Disclosures

• I have no conflicts of interest regarding the content of my presentation
Cholestasis
what is it, gall bladder? can't you see I have a lot to do?

I maked these

you made STONES?

YOU'RE JUST SUPPOSED TO HOLD WHAT I GIVE YOU!

GET OUT! GO ON!

I maked these
Functions: Liver Vs GB

• LIVER: 500

• GB: 2
1. Appendix
2. GB
3. Male Nipples
Cholestasis

- Greek in origin
- Means **bile stoppage**
- In its most overt form it presents as jaundice
- In early stages, cholestatic diseases lead to a preferential increase in the cholestatic liver enzymes: **AP and GGTP**
<table>
<thead>
<tr>
<th>Differential of Cholestatic Injury</th>
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</thead>
<tbody>
<tr>
<td>Biliary obstruction (stones, strictures, cysts, malignancy)</td>
</tr>
<tr>
<td>Infiltrative Diseases (Amyloid, Sarcoid, Malignancy, esp: Lymphoma)</td>
</tr>
<tr>
<td>Drug (Amox/Clav); TPN</td>
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<tr>
<td>Outflow (Right sided heart failure, Budd Chiari)</td>
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<tr>
<td>Sepsis</td>
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<tr>
<td>Cystic Fibrosis</td>
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<tr>
<td>Cholestatic Hepatitis (HBV/HCV)</td>
</tr>
<tr>
<td>Rejection; GVHD</td>
</tr>
<tr>
<td>Autoimmune Cholangitis</td>
</tr>
<tr>
<td>ICP, BRIC, PFIC</td>
</tr>
<tr>
<td>Secondary sclerosing diseases</td>
</tr>
<tr>
<td>Paraneoplastic</td>
</tr>
<tr>
<td>Idiopathic</td>
</tr>
</tbody>
</table>
Primary Biliary Cholangitis
&
Primary Sclerosing Cholangitis
• **18 papers and 4 abstracts** all published within last year with relatively high IF
Primary Sclerosing Cholangitis

- Chronic progressive disorder of unknown etiology (??Immune mediated) that is characterized by inflammation, fibrosis, and stricturing of medium size and large ducts in the intrahepatic and extrahepatic biliary tree
- Dx made on cholangiogram
  - MRCP > ERCP
- 40K cases in US
- 70% are male; average age dx 40
- ~80% of patients have concomitant IBD (UC)
  - Increased risk of colon cancer
PSC

- Increased risk of cholangiocarcinoma
- Increased risk of GB cancer
- No proven medical treatment
- ? 50% of patients will require OLTx at 15 years
Liver Transplants US Last Decade

- HCV
- NASH
- ALD
- HCV/ALD
- PBC/AIH
- PSC
- ALF

PSC pie slice is highlighted.
British Society Guidelines on PSC

Gut August 2019
Chapman et al

1. Recommend that UDCA not be routinely used for new dx of PSC
2. ERCP should be performed with expert multidisciplinary assessment
   – Mandatory that dominant strictures be sampled
3. Imaging should be prompted by change in symptoms or biochemical abnormalities
   – Recommend against routine monitoring of Ca 19-9
   – No recommendations on routine cholangio surveillance
4. GB US yearly
5. In patients with developing cirrhosis US +/- AFP per guidelines

Us guidelines Feb 2010
1. survey for cholangio and GB Ca in all adult patients with PSC regardless of disease stage especially in first year of dx and in patients with concomitant UC

2. US/CT or MRI with or without Ca 19-9 q6-12 months

3. no surveillance in patients less than 20 or those with small duct disease

4. strongly consider chole in pts with gb polyps 8mm or greater
Scheduled ERCP dilation of dominant stricture in patients with PSC

Gut, Dec 2019

• Germany, 1987–2017
• Group 1: scheduled ERCP with dilation of dominant stricture (even if asx) until resolution: 133–4 weeks from initial; then 3 months then q6 months
• Group 2: pts that refused scheduled and so ERCP only on demand: 153
• 268 patients, 10 year f/u
• Transplant free survival 51% versus 29% (p<0.01)
ERCP in Decompensated Cirrhosis

J Clin Exp Hepatol
Sept 2019; Jagtap et al

- India, January 2012 to December 2016
- 261 patients – 28% ETOH, 28% NASH, 22% Viral, 4% PSC – Childs A: 17%, B 52%, C 31%
- Cholangitis in 27% pts – Sphincterotomy performed 66%
- One month adverse events: 16.1%
- One month mortality 8.5% – Bleeding, cholangitis, post ercp pancreatitis, cardiac, sbp, variceal bleed (3), pse
- MELD > 18, OR 5.6 (adverse events)
Validation of Amsterdam-Oxford model for PSC

