

CASE:

Patient is a 53 yo man with end-stage liver disease secondary to alcohol and hepatitis C and resultant refractory ascites who was seen in clinic for regularly scheduled large volume paracentesis and routine laboratories. He was noted to be confused and have a creatinine of 2.7 from 1.6 four weeks prior. The patient has no specific complaints except fatigue. He is oriented only to self and is noted to have scleral icterus, dry mucous membranes and spider angiomas as well as tense ascites and 2+ pitting edema to the knees bilaterally. + asterixis. Admission laboratories include potassium 5.3, BUN 51; creatinine 2.7. Albumin was 2.0, total bilirubin 1.4, INR 1.4.

Does this patient have hepatorenal syndrome? What is his prognosis? How would you treat him?

Hepatorenal Syndrome (HRS)/Complications of End-Stage Liver Disease (ESLD)

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HRS: Major criteria: renal failure in the absence of shock, ongoing infection, recent treatment with nephrotoxic drugs or massive GI or renal losses. No sustained improvement following diuretic withdrawal and plasma expansion with 1.5 L isotonic saline; < 500 mg/dL proteinuria and no ultrasound evidence of obstructive uropathy or parenchymal kidney disease.

Epidemiology: 10-30% with cirrhosis and ascites; 1 year probability 20%; 5 year 40%; 30% of patients with SBP. High mortality especially in type 2. Can occur in acute alcoholic hepatitis or fulminant hepatic failure.

Two types:

Type 1: rapidly progressive: doubling of initial creatinine in < 2 weeks to > 2.5 mg/dL or halving of creatinine clearance to < 20mL/min; progressive oliguria; low GFR (usually < 20mL/min). Poor prognosis: median survival < 1 month without therapy. In-hospital survival < 10%

Type 2: slowly progressive renal failure that does not meet criteria for type 1 HRS; diuretic-resistant/refractory ascites. Creatinine > 1.5mg/dL and/or clearance < 40mL/min. Median survival ~6 months. Often managed as outpatient.

Pathophysiology: portal hypertension → splanchnic vasodilation → severe renal vasoconstriction → pronounced decrease in GFR. Tubular function preserved.

Diagnosis: *Diagnosis of exclusion.* If patient on diuretics, discontinue diuretics and give 1.5 L isotonic saline; recheck creatinine. Always rule-out infection prior to making diagnosis. Urine sodium may be low but can NOT reliably differentiate HRS from ATN.

Signs/symptoms: Ascites is universal. If renal failure but no ascites – look for another cause of renal failure. Na < 130 common; pulmonary edema rare (unless treated aggressively with plasma expanders).

Precipitating factors: bacterial infections/spontaneous bacterial peritonitis (SBP), large volume paracentesis w/o plasma expanders, GI bleeding

Prevention is key!!: If > 5 Liters of ascites removed, always consider albumin. Up to 15% of patients will develop HRS if ascites removed without plasma expanders. (6-10g albumin/Liter removed)

Consider albumin in SBP. One multi-center randomized (non-blinded) study (126 patients) showed decreased risk of HRS in patients with SBP who received albumin plus antibiotics versus antibiotics alone (10% vs. 33%) and decreased in-hospital (10 vs. 29%) and three month mortality (22 vs. 41%). Infection resolution rate was the same. Highest benefit in patients with total bilirubin > 4 mg/dL, baseline BUN > 30 and/or creatinine > 1.0. Albumin: 1.5 g/kg within 6 hours of dx and 1g/kg on day 3.

In alcoholic hepatitis pentoxifylline 400 mg TID decreased HRS occurrence (8% vs. 35%) and in-hospital mortality (24% vs. 46%) in one study. AVOID all NSAIDs in patients with cirrhosis!

Treatment:

Discontinue all diuretics and nephrotoxins. Challenge with 1.5 L isotonic saline.

Type 1: Hospitalize! Broad spectrum antibiotics if infected. Treatment of choice: liver transplant (cures liver and renal disease). Involve Nephrology and Hepatology early! HRS patients: higher rate of post-transplant dialysis; higher morbidity and in-hospital mortality than non-HRS patients after transplant – 3 year survival ~ 60%.

Vasoconstrictors plus albumin may serve as a bridge to transplant

- 1) effective ~ 2/3; recurrence after discontinuation 15%
- 2) treat 5-15 days
- 3) goal: reduce creatinine to < 1.5 mg/dL; recurrence after vasoconstrictors discontinued ~ 15%
- 4) vasopressin analogues (terlipressin (0.5-2.0 mg IV over 4-6 hours – GFR improves over days in 50-75% (younger patients and CTP < 13) but not available in US; expensive, 5-10% discontinue 2ry ischemia) and ornipressin (not recommended – cardiac ischemia in 1/3))
- 5) alpha-adrenergic agents (midodrine and norepinephrine (limited data but may be as effective as terlipressin)); recent study suggests that IV octreotide (25 micrograms after bolus) plus midodrine (2.5 mg/d po) plus albumin (+/- TIPS) is effective) or midodrine titrated to 12.5 mg po TID + albumin + octreotide subcutaneous
- 6) dopamine and prostaglandins not shown to be effective.

Dialysis may bridge to transplant but does not improve survival.

TIPS: (few studies): slow, moderate rise in GFR and decreased creatinine in ~ 60%. Median survival after TIPS in type 1 HRS 2-4 months (may be from improved renal function). TIPS versus vasoconstrictors: no studies. Efficacy appears similar but vasoconstrictors more available and less expensive.

N-acetylcysteine has been shown to have some efficacy in small series of patients; results need confirmation.

Type 2: (often managed in outpatient setting)

Serial large volume paracentesis with albumin. Vasoconstrictors may improve renal function (limited data).

TIPS improves renal function, controls ascites, and reduces risk of development of type 1 HRS. In randomized controlled study comparing TIPS and serial paracentesis with albumin: no survival benefit to TIPS.

Case Follow-Up

The patient was hospitalized because of confusion and inability to care for himself. His diuretics were held and with 1.5 Liter of normal saline his creatinine improved to 1.9. Urine output was 35-40cc/hour. Paracentesis showed no SBP. With lactulose his confusion improved. Over the next day his mental status and creatinine continued to improve and he was discharged to home on lower dose diuretics. He followed up in clinic for serial taps and he was referred for possible TIPS.

Three months later, the patient's creatinine increased to 4.2. On this admission, he underwent therapeutic paracentesis and was found to have SBP. He was treated with albumin and broad-spectrum IV antibiotics. His diuretics were held and he was given a fluid challenge with no improvement in his creatinine. Renal was consulted and recommended IV octreotide plus midodrine and albumin. Unfortunately the patient's creatinine continued to rise to a maximum of 8.9 and the patient developed oliguric then anuric renal failure. In discussions with the local transplant center, he was not a candidate for liver transplant given ongoing alcohol use. In accordance with his wishes, he was made comfort care and expired.

Clinical Pearls

- HRS is a **diagnosis of exclusion**; always rule-out other, potentially reversible, causes (e.g., pre-renal azotemia) first.
- Prevention is key!!
- Refer potential liver transplant candidates with HRS early. Involve Renal and Hepatology at the start.
- AVOID all NSAIDs in patients with cirrhosis!

References

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