Ascites in Cirrhosis: Pathophysiology and Management

Abstract:

Over 60% of patients with hepatic cirrhosis develop ascites at some stage of the disease. Ascites is usually symptomatic and it's continued presence predisposes to bacterial peritonitis. Complications of injudicious treatment can be life threatening.

The coexistence of liver and kidney disease and the importance of the development of ascites as a poor prognostic indicator, was recognised by Hippocrates as early as 400 BC. Until the introduction of effective diuretics, abdominal paracentesis was the mainstay of treatment for this condition. After 30 years of diuretic therapy for cirrhotic ascites the pendulum is beginning to swing in the direction of paracentesis once again.

PATHOPHYSIOLOGY OF ASCITES:

The pathogenesis of ascites formation involves changes in hepatic and intestinal lymph formation, and changes in renal sodium handling. Hepatic sinusoidal hypertension, by altering Starling's forces across the sinusoids, results in increased lymph formation. Intrahepatic (sinusoidal) hyperension and the consequent rise in portal pressure, along with an expanded peritoneal capillary bed, help to localise the collection of fluid in the peritoneal cavity. In patients with cirrhosis there is a five fold increase in the rate of lymphatic return via the thoracic duct compared to normal controls (1-1.5 L and 8-9 L/day respectively), while in cirrhosis with ascites it may reach 20 L/day. Renal sodium retention is an irrevocable finding in patients with cirrhotic ascites. The role of hypoalbuminemia as a primary event in the formation of ascites is not clear; a significant proportion of patients with cirrhosis have a normal or increased rate of albumin synthesis. The low serum albumin levels seen in patients with ascites is in part due to dilution.

Two major theories of ascites formation dominate current thinking. They have come to be known as the "Underfill" and "Overflow" theories (Fig. 1).

The "Overflow" theory:

According to this the primary event in the formation of ascites is renal retention of sodium leading to fluid retention and expansion of plasma volume with overflow into the extravascular space. Prostaglandins by indomethacin or other non steroidal anti inflammatory drugs, produces reversible

T he "Und er f ill" theory:

This proposes that ascites formation occurs when a critical imbalance in Starling's forces is reached across the hepatic and splanchic beds, resulting in an increase in the amount of lymph produced which exceeds the capacity of the thoracic duct for its return to the systemic circulation. Lymph then "weeps" out into the peritoneal cavity, drawing out fluid and electrolytes with a subsequent contraction of circulating plasma volume. Another factor contributing to underfill is the existence of a low systemic vascular resistance in patients with cirrhosis and ascites. This is partly due to the formation of systemic arteriovenous shunts and partly due to resistance vessel vasodilation, caused by circulating vasodilator substances. This combination of haemodynamic and physical factors results in a reduced "effective" plasma volume (ie. plasma volume with access to central volume receptors and baroreceptors situated in the heart and great vessels). Low "effective" blood volume stimulates the sympathetic nervous system, activates the renin-angiotensin-aldosterone system and results in increased renal sodium and water retention.

There is little doubt that the "underfill" mechanism plays an important role in cases of advanced decompensated liver disease. However most recent evidence (see above) points to the "overflow" mechanism as being the major mechanism responsible for ascites formation in the early stages of cirrhosis. Increased hepatic lymph formation and translocation into the peritoneum represents the final step in the physical process of ascites formation.

Prostaglandins:

An increased production of vasodialatory prostaglandins by the kidney (as detected in the urine) is an important compensatory mechanism against renal vasoconstriction in cirrhosis; Suppression of prostaglandins by indomethacin or other non steroidal anti inflammatory drugs, produces reversible
impairment of renal blood flow and a drop in glomerular filtration rate; their use is contraindicated in patients with chronic liver disease.

DIAGNOSIS:

The differential diagnosis of ascites is a lengthy one. More than 90% of cases of ascites in Europe are due to cirrhosis, malignancy, congestive cardiac failure; tuberculosis is often overlooked and may be a secondary infection in cirrhosis (Table 1). Ascitic fluid is divided into exudative (more than 3 g/dl of protein) and transudative (less than 3.0 g/dl) types. There may be a limited overlap between these two types particularly in patients undergoing diuresis. Pare et al. showed that the serum-ascites albumin gradient is a better discriminator of the two groups than the ascites total protein concentration. In their study 28 of 29 patients with liver disease and portal hypertension had serum-ascites albumin gradients of greater than 1.1.

Although progression of liver disease or failure to comply with medical treatment are common causes of first onset or recurrent ascites, other well recognised complications of chronic liver disease need to be excluded as the precipitating factor e.g., variceal haemorrhage, sepsis, hepatocellular carcinoma, and portal vein thrombosis (Table 1). Doppler-Ultrasound examination is of considerable value in the identification of most vascular causes listed and may give information on the presence of tumours. Cardiac causes should always be excluded with careful evaluation of the jugular venous pressure; in particular signs of congestive cardiac failure and of constrictive pericarditis should be sought.

