Liver disease in primary care: Approach to liver enzymes

Jordan J Feld MD MPH

Toronto Centre for Liver Disease
Sandra Rotman Centre for Global Health

Hemant Shah MD MScCH HPTE

Francis Family Liver Clinic
@hepatoMD

Disclosures

Jordan Feld:

- **Research:** Abbott, Abbvie, Gilead, Janssen, Merck
- **Consulting:** Abbvie, Contravir, Gilead, Merck

Hemant Shah:

- **Consulting Fees:** Abbvie, Gilead, Merck, Intercept, Lupin

Learning Objectives

1. Appreciate the significance of different patterns of abnormal liver enzymes
2. Develop an approach to the initial work-up of abnormal liver enzymes in primary care

Outline

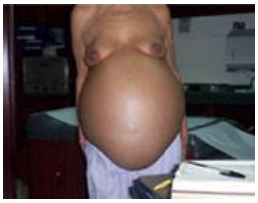
- Liver enzyme patterns
- Work-up for
  - Hepatocellular pattern
  - Cholestaic pattern
  - Mixed pattern
  - Liver enzymes over 1000!

What do you call these tests?

- ALT
- AST
- ALP
- GGT

Liver enzymes → NOT LFTs

Why?



56 yo man awaiting liver transplant

ALT 17
AST 27
GGT 43
ALP 93

"LFTs" are "Normal"!!

Actually – not true – LFTs VERY abnormal
INR 2.4
Bilirubin 4.8 g/dL
Albumin 2.8 g/dL

Liver tests/enzymes ≠ LFTs

- Liver Functions
  - **Synthesis:**
    - Protein – Albumin, Clotting factors (INR)
    - Glucose – gluconeogenesis (only impaired very late)
  - **Metabolism:**
    - Bilirubin conjugation
    - Ammonia breakdown (encephalopathy)
    - Drug/toxin breakdown
  - **(Portal Hypertension)**
    - Ascites
    - Varices
    - Encephalopathy

Liver function tests: INR, albumin, bilirubin (direct)

What do the liver enzymes mean?

- Ongoing injury
- **Hepatocellular injury**
  - ALT (SGPT) – **L for Liver** specific (small amount muscle)
  - AST (SGOT) – lots of other sources (RBC, muscle, heart)
  - Normal for both lower than the labs!
    - Men – ALT 30
    - Women – ALT 19
- **Cholestatic/infiltrative injury or obstruction**
  - ALP (alkaline phosphatase)
  - GGT

Categorization

- Most useful relative to upper limit of normal

- **Hepatocellular** pattern (ALT/ULN >> ALP/ULN)
- **Cholestatic/infiltrative** pattern (opposite)
- **Mixed** (ALT/ULN ≈ ALP/ULN)

- Helps with narrowing a broad differential
- Height & duration of elevation also important
  - Check trend ie historical labs

Hepatocellular Pattern (ALT/AST)

- Organization is key

- Infectious
- Toxic
- Metabolic

This should be the focus

- Genetic
- Autoimmune
- Other

Probably leave this stuff for us to do

Infectious

Screen EVERYONE!

- HBV (HBsAg, anti-HBc, anti-HBs)
- HCV (anti-HCV Ab)

Common enough to screen even if ALT normal

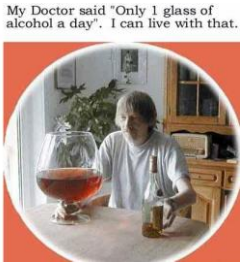
Screen Selectively

- HAV – very high ALT (>1000, exposure hx) – IgM
- CMV/EBV – immunosuppressed, ALP elevated

Toxin

- **Medications, medications, medications**
- Almost any drug can do it
- Take a good history → may have stopped the drug (ask about drugs in past 3 months)
  - Antibiotics (Amox/Clav!!, minocycline, nitrofurantoin)
- Don't forget herbals, OTC and **recreational drugs** – need to ask

Alcohol – how much is too much?



- History is everything
- AST>ALT (2:1) (+GGT)
- CAGE questionnaire
- Trust your patients (mostly)
- **If ALT>500 → not alcohol alone**

Men: 1-2 per day
Women: 1 per day

Avoid binge drinking
Avoid daily drinking

Metabolic – fatty liver

- ALT> AST (+ GGT)
- Metabolic risk factors
  - DM, HTN, lipids
  - Weight gain ***or loss***
- Still screen for **HCV, HBV & ETOH** – not mutually exclusive!
- More to come…

Genetic

- **Hemochromatosis**
  - Not rare in Caucasians (think Vikings – northern Europe)
  - Fe Sat > 50%, Ferritin
    - But both can be up in ETOH or Fatty liver disease
    - Again…not mutually exclusive!
  - More likely if also DM, arthritis, bronzing of the skin…etc
- **Wilson Disease**
  - Screen all if < 30 and maybe all up to age 50
  - Ceruloplasmin
  - Bad to miss this – deadly disease that is treatable

Autoimmune??

