


ACG ANNUAL SCIENTIFIC MEETING AND POSTGRADUATE COURSE • OCTOBER 23-28, 2009



Extrahepatic Manifestations of Chronic Hepatitis

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Dr. Zetterman has indicated that he has no relationships which, in the context of his presentation, could be perceived as a potential conflict of interest.

ACG Postgraduate Course • Saturday and Sunday, October 24-25, 2009

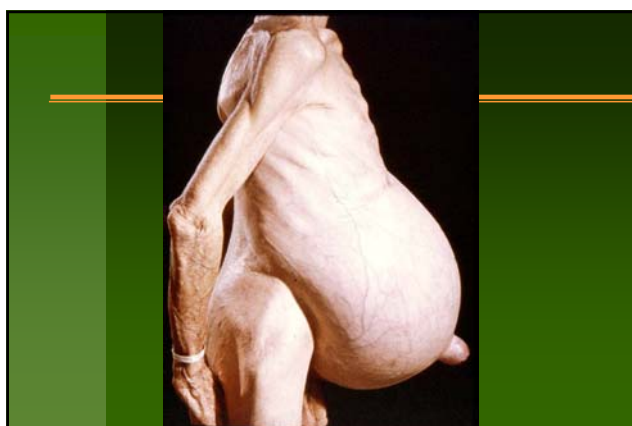
Extrahepatic Manifestations of Chronic Hepatitis and Cirrhosis

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Extrahepatic Manifestations

- Manifestations of portal hypertension
 - Ascites
 - Esophageal varices
 - Hepatic encephalopathy
- Other manifestations
 - Endocarditis
 - Portopulmonary hypertension
 - Hepatopulmonary syndrome

Ascites and Its Management



- ### Cirrhosis
- Compensated
 - No complications evident
 - Decompensated
 - Ascites the most common sign of decompensation
 - 35 to 50% develop ascites within 5 years of onset of cirrhosis

Natural History of Cirrhosis and Ascites

Clin Gastroenterol Hepatol 2006;4:1385

- 263 patients with cirrhosis and new onset of ascites followed for 41 ± 3 months
 - Hyponatremia developed in 28%
 - Refractory ascites developed in 11%
 - HRS developed in 8% (20 patients with type 1 in 7 of 20 and type 2 in 13 of 20)
- Probability of survival
 - 1-year 85% and 5-year 57%

Poor Prognostic Indicators of Survival in Cirrhotic Patients with Ascites

Mean arterial pressure	< 80 mm Hg
Urinary sodium	< 1.5 mEq/day
GFR	< 50 ml/minute
Norepinephrine level	> 570 pg/ml
Nutritional status	Poor
Hepatomegaly	Present
Serum albumin	< 2.8 gr/dL
Age	> 60 years
HCC	Present
Diabetes mellitus	Present

Treatment

- Low sodium diet
 - 1 gram sodium diet
 - Reduces calories
 - May increase dietary potassium as calories added by fruits, etc.
 - Compliance may be an issue
 - 15% will spontaneously diurese with low-sodium diet
- Water restriction
 - Only for those with serum Na < 120 mEq/L

Treatment

- **Spironolactone**
 - 100-200 mg/day (long half-life)
 - Maximum of 400 mg/day
 - Common side effects of hyperkalemia and gynecomastia
- **Furosemide**
 - 40 mg/day
 - Maximum of 160 mg/day
 - Side effects of hypokalemia, alkalosis, and hyponatremia

Albumin Infusions for Ascites

Dig Dis Sci 2005;50:1356-1360

- **19 patients** with diuretic-refractory ascites
 - IV albumin 50 grams weekly for 4 weeks
- **Outcome**
 - 17 patients improved weight
 - 2 patients gained weight

Diagnostic Criteria for Refractory Ascites

Heptology2003;38:258-266

- **Treatment duration**
 - Maximum spironolactone and furosemide > 1 week
- **Lack of response**
 - < 0.8 kg weight loss over 4 days of therapy
 - UNa < Na intake
- **Recurrence**
 - Moderate/severe ascites within 4 weeks of initial mobilization
- **Diuretic complications**
 - Renal impairment, encephalopathy, hyponatremia, hypo- or hyperkalemia

Large Volume Paracentesis (LVP)

- Paracentesis-induced **circulatory dysfunction**
 - Develops in **~20%**
 - Worsening hyponatremia, azotemia, renal failure
 - Hemodynamic changes
 - **Decreased SVR** seen in all patients after LVP
 - Greater in those with circulatory dysfunction
 - Further **activation of renin-angiotensin-aldosterone** system and sympathetic system
 - **Reduced effective arteriolar volume** and MAP
 - Decreased renal blood flow and GFR

