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Management of Ascites

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Abstract

The development of ascites indicates a pathological imbalance between the production and resorption of intraperitoneal fluid. The appearance and composition of ascites are variable, based on the underlying pathophysiology. Most commonly, ascites develops in the setting of decompensated cirrhosis, peritoneal infection, carcinomatosis, congestive heart failure or a combination (mixed ascites). The diagnosis can be difficult in some patients. Management options for ascites from decompensated liver disease focus on

low-sodium diets and diuretics supplemented by large-volume paracentesis, transvenous intrahepatic portosystemic shunts and liver transplantation. The development of refractory ascites, hepatic hydrothorax, hyponatraemia or hepatorenal syndrome presents unique challenges to the provider and the patient. In some of these patients, therapy with liver transplantation will be the only viable therapeutic option. The diagnosis of infectious ascites, such as tuberculosis, and carcinomatous ascites remain diagnostic and therapeutic challenges for the clinician.

Physiologically, the peritoneal space is a normally collapsed, well lubricated potential space that contains between 50–75 mL of serous fluid between the visceral and parietal peritoneum. Ascites is defined as the pathological accumulation of fluid within the peritoneal space.

Ascites is clinically apparent when the patient presents either symptomatically with abdominal distension, thus leading to further testing, or asymptomatically when radiological imaging shows unexpected peritoneal fluid accumulation. Serous ascites should be distinguished from intraperitoneal collections of blood, urine, chyle, pancreatic secretions or bile. There are no large, controlled, population-based studies that provide exact information regarding the prevalence, incidence and specific causality of ascites in the general population. It is generally assumed that most patients in North America with ascites have underlying cirrhosis (75%), followed by malignancy (10%), cardiac failure (3%) and tuberculosis (2%), with miscellaneous causes accounting for 10% of cases. Patients may present with a combination of causes for ascites ('mixed ascites').[1] The distribution of causes may be different in countries where tuberculosis is more prevalent.

General abdominal physical examination typically detects ascites when at least 1500 mL of peritoneal fluid is present.[2] Percussion dullness for a horseshoe distribution of fluid or the puddle sign can detect as little as 120 mL of fluid.[3,4] Auscultatory percussion has an increased sensitivity for the presence of ascites, but with a lower specificity than the puddle sign.[4] The precision and accuracy of these signs have been reviewed elsewhere.[5]

Trans-abdominal ultrasonography is the gold standard to establish the diagnosis of ascites and is more sensitive than abdominal CT. Furthermore, sonography can provide an estimated measurement of the ascitic volume.[6]

With the advent of endoscopic ultrasound (EUS) in the staging of upper gastrointestinal (GI) malignancies, the concept of 'low-volume ascites' (LVA) has been introduced.[7] LVA is defined as ascites that is undetectable by CT or MRI but can be identified by EUS.[7] EUS has shown that, while the presence of LVA is unlikely in most upper GI cancers (5.4–15%), when ascites is present, it indicates that the cancer is incurable in 76% of cases.[8]

Other clinical studies can also assist in the assessment of ascites aetiology. Retrospective studies have shown that diagnostic laparoscopy has a role in the work up of undefined ascites where tuberculosis is suspected even in the absence of known extra-abdominal tuberculosis.[9] The introduction of the concept of the serum-ascites albumin gradient (SAAG) has also resulted in better characterization of ascites than the traditional exudate or transudate concept.[1] Ascites can also contribute to the development of intra-abdominal hypertension and abdominal compartment syndrome.[10,11] The normal intra-abdominal pressure is <7 mmHg. Increases above 12 mmHg are defined as intra-abdominal hypertension. The development of abdominal compartment syndrome occurs when the pressure rises above 20 mmHg and organ dysfunction can be attributed to it.[11,12]

This article discusses the current understanding of the pathophysiology for each major cause of ascites, focuses on the established treatment of ascites and comments on newer management approaches.

1. Clinical Evaluation

Upon presentation, an initial and thorough history and physical examination is the most important step to establish the differential diagnosis of ascites aetiology (figure 1). Physical findings can include bulging flanks with dullness, a fluid wave or shifting dullness. In all instances, the work up of ascites should include a diagnostic paracentesis to provide a fast and cost-effective test that may determine the cause.[13] Pre-paracentesis laboratory studies or correction of coagulopathy are in most cases not required except in disseminated intravascular coagulation (DIC).[14] The prophylactic administration of frozen plasma or platelets is usually not recommended in patients with no inherited coagulation disorder.[13] Abdominal sonography has an important role in as far as it evaluates the liver for the development of hepatocellular carcinoma and assesses patency of portal and hepatic venous system.

The right or left lower quadrant laterally or the midline of the abdomen midway between the pubis and umbilicus are the best sites for paracentesis as large vessels can be avoided at those sites. Some suggest that a Z technique should be utilized by pulling the skin inferiorly as the needle is introduced in an effort to reduce leakage through the needle site following paracentesis. Paracentesis is generally safe, even in those with coagulopathy from cirrhosis.[13] Fluid should be examined for white blood cell and red blood cell count, total protein, albumin and bacterial culture. Based on pre-test probability, we would add glucose, lactate dehydrogenase, bilirubin, triglyceride, cytology and a tuberculosis smear to the fluid analysis.

The diagnosis of spontaneous bacterial peritonitis (SBP) is based on a polymorphonuclear leukocyte (PMN) count ≥250/mm^3.[15] The role of ascitic fluid lactoferrin for the diagnosis of SBP is emerging as a potential rapid bedside test. When

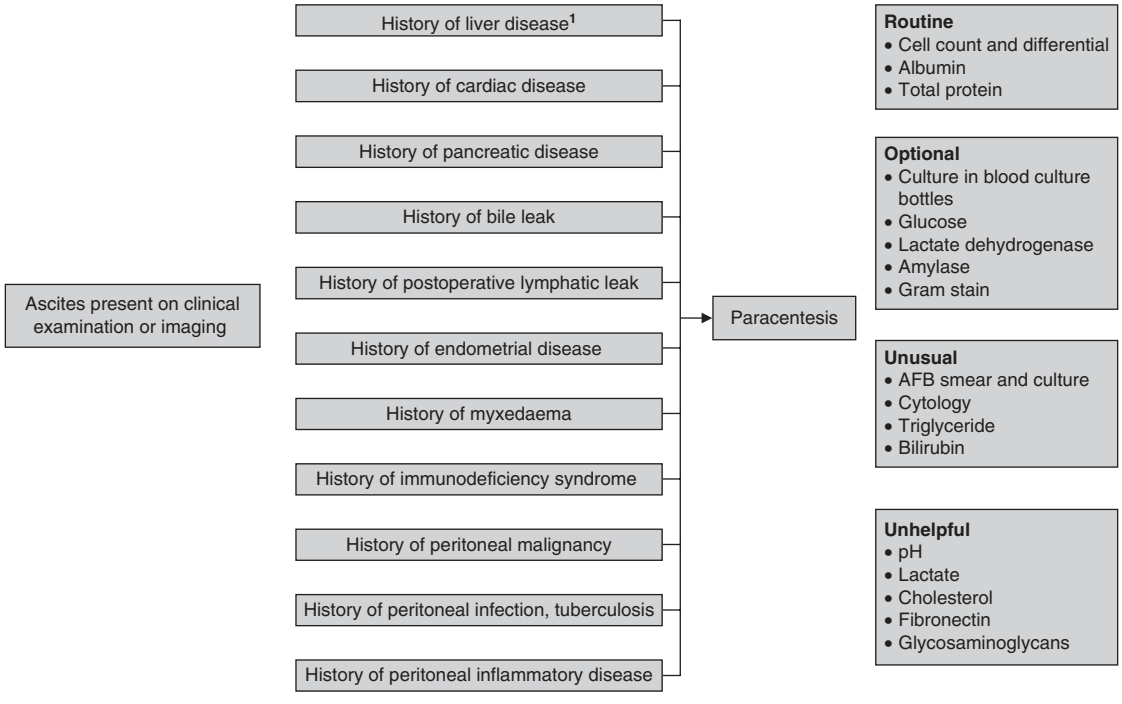

Fig. 1. Algorithm for clinical evaluation of patients with ascites. **1** indicates cirrhosis, alcoholic hepatitis, acute liver failure, Budd-Chiari syndrome. **AFB** = acid-fast bacillus.