- Diagnosis is not straightforward
- Variable presentation from asymptomatic liver test abnormalities to fulminant liver failure
- Useful diagnosis because it has a bad prognosis and it's treatable!
- Start with IgG → if high, follow with ANA, SMA (and LKM if children) and biopsy **(or just refer!)**

A few 'general' rules

- ALT>AST – most liver diseases
  - Viral hepatitis
  - NAFLD/NASH
  - Most drug induced liver injury
- AST>ALT
  - Alcohol – >2:1 ratio
  - Ischemia (low flow or congestion)
  - Wilson disease (hemolysis – 4:1)
  - **Cirrhosis!!** (AST>ALT but <2:1)

So bottom line – ALT/AST

- **Etiology Search**
  - History – meds, alcohol & other drugs
  - HBV, HCV for everyone, (HAV, other viruses in context)
  - Fe Sat/ferritin for everyone
  - (ceruloplasmin)
  - (IgG – if persistent)
- **Severity assessment**
  - CBC – low platelets suggest cirrhosis or acute alcohol
  - Bilirubin, INR, Albumin (if persistent)
  - Ultrasound (if persistent)

What about high ALP?

- First prove it's from the liver → GGT (usually up), ALP isoenzymes
- GGT is pretty useless on its own – VERY non-specific (almost any liver disease) and inducible (by meds)

- **Cholestatic**
  - Extra-hepatic obstruction (stone/tumor)
  - Intrahepatic duct disease
  - Cholestasis (poor bile flow) – e.g. alcohol!!
- **Infiltrative**
  - Granulomatous
  - Mass / tumor

Cholestatic

- Rule out obstruction → US usually adequate
  - If painless jaundice → need to see pancreas (CT or MRCP)

- If no obstruction (this is where we come in…):
  - **Large Ducts:** Primary/Secondary Sclerosing Cholangitis (stones, IgG4) → **MRCP**
  - **Small Ducts**: Primary Biliary Cholangitis, vanishing bile duct syndrome, portal biliopathy (PV thrombosis) → **biopsy**
  - **Drugs (or alcohol)** → **history +/- biopsy**

Granulomatous/Infiltrative

- **Granulomatous (biopsy)**
  - Sarcoid
  - TB/Fungal
  - Schistosomiasis – even years after leaving endemic area
- **Infiltrative (imaging +/- biopsy)**
  - Lymphoma
  - Mass lesion (HCC, mets, abscess, hydatid cyst)

High ALP – Work-up

History

- Symptoms – may be absent
  - Itch
  - Jaundice (dark urine – useful for timing)
  - Pain, Fever (stones)
  - Constitutional symptoms
- DRUGS + Herbals
- Risk factors for TB, HCC
- History of IBD (PSC), past stones, surgery (chole), bone disease

Labs/Radiology

- GGT – confirm liver (ie not bone, placenta etc)
- Imaging – US
  - If high suspicion, CT/MR even if US negative
- Etiology:
  - Anti-mitochondrial Ab (PBC)
  - Immunoglobulins (IgG, IgM)
  - Biopsy

Mixed Picture

- Similar approach to hepatocellular (AST/ALT)

- A few common ones:
  - Meds – antibiotics!
  - Alcohol – acute alcoholic hepatitis
  - Stones – AST/ALT up first followed by ALP (+/- Bili)
  - Sepsis
  - Viruses – CMV/EBV (not HBV, HCV)
  - Rarer conditions (overlap syndromes etc)

A good list to remember – ALT>1000

1. Virus
2. Toxin
3. Vascular
4. Stone
5. Autoimmune hepatitis

Not alcohol (unless alcohol plus)

Viral Infection (ALT>1000)

- **Hepatitis A to E**
  - A – HAV IgM – only order if ALT very high &/or exposure
  - B – flare or acute infection
  - C – rare unless acute (if high suspicion, HCV RNA)
  - D – super-infection with HBV or flare
  - E – think Hep A (travel history)
- **CMV/EBV**
  - Rare to be >1000, usually cholestatic too (ALP up)
- **HSV**
  - Important – if you think of it, start the acyclovir!
- Rare – VZV, SARS, influenza, adenovirus

Toxin (ALT>1000)

- **Medications, medications, medications**
- Take a good history → may have stopped the drug (ask about drugs in past 3 months)
  - Acetaminophen classic
  - Many others
- Don't forget herbals, OTC and recreational drugs – need to ask

Vascular (ALT>1000)

- **Forward flow – Shock Liver**
  - Usually underlying cardiac disease
  - Rapid increase and rapid normalization
  - Mild affect on liver function (INR may go up transiently)
- **Congestion**
  - Acute Budd-Chiari
  - Even severe heart failure (not very common)

Stone (ALT>1000)

