Management of Ascites

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Introduction

Although anti-viral treatment could delay the progression of chronic hepatitis B (CHB) infection, many patients in Hong Kong still suffer from the complications of this "silent" infection due to delayed treatment and lack of awareness. A Taiwan study showed that the annual incidence of CHB-related liver cirrhosis was 2.1% and the median age of diagnosis of cirrhosis was 35-40[1]. Once cirrhosis was established, about 5-7% of cases would progress from compensated to decompensated stage annually[2]. Ascites was usually the first sign of decompensation in this group of patients. Its occurrence was associated with a poor quality of life, increased risk of infection, and renal failure[3]. The cumulative survival rate 1 year and 3 years after the onset of ascites in CHB-related cirrhosis was 50.7% and 18.7% respectively in a recent Asian study[4]. The poor prognosis was related to the development of variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis and hepatocellular carcinoma as early as a median of 8-21 months. At low Model for End-stage Liver Disease (MELD) score (a scale of 6 to 40, with higher values indicating more severe disease) of less than 21, persistent ascites and hyponatraemia were shown to be the independent predictors of mortality[5]. In 2005, a consensus workshop on portal hypertension classified the presence of ascites in cirrhosis as stage 3 disease which carried a mortality rate of 20% per year[6]. Hence, it is recommended that all cirrhotic patients with ascites should be evaluated for liver transplantation.

Pathophysiology of Ascites (Fig 1)

The primary event that leads to portal hypertension is caused by the abnormalities in hepatic microcirculation as manifested by elevated hepatic resistance to portal flow[7]. Reduced endothelial nitric oxide (NO) production and vasodilatory response to NO are both considered as important pathogenic mechanisms. As portal hypertension develops, endothelial NO production by the arteries of the splanchnic and systemic circulation increases and leads to vasodilatation, the so-called "hyperdynamic circulatory state"[8]. When both portal hypertension and splanchnic arterial vasodilatation occur, capillary permeability and lymph formation in the splanchnic organs markedly increase and exceed the ability to return the lymph to the circulation by the thoracic duct, thus causing its accumulation in the peritoneal cavity.

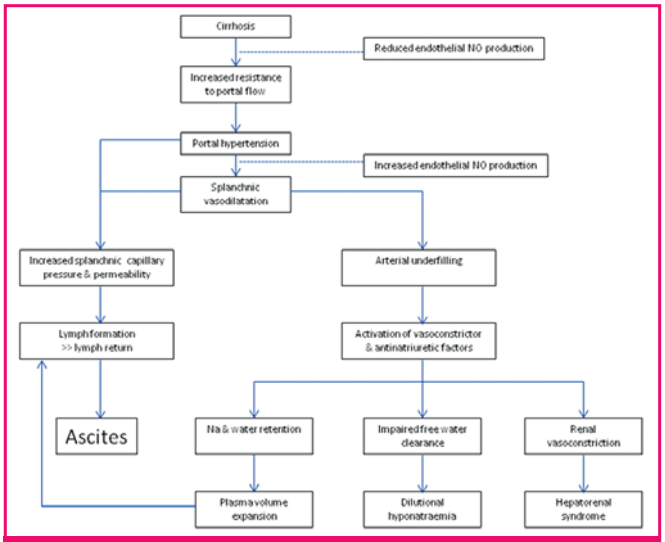

Figure 1. Pathogenesis of Ascites

Evaluation of Patients with Ascites

More than 75% of patients who present with ascites have underlying cirrhosis with the remaining being due to malignancy, cardiac failure, pancreatitis, tuberculosis and other rare causes[9]. In cirrhotic patients with ascites, physical examination may reveal splenomegaly, cutaneous venous collaterals over abdomen and other signs of chronic liver disease. Patients with gross ascites may have umbilical and inguinal hernias, leg oedema and muscle wasting due to poor nutritional status. Pleural effusion, which is known as hepatic hydrothorax, may occur in 5-12% of cirrhotic patients[10]. The proposed mechanism is the leakage of ascitic fluid via diaphragmatic defects facilitated by the negative intrapleural pressure. It occurs at the right-side in 65-87% of cases. During assessment, we should always look for evidence of hepatic encephalopathy, abdominal pain, fever and gastrointestinal bleeding so that prompt investigation and treatment can be initiated.