a cut-off level of 242 ng/mL for ascitic fluid lactoferrin level was applied, the sensitivity and specificity of the assay for diagnosis of SBP were 95.5% and 97%, respectively.[16] The sensitivity of reagent strips for the diagnosis of SBP was previously documented as between 83–100% and has been reviewed elsewhere.[17]

While the presence of red blood cells in ascites can indicate a traumatic tap during needle insertion, it can also be associated with hepatocellular carcinoma or tuberculous peritonitis. Ascitic fluid assumes a bloody appearance when the haematocrit is >0.5%.[18]

Massive haemoperitoneum can yield haematocrit values of 40% or higher.[18] The distinction between a traumatic tap and spontaneous haematoperitoneum is based on the results of an immediate second paracentesis stick at a different location. If the fluid is clear, then the first tap was traumatic.[18]

We recommend that aerobic and anaerobic blood culture bottles be immediately inoculated at the bedside to assist in the culturing of the ascitic fluid. In addition, as up to 50% of those with SBP will have bacteraemia, a blood culture should also be obtained when SBP is suspected. Anaerobic bacterial peritonitis is infrequent and most infectious agents will be aerobic or microaerophilic. The concurrent measurement of serum albumin levels at the time of ascites albumin measurement is needed to assess the SAAG, which is determined by subtracting the ascites albumin value from the serum albumin level. If the gradient is >1.1 g/dL, it suggests that portal hypertension is the aetiology of the ascites.[13]

2. Aetiology, Pathophysiology and Management

2.1 Ascites due to Portal Hypertension

Fluid accumulation occurs in about 50% of patients within 10 years of the diagnosis of cirrhosis.[19] The prognosis for patients with newly established ascites is a 1- and 5-year survival of 85% and 56%, respectively.[20] After development of ascites, 50% of patients will survive for 2–5 years.[21,22]

In cirrhotic patients, sinusoidal portal hypertension leads to peripheral arterial vasodilation and hence to a reduction of systemic vascular resistance, which occurs predominantly in the splanchnic circulation.[23] This vasodilator mechanism involves nitric oxide at its core[24-27] and may be driven by the presence of fragments of bacterial DNA in the blood of patients with advanced cirrhosis, which results in the production of nitric oxide and other cytokines (interleukin [IL]-2 and IL-12, tumour necrosis factor [TNF]-α, and interferon [IFN]-γ) by peritoneal macrophages.[28-30]

Increased transudation of fluid and proteins into the space of Disse follows. When the accumulation of interstitial fluid within the space of Disse and abdominal lymphatics exceeds the capacity of the abdominal lymphatics to remove excess lymph, ascites will develop. Transudation of fluid into the space of Disse is further enhanced by the presence of a low serum albumin. For every increase of 1 mmHg portal pressure within the sinusoid, there is a 60% increase in hepatic lymph volume production.[31-33]

In addition to splanchnic vasodilation, systemic vascular under-filling with activation of the sodium-retaining axis occurs (due to activation of the renin-angiotensin-aldosterone system, sympathetic nervous system and the release of antidiuretic hormone).[23] Sodium retention by the kidney also contributes to the formation of ascites, and the control of sodium intake with a low sodium diet and of sodium retention by administration of diuretics are important first steps in the management of the cirrhotic patient with ascites. Sodium retention by the kidney typically begins before the development of clinical ascites and is in part a consequence of activation of the renin-angiotensin-aldosterone system, which enhances tubular reabsorption of sodium. The avoidance of sodium-retaining medications such as NSAIDS by the patient cannot be overemphasized as this is a common, clinically occult reason why ascitic patients present with 'refractory' ascites. A detailed review of the pathophysiology of ascites is available in other publications.[23]

Recent evidence emerged from studies in Wistar rats to suggest that enhanced endothelial permeability is restricted to the hepatic and

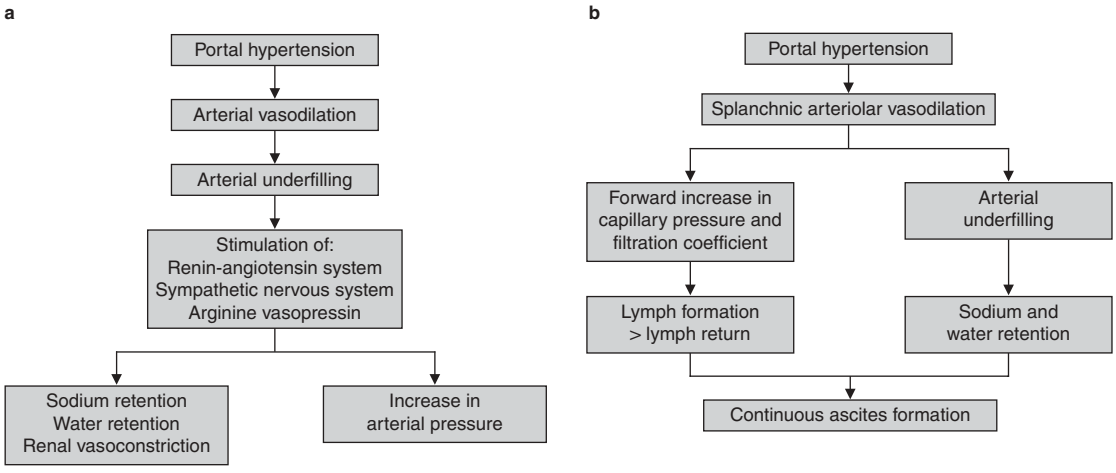

Fig. 2. Pathogenesis of ascites in patients with cirrhosis: (**a**) peripheral arterial vasodilation hypothesis and (**b**) forward theory of ascites formation (reproduced from Arroyo and Colmenero,[35] with permission from Elsevier).

mesenteric vascular beds in cirrhotic rats with ascites when using the Evan's Blue technique to measure capillary permeability to albumin.[34] Vascular endothelial growth factor (VEGF)-A and angiopoietin-2 are key factors in the signalling pathways regulating this dysfunction.[34] These factors may further increase the likelihood of transudation of fluid from the intravascular compartment into the space of Disse of patients with cirrhosis (figure 2).

The treatment of the patient with ascites is based on the findings obtained by diagnostic paracentesis, restriction of dietary sodium intake, the avoidance of sodium retaining factors (e.g. NSAIDs),[36] and natriuresis using single or multiple diuretics with the use of large-volume paracentesis or transvenous intrahepatic portosystemic shunts (TIPS) for those with refractory ascites. Most patients with ascites will respond to a sequential programme of reduced dietary sodium intake with the addition of diuretics in a stepwise fashion (figure 3).

Spironolactone is typically administered first followed by the addition of furosemide if diuresis does not occur. Some clinicians advocate the synergistic role of concurrent diuretic administration.[37] The implementation of a low-sodium diet of 80 mEq (2000 mg) per day calls for an initial consultation with a dietician and close follow-up in the persistently ascitic patient to ensure dietary compliance. A low-sodium diet alone typically leads to ascites clearance in <10% of patients.