SPONTANEOUS BACTERIAL PERITONITIS:

'Spontaneous' bacterial peritonitis develops in 15 to 30% of cirrhotic patients with ascites. It is mandatory to exclude bacterial peritonitis in all cases of ascites of recent onset, in patients with recent clinical deterioration, abdominal pain and tenderness, signs of encephalopathy, raised white blood cell count or fever. A diagnostic ascitic sample of 50 ml should be taken under aseptic conditions and sent for white cell and differential count, Gram stain and culture. Tubercle bacilli should be stained for and appropriate cultures set up, in each case. Cytology is often unhelpful. One third of all organisms implicated in spontaneous bacterial peritonitis are Gram positive organisms of non-enteric origin. Gran negative organisms E. coli and Klebsiella, and streptococci each account for around 10% of infections.

Since therapeutic decisions in spontaneous bacterial peritonitis must be made before the diagnosis is established on bacteriological grounds, it is important to use quick and reliable indices of infection. A number of recent studies have compared the sensitivity and specificity of ascites polymorphonuclear white cell count, pH, lactate and glucose levels, in the diagnosis of bacterial peritonitis. The combined results of these studies show the ascitic polymorphonuclear count to be the single most accurate diagnostic test. A white cell neutrophil count greater than 250 per cubic mm in the ascitic fluid is considered diagnostic of spontaneous bacterial peritonitis; such patients should be treated with intravenous broad spectrum antibiotics until a pathogen is identified. The antibiotic spectrum of Cefotaxime is similar to that of the combination of an aminoglycoside with ampicillin which cover the majority of pathogens causing spontaneous bacterial peritonitis. Cefotaxime has been shown to be both more effective than ampicillin-Tobramycin, as well as non-nephrotoxic. Several studies have shown that the majority of cases of spontaneous bacterial peritonitis occur after admission to hospital. These episodes may be precipitated by diagnostic and therapeutic procedures and there is a growing case for the use of antibiotic prophylaxis to cover these. Trials are in progress to assess this option. Bacterial peritonitis in liver disease carries a poor prognosis and must be treated in hospital. Renal failure often accompanies bacterial peritonitis and a rising serum creatinine may be the first indication of an underlying spontaneous bacterial peritonitis.

TREATMENT OF ASCITES IN CIRRHOSIS:

Dietary measures:

The aim of treatment is the induction of a negative sodium and water balance. Up to 15% of patients respond to dietary restriction of sodium alone. If the ascites is more than slight it is preferable for patients to be treated initially in hospital where they can be assessed fully. Where the cause is alcoholic liver disease, a period of hospital stay gives the opportunity to the patient to withdraw from alcohol, to realise the seriousness of his condition and to receive detailed dietary advice over a period of days. Patients with a mild degree of ascites should be given a trial of bed rest and sodium restriction before the introduction of diuretics. A 22 mmol daily sodium intake is usually effective; it may take between 2 and 4 weeks for an effective diuresis and natriuresis to occur on diet alone. Patients likely to respond to dietary measures alone display the following features: Recent onset of ascites, urinary sodium excretion greater than 10 mmol/day, normal renal function, ascites precipitated by high dietary sodium intake, and rarely, in the presence of reversible liver disease such as alcoholic hepatitis with fatty liver. Patients with normal serum sodium need not be fluid restricted. Hypotenaemic patients (130 mmol/l) should be restricted to 800-1000 ml of fluid daily.

Diuretics:

Indications for the use of diuretics along with
salt restriction include the presence of moderate or tense ascites, abdominal discomfort, respiratory impairment, marked umbilical oedema and rarely breakdown of the skin. Diuretics most commonly used are "distal tubule" potassium sparing diuretics, such as spironolactone or triamterene, and potassium losing loop diuretics such as frusemide, bumetanide and thiazides. Experience and controlled studies confirm the superiority of spironolactone to frusemide in non azotaemic patients. This effect is probably related to aldosterone antagonism by spironolactone. Spironolactone induced diuresis usually begins after 3 days treatment but may not occur for 8 to 12 days in some cases. The dose of spironolactone required ranges from 50 to 600 mg daily. Occasionally 800 to 1000 mg have been used. Combined therapy with spironolactone and a loop diuretic is sometimes necessary; it should be avoided outside hospital because of its tendency to cause marked electrolyte imbalance with frequent life threatening complications.

A reasonable regime would be to start with spironolactone 100 mg increasing by 100 mg every 2 days until there is a diuretic response. Electrolytes and urea and creatinine should be checked at least twice weekly or more and diuretic therapy adjusted accordingly. Where combined therapy is necessary frusemide doses of 40 to 80 mg on alternate days are usually sufficient to induce a diuresis. The aim of diuretic therapy should be to achieve weight loss not exceeding 0.75 kg per day in patients without peripheral oedema and up to 1.5 kg per day so long as peripheral oedema is present. An increase in urinary sodium is usually the earliest indication of an ensuing diuresis.

Non-steroidal anti-inflammatory drugs are contraindicated in cirrhosis (see above).

