ASCITES IN LIVER CIRRHOSIS AND ITS COMPLICATIONS

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INTRODUCTION
Ascites is a term used to describe accumulation of fluid in the peritoneal cavity. It is derived from the Greek term “askites” which means bag like.

CAUSES OF ASCITES
The most common cause of ascites is due to cirrhosis of the liver. Development of ascites is a sign of poor prognosis with a 50% 3 year survival\(^1\). About 60% patients with cirrhosis go on to develop ascites within 10 years of diagnosis\(^2\). A few of the less common causes of ascites are abdominal tuberculosis, intra-abdominal malignancies with peritoneal metastases, congestive heart failure, acute liver failure, Budd-Chiari syndrome, pancreatitis and Nephrotic syndrome.

EVALUATION OF A PATIENT WITH CIRRHOSIS AND ASCITES
The initial evaluation of ascites should include history, physical examination, abdominal ultrasound, liver function tests including serum albumin and INR, renal function tests, serum electrolytes and spot urinary electrolytes. An effort must also be made to ascertain the cause of cirrhosis. Ascitic fluid should be analyzed to calculate Serum Albumin to ascitic fluid albumin gradient (SAAG). A SAAG of more than or equal to 1.1 is defined as high SAAG ascites while it is low SAAG if this ratio is less than 1.1\(^3\).

If SAAG is more than 1.1, it usually means patient has portal hypertension\(^4\). Cirrhosis due to any cause leads to portal hypertension. Hepatitis C and Hepatitis B are the most common etiologies of cirrhosis leading to portal hypertension in Pakistan. Cirrhosis due to alcoholic liver disease, no-alcoholic fatty liver disease, Wilson’s disease and autoimmune hepatitis are less common causes of cirrhosis.

GRADES OF ASCITES\(^3\)

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SIGNS AND SYMPTOMS
Mild ascites does not cause symptoms. It is moderate or severe ascites that causes progressively increasing abdominal distension and shortness of breath when the excessive fluid exerts mechanical pressure on the diaphragm.

Moderate ascites is detected on physical examination by a bulge of the flanks and by shifting dullness in which the percussion note in the flanks changes from dull to resonant when the patient is shifted to the side (shifting dullness). A fluid wave travels from one side to the other on tapping (fluid thrill) in case of severe ascites.

Associated signs and symptoms may be prominent anterior abdominal veins, pedal edema, gynecomastia, palmar erythema, hematemesis and melena as a result of variceal hemorrhage and or drowsiness due to hepatic encephalopathy.

PATHOPHYSIOLOGY
Cirrhosis is a result of fibrosis in the liver parenchyma that leads to disruption in liver architecture and nodule formation. This leads to increased resistance to blood flow, which in turn results in portal hypertension. The normal hepatic vein pressure is 6-8mm.Hg, which can go up to 20mm.Hg in patients with portal hypertension and ascites⁴.

UNCOMPLICATED ASCITES
Uncomplicated ascites is defined as ascites that is not infected and is not associated with refractoriness to conventional medical treatment, development of hyponatremia, spontaneous bacterial peritonitis, or hepatorenal syndrome.

MANAGEMENT OF MODERATE AND UNCOMPLICATED ASCITES:
Management of ascites is aimed at bringing about relief of symptoms, prevent further progression and to prevent complications. In the meanwhile, the underlying cause of cirrhosis is sought and treated accordingly.

General Measures (Diet): A salt restricted diet of less than 88mmol of sodium is advised to patients with cirrhosis and ascites⁴. This is roughly equal to one heaped teaspoon or two flat teaspoons of table salt. It is therefore important to ask patients not to take added salt in diet. They must be advised not to avoid sprinkle salt on fruits and egg white before eating them. They must not eat chappattis prepared from salted dough. Foods with excessive salt for example nimko and pickles (achar) must also be avoided. Water and fluid intake does not need to be restricted unless the patient’s sodium falls to less than 125 mmol/l⁵.

Specific Measures: These include:

- Diuretics: The diuretic of choice is spironolactone, owing to its ability to block the secondary hyperaldosteronism that leads to sodium and water retention in patients with ascites. Starting dose is 100mg per day. Furosemide can be added to prevent hyperkalemia at a dose of 40mg once a day.
- Monitoring diuresis: checking the patient’s weight assesses the response to diuretics. The target weigh loss is 1.0kg per day in patients with peripheral edema and ascites while it is 0.5kg per day in cases with ascites alone. The dose of diuretics is increased in a ratio of 100:40 of spironolactone and furosemide according to this response. It is important to closely monitor for signs of drowsiness or altered conscious level, orthostatic hypotension, renal function and electrolytes⁶.
- **Prophylaxis against spontaneous bacterial peritonitis:** If on ascitic fluid analysis, the ascitic fluid has a total protein content of 1.5g/dl or less, the patient needs to be put on prophylaxis against spontaneous bacterial peritonitis with ciprofloxacin 500mg once a day or norfloxacin 400mg once a day.