Spironolactone is a distal tubular diuretic acting as an aldosterone antagonist. Other distal tubular diuretics that can be utilized include amiloride and triamterene in the setting of spironolactone intolerance. Spironolactone and its metabolites have a long half-life and the peak effect may not be reached until 3–7 days after initial administration. The starting dose of spironolactone is 100 mg/day and can be increased to 200 mg/day if weight loss of 0.5 kg/day does not ensue by the third day of therapy. Because spironolactone can cause hyperkalaemia, it may be necessary to limit oral dietary potassium intake. Furosemide is a loop diuretic that is readily absorbed and has a short half-life. It is effective in inducing diuresis and sodium loss in the majority of patients with ascites. Excessive sodium resorption in the proximal tubule can prevent generation of an adequate sodium concentrating loop of Henle and reduce furosemide effectiveness. After an initial low-sodium diet and administration of spironolactone, the addition of furosemide 40 mg/day is indicated and can be further increased in a stepwise fashion up to 160 mg/day if weight loss of 0.5 mg/day does

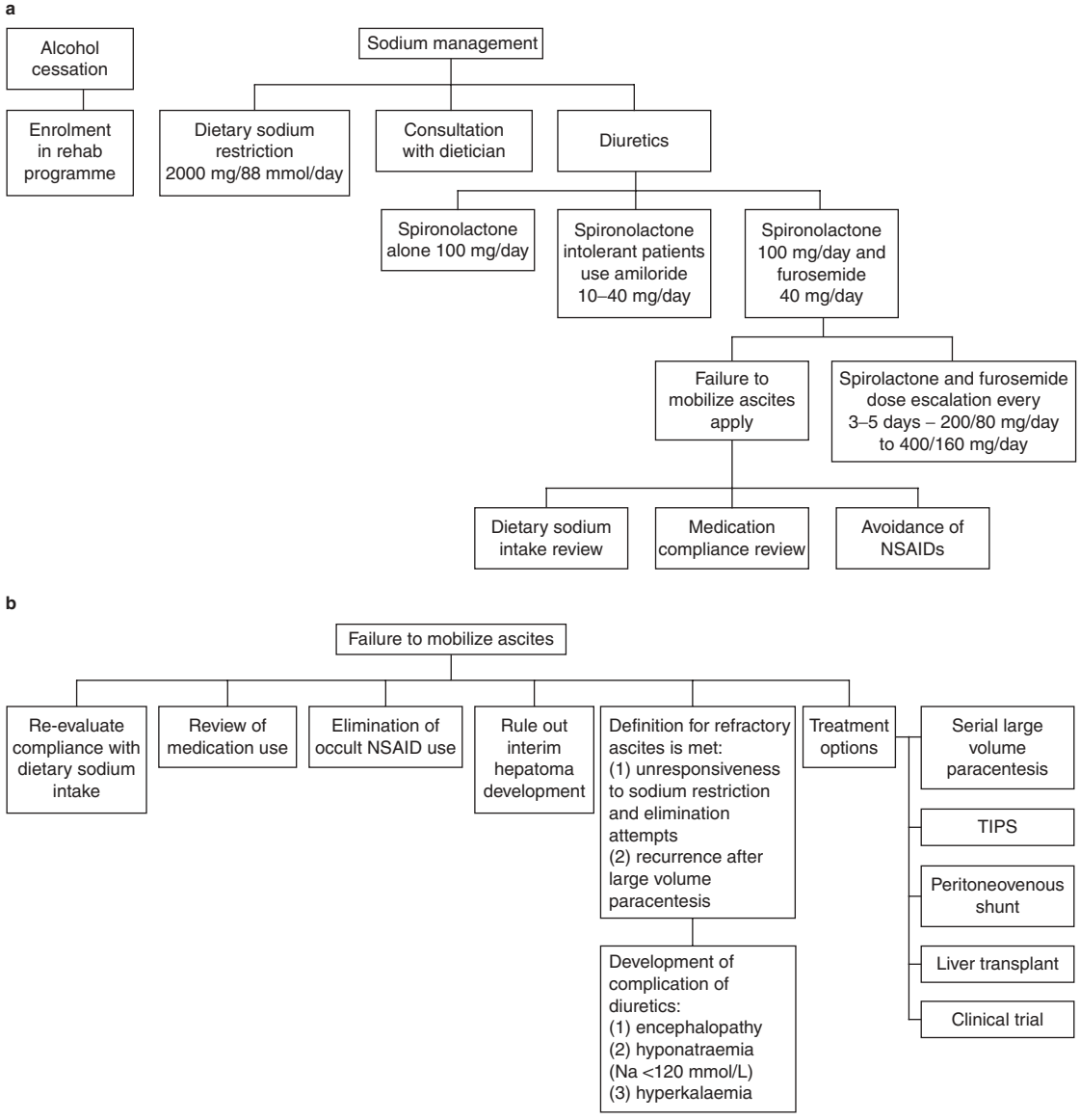

Fig. 3. Algorithm for treatment of patients with ascites due to portal hypertension: (**a**) initial steps and (**b**) follow up steps. **TIPS** = transjugular intrahepatic portosystemic shunt.

not ensue. We limit the maximum combination dose to spironolactone 400 mg/day and furosemide 160 mg/day. Serum creatinine, blood urea nitrogen and sodium/potassium determinations should be periodically assessed. Urinary sodium excretion predicts response to diuretics and is useful in the timely diagnosis of refractory ascites. The measurement of 24-hour urinary sodium provides one tool to assess for diuretic compliance and efficacy. A patient on a 2 g sodium diet (88 mmol/day) who excretes >78 mmol sodium (and has 10 mmol skin losses)

will go into negative sodium balance and mobilize ascites.

A random spot urine sodium concentration/spot urine potassium (Na_{urine}/K_{urine}) ratio that is >1 correlates with a 24-hour sodium excretion >78 mmol/day.[13] This correlation was confirmed by Pinto-Marques when, in patients with a confirmed 24-hour urine sodium excretion >78 mmol, a Na_{urine}/K_{urine} ratio of >1 showed a positive predictive value of 0.82.[38] The Na_{urine}/K_{urine} ratio thus provides a less cumbersome, cheaper and faster tool to assess diuretic response than the 24-hour collection of urine sodium.

Renal dysfunction may develop as a consequence of diuretic therapy. Discontinuation of diuretics should be considered when the creatinine concentration is >2 mg/dL. Other complications of diuretics can include hepatic encephalopathy from diuretic-induced hypokalaemia and alkalosis, or from increased ammonium production in the kidney. Breast tenderness and gynaecomastia may result from spironolactone therapy because it inhibits testosterone formation and enhances conversion of testosterone to estradiol.[39] The development of gynaecomastia would call for dose reduction or switching to amiloride. Eplerenone is a new aldosterone antagonist that is used in the management of heart failure and is not associated with an increased incidence of gynaecomastia when compared with placebo.[40] In a case series from Greece, four patients with decompensated hepatitis B virus (HBV)-induced cirrhosis were switched from spironolactone 100 mg to eplerenone 50 mg twice daily with a resultant decrease in breast size. However, detailed data on the effectiveness of ascites control using eplerenone were not provided by the authors.[41]

Tamoxifen has been evaluated in two studies for the treatment of painful gynaecomastia due to various causes. When given orally at a dosage of 10 mg twice daily for 1 month[42] or 2–4 months, symptomatic relief was reported.[43]

The development of lower extremity cramps (systremma) while taking diuretics can be related to hypokalaemia, hypomagnesaemia or volume contraction. Volume contraction appears to be a mechanism that is common to all classes of diuretics. Hypocalcaemia is a possible cause during therapy with loop-diuretics such as furosemide. Interestingly, potassium-sparing diuretics, such as amiloride, are also associated with cramping. Management of diuretic-associated leg cramps should involve correction of electrolyte abnormalities in the first instance. The efficacy of quinine for the treatment of nocturnal leg cramps has been reviewed.[44] Caution needs to be applied because of the issue of quinine toxicity, especially as the combination of quinine and diuretics could result in a prolongation of the QT interval. Supplementation with vitamin B complex capsules (fursulthiamine 50 mg, hydroxocobalamin 250 μg, pyridoxal phosphate 30 mg and riboflavin 5 mg) has been advocated for the treatment of leg cramps.[45] The use of diphenhydramine (sedative effect), verapamil (hypotension) and NSAIDs (sodium retention) can not be advocated in the cirrhotic patient population. The efficacy of tocopherol (vitamin E) has been studied in the haemodialysis population.[46] Painful muscle cramps in cirrhotic patients have been attributed to low vitamin E levels and responded to supplementation.[47,48] The use of gabapentin in dosages of 600–1200 mg/day has been studied in an open-label trial of patients with leg cramps[49] (see table I).