Large Volume Paracentesis (LVP)

- For ≥ 5 L of paracentesis
 - Administer **10 grams 25% albumin per 1 L** removed
 - Saline and plasma expanders less effective
 - **Terlipressin** may be as effective as albumin following LVP
 - Administration of **norepinephrine** may also reduce likelihood of paracentesis-induced circulatory dysfunction (J Int Med 2006;260:62-68)

Predictors of early mortality after transjugular intrahepatic portosystemic shunt

- Acute **bleeding** during TIPS insertion
- Pre-TIPS **encephalopathy**
- **ALT** > 100 IU/L
- **Bilirubin** > 3 mg/dL
- **Cardiac** dysfunction
- **Age** > 70 years
- **Child-Pugh score** > 12

TIPS vs. LVP: Cochrane Meta-analysis

Cochrane Database of Systematic Review 2006:Issue 4

- 5 trials (330 patients) of TIPS vs. LVP
- Assessment
 - TIPS more effective at removing ascites
 - No difference in mortality, GI bleeding, infection or acute renal failure
 - Encephalopathy follows TIPS significantly more often

Spontaneous Bacterial Peritonitis

Spontaneous Bacterial Peritonitis (SBP)

- Definition
 - Spontaneous infection of ascites in the absence of any intra-abdominal source
- General comments
 - Prevalence of 10-25% in hospitalized ascitics
 - Often monobacterial
 - Typically enteric organisms
 - Recurrence within 1 year in 70%
 - Hepatorenal syndrome develops in ~30% of patients with SBP

Spontaneous Bacterial Peritonitis (SBP)

- Risk factors
 - Severity of underlying liver disease
 - Most are Child-Pugh B or C
 - Large volume ascites
 - Low protein ascites
 - Reduction of opsonizing capacity
 - GI bleeding
 - Prior SBP

Spontaneous Bacterial Peritonitis

- Diagnosis
 - Paracentesis
 - 250 PMN's per μ L
 - Positive culture
 - Inoculate a blood culture bottle with ascites?
 - Blood culture
 - May be positive
 - Reagent strip for leukocyte esterase?
 - Sensitivity of 64-100%? J Hepatol 2005;20:187-192

Organisms Isolated in Spontaneous Bacterial Peritonitis

- Gram negative bacteria in 70%
 - E. coli, Klebsiella, Proteus or Enterobacter species, Citrobacter freundii
- Gram positive organisms in 25%
 - S. pneumoniae, S. aureus, S. viridans, Group D streptococcus
- Microaerophilic and anaerobic bacteria in 5%
 - Clostridia, bacteroides (rare), lactobacillus

Bacterascites

International Ascites Club 1999

- Recommendations:
 - Asymptomatic patient with ascites PMN < 250/ μ L and + culture should be re-evaluated (**repeat tap and culture**)
 - If > 250 PMN's, treat
 - If < 250 PMN's and culture +, treat
 - If < 250 PMN's and culture now negative, watch
 - Patient with ascites PMN < 250/ μ L and + culture and symptoms/signs of other infection, treat

Treatment for Spontaneous Bacterial Peritonitis

- Third-generation cephalosporin
 - Cefotaxime
 - Ceftriaxone
- Amoxicillin-clavulanic acid
- Piperacillin-tazobactam
- Fluoroquinolones
- Vancomycin

Primary Prophylaxis of Spontaneous Bacterial Peritonitis

- Who should receive **prophylaxis**?
 - Those with cirrhosis and **GI bleeding**
 - At least short-term
 - Antibiotics may also reduce risk of subsequent variceal hemorrhage
 - Those with **low ascites protein** content?
 - < 1 gr/dL (< 10g/L) J Hepatol 2008;48:774-779
 - Those with **poor hepatic function**

Gastroesophageal Varices

Portal Hypertension and Cirrhosis

- Portal hypertension is a progressive condition
 - Formation of esophageal varices is ~7% per year in patients with cirrhosis and portal hypertension
 - Higher in those with decompensated cirrhosis
 - Approximately 30% of those with compensated and 60% of those with decompensated cirrhosis have gastroesophageal varices
- The mortality rate for bleeding varices is approximately 15-20%

Why Do Varices Bleed?

