WGO Practice Guideline:
Condition: Management of Ascites Complicating Cirrhosis in Adults

Sections:

This guideline is concerned primarily with the management of ascites and with the diagnosis, treatment and prevention of spontaneous bacterial peritonitis (SBP) in adult patients with cirrhosis. The pathogenesis of ascites and SBP, a comprehensive differential diagnosis of ascites, the diagnosis and treatment of ascites due to causes other than cirrhosis, and the hepatorenal syndrome are beyond the scope of this guideline.

1. Initial evaluation

Comprehensive medical history

- Physical examination, including elicitation of increased flank dullness to percussion with patient supine and shifting dullness (>1500 ml free fluid)
- Abdominal ultrasound can be used to detect ascites in morbidly obese, to indicate appropriate site for paracentesis in patients with multiple abdominal surgical scars and with serum alpha-fetoprotein, to detect hepatic malignancy.
- Diagnostic ascitic fluid tap (20 ml)

2. Diagnostic ascitic fluid tap

- Indicated for inpatients or outpatients with clinically apparent ascites of recent onset, or any cirrhotic patient with ascites whose general condition deteriorates.
- Few contraindications, e.g. clinically evident fibrinolysis or disseminated intravascular coagulation.
- Prophylactic infusions of fresh frozen plasma or platelets not necessary.

3. Ascitic fluid analysis

- Cell count with differential and total protein and albumin concentration + serum albumin obtained routinely.
- Abnormal results are an indication for further non-routine tests on another specimen.
- If the polymorphonuclear leucocyte count is >250 cells/mm3, another specimen of ascitic fluid is injected into blood culture bottles at bedside.
- Serum-ascites albumin gradient = serum albumin - ascitic fluid albumin
    - o if $\geq$ 1.1 g/dL portal hypertension is present;
    - o if < 1.1 g/dL portal hypertension is not present (about 97% accurate).

  A high gradient is associated with diffuse parenchymal liver disease and occlusive portal and hepatic venous disease (as well as nephrotic syndrome, liver metastasis and hypothyroidism).

- Patients undergoing large volume paracenteses require cell count with differential only; culture not routine.
- Cytology and smear, and culture for mycobacteria – only if there is high index of suspicion of relevant disease.
- Cytology - only positive in peritoneal carcinomatosis.
  Sensitivity increased by centrifuging large volume.
- Bacterial growth occurs in about 80% of specimens with polymorphonuclear (PMN) count of $\geq$250 cells/mm^3.
- Lactate dehydrogenase >225mU/L, glucose <50mg/dL, total protein >1g/dL and multiple organisms on gram stain suggest secondary bacterial peritonitis (ruptured viscus or loculated abscess).
- A high level of triglycerides confirms chylous ascites.
- An elevated amylase level suggest pancreatitis or gut perforation.
- An elevated bilirubin level suggest biliary or gut perforation.

4. Treatment of diuretic-sensitive ascites

1. Significance of serum-ascites albumin gradient

Patients with low serum-ascites albumin gradient do not respond well to sodium restriction and diuretics, except when nephrotic syndrome is implicated. This guideline applies only to patients with a high gradient.

2. Alcohol

Abstinence from alcohol - decreases hepatocellular injury, allows improvement of reversible component of alcoholic liver disease, and may, in alcoholics, decrease portal hypertension.

3. Non-diuretic therapy

- Renal sodium retention is the phenomenon primarily responsible for fluid retention and ascites formation. It occurs months before impairment of renal free water clearance.
- Strict bed rest - not indicated
- Fluid restriction - not indicated unless serum sodium is < 120 mmol/L (reduced renal free water clearance). Aquaretic agents, such as antagonists of the V2

receptor of antidiuretic hormone or kappa-opioid receptor agonists, are experimental.
- Fluid loss and weight changes are directly related to sodium balance.
- Dietary sodium intake is restricted - usually to 88 mmol/day.
- Body weight - recorded daily until rate of diuresis is satisfactory.
- Measurements of urinary sodium excretion useful
- random concentrations of 0 mmol/L or > 100 mmol/L
- 24 hour excretion (with measurement of creatinine to assess completeness of collection)
- A major goal of treatment is to increase urinary sodium excretion to > 78 mmol/day, i.e. greater than intake of 88 mmol/day less non-urinary losses of 10 mmol/day.
- Only 10–15% of patients spontaneously excrete > 78 mmol/day.

4. Diuretic therapy

Initial conventional oral diuretic therapy consists of single morning doses of spironolactone 100 mg, or spironolactone 100 mg + furosemide 40 mg. If weight loss and natriuresis are inadequate the dose of spironolactone monotherapy is increased to 200 mg daily, and, if necessary to 400 mg daily, or the doses of both furosemide and spironolactone are increased simultaneously, maintaining the 2:5 ratio between the two doses, to facilitate maintenance of normokalemia, i.e. to 80 and 200 mg daily and to 160 and 400 mg daily, respectively. Maximum doses are 160 mg/day for furosemide and 400 mg/day for spironolactone.