JOH, Nov 2019
Goet et al

• 534 Patients with PSC
• Mean age 39 years; large duct in 87%
• 66% male; 92% on UDCA
• 60% UC
• 8 year f/u
• 7 parameters: large/small duct; age, albumin, AP, AST, TBr and platelets
## Input Parameters

**PSC Subtype**
- Large Duct

**Age at PSC Diagnosis**
- 24 Years

**Reset to original reference values**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Albumin</strong> (lower limit of normal (LLN))</td>
<td>35</td>
<td>g/L</td>
</tr>
<tr>
<td><strong>Alkaline Phosphatase (ALP)</strong> (upper limit of normal (ULN))</td>
<td>120</td>
<td>U/L μkat/L</td>
</tr>
<tr>
<td><strong>Aspartate Aminotransferase (AST)</strong> (upper limit of normal (ULN))</td>
<td>35</td>
<td>U/L μkat/L</td>
</tr>
<tr>
<td><strong>Bilirubin</strong> (upper limit of normal (ULN))</td>
<td>17</td>
<td>μmol/L mg/dL</td>
</tr>
<tr>
<td><strong>Platelets</strong> (lower limit of normal (LLN))</td>
<td>150</td>
<td>x10⁹/L</td>
</tr>
</tbody>
</table>
### Output Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amsterdam-Oxford PSC Score</td>
<td>3.55</td>
</tr>
<tr>
<td>5-year transplant-free estimated survival</td>
<td>53.70%</td>
</tr>
<tr>
<td>10-year transplant-free estimated survival</td>
<td>20.25%</td>
</tr>
<tr>
<td>15-year transplant-free estimated survival</td>
<td>7.03%</td>
</tr>
</tbody>
</table>

#### Prognosis of Patient

![Graph showing survival probability over years after diagnosis](image-url)
Patients with PSC and Development of Validation of a Risk Scoring System
Hepatology May 2019; Goode Et al

• UK-PSC research cohort
• 1001 pts!
• Age
• TBr dx and year 2
• Platelets dx and year 2
• Hg at dx
• AP dx and year 2
• Extrahepatic disease at dx
• Variceal bleed by year 2

• My same patient:
• 5 year transplant free survival ~ 46% (vs 53% with Amsterdam)
Farnesoid X Receptor Agonist Cilofexor (GS 9674) in PSC

Trauner et al
Hepatology Sept 2019

1. Phase II Double Blind Placebo Controlled
2. 13 sites; large duct, non cirrhotic
52 patients randomized (age 43, 58% male, 60% IBD; 46% UDCA)
Baseline AP 348 (288-439)
21% reduction in AP Cilofexor at 12 weeks (.029 vs placebo), independent of UDCA use
Well tolerated
Improved Outcomes of Patients With Primary Sclerosing Cholangitis

CGH, Stokkeland et al
August 2019

• 1. Sweden 2005-2014; 2914 patients!
• 61% male, 41 years of age
  – 60% of patients on UDCA
  – 75% 5-ASA
  – 75% Azathioprine
  – 34% 6MP
• 14% statin
• Statin associated with reduction in all cause mortality: HR 0.68 (CI 0.54-0.88) and the need for LT
  – Aza also with similar decrease in all cause mortality and LT
• UDCA did not affect mortality
Cholestatic and Autoimmune Liver Diseases
Prospective validation of the prognostic value of liver stiffness (LS) (FibroScan®) in PSC: the FICUS study

Aim:
To assess prospectively the prognostic value of liver stiffness (LS) as evaluated by FibroScan® in patients with PSC

Methods:
• 13 institutions, across 11 countries
• 616 PSC patients included, analysis at 2 years in 514 with valid LS at inclusion

Main Findings:
Strong and independent (adjusted for bilirubin, ALP, and Mayo Risk Score) predictive value of LS

Conclusions:
This study validates the prognostic value of LS (FibroScan®) in PSC and supports the role of LS as a risk stratifying tool and potential surrogate endpoint in clinical trials.

Chazouilleres O, et al., Abstract 47
Bile acid profiles predict hepatic decompensation in primary sclerosing cholangitis

Aim:
- Patients with PSC often demonstrate increased plasma bile acid (BA) concentrations due to ongoing cholestasis.
- We aim to establish whether bile acid profiles are predictive of hepatic decompensation (HD): ascites, variceal hemorrhage, or encephalopathy.

Methods:
Plasma BA profiles and alkaline phosphatase levels of 425 patients with PSC were measured using clinically available assays and gradient boosting was used to build multivariable models predicting development of HD.

