CASE: 46 yo man, previously healthy, presented to ED complaining of 4 weeks of increasing abdominal girth and diffuse abdominal pain and 5 days of "yellow eyes." He smokes 1 pack/day and drinks "a case of beer sometimes" Examination notable for a jaundiced man with scleral icterus, oriented to self and hospital but not date, moderately tense ascites with fluid wave, diffuse abdominal tenderness, no asterixis. Laboratories: AST 456, ALT 122, Alkaline phosphatase 206, Total bilirubin 5.1, INR 1.6, albumin 3.6, creatinine 1.1. No prior labs are available. What complications of end-stage liver disease does this patient have? What work-up would you do in the hospital? How would you manage his ascites?

Common Complications of End Stage Liver Disease: Ascites/Spontaneous Bacterial Peritonitis (SBP)

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SCOPE OF THE PROBLEM: In patients with cirrhosis and ascitis, 1-year risk of SBP is 30%. Risk of recurrence is 40-70% in 1 year. Prevalence in hospitalized cirrhotics is 10-30%. Mortality is 20-50% with a single episode of SBP; 1-year mortality is 70%. Hepatorenal syndrome develops in 20-33% of patients with SBP.

Ascites is the most common complication of ESLD; 80% with cirrhosis have ascites indicates poor prognosis and confers increased risk of infection and renal failure. One year survival ~50%. If cirrhosis and ascites, 1-year risk of SBP 30%. 1 year recurrence is 40-70%. Prevalence in hospitalized cirrhotics is 10-30%. Mortality is 20-50% with a single episode of SBP; 1-year mortality is 70%. Hepatorenal syndrome (HRS) develops in 20-33% of patients with SBP.

SBP Risk Factors: Gastrointestinal bleed, previous episode of SBP, and a serum albumin/ascites gradient (SAAG) > 1.1.

SBP Organisms: leave Enterobacteriaceae > E. coli >Streptococcus pneumoniae > Enterococci.

Physical Exam: Insensitive if <1-1.5 liters of ascites. Bulging flanks and shifting dullness are 60-90% sensitive, 40-70% specific. Fluid wave is 82-92% specific, 50-80% sensitive; LR 5.0. In SBP may or may not have fever and abdominal tenderness. Often, patients have altered mental status.

Imaging: Ultrasound can detect 100 cc of abdominal fluid; use CT to evaluate for masses.

Diagnostic Paracentesis. Early evaluation of ascitic fluid and diagnosis of SBP is key! Consider tap in new-onset ascites (if long-standing cirrhosis, rule out hepatocellular carcinoma); known ascites with new fever, abdominal pain, worse encephalopathy/altered mental status, or gastrointestinal (GI) bleed; and worsened hepatic or renal function in known cirrhosis; any hospitalized patient. Consider repeat tap at 48 hours if no improvement and WBC still high as there may be secondary peritonitis or a resistant organism.

NOTE: Coagulopathy is NOT a contraindication to diagnostic paracentesis! Bleeding risk is <1% with a 22-gauge needle.

Ascitic Fluid Evaluation

- Check cell count, culture, albumin, LDH and glucose; check serum albumin and LDH concurrently.
- Inoculate ascitic fluid directly into aerobic and anaerobic blood culture medium at the bedside.
- SAAG (serum albumin minus ascitic albumin) is 97% accurate in classifying etiology of ascites. A ratio $\geq$ 1.1 indicates portal hypertension associated with cirrhosis, alcoholic hepatitis, congestive

heart failure, portal vein thrombosis, Budd-Chiari syndrome. A ratio < 1.1 suggests tuberculosis (TB), pancreatic ascites, nephrotic syndrome, perintoneal carcinomatosis.

- SBP: suggested by >250 PMNs and culture growing of a single organism. If tap is bloody and >10,000 RBCs then subtract one PMN for every 250 RBCs.
- Secondary bacterial peritonitis: suggested by LDH > 225, glucose < 50, protein > 10 g/dL and polymicrobial growth on culture
- Obtain large volume of fluid for cytologic analysis and TB culture

Management Principles

- Bed rest increases GFR and Na excretion; low Na+ diet, 2 g/day, plus bed rest eliminates ascites in 10-20% if baseline urine Na excretion high (>50mEq/d) and moderate ascites.
- Diuretics: start with furosemide 40mg and spironolactone 100 mg daily (ratio optimizes potassium balance). Goal weight loss of half-kg/day and up to 1kg/day if peripheral edema
  - Spironolactone, aldosterone antagonist, has 3-4 day onset and 2 weeks to steady state.
  - Furosemide, a loop diuretic, can lead to azotemia, hypokalemia, and encephalopathy in 25%.
  - Complications include intravascular volume depletion/renal failure (25%), hyponatremia (28%), encephalopathy (26%). If renal dysfunction develops, hold diuretics, hydrate gently and resume diuretics at lower dose. Diuretics should never be initiated in patients with increasing creatinine, GI bleed or SBP.
- Fluid restriction: Consider if serum Na<120-130 with ascites or edema; goal is <1L of fluid/day, try to minimize free water.
- Consider large volume paracentesis.
- Reduce risk of co-morbidities e.g., varices, with non-selective beta blockade.
- Transcutaneous intrahepatic portosystemic shunt (TIPS): Consider in refractory ascites.

