End Stage Liver Disease: What is New?

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Natural History of ESLD

- Increasing liver fibrosis
  - Chronic liver disease
  - Compensated cirrhosis
  - Variceal hemorrhage
  - Ascites
  - Encephalopathy
  - Jaundice

- Development of HCC
  - Decompensated cirrhosis
  - Death
  - Alcohol
  - Hepatitis C/B
  - NASH
  - Cholestatic
  - Autoimmune

HCC, hepatocellular carcinoma; NASH, nonalcoholic steatohepatitis
Garcia Tsao CCO Hepatitis.com 2008
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

*Pineda, Hepatology 2005*
HCV SVR and All Cause Mortality

12,166: SVR 35%
1,119 died over 3.8y f/u

HCV SVR and All Cause Mortality

2904: 72% SVR
220 died in 3.8y f/u

Backus CGH 2011
HCV SVR and All Cause Mortality

1794 pts 62% SVR
196 died in 3.8y f/u

Backus CGH 2011: HTN 53%; DM 21%; COPD 14%; CAD, F4 13%
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

D’Amico 2006
HVPG to Predict Portal Hypertensive Event

Robic J Hep 2011: 100 pts followed for 2y: ETOH 38; v hep 28: 75 F3-4
LS to predict Portal Hypertensive Event

2y free of comps: 85.4 vs 29.5%
PHTN events only: 100 vs 47.5%

Robic J Hep 2011
Risk of Bleeding from Esophageal Varices

Cirrhosis

Prevalence
35%-80%

Risk of Bleeding
25%-40%

Survive
50%-70%

Die
30%-50%

Rebleed
70%

Risk of Bleeding from Esophageal Varices
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

Elastography to rule out Varices

• 211 patients with EGD and TE
  – Child’s A
  – 132 none or small varices
  – 79 large varices
• LS cut off 19.8 kPa
  – NPV 91%, PPV 55%
    • 7 pts with large varices misclassified
  – 157 HCV patients
    • NNP 98%, one patient misclassified
• Cut off >19.8 kPa for EGD and beta blockers
  – Cut offs vary with study most ≈ 20 (some 30)

Pritchett JVH 2011: Castera J Hep review 2012
Ascites: Pathogenesis and Mechanism of Action of Different Therapies

Cirrhosis

↑ Intrahepatic resistance

Portal (sinusoidal) hypertension

↓ Splanchnic/systemic vasodilation

↓ Effective arterial blood volume

Activation of neurohumoral systems

↓ Sodium retention

Ascites

Liver transplantation

TIPS

Albumin

PVS

Spironolactone ± Furosemide*

Paracentesis (LVP)

PVS

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

*Furosemide should only be used in conjunction with spironolactone.
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

• Hyponatremia
  – Fluid restriction, vasopression 2R antagonists, midodrine
6 mos Survival with Sodium <135

Jenq J Clin Gast 2010: 126 cirrhotics
Tolvaptan, Oral Vasopressin Antagonist for Hyponatremia- Cardenas J Hep 2012

- Thirst dry mouth: GIB 10% vs 2%
- D4 p=0.0002
- D30 p=0.08
- 15 mg/d increase to 30 mg then 60 mg

**Graph Details:**
- Serum sodium (mEq/L)
- X-axis: Day
- Y-axis: Serum sodium (mEq/L)
- Tolvaptan: Open circles with error bars
- Placebo: Filled squares with error bars
- Sample sizes:
  - Tolvaptan n = 63 62 62 63 61
  - Placebo n = 57 55 57 52 52
- Day-wise values: 55, 53, 48, 48, 50
- Day-wise values: 49, 42, 42, 38, 43
Pathogenesis Hepatorenal syndrome: HRS

1. Cirrhosis
2. Portal (sinusoidal) hypertension
3. Splanchnic/systemic vasodilation
4. Effective arterial blood volume
5. Activation of neurohumoral systems
6. Renal vasoconstriction
7. Hepatorenal syndrome

Garcia Tsao CCO Hepatitis.com 2008
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 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/mi
  – 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 $\rightarrow$ vasoconstriction
• Albumin to increase intravascular volume
Terlipressin, arterial vasoconstrictor for HRS. Sanyal 2008

35% Alc Hep
96.4% ascites

56 type 1 HRS 1 mg q6h. All albumin
Cr <1.5 48 h
Survival in days: Terlipressin for HRS
Sanyal 2008

SAE 9% vs 2% CV events
Spontaneous bacterial peritonitis (SBP)

- Most common type of bacterial infection in hospitalized cirrhotic patients
- Clinical suspicion:
  - unexplained encephalopathy, jaundice
  - worsening renal failure
  - <50%: fever, abdominal pain or tenderness, and leukocytosis
- Diagnose: tap ascites: WCC>500, PMN > 250 cells/mm³
  - 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 >12, if on DAA
Hepatic Encephalopathy

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

Bass NEJM 2010: 299 cirrhotics with PSE in remission 550 mg bid; 91% on lactulose
ESLD and HCV- What’s new?

• All HCV patients should be assessed for fibrosis stage prior to starting therapy
• SVR prolongs survival
• Progression to decompensated cirrhosis can occur with IFN based therapies
• Monitor varices with EGD (TE r/o)
• Ascites and hyponatremia- AVP antagonists + fluid restriction
• HRS: arterial vasconstrictors: terlipressin
• Hepatic encephalopathy- rifaximin
• Consider OLT when first decompensation occurs