Practical Approach to Patient with Liver Disease

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Best of EASL-Africa
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Addis Ababa, Ethiopia
Case 1

- An 18 YO student from Addis Ababa presented with malaise, anorexia, fatigue, myalgia, jaundice of 2 weeks

- P/E: Mild icterus and RUQ tenderness
### Case 1: Investigation

<table>
<thead>
<tr>
<th></th>
<th>1700</th>
<th>2031</th>
<th>1215</th>
<th>167</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>1700</td>
<td>2031</td>
<td>1215</td>
<td>167</td>
</tr>
<tr>
<td>AST</td>
<td>1070</td>
<td>1450</td>
<td>190</td>
<td>69</td>
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<tr>
<td>GGT</td>
<td>219</td>
<td>171</td>
<td>156</td>
<td>145</td>
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<td>ALP</td>
<td>200</td>
<td>165</td>
<td>116</td>
<td>95</td>
</tr>
<tr>
<td>INR</td>
<td>1.25</td>
<td>1.21</td>
<td>1.08</td>
<td>0.81</td>
</tr>
<tr>
<td>T. Bil</td>
<td>2.6</td>
<td>2.15</td>
<td>1.85</td>
<td>1.84</td>
</tr>
<tr>
<td>conjugated</td>
<td>1.90</td>
<td>1.83</td>
<td>1.05</td>
<td>0.68</td>
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<tr>
<td>T. protein</td>
<td>6.0</td>
<td>6.41</td>
<td>7.21</td>
<td>7.35</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.6</td>
<td>3.7</td>
<td>3.7</td>
<td>3.76</td>
</tr>
</tbody>
</table>

Oct 1  2016
Negative further tests

- HBV markers negative
- HCV Ab-negative
- Abdominal sonography-unremarkable
- What further tests?
Case 2

- A 40 year old farmer from Northern Ethiopia presented with fatigue and progressive abdominal distension of three months.
- He lost 5 family members recently from similar complaints. He noted similar problems among his neighbors.
- He was noted to have pallor, splenomegally, and ascites
- EGD reveled Esophageal varices and PHG
- Lab =ALP & Bil↑, pancytopenia
- Sonography=diffusely echogenic liver and ascites
- DDx?
Liver

- Biggest and busiest
- >1000 complex functions

- Too many DDx
- Several tests required for Dx
- Most tests non sensitive/specific

- Hepatocellular, choelstatic, mixed, external
Questions

- Normally abnormal and abnormally normal LBT?
- Methods of localization?
- How to differentiate so many DDx?
- How to assess prognosis?
- When to observe/ biopsy liver?
Diagnose Liver Ds

History

Exam

Investigation

Diagnosis
Approach to liver Ds

- **History**: Family, travel, tattoo, alcohol, blood Tx, contact, drug, toxin, HD, systemic Ds, Sx.

- Pregnancy (hyperemesis, PE, cholestasis, HELP, fatty

- **P.E.**: v/s, icterus, CLD, PHN, Murphy, LAP, systemic, urine, stool, rashes, ---

- **LBT**: Hepatocellular, cholest, mixed, 10% NI

- **Etiologic Tests**

- **Imaging**: US, EUS, CT, MRCP, ERCP, Fibroscan, venogram,
Challenges---

- But all these are **non specific**!
- 2.5% abnormal in **population**
- **Fluctuating** values
- Abnormally **normal**-fulminant/ESLD
Eg. Abnormal LBT in USA 249 blood donors

- Fatty liver 22-56% - Obesity↑*
- ALD 11-48% 
- HCV 17-20%
- Miscellaneous 4-8%
- Unexplained 2-9%

- Africa-HBV,HCV,toxin /DILI
Functional Organizations
Lobules, Acini, Cords/plates
Hepatic functions---

- **Secretory**
  1) Bile acid from cholesterol
  2) Conjugation of Bilirubin (Both secreted in bile)
  1) BSP
  2) Rose Bengal

- **Excretory**
  Excretion of exogenous dyes

- **Metabolic**
  1) Carbohydrate metabolism
  2) Lipid metabolism
  3) Amino acid metabolism
  4) Cholesterol synthesis and Esterification
  5) Ammonia formation
  6) Mineral metabolism
  7) Vitamin metabolism
  8) Nucleic acid metabolism
  9) Interconversion of sugars

