Interpreting Your Tests Results

Breakout Session I
1:30-2:15
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Tests routinely ordered (or at least discussed) in patients with PSC

- Blood Tests
- Imaging
- Liver Biopsy
- Endoscopy
I: BLOOD TESTS
Liver Function Tests (LFTs)

• Important to differentiate between liver *tests* and liver *function*
Liver Function Tests

LFTs

- **Total Bilirubin TBr (1.3)**
  - Conjugated/unconjugated; direct/indirect

- **Aspartate Aminotransferase AST (40)**
  - Serum Glutamic Oxaloacetic Transaminase (SGOT)

- **Alanine Aminotransferase ALT (40)**
  - Serum Glutamic Pyruvic Transaminase (SGPT)

- **Alkaline Phosphatase ALP (125)**

- **Gamma Glutamyltransferase GGT (55)**

**Markers of Liver Injury**

Hepatocytes

- Biliary Epithelium

Marked of Liver Injury
Alkaline Phosphatase
ALP

• Generally speaking a marker of ‘biliary injury’.

  – Liver
  – Bone
  – Placenta
  – Intestine

Other causes of ALP elevation
GGT

• A more sensitive marker of biliary injury
Cholestatic

• **90%** of patients with PSC will have elevated Liver enzymes

• The predominant liver injury in patients with PSC
  – AST/ALT is usually only minimally elevated

• The elevation in the cholestatic enzymes is typically mild/moderate
Other diseases causing Cholestatic liver injury

1. **PBC**
   - Typically seen in middle aged females; fatigue and itching are hallmark symptoms

2. **Obstruction**
   - Stones, stricture, malignancy

3. **Infiltrative Diseases**
   - Sarcoid, amyloid, lymphoma

4. **Other**
   - Sepsis, Congestive hepatopathy, TPN, cholestasis of pregnancy, BRIC, CF
LFTs

• Many times are not a good correlate of liver function

• Frustrating for patients and physicians

• The reason a fair amount of liver disease goes undiagnosed
54 year old male with alcoholic cirrhosis on the transplant list

• AST 29
• ALT 42
• AP 97
• GGTP 48
42 year old female with biopsy proven moderate/severe fatty liver disease

- ALT 57
- AST 49
- AP 128
58 y/o male with advanced PSC

- AST 22
- ALT 20
- AP 72
- GGTP 93
Cirrhosis

• Before we go further
• It is important that we understand the definition of
• Cirrhosis
30 YEARS
Varices/Bleeding

Ascites

HCC

Encephalopathy

30%

Ascites
What are the most common causes of chronic liver disease in the US

- 1. NAFLD
- 2. HCV
- 3. ETOH
- 4. HC
- 5. HBV
- 6. AIH
- 7. PSC
- 8. PBC
- 9. A1ATD
- 10. Wilson
Synthetic Function of Liver

- Total Bilirubin
- Albumin
- Prothrombin Time
  - International Normalized Ratio (INR)

- These tests are incorporated into our models for staging ‘severity’ of liver disease
  - Childs Class
  - MELD score
Childs Classification

• When a patient has cirrhosis
• We then further classify the cirrhosis
• On an A, B, C scale

• Childs A meaning although there is advanced scar in the liver, it is still functioning well
• Childs C meaning the life expectancy without a liver transplant is not good
# Child Turcotte Pugh Class

<table>
<thead>
<tr>
<th>Clinical and Lab Criteria</th>
<th>Points*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>Encephalopathy</strong></td>
<td>None</td>
</tr>
<tr>
<td><strong>Ascites</strong></td>
<td>None</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt; 3.5</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td></td>
</tr>
<tr>
<td>Seconds prolonged</td>
<td>&lt;4</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>&lt;1.7</td>
</tr>
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</table>

Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)

- **Class A** = 5 to 6 points (least severe liver disease)
- **Class B** = 7 to 9 points (moderately severe liver disease)
- **Class C** = 10 to 15 points (most severe liver disease)
Model End Stage Liver Disease

MELD

• $\text{MELD} = 3.78 \ln(\text{serum bilirubin (mg/dL)}) + 11.2 \ln(\text{INR}) + 9.57 \ln(\text{serum creatinine (mg/dL)}) + 6.43$

• Weighted
  - INR
  - Creatinine
  - Bilirubin
MELD score + blood type are the major determinants of *when* patients get transplanted

- 1. Score ranges from 6-40
- 2. Realistically speaking, most patients will not be transplanted until their scores > 20
This is why many patients with PSC are not well served by the MELD score

- Patient’s can have very active disease
- Recurrent bouts of cholangitis
- Severe itching, fatigue etc...
- But have no dysfunction in their synthetic parameters
48 y/o male with UC and PSC

- 4 documented bouts of cholangitis (2 with bacteremia)
- Severe disease on CT scan and ERC
- Severe fatigue, anorexia
- TBr 1.6
- AST 94, ALT 98
- AP 642, GGTP 486
- INR 1.1, Cr 0.9
- Childs A, MELD 9
Gastroenterology and Hepatology in Minnesota

The Revised Natural History Model for Primary Sclerosing Cholangitis

In the following model, survival probability of a patient with primary sclerosing cholangitis is estimated based on the following variables. Please enter data in the corresponding boxes.

