CHAPTER

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Ascites - From Basics to Bedside

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INTRODUCTION

The term ascites denotes the pathological accumulation of fluid in the peritoneal cavity. Healthy men have little or no fluid in the peritoneal cavity but women normally may have up to 20ml depending on the phase of menstrual cycle. Causes of ascites may be classified into two pathophysiologic categories: That associated with the normal peritoneum and that which occur due to a diseased peritoneum. Cirrhosis accounts for 84 percent of all cases of ascites, whereas Cardiac ascites, peritoneal carcinomatosis and mixed ascites resulting from cirrhosis and a second disease account for 10-15% of cases. Less common causes of ascites include massive hepatic metastasis, peritoneal tuberculosis, and pancreatitis and Nephrotic syndrome. Various causes of ascites are enumerated in Table 1.

Table 1: Causes of Ascites

Normal Peritoneum	**Diseased peritoneum (SAAG < 1.1g/dL)**
Portal hypertension (SAAG > 1.1g/ dL)	**Infections**
1. Hepatic congestion	Bacterial peritonitis
Congestive heart failure	Tuberculous peritonitis
Constrictive pericarditis	Fungal peritonitis
Tricuspid insufficiency	HIV-associated peritonitis
Budd-Chiari syndrome	**Malignant conditions**
Veno-Occlusive disease	Peritoneal carcinomatosis
2. Liver Disease	Primary mesothelioma
Cirrhosis	Pseudomyxoma peritonei
Alcoholic Hepatitis	Massive hepatic metastases
Fulminant hepatic failure	Hepatocellular carcinoma
Massive hepatic metastases	**Other Conditions**
Hepatic Fibrosis	Familial mediterranean fever
Acute Fatty liver of pregnancy	Vasculitis
3. Portal vein occlusion	Granulomatous peritonitis
Hypoalbuminemia (SAAG < 1.1g/dL)	Eosinophilic peritonitis
Nephrotic syndrome	
Protein- losing enteropathy	
Severe malnutrition with Anasarca	
Miscellaneous conditions (SAAG < 1.1g/dL)	
Chylous ascites	
Pancreatic ascites	
Bile ascites	
Nephrogenic ascites	
Myxedema (SAAG > 1.1g/ dL)	
Ovarian disease	

PATHOGENESIS

Pathogenesis of ascites is different in cases with cirrhosis and without the cirrhosis.

Pathogenesis in Cirrhosis Cases

The presence of portal hypertension contributes to the development of ascites in patients who have cirrhosis. There is an increase in Intrahepatic resistance, causing increased portal pressure, but there is also vasodilatation of the splanchnic arterial system, which in turn results in an increase in portal venous inflow. Both of these abnormalities result in increased production of splanchnic lymph. Vasodilating factors such as vascular endothelial growth factor and nitric oxide are responsible for the vasodilatory effect. These hemodynamic changes cause activation of the RAAS with the development of hyperaldosteronism and hence sodium retention. These renal effects of increased aldosterone also contribute to the development of ascites. Sodium retention causes

