

CLINICAL PRACTICE GUIDELINES

*Management of
Ascites due to Cirrhosis,
Spontaneous Bacterial
Peritonitis and
Hepatic Encephalopathy*

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1. Ascites due to Cirrhosis

1.1 Introduction

Chronic liver disease is one of the leading causes of death in Sri Lanka. Ascites is one of the commonest complications of decompensated cirrhosis. Development of ascites in a patient with cirrhosis carries a poor prognosis, as approximately 50% of such patients die within 2 years. Approximately 85% of patients presenting with ascites have cirrhosis of the liver as the cause of ascites. The other 15% have a non-hepatic cause for ascites, such as, carcinomatosis or tuberculosis. Approximately 5% of patients have more than one cause for ascites. eg cirrhosis with peritoneal carcinomatosis or peritoneal tuberculosis. Successful management depends on correct diagnosis of the cause of ascites. eg. ascites due peritoneal carcinomatosis does not respond to diuretic therapy.

The diagnosis of new onset ascites is suspected on the basis of the history and physical examination, and usually confirmed by an ultrasound scan of the abdomen. The diagnosis of the cause of ascites is initially based on the history and examination and ascitic fluid analysis. The liver is usually screened with an ultrasound scan for the presence of hepatocellular carcinoma, hepatic vein thrombosis and portal vein thrombosis.

Ascites is best managed in a General / Base Hospital setting under the supervision of a physician. However, follow-up of a stable patient should be possible at a more peripheral hospital under the supervision of a non-specialist medical officer though they need to have periodic (every 3 months) supervision by a physician. These patients should be screened for oesophageal and gastric fundal varices by upper GI endoscopy annually, and for hepatocellular carcinoma by abdominal ultrasonography and measurement of serum alpha-fetoprotein levels every 6 months. If a 'stable' patient develops complications, such as, fever or confusion, or if there is worsening of ascites while on treatment they should be referred to a physician in a hospital with facilities for further investigation.

Recommendations

1.2 Evaluation and diagnosis

1. Diagnostic abdominal paracentesis should be performed on all patients with new onset ascites. Diagnostic paracentesis should also be performed in patients with ascites whose ascites has not been analyzed previously and in patients previously analyzed who are presenting with a marked change in the clinical picture. (II)
2. Since bleeding during paracentesis is uncommon, the prophylactic use of fresh frozen plasma or platelets before paracentesis is not recommended unless there is history of bleeding disorder or clinical evidence of DIC. (III)

At least 20 ml of ascitic fluid should be aspirated preferably from the left lower quadrant of the abdomen 2 finger breadths above and medial to the anterior superior iliac spine.

1.3 Ascitic fluid analysis

3. The initial laboratory investigation of ascitic fluid should include an ascitic fluid cell count, the differential count and ascitic fluid total proteins. (II)

The serum ascites albumin gradient (SAAG) should be performed where available.(II).

If the SAAG is greater than or equal to 1.1g/dl the patient has portal hypertension with approximately 97% accuracy.

Serum ascites albumin gradient(SAAG) = Serum albumin - ascitic fluid albumin

4. Other studies can be ordered based on pretest probability of disease (Appendix-Table 1) in addition to routine investigations necessary in patients with decompensated cirrhosis.(Appendix-Table 2). (III)

5. Patients with ascites who are thought to have an alcohol component to their liver injury should abstain from alcohol consumption. (II)

1.4 Treatment of ascites

6. First-line treatment of patients with cirrhosis and ascites consists of sodium restriction (88 mmol per day) and diuretics (oral spironolactone and frusemide). (I)

One heaped teaspoonful of table salt contains slightly more than 88 mmol of sodium.

88mmol Na⁺ ==5g NaCl (table salt)

One heaped teaspoonful table salt= 6g NaCl

The usual diuretic regimen consists of a single morning dose of oral spironolactone 100mg and frusemide 40mg. The doses of both diuretics can be increased simultaneously every 3-5 days if weight loss and urinary sodium excretion are inadequate. Usual maximum daily doses are 400mg of spironolactone and 160mg of frusemide. Amiloride (10-40) mg a day can be substituted for spiranolactone in patients with tender gynacomastia.

Monitoring of daily body weight is recommended to asses the response of salt restriction and diuretics. Patients with massive oedema can be allowed to loose weight rapidly but once the oedema has subsided a 0.5 kg daily weight loss is considered appropriate.

Regular, if possible daily monitoring of blood urea/ serum electrolytes and serum creatinine is recommended.

Bed rest although traditionally used, has not been studied adequately and may not be practical.

