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# Ascites in Cirrhosis: A Review of Pathophysiology, Diagnosis and Treatment.

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**ABSTRACT**

Ascites is the commonest complication of liver cirrhosis with poor prognosis and reduced survival rate. Ascites is more common in liver cirrhosis followed by hepatic encephalopathy and variceal hemorrhage. Development of ascites worsens the prognosis of the patient. The aetiology of ascites in cirrhosis is considered to be multifactorial and there are many theories for ascites pathogenesis such as overfill, underfilling, peripheral arterial vasodilatation. These condition lead to sodium retention, water retention, hepatorenal syndrome, abnormalities in systemic and splanchnic haemodynamics. Laboratory investigation on ascitic fluid and blood helps in diagnosis of aetiology, secondary infection and assessment of electrolytes, albumin etc., and the treatment of choice for tense ascites will be large volume paracentesis with albumin infusion, compared to traditional method sodium restriction and diuretics. Refractory ascites may occur in advance stage in which TIPS (Transjugular Intrahepatic Portosystemic Shunt) is considered as more effective management, still in long term can impair hepatic function and chronic hepatic encephalopathy.

**Keywords:** Ascites, cirrhosis, diagnosis, pathophysiology, treatment

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## INTRODUCTION

Ascites is commonest complication of liver cirrhosis with poor prognosis and reduced survival rate [1]. Ascites refers to the pathological collection of fluid in the abdominal cavity. Ascites word derived from Greek origin "Askos" meaning sac/ bag [2]. Cirrhotic ascites is the leading cause 75% in patient with ascites followed by malignancy 10%, cardiac failure 3%, tuberculosis 2%, pancreatitis 1% and other rare causes [3]. If underlying course of cirrhosis is untreated 60% of patients can develop ascites in 10 years [4]. There is more than one pathophysiological process that leads to ascites formation, presence of cirrhosis causing portal hypertension which leads to vasodilatation in splanchnic and systemic circulation with vasoconstriction in renal circulation and alteration in renal auto regulation and reduction of functional liver cell mass together with cirrhotic cardiomyopathy. These result in increase in sodium and water retention. Portal hypertension localizes the excess fluid in the peritoneal cavity [5]. There are other diseases that contribute to ascites: nephrotic syndrome, congestive cardiac failure, pancreatitis, hypoalbuminemia, microbial infection of peritoneum, malignancy of organs etc [6].

At present, liver transplant is considered to be curative option for select group of patients; still pharmacological therapies can decrease the progression of decompensated cirrhosis. This concise overview will focus on diagnosis, pathophysiology and treatment of ascites due to cirrhosis liver and discuss clinical management of ascites with scientific developments [7].

## DEFINITIONS [8]

### Uncomplicated ascites

Ascites without infection and hepatorenal syndrome is termed as uncomplicated ascites.

### Refractory ascites

Ascites which does not respond to medical management is called as refractory ascites. It is of two types

1. **Diuretic resistant ascites**

   Ascites which does not respond to dietary sodium restriction, diuretic therapy

2. **Diuretic intractable ascites**

Ascites which does not respond to medical management or early recurrence of ascites which cannot prevented because of diuretic induced complication.

### Recidivant Ascites

Ascites which re-occurs at least three times within 12 months, in spite patient being already on dietary sodium restriction and adequate diuretic dosage.

### GRADING OF ASCITES [3]

Grade 1 – Ascites which is mild and detectable only by ultrasound examination
Grade 2- Ascites which is moderate and has a clinical finding of symmetrical distension of abdomen
Grade 3 –Ascites which is large or gross distension of abdomen.

