

15.22.2 Cirrhosis and ascites

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section 15 Gastroenterological disorders 3058 15.22.2 Cirrhosis and ascites Javier Fernández and Vicente Arroyo ESSENTIALS Ascites is the accumulation of fluid in the peritoneal cavity and the most common complication of cirrhosis, when it is associated with a poor prognosis. It occurs only when portal hypertension has developed and is mainly due to renal sodium retention secondary to splanchnic arterial vasodilation that leads to homeostatic activation of vasoconstrictor and sodium-retaining systems. Clinical presentation is with abdominal distension. Patients with tense ascites can also complain of backache or abdominal pain. Investigation The initial evaluation of a patient with ascites must include (1) history and physical examination; (2) liver and renal function tests including serum and urine electrolytes; (3) analysis of ascitic fluid (diagnostic paracentesis) for cell count and culture, and protein/albumin concentration; other tests such as cytology (suspicion of malignancy), amylase (pancreatic disease), and polymerase chain reaction and culture for mycobacteria (tuberculosis) should be done only when the diagnosis is unclear; (4) abdominal ultrasonography for evidence of cirrhosis, portal hypertension, or malignancy. Management First-line manoeuvres include dietary salt restriction (80–120 mmol/day), and therapeutic or total paracentesis. Water restriction is only recommended if there is severe dilutional hyponatraemia. Refractory ascites is managed by repeated paracentesis or insertion of a transjugular intrahepatic portosystemic shunt. Cirrhotic patients with ascites should be considered for liver transplantation. Complications All patients with cirrhosis and ascites are at risk of spontaneous bacterial peritonitis. Typical symptoms are abdominal pain and fever, but the condition may be asymptomatic. The gut is the most frequent source of organisms (bacterial translocation from intestinal lumen). Treatment with appropriate antibiotics (tailored according to the local epidemiological pattern of antibiotic resistance) should be started as soon as a presumptive diagnosis is made following diagnostic paracentesis (polymorphonuclear neutrophil count $\geq 250/\text{mm}^3$). Prophylactic norfloxacin reduces the risk of recurrent episodes. Mortality is around 10% for the acute episode and 75% at 1 year; hence (unless contraindicated), all patients with spontaneous bacterial peritonitis should be considered for liver transplantation. Patients with cirrhosis and ascites are also at high risk of other complications: (1) refractory ascites, (2) hyponatraemia, (3) hepatorenal syndrome, (4) paraumbilical hernia, and (5) pleural effusion.

Introduction Ascites is the accumulation of fluid in the peritoneal cavity. Studies on its pathogenesis began in the 17th century when Richard Lower (1631–1691), a physician based in Oxford, demonstrated that ascites developed in dogs following ligation of the inferior vena cava. Ernest Henry Starling (1866–1927), a physiologist based at University College London, made a major contribution to the study of oedema formation with the demonstration that both hydrostatic forces and oncotic forces were involved, and that the increase in thoracic lymph flow following obstruction of the inferior vena cava is mainly derived from the liver. Aetiology Ascites is the most common complication of cirrhosis and indicates the presence of portal hypertension and hepatic decompensation. It occurs in at least 50% of patients within 10 years of the diagnosis of cirrhosis, which accounts for over 75% of cases presenting with ascites. Ascites may also be caused by malignancy, pancreatitis, tuberculosis, cardiac failure, myxoedema, or other rarer causes, each of which may also occur in patients with cirrhosis (Table 15.22.2.1). Although ascites commonly occurs in patients with cardiac failure, it is rarely a presenting feature. Ascites does not occur in patients with portal vein thrombosis and is infrequent in other forms of noncirrhotic intrahepatic portal hypertension such as idiopathic portal hypertension. It frequently occurs in patients with the Budd–Chiari syndrome, severe alcoholic hepatitis, and subacute liver failure. Other (rare) causes of ascites include constrictive pericarditis, veno-occlusive disease, malnutrition, hypoalbuminemia (nephrotic syndrome and protein-losing enteropathy), stromal tumours and Meigs’ syndrome, hypothyroidism, lymphatic leak (chylous ascites), autoimmune inflammatory conditions (e.g. systemic lupus erythematosus), or Whipple disease. Rare infections include candidiasis, brucellosis, and filariasis. Granulomatous liver disease such as sarcoidosis may cause portal hypertension and (occasionally) ascites. Ascites may also occur in the

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Table 15.22.2.1 Underlying causes of patients presenting with ascites in the United States of America

Cause	% Total
Cirrhosis (alcoholic liver disease)	65
Cirrhosis (viral)	10
Cirrhosis (other)	6
Malignancy	10
Heart failure	3
Tuberculosis	2
Pancreatic disease	1
Other causes	3

15.22.2 Cirrhosis and ascites 3059 ovarian hyperstimulation syndrome in women undergoing fertility treatment. Epidemiology Cirrhosis is the fifth leading cause of death in the United Kingdom. It heralds the beginning of a usually rapid decline of liver function, with about half of patients dying within 2 years of the onset of ascites. Pathogenesis Ascites Until recently, the most widely accepted explanation for the pathogenesis of ascites and renal failure in cirrhosis has been based on the peripheral arterial vasodilation and the forward hypotheses of ascites formation proposed by Schrier et al. in 1988. This holds that the primary event stimulating renal sodium and water retention in cirrhosis is splanchnic arterial vasodilation caused by a massive release of local vasodilators (i.e. nitric oxide) secondary to portal hypertension. In the initial phases of cirrhosis, compensation occurs through the development of hyperdynamic circulation (high plasma volume, cardiac index, and heart rate). As cirrhosis progresses and splanchnic arterial vasodilation increases, this compensatory mechanism is insufficient to maintain circulatory homeostasis. Arterial pressure decreases, leading to stimulation of baroreceptors, homeostatic activation of the sympathetic nervous system (SNS) and the renin–angiotensin–aldosterone system (RAAS), and production of antidiuretic hormone (ADH, or vasopressin), all leading to renal sodium and water retention. Within the splanchnic microcirculation, the forward increase in capillary pressure and permeability from the greatly increased inflow of blood at high pressure into the splanchnic capillaries leads to the leakage of fluid into the abdominal cavity. The peripheral arterial vasodilation hypothesis has

