Potpourri for Transplant Hepatology Boards

AASLD Transplant Board Review Course 2020
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What’s Being Covered

- **Vascular Liver Diseases:**
  - Budd Chiari Syndrome
  - Sinusoidal Obstructive Syndrome (VOD)
  - Cardiac Cirrhosis
- **Autoimmune Liver Diseases**
  - Sarcoidosis
  - Celiac Disease

- Adherence to Medical Regimen
- Quality of Life
- Miscellaneous (not on blueprint)
  - Immunizations
  - Cancer screening after liver transplant
Budd-Chiari Syndrome (BCS)

- Hepatic venous outflow obstruction
  - Thrombosis of HV &/or IVC
    - Cardiac congestion/SOS excluded
  - 0.2-0.8 per million per yr
- West: HV obstruction
- East: Suprahepatic IVC (web)
  - Can be combined HV/IVC

Primary BCS
- Venous thrombosis or phlebitis

Secondary BCS
- External HV/IVC compression
- Benign/malignant/infectious
Risk Factors for Primary BCS

- 87% of pts have a prothrombotic RF
- 46% have > 1 prothrombotic RF
- Any hypercoagulable state, Factor V Leiden common
- Myeloproliferative d/o often present – easy to miss
- OCP (stop)
- Recent pregnancy

BCS Presentations
Variable

Fulminant liver failure (<5%)
Acute (weeks)
Subacute (3 months)
Chronic (adv fibrosis/cirrhosis)
Asymptomatic (incidental)

Symptoms:
Abdominal pain
Hepatomegaly
Ascites (SAAG > 1.1, T pro > 2.5)
Fever
Elevated liver enzymes
HE
Variceal bleeding
Diagnosis

- Doppler USG (in good hands)
- MR better than CT - Must exclude space occupying lesions
- Venography (select cases) – can be used for catheter based rx
- Liver biopsy – not helpful

BCS Management: Stepwise approach

- **Anticoagulation**
  - Urgent
  - Thrombosis eval
  - LMWH
  - Xa level 0.5-0.8
  - Warfarin
  - INR 2-3
  - Stop OCP

- **Thrombolysis**
  - Acute BCS only (<4wks)
  - Angioplasty +/- stenting
  - Symptomatic acute or subacute BCS
  - Esp for focal IVC web (Asia)
  - Stent in IVC can preclude OLT

- **Hepatic Decompression**
  - TIPS
  - Acute or subacute failing other treatments
  - Treat portal HTN complications
  - Can be technically challenging with clot
  - 5yr survival: 84%

- **Surgical shunt**
  - Mostly historical

- **Transplant**
  - Not candidates for or fail other treatments
  - 5yr survival: 85%

The usual management of ascites, varices, renal dysfunction of liver disease applies
Local expertise will vary
BCS survival scoring systems (Clichy, Rotterdam, BCS-TIPS): not clinically useful

BCS: Monitoring for Malignancy

- **HCC**
  - Prevalence HCC up to 15%
  - RFs for HCC
    - Combined HV & IVC thrombus
    - Long IVC segment thrombus, OR 6.5
    - Cirrhosis
    - Older age
  - Enhancing nodules can mimic FNH, likely d/t perfusion issues

- **Myelofibrosis and acute leukemia can occur**

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**Sinusoidal Obstructive Syndrome (VOD)**

**Seattle Criteria**
- 2 of 3 within 20d of transplant
  - Bili > 2 mg/dL
  - Tender hepatomegaly/RUQ pain
  - >2% weight gain from fluid

**Baltimore Criteria**
- Bili > 2 mg/dL plus 2 other criteria
  - Hepatomegaly, painful
  - > 5% weight gain
  - Ascites
- R/O other liver diseases
- Liver biopsy (not required)
  - Can be patchy
  - HVPG > 10 hi specificity for SOS

- **Circulatory d/o of sinusoids leading to non-thrombotic sinusoidal obstruction and can occlude central veins**
- **Associated with pre-SCT myeloablation and chemotherapy**
- **Presentation similar to BCS except patent HV/IVC**
- **Doppler USG – ascites/hepatomegaly**

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Paul et al. APT 2015;41:961-71,
Plessier et al. J. Hepatol 2012; 56: S25-S38

Plessier et al. J. Hepatol 2012; 56:S25-S38
Sinusoidal Obstructive Syndrome (VOD)

Agents associated with SOS

- Azathioprine/6MP/6TG
- Oxaliplatin
- Busulfan
- Cyclophosphamide
- Mephalan
- Dacarbazine
- Gemtuzumab-Ozogamicin

Teas/foods with pyrrolizidine alkaloids

Sinusoidal Obstructive Syndrome Prophylaxis and Treatment

- **Prophylaxis with myeloblation**
  - Urso – widely used, mixed data
  - Reduced intensity regimens
  - Lower body radiation <12 Gy
  - Careful pre-existing liver fibrosis
    - High dose myeloablation contraindicated in cirrhosis
    - Norethisterone contraindicated

