Core Curriculum In Hepatology And Liver Transplantation 2012-13

1) Hepatic Encephalopathy
2) Post AASLD Review – Top 5 Abstracts

November 20th, 2012

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Case History

- October, 2012
- 45 year old male
- Cirrhosis – HCV and alcohol
- Active alcohol use
- Recent detection of 2 cm HCC on screening US, confirmed on CT
- No history of GI hemorrhage, PSE
- Mild ascites, easily controlled on diuretics
- Told to stop drinking numerous times

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- Friday:
  - Admitted to OSH w confusion
  - P/E: A+O x 1-2, afebrile, asterixis, stigmata, mild ascites
  - Data:
    - Tox screen: pos BDZ only
    - WCC 9, BR 25, Creat 90, INR 1.3 (MELD 11)
  - Management:
    - Lactulose
    - ‘watched’

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Case History

- Progress
  - Sunday: still mildly confused, + asterixis
  - P/E: RR 18/m, 97% O2, BP 105/60. 37.1
  - No further lab data

Case History

- Progress
  - Monday 11.00 am: more confused,
  - P/E: RR 28/m, 90% O2, BP 80/35.
  - A diagnostic procedure was performed

Acute and Chronic Liver Disease

Acute Liver Failure
Liver Transplantation
Acute
Resolution

Chronic
Resolution
Compensated
Decompensated (ESLD)

Hepatocellular carcinoma
Cirrhosis
Portal Hypertension

Function:
↑PT, ↑INR, ↓Alb

Structure:
Variceal Hemorrhage, Ascites, Hepatic Encephalopathy

Liver Transplantation
Portal Hypertension

Hepatic Encephalopathy: Definition

- A spectrum of neuropsychiatric abnormalities that occur in patients with significant porto-systemic shunting, esp. in chronic liver disease (‘portosystemic encephalopathy’)
- Porto-systemic shunting must be present
- Cerebral edema is NOT present
- Portends poor prognosis:
  - 1-year survival estimated at 42%
  - 3-year survival estimated at 23%
  (Note: encephalopathy of acute liver failure is due to cerebral edema, leading to possible herniation and death – this does not occur in encephalopathy of chronic liver disease)

West Haven Classification

<table>
<thead>
<tr>
<th>Stage</th>
<th>Consciousness</th>
<th>Personality &amp; intellect</th>
<th>Neurologic</th>
<th>Ammonia level</th>
<th>EEG Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subclinical</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Stage 1</td>
<td>Insomnia, disturbed sleep pattern</td>
<td>Confusion, forgetfulness, agitation</td>
<td>Tremor, constructional apraxia, ataxia</td>
<td>↑</td>
<td>Slightly abnormal</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Lethargy</td>
<td>Disorientation, bizarre behavior</td>
<td>Asterixis, ataxia</td>
<td>↑↑</td>
<td>Severe altered consciousness</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Somnolence, but patient may be arousable</td>
<td>Disorientation, aggression</td>
<td>Asterixis, hyperactive reflexes, positive Babinski’s reflex</td>
<td>↑↑↑</td>
<td>Severe altered consciousness</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Coma, unresponsive</td>
<td>Coma</td>
<td>Oscillations of non-parallel lines</td>
<td>↑↑↑↑</td>
<td>Slow waves 2 to 3 cycles per second</td>
</tr>
</tbody>
</table>

Minimal Encephalopathy

- “Minimal HE” was proposed to replace the term “subclinical encephalopathy”
- Patients with minimal HE have no recognizable clinical symptoms of brain dysfunction
- Detected only by:
  - Neuropsychiatric testing
    - Standardized test battery including Number Connection Test (NCT) A and B, the line-tracing test, the serial-dotting test, and the digit-symbol test
  - Neurophysiologic tests
    - EEG with mean dominant frequency (MDF) or P300 auditory evoked potentials (EP)

