End-Stage Liver Disease in HIV
Liver Transplantation

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Presented at the Pre-workshop Educational Course, Milan, Italy, 1 June 2011
Survival Time from First Liver Decompensation to Death in HCV

- Death during study
  - 366/1037 HCV
  - 100/180 HIV/HCV
- Risk factors for death:
  - HIV
  - Baseline CTP
  - MELD >13
  - Age
Proportion of deaths due to ESLD in HIV+

- Neither HBV or HCV: 12% ESLD, 60% AIDS, 39% Other
- HBV alone: 22% ESLD, 38% AIDS, 40% Other
- HCV alone: 31% ESLD, 29% AIDS, 40% Other
- HCV and HBV: 44% ESLD, 22% AIDS, 34% Other

Salmon-Ceron, J Hepatol 2005
HIV immune reconstitution also improves survival from HCV liver disease

**Overall Mortality**

- Cumulative Survival
- Observation Time (days)
- HAART
- ART
- None

**Liver-related Mortality**

- Cumulative Survival
- Observation Time (days)

Qurishi, Lancet 2003
Natural History of ESLD

Chronic liver disease → Compensated cirrhosis → Decompensated cirrhosis → Death

Increasing liver fibrosis → Development of HCC

- Alcohol
- Hepatitis C/B
- NASH
- Cholestatic
- Autoimmune

- Variceal hemorrhage
- Ascites
- Encephalopathy
- Jaundice

HCC, hepatocellular carcinoma; NASH, nonalcoholic steatohepatitis
Garcia Tsao CCO Hepatitis.com 2008
Natural history of ESLD

• Transition to decompensated cirrhosis: 5% to 7% of patients per year.
• Best predictor of decompensation: hepatic venous pressure gradient (HVPG) > 10 mm Hg
• HCC
  – can trigger decompensation
  – predictor of death in decompensated cirrhosis
• Tools for predicting disease severity and death in decompensated cirrhosis
  – Child-Turcotte-Pugh (CTP) score
  – Model for End-Stage Liver Disease (MELD) score

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## Child-Pugh-Turcotte Score

<table>
<thead>
<tr>
<th>Points</th>
<th>1 (normal)</th>
<th>2</th>
<th>3</th>
</tr>
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<tbody>
<tr>
<td>Hepatic encephalopathy</td>
<td>None</td>
<td>1-2</td>
<td>3-4</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>slight</td>
<td>mod</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>&lt;2</td>
<td>2-3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Albumin</td>
<td>&gt;3.5</td>
<td>2.8-3.5</td>
<td>&lt;2.8</td>
</tr>
<tr>
<td>PT or INR</td>
<td>&lt;4 secs</td>
<td>4-6 secs</td>
<td>&gt;6 secs</td>
</tr>
<tr>
<td></td>
<td>&lt;1.7</td>
<td>1.7-2.3</td>
<td>&gt;2.3</td>
</tr>
</tbody>
</table>

A: 5-6; B: 7-9; C: > 9
### MELD: Model for End-Stage Liver Disease

<table>
<thead>
<tr>
<th></th>
<th>2</th>
<th>5</th>
<th>5</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin</td>
<td>1.1</td>
<td>2.0</td>
<td>2.0</td>
<td>3.0</td>
</tr>
<tr>
<td>INR</td>
<td>1.0</td>
<td>1.0</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Creatinine</td>
<td>10</td>
<td>20</td>
<td>27</td>
<td>31</td>
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</tbody>
</table>
Cirrhosis

Prevalence
35%-80%

Risk of Bleeding from Esophageal Varices

25%-40%

50%-70%
Survive

70%
Rebleed

30%-50%
Die
Variceal Surveillance
All cirrhotics require Esophagogastroduodenoscopy

No varices
- Repeat endoscopy in 3 years (well compensated); in 1 year if decompensated
- No beta-blocker prophylaxis