### AETIOLOGY [7, 9, 10]

There are multiple causes for ascites and liver cirrhosis is found to be leading cause for this. Ascites is due to high-pressure in the blood vessel (portal hypertension), due to low level of albumin, infections, malignancy

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**Table 1**

| | | |
|---|---|---|
| **Liver Related Problems** | a) Hepatic Cirrhosis | ➢ Alcoholic Hepatitis<br>➢ Chronic hepatitis B infection<br>➢ Chronic hepatitis C infection<br>➢ Non-alcoholic steatohepatitis<br>➢ Autoimmune hepatitis<br>➢ Wilsons disease<br>➢ Alpha 1 antitrypsin deficiency<br>➢ Chronic right heart failure<br>➢ Galactosemia<br>➢ Glycogen storage disease Type 4<br>➢ Cystic fibrosis |
| | b) Acute liver failure | ➢ Hepatotoxic drugs<br>➢ Toxins |
| | c) Budd-chiari syndrome<br>d) Hepatocellular carcinoma | |
| **Hypoalbuminemia** | a) Nephrotic syndrome<br>b) Protein losing enteropathy<br>c) Severe malnutrition | |
| **Diseased peritoneum** | Infections | ➢ Bacterial<br>➢ Tuberculous peritonitis<br>➢ Fungal peritonitis<br>➢ HIV associated peritonitis |
| | Malignant conditions | ➢ Peritoneal carcinomatosis<br>➢ Primary mesothelioma<br>➢ Pseudomyxoma peritonei |
| **Miscellaneous conditions** | a) Pancreatitis<br>b) Meigs syndrome<br>c) Vasculitis<br>d) hypothyroidism | |

**Table 2**

| Method | Fluid Level |
|---|---|
| Fluid Thrill | >2000ml fluid |
| Shifting Dullness | 1000ml fluid approx. |
| Puddle's Sign | 120ml fluid approx. |
| Ultrasound Abdomen | <30ml fluid |

## PATHOPHYSIOLOGY

### Vasodilatation theory

This is the most likely mechanism.

**(Flow chart 1)** that explains ascites in liver cirrhosis.

In liver cirrhosis, there is fibrosis with vascular smooth muscle dysfunction. These continued processes of inflammation and fibrosis in the liver leads to development of portal hypertension, where there is increased pressure in the portal veins of more than 8mmHg. Therefore there is stasis of vasodilators [11]. Nitric oxide (NO) is considered the main vasodilator, the others being adrenomedulin, carbon monoxide, endocannabinoids, prostacyclin [12], Glucagon, substance P and calcitonin gene related peptide were also considered in earlier studies [13].

These vasodilators result in vasodilatation in the splanchnic vascular compartment [8], which in turn results in reduction in effective arterial blood volume and decrease in systemic arterial pressure [12]. The blood supply to the kidney is reduced or there is hypo perfusion of the renal system [11]. Hypo perfusion of the kidney is a stimulus for the activation of the renin-angiotensin-aldosterone-system (RAAS) of the juxta

glomerular apparatus. Baroreceptor mediated activation of the sympathetic nervous system (SNS) is also a stimuli [12]. The activated RAAS is responsible for the formation of angiotensin 2 and release of aldosterone from zona glomerulusa of the adrenal cortex [11]. Aldosterone acts by increasing the sodium re -absorption from the collecting ducts and angiotensin 2, being a potent vasoconstrictor stimulates the non osmotic release of anti diuretic hormone (ADH) from the posterior pituitary [12]. The result is that there is sodium and water retention from the tubules and ducts.

The splanchnic arteriolar vasodilation also plays a role in increasing the micro vascular hydrostatic pressure and thus there is increase in escape of intravascular fluid to interstitial space [8, 13]. Ascites formation is therefore, also a consequence of increased rate of formation of hepatic and splanchnic lymph.

**OVERFILL THEORY**

One third of patients with ascites due to cirrhosis have normal levels of plasma renin, indicating that sodium retention occurs unrelated to vasodilatation in certain cases [12]. Also some investigations suggest that circulating blood volume is raised markedly in cirrhotic patients [8]. According to this theory there is primary sodium and water retention in response to certain hepatic signs.

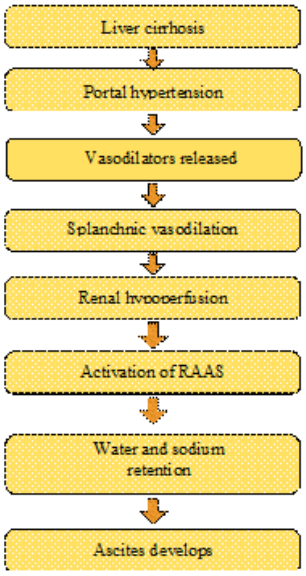
The signals may be due to reduced hepatic clearance of sodium retaining hormone, reduction in synthesis of natriuretic substance from hepatocytes or hepatorenal reflex [13]. Therefore, secondary increase in plasma volume and cardiac output occurs. To compensate the high blood volume, peripheral vascular resistance comes down [8]. The result is that the increased hydrostatic pressure in hepatic and splanchnic circulation leads to ascites formation [8].