- **Synthetic**
  Synthesis of:
  1) Albumin
  2) Alpha-1 and Gamma 2 globulins
  3) Clotting factors
  4) Binding proteins
  5) Transport proteins

- **Detoxification**
  Of
  1) Xenobiotics
  2) Steroids
  3) Thyroid hormone
  4) Endogenous metabolites

- **Storage**
  Storage of
  1) Glycogen
  2) B12
  3) Vitamin A
Functions of the Liver

- Metabolic activities
- Homeostasis,
- Nutrition & immune defense
- Synthesis
- Fetus-haemopoiesis.
- Detoxification/excretion
- Secretion
- Storage:
Transaminases could be NI but dysfn
DDx broad

- **Viral hep**--**Acute/ALF**>**chronic/ESLD**
- Metabolic: NAFLD, Wilson, Hemom, **DILI***
- Immunologic: AIH, PBC, PSC
- Infiltrative: Amyl/sarcoid, granuloma
- Vascular: VOD, BCS
- Neoplasm: HCC, Cholangio, Mest
- Non-hepatic: CHF, **shock***, myopathy, Thyroid, celiac, adrenal Ds
- *-->AMT>10UNL—others <5UNL
Aminotransferase level

- Reference range
- Liver cirrhosis
- Chronic hepatitis
- Alcoholic liver disease
- Autoimmune hepatitis
- Acute viral hepatitis
- Ischemic or toxic liver injury
Transaminitis

Agents in Clinical Cases

Acute Viral Hepatitis
- HBV
- HAV
- HCV
- Unknown

Chronic Viral Hepatitis
- HCV
- HBV
- HDV
- Unknown
LBT categories

- Detoxification & Excretory function
  - Serum Bilirubin
  - Urine Bilirubin
  - Blood Ammonia

- Biosynthetic function
  - Serum Albumin
  - Serum Globulin
  - Coagulation factors

- Hepatocyte injury
  - ALT
  - AST

- Cholestasis
  - Alk. Phosphatase
  - 5'-nucleotidase,
  - γ-glutamyl transpeptidase (GGT)
Liver Enzymes

- **thousands** in liver.

- **Drawbacks: sensitivity/Specificity**
  - <5x mild; Metabolic Ds
  - 5-10 Moderate: CVH, ALD
  - >Severity: toxic, Acute VH, shock
  - Fluctuating/progressive course
Aminotransferases

- AST
  - cytosol and mitochondria
  - liver, cardiac muscle, skeletal muscle, kidney, brain, pancreas, lung, leukocytes, RBC.

- ALT: Mainly liver cytosol

>Rise 1000x:
  - VH, Toxins, DILI, Ischemic (hospitalized*),
  - AIH, BCS, Fulminanat Wilson, OBJ

ALP GGT; Biliary membrane +:= cholestasis, infiltrative

Oct 1 2016
A) Hepatocellular necrosis

- Hepatocyte damage...CM injury... plasma ALT/ SGPT

- Degree of elevation in disease states:
  - **Minimal**: chronic hep
  - **Moderate** < 300 U/L  ALD
  - **Striking elevations**→1000 U/L—
    (viral hep, AIH, Wilson, ischemic hep, or toxin- or DILI)
AST:ALT De Rittis ratio > 2

- Depletion of *vit B6* in alcoholics → ALT synthesis
- Damage to *mitochondria* releasing mAST
- High ratio in recent *binge & advanced ALD*
- Could be normal in *chronic* alcoholics
Diagnostic Clues…

- Relative pattern of elevation of **AST** > **ALT**
  - Duration of disease **CLD** > 1:1
  - **Alcoholic** liver disease > 1:2-3

- Pattern of jaundice
  - Cholestatic Vs hepatocellular feature

- Enzymes **not prognostic**-normal in ESLD

- Follow disease activity- **serially.**
ALT predominant---pyrodoxine*

- <5-15 xUNL
- Acute/Chronic viral hep
- Ischemic Hep
- DILI, acute BCS, VOD
- NAFLD
- Hemochromatosis
- AIH
- AATD, Wilson, Celiac
AST predominant

- ALD—pyrodoxine def for ALT
- Cirrhosis—thrombocytopenia/spleen
- Myopathy, exercise
- Hemolysis
- Thyroid Ds
- Pancreas, bowel, Bone, placenta, ---
B) Enzymes for Cholestasis

