Gross and microscopic image of a normal and a cirrhotic liver

**Normal**
- Nodules

**Cirrhosis**
- Irregular surface
- Nodules surrounded by fibrous tissue
Cirrhosis Spectrum

- A continuum with a wide spectrum of clinical presentation
  - Liver synthesis; portal hypertension; hyperesplenism; ascites; HE
- Suboptimally represented by Child-Pugh (A, B, C) or MELD scores
- Fibroscan, a numeric continuum expressed in Kpa
Varices and Variceal Hemorrhage

**Cirrhosis**

- Resistance to portal flow
- Portal pressure
  - Varices present in 40-60% of cirrhotic patients

- **Portal blood inflow**
- **Splanchnic resistance** Due to nitric oxide

**Varices**

**Variceal Growth**
Varices Increase in Diameter Progressively

No varices

Small varices
Lower risk of bleeding
7-8%/year

Large varices
Higher risk of bleeding
7-8%/year

Merli et al. J Hepatol 2003;38:266
Bleeding Esophageal Varices

- Risk factors:
  - Large varices, Childs score C, cherry red/red wale markings (endoscopic red signs), HVPG > 12mm HG
  - 20% mortality with initial bleed

Bleeding Gastric Varix

- 10% of variceal hemorrhages
- Do not respond well to EBL
- Rule out splenic vein thrombus
Endoscopic Variceal Band Ligation: Current gold standard for bleeding varices

- Bleeding controlled in 90%
- Antibiotics are standard of care
- Rebleeding rate 30%
- Compared with sclerotherapy:
  - Less rebleeding
  - Lower mortality
  - Fewer complications
  - Fewer treatment sessions
Gastric Varices

Pretreatment cyanoacrylate

Post-treatment cyanoacrylate
Management of Acute Gastric (Fundal) Variceal Bleeding

Variceal Hemorrhage Suspected

Initial Management

- Transfuse to hemoglobin ~8 g/dL
- Early pharmacotherapy
- Antibiotic prophylaxis

Variceal obturation possible?

NO

- Not possible or rebleed

TIPS*

YES

Bleeding controlled?

NO

- Variceal obliteration + beta blockers

YES

*Surgical shunt may be considered for Child’s Class A

* Surgical shunt may be considered for Child’s Class A
Transjugular Intrahepatic Portosystemic Shunt (TIPS)

- TIPS is rescue therapy for recurrent variceal hemorrhage
  - At second rebleed for esophageal varices, at first rebleed for gastric varices
- Indicated in rebleed on combination endoscopic plus pharmacologic therapy
- Risk of hepatic encephalopathy
- In Child A cirrhosis, the distal spleno-renal shunt is as effective as TIPS
TIPS

- Portal access
- Intra hepatic placement
- Fixation of expandable stent
Early TIPS in Acute Variceal Bleed in Child B or C Patients

359 Patients were admitted for acute variceal bleeding

296 Were excluded
18 Declined to participate
72 Were in Child-Pugh Class A
40 Were in Child-Pugh Class B, but did not have active bleeding at endoscopy
18 Had Child-Pugh score >13 points
22 Had isolated gastric variceal bleeding
18 Had previous TIPS or drugs + EBL
17 Were older than 75 yr
34 Had hepatocellular carcinoma
20 Had portal-vein thrombosis
9 Had renal failure
6 Had prehepatic portal hypertension
22 Had other reasons

63 Underwent randomization

31 Were assigned to receive drugs + EBL and were included in the analysis
32 Were assigned to receive early TIPS and were included in the analysis

63 cases. Child B or C
Randomized during first 24 hours

Garcia Pagan, NEJM 2010
Early TIPS in Acute Variceal Bleed in Child B or C Patients

Freedom of uncontrolled bleeding or rebleeding
97 vs 50%

Survival differences at one year with early TIPS vs BL plus drugs

Garcia Pagan, *NEJM* 2010
Pathogenesis of Ascites

Cirrhosis

Nitric oxide synthesis by vascular endothelial cells is increased in cirrhosis

Arteriolar resistance (vasodilation)

Effective arterial blood volume

Activation of neurohumoral systems (renin, AVP, angiotensin, aldosterone)

Sodium and water retention

Ascites

Sinusoidal pressure (HVPG ≥ 10-12 mmHg)
Ultrasound is the Most Sensitive Method to Detect Ascites
Diagnostic Paracentesis

• **Indications**
  – New-onset ascites
  – Admission to hospital
  – Symptoms/signs of SBP
  – Renal dysfunction
  – Unexplained encephalopathy

• **Contraindications**
  – None: Can be done at any INR or platelet count
The Serum-Ascites Albumin Gradient (SAAG) Correlates With Sinusoidal Pressure