While at home patients should monitor their weight daily on bathroom scales and may also find a diary helpful in monitoring their sodium intake. Clinic or surgery visits can be arranged at appropriate intervals depending on clinical progress and serum electrolytes. Electrolytes should be checked once a month in the most stable patients and as frequently as twice weekly in the most unstable. The amount of dietary sodium may be increased cautiously over a period of a few months. For patients with improving liver function such as the truly abstinent alcoholic, it is often possible to increase sodium intake without recurrence of the ascites. Patients developing signs of complications such as encephalopathy (eg, ‘flap’), postural hypotension, deteriorating renal function, hyponatraemia or hyperkalaemia, that fail to respond to diuretic withdrawal should be admitted to hospital without delay because the speed of deterioration can be extremely rapid (Table 2).

The incidence of diuretic related complications is reported as: encephalopathy in 25% of patients, hyponatraemia (< 130 mmol/l) in 45%, and uraemia in 30%. Hypokalaemia occurs in up to 64% of patients receiving a loop diuretic alone and this therapy is not to be recommended (see Table 2).

Abdominal Paracentesis:

Limited volume paracentesis may be necessary in cases of diuretic resistant ascites to relieve pain, respiratory distress, or umbilical hernias. Large volume therapeutic paracentesis was abandoned after the introduction of diuretics because it was generally thought to carry a substantial risk of hypovolaemia, renal failure and encephalopathy. In the last two years a number of studies have re-examined this therapeutic option. Quintero et al. compared repeated paracentesis of 5 litres per day with albumin replacement to diuretic therapy and reported a smaller incidence of complications with paracentesis. Kao et al. recorded no adverse haemodynamic effects with a single 5 litre paracentesis in patients with peripheral oedema. Recently Simon et al. recorded central haemodynamic and renal function changes for 48 hours following single paracentesis, of 8 litres of ascitic fluid and found progressive drop in pulmonary capillary wedge pressure and central venous pressure as well as a 22% drop in glomerular filtration rate; renin levels were increased at 24 hours indicating a drop in intravascular volume. Patients selected for the above studies had near normal renal function and were not significantly hypoartaemic and would probably have responded to diuretic therapy. Further studies are needed, particularly in poor risk patients with refractory ascites, in order to assess the medium and long term efficacy of paracentesis before it can be accepted as a first line treatment.

Refractory Ascites:

Over 90% of patients respond to optimal diuretic therapy in combination with dietary measures; non responders almost invariably have poor renal function, less than 10 mmol/day urinary sodium excretion, hyponatraemia and hypoalbuminaemia. It has been suggested that paracentesis with albumin replacement may be helpful in these cases; further evaluation is necessary to determine the possible value of this therapeutic option. Methods of ascites ultrafiltration with reinfusion of ascitic protein into the vascular compartment have been largely abandoned although peritoneal-venous shunting (Le Veen shunt) is still used occasionally for cases of refractory ascites. The peritoneal cavity is drained through a plastic tube which passes subcutaneously to the neck and drains into the superior vena cava via the internal jugular vein; unidirectional flow is maintained by a valve. Pressure gradients related to respiration and coughing drive fluid from the peritoneal cavity towards the chest. The operative mortality of the procedure is 15%; only a third are patent at 1 year and there is a high incidence of infection and disseminated intravascular coagulation. Pul-
monary oedema and bleeding from oesophageal varices are frequent complications of peritoneovenous shunting.\textsuperscript{19, 20}

Dietary measures and the judicious use of diuretics remain the mainstay of treatment for cirrhotic ascites. Where they fail large volume paracentesis with albumin replacement is the therapeutic option most worth considering.

**REFERENCES**


Theories of ascites formation.

**UNDERFILL THEORY**

- ↓ Effective volume
- ↑ Renal sodium retention
- ↑ Extracellular fluid volume
- Ascites and oedema

**OVERFLOW THEORY**

- Primary renal tubular retention of sodium
- ↑ Plasma volume
- Translocation of fluid out of splanchic circulation as ascites

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**TABLE 1**

**Classification of ascites.**

**Transudate:**
- Right ventricular failure
- Constrictive pericarditis
- Parenchymal liver disease
- Budd-Chiari syndrome
- Portal vein occlusion

**Exudate:**
- Peritoneal metastases
- Pancreatitis
- Peritonitis - bacterial tuberculous
- Chylous ascites
- Myxoedema

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**TABLE 2**

**General principles in the treatment of ascites.**

**Measures:**
- Bed rest and 22 mmol sodium diet
- Fluid restriction if hyponatraemic
- Spironolactone 50-600 mg daily
- Frusemide 40-100 mg alt. days
- Paracentesis > albumin infusion

**Monitor:**
- Daily weight
- Fluid balance
- Urine sodium
- Electrolytes
- Encephalopathy
- Postural hypotension

**Complications of diuretic therapy.**

- All diuretics
  - Hypovolaemia
  - Uræmia
  - Hyponatraemia
  - Hyperkalaemia
  - Metabolic acidosis
  - Hypokalaemia
  - Metabolic alkalosis