- **Medication to avoid:** It is important to avoid continuing beta-blockers in patients with refractory ascites since they have been found to increase mortality. Aminoglycosides, Angiotensin converting enzyme inhibitors and angiotensin receptor blockers must not be prescribed to patients with cirrhosis and ascites. NSAIDs are best avoided and an alternate analgesia must be prescribed.

**MANAGEMENT OF LARGE VOLUME OR TENSE ASCITES:**

Treatment Options include paracentesis followed by diuretics.

**Paracentesis:** It is a procedure in which a needle or catheter is inserted into the peritoneal cavity to obtain ascitic fluid. It is either done to establish etiology of new-onset ascites or to rule out spontaneous bacterial peritonitis. It is also carried out for therapeutic purpose.

Large volume paracentesis (LVP) is removal of more than 5L of ascitic fluid and is performed: 1) when tense ascites leads to discomfort and respiratory embarrassment, or 2) in cases with refractory ascites. Large volume paracentesis followed by diuretics is appropriate in the management of patients with diuretic sensitive tense ascites. Up to 5 litres of fluid can be removed without colloid support. Large Volume Paracentesis should be carried out under cover of 8 g of albumin for every litre of ascitic fluid removed. Fresh frozen plasma (FFP) should not be used as an alternative form of colloid instead of albumin for paracentesis.

**COMPLICATED ASCITES**

Complicated ascites is defined as ascites with complications of one or more of the following: Spontaneous bacterial peritonitis (SBP), hepatorenal syndrome (HRS), and refractory ascites.

**SPONTANEOUS BACTERIAL PERITONITIS:**

Spontaneous bacterial peritonitis (SBP) is acute bacterial infection of the ascitic fluid. It is an ominous complication to occur and signifies poor long-term prognosis. Of the patients with cirrhosis and SBP, 70% have Child-Pugh class C cirrhosis.

**Signs and Symptoms:** The diagnosis of SBP requires a high index of suspicion in patients with cirrhosis who demonstrate sudden clinical deterioration. Patients may typically present with fever and chills and abdominal pain. Other symptoms are worsening of encephalopathy, new-onset ascites, worsening of ascites not responding to diuretics, worsening or new-onset renal failure, diarrhea and ileus.

**Diagnosis:** The diagnosis of SBP is made by aspirating ascitic fluid under aseptic measures in the emergency department before administration of any antibiotics. The fluid is sent for biochemical, microscopic and microbiologic analysis of ascitic fluid. Biochemistry includes Total protein, albumin, LDH and glucose content of ascitic fluid. The total leucocyte count and differential leucocyte count (TLC and DLC) must be checked and the sample for this is best sent in EDTA vials. Ascitic fluid must be sent for culture/sensitivity in blood culture bottles for better yield. SBP is diagnosed when the polymorphonuclear count (PMN) count in ascitic fluid is 250 cells /µL or more.
**Treatment:** Once SBP is suspected, empiric therapy with third generation cephalosporins should be started after sending a sample of the ascitic fluid for analysis as described above. Third generation cephalosporins need to be combined with 1.5g albumin per kg body weight within 6 hours of enrollment and 1.0g per kg body weight on day 3. Albumin is especially important when serum creatinine is > 1.0mg/dl, BUN > 30mg/dl and total bilirubin is > 4mg/dl. Antibiotics according to culture and sensitivity of ascitic fluid need to be continued for 7 days at least. The patient should be on prophylaxis against future episodes of SBP with ciprofloxacin or norfloaxacin as previously described.

**HEPATORENAL SYNDROME:**

**Definition:** Hepatorenal syndrome (HRS) is defined as the occurrence of renal failure in a patient with advanced liver disease, with portal hypertension and ascites, in the absence of an identifiable cause of renal failure. The diagnosis is hence established by excluding other possible causes of renal failure.

**Pathophysiology:** Proposed mechanisms of HRS are splanchnic vasodilation, which is accompanied by renal vasoconstriction. A decreased effective arterial blood pressure also contributes towards decreased renal perfusion.