Hoefs J, J Lab Clin Med 1983; 102:260
Management of Uncomplicated Ascites

Diuretic Therapy

- Dosage (initial ratio 5:2)
  - Spironolactone 100-400 mg/day
  - Furosemide (40-160 mg/d) for inadequate weight loss or if hyperkalemia develops
- Increase diuretics if weight loss <1 kg in the first week and <2 kg/week thereafter
- Decrease diuretics if weight loss >0.5 kg/day in patients without edema and >1 kg/day in those with edema
- Side effects
  - Renal dysfunction, hyponatremia, hyperkalemia, encephalopathy, gynecomastia
Refractory Ascites

- **Diuretic-intractable ascites**
  - Therapeutic doses of diuretics cannot be achieved because of diuretic-induced complications

- **Diuretic-resistant ascites**
  - No response to maximal diuretic therapy (400 mg spironolactone + 160 mg furosemide/day)

- **Therapy:** LVP, TIPS, Transplant
Major Criteria in the Diagnosis of Hepatorenal Syndrome

- Advanced hepatic failure and portal hypertension
- Creatinine >1.5 mg/dL or creatinine clearance <40 ml/min
- Absence of shock, bacterial infection, or nephrotoxic drugs
- Absence of excessive gastrointestinal or renal fluid loss
- No improvement in renal function after plasma volume expansion with 1.5 L of isotonic saline
- Urinary protein <500 mg/dL and normal renal ultrasound
Two Types of Hepatorenal Syndrome

**Type 1**
- Rapidly progressive renal failure (2 weeks)
- Doubling of creatinine to \(>2.5\) or halving of creatinine clearance (CrCl) to \(<20\) ml/min

**Type 2**
- More slowly progressive
- Creatinine \(>1.5\) mg/dL or CrCl \(<40\) ml/min
- Associated with refractory ascites

Arroyo et al., *Hepatology* 1996; 23:164
Survival in Different Types of Hepatorenal Syndrome (HRS)

Survival probability

Type 1

Type 2

\[ p = 0.001 \]

Gines et al., *Lancet* 2003; 362:1819
Therapy for Hepatorenal Syndrome

• In US
  – 25-50 gms of albumin daily
  – Midodrine (vasoconstrictor) 7.5 mg tid-12.5 mg tid for mean arterial pressure increase >15 mm Hg
  – Octreotide: 100 mcg-200 mcg tid or 50 mcg/hr IV

• Terlipressin (Europe)
  – Vasopressin analogue
  – 0.5-2.0 mg over 4-6 hrs IV with albumin
  – Currently being studied in US (granted Orphan Drug status), not available at this time

• Otherwise liver transplantation
  – Dialysis does not extend survival
Pulmonary Vascular Consequences of Liver Disease

- Hepatopulmonary syndrome (HPS)
  - Primarily a gas exchange problem characterized by arterial hypoxemia that may be severe

- Portopulmonary hypertension (PPH)
  - Primarily a hemodynamic problem which can result in right heart failure and death due to pulmonary vasoconstriction
Hepatopulmonary Syndrome
Diagnostic Criteria

- Chronic liver disease (portal hypertension)
- Arterial hypoxemia
  - \( \text{PaO}_2 < 70 \text{ mmHg} \), or
  - Alveolar-arterial oxygen gradient > 20 mmHg
- Pulmonary vascular dilatation
  - “Positive” delayed contrast echo
  - \(^{99}\text{TcMAA}\) lung perfusion with brain uptake > 6%
- Clubbing, cyanosis noted on exam
- Treatment: liver transplant
Contrast echocardiogram and presence of intrapulmonary vasodilatation
Diagnosis of Portopulmonary Hypertension

Established by right heart catheterization

- Mean pulmonary artery pressure (MPAP) ≥25 mmHg
- Pulmonary capillary wedge pressure (PCWP) ≤15mmHg
Portopulmonary Hypertension
Current Clinical Practice

• Not an indication for liver transplant alone
• Relative contraindication for liver transplant
  – $35 < \text{MPAP} < 50 \text{ mmHg}$ and
  – $\text{PVR} > 250 \text{ dynes.s.cm}^{-5}$ (3 Wood units)
• Absolute contraindication for liver transplant
  – $\text{MPAP} > 50 \text{ mmHg}$
• Pharmacologic therapies include: bosentan, sildenafil, and prostaglandins all of which act as vasodilators
Hepatic Encephalopathy Pathogenesis

- Bacterial action
- Protein load
- Failure to metabolize NH$_3$

NH$_3$ Shunting

GABA-BD receptors

Toxins
Hepatic Encephalopathy Is A Clinical Diagnosis

- **Clinical findings and history important**
- Ammonia levels are unreliable
  - Ammonia has poor correlation with diagnosis
  - Measurement of ammonia not generally necessary
- Number connection test
- Other psychometric tests
## Stages of Hepatic Encephalopathy

