Management of Adult Patients with Ascites Due to Cirrhosis: Update 2012
Of compensated cirrhosis patients develop ascites.

- Inability to excrete an adequate amount of sodium
  - secondary to arterial splanchnic vasodilation.
Diagnosis of ascites

- Hx, PE
- abdominal ultrasound,
- liver function, renal function
- serum and urine electrolytes, as well as an analysis of the ascitic fluid.
History

• Ascites usually is present for only a few weeks before the patient seeks medical attention.

• Alcohol
• Diabetes as nonalcoholic steatohepatitis
• body weight
• Past history of cancer, heart failure, renal disease, thyroid disease or tuberculosis

• peritoneal carcinomatosis does not respond to diuretic therapy.
Physical examination

- Shifting dullness: 500 ml
  - 83% sensitivity and 56% specificity

- Fluid thrill: 1500 ml

- Puddle sign: 120 ml

- JVP distention + ascites = cardiogenic causes/pulmonary hypertension

- The physical examination for detecting ascites in the obese patient may be problematic ➔ Ultrasounography: 10 ml
Puddle sign

• Prone for 3-5 min and then raise all fours
• Diaphragm is placed at the most dependent part.
• Flicking a finger over a localized flank area
• Move the stethoscope over opposite flank

Positive ➔ Sudden increase in intensity

JAMA 1992:267;2645-2648
Differential diagnosis of ascites

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Abdominal paracentesis

- Routine tests of coagulation do not reflect bleeding risk in patients with cirrhosis.
  - there were no hemorrhagic complications despite
    - a) no prophylactic transfusions
    - b) platelet counts as low as 19,000 cells/ mm³
    - c) INR > 8.7

• Prefer location
  – Lt. Lower quadrant
  – 2 finger breadths (3 cm) cephalad and
  – 2 finger breadths medial to the anterior superior iliac spine

may be a suboptimal choice in the setting of a dilated cecum (due to lactulose) or an appendectomy scar.

ultrasonography can be a useful adjunct in locating fluid

Needle

Diagnosis  21 or 22 gauge needle in lean patients.
22 gauge needle in obese patients.

Therapeutic  15 or 16 gauge, multihole needles
RECOMMENDATIONS

1. Diagnostic abdominal paracentesis should be performed and ascitic fluid should be obtained from inpatients and outpatients with clinically apparent new-onset ascites. (Class I, Level C)

2. Since bleeding is sufficiently uncommon, the routine prophylactic use of fresh frozen plasma or platelets before paracentesis is not recommended. (Class III, Level C)
**Ascites fluid analysis**

Gross appearance: water-clear to frankly purulent, bloody, or chylous.

Bacterial culture of the fluid in aerobic and anaerobic blood culture bottles

Urine dipstick to detect neutrophils (sensitivity 45%)

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Abbreviation: AFB, acid-fast bacteria. *Adapted from Runyon.*\(^{17}\) Reprinted with permission from Saunders Elsevier.
The SAAG retains accuracy despite fluid infusion and diuretic use. (Unlike Pleural effusion)

SAAG $\geq 1.1$ Portal hypertension

approximately 97% accuracy.
Fluid cytology

The sensitivity of cytology in detecting peritoneal carcinomatosis is 96.7% if 3 samples (from different paracentesis procedures) are sent and processed promptly hand-carried to the laboratory for immediate processing.

- Sensitivity of first sample is positive in 82.8%
- at least 1 of 2 samples is positive in 93.3%

50 ml of fluid
Mycobacteria

Sensitivity of smear for mycobacteria ➔ 0%

Sensitivity of culture for mycobacteria ➔ 50%

PCR for mycobacteria
most rapid and accurate methods of diagnosing tuberculous peritonitis.
Culture for bacteria

older methods, i.e. sending a syringe or tube of fluid to the laboratory ➔ Yield Culture positive 50%

inoculated into blood culture bottles at the bedside and prior to administration of antibiotics. ➔ Yield 80%

A single dose of an effective antibiotic usually leads to a negative bacterial culture.
RECOMMENDATIONS

3. The initial laboratory investigation of ascitic fluid should include an ascitic fluid cell count and differential, ascitic fluid total protein, and SAAG. (Class I, Level B)