Hyponatraemia from water retention by the kidney may occur as a consequence of impaired free water clearance. A reduction of oral fluid intake may improve serum sodium levels and should be considered when the serum sodium level is <125 mEq/L. Because hyponatraemia typically develops slowly in those with ascites and end-stage liver disease, complications from hyponatraemia are uncommon, although it can increase the risk of hepatic encephalopathy. Rapid correction of serum sodium levels should be avoided as this can lead to an osmotic demyelination syndrome (central pontine myelinolysis).[51,52] The use of hypertonic saline is discouraged in patients with hyponatremia.

The introduction of aquaretic drugs will potentially add to options in the treatment of hyponatraemia and ascites. Vasopressin receptor antagonists for the vasopressin V_{1a}, V_{1b} and V_2 receptors are available. The V_2 receptors regulate the antidiuretic response, the V_{1a} receptors result

Table I. Recommendations for use of diuretics including dosage summary and cost

Drug	Dosage and formulation (mg)	Name	Cost (no. C/T) [$US][a]	Initial dose (mg)	Higher dose (mg)	Highest dose (mg)
Spironolactone alone[b]	25 T	Aldactone®	35.69 (30)	100	200	400
		Generic	15.99 (30)			
	50 T	Aldactone®	54.59 (30)			
		Generic	21.99 (30)			
	100 T	Aldactone®	83.99 (30)			
		Generic	35.99 (30)			
Furosemide[c]	20 T	Lasix®	22.46 (30)	40	80	160
		Generic	13.99 (100)			
	40 T	Lasix®	26.01 (30)			
		Generic	13.99 (100)			
	80 T	Lasix®	33.10 (30)			
		Generic	12.99 (30)			
Amiloride hydrochloride[b]	5 T		50.45 (30)	10	20	40
		Midamor®	25.99 (30)			
Triamterene[d]	50 C	Dyrenium®	44.09 (30)			
	100 C		67.24 (30)			
Metolazone[e]	2.5 T	Generic	42.99 (30)	1	25	150
		Zaroxolyn®	77.80 (30)			
	5 T	Generic	37.37 (30)			
		Zaroxolyn®	83.36 (30)			
	10 T	Generic	40.99 (30)			
		Zaroxolyn®	76.17 (30)			
Hydrochlorothiazide[d]	12.5 C	Microzide®	30.99 (30)			
		Generic	14.99 (30)			
	25 T	Microzide®	12.99 (100)			
	50 T	Microzide®	15.99 (100)			

a Costs from Drugstore.com (accessed 12 July 2009).

b Initial, higher and highest dose as per AASLD guidelines.

c Dosage for furosemide in combination with spironolactone.

d No dose recommendations stated in AASLD guidelines.

e No dose recommendations stated in AASLD guidelines; data on dosage of metolazone were reported in Hillenbrand and Sherlock.[50]

AASLD = American Association for the Study of Liver Disease; **C** = capsule; **T** = tablet.

in vasoconstriction and the V_{1b} receptor mediates adrenocorticotropin release. Vasopressin receptor antagonists (vaptans) that are in development for the management of hyponatraemia include tolvaptan, satavaptan, lixivaptan, mozavaptan and M-0002, all of which are selective for the V_2 receptor. Conivaptan antagonizes both V_2 and V_{1a} receptors, and is the only drug approved in the US for the management of hospitalized hyponatraemic patients. The vaptans continue to be extensively evaluated for hyponatraemia in heart failure patients.[53,54] None of these drugs are currently approved for aquaresis in cirrhotic patients, although the study by Schrier et al.[55] established that tolvaptan can be given safely in the outpatient setting to patients with hyponatraemia due to various causes. In cirrhotic patients, three trials have been reported using vaptans.[56-58] Lixivaptan resulted in normalization of serum sodium concentration in 27%

and 50% of patients in the 100 and 200 mg/day groups, respectively.[57] Satavaptan improved control of ascites and increased serum sodium levels in patients with cirrhosis, ascites and hyponatraemia.[58] The reader is referred to reviews on the management of hyponatraemia and the therapeutic role of vaptans.[59,60]

For those patients who do not respond to diuretic management (diuretic-resistant ascites), large-volume therapeutic paracentesis of ascites is generally safe.[61,62]

Azotaemia can result from large-volume paracentesis and the simultaneous administration of 25% albumin for volume expansion may reduce the intravascular effects of paracentesis. Paracentesis without albumin administration is associated with a significant increase in blood urea nitrogen, a marked elevation in plasma renin activity and plasma aldosterone level, and a significant reduction in serum sodium concentration.[62]

Post-paracentesis circulatory dysfunction (PCD) is defined as an increase in plasma renin activity on the sixth day after paracentesis of >50% of the pretreatment value and occurred more frequently in patients treated with dextran 70 or polygeline than in those receiving albumin.[63] Recently, two studies reported on the use of the α-adrenoceptor agonist midodrine to prevent PCD after large-volume paracentesis.[64,65]

If renal insufficiency is present, the removal of 2 L or more of ascites should lead to consideration of intravenous albumin administration. When ≥5 L are removed or the patient has established renal insufficiency, for example type II hepatorenal syndrome (HRS) or a serum creatinine level >1.5 mg/dL, the replacement of 8 g of albumin for every litre of ascitic fluid removed is indicated. It has also been suggested that administration of noradrenalin (norepinephrine) following large-volume paracentesis may be as effective as albumin in preventing circulatory dysfunction. The American Association for the Study of Liver Disease (AASLD) practice guidelines from 2004 state that post-paracentesis albumin infusion may not be necessary for a single paracentesis of <4–5 L.[13] For large-volume paracentesis, an albumin infusion of 8–10 g/L of fluid removed can be considered.[13]

2.2 Ascites due to Cardiac Disease

Ascites with congestive hepatopathy can occur in advanced right heart failure from various causes such as constrictive pericarditis, mitral stenosis, tricuspid regurgitation, cor pulmonale and cardiomyopathy. Clinical signs seen in right heart failure include right ventricular heave, S3, tricuspid valve murmur, jugular venous distention, a Kussmaul sign and oedema to the point of anasarca. Oedema of the hepatic, renal and intestinal organs may result in impaired organ function, including the reduction of oral absorption of drugs. Increased renin secretion with congestive heart failure leads to increased vasoconstriction and sodium retention augmented by increased adrenergic activity and low cardiac output activity. Atrial natriuretic peptide (ANP) secretion may also be increased 2- to 10-fold, while the end-organ responsiveness to ANP is diminished. The ascites total protein content in patients with cardiac-related ascites is usually >2.5 g/dL and the SAAG is >1.1 g/dL.[66] Management of congestive hepatopathy has to focus on the underlying heart condition.