- How old is the patient? 43 (years)
- What is the bilirubin? 1.6 (mg/dl)
- What is the albumin? 3.7 (g/dl)
- What is the AST? 67 (IU/l)

Please choose one of the following for history of variceal bleeding.

- No history
- Past history

Risk score: 0.67922

Estimated Probability of Survival (%)

<table>
<thead>
<tr>
<th>Time</th>
<th>Year 0</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100</td>
<td>97</td>
<td>94</td>
<td>91</td>
<td>88</td>
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</table>
Almost all patients with PSC will have elevations in their cholestatic enzymes (ALP and GGTP)

Does this elevation correlate with disease severity or prognosis?
• The most recent evidence suggests that the answer to that question is:
  
• Yes
Reduction in ALP in patients with PSC is associated with improved survival

• Aim: to study the long term outcome of PSC patients on ‘medium’ dose UDCA (17-23 mg/kg)

• 198 patients

• Patients were categorized as biochemical responders if levels of ALP normalized or decreased by 40% after 1 year

AASLD 2012
• There was no difference in survival between treated (97) and untreated (101) patients.

• However, **ALP-responders** (regardless of UDCA) had a significantly better long term survival compared to non-responders (p 0.0001).
• Conclusions: Treatment with medium dose UDCA does not improve the long term survival in PSC patients.

• A reduction in ALP is associated with a better prognosis, regardless of UDCA treatment.
Kaplan-Meier analysis of survival UDCA vs. placebo and ALP-responders vs. non-responders

Figure 1a

Figure 1b
This observation was supported in a more recent study where achievement of ALP to 1.5x normal correlated with improved survival.

139 patients (63% males), followed mean 10 years.

- 40% achieved AP less than 1.5x ULN
- 60% did not
End points

Survival probability (%)

Years

SAP improvement to <1.5 ULN

NO SAP improvement

\( p = 0.001 \)

Number at risk

<table>
<thead>
<tr>
<th>Years</th>
<th>Group: SAP improvement to &lt;1.5 ULN</th>
<th>Group: No SAP improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>61</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>15</td>
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<td>0</td>
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<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
• 13/84 patients in the group who did not achieve improvement in ALP developed cholangiocarcinoma

• Versus none in the group that did improve

• The use of UDCA was similar in both group
What’s the deal with UDCA and PSC?

• I don’t know
  – I’m not sure anybody knows

• There are at least 10 studies showing UDCA leading to improvement in ALP

• So...
UDCA & PSC

• If normalization or near normalization of your ALP leads to a better prognosis
• &
• UDCA seems to improve alkaline phosphatase

• Can we infer that UDCA then leads to a better prognosis???
Long-term, high-dose UDCA therapy is associated with improvement in serum liver tests (TBr, AST and ALP) in PSC but does not improve survival and was associated with higher rates of serious adverse events.
• 150 patients
• Randomized, double-blinded, placebo, controlled
• High dose UDCA (28-30mg/kg) versus placebo
• 76 UDCA group versus 74 placebo
### Table 3. Biochemical Labs

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Alkaline Phosphatase</th>
<th>Aspartate Aminotransferase</th>
<th>Bilirubin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UDCA</td>
<td>Placebo</td>
<td>UDCA</td>
<td>Placebo</td>
</tr>
<tr>
<td>Baseline</td>
<td>76</td>
<td>73</td>
<td>3.3 (0.7-11.2)</td>
<td>3.2 (0.5-16.9)</td>
</tr>
<tr>
<td>12 Months</td>
<td>70</td>
<td>63</td>
<td>1.9 (0.6-9.1)</td>
<td>2.9 (0.6-13.6)</td>
</tr>
<tr>
<td>24 Months</td>
<td>65*</td>
<td>59†</td>
<td>1.8 (0.6-8.5)</td>
<td>2.6 (0.5-11.9)</td>
</tr>
<tr>
<td>36 Months</td>
<td>56‡</td>
<td>53</td>
<td>1.7 (0.6-16.5)</td>
<td>2.4 (0.4-12.1)</td>
</tr>
</tbody>
</table>

Data are presented as the median (range) unless otherwise indicated.