See annexure 1 for sodium content in common food items and a prototype diet chart.

7. Fluid restriction is not necessary unless serum sodium is less than 120 mmol/L. (III)
8. An initial therapeutic abdominal paracentesis of up to 5 litres should be performed in patients with tense ascites if the patient is otherwise well. Sodium restriction and oral diuretics should then be initiated. (II)
9. Diuretic-sensitive patients should preferably be treated with sodium restriction and oral diuretics rather than with serial paracentesis. (III)
10. Serial therapeutic paracentesis may be performed as necessary in patients with refractory ascites. (III)
11. Post-paracentesis albumin infusion may not be necessary for a single paracentesis of less than 5 L. For large-volume paracentesis, an albumin infusion of 8 to 10g per liter of fluid removed can be considered where available. (II)
Plasma is considered to be of no value as a substitute for human albumin. Plasma expanders may be considered if human albumin is not available
12. Peritoneovenous shunts or anastomosis should be considered for patients with refractory ascites who are not candidates for paracentesis, transplant, or TIPPS. (I)

1.5 Hepatorenal Syndrome.

Hepatorenal syndrome is a functional renal failure occurring in patients with advanced liver disease caused by intense vasoconstriction of renal arteries. There are two types of hepato renal syndrome, type 1 and type 2. The type 1 HRS is rapidly progressive and exhibits a very poor prognosis with a 90% 3 month mortality. The type 2 is a more stable less rapidly progressing renal impairment encountered in patients with advanced liver disease.

13. Albumin infusion plus administration of vasoactive drugs such as Terlipressin .5 - 2mg iv every 4-12 hrs should be considered in the treatment of type I hepatorenal syndrome. (II)
Vaso pressin may be useful in the absence of terlipressin.

1.6 Spontaneous Bacterial peritonitis.

14.A diagnostic paracentesis should be repeated in warded patients 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). (III)

15.If the preliminary analysis of the ascitic fluid shows a PMN count of >250 cells/Cumm patients should receive empiric antibiotic therapy after collecting ascitic fluid for culture in blood culture bottles at bedside, e.g., intravenous cefotaxime 1-2 g every 8 hours for 5 days(I)

16.Patients with ascitic fluid PMN counts less than 250 cells/mm³ ($0.25 \times 10^9/L$,) and signs or symptoms of infection (temperature $>100^\circ F$ or abdominal pain or tenderness) should also receive empiric antibiotic therapy, e.g., intravenous cefotaxime 1- 2 g every 8 hours for 5 days, while awaiting results of cultures. Antibiotics should be continued even in the absence of a positive culture.(II)

17.Patients with ascitic fluid PMN counts greater than or equal to 250 cells/mm³ ($0.25 \times 10^9/L$) and clinical suspicion of SBP should receive 1.5 g albumin per kg body weight within 6 hours of detection and 1.0 g/kg on day 3 where available.(II)

18.When the ascitic fluid of a patient with cirrhosis is found to have a PMN count greater than or equal to 250 cells/mm³ ($0.25 \times 10^9/L$), it should also be tested for total protein, LDH, glucose with a RBS,

and Gram's stain to assist with the distinction of SBP from secondary bacterial peritonitis (ascitic fluid infection caused by a surgically treatable intra abdominal source) Table 4. (II)

19. Oral ciprofloxacin (500 mg twice per day.) can be considered to substitute for intravenous cefotaxime in in-patients without vomiting, shock, grade II (or higher) hepatic encephalopathy, or serum creatinine greater than 3 mg/dL or other contraindications for use of ciprofloxacin. (I)

20. Short-term (7 days) inpatient twice-daily ciprofloxacin (or trimethoprim / sulfamethoxazole) should be given to prevent bacterial infections in patients with cirrhosis and gastrointestinal hemorrhage; a quinolone antibiotic can be given intravenously while the patient is actively bleeding. (I)

1.7 Prevention of Spontaneous Bacterial peritonitis (SBP)

21. Patients who have survived an episode of SBP should receive long-term prophylaxis with daily 400 mg of norfloxacin or cotrimoxazole because this is the most data-supported indication for long-term outpatient prophylaxis (I)

22. In patients with cirrhosis and ascites but no gastrointestinal bleeding, either short-term (inpatient-only) or long-term outpatient use of daily norfloxacin or cotrimoxazole can be justified when the ascitic fluid total protein is less than or equal to 1g/dL or serum bilirubin greater than 2.5 mg/dL. (I)