been revisited. Firstly, several studies have shown that cardiac function is increased in early stages of cirrhosis and ascites, but declines with the progression of the disease, being frequently normal in patients with hepatorenal syndrome. Hence, progression of circulatory dysfunction, the stimulation of the RAAS and the SNS, ADH production, and impairment of renal function in cirrhosis are caused by both progressive splanchnic arterial vasodilation and primary impairment in cardiac function (Fig. 15.22.2.1). Secondly, the peripheral arterial vasodilation hypothesis does not provide an explanation for the fact that patients with advanced cirrhosis frequently develop multiorgan failure (acute-on-chronic liver failure), a syndrome characterized by systemic inflammation and high short-term mortality. According to a new hypothesis, systemic inflammation could also contribute to the major clinical manifestations of advanced cirrhosis (Fig. 15.22.2.2). The sustained activation of the innate immune system caused by an abnormal translocation of bacteria and bacterial products from the intestinal lumen (pathogen-associated molecular patterns) could lead to the persistent activation of the innate pattern recognition receptors and subsequent chronic inflammation. Proinflammatory cytokines and oxidative stress could accentuate circulatory dysfunction (by enhancing arterial vasodilation and cardiac dysfunction) and damage the kidneys and other organs, worsening their function.

Renal dysfunction Renal function abnormalities (reduced ability to excrete sodium and free water and decreased renal perfusion and glomerular filtration rate) follow a progressive course in cirrhosis. Impairment of renal sodium handling can already be detected before the development of ascites, when cirrhosis is still compensated. In this phase, patients have subtle abnormalities in renal sodium excretion, for example, reduced natriuretic response to the acute administration of sodium chloride, and abnormal natriuretic responses to changes in posture. As cirrhosis progresses, patients become unable to excrete their regular sodium intake. Sodium is then retained together with water and fluid accumulates in the abdominal cavity as ascites. In the early phase, sodium retention is unrelated to the activation of the RAAS or of the SNS. However, when sodium retention is intense (urinary sodium excretion <10 mEq/day), the plasma renin activity and the plasma concentrations of aldosterone and noradrenaline are invariably increased. Aldosterone increases sodium reabsorption in the distal and collecting tubules, and increased renal SNS activity stimulates sodium reabsorption in the proximal tubule and loop of Henle. Sodium retention in this phase is therefore caused by increased sodium reabsorption throughout the nephron. Dilutional hyponatraemia (serum sodium concentration of <130 mEq/litre) develops in later phases when electrolyte-free water clearance is severely reduced. Finally, patients develop functional acute kidney injury secondary to intense renal hypoperfusion (type 2 hepatorenal syndrome). The degree of sodium retention in these patients is very intense and most of them do not respond to diuretics and have refractory ascites. Free water clearance is also markedly reduced.

Cardiac output Effective arterial hypovolemia Normal effective blood volume Splanchnic arterial vasodilation Systemic vascular resistance Extra-splanchnic vasoconstriction Degree of activation of RAAS, SNS, ADH Compensated cirrhosis Changes Ascites Time (years) Hyponatremia Type-2 HRS

Fig. 15.22.2.1 Pathogenesis of circulatory and renal dysfunction in cirrhosis (peripheral vasodilation hypothesis). ADH, antidiuretic hormone; HRS, hepatorenal syndrome; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system. Reprinted from Journal of Hepatology, Vol. 63, Bernardi M, et al., Mechanisms of decompensation and organ failure in cirrhosis: from peripheral arterial vasodilation to systemic inflammation hypothesis, Pages 1272–84, Copyright © 2015 European Association for the Study of the Liver, with permission from Elsevier.

section 15 Gastroenterological disorders 3060 reduced and most patients have significant hyponatraemia. Patients with type 2 hepatorenal syndrome are at increased risk of type 1 hepatorenal syndrome, a rapidly progressive acute kidney injury that frequently occurs in association with the failure of other organs and systems (acute-on-chronic liver failure). Clinical features Ascites is graded 1 to 3 depending on its severity. Grade 1 ascites is mild, and only detectable by ultrasound examination; grade 2 ascites is moderate, and is manifest by moderate symmetrical distension of the abdomen; and grade 3 ascites is large or gross, with marked abdominal distension. A grade 2 ascites is most easily detected by a shifting dullness. Grade 3 ascites is usually tense and easily detected by the presence of a fluid thrill on palpation. Aside from an unpleasant feeling of abdominal distension and/or abdominal pain, many patients will complain of backache. There is often divarication of the rectus abdominis muscles, and prominent veins may be evident on the abdominal wall (Fig. 15.22.2.3). Paraumbilical hernias develop in about 20% of patients with ascites, an incidence that increases to up to 70% in those with long-standing recurrent tense ascites, with the main risks being rupture and strangulation. Pleural effusions (hepatic hydrothorax) develop in about 5% of patients with cirrhosis and may develop in patients with no discernible ascites. The pleural effusions are right-sided in 85% of cases, left-sided in 13%, and bilateral in 2%. Laboratory diagnosis The cause of ascites is often obvious. Where there are no obvious clues to its aetiology, tests must be directed both at diagnosing the presumed cause of liver disease and at excluding other causes of ascites such as malignancy or tuberculosis. Other causes of abdominal distension such as huge masses, Meigs' syndrome, or pregnancy should be considered. The essential investigations on admission of a patient to hospital include the following:

- Liver and renal function tests, including serum and urine electrolytes—patients with cirrhosis and ascites are prone to hyponatraemia or renal impairment, either spontaneously or following diuretic therapy.
- Analysis of ascitic fluid (diagnostic paracentesis) for cell count, determination of protein concentration, and culture to confirm or exclude spontaneous bacterial peritonitis (SBP). A Gram stain is informative in patients with secondary peritonitis (polymicrobial). Cytology, amylase measurement, and polymerase chain reaction and culture for mycobacteria should be done when there is suspicion of other potential diagnosis (malignancy, pancreatic disease, and tuberculosis, respectively).
- Abdominal ultrasonography is needed to evaluate liver appearance (nodular in cirrhosis; congested in congestive cardiac failure), provide data on portal hypertension (splenomegaly, portal vein dilation, collaterals), portal vein flow (thrombosis is present in 8% of patients with cirrhosis), the presence of liver tumour(s) (hepatocellular carcinoma or metastases), and to semiquantify the amount of ascites.