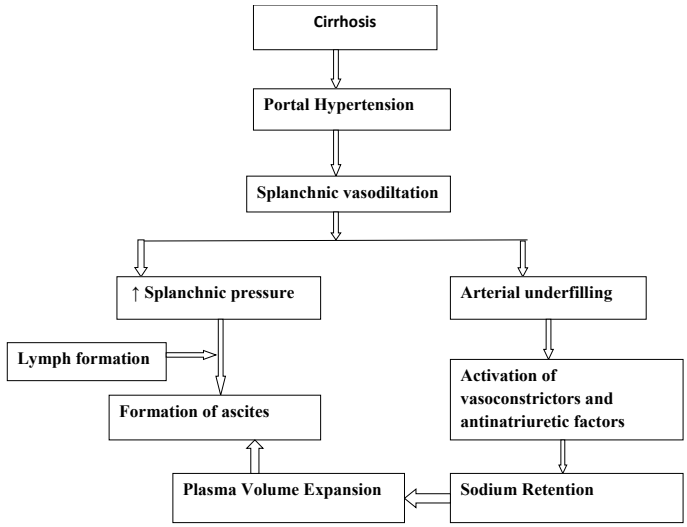

Fig. 1: Development of Ascites in Cirrhosis

fluid accumulation and expansion of extra cellular fluid volume which results in the formation of peripheral oedema and ascites. Sodium retention is the consequence of a homeostatic response caused by the under filling of arterial circulation secondary to arterial vasodilatation in the splanchnic vascular bed. Because the retained fluid is constantly leaking out of the intravascular compartment in to peritoneal cavity, the sensation of vascular filling is not achieved and the process continuous. Hypoalbuminemia and reduced oncotic pressure also contribute to the loss of fluid from the vascular compartment into the peritoneal cavity. Hypoalbuminemia is due to decreased synthetic function in the liver. Figure 1 is brief illustration of Pathogenesis of ascites in cirrhosis.

Pathogenesis in the Absence Of Cirrhosis

Ascites in the absence of cirrhosis generally results from peritoneal carcinomatosis, peritoneal infection or pancreatic disease. Peritoneal carcinomatosis can result from primary malignancies such as mesothelioma or sarcoma, secondary to abdominal malignancies such as gastric or colon adenocarcinoma, metastatic disease from breast or lung carcinoma or melanoma. Tumour cells lining the peritoneum produce a protein rich fluid that contributes to the development of ascites. Fluid from the extra cellular space is drawn into the peritoneum, further contributing to the development of ascites. Tuberculous peritonitis causes ascites via a similar mechanism; tubercles deposited on the peritoneum exude a proteinaceons fluid. Pancreatic ascites results from the leakage of pancreatic enzymes into the Peritoneum.

CLINICAL FEATURES

Symptoms and Signs

The history usually is one of increasing abdominal girth, with the presence of abdominal pain depending on the cause. Because most astices is secondary to chronic liver disease with portal hypertension, patients should be asked about risk factors for liver disease, especially alcohol consumption, transfusions, tattoos, injection drug use, a history of viral hepatitis or jaundice, and birth in an area endemic for hepatitis. A history of cancer or marked weight loss arouses suspicion of malignant ascites. Fever may suggest infected peritoneal fluid, including bacterial peritonitis (spontaneous or secondary). Patients with chronic liver disease and ascites are at greatest risk for developing spontaneous bacterial peritonitis. In immigrants, immunocompromised hosts, or severely malnourished alcoholics, tuberculous peritonitis should be considerd.

Physical examination should emphasize signs of portal hypertension and chronic liver disease. Elevated jugular venous pressure may suggest right-sided congestive heart failure or constrictive pericarditis. A large tender liver is characteristic of acute alcoholic hepatitis or Budd-Chiari syndrome. The presence of large abdominal wall veins with cephalad flow also suggests portal hypertension; inferiorly directed flow implies hepatic vein obstruction. Signs of chronic liver disease include palmar erythema, cutaneous spider angiomas, gynecomastia, and muscle wasting. Asterixis secondary to hepatic encephalopathy may be present. Anasarca results from cardiac failure or nephrotic syndrome with hypoalbuminemia. Finally, firm lymph nodes in the left superclavicular region or umbilicus may suggest intra-abdominal malignancy.

The physical examination is relatively insensitive for detecting ascitic fluid. In general, patients must have at least 1500mL of fluid to be detected reliably by this method. Even the experienced clinician may find it difficult to distinguish between obesity and small-volume ascites. Abdominal ultrasound establishes the presence of fluid.

Physical Examination

Physical examination should include an assessment for signs of systemic disease. The presence of lymphadenopathy, especially supraclavicular lymphadenopathy (Vorchow's node), suggests metastatic abdominal malignancy. Care should be taken during the cardiac examination to evaluate for elevation of jugular venous pressure (JVP); Kussmaul's sign (elevation of the JVP during inspiration); a pericardial knock, which may be seen in heart failure of constrictive pericarditis; or a murmur of tricuspid regurgitation. Spider angiomas, palmar erythema, dilated superficial veins around the umbilicus (caput medusae), and gynecomastia suggest chronic liver disease.

