Management of Complications of Cirrhosis: Hepatic Encephalopathy and Thrombocytopenia

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Gross and Microscopic Image of a Normal and a Cirrhotic Liver

Normal





Irregular surface





Cirrhosis

Nodules surrounded by fibrous tissue



Prevalence of Cirrhosis

- ~5.5 million people in the United States have cirrhosis
- 5th leading cause of adult deaths
- Ranks 8th in economic cost among major illnesses



Asymptomatic vs Symptomatic Cirrhosis

- Asymptomatic (Compensated)
 - Subtle clues may be overlooked
 - Thrombocytopenia
 - Muscle wasting
 - AST>ALT without alcohol consumption
 - Liver enzymes may <u>not</u> be abnormal
 - Etiology may be remote
 - Prior alcohol use
 - Uncontrolled diabetes mellitus and obesity
- Symptomatic (Decompensated)
 - Portal Hypertension: Ascites, hepatic encephalopathy, variceal bleeding
 - Hepatic failure: Jaundice, coagulopathy
- Child-Turcotte-Pugh (CTP) classification used to stratify patients
 - CTP-A: Compensated
 - CTP-B/C: Decompensated





Non-Invasive Markers

- Platelet count <100 x $10^9/L$
- Indirect biomarkers (e.g., APRI, FIB4)
- Direct biomarkers (e.g., Fibrotest, Fibrosure)
- Transient elastography (FibroScan)
- Clinically obvious cirrhosis does not require confirmation



Portal Hypertension

Increased Resistance

(Architectural changes secondary to fibrous tissue formation; active vasoconstriction due to decrease in formation of endogenous NO)

Increased Blood Flow

(Splanchnic arteriolar vasodilation)

Increased Portal Pressure

- Shunting (encephalopathy)
- Increased salt and water retention (ascites)
- Variceal formation (bleeding)

Adapted from Garcia-Tsao G, et al. Hepatology, 2017, 65:1; 310-335.



Portal Hypertension

- Consequences of portal hypertension produce symptoms:
 - Gastroesophageal varices
 - Ascites
 - Enlarged spleen
 - Hepatic encephalopathy



Hepatic Encephalopathy (HE)



Definition of Hepatic Encephalopathy (HE)

- HE is a brain dysfunction caused by liver insufficiency and/or porto-systemic shunting
- It manifests as a wide spectrum of neurological/psychiatric abnormalities ranging from subclinical alterations to coma



Characterization of HE Stages





West Haven Criteria

Grade	Features
0	No abnormalities detected
Ι	Trivial lack of awareness; Euphoria or anxiety; short attention span; Impairment of addition or subtraction
II	Lethargy or apathy, Disorientation for time, Obvious personality change, Inappropriate behavior
III	Somnolence to semi-stupor, Responsive to stimuli, Confused, Gross disorientation, Bizarre behavior
IV	Coma, unable to test mental state



Bajaj JS, et al. *Hepatology*. 2009;50:2014-2021.

Importance of Overt Hepatic Encephalopathy

- Associated with a poor prognosis
- Retrospective review of 111 cirrhotic patients for 12-17 months following first episode of acute OHE:
 - 82 (74%) died during follow-up period
 - Survival probability
 - 42% at 1 year
 - 23% at 3 years



Bustamante J et al. J Hepatol. 1999;30(5):890-895.

Diagnosis of Overt HE

- Limited to no role for serum ammonia levels
- Clinical recognition of the distinctive neurologic features of HE
- Knowledge that underlying cirrhosis is present
- Exclusion of all other etiologies of neurologic and/or metabolic abnormalities
- Identification of precipitating factors
- Portal-systemic encephalopathy score (PSE score; Conn score) to evaluate overall severity



General Principles of Management of OHE

- Acute HE in patients with cirrhosis is reversible in the majority of patients
- A precipitating cause of OHE, rather than worsening of hepatocellular function can be identified in most episodes
- Management of the precipitating events typically leads to prompt improvement
- Clinicians should simultaneously identify and resolve precipitating events while instituting pharmacologic therapy



Treatment Options for HE

Drug Name	Drug Class	Indication
Lactulose	Poorly absorbed disaccharide	Decrease blood ammonia concentration
		Prevention and treatment of portal-systemic encephalopathy
Rifaximin	Non-aminoglycoside semi- synthetic, non-systemic antibiotic	Reduction in risk of overt hepatic encephalopathy (HE) recurrence
Neomycin	Aminoglycoside antibiotic	Not to be used, renal and ototoxic risk
Metronidazole	Synthetic antiprotozoal and antibacterial agent	Not approved for HE
Vancomycin	Aminoglycoside antibiotic	Not approved for HE