*At 24 months, only 64 patients were tested for bilirubin in the UDCA group.
†At 24 months, only 58 patients were tested for alkaline phosphatase in the placebo group.
‡At 36 months, only 55 patients were tested for bilirubin in the UDCA group.
• Despite better LFTs at the end of the study
• 39% of patients in UDCA group went on to develop: cirrhosis, varices, cholangio, need for LT or death
• Versus 26% in placebo

• More patients in UDCA group develop adverse side effects
Recommendations:

28. In adult patients with PSC, we recommend against the use of UDCA as medical therapy (1A).

29. In adult patients with PSC and overlap syndrome, we recommend the use of corticosteroids and other immunosuppressive agents for medical therapy (1C).
• Seems (to me) as if patients fall into two groups
• Aggressive course
• Relatively mild/benign course

• Does UDCA have any role in altering the course of the disease?
• This remains a topic of immense controversy
  – With no clear consensus
• High dose UDCA seems to be harmful
• Is there a medium/lose dose that may be of benefit to a select group of patients with PSC?

• Ie UDCA responders
Off the Record:

• Trial of (low/medium dose) UDCA 1-2 years
• If you are able to decrease a patient’s ALP to 1.5 ULN (or by 40% of original?)
• This patient may be a UDCA ‘responder’
• And may in fact benefit

• **Bottom line**: we need better medical therapy for PSC!
Etiology of PSC

• Remains unknown
• ? Genetic
• ? Inflammatory reaction
  – Infection (bacteria)
  – Toxin
• ? Vascular
• ? Autoimmune
Autoantibodies

• At least one + Autoantibody seen in up to 97% of patients with PSC
• Antinuclear, Smooth Muscle, Immunoglobulins, Rheumatoid Factor
• Clinical significance of this is unclear and the presence of these antibodies does not seem to correlate with disease severity.
• Very rarely patients with PSC can have an overlap with other ‘autoimmune’ liver disease
• Ie: autoimmune hepatitis (AIH)

• AST/ALT higher than you would expect in ‘typical PSC’

• In the right clinical scenario, a liver biopsy may help distinguish this further
IgG4

• Subclass of immunoglobulins/antibodies
• Associated with plasma cells and T lymphocytes
• Have been linked to a variety of conditions
• Most famously ‘Autoimmune pancreatitis’
• One of the hallmarks of these diseases is their exquisite responsiveness to steroid therapy
Abstract from AASLD 2012

- Serum IgG4 was prospectively measured in 194 patients with PSC
- 26 patients had an elevated IgG4 (14%)
- IgG4 patients were more likely to decompensate, require liver transplant or die
- Mean f/u ~ 8 years
- 7/26 patients received a trial of steroids
- 71% had a ‘favorable’ clinical response
• I am checking IgG4 on all my patients with PSC
• Current guidelines support this practice

• What exactly to do with a positive result remains debatable
  — PSC with IgG4 or
  — IgG4 associated cholangiopathy (IAC)

• In the right clinical scenario a liver biopsy and trial of steroids is reasonable
PSC and Cancer

- Lifetime risk of bile duct cancer (cholangiocarcinoma) is 10-15% in patients with PSC
- Patients with PSC + cirrhosis are at a risk of developing primary liver cancer
- Risk of GB cancer
  - 3-14%
- Risk of Colon Cancer
  - Directly related to presence of IBD
Tumor Markers

• Ca 19-9
  – Not sensitive to cholangiocarcinoma
    • Pancreatic Cancer
    • Elevation can be seen in non-malignant conditions (esp cholangitis, jaundice)
  – A level of > 200 should increase suspicion for choalngio, especially the in setting of dominant stricture
  – An upward trend in a patients with chronic PSC should raise concern
CEA

• Elevated in multiple conditions:
  – Colon cancer
  – Liver disease ‘in general’
  – Inflammatory states
  – Non GI diseases (COPD, Diabetes)
• A level of > 5.2 (in the right setting) should raise concern

Study from UPCM (GIE 2002) noted an abnormal CEA + an abnormal Ca 19-9 (combo) was better than either test alone in detecting cholangiocarcinoma
• A level of > 20 in a patient with advanced liver disease should raise concern
• Up to 50% of patients with HCC will have no elevation in AFP
  – AFP not clearly recc as a surveillance tool by current AASLD guidelines
• The risk of HCC in patients with PSC is almost exclusively seen in the setting of cirrhosis
  – PSC patients not directly named in list of surveillance population in AASLD guidelines
Tumor Marker Surveillance

• Most experts recc CA 19-9 (+/- CEA) yearly
  – No strong evidence to support this

• AFP – controversial
  – In a patient with cirrhosis q 6 months is reasonable
Fat Soluble Vitamins

• D, A, K and E
  – D: bone deficiencies
  – A: night blindness
  – K: bleeding disorders
  – E: neurologic symptoms