- Clinical utility/ specificity
  - ALP
  - 5’- nucleotidase
  - GGT--Liver

- ALP
  - 4 different isozymes
  - Physiologic elevations: children/adolescent, pregnant

  > 4x: cholestatic, infiltrative: cancer, amyloidosis---.
ALKALINE PHOSPHATASE

- **Liver, bone, placenta, small intestine & kidney.**
  >4x Infiltrative cholestasis with GGTP & 5’NT-HB specific (Bone if without GGT/5NT)
  - 4 different isozymes-bound hep canalicular membrane
  - Physiologic milder elevations

- **Physiological**
  1. age > 60 can have ALP (1–1.5 X normal)
  2. Blood types O and B.
  3. children and adolescents-bone growth
  4. late in normal pregnancies
ALT: ALP ratio

- >5 = Hepatocellular
- <2 = Cholestasis
- 2-5 mixed
Isolated ALP↑

Hepatobiliary Disease

- Early cholestasis
- AIDS cholangiopathy
- Hepatic infiltration by tumor or granulomata. bone mets

- Jaundice may be absent

Others

- Hodgkin's disease
- Diabetes
- Hyperthyroidism
- CHF
- Amyloidosis
- IBD
Low ALP

- Reduced ALP activity due to displacement of the co-factor zinc by copper
- Eg.
  - Hypothyroidism,
  - Pernicious anemia,
  - Zinc deficiency,
  - Congenital hypophosphatemia
  - Fulminant hepatitis and hemolysis
Gamma Glutamyl Transpeptidase, GGTP

- liver (hepatocytes & cholangiocytes), kidney, pancreas, spleen, heart, brain, and seminal vesicles. T 1/2 = 26 days

- NOT in bone & pregnancy
- Localizes ALP to HB sources-R/o HB ds if N(90% NPV)

- High sensitivity but specif for hepatobiliary Ds
- HCC, CBD stones, CLD, phenytoin, alcohol, barbiturate, DILI, fever, CHF, pancreas, DM, IHD,
Disproportionate ALP GGT↑

- Ca, TB
- Amyloidosis
- Sarcoidosis
- Others
5′-Nucleotidase

- Hep canalicular and sinusoidal membranes
- intestine, brain, heart, B/vessels, pancreas.
- 2nd & 3rd trimesters of pregnancy
- Primarily in hepatobiliary Ds but NOT bone
LDH rise

- Hepatocellular necrosis
- Shock liver
- Cancer
- Hemolysis
- DILI
AIH

- 20% negative Ab
- ASMA, AMA, ANA,
- Electrophoresis: gamaglobulins ↑
- Rarely acute
ALD

- Mild-moderate transaminitis
- AST > ALT  2-3:1
- ALT normal or low
- GGT:ALP  >2.5

Oct 1 2016
Wilson Ds

- Genetic biliary Cu excretion
- Ceruloplasmin down in 80%
- Kayer-Fleisher ring
- Urin cu >100 microgm/day Dx
- Liver Bx > 250 microgm/day
Cholestasis Ds

- **A. Intrahepatic**
  - Viral hepatitis
  - ALD
  - DILI, VOD
  - PBC
  - Familial
  - Pregnancy

- TPN
- Post Op, LTx
- Sepsis
- Paraneop syndrome
- Infiltrative: TB, NHL, Amyl/sarcoid---
Cholestasis---

- B. Extra hepatic:
  - HBP cancers
  - Choledocholithiasis
  - Biliary stricture
  - Chronic pancreatitis
  - AIDS cholangiopathy
  - Mirizzi’s syndrome - GB/cystic D stone compress CBD
  - Ascariasis
C) Mixed : HC& Cholestasis

- Viral Hepatitis
  - HAV, HBV, HCV---fibrosing
  - Others: EBV, CMV

- Alcoholic hepatitis
- DILI

- Solid organ transplantation
2) Bilirubin

- Breakdown product: porphyrin ring of heme-proteins.

- Daily synthesis = 250 – 300mg (95% RES Hb)

- Exists in 2 forms
  - Indirect/ Unconjugated
  - Direct/ conjugated –dixo reactant
  - **Delta Bil-albumin t1/2=14-21 days** (vs 4hrs-lagging jaundice)
  - Bilirubinuria-Dx Liver Ds early=direct Bil

- Normal serum T.Bilirubin-van den Bergh Rxn
  - Total =0.2 - 0.9 mg/dl - in 95% population (15% conjugated.)
Metabolism
Hyperbilirubinemia

**Sources:**

1. **Overproduction:**
   - Hemolysis, ineffective hemop, Thalassemia, Sickle, Anemias, malaria, 
   - ... 