In a hospitalized patient with moderate or tense ascites, first line therapy includes therapeutic paracentesis with albumin (see below) followed by diuretics and salt restriction. This regimen can accelerate recovery and hospital discharge. Although there is no survival benefit, therapy improves quality of life and reduces incidence of SBP.

"Therapeutic" or large-volume paracentesis: Fewer complications than diuretics (less azotemia, encephalopathy), faster ascites resolution. Fluid reaccumulates an average of 5-7% per day though sometimes faster. Infection and intestinal perforation are rare. Serious bleeding is rare but studies exclude pts with INR>1.6, platelets <50,000. Serious complications include dilutional hyponatremia in 20% and (HRS) in a few, which may confer shortened survival.

Albumin infusion: Controversial and expensive. Randomized studies have shown no consistent survival benefit except in SBP. Consider albumin if 5 liters or more of ascites is removed, since 15% of patients may develop HRS; give 6-10g albumin/liter of ascites removed. May help with hyponatremia and transient electrolyte abnormalities.

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

Refractory ascites is defined as ascites resistant to diuretics and/or associated with encephalopathy, hyponatremia, and azotemia. Affects 5-10% of patients with ascites and confers increased risk of HRS with 1-year survival of 25-40%.

Treatment: Perform large-volume paracentesis with albumin and initiate diuretics after tap. In a randomized, double-blind placebo-controlled trial, ascites recurred less frequently in four-week

follow-up (18% vs. 93%) in patients on spironolactone. Restrict sodium. In 2 prospective randomized trials, TIPS is more effective than a large volume tap in controlling ascites, as partial response is 84% vs. 43%, but mortality data are mixed. 40-75% of TIPS are occluded at 1 year; TIPS may exacerbate encephalopathy.

SBP Treatment: Goals: 1) treat infection, 2) prevent recurrence, 3) initiate prophylaxis against future episodes. Initiate empiric treatment early.

Treatment of choice for presumed or confirmed SBP is cefotoxime, ceftriaxone, piperacillin/ tazobactam, or ampicillin/sulbactam. If resistant E coli or Klebsiella, use imipenem or fluoroquinolone. Avoid aminoglycosides. 5-day therapy with cefotaxime is as effective as 10 days. RCT in 2000 showed that 5 days of oral ciprofloxacin after 2 days of IV therapy is as effective as 1 week of IV therapy. See also section on albumin infusion – previous page.

Primary prophylaxis is indicated in all cirrhotic patients with a history of upper gastro-intestinal variceal bleeding; use a fluoroquinolone x 7 days. Survival benefit has been demonstrated with this approach.

Use secondary prophylaxis, if history of SBP plus:

- Cirrhosis and upper GI bleed: use ciprofloxacin 750 mg q week.
- Cirrhosis and ascites: trimethoprim/sulfamethoxazole DS 5 days/week or cipro 750 mg weekly. Long-term prophylaxis has proven survival benefit.
- Insufficient data for use of long-term prophylactic antibiotics in patients with ascites without history of SBP or upper GI bleed. In a double-blind, placebo controlled study, continuous oral norfloxacin 400 mg oral daily decreased 1-year recurrence of SBP from 68% to 20%; survival not assessed.
- Prophylactic concept: poorly absorbed oral antibiotics reduce the concentration of gram-negative gut bacteria without affecting gram-positive organisms.

Case Follow-up. *The patient was admitted and underwent diagnostic and therapeutic tap with albumin infusion with improvement in his abdominal discomfort. Tap showed 357 wbc; culture grew out E. coli. The patient was treated with IV cefotaxime for 5 days and received an additional infusion of albumin on hospital day #3. His mental status improved. The patient was discharged on HD#5 with close follow-up with his primary care doctor to initiate furosemide/spironolactone therapy. He was discharged with weekly oral ciprofloxacin.*

Clinical Pearls

Ascites

- Diagnostic paracentesis is indicated in new-onset ascites or known ascites with fever, abdominal pain, encephalopathy, or GI bleed. Consider paracentesis during hospitalization if there is significant change in clinical status.
- Albumin infusion probably benefits patients undergoing large volume (>5L) paracentesis.
- First-line therapy for hospitalized patients with moderate-tense ascites is therapeutic paracentesis plus albumin (if >5L of fluid removed) followed by diuretics and salt restriction.
- Diuretics should never be initiated in patients with increasing creatinine, GI bleed or SBP.
- In patients with new ascites and known, compensated cirrhosis, rule-out hepatocellular carcinoma.

SBP

- Albumin infusion on day 1 and 3 has been shown to decrease risk of HRS in patients with SBP, particularly in patients with total bilirubin>4 mg/dL, baseline BUN>30 and/or creatinine >1.0.
- Long-term SBP prophylaxis in patients with history of SBP has known survival benefit.

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