• Should be checked in patients with PSC
• Supplemental therapy should be administered when necessary
II: IMAGING
Ultrasound

- Low risk (no radiation)
- Low cost (comparatively speaking)
- User dependent
- Decent initial test of hepatic parenchyma
  - Can also assess vessel patency
- **Good for evaluation of gallbladder** (stones, polyps, masses)
- Good for evaluation of bile duct stone, large CBD stricture
- Not particularly good in patient’s with advanced disease
- Remains the **test of choice for surveillance of HCC**
  - AASLD
Computed Tomography
CT scan (with contrast)

- Fast
- Can evaluate entire abdominal viscera
  - Pancreas, stomach, intestines, kidneys
- **Not affected by obesity**
- Better at distinguishing masses, hepatic parenchyma
- Vasculature can also be assessed
- Disadvantages
  - Cost
  - Radiation Exposure
  - **Contrast**
    - Renal Injury
Magnetic Resonance Imaging

- Magnetic Resonance Imaging
- Comparable in efficacy in detecting lesions
  - Probably slightly better
  - Lesion in question on CT almost always prompts MRI

Advantages
- No radiation

Disadvantages
- Cost
- Takes longer (patient has to be cooperative – claustrophobia)
- Pacers/metal
- Renal Insuff?
- Difficult to read
Cholangiogram

Radiographic evaluation of biliary system

- MR
  - radiology
- ERC
  - endoscopy
- PTC
  - Interventional radiology
1. Needle inserted
2. Needle injects contrast medium into the **right** bile ducts
3. Needle injects contrast medium into the **left** bile ducts

![Image of liver and bile ducts with numbered steps and diagrams](image-url)
• MRCP has become the diagnostic test of choice for evaluation of biliary system

• Ie: You’re evaluating a patient with ulcerative colitis and they have a persistent elevation in ALP.

• The test to order is an MRCP.
185 patients with PSC
ERCP and PTC as reference standard
MRCP had a sensitivity and specificity 85% and 94% respectively

In most cases of suspected PSC, MRCP is sufficient for diagnosis, and thus, the risks associated with ERCP can be avoided
• When there is an otherwise unexplained elevation in a patient’s labs
  – Rise in TBr
  – Increase in Cholestatic Enzymes
  – Elevation in Ca 19-9/CEA
• Most will go to MRCP prior to ERC
Osteoporosis

- 15% of patients with PSC
- 24x higher than the regular (age, sex matched) population
- Risk factors for osteoporosis in patients with PSC
  - Risk factors for OP in patients with PSC
    - Age > 54 years
    - BMI < 24
    - Long standing IBD
**Dual-Energy X-ray Absorptiometry**

- DEXA
- The most widely used method to measure bone mineral density
- Recommend by AASLD in all patients with PSC at the time of diagnosis and then q2-3 years after
III: LIVER BIOPSY
• PSC is one of the few liver diseases where liver biopsy is NOT the gold standard in diagnosis

• AASLD guidelines recommends against routine liver biopsy for diagnosis of patients with PSC with typical cholangiographic findings

• Because of the nature of PSC, there is a high degree of sampling error (in terms of fibrosis)
Liver Biopsy in patients with PSC

- It can however be helpful in patients with:
  - Suspicion of very early disease
    - Small duct PSC
  - Sometimes is the only way to determine exactly how much scar tissue has developed in the liver
  - Patients with overlap (PSC/Autoimmune)
  - ? Patients with IgG4

- Some experts recommend that antibiotics be given to patients with PSC prior to liver biopsy in order to minimize risks of cholangitis
IV: ENDOSCOPY
1. EGD
   – Surveillance of portal hypertension
30 YEARS
Varices/Bleeding

Ascites

Encephalopathy

HCC

30%
PSC and Inflammatory Bowel Disease

• The incidence of IBD (mainly Ulcerative Colitis) ~ 80% in patient’s with PSC

• UC + PSC incurs a **fourfold risk in CRC** (compared to UC alone).

• Best established risk factors are:
  
  – 1. **Duration** of colitis
  
  – 2. **Extent** of colitis
    
    • Pan-colitis>rectal disease
• Colonoscopy
  – Required in all patients with a diagnosis of PSC
  – Even if bowel appears endoscopically normal, random biopsies should be obtained

• If and when a diagnosis of IBD is made in a patient with PSC

• Regular surveillance for CRC
ERCP

• Because of the risks associated with ERCP
  – Namely post ERCP Pancreatitis
  – Cholangitis

• Generally no longer considered a diagnostic test

• Reserved for:
  – Evaluation of concerning stricture
    • Biopsy/brushing
  – Removal of stones in patients with cholangitis
  – Dilation/stenting of stricture
Questions?
SAVE LIVERS
SAVE LIVES