- Associated factors
 - Portal pressure > 12 mm Hg
 - Large varices (especially those with red wales)
 - Diurnal variation of hemorrhage
 - 0800 and 2000 hours
 - Decompensated cirrhosis
- Implosion vs. Explosion
 - Esophagitis erodes into the varix vs. varix rupture from high intra-variceal pressure

Prevention of First Variceal Bleed

Options for Prevention of First Bleed

- Drug therapy
 - Beta-blockers
- Endoscopic Therapy
 - Sclerotherapy
 - Band ligation
- TIPS
- Surgery
 - Portosystemic shunt

Beta-blockers vs. Band Ligation

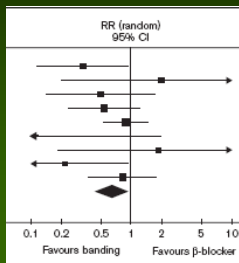
Eur J Gastroenterol and Hepatol 2007;19:835-845

- Meta-analysis of 9 randomized controlled trials
 - Patients received either non-selective beta-blockers (BB) or endoscopic band ligation (BL) as preventive therapy
 - Endpoints were first variceal bleed, overall mortality, bleeding mortality, and adverse events
 - 734 patients randomized (378 BB, 356 BL)
 - Grade II or larger varices

Beta-blockers vs. Band Ligation

Eur J Gastroenterol and Hepatol 2007;19:835-845

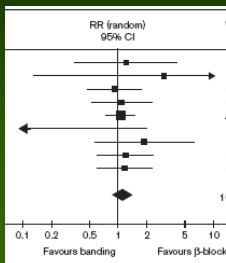
First Variceal Bleed



Beta-blockers vs. Band Ligation

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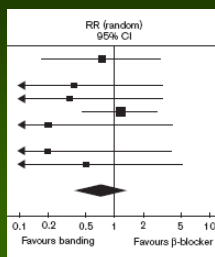
Overall Mortality

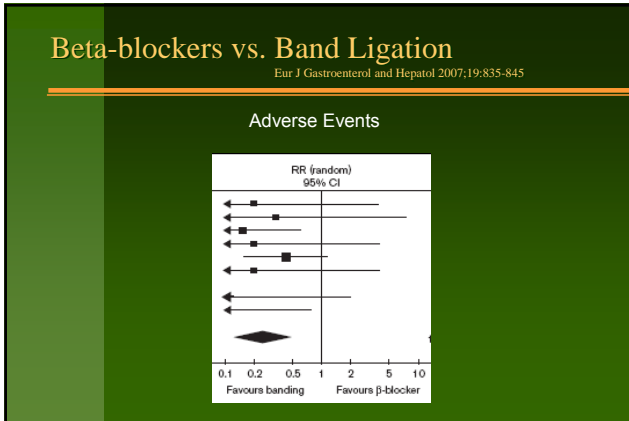


Beta-blockers vs. Band Ligation

Eur J Gastroenterol and Hepatol 2007;19:835-845

Bleeding Mortality





Management of Bleeding Gastro-Esophageal Varices

- ### Acute Variceal Hemorrhage
- Resuscitation
 - Administration of **octreotide**
 - Administration of prophylactic antibiotics
 - 3rd generation cephalosporins may be more effective than fluoroquinolones
 - Be sure to **administer** some form of broad spectrum **antibiotics**
 - Endoscopy
 - Rarely balloon tamponade

Endoscopic Therapy

- Acute therapy
 - Sclerotherapy
 - Band ligation
- Adjunctive therapy
 - Sclerotherapy and band ligation?
- Prophylaxis
 - Band ligation

Meta-analysis of Band Ligation (BL) and Sclerotherapy (ES)

Ann Intern Med 1995;123:280-287

- Immediate control of bleeding similar
- Re-bleeding due to varices less with BL
- Mortality rate less with BL
- Rate of death due to bleeding less with BL
- No difference in infection rates
- BL required fewer endoscopies to achieve variceal obliteration

Minimal Hepatic Encephalopathy

Hepatic Encephalopathy

- Types of hepatic encephalopathy
 - Minimal hepatic encephalopathy
 - Lactulose and rifaximin of limited value or not?
 - Precipitant-induced encephalopathy
 - Removal of the precipitant
 - Persistent encephalopathy
 - Lactulose and/or antibiotics
 - Liver transplantation

Minimal Hepatic Encephalopathy

- First stage of hepatic encephalopathy
 - But lack overt signs
- Manifestations
 - Alteration of quality of life
 - Difficulty with driving a vehicle
 - Altered learning
- Diagnosis
 - Psychometric studies

Minimal Hepatic Encephalopathy

- Clinical issues
 - Not a specific type of hepatic encephalopathy
 - The early component of the spectrum of encephalopathy from liver disease
 - A predictor of eventual overt encephalopathy
 - Prevalence of neuropsychological deficits is variable
 - Clinical effects impair aspects of daily living
 - Automobile driving
 - Computation – business, paying bills, etc.