2.3 Ascites due to Pancreatic Disease

The incidence of pancreatic ascites is low and data from randomized controlled trials are not available for the best therapeutic approach.[67] Treatment focuses on conservative and interventional approaches. Pancreatic ascites is often due to pancreatic duct disruption either in the presence or absence of a pancreatic pseudocyst.[68] Pancreatic duct disruption is usually anterior, thus resulting in direct accumulation of pancreatic secretions in the peritoneal space. Pancreatic ascites can develop in the setting of pancreatic malignancy, acute and chronic pancreatitis, or traumatic pancreatic duct disruption as a result of blunt or sharp abdominal trauma. Pancreatic ascites has been reported in approximately 4% of patients with chronic pancreatitis and in 6–14% of those with pancreatic pseudocysts. The aetiology is usually established based on history followed by cross-sectional abdominal imaging (CT) and endoscopic retrograde cholangiopancreatography (ERCP) in conjunction

with an ascitic fluid amylase concentration that is generally >1000 IU/mL. The ascitic fluid to serum amylase ratio is elevated (>6-fold) and the combination of this with a serum-albumin ascites gradient <1.1 g/dL, a total protein level >3 gm/L and an elevated ascitic amylase is generally diagnostic of pancreatic ascites. Therapeutic efforts to reduce exocrine pancreatic secretions to control ascites should be considered, including total parenteral nutrition (TPN) and enteric feeding distally to the ligament of Treitz as well as octreotide.[69] Treatment of duct disruption may require the placement of a transpapillary pancreatic stent.[68,70,71] The surgical management of persistent pancreatic ascites often includes the creation of an anastomosis between the ruptured duct and a Roux-en-Y jejunal loop, internal drainage of a pancreatic pseudocyst or distal pancreatic resection with duct ligation in the case of pancreatic tail leakage.[67]

The role of somatostatin and octreotide given intravenously or subcutaneously as a first- or second-line treatment option has been reviewed.[67] The rationale for these drugs is based on the reduction of exocrine secretions, which would then result in closure of fistulas. While the analysis of case reports and case series by Gomez-Cerezo et al.[67] did not show any benefits for these drugs, Segal et al.[72] showed resolution of pancreatic ascites in a case series when octreotide was given subcutaneously for 21 days.

2.4 Ascites due to Bile Leakage

A bile leak can occur in the setting of open and laparoscopic cholecystectomy from cystic duct or bile duct injury, from a post-operative patent duct of Luschka, or following liver resection, liver transplantation with duct dehiscence or blunt abdominal trauma. The diagnosis is based on imaging (CT scan, hepatobiliary iminodiacetic acid [HIDA] scan and/or ERCP) and ascitic fluid analysis. In biliary ascites, the fluid may appear green and the bilirubin concentration is greater than in plasma. Biliary ascites usually occurs in the postoperative setting of biliary tract operations or after abdominal trauma. Bile peritonitis following a gallbladder perforation or bile duct leak is typically associated with severe signs of peritoneal irritation.[73] The management of patients with biliary ascites is best provided by a multidisciplinary team including surgeons, therapeutic endoscopists and radiologists,[74] and often involves endoscopic placement of transpapillary or transhepatic stents.[75-78] Interventional radiology can aid in percutaneous bile collection (biloma) drainage, percutaneous transhepatic biliary drainage, biliary leak site embolization/sclerosis or leaking biliary segment ablation.[79] Surgical intervention is required when endoscopic or radiological management fails, or the clinical status of the patient deteriorates.

2.5 Ascites due to Ovarian Disease

The presentation of a benign ovarian tumour with ascites and hydrothorax that resolves after tumour resection is known as Meigs syndrome and is a rare clinical entity. The development of ascites in the setting of ovarian carcinoma correlates with a significantly decreased 5-year survival rate (5% with ascites vs 45% without ascites) among women with stage III or IV epithelial ovarian carcinoma.[80]

The role of the renin-angiotensin system in malignancy has been reviewed elsewhere.[81] Angiotensin II is a growth promoter via angiotensin II type 1 receptors (AT_1R), which are functionally expressed in ovarian carcinoma and involved in both tumour progression and angiogenesis. Therapy with AT_1R antagonists or blockers may become a novel and promising strategy for ovarian cancer treatment.[82]

VEGF protein levels in ovarian, gastric and colon cancer-related ascites are increased 45, 23, and 12 times, respectively, when compared with levels in patients with cirrhotic ascites. Malignant ascites from patients with colon and gastric cancer cause an increase in permeability in human umbilical vein endothelial cells (HUVECs). Controlling VEGF activity in patients with ascites caused by colon cancer decreased *in vitro* HUVEC permeability in three of four cases.[83] Bevacizumab (a humanized recombinant anti-VEGF monoclonal antibody) inhibited intraperitoneal tumour growth and ascites production in the nu/nu mouse xenograft model, and enhanced the therapeutic efficacy of cisplatin with a significantly

prolonged survival.[84] Bevacizumab is currently not indicated for malignant ascites.

2.6 Ascites due to Endometrial Disease

Ascites formation is a rare occurrence with endometriosis, and when it does occur, it is usually massive with the volume of serosanguineous, sanguineous or brown coloured fluid ranging from 1500 to 10 000 mL.[85] Cancer antigen (CA)125 values as high as 7900 mIU/mL associated with endometriosis have been reported, thus raising the possibility that the patient may have an ovarian carcinoma as the cause for the ascites rather than endometriosis.[86] Endometrial carcinoma may also present with ascites, often as a consequence of spread from the fallopian tube to the abdominal cavity.

2.7 Chylous Ascites

Chylous fluid in the chest and abdomen is defined by its appearance and chemical composition. The criteria for chylous ascites established in 1944 by Jahsman[87] for the diagnosis of chylothorax still apply today, including its milky appearance, its separation into a creamy layer upon standing, a specific gravity of >1.012, its bacteriostatic properties, a 3% total protein level, staining of fat globules by Sudan Red, a fat content of 0.4–4% and total solids >4%. Triglyceride concentrations are 2–8 times plasma levels and typically >110 mg/dL. The history and pathophysiology of chylous ascites have been reviewed elsewhere.[88] Normally, chylomicrons and very low-density lipoproteins (VLDL) diffuse into the central lacteal of the intestinal villus and are transported by the lymphatic system to the circulatory system. This mechanism can be disrupted by trauma, or obstruction or interruption of the lymphatic system. The management of chylous ascites is aimed at restoring lymphatic drainage or the initiation of a medium-chain triglyceride (MCT) diet with avoidance of long-chain triglycerides to reduce lymph formation from triglyceride intake. Peritoneovenous shunts can be utilized, although they may be associated with the development of DIC. The successful use of TIPS in patients with chylous ascites has been reported.[89] Octreotide alone[90] or in combination with a MCT-supplemented diet and TPN has also shown some promise in iatrogenic chyloperitoneum.[91] Lymphangiography[92] may provide diagnostic information before operative treatment is considered and has also resulted in spontaneous healing of chyle leakage probably because of the oil embolization effect of lipiodol contrast agents used in the procedure.[93]

2.8 Ascites due to Myxoedema

The mechanism of ascites formation in myxoedema is obscure.[94,95] Some have suggested that low levels of thyroid hormone cause an increased leakage of plasma proteins into the peritoneal cavity with a concurrent lack of compensatory lymphatic return flow. Another possibility is that hyaluronic acid may exert a direct hygroscopic effect in the dermis by interaction with albumin preventing its return into the intravascular compartment resulting in a reduction of serum albumin levels. Approximately 50 case reports of myxoedema ascites have been published. The fluid characteristics are an ascites protein >2.5 gm/dL in 98% of cases with the SAAG between 0.8–2.3, and a white blood cell count of 10–400 cells/mL (predominantly lymphocytes). The treatment of myxoedema ascites is thyroid hormone replacement, which should result in complete resolution of ascites upon re-establishment of a euthryoid state.