4. If ascitic fluid infection is suspected, ascitic fluid should be cultured at the bedside in aerobic and anaerobic blood culture bottles prior to initiation of antibiotics. (Class I, Level B)

5. Other studies of ascitic fluid can be ordered based on the pretest probability of disease (Table 3). (Class IIa, Level C)

6. Testing serum for CA125 is not helpful in the differential diagnosis of ascites. Its use is not recommended in patients with ascites of any type. (Class III, Level B)
# TREATMENT OPTIONS FOR PATIENTS WITH CIRRHOSIS AND ASCITES

## First-Line
- Cessation of alcohol use, when present
- Sodium restricted diet and diet education
- Dual diuretics, usually spironolactone and furosemide, orally with **single daily dosing**
- Discontinue non-steroidal anti-inflammatory drugs
- Evaluation for liver transplantation

## Second-Line
- Discontinue beta blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers
- Consider adding midodrine especially in the profoundly hypotensive patient
- Serial therapeutic paracenteses
- Evaluation for liver transplantation
- Transjugal intrahepatic portasystemic stent-shunt (TIPS)

## Third-Line
- Peritoneovenous shunt
Cessation of alcohol

• Abstinence
  – dramatic improvement in the reversible component of alcoholic liver disease.

• Baclofen 5 mg orally tid for 3 days and then 10 mg tid
  – Reduce alcohol craving and alcohol consumption
DIET AND DIURETICS

• Sodium restriction 2 gm/day
  – Too much restriction ➔ less palatable and may further worsen the malnutrition

sodium restriction, not fluid restriction

• Oral diuretics
URINE SODIUM MONITORING

• Random urinary sodium concentrations

  Grey zone (Unhelpful)  High Sodium excretion

  0 mmol/L  100 mmol/L

• 24 hr urinary sodium concentrations

  goals of treatment is to increase urinary excretion of sodium
  (exceeds 78 mmol per day)
  [88 mmol intake – 10 non-urinary sodium excretion = 78 ]

• Urinary Sodium / Potassium ratio

  ratio is >1, the patient should be losing fluid weight.
FLUID RESTRICTION

not necessary in treating most patients with cirrhosis and ascites.
Hyponatremia

The chronic hyponatremia usually seen in cirrhotic ascites patients is seldom morbid unless it is rapidly corrected.

- rapidly correct hyponatremia with hypertonic saline ➔ more complications than the hyponatremia itself.

no data-supported specific threshold for initiating fluid restriction
no data-supported level of restriction.

VAPTANS

- Hyponatremia recurs when the drug is discontinued.
- “not clinically beneficial in the long-term management of ascites in cirrhosis”
- Satavaptan ➔ higher mortality VS placebo.
- serum sodium ≤120 mmol/L remains unproven.
DIURETICS

• Initial dose
  – Spironolactone 100 mg
  – Furosemide 40 mg

Oral route ➔ Prefer
Starting both drug ➔ Prefer

Acute reductions in GFR associated with IV furosemide can be increased simultaneously every 3 to 5 days (maintaining the 100 mg:40 mg ratio)

Single morning dosing maximizes compliance.
INTRA VENOUS ALBUMIN

- weekly 25 g infusions of albumin for 1 year followed by infusions every 2 weeks improved survival compared to diuretics alone.

SPEED OF WEIGHT LOSS

- Edema: no limit to the daily weight loss

- No edema: 0.5 kg/day (maximum).

- Cessation of diuretics
  - Uncontrolled or recurrent encephalopathy
  - Serum sodium less than 120 mmol/L despite fluid restriction
  - Serum creatinine greater than 2.0 mg/dL (180 μmol/L)
  - GI bleed
  - Bacterial infection
  - Hypotension
DRUGS TO BE AVOIDED OR USED WITH CAUTION

- **ACEI / ARB**
- **Betablocker** (include propranolol) in refractory ascites (negative impact on BP)
  - not initiating beta blockers in those patients with refractory ascites

Risks versus benefits of beta blockers must be weighed carefully

- **nonsteroidal antiinflammatory drugs**
  - can reduce urinary sodium excretion
MANAGEMENT OF TENSE ASCITES.