Diagnostic abdominal paracentesis (30ml) should be performed in all patients when first presented with ascites and in all patients with any evidence of clinical deterioration as stated above. Abnormal coagulation profile should not preclude paracentesis unless there is clinical evidence of hyperfibrinolysis or disseminated intravascular coagulation[11].

Ascitic Fluid Analysis

Ascitic fluid should be sent for cell count and differential,

albumin and total protein concentration if uncomplicated cirrhotic ascites is suspected. To diagnose ascitic fluid infection, ascitic fluid should be inoculated into blood culture bottles instead of plain bottles for higher diagnostic yield[12]. An ascitic fluid neutrophil count of 250/mm^3 has >90% sensitivity and specificity for the diagnosis of spontaneous bacterial peritonitis (SBP)[13]. Urine dipstick has recently been suggested to facilitate the diagnosis of SBP. However, a review of 19 studies on the use of reagent strips showed a low sensitivity and a high false-negativity rate[14]. The conventional concept of transudate-exudate based upon the ascitic protein concentration (<25g/L or >25g/L) should not be used due to inaccuracy in distinguishing the cause of ascites. The serum-ascites albumin gradient (SAAG= serum albumin - ascitic albumin concentration) is more specific and sensitive in classifying ascites with 97% accuracy[15]. Values greater than 11g/L signify cirrhotic ascites whereas values lower than 11g/L suggest other causes (Table 1).

Table 1. Serum ascites-albumin gradient (SAAG)

SAAG >11g/L	SAAG <11g/L
Cirrhosis	Malignancy
Cardiac failure (cardiac ascites)	Pancreatitis
Budd-Chiari syndrome	Tuberculosis
	Nephrotic syndrome

Stages of Ascites

In a consensus meeting report published in 1996, ascites was classified as uncomplicated ascites and refractory ascites (Table 2)[16]. Refractory ascites is defined as ascites that cannot be mobilised or the early recurrence of which cannot be satisfactorily prevented by medical therapy. About 5-10% of all cases of ascites fall into this category. It is frequently associated with type 2 hepatorenal syndrome and dilutional hyponatraemia.

Table 2. Stages of ascites

Stage	Severity of ascites	Treatment
1	Only detectable by ultrasound	Salt restriction
2	Moderate ascites; abdominal distension	Salt restriction,, diuretics
3	Massive ascites; marked abdominal distension	Diuretics, therapeutic paracentesis, TIPS
Refractory (5-10%)	Diuretic-resistant (unresponsive to sodium restriction and diuretics or rapid recurrence)	Therapeutic paracentesis, TIPS, OLT
	Diuretic-intractable (develop complication due to diuretic use)	

Treatment

Bed Rest
Although studies demonstrated an improved diuretic effect in patients with cirrhotic ascites when assuming a supine position, bed rest is not advisable as it may lead to muscle atrophy and prolonged hospital stay[17].

Sodium Restriction
Loss of ascites can be achieved by sodium restriction alone in 10-15% of patients[18]. However, patient compliance is usually a problem and severe salt restriction may lead to poor nutrition. Hence moderate restriction to 5.2g/d (90 mmol) is advisable[19].

Water Restriction
Many ascitic patients were advised by their physicians to restrict water intake. However there have been no studies on its benefit or harm on the resolution of ascites. Besides, this treatment may exacerbate the severity of effective central hypovolaemia that enhances the secretion of antidiuretic hormone and results in further decline in renal function and aggravates dilutional hyponatraemia. Fluid restriction is not necessary in most patients with cirrhotic ascites.