<table>
<thead>
<tr>
<th>Stage</th>
<th>Mental state</th>
<th>Neurologic signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Minimal hepatic encephalopathy (MHE)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Mild confusion: limited attention span, irritability, inverted sleep pattern</td>
<td>Incoordination, tremor, impaired handwriting</td>
</tr>
<tr>
<td>2</td>
<td>Drowsiness, personality changes, intermittent disorientation</td>
<td>Asterixis, ataxia, dysarthria</td>
</tr>
<tr>
<td>3</td>
<td>Somnolent, gross disorientation, marked confusion, slurred speech</td>
<td>Hyperreflexia, muscle rigidity, Babinski sign</td>
</tr>
<tr>
<td>4</td>
<td>Coma</td>
<td>No response to pain, decerebrate posture</td>
</tr>
</tbody>
</table>
Hepatic Encephalopathy is an Independent Risk Factor for Mortality in Patients Awaiting Liver Transplantation

Fig. 1. Kaplan Meier survival estimate (months) of all patients until death according to the presence or absence of hepatic encephalopathy (HE) in patients listed for liver transplantation.

Coenraad et al, EASL 2013 Abs. 147
Treatment of Hepatic Encephalopathy

• Identify and treat precipitating factor
  – Infection
  – GI hemorrhage
  – Dehydration
  – Sedatives
  – Constipation
  – Non-compliance
• Lactulose (adjust to 2-3 bowel movements/day)
• Rifaximin
• Protein restriction, short-term (if at all)
Lactulose in those with intermittent (breakthrough) encephalopathy

How does one convince an “asymptomatic” patient to take a medication that makes them unsure of their bowels indefinitely?
Rifaximin Treatment in HE

- RCT with rifaximin vs placebo in maintaining HE remission
  - Individuals with $\geq 2$ HE episodes w/in 6 mo
  - HE breakthrough reduced by 58% (HR 0.42 $p<0.0001$)
  - HE hospitalization reduced by 50% (HR 0.50 $p=0.0129$)

Treatment of Overt Hepatic Encephalopathy

- **After recovery from overt HE episode**
  - Assess need to maintain remission with lactulose or rifaximin
    - **Lactulose**
      - Historical standard of care with lower medication cost
      - High adverse event profile leads to non-compliance
    - **Rifaximin**
      - Excellent tolerability and safety profile
      - Large RCT efficacy in maintaining remission
      - Favorable direct comparison to lactulose
      - Reduced hospitalization(s)/costs
ALBUMIN FOR ACUTE EPISODIC HEPATIC ENCEPHALOPATHY (ALFAE STUDY)

EASL 2013; Abstract 243

M. Simón-Talero¹*, R. García-Martínez¹,², M. Torrens¹, G. Pereira³, M. Guevara³,⁴,⁵, E. Roman⁴,⁶, G. Soriano⁴,⁶, J. Sánchez-Delgado⁴,⁷, J. Córdoba¹,⁴

¹Internal Medicine-Hepatology, Hospital Vall d´Hebron, University Autonoma of Barcelona, Barcelona, Spain, ²Liver Failure Group, UCL Hepatology, The Royal Free Hospital, University College London, London, UK, ³Liver Unit, Hospital Clínic, University of Barcelona, ⁴CIBERehd., ⁵IDIBAPS, ⁶Department of Gastroenterology, Hospital Sant Pau, Barcelona, ⁷Gastroenterology Unit, Hospital Parc Taulí, University Autonoma of Barcelona, Sabadell, Spain.
RIFAXIMIN IMPROVES COGNITION AND ENDOTOXEMIA IN MINIMAL HEPATIC ENCEPHALOPATHY BY SHIFTING GUT MICROBIAL FUNCTIONALITY WITHOUT ALTERING THEIR ABUNDANCE

EASL 2013; Abstract 192

AST-120 (SPHERICAL CARBON ADSORBENT) IN COVERT HEPATIC ENCEPHALOPATHY: RESULTS OF THE ASTUTE TRIAL

EASL 2013; Abstract 190

J.S. Bajaj*, M.Y. Sheikh, M. Chojkier, L. Balart, A.H. Sherker, R. Vemuru, N.L. Sussman, J. Vierling, G. Morelli, K.E. Anderson, M.S. Harris, K.D. Mullen, McGuire DVAMC, Richmond, VA, UCSF, Fresno Community Regional Medical Center, Fresno, Veterans Medical Center, San Diego, CA, Tulane University Health Sciences Center, New Orleans, LA, National Institute for Health, NIDDK, Bethesda, MD, Permian Research Foundation, Odessa, Baylor College of Medicine, Houston, TX, University of Florida, Gainesville, FL, Ocera Therapeutics Inc., San Diego, CA, Georgetown University School of Medicine, Georgetown, DC, Case Western Reserve MetroHealth Medical Center, Cleveland, OH, USA.
Cirrhosis is 12th leading cause of death in US and rising

Expected increase in incidence of decompensated cirrhosis over next decade

Complications with highest risk of death
- Bleeding, infection, renal failure

Complication with greatest impact on QOL
- Refractory ascites, hepatic encephalopathy