Lactulose

- Currently the mainstay of therapy of HE; ~70% to 80% of patients with acute and chronic HE improve with lactulose treatment
- Mechanism of action:
 - A non-absorbable dissacharide that is fermented in the colon
 - Metabolism by the bacterial flora in the colon to lactic acid lowers the colonic pH
 - Cathartic effect can increase fecal nitrogen excretion with up to a 4-fold increase in stool volume
- Administered orally or through a nasogastric tube or via retention enemas
- Dose: 45 to 90 g/day, titrated to achieve 2 to 3 soft stools per day with a pH below 6
- Main side effects include abdominal distension, cramping, diarrhea, electrolyte changes, and flatulence



Rifaximin

- Oral minimally absorbed (<0.4%) antibiotic
- Broad-spectrum in vitro activity against aerobic and anaerobic enteric bacteria
- No drug interactions
- No dosing adjustment required in patients with liver disease or renal insufficiency
- Can be used long-term with or without lactulose
- Approval of 550 mg tablets was granted March 24, 2010 for reduction in risk of HE recurrence and was based on a large, double-blind, placebo-controlled, Phase 3 trial published in *The New England Journal of Medicine*



Bass NM. Semin Liver Dis. 2007;27(suppl 2):18-25; Mullen KD et al. Semin Liver Dis. 2007;27(suppl 2):32-47.

Management Goals for HE

- Provision for supportive care
- Identification and removal of precipitating factors (e.g., infection, GI bleed, dehydration)
- Correct electrolyte abnormalities
- Diet: daily energy intake between 35-40 kcal/kg ideal body weight, daily protein intake of 1.2-1.5 g/kg/day (do not restrict protein), small meals/liquid nutritional supplements throughout the day with late-night snack)
- Assessment of the need for long-term therapy
 - Control of potential precipitating factors
 - Higher likelihood of recurrent encephalopathy
 - Assessment of the need for liver transplantation
- Difficult on the caregiver so assure necessary support



Managing Thrombocytopenia in the Cirrhotic Patient



Liver Disease and Thrombocytopenia

- Liver disease impacts all aspects of "clotting" including hemostasis, coagulation and fibrinolysis
- Thrombocytopenia, defined as platelet count <100 x 10⁹/L, is estimated to affect up to 70% of patients with cirrhosis
 - Worsens with the severity of portal hypertension and cirrhosis
- Higher risk of bleeding
- May be deemed ineligible for elective surgical or diagnostic procedures



Procedures, Thrombocytopenia and Chronic Liver Disease (CLD)

- CLD patients require 1-3 procedures annually
- Different procedures are associated with different risks of bleeding
- Thrombocytopenia can lead to serious uncontrolled bleeding in these patients negatively impacting clinical care
 - Prolonged hospitalizations
 - Serious complications
 - Poor clinical outcomes
- Until recently, platelet transfusions were the recommended option for platelet counts <50 x 10⁹/L



Relative Bleeding Risk Associated With Common Medical Procedures Performed in Patients With Chronic Liver Disease

Low

- Thoracentesis
- Paracentesis
- Endoscopy
- Upper GI endoscopy
 - ± biopsy
 - ± variceal banding ± sclerotherapy
- Colonoscopy ± polypectomy biopsy

Medium

- Liver biopsy
- Bronchoscopy ± biopsy
- Ethanol ablation
- Chemoembolization for HCC

High

- Biliary interventions
- Dental procedures
- Transjugular intrahepatic
 portosystemic shunt
- Laparoscopic interventions
- Nephrostomy tube placement
- Radiofrequency ablation
- Renal biopsy
- Vascular catheterization



New Option: Thrombopoietin Receptor Agonists

- Both avatrombopag and lusutrombopag were approved in 2018
- Oral meds which are dosed for a few days prior to scheduled procedure
- Can be used instead of platelet transfusion
- Platelet levels gradually decrease to pretreatment level



Avatrombopag in Chronic Liver Disease Patients Undergoing Scheduled Procedures

- Significantly reduced the need for platelet transfusion prior to undergoing invasive procedure
- Safe and well tolerated

No Platelet Rescue Procedure Required



UT Healt San Antonio Lusutrombopag in Chronic Liver Disease Patients Undergoing Scheduled Procedures

- Significantly reduced the need for platelet transfusion prior to undergoing invasive procedure
- Safe and well tolerated



Key Outcomes

Managing the Cirrhotic Patient...

- Recognize signs of hepatic encephalopathy
- Assure liver cancer screening
- Recognition of ascites
- Life style and nutrition counseling
- Assure thrombocytopenia managed when elective procedures required
- Intervene early when decompensation first recognized in order to minimize morbidity and mortality