- **Treatment of SOS**
  - Defibrotide tho data mixed
  - Manage fluid overload
  - No TIPS
    - Helps ascites, not survival
  - OLT case reports for benign condition or favorable prognosis malignancy

Images courtesy J. Hart, MD
Cardiac Cirrhosis
(congestive hepatopathy)

Presentation
- RUQ pain
- Hepatomegaly (often tender)
- Ascites
- Pulsatile liver
- Hepatojugular reflux

Diagnostic studies
- ECHO
- Doppler USG
- Dilated IVC / HV
- Liver biopsy – select cases
- Prior to cardiac transplant
- Sampling error – bi-lobar

Labs
- TB elevation, predictor of morbidity and mortality
- Transaminases elevation 1/3 (2-3 ULN)
- Consider ischemic hepatitis from dec CO with massive transaminase elevations

Cardiac ascites
- SAAG > 1.1, ascites total protein > 2.5
- Serum BNP > 364 pg/mL, 98% sens & 99% spec for cardiac ascites
- Serum BNP < 182 pg/mL r/o cardiac ascites

Treat underlying heart disease
- Combined heart-liver txp
  - CHLT: 0.3% of all heart txp
  - CHD, amyloid, CMP
  - CHLT survival 1yr 86-92%
    5yr 83-92%
  - CHLT survival similar to heart alone
- Heart/liver/kidney transplant reports
- HCC has been reported many years after Fontan’s
Sarcoidosis

- 20-40% of sarcoid pts with elevated ALP or GGT
- 50-65% of sarcoid pts have portal or periportal granulomas on liver biopsy (often do not biopsy)
  - <5% develop symptoms (fever/weight loss/ jaundice)
  - Rare advanced disease (cirrhosis/portal HTN/ Budd Chiari)
- Look for extra-hepatic disease if no previous sarcoid dx

Judson. Semin Respir Crit Care Med 2007; 28:83
**Sarcoidosis - Diagnosis**

**Clinical Features**

- Elevated ALP and GGT
- Elevated ACE
- Extrahepatic sarcoid diagnosis strengthens
- Abdominal pain, fatigue, fever, weight loss and hepatomegaly
- Presents with hilar LAD with obstruction, HVT, jaundice, intrahepatic biliary strictures (rarely)
- Portal HTN from progressive fibrosis or periporal granuloma restricting portal flow

Exclude alternative causes:
- Infectious: TB, fungal, Q fever, brucellosis
- PBC/PSC
- Hodgkin’s, NHL
- DILI

Image courtesy J. Hart MD


**Hepatic sarcoidosis - Treatment**

- Asymptomatic (most) no rx
- Symptomatic
  - Extrahepatic dz dictates rx
  - Immunosuppression (6-12mos):
    - Steroids
      - 1/3 resolve, 1/3 partial, 1/3 no response
    - MTX or AZA
    - Urso
- Transplant - rarely indicated
  - 0.12 % sarcoid OLT in UNOS
- UNOS OLT survival 1987-2007:
  - Sarcoid: 1yr - 78% 5yr - 61%
  - PSC/PBC: 1yr - 90% 5yr - 79%
  - Sarcoid factor for poor survival
- Sarcoid recurs post transplant
  - Noted cause of death post-tpx
- OLT reports for HVT,Budd-Chiari

Kennedy et al. Eur J Gastroenrrol Hepatol 2006; 18:721
Vanatta et al. Liv Transplant 2011; 7:1027-1034

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The Liver in Celiac Disease (CD)

New celiac diagnosis:
- Transaminase elevations in 40% adults & 60% kids
- Usually asymptomatic, fatigue & malaise reported
- HBV vaccine not as effective

Celiac hepatitis “classic disease”
- Transaminases normalize 75-95% on GFD
- Biopsy mild steatosis or portal inflammation, usu. not needed
- Look for CD in unexplained elevated LTs
- CD has been implicated in unexplained advanced fibrosis

Celiac pts:
- 2-6 fold increase in liver disease
- 8 fold inc risk of death in cirrhosis vs gen pop
- CD prevalence in OLT pts reported 3-4.3%
- Associated with PBC, PSC and AIH

Rubia-Tapia et al. Hepatology 2007; 46: 1650-1658

Images courtesy J. Hart, MD

Adherence to Medical Regimen
**Adherence to Medical Regimen**

- **Self-report NA:** 62% at least once last 3 months
  - 2% NA “frequently” or “always”

- **Clinician report NA:** 22%
  - Includes missed labs / appts

- **Biochemical NA (Standard deviation of TAC levels):** 32%
  - SD TAC >2.5 mcg/dl is predictive of graft failure and NA

- **Reports of NA higher in the US**
  - NA of IS for kidney transplant worse than liver and other organs