2. **Impaired uptake:**
   - Rif, probenicid, Ribvn, contrast 
   - Conjugation: Gilbert, Criglar-Najjar 
   - Or excretion (direct): Dubin-Johnson, Rotor 

3. **Regurgitation:**
   - Damaged hepatocytes or bile ducts.

4. **Cholestasis:**
   - Intra/extrahep
Unconjugated hyperbilirubinemia

• UGTA mutation - Gilbert synd

• UGTA inhibition: Indina/Atazanivir

• Bil uptake inhibition: Rifampin, CAF, genta
Conjugated Hyperbilirubinemia

1. **Extra hepatic**
   - Biliary obstruction: Stone, Ca
   - Pancreatic: Ca, stricture

2. **Intrahepatic**
   - PSC, PBC = AMA
     - Dubin-Jo, Rotor synd = transporter mutation
     - Cholestasis: AIH, Viral: ANA, ASAM, LKM
Elevated serum bilirubin

History and Physical Examination, Liver Chemistries

Unconjugated bilirubin
Normal Alk Phos, ALT, AST

Hemolysis Studies
Review Medications

Conjugated bilirubin
Abnormal Alk Phos, ALT, AST

RUQ ultrasound to assess ductal dilatation

present

ERCP or MRCP

absent

*Elevated ALT evaluation
Review medications, AMA, ERCP or MRCP
liver biopsy
Synthetic
Hypoalbuminemia

- 3.5 to 5.0g/dL t1/2 18-21 days-chronic Ds
- hepatocellular dysfunction
- Malnutrition

- protein-losing enteropathy
- nephrotic syndrome

- Chronic inflammatory conditions
- hormonal imbalances
B) Serum Globulins: electropheresis

- 3 types – α, β & γ

- Increased γ - chronic hepatitis and cirrhosis
  Eg.
  - IgG = AIH; IgM = PBC; IgA = ALD.
C ) Coagulation Factors

- Acute Ds
  - **PT**
    - vitamin K deficiency
    - obstructive jaundice
    - fat malabsorption of any kind.
    - hepatocellular dysfunction
  - **INR**
    - Component of MELD score
LDH ↑

- **Ischemic** hepatitis

- ALT > LDH - acute viral > ischemic hepatitis

- **Malignancy**
Hyperammonemia

- ALF
- Hepatic encephalopathy
- Decompensated cirrhosis
# Dx Clues

**Table 302-1 Liver Test Patterns in Hepatobiliary Disorders**

<table>
<thead>
<tr>
<th>Type of Disorder</th>
<th>Bilirubin</th>
<th>Aminotransferases</th>
<th>Alkaline Phosphatase</th>
<th>Albumin</th>
<th>Prothrombin Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemolysis/Gilbert’s syndrome</td>
<td>Normal to 86 μmol/L (5 mg/dL)</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>85% due to indirect fractions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No bilirubinuria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute hepatocellular necrosis (viral and drug hepatitis, hepatotoxins, acute heart failure)</td>
<td>Both fractions may be elevated</td>
<td>Elevated, often &gt;500 IU</td>
<td>Normal to &lt;3 times normal elevation</td>
<td>Normal</td>
<td>Usually normal. If &gt;5X above control and not corrected by parenteral vitamin K, suggests poor prognosis</td>
</tr>
<tr>
<td></td>
<td>85% due to indirect fractions</td>
<td>ALT &gt; AST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No bilirubinuria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic hepatocellular disorders</td>
<td>Both fractions may be elevated</td>
<td>Elevated, but usually &lt;300 IU</td>
<td>Normal to &lt;3 times normal elevation</td>
<td>Often decreased</td>
<td>Often prolonged Fails to correct with parenteral vitamin K</td>
</tr>
<tr>
<td></td>
<td>Bilirubinuria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcoholic hepatitis Cirrhosis</td>
<td>Both fractions may be elevated</td>
<td>AST:ALT &gt; 2 suggests alcoholic hepatitis or cirrhosis</td>
<td>Normal to &lt;3 times normal elevation</td>
<td>Often decreased</td>
<td>Often prolonged Fails to correct with parenteral vitamin K</td>
</tr>
<tr>
<td></td>
<td>Bilirubinuria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra- and extra-hepatic cholestasis (Obstructive jaundice)</td>
<td>Both fractions may be elevated</td>
<td>Normal to moderate elevation</td>
<td>Elevated, often &gt;4 times normal elevation</td>
<td>Normal, unless chronic</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Bilirubinuria</td>
<td>Rarely &gt;500 IU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infiltrative diseases (tumor, granuloma); partial bile duct obstruction</td>
<td>Usually normal</td>
<td>Normal to slight elevation</td>
<td>Elevated, often &gt;4 times normal elevation</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fractionate, or confirm liver origin with 5’ nucleotidase or 1 glutamyl transpeptidase</td>
<td></td>
<td></td>
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</tbody>
</table>
PROGNOSIS

