

Hepatorenal Syndrome

Background

1. Functional renal failure, not due to intrinsic renal dz, in setting of advanced liver dz
 - Renal biopsy is normal if done

Pathophysiology

1. Portal hypertension causes splanchnic arterial vasodilation (via nitric oxide)
 - Leads to systemic arterial under filling
2. Stimulates renin-angiotensin-aldosterone and arginine-vasopressin axes, and sympathetic nervous system
3. Results in renal arterial vasoconstriction and reduction in GFR
 - Tubular function remains preserved
4. Sodium retention w/disproportionate free water retention
 - Results in dilutional hyponatremia and increased ascites/edema
5. Incidence/prevalence
 - Among non-azotemic pts with cirrhosis and ascites
 - 18% at 1 yr
 - 39% at 5 yrs
6. Risk factors
 - Decompensated cirrhosis
 - Ascites
 - Portal hypertension
 - Spontaneous bacterial peritonitis (SBP)
 - Large volume (>5 L) paracentesis without plasma expansion (albumin)
 - Hyponatremia

Diagnostics

1. History
 - Progressive oliguria
 - Hx of chronic liver dz (esp alcoholic)
 - Use of nephrotoxic agent (NSAIDs and aminoglycosides)
2. Physical exam
 - Ascites (often tense)
 - Jaundice
 - Hepatic encephalopathy
 - Signs of portal hypertension
 - Signs of acute/chronic liver dz
 - Hypotension
 - Tachycardia
3. Diagnostic tests
 - Suspect HRS when serum creatinine >1.5 mg/dL in pt with evidence of advanced liver dz, ascites, and portal hypertension
 - Type 1:
 - Doubling of serum creatinine to value >2.5 mg/dL, or creatinine clearance <20 mL/min, within a 2 wk period

- Type 2:
 - All others
 - Not as severe decline in creatinine and creatinine clearance
 - Generally better prognosis
- Labs
 - Serum chemistry panel
 - Electrolytes, BUN/Cr, glucose, ammonia level
 - Liver enzymes
 - PT/PTT (elevated in hepatic failure)
 - CBC
 - Urinalysis with microscopy
 - Urine osmoles
 - FeNa
 - 24-hr urine for protein
 - Ascitic fluid cell count and albumin
 - Helpful if not previously evaluated
 - Critical if SBP suspected
- Indicators of low GFR (CrCl <40 ml/min: 24 hour urine sodium and Cr/serum and urine osmolality)
 - Hyperosmolar urine
 - Urine: plasma Cr > 30:1
 - Fractional excretion of sodium <1%
 - Spot urine sodium <10 mEq/L [10 mmol/L]
- Blood, ascitic fluid, and urine culture as indicated
- Urinary beta-2 microglobulin: marker of acute tubular damage
- Imaging
 - Ultrasound to evaluate for post-renal obstruction and ascites or noncontrast CT
 - CXR: look for CHF
 - Renal US: rule out renal obstruction as etiology
- Other tests
 - ECG: look for dysrhythmia/hyperkalemia
 - CVP measurements

4. Major Criteria: (all must be present for diagnosis)

- Advanced hepatic failure and portal hypertension
- Low GFR (serum creatinine >1.5 mg/dL, or creatinine clearance <40 mL/min)
- Absence of treatment w/nephrotoxic drugs, shock, infection, and substantial recent fluid losses
- No improvement in renal function following diuretic withdrawal and volume expansion with 1.5 L of isotonic saline
- Urine protein <500 mg/dL
- No evidence of parenchymal dz or obstruction

5. Minor Criteria: (provide support for diagnosis)

- Oliguria <500 mL/day
- Urine sodium <10 mEq/L

- Urine osmolality > plasma osmolality
- Urine RBCs <50/high power field
- Serum sodium <130 mEq/L

Differential Diagnosis

1. Volume depletion
2. Acute Tubular Necrosis (ATN)
3. Sepsis
4. Nephrotoxic medications
5. Parenchymal renal dz/glomerulonephritis

Therapeutics

1. Immediate
 - Discontinue any nephrotoxic drugs (NSAIDs, ACE inhibitors, etc)
 - Close monitoring of vital signs, urine output, blood chemistries
 - Sodium and fluid restriction (1 L/d)
 - Paracentesis with albumin
 - Diuresis, avoid potassium-sparing diuretics
 - Treat bacterial infections
 - Vasoconstrictors may be helpful
 - Cochrane review of Terlipressin for HRS suggests reduction in mortality, but
 - Evidence not strong enough to allow recommendations for clinical practice
2. Further management
 - Hemodialysis
 - Transjugular Intrahepatic Portosystemic Shunts (TIPS)
 - Liver transplantation

Follow-Up

1. Admit to hospital
 - Admit all pts suspected of having hepatorenal syndrome with GI and nephro
 - Consult; ICU admission for associated
 - Cardiopulm dz
 - Hepatic encephalopathy, or
 - Marked electrolyte imbalance

Prognosis

1. HRS type 1
 - Hospital survival <10%
 - Median survival time 2 wks
2. HRS type 2
 - Median survival <6 months

Prevention

1. Lower risk of renal impairment if albumin given with antibiotics in pts with SBP (NNT 4.3)⁵, or if pentoxifylline given to pts admitted with dx of acute alcoholic hepatitis (NNT 3.8)⁶

References

1. Gines P, Guevara M, Arroyo V, Rodes J. Hepatorenal syndrome. *Lancet* 2003; 362: 1819-27.
2. Heidelbaugh JJ, Sherbondy M. Cirrhosis and Chronic Liver Failure: Part II. Complications and Treatment. *Am Fam Physician* 2006;74:767-76. <http://www.aafp.org/afp/20060901/767.html> (accessed 8.19.2008)
3. Arroyo V, Gines P, Gerbes A, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. *Hepatology* 1996;23:164-76.
4. Gluud LL, Kjaer MS, Christensen E. Terlipressin for hepatorenal syndrome. *Cochrane Database of Systematic Reviews* 2006, Issue 4. Art. No.: CD005162. DOI: 10.1002/14651858.CD005162.pub2.
5. Sort P, Navasa M, Arroyo V, et al. Effect of plasma volume expansion on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med* 1999;341:403-9.
6. Akriviadis E, Botla R, Briggs W, Han S, Reynolds T, Shakil O. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000; 119: 1637-48.

Author: Manuel Alsina, MD, *Puget Sound FM Naval Hospital, WA*

Editor: Vince WinklerPrins, MD, *Georgetown University-Providence Hospital, Washington DC*