Diuretics
Spironolactone, an aldosterone antagonist acting on the distal tubules, is more effective in cirrhotic patients with ascites than non-cirrhotics. Its major active metabolite, canrenone, has a half-life of 10-35 hours in healthy subjects (T 1/2 may be longer in cirrhotic patients). It can be started from 25-50 mg/d to a maximum dose 400mg/d. Hyperkalaemia and painful gynaecomastia are the most common side-effects. A loop-diuretic, frusemide, can be used concomitantly if the response to spironolactone is not sufficient. The recommended initial dose should be 20-40mg/d (max 160mg/d). Inadvertent use of this drug may precipitate pre-renal failure and hepatic encephalopathy due to increased renal ammonia production as a result of diuretic-induced hypokalaemia and alkalosis[20]. Amiloride (10-40mg/d) can replace spironolactone in patients with tender gynaecomastia though it is more expensive and less effective than canrenone[21]. When diuretics are used, it is recommended that the rate of weight loss should not exceed 0.5 kg/d in the absence of oedema, or 1 kg/d when oedema is present[22].

Large Volume Paracentesis (LVP)
LVP involves drainage of >5 L ascitic fluid. When compared with diuretics, it is more effective in eliminating ascites and shortening the duration of hospitalisation. If done alone, it is associated with postparacentesis circulatory dysfunction (PPCD) in 20% cases. PPCD is found to be associated with increased risk of renal failure and mortality up to 30 days after LVP[23]. When compared with synthetic plasma expanders, albumin infusion before the procedure is more effective in preventing PPCD especially if >5 L ascites are removed. It is usually given at a dose of 6 to 8 g for each litre of ascites removed[23]. As albumin is expensive, some studies showed that intravenous use of terlipressin, a vasopressin pro-drug, is nearly equivalent to albumin in the prevention of PPCD[24,25]. More studies are needed to assess the long-term safety of this approach.

Aquaretic Agents
Aquaretics are specific vasopressin receptor (V2) antagonists which act on the collecting tubules of the kidney by counteracting vasopressin (AVP) and inducing free-water excretion without affecting electrolyte balance. In a short-term study, satavaptan, a highly selective non-peptide V2 receptor antagonist, when given to spironolactone treated patients with cirrhotic ascites and hyponatraemia for 14 days was shown to improve ascites control and increase serum sodium level[26]. We await long-term studies to define the role of these agents in the management of cirrhotic ascites.

Transjugular Intrahepatic Portosystemic Shunt (TIPS)
TIPS is more effective at removing ascites as compared with paracentesis without a significant difference in

mortality, gastrointestinal bleeding, infection, and acute renal failure[27]. However, TIPS patients develop hepatic encephalopathy significantly more often (~30%) and may be more expensive due to stent replacement for stent dysfunction (up to 75%). In general, TIPS should not be performed in patients who have a bilirubin level of greater than 3 mg/dL (51 µmol/L), prothrombin time greater than 20 seconds, and a serum creatinine level of greater than 2 mg/dL (152µmol/L), because it is associated with a 3-month mortality exceeding 90%.

Peritoneovenous Shunts

Due to their poor long-term patency, excessive complications, and no survival advantage compared to medical therapy in controlled trials, peritoneovenous shunts (e.g. LeVeen or Denver) have little role in the treatment of refractory ascites.

Liver Transplantation

All cirrhotic patients who develop ascites should be assessed for liver transplantation due to poor long-term prognosis.

Summary

Ascites is the most common complication of liver cirrhosis which develops in 50% of patients over a 10-year period. The management of ascites is determined by the severity of the symptoms. The therapeutic options include salt restriction, diuretics, LVP, and TIPS. Newer pharmacological agents such as aquaretics are being studied. Close monitoring of both the treatment-related efficacy and adverse effects are equally important. Liver transplantation should be considered for all patients with cirrhotic ascites.

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