Investigating the patient with ascites

Each month we present authoritative advice on the investigation of a common clinical problem, specially written for family doctors by the Board of Continuing Medical Education of the Royal Australasian College of Physicians.

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Ascites is excessive fluid in the peritoneal space (Figure). It is suggested clinically by the finding of shifting dullness and confirmed by imaging such as ultrasonography. There are many possible causes. These can be broadly categorised as portal or non-portal hypertension-related processes (Table 1). The latter include reduced plasma oncotic pressure, peritoneal inflammation, disruption to lymphatic drainage and increased vascular permeability (see the flowchart on page 50).

Despite the aetological diversity, portal hypertension due to cirrhosis accounts for about 80% of cases of ascites in western countries. Peritoneal malignancies and right heart failure account for most of the remaining cases. Although acute portal vein thrombosis often results in transient ascites, chronic portal vein obstruction does not usually cause ascites in the absence of underlying liver disease. Tuberculosis is a common cause in patients from areas in which this disease is endemic.

In Australia, an increasing number of patients will be expected to present with ascites, given that the incidence of cirrhosis due to hepatitis C viral infection alone is predicted to at least double in the next decade.

Spontaneous bacterial peritonitis is a serious disorder that may complicate pre-existing ascites, often resulting in an exacerbation of peritoneal fluid accumulation. Less often, ascites develops *de novo* as a consequence of spontaneous bacterial peritonitis. Most instances of spontaneous bacterial peritonitis occur in cirrhotic patients with advanced hepatic dysfunction, but this condition may also occur in patients with acute liver failure, nephrotic syndrome, or other hypoproteinaemic states. Conversely, spontaneous bacterial peritonitis rarely, if ever, complicates ascites due to other causes.

IN SUMMARY

- **Portal hypertension due to cirrhosis is the most common cause of ascites in western countries, accounting for about 80% of cases.**
- **Peritoneal malignancies and right heart failure account for most of the remaining cases.**
- **The serum-to-ascites albumin gradient correctly differentiates patients with ascites related to portal hypertension from those with non-portal hypertension-related aetiologies in over 97% of instances.**
- **The ascitic white cell count is usually normal in patients with uncomplicated portal hypertension-related ascites and raised in those with non-portal hypertensive aetiologies, with the exception of hypoproteinaemic states and disorders associated with increased vascular permeability.**
- **A simple initial algorithm based on the patient's medical history, physical examination and results of diagnostic paracentesis allows a focused approach to further investigation.**

Initial investigation

Initial investigations are aimed at categorising patients into those with portal hypertension-related ascites and those with non-portal hypertension-related ascites. This enables a focused approach to further investigations.

The key initial components in determining the cause of ascites are the patient's history, physical examination and determination of the serum-to-ascites albumin gradient following diagnostic paracentesis. History taking and physical examination are directed towards the range of possible aetiologies listed in Table 1. Particular emphasis should be placed on the more common causes, such as liver disease and right heart failure (in which ascites is due to portal hypertension) and peritoneal malignancies (in which ascites is unrelated to portal hypertension).

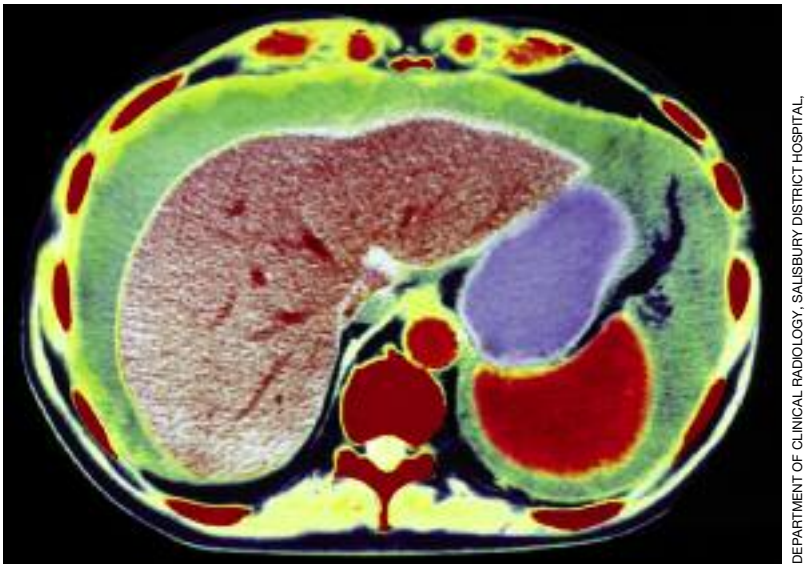

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Figure. Coloured CT scan of an axial section through the abdomen showing ascites. The liver (pale red), stomach (centre right, blue) and spleen (lower right, red) are surrounded by fluid (green), giving rise to the condition of ascites.