Small varices (< 5 mm), Child B/C
- Nonselective Beta-blocker prophylaxis

Medium or large varices
- Child Class A, no red wales: beta blockers
- Child class B/C, red wales: beta blockers or band ligation

**Ascites: Pathogenesis and Mechanism of Action of Different Therapies**

- **Cirrhosis**
  - $\uparrow$ Intrahepatic resistance
  - **Portal (sinusoidal) hypertension**
    - **Splanchnic/systemic vasodilation**
      - $\downarrow$ Effective arterial blood volume
      - **Activation of neurohumoral systems**
        - **Sodium retention**
          - **Ascites**

- **Liver transplantation**
  - **TIPS**
  - **Albumin**
  - **PVS**
  - **Spironolactone $\pm$ Furosemide**
  - **Paracentesis (LVP)**
    - **PVS**

*LVP, large-volume paracentesis; PVS, peritoneovenous shunt.*

*Furosemide should only be used in conjunction with spironolactone.*

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Garcia Tsao CCO Hepatitis.com 2008
Stages of ascites

- Diuretic-responsive ascites
- Refractory ascites
- Hyponatremia
- Hepatorenal syndrome (HRS)

Each stage reflects a more deranged circulatory state.
Treatment of ascites

• Diuretic-responsive ascites
  – Sodium restriction
  – Spironolactone (75-100 mg) and furosemide (20-40 mg)

• Refractory ascites
  – Large volume paracentesis with 25% albumin (50 cc/L)
  – TIPS- higher OLT free survival, higher PSE
  – TIPS HVP <12 mm Hg
  – Albumin, midodrine and octreotide- vasoconstriction
  – Experimental: clonidine, vasopression 2 R antagonists

• Hyponatremia
  – Fluid restriction, vasopression 2R antagonists, midodrine
Pathogenesis Hepatorenal syndrome: HRS

- Cirrhosis
  - Portal (sinusoidal) hypertension
    - Splanchnic/systemic vasodilation
      - Effective arterial blood volume
        - Activation of neurohumoral systems
          - Renal vasoconstriction
            - Hepatorenal syndrome

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Hepatorenal syndrome (HRS)

• Acute renal failure occurs in 14% to 25% of hospitalized patients with cirrhosis
• Most commonly prerenal failure (accounting for 60% to 80% of the cases)
  – HRS is a form of prerenal failure
• Then acute tubular necrosis (20% to 40%)
Hepatorenal syndrome

- results from vasodilatation and marked reduction in effective arterial blood volume leading to renal vasoconstriction
- occurs in patients with refractory ascites and/or hyponatremia.
- **Type 1 HRS**: rapidly progressive renal failure in 2 weeks
  - with a doubling of serum creatinine to a level > 2.5 mg/dL
  - or halving creatinine clearance to < 20 mL/min
  - Prognosis: < 50% survival at 1 month
HRS-contd

- **Type 2 HRS**: slowly progressive
  - increase in serum creatinine level to > 1.5 mg/dL
  - a creatinine clearance of < 40 mL/min
  - or a urine sodium < 10 mEq/d
  - associated with ascites that is unresponsive to diuretic medications
  - median survival: ~ 6 months
HRS treatment

- OLT
- Midodrine and octreotide
  - HRS due to extreme splanchnic and systemic vasodilatation
  - Drugs → vasoconstriction
- Albumin to increase intravascular volume
Spontaneous bacterial peritonitis (SBP)

- Most common type of bacterial infection in hospitalized cirrhotic patients
- Clinical suspicion:
  - <50%: fever, abdominal pain or tenderness, and leukocytosis
  - unexplained encephalopathy, jaundice
  - worsening renal failure
- Diagnose: tap ascites: WCC>500, PMN > 250 cells/mm$^3$
  - Place ascites in blood culture bottles
- Start treatment immediately before culture results
SBP treatment