Compensated cirrhosis Early decompensated cirrhosis Decompensated cirrhosis Acute-on-chronic liver failure Mild/moderate BT Moderate SAV compensated by increased CO No systemic or organ inflammation Significant SAV No further increase in CO Moderate systemic and organ inflammation Severe SAV Decreased CO Significant systemic and organ inflammation Extreme circulatory and cardiac dysfunction Organ hypoperfusion Severe organ inflammation and oxidative stress Organ damage Organ failures Acute-on-chronic liver failure Marked effective hypovolaemia organ dysfunction Renal failure Effective hypovolaemia Organ dysfunction No organ failure No effective hypovolaemia No organ dysfunction Significant BT Severe BT Bacterial infection Acute sterile inflammation Severe burst of BT

Fig. 15.22.2.2 The systemic inflammation hypothesis of decompensation and acute-on-chronic liver failure in cirrhosis. Bacterial translocation (BT) progressively impacts the natural course of cirrhosis causing circulatory and cardiac dysfunction and finally acute-on-chronic liver failure. CO, cardiac output; SAV, splanchnic arterial vasodilation. Modified from Journal of Hepatology, Vol. 63, Bernardi M, et al., Mechanisms of decompensation

and organ failure in cirrhosis: from peripheral arterial vasodilation to systemic inflammation hypothesis, Pages 1272–84, Copyright © 2015 European Association for the Study of the Liver, with permission from Elsevier. Fig. 15.22.2.3 Alcoholic cirrhosis with ascites is often associated with marked anorexia and malnutrition.

15.22.2 Cirrhosis and ascites **3061 Paracentesis** An ascitic tap is performed for either diagnostic purposes or for the removal of large volumes of ascites. The most common site for paracentesis is about 15 cm left lateral to the umbilicus (approximately 5 cm superior and medial to the left anterior superior iliac spine), with care being taken to avoid an enlarged spleen. The epigastric arteries run just lateral to the umbilicus towards the midinguinal point and should be avoided. For diagnostic purposes, 20 ml of ascitic fluid should be withdrawn, and 5 to 15 ml placed under aseptic conditions (i.e. the needle changed) into each of two blood culture bottles. A 2- to 5-ml aliquot of fluid should also be sent in a plastic container (containing ethylenediaminetetraacetic acid (EDTA) if the sample has a tendency to clot) to the lab for cell count (polymorphonuclear neutrophil (PMN) or lymphocyte count) and ascitic fluid protein determination. Cytological examination requires 20 to 50 ml of ascitic fluid.

Ascitic fluid investigations A diagnostic paracentesis should be performed in all patients with new-onset grade 2 or 3 ascites, and in all patients hospitalized for worsening of ascites or any other complication of cirrhosis, in order to rule out SBP. An appropriate ascitic fluid analysis must include cell count and the determination of total protein concentration. Ascitic protein concentration and serum-ascites albumin gradient Conventionally, ascites is described as being an exudate or a transudate depending on whether ascitic protein concentration is respectively more or less than 25 g/litre, the purpose of this subdivision being to narrow the differential diagnosis of its cause. The causes of transudative and exudative ascites are given in Table 15.22.2.2. Cardiac ascites, malignancy, and tuberculous peritonitis usually have a high ascitic protein content. However, 20% of patients with a malignancy and 30% of those with tuberculosis have low-protein ascites. Ascites in cirrhosis is normally a transudate (85%), but about 15% of cases of cirrhotic ascites have an ascitic protein level of more than 25 g/litre. Measuring the difference between serum and ascites albumin levels (high gradient, >11 g/litre vs low gradient, <11 g/litre) considerably improves the capacity to subdivide exudative or transudative causes. The overall accuracy of this method is high, although its actual impact in day-to-day clinical practice is small (Table 15.22.2.3). In patients with cirrhosis, a very low ascitic protein level (<10–15 g/litre) is associated with an increased risk of SBP. Moreover, protein concentration in ascites (>10 g/litre) has been suggested as a criterion to distinguish between spontaneous and secondary peritonitis (Runyon's criteria). Ascitic amylase The ascitic fluid amylase level should always be measured in patients with an exudative or unexplained ascites. A very high value is obtained when ascitic fluid results from a pancreatic pseudocyst. Patients with secondary peritonitis due to gut perforation also present high levels of amylase and bilirubin in ascitic fluid.

Ascitic fluid cell count An ascitic neutrophil count of at least 250 PMNs/mm³ is diagnostic of SBP. An elevated lymphocyte count should raise the possibility of tuberculous peritonitis or malignancy. Excess red blood cells are most commonly due to a traumatic tap, but should also raise the possibility of malignancy (i.e. haemoperitoneum due to hepatocellular carcinoma in cirrhosis).