- single 5-L paracentesis can be performed safely.

- Larger volumes of fluid have been safely removed with the administration of intravenous albumin (8 g/L of fluid removed)
RECOMMENDATIONS

7. Patients with ascites who are thought to have an alcohol component to their liver injury should abstain from alcohol consumption. (Class I, Level B)

8. Baclofen can be given to reduce alcohol craving and alcohol consumption in patients with ascites in the setting of alcoholic liver disease. (Class IIb, Level C)

9. First-line treatment of patients with cirrhosis and ascites consists of sodium restriction (88 mmol per day [2000 mg per day], diet education,) and diuretics (oral spironolactone with or without oral furosemide). (Class IIa, Level A)

10. Fluid restriction is not necessary unless serum sodium is less than 125 mmol/L. (Class III, Level C)

11. Vaptans may improve serum sodium in patients with cirrhosis and ascites. However their use does not currently appear justified in view of their expense, potential risks, and lack of evidence of efficacy in clinically meaningful outcomes. (Class III, Level A)

12. An initial therapeutic abdominal paracentesis should be performed in patients with tense ascites. Sodium restriction and oral diuretics should then be initiated. (Class IIa, Level C)

13. Diuretic-sensitive patients should preferably be treated with sodium restriction and oral diuretics rather than with serial paracenteses. (Class IIa, Level C)

14. Use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers in patients with cirrhosis and ascites may be harmful, must be carefully considered in each patient, monitoring blood pressure and renal function. (Class III, Level C)

15. The use of nonsteroidal anti-inflammatory drugs should be avoided in patients with cirrhosis and ascites, except in special circumstances. (Class III, Level C)

16. Liver transplantation should be considered in patients with cirrhosis and ascites. (Class I, Level B)
Refractory Ascites
REFRACTORY ASCITES

• Defined as

  – (1) is unresponsive to sodium-restricted diet and highdose diuretic treatment (400 mg per day of spironolactone and 160 mg per day furosemide)
  
  – (2) recurs rapidly after therapeutic paracentesis

<10% of patients with cirrhosis and ascites are refractory to standard medical therapy.
MEDICAL TREATMENT OPTIONS

• Oral midodrine 7.5 mg three times daily
  – increase urine volume, urine sodium, mean arterial pressure, and survival
  – added to diuretics to increase blood pressure
  – convert diuretic-resistant patients back to diuretic-sensitive.

Second-Line
Discontinue beta blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers
Consider adding midodrine especially in the profoundly hypotensive patient
Serial therapeutic paracenteses
Evaluation for liver transplantation
Transjugular intrahepatic portasystemic shunt (TIPS)

Third-Line
Peritoneovenous shunt
SERIAL THERAPEUTIC PARACENTESIS

• effective in controlling ascites.
• Diuretic resistant ➔ discontinue diuretics.
• Serial paracenteses ➔ deplete proteins, (may aggravate malnutrition and predispose to infection.)
Studies have infused between 5 and 10 g of albumin per liter of fluid removed; 6-8 g/L have been the most common doses.
TIPS VS Large volume paracentesis

Better control of ascites
More hepatic encephalopathy
No survival benefit
Less hepatorenal syndrome ??
No effect on quality of life

LVEF < 60% or diastolic dysfunction ➔ Less post TIPS survival
PERITONEOVENOUS SHUNTS

- poor long-term patency
- excessive complications
- No survival advantage

- reserved for diuretic-resistant patients who are not candidates for ...
  - Transplant
  - TIPS
  - serial paracenteses
RECOMMENDATIONS

17. The risks versus benefits of beta blockers must be carefully weighed in each patient with refractory ascites. Systemic hypotension often complicates their use. Consideration should be given to discontinuing or not initiating these drugs in this setting. (Class III, Level B)

18. The use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers should be avoided in patients refractory ascites. Systemic hypotension often complicates their use. (Class III, Level B)

19. Oral midodrine has been shown to improve clinical outcomes and survival in patients with refractory ascites; its use should be considered in this setting. (Class IIa, Level B)

20. Serial therapeutic paracenteses are a treatment option for patients with refractory ascite (Class I, Level C)

21. Post-paracentesis albumin infusion may not be necessary for a single paracentesis of less than 4 to 5 L. (Class I, Level C)