**UNDERFILL THEORY [8, 13]**

This is a traditional concept also called as the backward theory.

It considers that there is a backward increase in the hydrostatic pressure in hepatic sinusoids and splanchnic micro circulation due to intra hepatic obstruction of the blood flow as a result of portal hypertension. Due to pressure difference in the micro circulation, excessive fluid moves into the interstitial space forming excessive lymph. This excessive fluid leaks into the peritoneal cavity forming ascites when lymph formation exceeds that of the lymphatic return. This results in decrease in circulating blood volume and secondary renal dysfunction.

**Flow Chart 1**



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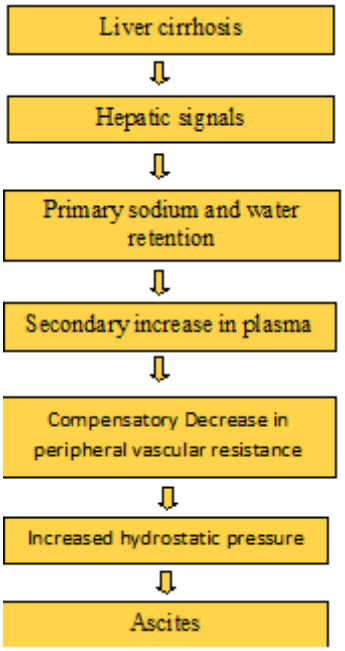
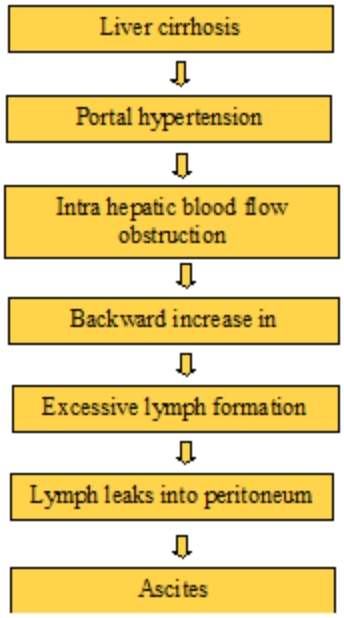
**Flow Chart 2**




**Flow Chart 3**




## DIAGNOSIS OF ASCITES

**Natural History [14]**

Patient with ascites may have different underlying pathology mentioned in the aetiology hence these patient should be reviewed about risk factor for liver disease, since ascites is most commonly caused due to liver cirrhosis and other disease such as renal disease, tuberculosis, congestive heart failure, it is very essential to identify the underlying disease since treatment differ for each condition.

**Examination of abdomen [15]**

- Inspection
  - Abdomen distended
  - Flanks full
  - Umbilicus everted in severe cases
  - Enlargement of veins seen in portal hypertension (around umbilicus-caput medusa) and also in lumbar region.
- Percussion
  - Shifting dullness

When patient lies on supine position percuss laterally from midline by keeping finger in the longitudinal axis. In the normal individual flanks are resonant. In moderate ascites, flanks are dull but if patient is made to right or left lateral decubitus position the previous dull area becomes resonant. This is known as shifting dullness.

  - Fluid thrill

With the patient lies on supine position, place one hand over the lumbar region and ask the patient to put his hand in the midline of abdomen firmly. Tap gently the lumbar region of another side. A fluid waves or thrill is felt by detecting hand on the lumbar region. This test is positive when there is large amount of (>2000ml) fluid accumulation.

  - Puddle's sign

It can be done by percussion and auscultation. Patient put on prone position for 5 min and goes on all 4 limbs ( arm knee position) so the middle portion of the abdomen is dependent and his horizontal. Then percuss around the umbilical region which will be dull ( normal patient resonant). This test is positive with fluid around 120 ml.