The abdominal examination should begin with inspection for the presence of uneven distention or an obvious mass. Auscultation should follow. The absence of bowel sounds or the presence of high-pitched localized bowel sounds points toward an ileus or intestinal obstruction. An umbilical venous hum may suggest the presence of portal hypertension, and a harsh bruit over the liver is heard rarely in patients with hepatocellular carcinoma. Abdominal swelling caused by intestinal gas can be differentiated from swelling caused by fluid or a solid mass by percussion; an abdomen filled with gas is tympanic, whereas an abdomen containing a mass or fluid is dull to percussion. The absence of abdominal dullness, however, does not exclude ascites, because a minimum of 1500 ml. of ascites fluid is required for detection on physical examination. Finally, the abdomen should be palpated to assess for tenderness, a mass, enlargement of the spleen or liver, or presence of a nodular liver suggesting cirrhoses or tumor. Light palpation of the liver may detect pulsations suggesting retrograde vascular flow from the heart in patients with right-sided heart failure, particularly tricuspid regurgitation.

EVALUATION

Once the presence of ascites has been confirmed, the etiology of the ascites is best determined by paracentesis. The left lower quadrant is preferred because of the greater depth of ascites and the thinner abdominal wall. Paracentesis is a safe procedure even in patients with coagulopathy; complications, including abdominal wall hematomas, hypotension, hepatorenal syndrome, and infection are infrequent.

Once ascitic fluid has been extracted, its gross appearance should be examined. Turbid fluid can result from presence of infection or tumor cells. White, milky fluid

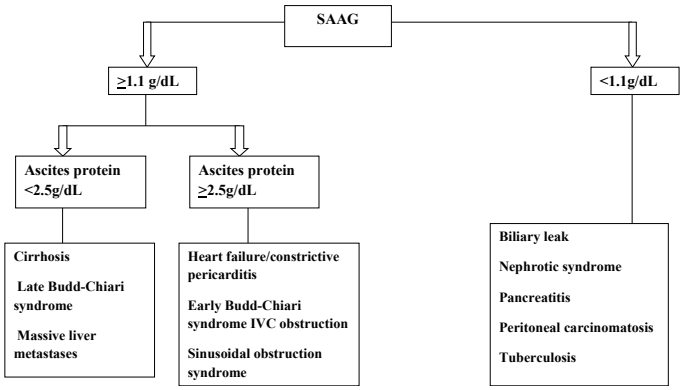

Fig. 2: Algorithm for the diagnosis of Ascites

indicates a triglyceride level>200 mg/dL (and often >1000 mg/dL), which is hall mark of chylous ascites. Chylous ascites results from lymphatic disruption that may occur with trauma, cirrhosis, tumor, tuberculosis, or certain congenital abnormalities. Dark brown fluid can reflect a high bilirubin concentration and indicates biliary tract perforation. Black fluid may indicate the presence of pancreatic necrosis or metastatic melanoma.

The ascitic fluid should be sent for measurement of albumin and total protein levels, cell and differential counts, and if infection is suspected, Gram's stain and culture, with inoculation into blood culture bottles at the patient's bed side to maximize the yield. A serum albumin level should be measured simultaneously to permit calculation of the serum ascites albumin gradient (SAAG).

The SAAG is useful for distinguishing ascites caused by portal hypertension from non portal hypertensive ascites. (Figure 2). The SAAG reflects the pressure within the hepatic sinusoids and correlates with the hepatic venous pressure gradient. The SAAG is calculated by subtracting the ascitic albumin concentration from the serum albumin level and does not change with diuresis. A SAAG > 1.1g/dL reflects the presence of portal hypertension and indicates the ascites is due to increased pressure in the hepatic sinusoids. According to Starling's law, a high SAAG reflects the oncotic pressure that counterbalances the portal pressure. Possible causes include cirrhosis, cardiac ascites, hepatic vein thrombosis (Budd-Chirari Syndrome), sinusoidal obstruction syndrome (Veno-Occlusive Disease), or massive liver metastases. A SAAG < 1.1g/dL indicates that the ascites is not related to portal hypertension, as in tuberculousis peritonitis, peritoneal carcinomatosis, or pancreatic ascites.