- ALT and AST go up ***BEFORE*** ALP and Bilirubin
- Typically associated with pain +/- fever (others may be asymptomatic)
- Prompt normalization with passing of the stone

Autoimmune Hepatitis (ALT>1000)

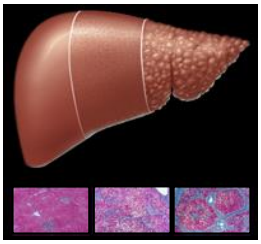
- Not all that common but you have to think of it
- Diagnostic tests:
  - Quantitative immunoglobulins → IgG
  - ANA
  - Smooth Muscle Antibody
  - Liver Kidney Microsomal (Type II – children)
  - Liver biopsy

Liver Disease Catches You By Surprise…

"Move back just a little Fred....Fred!?!"

Liver May Look Normal Even with Cirrhosis

- Stages F1-3 and even early F4 may "look normal" on imaging
- A "normal" liver ultrasound does not exclude fibrosis and may miss cirrhosis



The Spectrum of Cirrhosis: From Subtle to Overt

Compensated Cirrhosis

- Diagnosis subtle
- Few or no symptoms
  - Possibly fatigue
- Subtle or no physical exam abnormalities
- Subtle or no laboratory abnormalities
  - Low platelet count, AST > ALT

Decompensated Cirrhosis

- Diagnosis usually obvious
- Complication(s) of cirrhosis
  - Ascites/edema
  - Variceal hemorrhage
  - Encephalopathy
  - Jaundice
- Abnormal liver function
  - Bilirubin
  - Albumin
  - INR

Tools to Assess Fibrosis

- **Exam & radiology – very insensitive!!**
- **Laboratory tests**
  - Liver enzymes (AST/ALT) may be normal even with cirrhosis – not helpful
  - Liver function (bilirubin, albumin, INR) normal until advanced cirrhosis

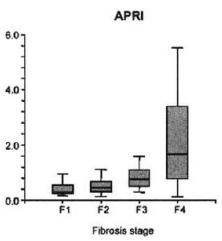
Tests suggesting advanced fibrosis/cirrhosis

- Platelet count < 150 x 10E9/µl
- AST:ALT ratio > 1 (typically < 1 in HCV & most liver dx)
- Elevated IgG (polyclonal)
- (Abnormal bilirubin, INR, albumin → late finding)

Simple Test: APRI

- Cirrhosis
  - Platelets fall
  - AST > ALT
- Very useful to exclude cirrhosis
  - Low is good
    - <0.5 is good – 98% NPV for cirrhosis!
  - High is bad
    - >2.0 – worry about cirrhosis
- **Caveat** – AST high if active inflammation

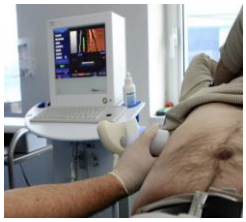
$$\frac{\text{AST/ULN} \times 100}{\text{Platelet count}}$$



Castera et al., 2005

Liver Stiffness by Transient Elastography (Fibroscan)

- Ultrasound-based technique
- Determines liver "stiffness"
- Correlates with liver fibrosis
- No ceiling, ie, increases with worsening cirrhosis → predicts complications (eg, varices)
- Simple to use – minimal training



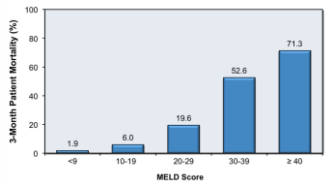
Caveats: May fail with obesity
Influenced by inflammation – it falsely elevates measurements

Child-Pugh-Turcotte Assessing Severity of Cirrhosis

Lab	1	2	3
INR (N<1.2)	<1.7	1.7-2.2	>2.2
Albumin (N>40)	>35	28-35	<28
Bilirubin (N<17)	<34	34-54	>54
Clinical			
Ascites	none	mild	severe
Encephalopathy	none	mild	severe

Child's	CPT score	Surgical Mortality	Survival
A	5-6	~10%	10-15 yrs
B	7-9	~30%	5 yrs
C	10-15	~80%	2 yrs

MELD – Very objective



Baseline MELD	10 Yr Mortality
<8	17%
8-10	18%
10-13	32%
>13	66%

MELD = (3.8 ln Bili (mg/dL)) + 11.2 (ln INR) + 9.6 (ln Creat (mg/dL)
(or use an online calculator!)

Bruno Am J Gastro 2009

MELD - Model End Stage Liver Disease

Summary

- Enzymes are not liver function tests!
- Categorize by pattern
  - Hepatocellular (ALT/AST)
  - Cholestatic (ALP)
  - Mixed (ALT & ALP)
- Directed work-up: history & physical, labs, imaging
- Fibrosis assessment critical for prognosis
  - Remember low platelets → think cirrhosis!
  - New tools – biopsy rarely required
  - CP & MELD score very useful for prognosis