Hepatorenal Syndrome

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PURPOSE:

To delineate clinical guidelines for the diagnosis and management of patients with hepatorenal syndrome. This protocol is only meant to provide a general guideline to care. The clinical circumstances and treatment of each patient will be determined on a case-by-case basis.

DEFINITION:

Hepatorenal syndrome (HRS) is defined as the occurrence of renal failure in a patient with advanced liver disease with associated portal hypertension in the absence of another identifiable cause of renal failure. Thus, the diagnosis is essentially one of exclusion of other causes of renal failure.

Clinical criteria (1):

1. Cirrhosis with ascites
2. Serum creatinine >1.5 mg/dl
3. Absence of shock
4. Absence of hypovolemia as defined by no sustained improvement of renal function (creatinine decreasing to 1.5 mg/dL or less) following at least 2 days of diuretic withdrawal (if on diuretics), and volume expansion with albumin at 1 g/kg/day up to a maximum of 100 g/day
5. No current or recent treatment with nephrotoxic drugs
6. Absence of parenchymal renal disease as defined by proteinuria <0.5 g/day, no microhematuria (<50 red cells/high powered field), and normal renal ultrasonography

- Caution: Patients with hepatorenal syndrome may have renal dysfunction that is substantially more severe than is suggested by the serum creatinine alone. Both urea and creatinine production may be substantially reduced in the setting of chronic liver disease due to decreased muscle mass and decreased protein and meat intake.
  - Use GFR calculations, using MDRD, and 24 hour CrCl to estimate renal function

There are 2 types of hepatorenal syndrome based upon clinical severity.

1. Type 1
   a. Increase in serum creatinine by at least two fold to a value greater than 2.5 mg/dL during a period of less than 2 weeks
   b. Median survival of 2 weeks
   c. Frequently develops in temporal relationship with a precipitating factor for sudden deterioration of liver function (i.e. infection such as SBP or acute alcoholic hepatitis) and is associated with deterioration of other organ function

2. Type 2
   a. Less progressive renal failure with more insidious and less rapid onset typically with avid sodium retention
   b. Median survival 4-6 months
   c. Occurs most often in patients with refractory ascites
   d. Can develop into type 1 hepatorenal syndrome either spontaneously or following a precipitating event

**PATHOPHYSIOLOGY:**

There are 4 factors involved in pathogenesis (2):

1. Development of splanchnic vasodilatation which causes a reduction in effective arterial blood volume and a decrease in mean arterial pressure.
2. Activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system which causes renal vasoconstriction and a shift in the renal autoregulatory curve which makes renal blood flow much more sensitive to changes in mean arterial pressure.
3. Impairment of cardiac function due to the development of cirrhotic cardiomyopathy, which leads to a relative impairment of the compensatory increase in cardiac output secondary to vasodilatation.
4. Increased synthesis of several vasoactive mediators which may affect renal blood flow or glomerular microcirculatory hemodynamics.
TREATMENT

General Measures:

1. Careful monitoring of vital signs as well as accurate input and output measurements are crucial
2. Evaluation for precipitating infection is necessary including rapid diagnostic paracentesis, UA/culture, blood cultures and possibly CXR
3. Cessation of all diuretics
4. Cessation of all nephrotoxic meds including NSAIDs, ACE/ARB, Neomycin, Aminoglycosides
5. Initial attempts at volume expansion with albumin (1 g/kg/d) for 2 days is part of diagnostic criteria and should be given in those with cirrhosis and AKI
6. Nephrology consultation
7. Evaluate the patient for hepatoadrenal syndrome if systolic BP is less than 90 or MAP is less than 70

Specific Measures:

1. Vasoconstrictor drugs in combination with albumin (1 g/kg for 1-2 days followed by 25-50 grams/day). Maintain treatment until serum Cr <1.5 mg/dL.
   a. Norepinephrine (3)
      i. Used in those who are critically ill in the ICU
         1. If systolic BP is less than 90 or MAP is less than 70
      ii. 0.5-3 mg/hr with goal of increasing mean arterial pressure by 10 mm Hg
   b. Midodrine and octreotide (4)
      i. Initial dose of midodrine is 2.5-7.5 mg orally every 8 hours and titrating up to 12.5 mg every 8 hours,
         1. Ideal systolic pressure 95-100mm/Hg
      ii. Initial dose of octreotide is 100 mcg subcutaneously every 8 hours and titrating up to 200 mcg every 8 hours
   c. Terlipressin
      i. Currently available only in Europe but being evaluated in the United States (5)
      ii. 1-2 mg bolus every 4-6 hours
      iii. Recent study indicates increased efficacy compared to midodrine and octreotide (6)
      iv. Most common side effects include cardiovascular or ischemic events
2. Liver transplantation
   a. Expedited referral for transplant is needed in those who are potential candidates for liver transplant
   b. Most effective treatment for both types of hepatorenal syndrome
   c. Vasoconstrictor therapy should be continued while transplant evaluation is being performed
If dialysis is performed prior to liver transplant for >8-12 weeks, consideration for combined liver-kidney transplant is needed

3. **TIPSS**
   a. Has been shown to improve renal function in those with type 1 and 2 hepatorenal syndrome in uncontrolled trials but has not been compared to standard medical therapy

4. **Dialysis**
   a. Should be considered in those who are transplant candidates and suffer from electrolyte disturbance, acidosis, volume overload

**PREVENTION**

1. Albumin use in conjunction with antibiotics in those with spontaneous bacterial peritonitis. (7)
   a. Dose: 1.5 grams/kg day 1 and then 1 gm/kg day 3
   b. See SBP guidelines
2. Ciprofloxacin 500 mg/day in those with cirrhosis and ascites that has total protein level <1.5 g/dL and either of the following: (8)
   a. CTP score ≥9 and total bilirubin ≥3.0 mg/dL
   b. Serum Cr ≥1.2 mg/dL or BUN ≥25 mg/dl or sodium ≤130 mEq/L
3. Possibly pentoxifylline 400 mg TID in those with severe acute alcoholic hepatitis based on recent meta-analysis although several low quality studies were included in this study. (9) Should generally be reserved for those patients who have contraindications to steroid use.

**REFERENCES:**