Hepatic Encephalopathy

- Fetor hepaticus may be evident
- Ammonia (venous) level usually unhelpful
- CT brain to exclude other pathology, esp bleed
- EEG, typical pattern, rarely used

Economic Burden of Chronic Liver Disease: Direct Costs

Total = $2.1 billion

*Based on 1995 National Health Interview Survey and adjusted to 1998
†Based on 2004 data - current costs is over $1 billion per year

### Trends in Hospital Admissions for HE

**Chart:**
- Trends in hospital admissions for HE (All Diagnoses)
- **Note:** Total number of discharges includes alcoholic (code 571.2) and non-alcoholic cirrhosis (code 571.5).

### Pathogenesis of HE

**Because of portal-systemic shunting and impaired hepatic function, toxic substances normally metabolized in the liver cross the blood–brain barrier and exert direct or indirect neurotoxic effects on CNS.**

- **End result:**
  - Changes in brain energy levels
  - Metabolic abnormalities in structure and function of neuronal and synaptic membranes
  - Alterations in neurotransmitter function

### Pathogenesis of HE: Hypotheses

- **Endogenous neurotoxins**
  - NH₃
  - Mercaptans
  - Phenols
  - Short- and medium-chain fatty acids
  - Endogenous benzodiazepine analogues

- **Increased permeability of blood–brain barrier:**

- **Change in neurotransmitters and receptors:**
  - γ-Aminobutyric acid/benzodiazepine
  - "False" neurotransmitters
  - True neurotransmitters (e.g., glutamate, dopamine)
  - Serotonin (5-hydroxytryptamine)

- **Other theories:**
  - Zinc deficiency
  - Excessive cerebral deposition of manganese

### HE: Look For Precipitating Factors

- **Increased nitrogen load**
  - (gastrointestinal bleeding, dietary intake)
  - FOB stools, Hb level

- **Deterioration of liver function**
  - BR, INR
  - Superimposed new, growing HCC, new PVT
  - US Liver, CT/MRI

- **Infection (local or systemic)**
  - Culture urine, blood, ascites - r/o SBP, CXR, empiric Abx

### HE: Look For Precipitating Factors

- **Hypovolemia (excessive diuresis/paracentesis)**
  - Hold diuretics, give volume, U&E

- **Tox screen - avoid any centrally sedating agents (BDZ, opiates, antiemetics)**

- **Electrolyte or acid-base imbalance**
  - U&E, replete

- **Increased portal-systemic shunting**
  - e.g., recent TIPS - Doppler to evaluate patency

### Transjugular Intrahepatic Portosystemic Shunt - TIPS

- **Stent placement by hepatic venous placement, through hepatic parenchyma, from hepatic vein branch to portal vein branch**
- **90% success**
- **Lowers HFVG to < 12 mmHg**

- **Indications:**
  - Refractory variceal bleeding – either esophageal / gastric
  - Refractory ascites
TIPS Complications

- Procedure-related
- Stenosis - early, late (↓ with coated stents)
- Hepatic encephalopathy
  - 20–40% (mild)
  - 1-3% severe
- Hepatic decompensation, esp. if MELD > 15

Predictors of Encephalopathy
- Previous encephalopathy
- Age
- Severity of liver disease
- ? Stent diameter

HE: Diagnosis

- Clinical context
- Asterixis
- Exclude other causes of encephalopathy
- Evaluate stage of hepatic encephalopathy

Hepatic Encephalopathy: Management

- Identify and treat precipitating factors
- Lactulose: limited controlled data regarding effectiveness though sound rationale
- Non-absorbable antibiotics: Rifaxamin
- Do NOT use neomycin!
- Avoid low protein diets – change source to vegetable and dairy protein
- Zinc increases hepatic urea production

Rationale for Use of Nonabsorbable Disaccharides

- Non-absorbable disaccharides lower \( \text{NH}_3 \) by protonation and trapping as ammonium; inhibition of bacterial \( \text{NH}_3 \) production; purging of bacteria from colon.