Table 1. Causes of ascites

Portal hypertension-related

With liver damage

Cirrhosis with or without portal vein thrombosis or infiltration by hepatocellular carcinoma
Right heart failure*
Alcoholic hepatitis
Diffuse liver infiltration:
- metastases
- lymphoma†
- leukaemia

Presinusoidal pathologies:
- nodular regenerative hyperplasia
- schistosomiasis

Acute liver failure
Veno-occlusive disease
Budd-Chiari syndrome:*
- hypercoagulable state
- tumours (hepatocellular carcinoma, renal cell carcinoma, adrenal carcinoma)
- membranous webs

Without liver damage

Acute portal vein obstruction:
- trauma
- acute pancreatitis
- intra-abdominal sepsis
- hypercoagulable state

Non-portal hypertension-related

Peritoneal inflammation

Spontaneous bacterial peritonitis‡
Tuberculosis
Pancreatic enzyme leakage
Bile leakage
Pelvic inflammatory disease
Connective tissue disorders

Reduced plasma oncotic pressure§

Nephrotic syndrome
Protein losing enteropathy
Malnutrition

Impaired lymphatic drainage

Lymphatic obstruction:
- lymphoproliferative disorders
- peritoneal malignancies
- tuberculosis

Lymphatic tear:
- trauma
- cirrhosis

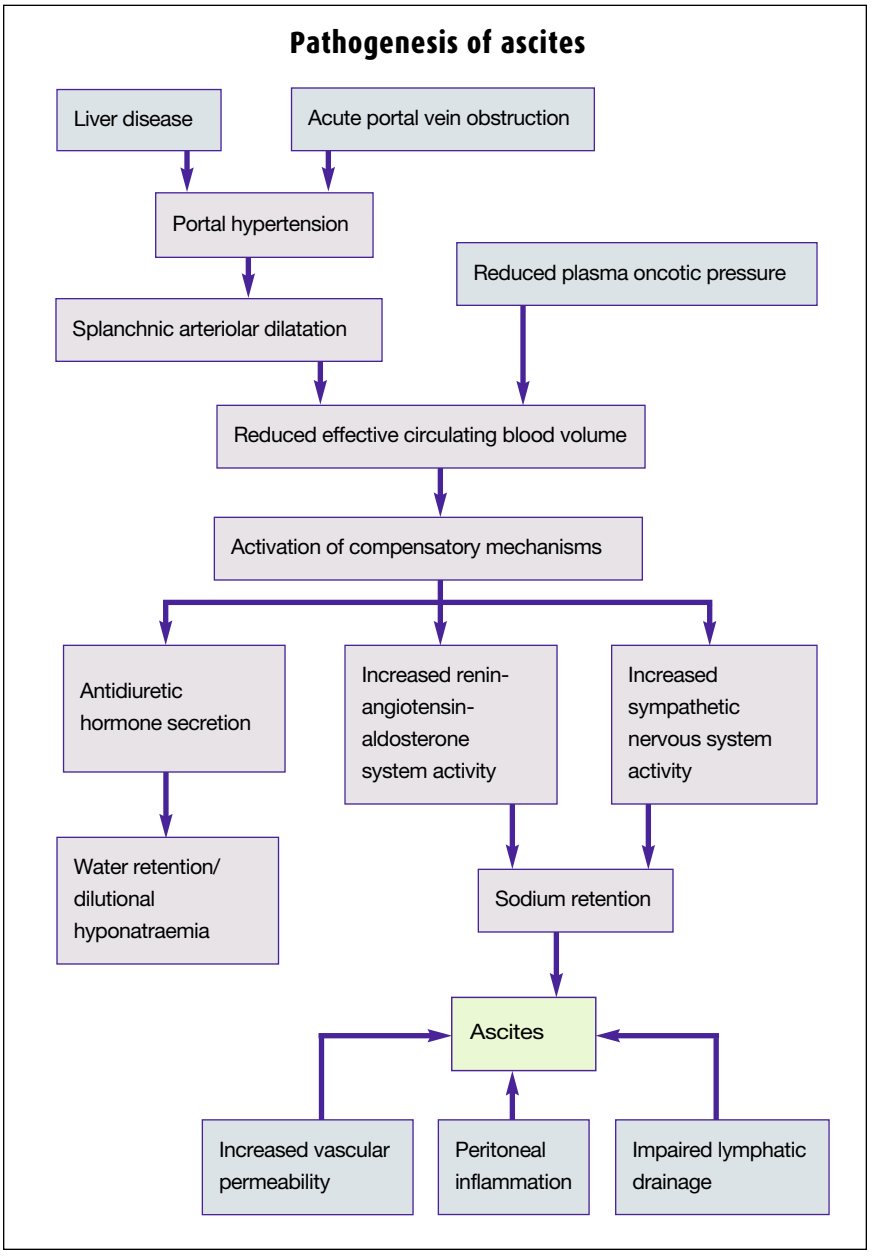
Increased vascular permeability

Peritoneal malignancies
Ovarian hyperstimulation syndrome

* Resultant hepatic congestion usually also results in impaired lymphatic drainage, exacerbating potential for ascites. † Predominant sinusoidal infiltration may lead to portal hypertension without diffuse liver infiltration. ‡ Usually complicates pre-existing ascites, especially in patients with advanced liver damage. § In the absence of liver disease.