2.9 Ascites due to Immunodeficiency Syndrome

The differential diagnosis of ascites in immunodeficiency syndrome is broad. The early literature on HIV and ascites focused on noncirrhotic patients with AIDS presenting with new-onset high-protein ascites.[96]

Subsequently, other associations were described with ascites including cirrhosis due to HBV, hepatitis C virus and hepatitis D virus, malignancy (B-cell non-Hodgkin's lymphoma or Kaposi's sarcoma[97]), prolonged exposure to antiretroviral drugs,[98] and infections including toxoplasmosis,[99] *Mycobacterium tuberculosis* and *M. avium intracellulare*,[100] coccidioidomycosis,[101]

pneumocystis[102] and bacillary angiomatosis.[103] It is now recognized that ascites in HIV patients is usually due to portal hypertension with AIDS-related conditions starting to prevail when the CD4+ cell count reaches <40 cells/mm^3.[83] The development of ascites in the cirrhotic patient with HIV entails a poor prognosis and liver transplantation should be considered.

2.10 Ascites due to Peritoneal Malignancy

The development of malignant ascites is due to direct invasion of the parietal or visceral peritoneum, liver metastasis, portal vein or hepatic vein compression, or direct lymphatic obstruction with chylous ascites formation. The diagnosis is established by the presence of tumour cells on cytology or biopsy. The classification of malignant ascites into four categories has been proposed by Enck,[104] including (i) peripheral, when the peritoneal membrane is directly infiltrated by tumour cells; (ii) central, when the liver or portal vein is invaded; (iii) mixed, which represents a combination of peripheral and central mechanisms; and (iv) chylous, where tumour cells obstruct or involve the lymphatic drainage.

2.10.1 Primary Peritoneal Malignancies

Serous surface papillary carcinoma, malignant mesothelioma, benign papillary mesothelioma, desmoplastic small round cell tumours, benign and malignant mesenchymal tumours, peritoneal angiosarcoma, leiomyomatosis peritonealis disseminata, peritoneal hemangiomatosis, lymphoproliferative disorders and ovarian carcinoma in the setting prior to oophorectomy are defined as primary peritoneal malignancies.[105,106] All of these various conditions can present with ascites as their principal manifestation and treatment often involves debulking operations in combination with adjuvant systemic or intraperitoneal chemotherapy.

2.10.2 Secondary Peritoneal Carcinomatosis with Ascites

More commonly than primary peritoneal carcinomatosis, the peritoneum is affected by metastatic carcinomas where the primary tumour originates from breast, ovaries, endometrium, and the GI tract (in particular the colon) or pancreas. The treatment of malignant ascites includes the supportive use of diuretics, periodic paracentesis, intermittent or permanent peritoneal catheter placements to avoid repeated paracentesis, intraperitoneal radioisotope therapy, intracavitary chemotherapy, biologic agents, and shunt creation utilizing peritoneovenous shunts or TIPS.[107,108] The complications of peritoneovenous shunts for malignant ascites have been reviewed by others.[109]

Combined treatments have also involved resection of macroscopic peritoneal disease and administration of hyperthermic chemotherapy with mitomycin, fluorouracil, cisplatin, paclitaxel or gemcitabine, depending on tumour histology (see comprehensive reviews by Becker et al.[110] and Adam and Adam[111]).

An earlier report from 1997 described the successful palliative treatment of two cancer patients with portal hypertension who presented with tense ascites, mesenteric congestion and variceal bleeding with the placement of TIPS.[112] Recently, percutaneously placed peritoneovenous shunts (PVS) in patients with refractory ascites due to cirrhosis and malignancy has shown promise in an uncontrolled case series.[113] A report from Japan[114] suggests that PVS placement can be an effective treatment option for patients with refractory malignant ascites in advanced cancer, and yields a higher likelihood of hospital discharge for the patient when compared with conventional paracentesis. Different techniques of placement for these shunts have been compared, and a recent report shows that dissection of the jugular vein is not mandatory for placement and the percutaneous technique is the easiest, fastest and least invasive procedure.[115]

Laparoscopic-assisted positioning of these shunts is recommended if a peritoneal biopsy and/or abdominal exploration is required for a definitive diagnosis.[115]

2.11 Ascites due to Peritoneal Infection

2.11.1 Tuberculosis

Peritoneal tuberculosis with the formation of ascites results from haematogenous spread of mycobacteria from a primary pulmonary source.[116]

The presence of unexplained lymphocytic ascites with a SAAG of <1.1 g/dL and an ascites fluid protein content >3 mg/dL should alert the clinician to the possibility of tuberculosis. Peritoneal dialysis patients with tuberculosis may present with neutrophilic ascitic fluid.[117] Risk factors for peritoneal tuberculosis include cirrhosis,[118] peritoneal dialysis, diabetes mellitus, malignancy, systemic corticosteroids and AIDS.[119,120] Treatment with TNFα inhibitors is also known to increase the risk of tuberculosis and cases of reactivation of tuberculosis in patients treated with infliximab have been reported.[121] Confirmation should be sought with cultures of *M. tuberculosis* or a peritoneal biopsy that identifies tubercle bacilli. The utility of the adenosine deaminase (ADA) test is limited in the US.[122] In other countries, the significantly higher level of ADA in effusions of tuberculous aetiology has a sensitivity of 91–100% and a specificity of 81–100%. Polymerase chain reaction (PCR) assay alone should not be relied upon to make the diagnosis of tuberculosis as a study by Mishra et al.[123] in children from India showed that fluid PCR for *M. tuberculosis* was positive in 74% of tuberculous effusions and falsely positive in 13% of the non-tuberculous group. In the future, the diagnosis of latent tuberculosis using the tuberculin skin test may be supplanted by assay platforms involving T-cell IFN-γ-release assays (enzyme-linked immunosorbent spot [ELISpot] and QuantiFERON®-TB Gold test).[124] The mortality rate from tuberculous peritonitis approaches 50%.

The diagnostic work up has to include obtaining laparoscopic biopsy samples from the peritoneum, which should be stained for acid-fast bacilli, and cultures should also be obtained.[125] The yield of simple culture of the ascitic fluid is too low when dealing with tuberculous peritonitis and ascites.[126]

A 6- to 9-month regimen (2 months of isoniazid, rifampicin [rifampin], pyrazinamide and ethambutol, followed by 4–7 months of isoniazid and rifampicin) is recommended as initial therapy for all forms of extrapulmonary tuberculosis unless the organisms are known or strongly suspected to be resistant to the first-line drugs.[116,127] Resolution of symptoms, disappearance of ascites and normalization of laboratory-based tests of disease activity are supportive of response to treatment.[116] Nonresponse should prompt an evaluation of whether orally administered drugs are absorbed and drug sensitivity testing needs to be considered. Adjunctive treatment with corticosteroids for tuberculous ascites cannot be recommended based on limited data available. The occurrence of drug-induced hepatotoxicity constitutes a major dilemma, especially in patients with established liver disease and treatment guidelines have been published.[128]

The management of tuberculosis of the GI tract and peritoneum has also been reviewed elsewhere.[116,129]

2.11.2 Chlamydia

Chlamydia trachomatis infection may present in the context of a sexually acquired transmission. The association of chlamydia with ascites was first reported in 1980[130] and its association with ascites in chronic liver disease patients has been confirmed by others.[131] Treatment with appropriate antibacterials can result in complete resolution.[132]

2.11.3 Fungal

Isolated fungal infection as a cause of ascites in the absence of peritoneal dialysis is a rare event.