For high-SAAG (> 1.1) ascites, the ascitic protein level can provide further clues to the etiology (Figure 2). An ascites protein level of >2.5 g/dL indicates that the hepatic sinusoids are normal and are allowing passage of protein into the ascites, as occurs in cardiac ascites, early Budd-Chiari syndrome, or sinusoidal obstruction syndrome. An ascitic protein level <2.5g/dL indicates that the hepatic sinusoids have been damaged and scarred and no longer allow passage of protein, as occurs with cirrhosis, late Budd-Chiari syndrome, or massive liver metastases. Pro-brain type natriuretic peptide (BNP) is a natriuretic hormone released by the heart as a result of increased volume and ventricular wall stretch. High levels of BNP in serum occur in heart failure and may be useful in identifying heart failure as the cause of high-SAAG ascites.

Further tests are indicated only in specific clinical circumstances. When secondary peritonitis resulting from a perforated hollow viscus is suspected, ascitic glucose dehydrogenase (LDH) levels can be measured. In contrast to "spontaneous" bacterial peritonitis, which may complicate cirrhotic ascites. Secondary peritonitis is suggested by an ascitic glucose level <50.0Mg/dL, an ascitic LDH level higher than the serum LDH level, and the detection of multiple pathogens on ascitic fluid culture. When pancreatic ascites is suspected, the ascitic amylase level should be measured and is typically >1000mg/dL. At least 50mL of fluid should be obtained and sent for immediate processing. Tuberculous peritonitis is typically associated with ascitic fluid lymphocytosis but can be difficult to diagnose by paracentesis. A smear for acid-fast bacilli has a diagnostic sensitivity of only 0 to 3%; a culture increases the sensitivity to 35-50%. In patients without cirrhosis, an elevated ascitic adenosine deaminase level has a sensitivity of>90%when a cut-off value of 30-45% U/L is used. When the cause of ascites remains uncertain, laparotomy or laparoscopy with peritoneal biopsies for histology and culture remains the gold standard.

Laboratory Evaluation

Laboratory evaluation should include liver biochemical testing, serum albumin level measurement, and prothrombin time determination (international normalized ratio) to assess hepatic function as well as a complete blood count to evaluate for the presence of cytopenias that may result from portal hypertension or of leukocytosis, anemia, and thrombocytosis that may result from systemic infection. Serum amylase and lipase levels should be checked to evaluate the patient for acute pancreatitis. Urinary protein quantitation is indicated when nephrotic syndrome, which may cause ascites, is suspected.

In selected cases, the hepatic venous pressure gradient (pressure across the liver between the portal and hepatic veins) can be measured via cannulation of the hepatic vein to confirm that ascites is caused by cirrhosis. In some cases, a liver biopsy may be necessary to confirm cirrhosis.

Imaging

Abdominal ultrasound is useful in confirming the presence of ascites and in the guidance of paracentesis. Both ultrasound and CT imaging are useful in distinguishing between causes of portal and non-portal hypertensive ascites. Doppler ultrasound and CT can detect thrombosis of the hepatic veins (Budd-Chiari syndrome) or portal veins. In patients with non-portal hypertensive ascites, these studies are useful in detecting lymphadenopathy and masses of the mesentery and of solid organs such as the liver, ovaries, and pancreas. Furthermore, they permit directed percutaneous needle biopsies of these lesions. Ultrasound and CT are poor procedures for the detection of peritoneal carcinomatosis; the role of position emission tomography (PET) imaging is unclear.

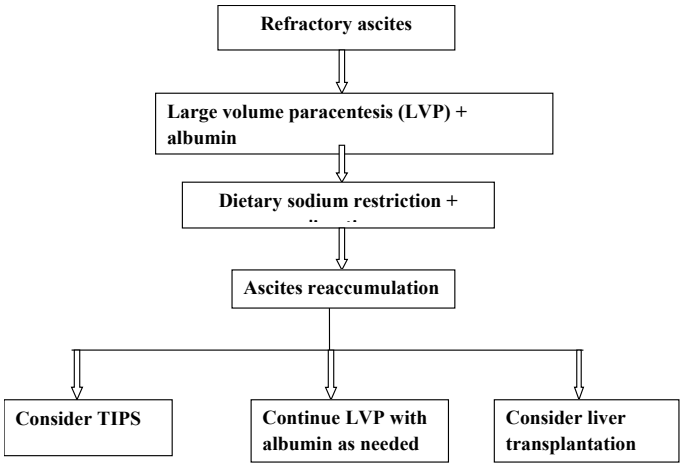

Fig. 3: Treatment of Refractory Ascites

Laparoscopy

Laparoscopy is an important test in the evaluation of some patients with non-portal hypertensive ascites (low SAAG) or mixed ascites. It permits direct visualization and biopsy of the peritoneum, liver, and some intra-abdominal lymph nodes. Cases of suspected peritoneal tuberculosis or suspected malignancy with non-diagnostic CT imaging and ascitic fluid cytology are best evaluated by this method.