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**Risk Factors for Non Adherence**

- Limited literacy
- Limited finances
- Adolescence
- Unemployment at time of listing
- Pretransplant non-adherence
- H/O Substance abuse
- Higher number of medications

**Improving Adherence**

- Motivational pharmacy counseling
- Structured education (including testing knowledge)
- Pt demonstration of regimen use (filling pill boxes)
- Cell phone/text reminders (kidney)

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**Quality of Life**
Quality of Life

Liver Transplant vs Pre-operative Status

- LT improves QOL and physical function
- Improves loneliness, anxiety & hopelessness
- Better social interactions
- Durable up to 20 yrs

Liver Transplant vs General Population

- QOL similar but physical function reduced in LT
- Postoperative activity is key for better outcome
- Lower QOL with increased post-op complications
- Esp physical domains

Employment

- Pre-op: lack of disability & hours worked pre-txp predicts post-op employment
- Recover short term (50% employed)
- Decline after 5 yrs (2/3 retired 8yrs out)
- PSC better than ALF, PBC, alcohol

Yang et al. Liver Int. 2014; 34: 1298-1313
Desai et al. Liver Transpl 2008; 14: 1473-1479
Yang et al. Liver Int 2014; 34: 1298-1313
### Immunizations for transplant patients

<table>
<thead>
<tr>
<th>Vaccines safe to give post-transplant (inactive, killed or recombinant)*</th>
<th>Live vaccines-contraindicated after transplant^</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seasonal influenza</td>
<td>Zoster live (ZVL)</td>
</tr>
<tr>
<td>Pneumococcus q3-5 yrs</td>
<td>Varicella (VAR)</td>
</tr>
<tr>
<td>Hepatitis A Virus</td>
<td>Measles/Mumps/Rubella (MMR)</td>
</tr>
<tr>
<td>Hepatitis B Virus (2 and 3 dose series)</td>
<td>Rotavirus (kids only)</td>
</tr>
<tr>
<td>Meningococcus</td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenzae (Hib)</td>
<td></td>
</tr>
<tr>
<td>Human papilloma (HPV) (up to age 26)</td>
<td></td>
</tr>
<tr>
<td>Tetanus/diptheria/perussis (Tdap/Td)</td>
<td></td>
</tr>
<tr>
<td>Recombinant zoster vaccine (Shingrix) RZV</td>
<td></td>
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</tbody>
</table>

* Best if give vaccinations at least 4 wks prior to txp to maximize immune response

^ Live vaccines can be given BEFORE transplant (at least 4 wks)
**Newer vaccines**

- **Heplisav (HepB-CpG)**
  - 2 dose series, 1 month apart
  - Immunostimulatory adjuvant
    - sAb: 90-100% HepB-CpG vs 70-90% conventional Engerix-B
    - Better in DM/obese than conventional
    - Limited data in cirrhosis & post-LT
    - Theoretical risk alternating immunotolerance post LT
  - Conventional HBV vaccines in cirrhosis (Engerix-B or Recombivax-HB): seroconvert 28-62% (double dose)

- **Shingrix (Recombinant Zoster Vaccine)**
  - 2 dose series, 2-6 months apart
  - Recombinant, can give post-LT
  - Age 50
  - RZV superior to zoster virus live (ZVL) preventing Zoster and postherpetic neuralgia

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**Cancer screening post liver transplant**

<table>
<thead>
<tr>
<th>Cancer (source/yr)</th>
<th>Recommendation from AST/AASLD and USPSTF for Cancer Screening in Liver Transplant Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast (US 2016)</td>
<td>Biennial mammogram women age 50-74, individualize age 40-49</td>
</tr>
<tr>
<td>Skin (AST 2012)</td>
<td>Self exam monthly, Derm exam yearly starting 5yrs post LT</td>
</tr>
<tr>
<td>Cervical (US 2018)</td>
<td>21-29 y/o PAP q3 yr 30-65 y/o q 3yr PAP, alternative PAP+HPV q5 yr</td>
</tr>
<tr>
<td>Prostate (2018 US)</td>
<td>Individualize men 55-69 y/o yearly PSA. Do not screen above 70 y/o</td>
</tr>
<tr>
<td>Colon (AST 2012)</td>
<td>IBD with PSC yearly colonoscopy. Multiple societies general CRC recommendations</td>
</tr>
<tr>
<td>Lung (US 2013)</td>
<td>Annual low-dose chest CT age 55-80 with 30 PY smoking history (smokers and ex-smokers)</td>
</tr>
<tr>
<td>Oropharyngeal (US 2013)</td>
<td>Not enough evidence to recommend screening</td>
</tr>
<tr>
<td>HCC (AST 2012)</td>
<td>Cirrhosis of graft require abdominal imaging q 6-12 months</td>
</tr>
</tbody>
</table>
Best of luck!