Spironolactone monotherapy may suffice if fluid overload is minimal and is more effective than furosemide monotherapy. Spironolactone monotherapy may be complicated by hyperkalemia and tender gynecomastia. The onset of the action of spironolactone may not be apparent until several days after starting therapy. Tolerance of spironolactone may be reduced in the presence of parenchymal renal disease, due to hyperkalemia. Amiloride and triamterene are substitutes for spironolactone.

Furosemide may be temporarily withheld if hypokalemia occurs.

When edema is present there is no limit to daily weight loss. When edema has resolved, maximum daily weight loss should be about 0.5 kg, to avoid azotemia due to intravascular volume depletion.

Diuretic sensitive patients should not be treated with serial large paracenteses.

5. Large volume paracentesis

If tense ascites is causing clinically significant symptoms, a single large volume paracentesis (4–6 L) can be performed safely, without adversely affecting hemodynamics, and without the necessity of concomitant colloid infusion, as an initial treatment to relieve the symptoms. If the paracentesis is > 6 L, intravenous infusion of albumin, 6–8 g/L removed, is recommended.

To prevent reaccumulation of fluid, dietary sodium restriction and diuretic therapy are instituted.

Large volume paracentesis is not first line therapy for all patients with tense ascites.

6. Outpatient management

- When a patient is responding to medical treatment, hospitalisation is not necessary.

- Body weight, orthostatic symptoms, and serum electrolytes, urea and creatinine are monitored.
- Random urinary sodium concentration is measured if weight loss is inadequate. If urinary sodium is > 0 and < 100 mmol/L, or if refractory ascites or non-compliance with diet is suspected, a measurement of urinary sodium excretion in 24 hours is obtained. Patients, who are excreting > 78 mmol/day and who are not losing weight, should be counselled further about restricting their sodium intake. Patients, who do not lose weight and who excrete < 78 mmol/day, should be treated with higher doses of diuretics.
- Intravenous albumin, 12.5 g/day, may enhance diuretic efficacy.

7. Liver transplantation

The development of ascites as a complication of cirrhosis is associated with an approximately 50% 2-year survival.

5. Indications to stop diuretics

1. Encephalopathy
2. Serum sodium <120 mmol/L despite fluid restriction
3. Serum creatinine > 2.0 mg/dL
4. Clinically significant complications of diuretics
5. Hyperkalemia and metabolic acidosis (spironolactone)

6. Treatment of refractory ascites

1. Definition

Refractory ascites is defined as fluid overload that is non-responsive to restriction of dietary sodium to 88 mmol/day and maximal-dose diuretic therapy (furosemide + spironolactone), in the absence of ingestion of prostaglandin inhibitors, such as non-steroidal anti-inflammatory drugs. Ascites is also considered to be refractory when there is intolerance of diuretic therapy.

Indications of failure of diuretic therapy include minimal or no weight loss, together with inadequate urinary sodium excretion (< 78 mmol/day).

Less than 10% of patients with ascites complicating cirrhosis meet the criteria of the definition of refractory ascites.

2. Serial large-volume paracenteses

Serial large-volume paracenteses (6-10 L) are safe and effective in controlling refractory ascites.

In patients with no urinary sodium excretion and a dietary intake of 88 mmol sodium daily, the required frequency is about every two weeks. The frequency is influenced by the degree of compliance with the low sodium diet. The sodium content of ascitic fluid is about 130 mmol/L. Thus, a 6 L paracentesis removes 780 mmol sodium. Patients, who ingest 88 mmol sodium per day and excrete 10 mmol sodium in non-urinary losses and no sodium in the urine, retain 78 mmol sodium per day. Accordingly, a 6 L paracentesis removes the sodium retained over a period of 10 days, and a 10 L paracentesis removes the sodium retained over approximately 17 days.

Patients with urinary sodium excretions greater than zero should require paracenteses less frequently.

Patients requiring paracenteses of 10 L more frequently than every 2 weeks are not complying with the low sodium diet.

Intravenous colloid replacement, e.g. albumin 6-8 g/L ascitic fluid removed is recommended immediately following a large-volume paracentesis (> 5 L), to minimize intravascular hypovolemia, activation of vaso-constrictor and antinatriuretic systems, and impairment of renal function. Dextran 70 is less efficacious than albumin. If a paracentesis is < 5 L, colloid replacement appears to be unnecessary.

3. Transjugular intrahepatic portal-systemic stent-shunt (TIPSS)

A TIPSS is a side-to-side portal-systemic shunt placed by an interventional radiologist.

TIPSS is an efficacious treatment for patients with refractory ascites. The incidence of encephalopathy is not necessarily increased and survival may be better than in patients treated with serial large-volume paracenteses. TIPSS is associated with suppression of antinatriuretic systems, and an improvement in renal function and renal response to diuretics.

4. Peritoneovenous shunt

Peritoneovenous shunts (e.g. LeVeen or Denver) have been shown to have poor long-term patency. They are associated with excessive complications, including peritoneal fibrosis, and confer no survival advantage relative to standard therapy.

Peritoneovenous shunting should be reserved for diuretic-resistant patients who are candidates for neither liver transplantation nor serial large-volume paracenteses (because of multiple surgical scars or distance from a physician able to perform paracentesis).