Rationale for Use of Metabolic Trapping

- Metabolic trapping “binds” \( \text{NH}_3 \) through amination reactions.

Rationale for Use of Nonabsorbable Antibiotics

- Antibiotics ↓ gut-derived ammonia (\( \text{NH}_3 \)) by eliminating the bacteria that produce it.
**Antibiotic Treatment of HE**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Activity</th>
<th>Total Daily Dosage</th>
<th>Potential Drawbacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neomycin</td>
<td>Aerobes</td>
<td>4–8 g</td>
<td>Ototoxicity, nephrotoxicity</td>
</tr>
<tr>
<td>Paromomycin</td>
<td>Broad</td>
<td>4 g</td>
<td>Ototoxicity, nephrotoxicity</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Anaerobes</td>
<td>2 g</td>
<td>VRE</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Anaerobes</td>
<td>0.5–0.8 g</td>
<td>Neurotoxicity, dose-dependent peripheral neuropathy</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>Broad (in vitro)</td>
<td>1.2 g</td>
<td>None</td>
</tr>
</tbody>
</table>

**VRE = vancomycin-resistant enterococci**

**Properties of XIFAXAN**

- Non-systemic (<0.4%)
  - Low risk for drug interactions
    - No effect on drugs metabolized by cytochrome p450 enzyme system
  - Adverse events comparable to placebo
- Concentrated in gastrointestinal (GI) tract and primarily excreted unchanged in feces
- Binds to the beta subunit of bacterial DNA-dependent RNA polymerase (inhibits bacterial RNA synthesis)

**Rifaximin Treatment in Hepatic Encephalopathy**

- Placebo-controlled, randomized trial
- Patients with a history of recurrent hepatic encephalopathy resulting from chronic liver disease
- Rifaximin (550 mg twice daily) prevented episodes of hepatic encephalopathy and hospitalizations involving hepatic encephalopathy

**Rifaximin for HE**

- Over a 6-month period, treatment with rifaximin maintained remission from hepatic encephalopathy more effectively than did placebo ($P<0.001$)
- A breakthrough episode of hepatic encephalopathy occurred in 22.1% of patients in the rifaximin group, as compared with 45.9% of patients in the placebo group
- Rifaximin treatment also significantly reduced the risk of hospitalization involving hepatic encephalopathy:
  - 13.6% of the patients in the rifaximin group had a hospitalization involving HE as compared with 22.6% of patients in the placebo group ($P=0.01$)
  - More than 90% of patients received concomitant lactulose therapy
- Incidence of adverse and serious adverse events reported during the study was similar in the two groups
Case History: Follow-up

Monday 12.30pm
- T/F to SVUH ED
- Hypoxic, I & V stat
- BP 70/25 - started on norepi, BS Abx
- T/F to ICU

Within 12 hours
- CVVH, Max norepi, comatose
- Ascites WCCC > 10,000, 99% PMNs, (*E. coli*)

Case History: Follow-up

Tuesday 5.00am
- Max pressors, pupils fixed + dilated, anuric
- Family discussion

Tuesday 5.30am
- Asystolic arrest, not resuscitated

Take Home Lessons...........

Post AASLD Review:
Top 5 Abstracts

**ABSTRACT ID: 112**
**TITLE:** Randomized, Controlled, Double Blind Study Of Glycerol Phenylbutyrate In Patients With Cirrhosis And Episodic Hepatic Encephalopathy

**Background:** Glycerol Phenylbutyrate (GPB) is an investigational drug which lowers ammonia (NH3) through metabolism to phenylacetylglutamine, a urea surrogate excreted in urine.

**Methods:** This randomized, placebo-controlled, double-blind study enrolled patients with ≥2 West Haven (WH) Grade ≥2 HE episodes in the prior 6 months while on standard of care (SOC), including lactulose and/or rifaximin. Enrollment was stratified for rifaximin use. Patients could remain on study and SOC could be changed after their first HE event.