**Diagnosis:** There are two types of HRS:

1) *Hepatorenal syndrome type of acute kidney injury (HRS-AKI)*, previously known as Type-1 HRS, is a rapidly progressive renal failure in patients with advanced liver failure and is associated with poor prognosis. HRS-AKI, if left untreated, can lead to death within a month.

2) *Hepatorenal syndrome type of chronic kidney disease*, previously known as Type-2 HRS, is a slowly progressive renal failure in patients with cirrhosis and refractory ascites. Those with HRS have a poor prognosis with average median survival of 3 months.

**Management:** These include:

- **General Measures:** Once diagnosed, HRS-AKI should be treated promptly so as to prevent further deterioration of renal function. It is important to assess for other complications of cirrhosis and to monitor vital signs, urine output, serum electrolytes, renal and liver function tests. Such patients should ideally be managed in an intensive care unit and an effort should be made to measure the central venous pressure.

- **Specific Measures:** These include vasoconstrictor agents and albumin. Vasoconstrictor agents such as terlipressin, midodrine/octreotide and norepinephrine have been evaluated in combination with albumin for treatment of HRS-AKI. These agents bring about vasoconstriction in the splanchnic vasculature and increase the mean arterial pressure. Albumin is of benefit in patients with sepsis owing to its scavenging, anti-oxidant as well as endothelial stabilizing effect apart from its additional benefit of volume expansion.

- Once diagnosed with hepatorenal syndrome, the patient is best referred to a tertiary care unit to be managed in ICU setting by experts in the field of hepatology.

**REFRACTORY ASCITES:**

**Definition:** Ascites that cannot be mobilized or the early recurrence of which (i.e., after Large Volume Paracentesis) cannot be satisfactorily prevented by medical therapy.

**Types:** Refractory ascites has two subtypes:

1) *Diuretic-resistant ascites:* Ascites that cannot be mobilized or the early recurrence
of which cannot be prevented because of a lack of response to sodium restriction and permissible dose of diuretics

2) *Diuretic-intractable ascites:* Ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of the development of diuretic induced complications that preclude the use of an effective diuretic dosage

**Prerequisites** for a diagnosis of refractory ascites:

1) *Treatment duration:* Patients must be on intensive diuretic therapy (up to spironolactone 400 mg/day and furosemide 160 mg/day) for at least 1 week and on a sodium-restricted diet of less than 88 mmol/day

2) *Lack of response:* Mean weight loss of <0.8 kg over 4 days and urinary sodium output less than the sodium intake.

3) *Early ascites recurrence:* Reappearance of grade 2 or 3 ascites within 4 weeks of initial mobilization.

4) *Diuretic-induced complications:*
   a. *Diuretic-induced hepatic encephalopathy* is the development of encephalopathy in the absence of any other precipitating factor.
   b. *Diuretic-induced renal impairment* is an increase of serum creatinine by >100% to a value >2 mg/dl (177 mmol/L) in patients with ascites responding to treatment.
   c. *Diuretic-induced hyponatremia* is defined as a decrease of serum sodium by >10 mmol/L from baseline to a serum sodium of <125 mmol/L.
   d. *Diuretic-induced hypo- or hyperkalemia* is defined as a change in serum potassium to <3 mmol/L or >6 mmol/L despite appropriate measures

**Treatment Options for Refractory Ascites:** These include: large volume paracentesis, TIPS, peritoneovenous shunt, liver transplantation, and ALFA pump

- **Large Volume Paracentesis (LVP):** It is removal of more than 5L of ascitic fluid and is performed when tense ascites leads to discomfort and respiratory embarrassment or in cases with refractory ascites.
- **Transjugular Intrahepatic Portosystemic Shunt (TIPS):** It is a side-to-side portocaval shunt placed between the high pressure portal vein and low pressure hepatic vein to decompress the portal system. It is used in patients with refractory ascites and for patients with variceal hemorrhage that is poorly controlled by endoscopic methods.
- **Peritoneovenous Shunt:** It is a shunt that drains peritoneal fluid from the peritoneum into the systemic veins, either the internal jugular vein or the superior vena cava.
- **Liver Transplantation (LT):** It is a procedure in which the patient’s diseased liver is replaced by a whole healthy liver (Deceased donor) or part of a healthy liver of a willing donor (Living donor). The presence of refractory complicated ascites is one of the indications for liver transplantation in patients with decompensated cirrhosis.
- **Automated Low Flow Ascites (ALFA) Pump:** A surgically implanted pump that automatically transfers peritoneal fluid to the bladder has been undergoing trials for some time (Developed by Sequana Medical AG http://www.alfapump.com/alfapump).
REFERENCES