Cryptococcal peritonitis in decompensated Laennec cirrhosis has been reported.[133] The diagnosis of fungal peritonitis is based on a positive culture of the dialysate or ascetic fluid. The 2005 guidelines for the treatment of fungal peritonitis state that catheters should be removed immediately after fungi are identified by microscopy or by culture.[134] The International Society for Peritoneal Dialysis have also published guidelines for peritoneal infections (see http://www.ispd.org/lang-en/treatmentguidelines/guidelines).

Treatment of fungal infections depends on culture results and sensitivities. The guidelines established by the Infectious Diseases Society of America should be followed (see http://www.idsociety.org/Content.aspx?id=9088). Drugs that have been used successfully include azole drugs and for azole-exposed patients, amphotericin B,[135] caspofungin,[136] micafungin[137] and anidulafungin,[138] as well as combinations of drugs.[139]

2.12 Ascites due to Peritoneal Inflammatory Conditions

2.12.1 Sarcoidosis

Peritoneal sarcoidosis involvement with ascites and abdominal pain is a rare manifestation of the disease, usually presenting in women between the ages of 20 and 40 years. Establishing the diagnosis may require laparoscopic evaluation in patients with tense exudative ascites and include a peritoneal biopsy to document the presence of noncaseating granulomas. More commonly, ascites develops as a result of the sarcoidosis causing pulmonary hypertension and right heart failure or portal hypertension due to biliary cirrhosis. Corticosteroids remain the mainstay of treatment when organ dysfunction occurs.[140,141]

2.12.2 Vasculitis

Numerous syndromes with vasculitis have been associated with the development of ascites.

The GI manifestations of systemic lupus erythematosis (SLE) have been well reviewed.[142] SLE can be associated with massive ascites and pleural effusion.[143] Management with corticosteroids can result in resolution of the ascites as the vasculitis is controlled.

Ascites has also been noted as the first manifestation of polyarteritis nodosa.[144] The formation of chylous ascites in Henoch-Schoenlein purpura has been reported in the context of development of a chylothorax and Meigs' syndrome[145] (ascites and pelvic mass) in a patient with Takayasu arteritis. Budd-Chiari syndrome is a rare vascular complication of Behçet's disease with the ascites responding to percutaneous transluminal angioplasty of the hepatic vein.[146] Incomplete septal cirrhosis associated with Wegener's granulomatosis presented with ascites and encephalopathy in a Japanese patient.[147]

2.13 Ascites due to a Combination of Aetiologies (`Mixed Ascites')

Two causes of ascites that are simultaneously present currently defines the entity of mixed ascites. The usual combination is cirrhosis with tuberculosis or carcinomatosis. Overall, mixed ascites accounts for 5% of all cases of ascites and has been recognized since 1960 when 43% of patients with peritoneal tuberculosis were noted to have underlying cirrhosis.[148] In a prospective cohort of 448 patients with ascites, malignancy was seen in conjunction with cirrhosis in 11% of patients.[149] The prognosis for patients with mixed causes of ascites is guarded as the simultaneous presence of portal hypertension indicates that decompensated liver disease is already present. The SAAG is usually >1.1 as defined by the presence of portal hypertension.[36]

3. Complications

In this review, we limit the discussion of specific complications of ascites to those that occur in the setting of underlying cirrhosis and portal hypertension (see figure 3).

3.1 Refractory Ascites

True, medically refractory ascites or diuretic-resistant ascites is defined by the rapid reaccumulation of fluid after therapeutic paracentesis or associated with resistance to adequate diuretic management (e.g. furosemide 160 mg/day and spironolactone 400 mg/day), and occurs in <10% of patients with cirrhotic ascites (those with a SAAG >1.1). The management of refractory ascites involves the use of recurrent large-volume paracentesis or utilization of TIPS (figure 4). Refractory ascites should also be considered as an indication for evaluation for liver transplantation.[13]

The previous use of peritoneovenous shunting (e.g. LeVeen or Denver) has declined because of development of shunt occlusion,[151] thrombosis of major vessels, seroma formation and leaking, and pulmonary oedema.[109,152] In patients with cirrhosis, peritoneovenous shunt placement is associated with DIC.[153]

Several large-scale, randomized, controlled trials of TIPS compared with large-volume paracentesis in Europe[154-156] and the US[157] have been recently re-analyzed in a meta-analysis[158] and indicate that TIPS significantly improves the transplant-free survival of cirrhotic patients with refractory ascites. However, in a recent review, Gines et al.[23] stated that the use of TIPS should

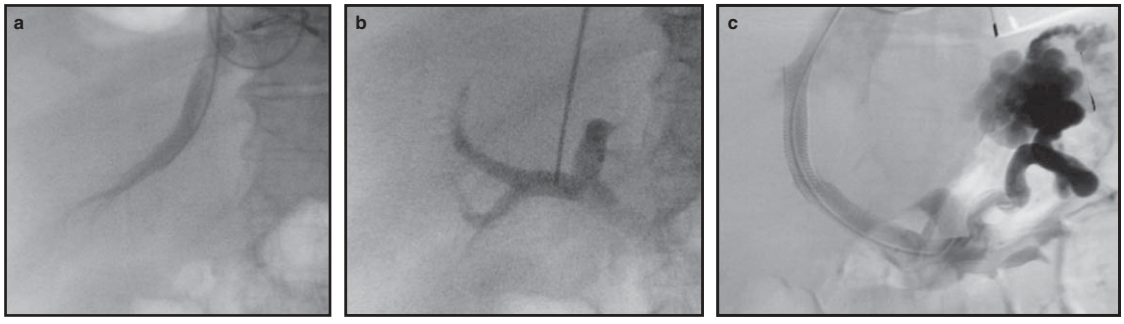

Fig. 4. Steps involved in creation of transjugular intrahepatic portosystemic shunt (TIPS): (**a**) a curved catheter is placed into the right hepatic vein; (**b**) advancement of Colapinto needle via right hepatic vein into right portal vein; and (**c**) a TIPS (10×68 mm Wallstent dilated with 10 mm×4 cm balloon) has been placed. Note the flow through the Wallstent and filling of the splenorenal shunt. The intrahepatic portal flow became reversed after TIPS placement (reproduced from Novelli,[150] with permission from eMedicine.com, 2009).

not be recommended as the treatment of choice for refractory ascites because studies have not shown that TIPS improves survival in patients with refractory ascites. Midodrine alone in the treatment of non-azotaemic patients with cirrhosis and ascites is associated with a significant improvement in systemic haemodynamics.[159] This observation was confirmed in non-azotaemic patients.[160] Administration of midodrine, octreotide (as Sandostatin® LAR®) and albumin to ten patients with refractory ascites demonstrated that a significant reduction in plasma renin and aldosterone concentration will occur.[161] This was also coupled with a trend towards a reduction in the volume of ascites that must be removed by paracentesis without any deterioration of renal function. However, these beneficial effects were at the expense of a reversible deterioration in the Model for End-stage Liver Disease (MELD) score.

In addition to splanchnic vasodilation, the sympathetic nervous system is activated in some cirrhotic patients. Clonidine via a centrally acting α_2-adrenoceptor agonist mechanism has been shown to offer sympatholytic activity in patients with arterial hypertension or cirrhosis. The effects of the addition of clonidine to diuretics on the mobilization of ascites in the short term (diuretic response and requirement of diuretics) and long term (readmissions for tense ascites and requirement of diuretics) have been examined in patients with cirrhosis and with increased sympathetic nervous system activity.[162,163] Coadministration of clonidine and spironolactone resulted in natriuresis and weight loss more effectively than spironolactone alone in patients with cirrhosis and ascites.[163] Further evaluation of this observation with a randomized controlled trial seems warranted.