The primary endpoint was the proportion of patients with at least one HE event. Secondary endpoints included total HE events, hospitalizations, symptomatic days assessed using Clinical Hepatic Encephalopathy Staging Scale (CHESS) and venous NH3.

**Results:** Study met its primary and key secondary endpoints.
- Adverse events (AEs) were similar on GPB (78.9%) vs. placebo (76.1%); nausea, diarrhea, abdominal pain and increased AST were most common. There were no changes in MELD score, liver or other laboratory tests. Three patients died (2 on GPB, 1 on placebo; all unrelated). Serious AEs (SAEs) occurred in 20 patients on GPB (1 related) and 12 patients on placebo (4 related). GI bleeding and UTIs were the most common; 66% of CPC patients experienced SAEs.
- GPB significantly reduced NH3, which correlated with HE events at baseline (p = 0.0001) and during the study (p = 0.0019).

**Conclusions:** The results indicate that GPB reduces HE events in patients with episodic HE, that NH3 is important in HE pathogenesis and that GPB warrants further development for this condition.
ABSTRACT ID: 81
TITLE: Up to 100% SVR4 rates with ritonavir-boosted danoprevir (DNV1), mericitabine (MCB) and ribavirin (R) ± peginterferon alfa-2a (40KD) (P) in HCV GT 1-infected partial and null responders: results from the MATTERHORN study

Methods: PegIFN-RBV ±/ PegIFN/RBV: PegIFN/RBV + PegIFN/RBV = PegIFN/RBV, PegIFN-RBV + PegIFN/RBV = PegIFN/RBV, PegIFN-RBV + PegIFN/RBV = PegIFN/RBV

Results: Addition of MCB in DNV/PR for 24 wks of treatment results in SVR4 in 100% of G1b and up to 85% of G1a partial PR partial/null responders

MCB-containing QUAD therapy was well-tolerated and is a promising approach for the treatment of partial/null responders

ABSTRACT ID: 229
TITLE: Once Daily Sofosbuvir (GS-7977) Plus Ribavirin in Patients with HCV Genotypes 1, 2, and 3: The ELECTRON Trial

Results: About 65% of study participants in the sofosbuvir/ribavirin arms were men, in the triple-therapy arms, only 32% of treatment-naive patients were men, rising to 78% of prior null responders.

Across all arms, most participants (80%) were white and the average age was similar at approximately 48 years.

Nearly 90% of participants had difficult-to-treat HCV subtype 1a – typical of the hepatitis C population in Australia.

Subjects were men and/or women.

Among treatment-naive patients assigned to either regimen, about 40% had the IL28B CC genotype associated with good response to interferon, as expected, only 20% of null responders in the dual-therapy arms and none in the triple-therapy arm.

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- **Results:**
  - All patients – end-of-treatment response rate of 100%
  - No participants experienced viral breakthrough during treatment.
  - Outcomes diverged dramatically, however, after completing treatment.
    - Among recipients of sofosbuvir/ribavirin dual therapy: 4 treatment-naive people and 9 out of 10 prior null responders experienced virologic relapse within 4 weeks post-treatment, yielding SVR4 rates of 88% and 100%, respectively. An additional treatment-naive person relapsed later, resulting in 12-week sustained virological response (SVR12) rates of 84% and 100%, respectively.
  - In contrast, the 3-drug regimen containing GS-5885 continued to perform well.
  - None of the 25 total participants in the treatment-naive arm, nor the 3 patients who reached this time point in the null responder arm, relapsed post-treatment week 4, or SVR12 rates remained at 100%.

- Side effects were uncommon, and they mostly occurred with similar frequency across study arms.