22. For large-volume paracenteses, an albumin infusion of 6-8 g per liter of fluid removed appears to improve survival and is recommended (Class IIa, Level C)

23. Referral for liver transplantation should be expedited in patients with refractory ascites, if the patient is otherwise a candidate for transplantation. (Class IIa, Level C)

24. TIPS may be considered in appropriately selected patients who meet criteria similar to those of published randomized trials. (Class I, Level A)

25. Peritoneovenous shunt, performed by a surgeon or interventional radiologist experienced with this technique, should be considered for patients with refractory ascites who are not candidates for paracenteses, transplant, or TIPS. (Class IIb, Level A)
Spontaneous bacterial peritonitis

• diagnosis of spontaneous bacterial peritonitis (SBP) is made in the
  presence of an elevated ascitic fluid absolute polymorphonuclear leukocyte (PMN) count (i.e., ≥250 cells/mm³ [0.25 x 10⁹/L])
  without an evident intra-abdominal, surgically treatable source of infection.

• Clinical ➔ Not adequate for rule in /rule out
EMPIRIC TREATMENT.

- culture-negative neutrocytic ascites (CNNA)
  - similar signs, symptoms, and mortality as patients with SBP
  - empiric antibiotic treatment

- monomicrobial nonneutrocytic bacterascites (MNB)
  - 62% in one study — resolve the colonization without antibiotics and without a neutrophil response.

- alcoholic hepatitis can masquerade as SBP.
EMPIRIC TREATMENT.

- **Cefotaxime**
  - used to cover 95% of the flora including the 3 most common isolates:
    - *Escherichia coli*, *Klebsiella pneumoniae*, and *Streptococcal pneumoniae*
    - Dosing of cefotaxime 2 g intravenously every 8 hours

- **Ceftriaxone**
  - An uncontrolled study
  - ceftriaxone 1 g intravenously twice a day × 5 days was effective in treating culture-negative neutrocytic ascites
ORAL TREATMENT

• Oral ofloxacin (400 mg bid for an average of 8 days)

• as effective as parenteral cefotaxime in the treatment of SBP in patients without
  – Vomiting
  – Shock
  – grade II (or higher) hepatic encephalopathy
  – serum creatinine greater than 3 mg/dL

• treatment was given in hospitalized patients
<table>
<thead>
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<th>REF NO.</th>
<th>STUDY DESIGN</th>
<th>METHOD OF RANDOMIZATION AND ANALYSIS</th>
<th>N</th>
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<td>Renal failure 10% vs 33%</td>
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Abbreviation: NS, not significant
### INTRAVENOUS ALBUMIN INFUSION IN ADDITION TO CEFOTAXIME.

#### Cefotaxime alone

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<td>Resolution of infection — no. (%)†</td>
<td>59 (94)</td>
<td>62 (98)</td>
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<td>Duration of antibiotic therapy — days</td>
<td>6 ± 1</td>
<td>5 ± 1</td>
<td>0.48</td>
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<td>16 (25)</td>
<td>14 (22)</td>
<td>0.83</td>
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<td>Hospital stay — days</td>
<td>13 ± 1</td>
<td>14 ± 1</td>
<td>0.48</td>
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<td>Renal impairment — no. (%)</td>
<td>21 (33)</td>
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<td>Death — no. (%)</td>
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<td>In hospital§</td>
<td>18 (29)</td>
<td>6 (10)</td>
<td>0.01</td>
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<tr>
<td>At three months¶</td>
<td>26 (41)</td>
<td>14 (22)</td>
<td>0.03</td>
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Secondary peritonitis

- free perforation of a viscus
  - e.g., duodenal ulcer

- *loculated abscesses in* the absence of perforation
  - e.g., periappendiceal abscess
SBP VS secondary peritonitis (2)

Characteristic analysis in the setting of free perforation

- PMN count $\geq$ equal to 250 cells/mm$^3$ (usually many thousands)
- Polymicrobial (frequently including fungi and enterococcus) Gram’s stain and culture

- At least two of the following criteria:
  - T. protein greater than 1 g/dL
  - LDH greater than the upper limit of normal for serum
  - Glucose less than 50 mg/dL.