Ascitic fluid culture Ascitic fluid must be processed in the same way as blood cultures, and ascitic fluid inoculated directly into blood culture bottles at the bedside. This policy doubles the positive culture rate. If an ascitic cell count is reported as showing less than 250 PMNs/mm³ but subsequent culture is positive (bacterascites), then the ascitic tap should be repeated since the patient may have developed SBP and thus require treatment with

antibiotics and albumin. Ascitic fluid cytology Ascitic cytology should involve liaison with the cytopathologist so that the index of suspicion and type of potential tumour are discussed. A 20- to 50-ml sample of ascitic fluid is required to produce a cell concentrate for cytology—obtained by centrifuging the ascites fluid, removing supernatant, and resuspending the cells. A sample of the concentrate then undergoes a cytospin to deposit cells on to microscope slides, following which the cells are stained. Typical stains include the Papanicolaou and May-Grünwald-Giemsa stain.

Ascitic volume Ascitic volume is not usually determined in clinical practice. It can, however, be quantified radiologically or by indicator-dilution (radiolabelled ^{99}Tc -macroalbumin). As a rough guide, patients with barely detectable ascites usually harbour between 1 and 4 litres,

Table 15.22.2.2 Subdivision into exudative and transudative ascites Exudative ascites (protein >25 g/litre) Transudative ascites

(protein <25 g/litre) Malignancy (80%) Cirrhosis (85%) Tuberculosis (70%) Malignancy (20%) Congestive cardiac failure Protein-losing enteropathy Cirrhosis (15% of cases) Tuberculosis (30%) Pancreatitis Budd-Chiari syndrome Myxoedema Constrictive pericarditis Nephrotic syndrome

Table 15.22.2.3 Subdivision of patients into high and low ascitic albumin gradient Serum-ascites albumin

gradient <11 g/litre (low gradient) Serum-ascites albumin

gradient >11 g/litre (high gradient) Malignancy Cirrhosis Tuberculosis Cardiac failure Pancreatic Budd-Chiari syndrome Biliary Myxoedema Nephrotic syndrome Connective tissue disease

section 15 Gastroenterological disorders 3062 those with moderate ascites 4 to 8 litres, and those with marked ascites more than 8 litres of fluid. Management Patients with ascites can be divided into those who are easy to treat and those who are difficult. In general, patients with their first presentation of ascites and normal renal function, who have a spot urine sodium concentration of greater than 20 mmol/litre, or an identifiable source of dietary sodium excess, respond well to simple measures. Likewise, when ascites has developed as a consequence of bleeding or infection, it usually resolves more readily. The treatment of ascites is summarized in Box 15.22.2.1.

Bed rest There is no evidence to recommend bed rest as part of the treatment of ascites. Moreover, bed rest accentuates muscle atrophy, a very significant problem in advanced cirrhosis.

Dietary salt restriction There is a consensus that dietary salt restriction is an important component of the management of patients with cirrhosis and ascites. Standard practice is to restrict sodium intake to 80 to 120 mmol/day, which in effect is equivalent to a 'no added salt' diet with avoidance of preprepared meals. A greater reduction in sodium intake interferes with nutrition and is not advisable. In most cases, however, urinary sodium excretion is very low, and a negative sodium balance cannot be achieved without diuretics. Even in these cases, sodium restriction is important because it reduces diuretic requirements.

Water restriction As a general recommendation There are no data to support fluid restriction in patients with ascites and normal serum sodium concentration. It is well known that water follows salt, hence fluid loss will occur if a patient achieves negative sodium balance with dietary salt restriction and/or diuretics. In patients with hyponatraemia Dilutional hyponatraemia in cirrhosis is related to severely impaired renal free water excretion, due mainly to ADH hypersecretion. Other mechanisms involved are impaired renal production of prostaglandin E₂ (a powerful antagonist of the tubular effect of ADH), and reduced sodium and water delivery to the ascending limb of the loop of Henle and the distal convoluted tubule, where urinary dilution occurs. Treatment of dilutional hyponatraemia in cirrhosis with ascites should, therefore, be directed towards reducing total body water. The administration of sodium may produce a transient increase in serum sodium, but at the expense of increasing the

rate of ascites formation. Fluid restriction has been the standard of care in patients with severe hyponatraemia, but is rarely effective in improving serum sodium concentration, although it can be helpful in preventing a further decrease in serum sodium level. The lack of efficacy is probably due to the fact that in clinical practice total daily fluid intake cannot be restricted to less than 1 litre/day. A more recent approach has been the use of highly selective vasopressin V2 antagonists (vaptans) with the aim of improving serum sodium concentration by increasing solute-free water excretion. These drugs produce a rapid and marked increase in urine volume with a reduction in urine osmolality and an increase in serum osmolality and serum sodium concentration. They have consistently been demonstrated to improve control of ascites and serum sodium in the short term, but seem to increase mortality in phase III studies. Diuretics Furosemide and spironolactone are the diuretics most commonly used in the treatment of ascites in cirrhosis. Spironolactone is the preferred drug, because—in contrast to healthy subjects—it is generally more effective than furosemide. Cirrhotic patients with ascites and marked hyperaldosteronism (50% of patients with ascites) do not respond to furosemide, whereas most will respond to spironolactone. Patients with normal or slightly increased plasma aldosterone concentration respond to low doses of spironolactone (100 to 150 mg/day), but as much as 300 to 400 mg/day may be required in those with marked hyperaldosteronism. The goal of treatment is to maintain patients free of ascites with the minimum dose of diuretics. Thus, once the ascites has largely resolved, the dose of diuretic should be reduced to the minimum, or discontinued if possible. The safe upper limit of the rate of weight loss is unclear, but most experts agree that the diuretic dose should be adjusted to achieve a rate of weight loss below an average of 500 g per day in patients without peripheral oedema, or 1 kg per day in those with peripheral oedema. Patients not responding to 400 mg/day of spironolactone and 160 mg/day of furosemide will not respond to higher diuretic doses.