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**ABSTRACT ID: LB 1**

**TITLE:** 12 week IFN-free Treatment Regimen with with 4-drug regimen of ABT-450/ritonavir, ABT-267, ABT-333, and ribavirin (RBV) ... in non-cirrhotic patients infected with GT 1 HCV

- **Background:**
  - ABT-450: potent HCV NS3/4A protease inhibitor once daily, boosted with low-dose ritonavir
  - ABT-267: NS5A inhibitor dosed once daily
  - ABT-333: non-nucleoside HCV NS5B polymerase inhibitor dosed twice daily

- **AIM:** Current study evaluated efficacy, safety, and tolerability of various interferon-free regimens containing ABT-450/ritonavir in combination with ABT-267 and/or ABT-333 in treatment-naive and treatment-experienced patients with genotype 1 HCV

### Treatment-Naive Patients

<table>
<thead>
<tr>
<th>Genotype 1a</th>
<th>Genotype 1b</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 8%</td>
<td>&lt; 8%</td>
</tr>
<tr>
<td>8% - 10%</td>
<td>10% - 20%</td>
</tr>
<tr>
<td>20% - 30%</td>
<td>30% - 40%</td>
</tr>
<tr>
<td>&gt; 40%</td>
<td>&gt; 40%</td>
</tr>
</tbody>
</table>

### Null Responders

<table>
<thead>
<tr>
<th>ITT analysis</th>
<th>Observed data analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>87.5</td>
<td>88.6</td>
</tr>
<tr>
<td>85.4</td>
<td>87.5</td>
</tr>
<tr>
<td>89.9</td>
<td>92.2</td>
</tr>
<tr>
<td>87.3</td>
<td>92.0</td>
</tr>
<tr>
<td>97.5</td>
<td>98.7</td>
</tr>
</tbody>
</table>

- **Conclusions:**
  - SVR12 rate 97.5% in treatment-naive patients, 93.3% in previous null responders
  - SVR12 rates ≥ 89% in several difficult-to-treat populations, including those with HCV genotype 1a infection, and non-CC1221b genotype
  - Virologic breakthrough and relapse infrequent
  - SVR12 rates with various 3-drug combinations also high (85.4% to 89.9%), but slightly lower than with 4-drug regimen
  - All regimens relatively well tolerated:
    - ≤ 2% of patients discontinued treatment because of adverse events
    - Most common adverse event included fatigue, headache, nausea, insomnia
  - Regimens of ABT-450/ritonavir, ABT-267, and ABT-333, with or without RBV, selected for further clinical development
  - Co-formulated tablet containing ABT-450/ritonavir and ABT-267 in development
**ABSTRACT ID: LB 4**

**TITLE:** High efficacy of GS-7977 in combination with low or full dose ribavirin for 24 weeks in difficult to treat HCV infected genotype 1 patients: interim analysis from the SPARE trial.

**Methods:**
- **Part 1:** stage 0-2
- **Part 2:** all stages, including Child-Pugh Class A

**Results:**

<table>
<thead>
<tr>
<th></th>
<th>Part 1</th>
<th>Part 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SVR4</strong></td>
<td>90</td>
<td>56</td>
</tr>
<tr>
<td><strong>SVR12</strong></td>
<td>NYA</td>
<td>NYA</td>
</tr>
</tbody>
</table>

**Conclusions:**
- Peginterferon-free regimen of sofosbuvir (GS-7977) plus ribavirin (RBV) for 24 weeks produced sustained virologic response rates at 4 weeks posttreatment (SVR4) in majority of difficult-to-treat patients chronically infected with genotype 1 HCV.
- **SVR4 77% with full-dose RBV**
- **SVR4 56% with low-dose RBV**

- Sofosbuvir plus RBV very well tolerated
- No safety signals, drug-related discontinuations
- Only 2 grade 3 adverse events reported; no grade 4 adverse events

**The Long And Winding Road Of HCV To . . . The Ideal HCV Therapeutic…Sept 2012**

- Safe and tolerable
- Simple regimen and stopping rules, short duration, easy dosing
- Pan-genotypic - 1a/b, 2, 3
- High SVR
  - > 90%, durable response, low resistance, esp. in 'challenging' populations
- All oral, non-interferon backbone