5. Liver transplantation

In a patient with cirrhosis, the development of ascites refractory to standard medical therapy is associated with an approximately 50% 6-month survival, and an approximately 25% 12-month survival.

7. Spontaneous bacterial peritonitis

1. Diagnosis

A diagnostic ascitic fluid tap is mandatory and should be repeated if symptoms, signs and/or laboratory findings consistent with infection develop.

A diagnosis of SBP is made when an ascitic fluid bacterial culture is positive (e.g Escherichia coli, Klebsiella pneumoniae, or pneumococcus) with an elevated ascitic fluid absolute PMN leucocyte count ($\geq$ 250cells/mm^3), without an evident intra-abdominal and surgically treatable source of infection.

A presumptive diagnosis of SBP is made in patients with negative ascitic fluid cultures, but ascitic fluid PMN leucocyte counts of $\geq$ 250 cell/ mm^3 and symptoms and/or signs consistent with infection (temperature >100 degrees F, chills, abdominal pain, rebound tenderness, reduced bowel sounds).

In patients with alcoholic hepatitis and fever, leucocytosis and/or abdominal pain, a diagnosis of SBP should not be made in the absence of an elevated ascitic fluid PMN leucocyte count.

In most patients with culture positive ascitic fluid, bacterial and PMN leucocyte counts are increasing during the period immediately before treatment.

Ascitic fluid cultures may be positive before there is a neutrophil response.

2. Treatment

Patients with a definitive diagnosis or presumptive diagnosis of SBP, should be treated with antibiotics. Treatment should not be delayed in those with a presumptive diagnosis until a positive culture is obtained. Those with positive ascitic fluid cultures in the absence of a neutrophil response, should also be treated with antibiotics, if symptoms and/or signs of infection are present.

When treating empirically a broad spectrum, non-nephrotoxic, antibiotic is administered intravenously, e.g cefotaxime (third-generation cephalosporin) 2 g 8 hourly.

In well-characterised patients with SBP a 5-day course is as efficacious as a 10-day course of intravenous antibiotics.

Lack of antibiotic-induced clinical improvement is an indication for repeat diagnostic paracentesis. If the ascitic fluid PMN leucocyte count is lower and the culture negative, a further course of antibiotic is given. If the ascitic fluid PMN leucocyte count is higher and culture yields a new organism, a different antibiotic is chosen. Alternatively, if reculture yields the same organism secondary bacterial peritonitis is suspected.

Co-treatment with intravenous albumin, 1.5 g/kg at the time of diagnosis and 1 g/kg on day 3, reduces the incidence of renal impairment and improves survival.

Oral ofloxacin has been reported to be as efficacious as intravenous cefotaxime in the treatment of patients with SBP, who are not azotemic, vomiting or in shock. However, until more data are available, an intravenous antibiotic regimen is preferred.

3. Follow-up paracentesis

A follow-up paracentesis is only necessary if there are atypical features (symptoms, clinical setting, ascitic fluid analysis, organism(s), response to therapy) suggestive of secondary peritonitis.

4. Liver transplantation

The prognosis in patients who develop SBP is so poor, that liver transplantation should be considered in all survivors of SBP.

5. Prevention

Cirrhotic patients, with low ascitic fluid total protein levels (< 1 g/dL) or gastrointestinal hemorrhage or those who have recovered from an episode of SBP, are at high risk of developing SBP and are candidates for long-term prophylactic therapy with oral antibiotics.

Oral antibiotic primary prophylaxis, with norfloxacin, ciprofloxacin or cotrimoxazole, appears to be effective in preventing an initial episode of SBP or a recurrence of SBP. The

emergence of infections caused by bacteria resistant to specific antibiotics is a potential problem.

8. Links to Useful Websites

The American Association for the study of Liver Diseases AASLD)
: Excellent AASLD Guideline by Bruce AQ Runyon - if a little dated . "Management of adult patients with Ascites caused by cirrhosis"

PUBMED Medline Plus
: The best starting point for consumer/patient information; type "ascites" in the search box.

The National Guidelines Clearinghouse
: The best starting point for guidelines; type "ascites" in the search box.

Society of American Gastrointestinal Endoscopic Surgeons
: Guideline for diagnostic laparoscopy.

American College of Radiology
: ACR Appropriateness Criteria™ for percutaneous catheter drainage of infected intra-abdominal fluid collections.

The British medical Journal
: ABC of diseases of liver, pancreas, and biliary system: Portal hypertension 2. Ascites, encephalopathy, and other conditions, J E J Krige and I J Beckingham, BMJ 2001; 322: 416-418. Pubmed-Medline

The Cochrane Collaboration
: Antibiotics for spontaneous bacterial peritonitis in cirrhotics (Cochrane Review)

9. Queries and Feedback from you

INVITATION TO COMMENT

The Practice Guidelines Committee welcomes any comments and queries that readers may have. Do you feel we have neglected some aspects of the topic? Do you think that some procedures are associated with extra risk? Tell us about your own experience. You are welcome to click on the link below and let us know your views.

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