Spironolactone Spironolactone is an aldosterone antagonist, acting mainly on the distal tubules to increase natriuresis and conserve potassium. Natriuretic effect occurs between the third and the fifth day. The main problem with clinical use in men is the development of gynaecomastia, which is often painful. Other side effects of spironolactone include hyponatraemia, impotence, menstrual disturbance (although most ascitic patients are amenorrhoeic), and osteomalacia. Eplerenone is a useful alternative for patients who develop gynaecomastia and other sex-related adverse effects on spironolactone. It binds specifically to mineralocorticoid receptors and less to progesterone and androgen receptors than spironolactone, hence it has a much lower propensity to induce these side effects.

Box 15.22.2.1 Summary of treatment of ascites

- Sodium restriction to 80 to 120 mmol/day
- Diuretic therapy should use spironolactone as the first-line drug
- Water restriction should only be used in severely hyponatraemic patients with caution
- Total paracentesis should initially be carried out on patients with marked ascites
- Shunts (TIPS) may be used in those with refractory ascites in whom recurrent paracentesis is too frequent or poorly tolerated, or in those with a hepatic hydrothorax

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3063 Amiloride Amiloride, a diuretic acting in the collecting duct, is less effective than aldosterone antagonists and should only be used in those patients who do not tolerate spironolactone. Furosemide Furosemide is a loop diuretic generally used as an adjunct to spironolactone treatment. The simultaneous administration of both agents increases their natriuretic effect and reduces the incidence of hypo- or hyperkalaemia that may be observed when these drugs are given alone.

Complications and benefits of diuretic therapy Diuretic therapy generally improves morbidity and well-being, since it leads to resolution or amelioration of ascites, allows a more liberal diet, decreases portal pressure, and increases the opsonic activity of ascitic

fluid, thereby decreasing the risk of SBP. However, diuretic use in cirrhosis often leads to complications (Box 15.22.2.2), particularly in patients requiring high diuretic doses. Approximately 20% develop significant renal impairment, which is usually moderate and reversible after diuretic withdrawal. Hyponatraemia secondary to a decrease in the renal ability to excrete free water also occurs in approximately 20% of these patients. The most severe complication related to diuretic treatment is hepatic encephalopathy, which occurs in approximately 25% of those who are hospitalized with tense ascites and treated with high doses of diuretics.

Therapeutic paracentesis Large-volume paracentesis has been in use for at least 2000 years, and was widely used in the earlier part of the last century. When diuretics first became available in the 1940s, the practice declined, but it was still used as an adjunct to therapy until the early 1960s, when it gradually fell into disrepute with the recognition that repeated paracentesis resulted in salt depletion and oliguria, and became virtually banned as a treatment. However, it re-emerged in the mid 1980s when several controlled clinical studies demonstrated that (1) large-volume paracentesis combined with albumin infusion was more effective and associated with fewer complications (hyponatraemia, renal impairment, and hepatic encephalopathy) than diuretic therapy in patients with grade 3 ascites; (2) it shortened hospital stay; and (3) it was a safe procedure with a very low rate of local complications. Total paracentesis is a rapid, effective, and safe treatment of ascites in cirrhosis and is the treatment of choice for tense ascites. The mobilization of ascites by paracentesis is associated with a deterioration of circulatory function, as manifested by a marked increase in plasma renin activity and aldosterone concentration, in 60 to 70% of patients. This impairment in circulatory function results from accentuation of the arterial vasodilation already present in these patients, but the incidence of this complication is reduced to 30 to 40% if paracentesis is followed by plasma volume expansion with synthetic plasma volume expanders (dextran 70 or polygeline), and to only 18% if it is accompanied by plasma volume expansion with albumin (8 g per litre of ascitic fluid removed).

Practical aspects Paracentesis cannulas should have multiple side perforations to avoid obstruction by omentum. All ascitic fluid should be drained in a single session as rapidly as possible over 1 to 4 h. The old dogma that rapid paracentesis causes marked hypotension is false. There is an immediate fall in right atrial pressure (within 30 min), due to a decrease in intra-abdominal pressure and a decrease in compression of the right atrium. There is a rapid decrease in systemic vascular resistance and increase in cardiac output that peaks at 3 h. Pulmonary capillary wedge pressure remains constant for 6 h (in the absence of colloid), and decreases after this interval in the absence of colloid replacement. Mean arterial pressure decreases by about 8 mmHg. These changes are shown in Fig. 15.22.2.4. The drainage system should never be left in place overnight since this carries a high risk of infection and bleeding complications.

Colloid replacement As commented before, it is very important that colloid replacement is given following large-volume paracentesis to prevent circulatory dysfunction. After total paracentesis, synthetic plasma expanders may be used if the volume of ascites removed is less than 5 litres, but albumin should be used when more than 5 litres is removed. All or most trials have used albumin at a dose of 8 g/litre of ascites.

Box 15.22.2.2 Complications of diuretics in the management of ascites

- Hyponatraemia (20–30%)
- Hyperkalaemia (spironolactone) or hypokalaemia (loop diuretics)
- Hepatic encephalopathy (secondary to electrolyte disturbance)
- Renal impairment
- Hyperuricaemia (30%)
- Gynaecomastia, osteomalacia, and mild metabolic acidosis with spironolactone

Mean arterial pressure (mmHg) Cardiac output (litres/min) Right atrial pressure (mmHg) PCWP (mmHg)

13	12	11	10	9	8	7	6	Time (h)	24	48	11	6	3	2	1	100	90	80														
70	60	Time (h)	0	0.5	24	48	6	3	2	1	0	0.5	24	48	6	3	2	1	0	0.5	10	9	8	7	6	5	Time (h)	10	9	8	7	6

Fig. 15.22.2.4 Haemodynamic changes following acute total paracentesis of

approximately 10 litres of ascites over 1 h. Paracentesis was commenced at time 0 h and sequential changes were monitored by a Swan-Ganz catheter, without albumin replacement. PCWP, pulmonary capillary wedge pressure. Modified from Panos MZ, et al. (1990). Single, total paracentesis for tense ascites: sequential haemodynamic changes and right atrial size. *Hepatology*, 11, 662-7.