Minimal Hepatic Encephalopathy

J Hepatol 2006;44:106

- Neurocognitive disorder
 - Attention and psychomotor tests most abnormal
 - Memory inconsistently altered
 - Learning impairment identified
 - Auditory verbal learning abnormal
 - Consistent with attention deficit secondary to minimal hepatic encephalopathy
 - Thus, both attention and learning impairment co-exist

Minimal Hepatic Encephalopathy

- Diagnostic criteria
 - Careful history and physical examination
 - Exclude other metabolic encephalopathies
 - Exclusion of other neurologic disorders
 - Performance of neuropsychological and neurophysiologic tests with high specificity for MHE
 - Number connection test
 - Digit symbol test
 - Block design test

Lactulose Therapy for MHE

Hepatology 2007;45:549

- 61 patients with MHE
 - Randomized to lactulose or no treatment
 - Significant improvement in psychometric tests and cognitive tests with lactulose

Lactulose or Probiotics for MHE

Eur J Gastroenterol Hepatol 2008;20:506-511

- 105 patients with cirrhosis
 - 55% had MHE
 - Treated with
 - Lactulose
 - Probiotics
 - Lactulose + probiotics
 - Lactulose, probiotics, and both were **all equally effective in reversing MHE**

Cardiac Changes in Cirrhosis

Circulatory Changes in Cirrhosis

- 4 major issues:
 - Cardiac output is **increased**
 - SVR is **reduced**
 - Systemic blood pressure **reduced**
 - Cardiac response to physiologic stimuli is subnormal – **cardiac cardiomyopathy**

Circulation Changes in Cirrhosis

- Cardiac output increased
 - Increased heart rate, increased myocardial contractility, increased venous return
 - Increased venous return due to
 - Decreased SVR
 - Vasodilation
 - Increased intravascular volume
 - Arteriovenous communications

Cardiomyopathy of Cirrhosis

- Principally left-sided changes
 - Left atrial enlargement with LVH
- Response to stimuli blunted
 - β -adrenergic drugs
 - Physiologic exercise
 - Stressors such as OLTx, infection, TIPS, etc.
- Overt heart failure rare

Portopulmonary Hypertension

Portopulmonary Hypertension

- Definition
 - The elevation of pulmonary artery pressure in the setting of chronic liver disease due to increased pulmonary vascular resistance
 - Occurs in conjunction with portal hypertension with or without end-stage liver disease
 - Criteria
 - Pulmonary artery mean pressure > 25 mm Hg, pulmonary vascular resistance > 240 dynes/d/cm-5, pulmonary capillary wedge pressure < 15 mm Hg

Portopulmonary Hypertension

- Circulatory changes in portopulmonary hypertension
 - Cardiac output typically increased, systemic vascular resistance reduced, pulmonary vascular resistance increased
 - Cardiac output typically higher in portopulmonary hypertension than pulmonary hypertension of other causes
 - Cardiac output may decrease as portopulmonary hypertension worsens

Portopulmonary Hypertension

- Epidemiology
 - Current studies suggest the prevalence of 2 to 5% of patients with cirrhosis Chest 2002;123:562
 - Typically identified after portal hypertension recognized Gastroenterology 1991;100:520
 - Age of onset typically 40 to 55 years
 - Male to female ratio = 1:1

Portopulmonary Hypertension

Hepatology 2008;48:196

- Associations
 - Women = men
 - Autoimmune hepatitis cirrhosis increased risk
 - HCV-induced cirrhosis reduced risk
 - Severity of liver disease not associated

Portopulmonary Hypertension

- Clinical findings
 - History
 - Dyspnea on exertion
 - Ankle swelling
 - Fatigue
 - Hemoptysis
 - Orthopnea
 - Physical
 - Signs of right heart failure
 - Increased P2, tricuspid insufficiency murmur, split S2

Portopulmonary Hypertension

- Echocardiogram 97% sensitive
 - Increased pulmonary artery mean pressures
 - Increased RV systolic pressures
 - Right ventricular hypertrophy
 - Tricuspid or pulmonary insufficiency
 - Paradoxical septal motion

Portopulmonary Hypertension

- **Right heart catheterization**
 - Anyone with suspected pulmonary hypertension or RV systolic pressure > 50 mm Hg being considered for liver transplantation should undergo a right heart catheterization