**Diagnosis of ascitic fluid volume by different method to know the volume [16]**.

**Laboratory Investigation [11, 17]**

Proper evaluation rests up on direct assessment by paracentesis: to know fluid origin, whether it is infectious, sterile or malignant .Gross examination should be done before sending sample to laboratory investigation to rule out if it is a transudate or exudate or blood stained.
**(table 3) [**18]

Routine laboratory test: Differential cell count, albumin assay and cultures. The table 3 and 4 will explain ascites fluid characters in specific disease conditions.
**(Table 4) [14]**

- Inspection

Ascitic fluid will be usually transluscent and yellow. Fluid of other colour and consistency will reflect specific disease.

- Cell count

Helps to differentiate bacterial infection from others

- Albumin

Total ascitic fluid protein concentration measured to assess risk of Spontaneous Bacterial Peritonitis (SBP). Since protein concentration <15g/litre increases risk of SBP. Serum-ascites albumin gradient

(SAAG) is calculated by SAAG=Serum albumin- ascitic albumin. If SAAG >= 1.1g/dl, it is ascribed to be portal hypertension with 97% accuracy.

**Table 3**

| Transudative ascites (Serum Albumin - Ascites Albumin >1.1 gm/dl) | Exudative ascites (Serum Albumin - Ascites Albumin <1.1 gm/dl) |
|---|---|
| 1. Liver cirrhosis<br>2. Congestive heart failure<br>3. Hepatic vein obstruction (Budd Chiari syndrome)<br>a. Assoc. with tumors (hepatoma, hypernephroma, pancreatic Ca.<br>b. Assoc. with hematologic disorders (myeloproliferative disease, polycythemia vera, myeloid metaplasia<br>c. Due to infections<br>4. Nephrotic syndrome<br>5. Meig's ovarian tumor syndrome<br>6. Constrictive pericarditis<br>7. Inferior vena cava obstruction<br>8. Viral hepatitis with submassive or massive hepatic necrosis | 1. Neoplastic diseases involving the peritoneum: Peritoneal carcinomatosis, Lymphomatous disorders<br>2. Tuberculous peritonitis<br>3. Pancreatitis<br>4. Post surgery talc or starch powder peritonitis<br>5. Transected lymphatics following portal caval shunt surgery<br>6. Myxedema<br>7. Sarcoidosis<br>8. Lymphatic obstruction: a. Intestinal lymphangiectasia, b. Lymphoma<br>9. Pseudomyxoma peritonei<br>10. Struma ovarii<br>11. Amyloidosis<br>12. Prior abdominal trauma with ruptured lymphatics<br>13. Hemodialysis CRF related ascites |

**Table 4**

| | |
|---|---|
| Routine Investigation | ▪ Total Cell count<br>▪ Differential cell count<br>o Neutrophils increased in bacterial infections<br>o Lymphocytes increased in tuberculous peritonitis<br>▪ Albumin-SAAG-portal hypertension > 1.1g/dl<br>▪ Total protein concentration<br>o <1gm/dl in spontaneous peritonitis<br>o >1gm/dl in secondary peritonitis |
| In case of suspected infection | ▪ Bacterial culture<br>▪ Urine dipstick – to detect neutrophils in ascitic fluid<br>▪ Automated cell count<br>▪ LDH (Lactate Dehydrogenase)<br>▪ Glucose<br>▪ Amylase<br>▪ Gram Stain |
| In case of perforated Gut | ▪ Carcinoembryonic antigen > 5mg/ml<br>▪ Alkaline phosphatise >240U/L |
| In case of suspected Tuberculosis | ▪ Cytology, smear and culture for Mycobacteria |

**Culture and Gram staining [19]**

The best method of determining the presence of infection is by culture. Apparently 10bacteria/µl of fluid is required for a positive gram stain. Gram stain is insensitive in spontaneous bacterial peritonitis where the concentration of bacteria is $10^3$ organisms/µl of fluid. Gram stain is helpful in free gut perforation.

## MANAGEMENT OF ASCITES

**Treatment of underlying cause [3, 7]**

In case of patient with alcoholic cirrhosis (one of the most common cause for ascites), stoppage of alcohol consumption found to have improvement in liver function and subsequently resolution of ascites. Interferon based antiviral drugs are useful for patients with HCV liver damage.