MELD score vs CP class for LTx priority

Table 301-4 Child-Pugh Classification of Cirrhosis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Units</th>
<th>1</th>
<th>2</th>
<th>3</th>
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</thead>
<tbody>
<tr>
<td>Serum bilirubin</td>
<td>μmol/L mg/dL</td>
<td>&lt;34</td>
<td>34-51</td>
<td>&gt;51</td>
</tr>
<tr>
<td></td>
<td>mg/dL</td>
<td>&lt;2.0</td>
<td>2.0-3.0</td>
<td>&gt;3.0</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>g/L g/dL</td>
<td>&gt;35</td>
<td>30-35</td>
<td>&lt;30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;3.5</td>
<td>3.0-3.5</td>
<td>&lt;3.0</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>seconds prolonged INR</td>
<td>0-4</td>
<td>4-6</td>
<td>&gt;6</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Easily controlled</td>
<td>Poorly controlled</td>
<td></td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>None</td>
<td>Minimal</td>
<td>Advanced</td>
<td></td>
</tr>
</tbody>
</table>

Note: The Child-Pugh score is calculated by adding the scores of the five factors and can range from 5 to 15. Child-Pugh class can be A (a score of 5-6), B (7-9), or C (10 or above). Decompensation indicates cirrhosis with a Child-Pugh score of >7 (class B). This level has been the accepted criterion for listing liver transplantation.

MELD provides a more objective means of assessing disease severity and has less center-to-center variation than the Child-Pugh score and has a wider range of values. MELD is currently used to establish priority listing for liver transplantation in the United States. A similar system using bilirubin, INR, serum albumin, age, and nutritional status is used for children below the age of 12 years [pediatric end-stage liver disease (PELD)].

Oct 1 2016
Further Ix

- LBT--
- Etiologi tests: Viral, Wilson, AIH, Toxin
- Sonography/EUS/Fibroscan
- CT, MRCP/ERCP
- Liver biopsy
- EGD
- FNA-cytology
- Ascites analysis
Tests to detect hepatic fibrosis

- Biological
  - Scores: APRI, FIB4

- Physical
  - Transient Elastography
Liver Bx Indications

(A) Diagnostic

- (1) Unspecified Hepatocellular disease
- (2) Unexplained hepatomegaly
- (3) Unexplained splenomegaly
- (4) Hepatic filling defects
- (5) FUO

(B) Staging & grading of CLD/malignant.
When to observe?

- LBT < 2x UNL
- No CLD s/s
- Normal imaging
- Young/pregnant - ALP
- Non rising LBT
- Seroius DDx excluded
When to biopsy Liver?

- Rising LBT > 2x
- CLD s/s
- Focal lesion
- Aging
- Obesity/comorbidity
- Recurrent/fluctuating
Local experiences: Cases

- HAV children and young- late exposure
- VOD-PA epidemic -PA-pyrole
- Epidemic dropsy-alkaloid outbreak≈case
- Cholestatic/Portal HTN
- HBV-Young family e neg& carrier/ tolerant
- HCV-Chronic hepatitis-adults and old
Summary

- Clinical triad approach: HIP
- Normally abnormal vice versa
- Transient abnormal LBT
- **Serial LBT**—Dx prognosis
- Localization for DDx: HC, cholestat-i/entra
- Imaging
- Etiologic tests
- **CIN VIM TTA** DDx---Clinic senario/epidm
THANK YOU!