Treatment

1. The initial treatment for cirrhotic ascites is restriction of sodium intake to 2 gl /day.
2. When sodium restriction alone is inadequate oral diuretics typically the combination of spironolactone and furosemide are used. Spioronolactone is an aldosterone antagonist that inhabits sodium resorption in the distal convoluted tubule of kidney. Prolonged use of spironolactone may lead to hyponatremia, hyperkalemia and painful gynecomastia. In such cases amiloride 5-40mg/day may be substituted for speronolactone.
3. Malignant acites does not respond to sodium restriction or diuretics. Patient may undergo large volume paracentesis (LVP's), transcutaneous catheter placement or rarely creation of peritoneovenous shunt.
4. Ascites caused by tuberculous peritonites is treated with standard antituberculous therapy.

Refractory Ascites

Refractory cirrhotic ascites is defined by the presence of ascites despite sodium restriction and maximal diuretic dose. Pharmacological therapy for these cases (Figure 3) include the addition of Midodrine and a adrenergic antagonist or clonidine an a_2 adrenergic antagonist to diuretic therapy. These agents act as vasoconstrictors, counteracting splanchnic vasodilatalion. Beta blockers are often prescribed to prevent variceal hemorrhage in patient with cirrhosis.When medical tharpy alone is insufficient refractory ascites can be managed by repeated large volume paracentesis (LVP) or transjugular intrahepatic peritoneal shunt (TIPS) to decompress the hepatic sinusoids. I/V infusion of albumin (6-8 gm/l of fluid drained) accompanying LVP decrease the risk of post paracentesis circulatory dysfunction. TIPS is superior to LVP in reducing the reaccumulation of ascites but is associated with increased frequency of hepatic encephalopathy.

Tuberculous Ascites

Tuberculous involvement of the peritoneum is significant problem in the developing world including India. The incidence is higher in those with uncontrolled HIV disease, the urban poor, patients with cirrhosis and nursing home residents.

The presenting symptoms include low grade fever, abdominal pain, anorexia and weight loss. Most patients have symptoms for months before the diagnosis is established. On physical examination patient may have generalized abdominal tenderness and distention. There may be clinically evident ascites. Ultrasonography or CT imaging of the abdomen reveals free or localated ascites in >80% of patients. Mantoux test is positive in 50% of cases. Ascitic fluid smear for AFB is usually negative and fluid cultures are positive in 35% cases. Ascitic fulid total protein is more than 3g/dL, LDH >90 units/L or mononuclear cell predominant leucocytes >500/cc. Ascitic adenosine deaminase activity > 36-40 IU/L has a sensitivity of 100% and a specificity of 97% for diagnosis of tuberculous peritonitis. In doubtful cases laparoscopy confirms the diagnosis.

Malignant Ascites

Two-thirds of cases of malignant ascites are caused by peritoneal carcinomatosis. The most common tumors causing carcinomatosis are primary adenocarcinomas of the ovary, uterus, pancreas, stomach, colon, lung or breast. The remaining one-third is due to lymphatic obstruction or portal hypertension due to hapatocellular carcinoma or diffuses hepatic metastases. Patients present with non specific abdominal discomfort and weight loss associated with increased abdominal girth. Nausea or vomiting may be caused by partial or complete intestinal obstruction. Abdominal CT may be useful to demonstrate the primary malignancy or hepatic metastases but seldom confirms the diagnosis of peritoneal carcinomatosis. In patients with carcinomatosis, paracentesis demonstrates a low serum ascites-albumin gradient (<1.1 mg/dL), an increased total protein (> 2.5 g/dL), and an elevated white cell count (often both neutrophils and mononuclear cells) but with a lymphocyte predominance. Cytology is positive in over 95%, but laparoscopy may be required in patients with negative cytology to confirm the diagnosis and to exclude tuberculousis peritonitis, with which it may be confused. Malignant ascites attributable to portal hypertension usually is associated with an increased serum ascites-albumin gradient (>1.1 g/dL), a variable total protein, and negative ascitic cytology. Ascites caused by peritoneal carcinomatosis does not respond to diuretics.