1.8 Annexure

- 23. Trans jugular intrahepatic portosystemic shunt is to be considered in patients with refractory ascites provided transplantation is considered if available. (I)
- 24. Liver transplantation should be considered in patients with cirrhosis and ascites where available. (I)
- 25. Patients with cirrhosis and ascites and hepatorenal syndrome(type 1) should have an expedited referral for liver transplantation where available. (II)

1.9 Appendix

Table 1 - Additional investigations recommended in ascites on ascetic fluid

Additional investigation	Relevance
Culture	When PMN Count greater than 250/ Cumm before starting antibiotics
Cytology and smear	When intra abdominal malignancy is suspected
Smear for AFB and culture for TB	If tuberculosis is suspected
Glucose	When secondary bacterial peritonitis is suspected
LDH	When secondary bacterial peritonitis is suspected

Table 2 - Routine investigations in patients with cirrhosis and ascites

1. Blood glucose
2. UFR and urine for culture
3. Full blood count
4. Liver profile
5. Blood urea
6. Serum creatinine
7. Serum electrolytes
8. Chest Xray
9. Ultrasonography of the abdomen
10. Alpha fetoproteins if available

Table 3 - Criteria for diagnosis of hepatorenal syndrome

Criteria for diagnosis of hepatorenal syndrome
<ul style="list-style-type: none">• Advanced liver failure with portal hypertension.• Serum creatinine concentration >1.5mg/dl or 24 hr creatinine clearance < 40ml/min• Absence of shock, ongoing bacterial infection and fluid loss and no current treatment with nephrotoxic drugs• Absence of sustained improvement in renal function after discontinuation of diuretics and trial of plasma expansion• Absence of proteinuria(500mg/day) or haematuria• Absence of ultrasonographic evidence of obstructive uropathy or parenchymal renal disease

Table 4 - Characteristic features of Bacterial peritonitis with underlying perforation

<ol style="list-style-type: none">1. PMN count greater than 250/Cumm (Usually many thousands)2. Multiple organisms on gram stain and culture3. Total proteins greater than 1g/dl4. LDH greater than upper limit for normal for serum5. Glucose less than 50 mg/dl

Table 3 - Dietary Recommendations

Cirrhotic patients with ascites need sodium restriction. Their daily intake of sodium should not exceed 2000mg (88mmol) per day. One heaped tea spoonful of salt contains 100mmol of sodium.

These patients should not receive food rich in sodium. Moderate sodium foods are limited. An intake of no more than ¼ tea spoonful of table salt is allowed daily. Animal protein foods are generally high in sodium. Some vegetables also contain higher sodium content. Patients should be careful about the salt used when cooking rice and making bread. Approximate sodium content in some commonly used food items are given below.

- 1 tea spoon of salt = 6 g
- 6 g of salt = Na 2400 mg (100 mmol)
- 1 tea spoon of salt = 6g of salt = 2400 Na

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Low	Medium	High	Very high
Potato	Cabbage	Beef	Cheese
Rice	Garlic	Carrot	Preserved
Oranges	Mushrooms	Beet	meat
Pineapple	Broccoli	Egg	Canned
Dates	Yeast	Yolk	fish
Cucumber	Brown sugar	Tuna	Pickles
Pea nuts	Fish	Yoghurt	Butter
Refined		Spinach	Margarine
sugar		Bread	Chutney
			Marmite
			Dried fish
			Sprats
			King Coconut
			“Lunu Dehi”
			Soup cubes
			Sauces
			Ajinomoto

A model diet plan for daily main meals

Food Item	Servings	Total Na
25g of Milk	2	60 x 2 = 120 mg
1 cup of rice	2	10 x 2 = 20 mg
2 slices of bread	1	300 x 1 = 300 mg
2 crackers	2	40 x 2 = 80 mg
50g of fish	2	60 x 2 = 120 mg
1 cup of vegetables	2	40 x 2 = 80 mg
1 cup of fruit	2	2 x 2 = 4 mg
Total		684 mg of Na

* Half a teaspoon of salt (3g/1200 mgs of Na) can be added if only the above diet plan is used for the day.

2. Hepatic encephalopathy

The Guideline Committee bases these recommendations on currently available data on the management of hepatic encephalopathy. Multiple treatments have been used for the treatment of hepatic encephalopathy. However their efficacy has not been assessed adequately by well-designed randomized clinical trials. Despite these limitations a review of the currently available literature on the subject renders it possible to outline a rational approach to the management of hepatic encephalopathy.