100% Sensitivity
45% Specificity

- An ascitic fluid carcinoembryonic antigen $\geq$5 ng/mL or
- Ascitic fluid ALP >240 units/L

92% Sensitivity
88% Specificity

Not useful in nonperforation secondary peritonitis.

Patients who fulfill either set of criteria for gut perforation should undergo emergent computed tomographic scanning.
secondary peritonitis

Anaerobic coverage
+ 3rd generation cephalosporin

Laparotomy
FOLLOW-UP PARACENTESIS

Not needed in many patients with infected ascites.

In the setting, symptoms, analysis, organism(s), or response are atypical
RECOMMENDATIONS

26. Patients with ascites admitted to the hospital should undergo abdominal paracentesis. Paracentesis should be repeated in patients (whether in the hospital or not) who develop signs or symptoms or laboratory abnormalities suggestive of infection (e.g., abdominal pain or tenderness, fever, encephalopathy, renal failure, acidosis, or peripheral leukocytosis). (Class I, Level B)

27. Patients with ascitic fluid PMN counts greater than or equal to 250 cells/mm$^3$ (0.25 x $10^9$/L) in a community-acquired setting in the absence of recent $B$-lactam antibiotic exposure should receive empiric antibiotic therapy, e.g., an intravenous third-generation cephalosporin, preferably cefotaxime 2 g every 8 hours. (Class I, Level A)

28. Patients with ascitic fluid PMN counts greater than or equal to 250 cells/mm$^3$ (0.25 x $10^9$/L) in a nosocomial setting and/or in the presence of recent $B$-lactam antibiotic exposure should receive empiric antibiotic therapy based on local susceptibility testing of bacteria in patients with cirrhosis. (Class IIa, Level B)

29. Oral ofloxacin (400 mg twice per day) can be considered a substitute for intravenous cefotaxime in inpatients without prior exposure to quinolones, vomiting, shock, grade II (or higher) hepatic encephalopathy, or serum creatinine greater than 3 mg/dL. (Class IIa, Level B)

30. Patients with ascitic fluid PMN counts less than 250 cells/mm$^3$ (0.25 x $10^9$/L) and signs or symptoms of infection (temperature >100°F or abdominal pain or tenderness) should also receive empiric antibiotic therapy, e.g., intravenous cefotaxime 2 g every 8 hours, while awaiting results of cultures. (Class I, Level B)
31. When the ascitic fluid of a patient with cirrhosis is found to have a PMN count greater than or equal to 250 cells/mm$^3$ ($0.25 \times 10^9$/L) and there is high suspicion of secondary peritonitis, it should also be tested for protein, LDH, glucose, Gram’s stain, carcinoembryonic antigen, and alkaline phosphatase to assist with the distinction of SBP from secondary peritonitis. Computed tomographic scanning should also be performed. (Class IIa, Level B)

32. Patients with ascitic fluid PMN counts greater than or equal to 250 cells/mm$^3$ ($0.25 \times 10^9$/L) in a nosocomial setting and/or in the presence of recent $B$-lactam antibiotic exposure and/or culture an atypical organism(s) or have an atypical clinical response to treatment, should undergo a follow-up paracentesis after 48 hrs of treatment to assess the response in PMN count and culture. (Class IIa, Level C)

33. Patients with ascitic fluid PMN counts greater than or equal to 250 cells/mm$^3$ ($0.25 \times 10^9$/L) and clinical suspicion of SBP, who also have a serum creatinine $>1$ mg/dL, blood urea nitrogen $>30$ mg/dL, or total bilirubin $>4$ mg/dL should receive 1.5 g albumin per kg body weight within 6 hours of detection and 1.0 g/kg on day 3. (Class IIa, Level B)
PREVENTION OF SBP

- PPI associated with risk of SBP.

- Risk factors for development of SBP:
  - Total protein concentration $\leq 1.0 \text{ g/dL}$ or $1.5 \text{ g/dL}$
  - Variceal hemorrhage
  - Prior episode of SBP has led to randomized controlled trials of prophylactic antibiotics
PREVENTION OF SBP

• Norfloxacin 400 mg per day orally has been reported to successfully prevent SBP in...