Portopulmonary Hypertension

- **Treatment**
 - Consider treating those with mean PA pressures > 35 mm Hg
 - No proven pharmacotherapy
 - Diuretics to control blood volume?
 - **Oxygen** supplementation for hypoxemia
 - IV **epoprostenol** (prostacyclin pathway)
 - Oral **bosentan** (endothelin pathway)
 - Oral **sildenafil** (nitrous oxide pathway)
 - Liver transplantation

Portopulmonary Hypertension

- **Liver Transplantation**
 - Mean pulmonary artery pressures > 50 mm Hg → **contraindication** to OLTx
 - Goal of vasodilator therapy →
 - Mean PAP < 35 mm Hg
 - Pulmonary artery resistance < 400 dynes/s/cm-5
 - Post-OLTx
 - Increased peri-operative mortality
 - Slow resolution of symptoms
 - Some may have progressive pulmonary hypertension
 - Recurrence of pulmonary hypertension with graft failure

Portopulmonary Hypertension

- Prognosis
 - Increased perioperative mortality with liver transplantation?
 - Increased mortality without liver transplantation?
- Associations
 - Right-sided congestive heart failure
 - Beta blockers for prophylaxis of variceal hemorrhage may worsen exercise tolerance Gastroenterology 2006;130:120

Hepatopulmonary Syndrome

Hepatopulmonary Syndrome

- Definition
 - Increased alveolar-arterial oxygen gradient due to intrapulmonary vasodilation (while breathing room air) in the patient with liver disease or portal hypertension
 - > 15 mm Hg gradient in those < 64 years
 - > 20 mm Hg gradient in those > 64 years

Hepatopulmonary Syndrome

- Screening patients for hepatopulmonary syndrome
 - Finding a $\text{PaO}_2 < 70 \text{ mm Hg}$ while breathing room air
- Hepatopulmonary syndrome identified in 5-32% of those considered for orthotopic liver transplantation

Gut 2002;51:853

Hepatopulmonary Syndrome

- Associations
 - All ages affected
 - Most common in cirrhosis
 - May not correlate with severity of liver disease
 - Typically occurs with portal hypertension but can occur in its absence
 - Also seen in portal hypertension without cirrhosis
 - e.g. Nodular transformation, PV thrombosis, congenital hepatic fibrosis, acute and chronic hepatitis without cirrhosis

Hepatopulmonary Syndrome

- Clinical findings
 - History
 - Dyspnea, worsened by exertion
 - Platypnea (dyspnea improved when supine, and worsened when sitting)
 - Physical
 - Clubbing
 - Cyanosis
 - Spider angiomata?

Hepatopulmonary Syndrome

- Oxygenation studies
 - Increased alveolar-arterial oxygen gradient
 - Age adjusted
 - Screening with oximetry may work (can overestimate oxygen saturation in cirrhosis) but needs confirmation with arterial gases
 - Orthodeoxia
 - Hypoxemia worsened when upright (>4 mm decrease)

Hepatopulmonary Syndrome

- Other studies if hepatopulmonary syndrome is suspected
 - Pulmonary function studies
 - Chest x-ray
 - Arterial blood gases
 - Contrast echocardiography

Hepatopulmonary Syndrome

- Pulmonary function studies
 - Typically normal except for diffusing capacity
- Radiography
 - Chest x-ray to exclude other pulmonary disease
 - Radionuclide study with macroaggregated albumin
 - Macroaggregates of 20 μ M particles should be trapped in the lung
 - Uptake in other organs indicates intra-pulmonary shunting

Hepatopulmonary Syndrome

- Arterial blood gases
 - Done on room air
 - Age-adjusted for oxygen saturation
 - Severity of hepatopulmonary syndrome
 - < 50 mm Hg = very severe
 - 50-59 mm Hg = severe
 - 60-79 mm Hg = moderate
 - > 80 mm Hg = mild

Hepatopulmonary Syndrome

Gastroenterology 1995;109:1283

- Microbubble echocardiography
 - Appearance of microbubbles in the left ventricle 3-6 beats after the right ventricle may indicate a right to left shunt
 - Some cirrhotics have a positive microbubble study without hepatopulmonary syndrome

Hepatopulmonary Syndrome

- Clinical course
 - May be progressive
 - Overall survival less than those without hepatopulmonary syndrome
 - Median survival of 24 months
 - May have higher liver transplantation peri-operative mortality
 - Especially those with very severe hepatopulmonary syndrome
 - Oxygen saturation < 50 mm Hg

Hepatopulmonary Syndrome

- Treatment
 - Oxygen supplementation
 - Liver transplantation
 - Those with very severe hepatopulmonary syndrome have the poorest outcome
 - Time to normalization of post-operative oxygenation may be up to a year or more

Thank you for your attention