Hepatic encephalopathy (HE) may be defined as a disturbance in central nervous system function because of hepatic insufficiency. This definition reflects the existence of a spectrum of potentially reversible neuropsychiatric manifestations characterized by changes in the cognitive function, behavior and personality, and transient neurological symptoms present in both acute and chronic liver failure.

Table -4 shows the grading of hepatic encephalopathy

Hepatic encephalopathy is a frequent complication of cirrhosis, that is usually observed in association of severe hepatic insufficiency .The characteristic presentation is the development of acute encephalopathy with an abrupt decline in the level of consciousness leading to coma. In acute encephalopathy a precipitating factor is frequently found. However, in patients with poor hepatic function subtle neurological manifestations may be present as a form of chronic encephalopathy.

The exact mechanism for the development of HE is unknown. A number of gut derived toxic factors have been implicated. Most evidence suggests ammonia as a key factor in the pathogenesis of hepatic encephalopathy. Therefore, most of the treatment options are aimed at either reducing the production of ammonia in the gut or reducing the absorption of ammonia that is produced from the Gut.

In these guidelines, we separately outline the

recommended management plan for a patient with chronic liver disease presenting with acute hepatic encephalopathy and the management of a more stable patient with advanced liver disease and chronic encephalopathy.

Acute encephalopathy should be managed in a General / Base Hospital under the supervision of a physician. The follow-up of a more stable patient with chronic encephalopathy could be carried out at a more peripheral level, under the supervision of a non-specialist medical officer with periodic reviews by a physician.

2.1 Management of acute encephalopathy in a patient with cirrhosis

Recommendations

1. A vigorous search to identify and eliminate a precipitating factor or factors should be started immediately.

Well-known precipitating factors are:

1. Gastrointestinal haemorrhage,
2. Infections,
3. Renal and electrolyte disturbances,
4. Medications (specially sedatives),
5. Constipation,
6. Dehydration
7. Excessive dietary protein intake in some patients

Blood cultures and ascitic fluid cell counts are recommended even if the other signs of infection are absent. It is wise to assume that a patient with cirrhosis who has a major change in mental status has an infection and started on intra venous broad spectrum antibiotics unless proven otherwise.

Encephalopathy may occur spontaneously in patients with advanced liver disease and carries a poor prognosis.

2. Adequate supportive care is critical during all stages of encephalopathy.

As the level of consciousness varies rapidly prevention of bodily harm by adequate nursing care is important. I.V. line should be in place. Prevention of line sepsis needs special attention.

3. A nasogastric tube (NG tube) and urinary catheter should be in place in deep encephalopathy and NG nutrition started. A NG tube will also help the administration of medications specially lactulose.

4. In patients in deep coma endotracheal intubation and ventilation should be considered if possible.

5. Patients should receive adequate fluid intake even if the oedema and ascites present. An input out put chart should be maintained.

The preferred intra venous solution is 5% dextrose. In patients with diabetes use of 5 % with adequate control blood sugar with insulin is preferred over normal saline. Thiamine 100mg/d i.v should be added till the patient recovers. This is to avoid precipitating Wernicke's encephalopathy in alcohol dependant patients.

In general diuretics should be avoided in acute encephalopathy unless pulmonary oedema is present. If tense ascites is present paracentesis could be considered over diuretics.

6. Measures to reduce the nitrogen load from the gut should be implemented

Bowel cleansing is a standard therapeutic measure in HE. Lactulose is a first line pharmacological treatment in HE. In acute HE lactulose 45ml should be given via NG tube followed by dosing every hour until bowel evacuation occurs. After the initial bowel evacuation dosing is adjusted to an objective of 2-3 soft bowel movements a day. Alternatively phosphate enemas could be used for

the initial bowel evacuation with lactulose. After achieving the initial bowel movement, as before, the dose of lactulose should be adjusted to achieve 2-3 bowel openings a day. There is no evidence for continuation of enemas or bowel washes after achieving bowel movements with lactulose. So enemas may be stopped after achieving regular (at least twice a day) soft bowel movements with lactulose. If the patient is incapable of receiving lactulose orally, for example during active upper GI bleeding, bowel cleansing should be continued with phosphate enemas. A tap water enema may be considered for the initial bowel evacuation if phosphate enemas are not available. There is no evidence for use of the high bowel washes that are traditionally used in hepatic encephalopathy. Repeated high bowel washes may not be practical in an unconscious patient and results in an additional strain on the staff in an inadequate resource setting. Repeated phosphate enemas or bowel washes may be considered if lactulose is not available.

Antibiotics are a therapeutic alternative to non-absorbable disaccharides in the treatment of acute encephalopathy. Metronidazole 200mg tds is preferred over neomycin. There is no evidence for or against the combined use of lactulose and antibiotics.

