Full First Name:	Fax No:	Patient Address:
Facility Name/Address:	Phone No:	Demographics verified: ❑ Health Card ❑ Armband ❑ eChart/CR ❑ Other

Collection Information (fields marked with ♦required by person collecting sample)

♦ Collector:	♦ Collection Date:	♦Collection: ❑ Venipuncture ❑ Capillary ❑ Indwelling Line
♦ Collection Facility/Lab:	♦ Collection Time:	
# Serum vial(s)	# Plasma vials(p)	Referring Lab: # of tubes sent Samples shipped frozen ❑

Clinical Information/Diagnosis:

LAB USE ONLY PLACE BARCODE HERE

Liver Disease (IFA)

☐	LDP	HEP2, LKS
	HEP2	Antinuclear AB Hep20/10 Substrate
	LKS	Mitochondrial, Smooth Muscle & Liver-Kidney-Microsome

Myasthenia Gravis (EIA/IFA)

☐	ACHR	Acetylcholine Receptor
☐	STR	Striated Muscle

Inflammatory Bowel Disease (EIA/IFA/Multiplex)

☐	IBD	ASCA, ANCA
	ASCA	Anti-Saccharomyces Cerevisiae (IgG/IgA)
	ANCA	Cytoplasmic Neutrophilic Ab

Celiac Disease (Multiplex)

☐	GLUG	Tissue Transglutaminase IgA
☐	TTG	Tissue Transglutaminase IgG (IgA <0.07g/L)

Phospholipid Syndrome (Multiplex)

☐	APHL	Cardiolipin IgG/IgM, Beta-2-glycoprotein IgG/IgM

Vasculitis Disease (IFA/Multiplex)

☐	ANCA	Cytoplasmic Neutrophilic Ab
☐	MPO	Myeloperoxidase
☐	PR3	Proteinase 3

Bullous Dermatoses (IFA)

☐	ABD	PGUS, PGOID, DSG1 & 3, BP180 & 230, Salt Split Skin

Other (IFA/Multiplex)

☐	PCA	Parietal Cell
☐	AEMA	Endomysial IgA
☐	GBM	Glomerular Basement Membrane

Shared health Soins communs Manitoba

Immunology Laboratory, St. Boniface Hospital
L1011, 409 Tache Avenue
Winnipeg, MB R2H 2A6
Phone: 204-237-2026
Fax: 204-233-0826

Additional requisitions and sample requirements available at:
https://apps.sbgh.mb.ca/labmanual/

R250-10-85 V01
Effective date: 03-FEB-2020

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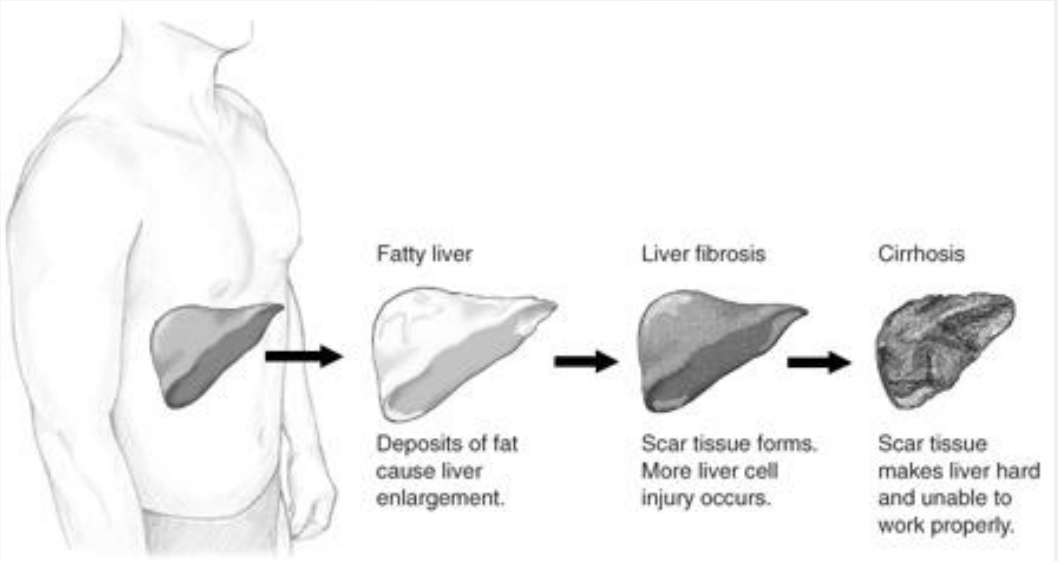
Cirrhosis

- Compensated -
  - (Prognosis Variable- Median 12 years)
  - **Key:** Treatment can still improve fibrosis in Alcohol Use Disorder, Hep B/C and NAFLD
- Decompensated
  - (Prognosis Median 2 Years)
  - Jaundice
  - Ascites
  - Hepatic Encephalopathy
  - Variceal Hemorrhage



Cirrhosis- Monitoring

- Metabolic panel, INR, CBC, albumin, Billi q 6mo (MELD Score/Child Pugh)
- Hepatocellular Carcinoma- Liver Ultrasound q 6months
- Varices- EGD at dx, then q 2-3 years if none, 1-2 years if small, more frequently if

MELD Score (?dialysis, creat, INR, Na, Billirubin)

- Predicts survival in Cirrhosis/transplant list
- Can prognosticate in other conditions need to interpret

- Child-Pugh Score (Bilirubin, Albumin, INR, Ascites, Hep Encephalopathy)
  - Older, predicts surgical mortality

Cirrhosis- Complications

Complication	Dx	Intervention
Ascites	Clinical, Paracentesis if New or SBP concern	Moderate-Severe: Salt restriction only, Spironolactone +/- Lasix Large- High volume paracentesis with albumin
Esophageal Varices	EGC	Monitoring, Medium to Large: Non selective BB- titrate 25 % decrease in HR and >55. Discontinue if : sepsis, SBP, acute GI bleeding, refractory ascites, systolic bp < 90 mm Hg, Low Na
Hepatic Encephalopathy	Clinical, limited role for ammonia	Avoid precipitants 1st episode: Lactulose, 2nd: Rifaximin
Spontaneous Bacterial Peritonitis (SBP)	Clinical, Paracentesis- Neutrophil>250/mm^3	Tx- Empiric IV abx, Ceftriaxone/Cefotax/Pip-Tazo Prophylaxis: GI bleed- Child pugh B/C- Ceftriaxone IV, A- oral SBP+ low ascitic protein + advanced liver disease or kidney disease
others	Refer to Smith et al. Cirrhosis: Diagnosis and Management. Am Fam Physician. 2019;100(12):759-770	

Summary

- 4 Questions:
- **Is the patient sick?**
  - Look for Liver badness-signs and symptoms
  - Non Liver disease
- **Is it Failing?** LFTs
  - Abnormal liver function=failure
  - New increase in Billi-Rule out obstruction then look for cause and manage
- **Is there damage?** Liver Enzymes
  - First Consider Meds/Non-liver
  - Cholestatic VS Hepatocellular
  - Hepatocellular- if Mild, Hx and initial investigations, Think NAFLD
  - Etiology identified-manage/refer if NYD
- **Is Help Needed?**
  - Refer Acute, persistent or clinical signs and NYD, Chronic Viral, Cirrhosis MELD>14 or complications

Mitigating Bias

Sources

- Smith A, Baumgartner K and Bositis C. Cirrhosis: Diagnosis and Management. Am Fam Physician. 2019 Dec 15;100(12):759-770.
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