Patient may be treated with periodic large-volume paracentesis for symptomatic relief. Intra peritoneal chemotherapy is some time used to shrink the tumor, but the overall prognosis is extremely poor, with only 10% survivor at 6 month. Ovarian cancers represent an

exception to this rule. With newer treatments consisting of surgical debulking and intraperitoneal chemotherapy, long term survival from ovarian cancer is possible.

Chylous Ascites

This is a accumulation of lipid rich lymph in the peritoneal cavity. Ascites fluid is milky in appearance with triglyceride level >1000 mg/dL. Usual causes in adults is lymphatic obstruction or leakage caused by malignancy especially lymphoma. Non malignant causes include postoperative trauma, cirrhosis, tuberculosis, pancreatitis and filariasis.

Pancreatic Ascites

It is intra peritoneal accumulations of massive amount of pancreatic secretion due either to disruption of pancreatic duct or to a pancreatic pseudocyst. Its most commonly seen in patients with chronic pancreatitis. Ascitic fluid is characterized by high protein level (>2.5 g/dL) but a low SAAG, Ascitic fluid amylase levels are in excess of 1000 units/L. Non surgical cases are treated by bowel rest, total parenteral nutrition and octreotide to decreased pancreatic secretion.

Spontaneous Bacterial Peritonitis

"Spontaneous" bacterial infection of ascitic fluid occurs in the absence of an apparent intraabdominal source of infection. It is seen with few exception in patients with ascites caused by chronic liver disease. Translocation of enteric bacteria across the gut wall or mesenteric lymphatic leads to seeding of the ascitic fluid, as may bactiremia from other sites. Approximately 20-30% of cirrhotic patients with ascites develop spontaneous peritonitis; however the incidence is >40% in patients with ascitic fluid total protein <1g/dL, probably due to decreased ascitic fluid osmotic activity.

Virtually all cases of spontaneous bacterial peritonitis are caused by a monomicrobial infection. The most common pathogens are enteric gram-negative bacteria Ecoli, klebsiella Pneumonae or gram-positive bacteria. (Streptococcus pneumoniae, viridans streptococci, enterrococcus species). Anaerobic bacteria are not associated with spontaneous bacterial peritonitis.

Symptoms and Signs

Eighty to 90percent of patients with spontaneous bacterial peritonitis are symptomatic; in many cases the presentation is subtle. Spontaneous bacterial peritonites may be present in 10-20% of patients hospitalized with chronic liver disease, sometimes in the absence of any suggestive symptoms or signs.

The most common symptoms are fever and abdominal pain, present in two-thirds of patients. Spontaneous bacterial peritonitis may also present with the change in mental status due to exacerbation or precipitation of hepatic encephalopathy, or sudden worsening of renal function. Physical examination typically demonstrates signs of chronic liver disease with ascites. Abdominal tenderness is present in <50% of patients and its presence suggests other causes.

Treatment

Empiric therapy for spontaneous bacterial peritonitis should be initiated with a third-generation cephalosporin (such as cefotaxime, 2 g intravenously every 8-12 hours, or ceftriaxon 1-2 gm I-V every 24 hours, or a combination of β-lactam/ β-lactamase agent (such as ampicillin/ sulbactam, 2g/1g intravenously every 6 hours). A course of 5-10 days is sufficient in most patients, or until the ascites fluid PMN count decreases to < 250 cells/cc.

Kidney injury develops in up to 40% of patients and is a major cause of death. Intravenous albumin increases effective arterial circulating volume and renal perfusion, decreasing the incidence of kidney injury and mortality. Intravenous albumin, 1.5g/kg on day 1 and 1g/kg on day 3, should be administrated to patients at high risk for hepatorenal failure (ie, patients with baseline creatinine > 1mg/dl, blood urea nitrogen (BUN) > 30 mg/dL, or bilirubin > 4 mg/dL.

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