3.2 Spontaneous Bacterial Peritonitis

Infection of ascitic fluid is classified based on ascitic fluid PMN count, culture and presence or absence of a surgical cause into: (i) spontaneous ascites infection with three subcategories of SBP, culture-negative neutrocytic ascites and monomicrobial non-neutrocytic bacterascites; (ii) secondary bacterial peritonitis; and (iii) polymicrobial bacterascites.[164]

SBP is defined by the presence of >250 PMN per mm^3 and occurs in up to 10% of patients with cirrhosis who develop ascites. Patients with SBP may be asymptomatic and paracentesis should be performed on all those patients with cirrhosis and new-onset ascites, or in any patient with ascites who is symptomatic with signs of infection, encephalopathy, nausea or vomiting, or concomitant GI bleeding. Enteric organisms are the most common causes of SBP. Organisms are invariably aerobic or microaerophilic in type. If the patient has undergone prior paracentesis, skin organisms such as staphylococci should be considered as possible causes. We would add vancomycin to treatment in the latter scenario. Despite appropriate studies and cultures, up to 40% of

patients with symptoms and signs suggesting spontaneous peritonitis will be culture negative. Cefotaxime is the treatment of choice. The addition of intravenous albumin 1.5 g/kg bodyweight on days 1 and 3 has been shown to reduce the mortality of SBP from 29% to 10%.[165]

Patients at risk for the development of SBP include those with low ascitic protein concentrations of <1 g/dL, prior SBP or active variceal bleeding. SBP may also develop following an upper GI bleed in those with cirrhosis and ascites.[13] Administration of oral norfloxacin as prophylaxis for patients with upper GI bleeding can reduce the risk of SBP, although up to 30% of enteric organisms may be resistant to fluroquinolones.[166] Current recommendations include the use of a third-generation cephalosporin or a β-lactam antibacterial for prophylaxis in those patients with GI bleeding and ascites.[13]

3.3 Hepatorenal Syndrome

Among individuals with ascites, HRS develops in 20% and 40% of individuals within 1 and 5 years, respectively.[167] The development of HRS in patients with end-stage liver disease and ascites is a poor prognostic sign. The diagnostic criteria for HRS were established by the International Ascites Club.[168] Type 1 HRS is defined by a doubling of creatinine to ≥2.5 mg/dL, or by a 50% decrease of creatinine clearance to a level of <20 mL/min in an interval of <2 weeks. Type 2 HRS is a more slowly progressive renal failure with a serum creatinine >1.5 mg/dL usually developing in the setting of refractory ascites (table II).

TIPS is an effective treatment for type 1 HRS in suitable patients with cirrhosis and ascites, following the improvement of renal function with combination therapy of midodrine, octreotide and albumin.[170] In the US, the combination of albumin, octreotide and midodrine remains the standard of care as outlined in the AASLD guidelines.[13]

Terlipressin is a V_1 receptor agonist that has shown efficacy and safety in the treatment of HRS.[171] Terlipressin is approved in Europe and Asia for the treatment of HRS 1. Two smaller studies by Hadengue et al.[172] and Solanki et al.[173] showed evidence that terlipressin could reverse HRS 1. In a prospective, randomized, double-blind, placebo-controlled clinical trial of intravenous terlipressin 1 mg every 6 hours or placebo plus albumin in both groups for type 1 HRS, Sanyal et al.[174] showed an improvement in azotaemia with terlipressin that was twice that of placebo (25% vs 12.5%; p = 0.093). In this study, the serum creatinine level improved from baseline and HRS reversal was noted, as defined by a decrease in serum creatinine level ≤1.5 mg/dL, when terlipressin was compared with placebo. The TAHRS (Terlipressin and Albumin for Hepatorenal Syndrome) investigators evaluated the safety and efficacy of terlipressin plus albumin in patients with HRS type 1 or 2. They showed that terlipressin and albumin resulted in an improvement of renal function over albumin treatment alone, but no difference in mortality.[175] Future studies will have to address establishment of an optimal dosing regimen for terlipressin and provide more insight into the selection of patients who are more likely to respond to terlipressin.

Table II. Criteria for diagnosis of hepatorenal syndrome (reproduced from Salerno et al.,[169] with permission from BMJ Publishng Group Ltd)

Cirrhosis with ascites
Serum creatinine >133 μmol/L (1.5 mg/dL)
No improvement of serum creatinine (decrease to a level ≤133 μmol/L) after at least 2 days with diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg bodyweight/day up to a maximum of 100 g/day
Absence of shock
No current or recent treatment with nephrotoxic drugs
Absence of parenchymal liver disease as indicated by proteinuria (500 mg/day), microhaematuria (>50 red blood cells per high power field) and/or abnormal renal ultrasonography

3.4 Hepatic Hydrothorax

Hepatic hydrothorax is defined as a pleural effusion (right sided in 67–85%) that develops in patients with cirrhosis in the absence of cardiopulmonary disease.[176] The characteristics of the pleural fluid include a PMN count of <250 cells/mm^3, protein <2.5 g/dL, pleural fluid/serum total protein ratio <0.5, pleural fluid/lactate

dehydrogenase ratio >0.6, pleural fluid/serum albumin gradient >1.1, pleural fluid/serum bilirubin ratio <0.6, pH >7.4 and a glucose level similar to serum glucose.[177,178] The proposed mechanisms of formation have been reviewed and include hypoalbuminaemia, azygous vein hypertension, leakage of fluid via diaphragmatic defects and diaphragmatic lymphatic channel passage of fluid.[179,180] Infection of the fluid (spontaneous bacterial empyema) is defined by a positive culture or PMN count >500 cells/mm^3. The management of uncomplicated hepatic hydrothorax includes the same measures as taken for ascites. Patient evaluation for liver transplant is indicated. The role of TIPS for hepatic hydrothorax has evolved over the last years with response rates of 70%.[181-184] The postoperative mortality of up to 20% with the LeVeen shunt precludes its application in the management of hepatic hydrothorax.[185] Video-assisted thoracoscopic (VATS) repair of the diaphragmatic defects, which was first proposed in 1996,[186] utilizes the application of talc pleurodesis.[186-188] Recently, VATS using intra-abdominal insufflation of saline with indocyanine green or carbon dioxide followed by suture closure of defects using fibrin glue showed improvement in the effusions.[189]

4. Conclusions

The formation of ascites in cirrhosis, carcinomatosis and infections (e.g. tuberculosis) provides for unique management challenges in clinical medicine. The complexity of the pathophysiological mechanisms in ascites formation presents diagnostic and therapeutic challenges. In the patient with established cirrhosis with obvious decompensation, the diagnosis is usually straightforward and the management of ascites focuses on compliance with an established regimen of diuresis and salt restriction. The difficult challenges in patients with portal hypertension are presented when the patients develop refractory ascites, SBP or hepatic hydrothorax. Patients with ascites due to cirrhosis should be considered for evaluation for liver transplantation. Patients with hyponatraemia may one day benefit from the judicious use of vaptans. There is hope that patients with malignant ascites will eventually benefit from advances in the understanding of cytokine-mediated pathways. The role of multimodality treatment of malignant peritoneal disease is evolving, utilizing a combination of systemic and intraperitoneal therapy as well as debulking surgery. The patient with mixed ascites faces the dilemma of typically decompensated liver disease coupled with infection or carcinomatosis and the outcome of these patients will depend on whether liver transplantation is an option.

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