• Cephalosporins
• Renal dysfunction is main cause of death
  – prevented by the use of intravenous albumin if
  – serum bilirubin > 4 mg/dL
  – serum creatinine > 1 g/dL
  – or blood urea nitrogen level > 30 mg/dL
• Prevent recurrence: ciprofloxacin, TMP/SMX, norfloxacin
• Primary prophylaxis: ciprofloxacin weekly if MELD > 9
Hepatic Encephalopathy

• Classified as
  – episodic (previously acute)
  – persistent (previously chronic)
  – or minimal (previously subclinical)

• Results from a combination of
  – Portosystemic shunting and
  – failure to metabolize neurotoxic substances
  – Ammonia remains the most important neurotoxic substance but poorly correlates with stage
Hepatic Encephalopathy

• Precipitants
  – Infection- especially SBP or UTI
  – Bleeding
  – Electrolyte imbalance
  – Portal vein thrombosis
  – Worsening liver disease
Hepatic Encephalopathy

- Treatment aims to reduce production of ammonia from the colon through
  - nonabsorbable disaccharides
    - lactulose, lactitol, and lactose
  - nonabsorbable antibiotics
    - neomycin, rifaximin
  - Protein restriction promotes protein degradation and, if maintained for long periods, worsens nutritional status and decreases muscle mass
    - No longer recommended
HCC Monitoring Guidelines for HIV Cirrhotic Patients

- All patients with cirrhosis
- Patients with HBV (>40y) and family history
- Screening strategy
  - serum alpha-fetoprotein (AFP) testing
  - ultrasonography at intervals of 6 or 12 months
- Based on
  - low incidence of HCC in those at risk: 1-4% /y
  - slow growth of these tumors, mean estimated doubling time of 136 days
Indications for Liver Transplantation

• Development of decompensation (ascites, variceal hemorrhage, HE) in patients with cirrhosis is associated with a median survival of only 1.5 years.
Liver Transplantation

- MELD
- Serum sodium
- Underestimated
  - chronic encephalopathy
  - hepatic hydrothorax
  - hepatopulmonary syndrome
  - portopulmonary hypertension
OLT in HIV: Why Now?

- HAART-associated improvements:
  - decreased mortality
  - decreased incidence of opportunistic infections
  - decreased hospitalization rates

- Immunosuppressives may have anti-HIV effects
  - cyclosporine, MMF, rapamycin

- Better prophylaxis for opportunistic infections
Patient and Graft Survival
HBV vs HBV-HIV*

*No deaths due to recurrent HBV

Survival Post-Transplantation (mos)

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Terrault 2007
Patient Survival: HCV

P = .01

HCV mono-infected: n=135, n=67, n=22
HCV-HIV co-infected: n=46, n=28, n=14

Potential factors contributing to poor outcomes in HCV+ liver recipients

- Donor HCV+ ($p=0.02$)
- MELD ($p=0.01$)
- BMI <21 at enrollment ($p=0.0001$)
- Dual organ ($p=0.01$)
- Detectable HIV RNA at enrollment ($p=0.005$)
- Initial IS of tacrolimus vs CsA: $p=0.04$
- Donor age? No difference seen between age groups >40 vs ≤40 ($p=0.75$)
HIV OLT SUMMARY

- Recurrent hepatitis B controlled with combination therapy and monthly HBIg
- Recurrent HCV may be a significant problem, with an increased risk of morbidity and mortality
- HPV – anal CA; HHV8 – KS - problematic
- HAART regimens including PI require major adjustments in Calcineurin inhibitor dosing
ESLD and HIV

- Liver disease has become a major cause of death in people infected with HIV
- Prevalence of HCV coinfection is high (30%)
- Prevalence of HBV coinfection ~ 10%
- Progression to cirrhosis is rapid in coinfected pt
- ESLD common
- Monitor ascites and infection (SBP prophylaxis)
- EGD for varices, imaging for HCC
- Consider OLT early