Main Findings:
Using a machine learning technique, BA profiles are independently capable of predicting future HD events in PSC patients over 5 years.

Conclusions:
BA profiles have prognostic value and should be considered in disease management and as an exploratory endpoint in future clinical trials.

Mousa OY, et al., Abstract 188
PBC
Primary Biliary Cholangitis  
formerly known as Primary Biliary Cirrhosis (2015)

- Chronic liver disease resulting from progressive immunologic destruction of the small intralobular bile ducts that may result in cirrhosis and liver failure
- 95% of patients are female
- Diagnosis typically made 4\textsuperscript{th}/5\textsuperscript{th} decades of life
- Fatigue, itching (pruritus), abdominal discomfort (less common)
- 50% of pts are asymptomatic
PBC diagnosis: 2 of the following 3

- Elevation in LFTs – specifically AP/GGTP (cholestatic enzymes)
- Antimitochondrial antibodies (AMA) are the serologic hallmark; present in 95% of patients
- Liver biopsy classically shows ‘florid duct lesion’
PBC

- PBC used to be one of the more common indications for liver transplant
- But since the approval of UDCA, the prognosis of pts with PBC (diagnosed before onset of cirrhosis) is quite good
Onion Skinning: PSC

Florid Duct Lesion: PBC
Boston
I don't often hate, but when I do...
I prefer to hate the New England Patriots.
Boston 2009

• Wife: So...what do you do?
• Me: I’m a hepatologist
• Wife: What the heck is that
• Me: I’m a liver physician
• Wife: a liver what?
• Me: I’m a doctor
• Wife: I DO!
10 year anniversary
Age and Sex Response to UDCA and Tx Free Survival in PBC

Cheung et al, CGH Sept 2019

• Global PBC Study Group
• Retrospective study of 4355 patients with PBC
• 1961-2014
• Male patients were older at the start of treatment (58 versus 54)
• Younger pts (male and female; 45 years or less) were less likely to respond to therapy
• Risk of LT or death decreased significantly with advancing age
• Patients less than 35 especially (HR 14.59)
Incidence, Prevalence and Outcome of PBC in Sweden
Marschall et al; Sci Rep August 2019

• 1. 1987-2015
• 2. 5K patients with PBC matched to 10 controls
• Prevalence of PBC increased from 5/100K to 37 between 87 and 2014
• Female male ratio 4:1
• PBC individuals aged 15-39 had a substantially high risk of death (HR 12.7); risk was highest in men
Factors associated with progression of Early Stage PBC
CGH; August 2019
Gatselis et al

• 1. 1615 patients, mean age 55 with early stage PBC (based on albumin and br)
• Median f/u 8 years
• Of the patients: 904 developed ‘moderate’ disease and 201 ‘advanced’ disease over the study period
• 236 patients had a ‘clinical event’
• UDCA and LFTs are biggest predictors!
BEZAFIBRATE AND PBC

• Placebo controlled trial of bezafibrate in PBC

NEJM June 2018

• Phase III trial, Paris

• 100 patients who had inadequate response to UDCA

• 50/50 bezafibrate (500mg) vs placebo

• AP normalized 67% of pts in study arm versus 2% placebo
Bezafibrate

- is a fibrate drug used as a lipid-lowering agent to treat hyperlipidemia. It helps to lower LDL cholesterol and triglyceride in the blood, and increase HDL.

- It was patented in 1971 and approved for medical use in 1978
  - Not available in US
  - Gemfibrozil and fenofibrate
Bezafibrate and long term outcomes in PBC
Hepatology, Honda et al
Feb 2019

• Bezafibrate is 2nd line agent in Japan for PBC
• From a cohort of 873 patients with PBC
• Enrolled 118 patients treated with combo UDCA and bezafibrate
• Combo therapy significantly decreased prognostic scores (GLOBE and UK-PBC) and long term prognosis (Tx free survival and liver related death)– especially in those with early PBC
Pruritus is common and undertreated in PBC in the UK

CGH June 2019
Hegade et al

• 1. > 2000 patients, self reported data
• 73% experienced pruritus
• Severe in 12%
• Younger age and AP elevation were associated with pruritus
• Less than 50% patients received medical therapy (cholestyramine, rifampin, naltrexone)
Smoking and risk of PBC: systemic review and Meta analysis

J Gastrointestin Liver Dis June 2019
Wijarnpreecha et al

• 1. Nine case control studies; 21K participants
• Smoking OR 1.31 risk of PBC versus non smokers
Trends in LT for PBC in Europe