section 15 Gastroenterological disorders 3064 removed: there are no data on whether smaller amounts of albumin have differing degrees of efficacy. A recent meta-analysis shows that albumin administration improves survival in patients receiving large-volume paracentesis. Colloids should be given after paracentesis has been completed. Benefits Paracentesis most obviously provides immediate relief from ascites and a tense abdomen, but also a number of other benefits, including (1) relief of respiratory muscles—tense ascites clearly restricts breathing, and increases both the workload of respiration and energy expenditure, with paracentesis providing immediate relief; (2) reduction in resting energy expenditure, which is increased by ascites; and (3) enhanced salt and water excretion—due to acute reduction of renal venous pressure and consequent increase in renal perfusion, also an acute decrease in plasma ADH levels, which are directly related to intrathoracic or intra-abdominal pressure, with both of these perhaps making patients more responsive to diuretic therapy. Contraindications It is generally agreed that there are no contraindications to paracentesis, although studies to date have excluded several subsets of patients, primarily because of inadequate data. In practice, some clinicians have concerns about carrying out paracentesis in patients who have a severe coagulopathy or marked thrombocytopenia in case localized bleeding complications arise, but there are no data to support this view. Patients with severe thrombocytopenia usually receive platelet transfusion before large-volume paracentesis. Intravenous albumin infusion There is clear evidence that the infusion of albumin is beneficial to patients with cirrhosis. It has a useful role in relation to large-volume paracentesis (see 'Therapeutic paracentesis'), prevents hepatorenal syndrome, improves short-term survival in SBP (see SBP 'Prognosis and management' section), and is essential in the treatment of type 1 hepatorenal syndrome together with vasoconstrictors (mainly terlipressin). Some studies have demonstrated that periodic albumin administration improves the response to diuretics in patients with ascites. A recent randomized controlled trial showed that regular albumin administration (40 g every week) prevented renal failure, hyponatraemia, and SBP, decreased the need for repeated large-volume paracentesis and hospital readmissions and improved long-term survival in patients with cirrhosis and ascites. Management of refractory ascites Refractory ascites is defined as ascites that cannot be mobilized, or early recurrence of ascites after paracentesis which cannot be prevented because of lack of response to maximal diuretic therapy and salt restriction (<80-120 mmol salt/day), or when there is inability to reach an effective diuretic dose because of side effects. Assessment of the response of patients with ascites to diuretic therapy and salt restriction should only be made in stable patients without associated complications such as bleeding or infection. Five to ten per cent do not respond adequately. This may be because the diuretics induce an electrolyte disturbance or encephalopathy, necessitating a temporary and recurrent withdrawal of medication, or alternatively the patient may be genuinely resistant. In both these groups, there is invariably significant renal dysfunction when assessed by creatinine clearance or other techniques measuring glomerular filtration rate. The mainstay of treatment for these patients is repeated large-volume paracentesis or insertion of a transjugular intrahepatic portosystemic shunt (TIPS). Shunts Transjugular intrahepatic portosystemic shunts TIPS is the most recent treatment introduced for the management of portal hypertension. It works

as a side-to-side portacaval shunt and is extremely effective in improving circulatory and kidney function, and reducing ascites. TIPS induces a marked increase in cardiac output, a decrease in systemic vascular resistance, an elevation in right atrial pressure and pulmonary wedge pressure, and a significant reduction in the plasma levels of renin, aldosterone, noradrenaline, and ADH, indicating an improvement in effective arterial blood volume. The improvement in circulatory function induces a rapid increase in urinary sodium excretion, which occurs within the first 1 to 2 weeks. Significant increases in serum sodium concentration and glomerular filtration rate are also observed over 1 to 3 months, indicating improved renal perfusion and free water clearance. The improvement in systemic and splanchnic haemodynamics is associated with a complete disappearance of ascites or a partial response (sufficient improvement so that paracentesis is no longer required) in most patients. Only 10% of patients fail to respond to TIPS. Ascites characteristically resolves very slowly (1–3 months), but continuous diuretic treatment at lower doses is required in more than 90% of cases, either for the treatment of ascites or to reduce the peripheral oedema. Hepatic encephalopathy is the most important complication, seen in more than 40% of cirrhotic patients with refractory ascites treated by TIPS. In most instances, it responds to standard therapy. Peritoneovenous shunts (Le Veen shunts or Denver shunts) Peritoneovenous shunting became very popular in the 1970s, with numerous publications on its benefits to renal function and resolution of ascites. However, it soon became apparent that many shunts became blocked or infected and caused scarring of the peritoneum, which can make liver transplantation difficult. This old technique offers no survival advantage over medical therapy, TIPS, or repeated paracentesis and has been abandoned. Prognosis The occurrence of ascites in patients with cirrhosis is associated with a poor prognosis, and patients with ascites may have a much worse prognosis than currently reflected in the Model for End-Stage Liver Disease (MELD) or United Kingdom Model for End-Stage Liver Disease (UKELD) score system, commonly used in organ allocation for liver transplantation. Survival rates are around 50% at 1 to 2 years, but somewhat better in alcoholic patients with ascites who stop drinking. The development of SBP in patients with ascites is associated with a mortality of 75% at 1 year, hence the development of this complication is