Neomycin has been in use for hepatic encephalopathy for the past 40 years. There is no firm evidence to support that neomycin is beneficial in HE. Neomycin is also potentially nephrotoxic.

7. Adequate nutritional support is recommended.

Current recommendation is to provide 25-35 kcal/kg/d and proteins 0.5 - 1.2g/kg/d.

Proteins can be withdrawn for the first day (even 2-3 days). Thereafter patient should receive the maximal tolerable protein intake aiming at 1.2g/kg/d (40-60g/d).

8. L-Ornithine L-Aspartate (LOLA) has been shown to be beneficial in HE in several randomized studies. LOLA increases ammonia removal. The place for LOLA in the management of hepatic encephalopathy is still unclear. However, if available, it may be considered in patients with moderate to severe hepatic encephalopathy not responding to standard treatment. The dose is 20 mg iv infusion daily for 4 days.

2.2 Management of chronic encephalopathy in patients with cirrhosis

Patients with cirrhosis are at risk of developing new episodes of encephalopathy. In patients with recurrent encephalopathy the main objective is to avoid the acute episodes.

In patients with chronic low-grade symptoms like mild impairment of memory due to chronic encephalopathy, the objective is to improve the quality of life.

Recommendations

1. In patients with advanced liver disease avoiding potential precipitating factors for HE is recommended.

These include:

1. Avoidance of constipation
 2. Prophylactic treatment to prevent bleeding from oesophageal varices
 3. Prophylaxis against spontaneous bacterial peritonitis (SBP) when indicated
 4. Judicious use of diuretics. This will prevent dehydration and electrolyte disturbances.
 5. Avoidance of sedatives.
2. Non-absorbable disaccharides should be prescribed.

Lactulose is the widely used drug for this purpose. Patients should be advised to have 2 or 3 soft

bowel movements a day. Care is needed to avoid excessive diarrhoea which may lead to dehydration and electrolyte disturbances. Lactulose may not be well tolerated by some patients due its sweet taste or due to flatulence associated with its use.

If the patient is intolerant of non-absorbable disaccharides, antibiotics are an alternative. Neomycin or metronidazole can be used. Metronidazole is preferred over neomycin in view of the adverse effects. There is no firm evidence for or against using lactulose in combination with antibiotics. If neomycin is used, tests must be done to detect toxicity, eg. blood urea should be performed regularly. The continuous use of antibiotics for more than 6 months is not recommended.

3. Careful management of other complications associated with advanced liver disease is recommended.

In patients with chronic encephalopathy, ascites is better managed with regular paracentesis or low dose diuretics. It is useful to record the patient's weight regularly and the diuretic dose. It is important that the patient and relatives understand that mild degrees of fluid retention are not harmful, and it is better to have this than risk an episode of hepatic encephalopathy.

4. Correct advice on nutrition is recommended.
Protein intake is extremely important in chronic liver disease due to the on going hypercatabolic state.

Low protein diets have been traditionally recommended in patients with chronic liver disease and hepatic encephalopathy. There is no scientific evidence that a low protein diet reduces the number of encephalopathy episodes or improves persistent neurological manifestations. A minority of patients may not be tolerant of a high protein intake, and develop encephalopathy. Therefore, the protein intake should be gradually increased up to 1.5g/

kg/d (80g/d). An increase in protein tolerance can be achieved by increasing the protein intake in combination with other therapeutic measures, such as, lactulose. Substitution of animal proteins with vegetable proteins could be considered, as these patients generally tolerate vegetable proteins better than meats. However, dairy proteins may be allowed. Since patients with chronic liver disease have a reduced appetite several small meals should be encouraged for a day (5-6 meals a day). Whenever available, the help of an experienced nutritionist / dietitian is recommended for this purpose.

Zinc supplementation is considered to be useful in patients with chronic liver disease, together with vitamins.

Oral Branched chained amino acids are reserved for protein intolerant patients, and are not recommended for routine use.

2.3 Appendix 1

Table 4 - Grading in hepatic encephalopathy.

Grade	Symptoms and signs
Grade I	Euphoria or depression, mild confusion, monotonous voice, sleep cycle changes +/- asterixis
Grade II	Lethargy and /or confusion, asterixis, triphasic waves on EEG
Grade III	Severe confusion, incoherent language, semistupor but awakes with language, asterixis, triphasic waves on EEG
Grade IV	Coma, initially can respond to painful stimuli, asterixis, delta activity on EEG