**Sodium restriction [5]**

The main stay in the treatment of ascites is to induce a negative sodium balance. It can be achieved either by reducing dietary sodium intake or by increasing sodium output from kidney using diuretics.

**DIURETICS**

**Potassium sparing diuretics [3, 5]**

Spironolactone is the first choice of drug for ascites since secondary hyperaldosteronism is main reason for renal sodium retention in distal nephron. The dose is 100-200mg per day which may be increased to 400mg per day in severe cases. Gynecomastia is the main side effect. Sometimes metabolic acidosis can occur. Potassium canrenoate (popular in Europe) can also be used with initial dose of 200mg per day which may be increased to maximum of 400mg per day

**Other potassium sparing diuretics [3]**

Amiloride (20-60mg/day) can be used but it is less potent than spironolactone.

**Loop diuretics [3, 5]**

It can be added if aldosterone antagonist is not producing desired effect. But it may lead to renal failure due to potassium depletion, metabolic hypochloremic alkalosis, hyponatremia. Most successful regime involves combination of spironolactone 100mg plus furosemide 40mg and the dosage can be increased in the stepwise pattern with the same ratio to maintain normal potassium levels.

Almost 90% of patients can respond to sodium restrictions so diuretics without renal failure in controlled clinical trials. In case of patients with refractory ascites which cannot be mobilized despite spironolactone 400mg/day or Amiloride 30mg/day plus Furosemide 160mg/day along with sodium restriction of $\leq$90mmol/day for more than one week and Diuretic Intractable Ascites (cannot tolerate Ascites because of its complications). *Eg* - Furosemide, Torsemide, Bumetanide.

**Large volume paracentesis (LVP) [5]**

From many randomized controlled trials, it is concluded that LVP of 4-6lit is safer and effective than the use of diuretics in treatment of tense ascites. Moreover the complications such as systemic and hemodynamic disturbance, renal impairment, electrolyte disturbance and encephalopathy are lowered in patients with LVP than with diuretics.

Re accumulation of Ascites following LVP leads to condition called paracentesis - induced circulatory dysfunction (PICD) which is characterized by reduction in central circulatory volume, increase in plasma renin activity by more than 50% and subsequently can end in renal impairment but not all the patients who developed PICD, develops renal impairment. PICD can be reduced using plasma expanders after LVP. International ascites club recommends infusing albumin 6-8litre of ascitic fluid removed for every LVP > 5-6 litre. Recent study from Toronto states that as long as the ascitic volume removed is less than 8 litre, and standard dose of Albumin 6-8 g/litre of ascitic fluid removed is given, there is no association of PICD with any renal impairment.

**Transjugular Intra hepatic Porto systemic shunt (TIPS) [3]**

A self expanding shunt is inserted to create shunt between hepatic vein (low pressure) and portal vein (high pressure). It results in improved renal performance and there by Na+ excretion and consequently the resolution of ascites complication of TIPS are intra abdominal bleeding, thrombosis and stenosis of shunt. In patients with cardiac diseases, TIPS may result in cardiac failure .Since there is shunting of blood away from liver in TIPS, liver function can also reduce to some extent.

**Liver Transplantation [5, 3]**

It is the ideal treatment for advanced cirrhosis and refractory ascites. The success of liver transplantation in these patients has resulted in rapid growth of number of patients waiting for transportation, clearly in excess of available donors.

## NEWER TREATMENT APPROACHES

**Vasoconstrictors**

Midodrine (long time administration) with weekly Albumin infusion and long acting octreotide shown to reduce plasma renin and aldosterone concentration, but only a trend towards reduction in ascites by paracentesis without affecting renal function.

**Vasopressin V2 receptor antagonist or vaptans**

These agents compete with vasopressin to bind V2 receptors at renal collecting tubule and inhibits water re absorption. It is used to reduce the extent of ascites in patient with cirrhosis.

**ALFA Pump system**

It is subcutaneously implanted battery powered peritoneo-vesical shunt. It pumps excess fluid in the peritoneum into urinary bladder which can be voided by urination.

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