Approach to Abnormal Liver Test: Approach to liver enzymes

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
• Brief intro to ECHO
• Liver enzyme patterns
• Work-up for
  • Hepatocellular pattern
  • Cholestaic pattern
  • Mixed pattern
  • Liver enzymes over 1000!

The father of ECHO

ECHO
(Extension for Community Health Outcomes)
Made in New Mexico

Project ECHO
- Linking PCPs to specialists
- Facilitates linkage to care
- Allows people to be treated by people and in settings they know & trust

Arora NEJM 2011  Perfected in Canada!

The Methods
- **Use Technology** to leverage scarce resources
- **Sharing “best practices”** to reduce disparities
- **Case based learning** to master complexity
- Web-based database to monitor outcomes


ECHO in Canada
- First proposed to do ECHO Hepatitis in Canada
  - Limited interest and no support from MOH
  - Developed HepC Net program – Hemant Shah – similar model to support HCV treatment teams around Ontario
- 2014 – ECHO Pain
  - Chronic pain team led by Andrea Furlan
  - Support from MOH
  - Highly successful
- 2016 – Add ECHO Hepatitis + Arthritis...initially only HCV
- 2018 – expanded ECHO hepatitis to cover liver disease

The ECHO Hub Team
- Hepatology: Jordan Feld & Hemant Shah - Toronto
- Family Medicine/Addiction: Craig Kuhn - Niagara
- Nursing: Magdalena Kuczynski, Elizabeth Lee
- Pharmacist: Ruifen Su
- ECHO Team: Rhonda Mostyn – Project Manager
  Ralph Fabico – Program Coordinator
  Jane Zhao – Research Coordinator
  Shamini Martin- Education Coordinator
  Ashley Grilo – Admin Coordinator

The Sessions
- ‘Didactic session’
  - HCV curriculum – 15 topics
  - Hub + ‘guest’ speakers – 40 min + discussion
- Case presentations
  - Community site
  - Key points and clear question
  - Discussion – community sites + hub
  - Collective consensus on best strategies
  - Follow-up of previous cases
  - Pre + Post questionnaires + survey

After the Curriculum
- Welcome to join any time!
- Bring cases or just participate in the discussion
- With time...the goal is that everyone becomes a local HCV expert but still value in joining the sessions
  - Updates from meetings
  - New literature
  - Challenging cases
Approach to Abnormal Liver Test: Approach to liver enzymes

Jordan J Feld MD MPH
Toronto Centre for Liver Disease
Sandra Rotman Centre for Global Health

Hemant Shah MD MScCH HPE
Francis Family Liver Clinic @hepatoMD

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”!!

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 i.e. historical labs

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

INR – International normalized ratio
LFT – liver function tests

ALT - Alanine aminotransferase | AST – Aspartate aminotransferase
ALP - Alkaline phosphatase | GGT - Gamma-glutamyl transferase

ULN - Upper Limit of Normal
Hepatocellular Pattern (ALT/AST)
- Organization is key
- Infectious
- Toxic
- Metabolic
- Genetic
- Autoimmune
- Other

This should be the focus

Infectious
- Screen EVERYONE!
- Common enough to screen even if ALT normal
- HBV (HBsAg, anti-HBc, anti-HBs)
- HCV (anti-HCV Ab)

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
  - Ceruloplasmmin
  - 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!)

IgG - Immunoglobulin G | ANA - Antinuclear antibody

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)

So bottom line – ALT/AST

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

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

Granulomatous/Infiltrative

• Granulomatous (biopsy)
  • Sarcoïd
  • 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 + Herbs
- 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

When to refer...(or bring to ECHO)

- Persistent enzyme elevation without a diagnosis
- Management after a diagnosis
  - HBV, HCV, AIH etc
- Signs of cirrhosis or liver failure (ascites, encephalopathy, variceal bleed)
- What we need:
  - Serial enzymes – AST, ALT, ALP, (GGT)
  - Serial liver function – bilirubin, INR, albumin
  - Serial CBC, Cr
  - Any work-up done – at least viral hep, Fe, IgG/Ab’s
  - Imaging – US usually adequate

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

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

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

Castera et al., 2005

Child-Pugh-Turcotte Assessing Severity of Cirrhosis

<table>
<thead>
<tr>
<th>Lab</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR (N&lt;1.2)</td>
<td>&lt;1.7</td>
<td>1.7-2.2</td>
<td>&gt;2.2</td>
</tr>
<tr>
<td>Albumin (N&gt;40)</td>
<td>&gt;35</td>
<td>28-35</td>
<td>&gt;28</td>
</tr>
<tr>
<td>Bilirubin (N&lt;17)</td>
<td>&lt;34</td>
<td>34-54</td>
<td>&gt;54</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical</th>
<th>none</th>
<th>mild</th>
<th>severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites</td>
<td>none</td>
<td>mild</td>
<td>severe</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>none</td>
<td>mild</td>
<td>severe</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Child’s CPT score</th>
<th>Surgical Mortality</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 5-6</td>
<td>~10%</td>
<td>10-15 yrs</td>
</tr>
<tr>
<td>B 7-9</td>
<td>~30%</td>
<td>5 yrs</td>
</tr>
<tr>
<td>C 10-15</td>
<td>~80%</td>
<td>2 yrs</td>
</tr>
</tbody>
</table>
MELD – Very objective

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

<table>
<thead>
<tr>
<th>Baseline MELD</th>
<th>10 Yr Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;8</td>
<td>17%</td>
</tr>
<tr>
<td>8-10</td>
<td>18%</td>
</tr>
<tr>
<td>10-13</td>
<td>32%</td>
</tr>
<tr>
<td>&gt;13</td>
<td>66%</td>
</tr>
</tbody>
</table>