Hepatorenal Syndrome

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

Pathophysiology
1. Portal hypertension causes splanchnic arterial vasodilation (via nitric oxide)
   o 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
   o Tubular function remains preserved
4. Sodium retention w/disproportionate free water retention
   o Results in dilutional hyponatremia and increased ascites/edema
5. Incidence/prevalence
   o Among non-azotemic pts with cirrhosis and ascites
     • 18% at 1 yr
     • 39% at 5 yrs
6. Risk factors
   o Decompensated cirrhosis
   o Ascites
   o Portal hypertension
   o Spontaneous bacterial peritonitis (SBP)
   o Large volume (>5 L) paracentesis without plasma expansion (albumin)
   o Hyponatremia

Diagnostics
1. History
   o Progressive oliguria
   o Hx of chronic liver dz (esp alcoholic)
   o Use of nephrotoxic agent (NSAIDs and aminoglycosides)
2. Physical exam
   o Ascites (often tense)
   o Jaundice
   o Hepatic encephalopathy
   o Signs of portal hypertension
   o Signs of acute/chronic liver dz
   o Hypotension
   o Tachycardia
3. Diagnostic tests
   o 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

  o 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

  o 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]

  o Blood, ascitic fluid, and urine culture as indicated

  o Urinary beta-2 microglobulin: marker of acute tubular damage

  o 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

  o 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**


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