• (1) patients with low-protein ascites
• (2) patients with prior SBP

• Alternative
  – DS Bactrim x 5 dose/wk
  – Ciprofloxacin 750 mg/wk

But…may select resistant flora

Inclusion criteria in most RCT
ascitic fluid total protein less than 1.5 g/dL and with impaired renal function (creatinine ≥1.2, BUN ≥25 or serum Na ≤130) or liver failure (Child score ≥9 and bilirubin ≥3
34. Intravenous ceftriaxone for 7 days or twicedaily norfloxacin for 7 days should be given to prevent bacterial infections in patients with cirrhosis and gastrointestinal hemorrhage. (Class I, Level A). Perhaps parenteral antibiotic, while the patient is bleeding and oral antibiotic after oral intake is resumed, for a total of 7 days, is a practical treatment regimen.

35. Patients who have survived an episode of SBP should receive long-term prophylaxis with daily norfloxacin (or trimethoprim/sulfamethoxazole). (Class I, Level A)

36. In patients with cirrhosis and ascites, longterm use of norfloxacin (or trimethoprim/sulfamethasoxazole) can be justified if the ascitic fluid protein <1.5 g/dL along with impaired renal function (creatinine ≥1.2, BUN ≥25 or serum Na ≤130) or liver failure (Child score ≥9 and bilirubin ≥3. (Class I, Level A)

37. Intermittent dosing of antibiotics to prevent bacterial infections may be inferior to daily dosing due to the development of bacterial resistance) and thus daily dosing should preferentially be used. (Class IIb, Level C)
Hepatorenal syndrome

Major Criteria

1) Cirrhosis with ascites
2) Serum creatinine > 1.5 mg/dl
3) Not improve with diuretic withdraw or volume expansion with albumin at least 2 days
4) Absence of shock
5) No current nephotoxic drug
6) Absence of renal parenchymal disease

   (Protein urea > 500 g/day or U/S kidney)
Hepatorenal syndrome

Type I (Rapid progressive)

doubling of the initial serum creatinine to a level greater that 2.5 mg/dL or a 50% reduction of the initial 24-hour CrCl < 20 mL per minute in less than 2 weeks

Type II

Cr 2.5 mg/dl

50%

2X

CrCl <20 ml/min
Prevention

• Pentoxifylline
  – preventing hepatorenal syndrome in patients with cirrhosis, ascites, and creatinine clearances between 41 and 80 mL/min
Treatment

- Albumin infusion
- Pentoxifylline creatinine clearances between 41 and 80 mL/min
- Hemodialysis (may cause hypotension)
- Liver transplantation

Type I
- Octreotide (200 ug SC tid) and midodrine (12.5 mg orally 3 times per day)
- *Plus* albumin infusion (10-20 gm/day x 20 days)

Type I+II
- terlipressin and albumin ?? (improve renal function but no survival benefit) $P=0.059$
- Norepinephrine/vasopressin and albumin (Need ICU)
RECOMMENDATIONS

38. Urinary biomarkers such as neutrophil gelatinase associated lipocalin may assist in the differential diagnosis of azotemia in patients with cirrhosis. (Class IIa, Level B)

39. Albumin infusion plus administration of vasoactive drugs such as octreotide and midodrine should be considered in the treatment of type I hepatorenal syndrome. (Class IIa, Level B)

40. Albumin infusion plus administration of norepinephrine should also be considered in the treatment of type I hepatorenal syndrome, when the patient is in the intensive care unit. (Class IIa, Level A)

41. Patients with cirrhosis, ascites, and type I or type II hepatorenal syndrome should have an expedited referral for liver transplantation. (Class I, Level B)
Hepatic hydrothorax

Confirm by injecting technetium-radiolabeled sulfur colloid into the abdomen and detecting rapid passage of isotope into the chest cavity.
Hepatic hydrothorax

RECOMMENDATIONS

45. Chest tube insertion is contraindicated in patients with hepatic hydrothorax. (Class III, Level B)

46. First-line therapy of hepatic hydrothorax consists of dietary sodium restriction and diuretics. (Class IIa, Level B)

47. TIPS can be considered as second-line treatment for hepatic hydrothorax, once it becomes refractory. (Class IIb, Level B)