15.22.2 Cirrhosis and ascites 3065 associated with an overall poor prognosis and, unless contraindicated, all patients should be considered for liver transplantation. Complications The complications of ascites are shown in Box 15.22.2.3. Spontaneous bacterial peritonitis Diagnosis and epidemiology The diagnosis of SBP is based on clinical suspicion and on ascitic fluid analysis. It is defined as an ascitic fluid PMN count of at least 250 cells/mm³ (independently of the results of the ascitic fluid and blood cultures), with no evident intra-abdominal source of infection. In patients with haemorrhagic ascites, a subtraction of 1 PMN per 250 red blood cells should be made. Ascitic fluid cell count is generally performed manually, although automated cell counts may give comparable results. The measurement of lactic dehydrogenase concentration, glucose levels, and total protein concentration in ascitic fluid is important to establish a differential diagnosis between spontaneous and secondary peritonitis. A secondary peritonitis must be suspected when at least two of the following features are present in ascitic fluid: glucose levels less than 50 mg/dl, protein concentration greater than 10 g/litre, or lactic dehydrogenase concentration greater than normal serum levels. Gram's stain is frequently negative in SBP but may identify patients with ascites and gut perforation (polymicrobial). Patients with gut perforation also present with high levels of amylase and bilirubin in ascitic fluid. Prompt CT scanning and surgical intervention are required in patients with secondary peritonitis. Culture of ascitic fluid directly into blood culture bottles

(aerobic and anaerobic media) at the bedside is positive in 40 to 60% of cases of SBP. Moreover, blood cultures are positive in many patients. The most common organisms isolated are shown in Table 15.22.2.4. About 11% of patients presenting with ascites will develop SBP within 1 year, and 15% within 3 years. For patients admitted to hospital with ascites, with or without other complications (e.g. bleeding), the incidence of SBP on admission is about 10%. Pathogenesis The pathogenesis of SBP is shown in Fig. 15.22.2.5. Most organisms causing this infection are Gram-negative bacteria of enteric origin, and colonization of ascitic fluid is presumed to occur following an episode of bacteraemia. Two major alterations are involved in the development of SBP: intestinal bacterial overgrowth and translocation of bacteria from the intestinal lumen to the systemic circulation. Patients with advanced cirrhosis also have alterations in the innate immune system that facilitate bacterial translocation, prolong bacteraemia, and decrease their capacity to eliminate bacteria from the blood and ascitic fluid. Risk factors The risk factors for the development of SBP are summarized in Box 15.22.2.4. Decreased opsonic activity Patients with a low protein content (<10–15 g/litre) have an increased risk of developing SBP compared to those with a high ascitic protein content. Consequently, patients with cirrhotic and nephrotic ascites are prone to infection, whereas those with malignant ascites or cardiac ascites are not. For those cirrhotic patients with an ascitic protein level less than 10 g/litre, the risk is 24% within 3 years, increasing to 60% at 1 year in patients with poor liver and/or renal function. When bacteria enter ascitic fluid they may be lysed by the activity of complement or coated with opsonins. Complement deficiency also predisposes to infection. The opsonic activity of ascitic fluid correlates with the total protein, as well as that of CH₅₀ (total haemolytic complement), C3, and C4 concentration. These concentrations may be increased by diuretics, thus decreasing the risk of SBP. Recent instrumentation A high degree of instrumentation increases the risk of secondary bacteraemia and potentially of SBP, but the risk is not increased by large-volume paracentesis. Upper gastrointestinal haemorrhage Upper gastrointestinal haemorrhage increases the risk of SBP and other infections during or immediately after the bleeding episode (first 5–7 days), with an incidence ranging between 16% (compensated cirrhosis) and 66% (advanced cirrhosis). Bacterial infections

Box 15.22.2.3 Complications of ascites • SBP • Hepatorenal syndrome • Pleural effusion • Respiratory difficulties • Paraumbilical hernia • Hypercatabolic state

Table 15.22.2.4 Organisms causing spontaneous bacterial peritonitis

Enteric organisms (75–80%) *Escherichia coli* (55%) *Klebsiella* spp. (15%) *Enterobacter* spp. (4%) *Enterococcus faecalis* (6%) Anaerobes (<1%)

Nonenteric organisms (20–25%) Gram-positive cocci: *Streptococcus pneumoniae* (10%) Other *Streptococcus* spp. (5–10%) *Staphylococcus* spp. (2–4%) Others (2%)

Box 15.22.2.4 Risk factors for SBP • Upper gastrointestinal haemorrhage • Previous SBP • Low protein ascites (<10–15 g/litre: decreased opsonic activity) • Instrumentation

section 15 Gastroenterological disorders 3066 in this setting increase the probability of failure to control bleeding, rebleeding, and hospital mortality. Antibiotic prophylaxis reduces the mean incidence of in-hospital infections, including SBP, rebleeding and improves survival. Previous SBP The recurrence rate for SBP is 47% at 6 months and 69% at 1 year. Patients recovering from a previous episode of SBP should receive antibiotic prophylaxis (norfloxacin 400 mg/day or ciprofloxacin 500 mg/day). Clinical features The clinical presentation of SBP depends on the stage at which the infection is diagnosed. Most patients present signs or symptoms clearly suggestive of peritoneal infection, although SBP may be asymptomatic, especially in the initial stages. Abdominal pain and fever are the most characteristic symptoms (Box 15.22.2.5). Other signs and symptoms are vomiting, ileus, diarrhoea, hepatic encephalopathy, gastrointestinal bleeding, renal