Ailment Pharmacol Ther
Feb 2019; Harms et al

- Patients undergoing LT from 1986 to 2015 in European LT Registry
- 6029 pts with PBC (5.3% of all transplants)
- Indication dropped from 20% in 1986 to only 4% of all transplants in 2015
- PBC was the only indication showing consistent decrease throughout all decades
Outcomes of LT for PBC; SRTR Database
DDS, Sayiner et al
August 2019

• 1994-2016
• 223,000 LT; **8K for PBC (3.6%)**
• Mean age 55; 80% white; 86% female
• Mean MELD 21
• 6.6% retx
• Waitlist mortality 18%
• Tx rate was 57.7% (versus 53% HCV)
• Waitlist dropout 25%
• Mortality and graft loss were significantly lower compared to HCV
Recurrence of PBC after LT

Gastro Jan 2019
Montano-Loza et al

- 785 (89% female) patients with PBC who underwent LT; mean age 54 years; mean f/u 7 years
- 1983-June 2016; USA and Europe
- Recurrence occurred in 22% of patients at 5 years and 36% at 10 years
- Factors associated with recurrence:
  - 1. age < 50 at diagnosis of PBC
  - Age of LT less than 60 years
  - Use of FK (HR 2.31)
  - Increased AP and TBr 6 months post LT
  - Recurrence was associated with increase risk of graft loss
    - We were not in this study, but for the record UPMC alone has done 600 PBC transplants! This study was the composite of 16 European centers
Cholestatic and Autoimmune Liver Diseases
Bezafibrate is superior to placebo in improving pruritus in chronic cholestatic liver disease: the FITCH trial

Hypothesis:
Bezafibrate may relieve cholestasis-associated pruritus by alleviating hepatobiliary inflammation and thereby reducing secretion of a biliary itch factor (Hepatology 2014;60:399-407).

Methods:
Double-blind, randomized, placebo-controlled trial in patients with PSC (n=44), PBC (24), or secondary sclerosing cholangitis (2) with moderate to severe cholestasis-associated pruritus.

Main Findings:
Bezafibrate (400 mg daily) led in 38% of the patients to ≥50% reduction of pruritus whereas patients treated with placebo reached the primary endpoint in 12% (p=0.03; see figure).

Conclusions:
Bezafibrate is superior to placebo in improving pruritus in chronic cholestatic liver diseases such as PSC and PBC.

Vries de ES, et al., Abstract 13
Durable response in the markers of cholestasis through 5 years of OLE study of OCA in PBC patients

Objective:
Open-label extension (OLE) of the POISE phase 3, randomized, double-blind, placebo-controlled, study in patients with PBC to assess long-term safety of obeticholic acid (OCA) and durability of effects on serum markers of cholestasis.

Methods:
Following the 1-year double-blind phase, patients on placebo started OCA and were then pooled with OCA-treated patients to evaluate the efficacy and safety of up to 6 years of OCA treatment.

Main Findings:
- ALP, AST, GGT, and key inflammatory markers were significantly reduced; reductions were sustained for the duration of treatment.
- Total bilirubin was maintained within the normal range.

Conclusions:
Six years of treatment with OCA resulted in sustained improvements in markers of cholestasis and inflammation and in stabilization of liver stiffness with no new safety observations.

Nevens F, et al., Abstract L06
Eleven Take Home Points

1. **Scheduled dilation of dominant stricture** may have mortality benefit in patients with PSC.

2. **ERCP should be performed with** expert multi-disciplinary assessment.
   - ERCP in pts with cirrhosis (esp B/C; MELD > 18) carries a one month mortality near 10%.

3. The Amsterdam-Oxford and UK-PSC online validation scores offer **prognostic information** with readily available clinical data.

4. **FibroScan** also has very good prognostic value in PSC.

5. **Statins** may have mortality benefit in pts with PSC.
   - Ongoing study of **FXR Agonist**.
Take home points (cont)

6. Younger patients (less than 35) dx with PBC have a more aggressive course

7. Although many patients with PBC will respond to UDCA up to a 1/3rd will not and AP is probably the best short term clinical predictor

8. Role of Bezafibrate in mortality benefit and sx relief

9. OCA has durable (biochemical) response at 5 years in patients with PBC

10. PBC as an indication for LT has dropped nearly five fold; Recurrence of PBC post LT is not uncommon

11. Probably should think twice before agreeing to give a talk on a Saturday the day following your ten year anniversary
SAVE LIVERS
SAVE LIVES
2019 Annual Update in Medical Hepatology

Latest Advances in Cholestatic Diseases

Shahid M. Malik, MD
Assistant Professor of Medicine
Program Director Transplant Hepatology Fellowship