impairment, septic shock, and hypothermia. Early diagnosis of SBP relies on the performance of diagnostic paracentesis at hospital admission in all cirrhotic patients with ascites and in hospitalized patients with ascites whenever they deteriorate. Prognosis and management The mortality associated with SBP is now about 10%. Adequate anti-biotics must be started as soon as a presumptive diagnosis is made following diagnostic paracentesis. For patients with bacterascites but no rise in the neutrophil count, the ascitic tap should be repeated. The treatment of SBP is summarized in Box 15.22.2.6. Empirical antibiotic schedules must be adapted to the site of acquisition of infection and to the local epidemiological pattern of antibiotic resistance given the higher rate of infections caused by multidrug-resistant bacteria in nosocomial infections (e.g. β -lactams in community-acquired infections and carbapenems $\pm$ glycopeptide in nosocomial infections). Treatment is continued until complete resolution of all signs of infection and the ascitic neutrophil count decreases to within the normal range, which is generally achieved within a week. The administration of albumin at a dose of 1.5 g/kg at the time of diagnosis and 1 g/kg on day 3 decreases the incidence of renal dysfunction and decreases mortality from 29 to 10%. Prevention Antibiotic prophylaxis in cirrhosis must be restricted to selected patients at a very high risk of SBP in order to prevent the development ENTERIC BACTERIA BACTERIAL TRANSLOCATION TO MLN SBP BACTERAEMIA PORTAL VEIN Intestinal bacterial overgrowth Increased gut permeability RES dysfunction Portosystemic shunts Alterations in mucocutaneous barriers Decreased systemic clearance capacity Alterations in antimicrobial activity in ascites COLONIZATION OF ASCITIC FLUID NON-ENTERIC BACTERIA Fig. 15.22.2.5 Pathogenesis of SBP. Enterobacteria translocate from the intestinal lumen to the systemic circulation through the mesenteric lymph nodes (MLN). Bacteria reach ascites after sustained bacteraemia. If local host defence is poor, bacteria colonize ascitic fluid and cause SBP. RES, reticuloendothelial system. Box 15.22.2.5 Symptoms of SBP • Asymptomatic: 10% • Abdominal pain: 70% • Abdominal tenderness: 10% • Fever: 50% • Encephalopathy: 10% • Shock: <5% Box 15.22.2.6 Management of SBP 1 Diagnosis of SBP on ascitic fluid cell count (≥ 250 PMNs/mm³) 2 Initiate appropriate intravenous antibiotics tailored according to the local epidemiological pattern of antibiotic resistance 3 Infuse albumin at 1.5 g/kg at diagnosis and 1 g/kg on day 3 4 Treat with antibiotics until 1 to 2 days after confirming resolution (repeated paracentesis) 5 Commence prophylaxis against future SBP (norfloxacin 400 mg/day or ciprofloxacin 500 mg/day) 6 Consider liver transplantation as 1-year mortality is 75%

15.22.2 Cirrhosis and ascites 3067 of antibiotic resistance. Current indications of antibiotic prophylaxis are (1) upper gastrointestinal bleeding, (2) previous episode of SBP, and (3) low protein ascites (<15 g/litre) and advanced cirrhosis (poor liver and/or renal function). Hepatorenal syndrome Hepatorenal syndrome is the development of functional acute kidney injury in patients with advanced cirrhosis in the absence of any pathological cause of renal failure. It is due to a reduction of renal blood flow in the setting of a marked activation of the RAAS and the SNS. Systemic inflammation is also a major factor involved in pathogenesis. See Chapter 21.5 for further discussion. Pleural effusion Pleural effusions (hepatic hydrothorax) develop in about 5% of patients with cirrhosis. Fluid tracks up into the pleural cavity via defects in the diaphragm (e.g. holes or blebs), which occasionally close spontaneously. Hepatic hydrothorax may develop in patients with no discernible ascites. The pleural effusions are right-sided in 85% of cases and bilateral in 2% of cases. Management is as for conventional ascites unless it is unresponsive and causing severe dyspnoea, in which case a TIPS could be inserted. Respiratory difficulties Increasing abdominal distension due to the accumulation of peritoneal fluid increases the effort required for breathing. Occasionally this may precipitate extreme difficulty in breathing that should be treated by rapid large-volume paracentesis. Paraumbilical hernia Paraumbilical hernias develop in about 20% of

patients with ascites, an incidence that increases up to 70% in those with long-standing recurrent tense ascites. The main risks are rupture and strangulation, complications that require emergency surgery.

Hypercatabolic state Many patients with ascites present in a hypercatabolic state, which may be secondary to chronic systemic inflammation probably related to translocation of bacterial products from the intestinal lumen to the systemic circulation, together with their general state of malnutrition.

Other issues

Drug prescribing When prescribing a drug for any patient with liver disease it is always sensible for the physician to check the product literature or some source such as the British National Formulary, but in patients with ascites, the following are worthy of particular comment:

- Nonsteroidal anti-inflammatory drugs are contraindicated in cirrhosis because of the high risk of developing renal failure.
- Drugs that can cause a reduction in arterial pressure or decrease renal blood flow (e.g. angiotensin-converting enzyme inhibitors, and angiotensin II and $\alpha 1$ -adrenergic receptor blockers) should be avoided in patients with cirrhosis and ascites because of an increased risk of renal impairment.
- Aminoglycosides are associated with an increased risk of nephrotoxicity and renal failure, hence their use should be reserved for patients with bacterial infections that cannot be treated with less toxic antibiotics.
- Contrast media for radiological investigations should be used with care, particularly if the patient has significant renal impairment (beware the patient whose serum creatinine is 'not too bad' as a consequence of low muscle mass or body mass index). However, the only study assessing renal function after the administration of contrast media showed a very low incidence of nephrotoxicity.
- Nonselective β -blockers should be used with caution in the setting of refractory ascites and in any patient with a systolic blood pressure less than 90 mmHg, hyponatraemia (<130 mEq/L), or acute kidney injury.

Fertility Women with cirrhosis and ascites rarely, if ever, become pregnant, since ovulation has usually ceased before the onset of ascites.

Areas of controversy and for further research The roles of inflammation, oxidative stress, and immune paralysis in the development of decompensation and acute-on-chronic liver failure in cirrhosis should be clarified in the near future. The mechanisms of organ failure also require investigation. New indications for albumin administration should be investigated (i.e. non-SBP infections and advanced cirrhosis, and long-term albumin administration in patients with ascites). Current areas of controversy are mainly focused on safety issues of two treatments: nonselective β -blockers in patients with ascites (there are contradictory data regarding their impact on mortality) and automated low-flow pumps in refractory ascites (preliminary reports suggest an increased morbidity associated with this device).

Regarding SBP and antibiotic therapy, in the near future we will probably face a spread in antibiotic resistance in the cirrhotic population. Research on new antibiotics, early markers of bacterial translocation and infection, and microbiological techniques is required.

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