The possibility of underlying cirrhosis should not be dismissed in patients without peripheral stigmata of chronic liver disease, such as palmar erythema and spider naevi, as these are often absent, especially in those with nonalcoholic aetiologies of cirrhosis.

Calculation of the serum-to-ascites albumin gradient complements the clinical assessment. This gradient correctly differentiates patients with ascites related to portal hypertension (gradient ≥11 g/L) from those with non-portal hypertension-related aetiologies (gradient <11 g/L) in over 97% of cases. The accuracy of this ratio usually obviates the need for more invasive investigations for portal hypertension, such as measurement of the hepatic venous pressure gradient.



Further investigation

Further investigation is mandatory to determine the actual cause of ascites. The ascitic total and differential white cell counts are of particular value (Table 2). In practice, ascitic samples for white cell counts and albumin concentration determination are taken at the same time.

The ascitic white cell count is usually normal (total count <500/μL, neutrophil count <250/μL) in patients with uncomplicated portal hypertension-related ascites, such as that due to cirrhosis. It is usually raised in all non-portal hypertensive aetiologies, with the exception of hypoalbuminaemic states and disorders associated with increased vascular permeability. An example of the latter is ovarian hyperstimulation syndrome, which may complicate assisted conception treatments.

Ascites due to portal hypertension

Investigation for liver disease and its causes will be needed in patients with portal hypertension-related ascites (i.e. those with a serum-to-ascites albumin gradient ≥11 g/L).

Standard liver function tests and liver imaging to assess for features of cirrhosis or extensive infiltration, generally with ultrasound in the first instance, are important. Liver biopsy may be required. To minimise the risk of haemoperitoneum, this should be performed only after ascites has been effectively treated. The transjugular biopsy route is an alternative to a percutaneous approach if this is problematic. Coagulopathy must be reversed with fresh frozen plasma and/or platelet transfusions before biopsy.

If right heart failure is suspected investigations such as echocardiography and lung function tests may be needed to establish the cause.

Patency of the portal and hepatic veins is usually adequately assessed by Doppler ultrasound or dynamic computerised tomography. A high index of clinical suspicion is important for diagnosing

hepatic veno-occlusive disease (which often complicates bone marrow transplantation) and Budd-Chiari syndrome (resulting from hepatic venous outflow block). Tender, nonpulsatile hepatomegaly is a clinical hallmark of these disorders, although this can be difficult to detect when ascites is tense. An underlying hypercoagulable state, most often related to a myeloproliferative disorder, is present in about 75% of patients with Budd-Chiari syndrome and should be sought. The possibility of an underlying malignancy should also be excluded. Associated thromboses in the inferior vena cava and/or portal vein are present in up to 20% of cases.

Ascites due to other causes

Several investigations are useful to help determine the cause of non-portal hypertension-related ascites (i.e. serum-to-ascites albumin gradient <11 g/L).

Cytological examination of ascitic fluid remains the gold standard test for ascites due to peritoneal malignancy, although sensitivity is as low as 40 to 60% in some series, even when up to 500 mL of fluid is analysed. Ascitic fluid fibronectin levels have recently been reported to have high diagnostic accuracy in discriminating between malignant and nonmalignant causes of ascites. Laparoscopy-guided peritoneal biopsy may be required.

Laparoscopy-guided peritoneal biopsy is the most reliable test for tuberculous peritonitis. Raised adenosine deaminase levels in ascitic fluid have a specificity for tuberculosis peritonitis of over 90%, although reported sensitivities are widely variable. Mycobacteria are identified on culture of ascitic fluid in fewer than 20% of cases. Molecular diagnosis by polymerase chain reaction techniques is becoming more routinely available. Over 70% of patients with tuberculous peritonitis have no evidence of pulmonary disease.

A raised ascitic amylase level, generally in the order of 2000 IU/L, is typical of pancreatic ascites, while an ascitic bilirubin value in excess of that in serum is compatible with a biliary aetiology. Further imaging of the pancreas and biliary tree, respectively, should be undertaken in these circumstances.

Spontaneous bacterial peritonitis

An ascitic fluid neutrophil count of ≥250/μL is the single most reliable test for spontaneous bacterial peritonitis, with a sensitivity approaching 90%. Other causes of neutrocytic ascites (see Table 2) must be excluded depending on the clinical context; however, most instances of a raised ascitic neutrophil count are due to spontaneous bacterial peritonitis, especially in patients with cirrhosis.

The sensitivity of traditional ascitic fluid culture in determining spontaneous bacterial peritonitis is only 33%. This is increased to about 75% by the bedside inoculation of ascitic fluid into blood culture bottles. Gram stain of

Table 2. Causes of ascites according to diagnostic paracentesis results

	Serum-to-ascites albumin gradient	
	Normal (<11 g/L)*	**Increased (≥11 g/L)†**
Normal white cell count and differential‡	Nephrotic syndrome Protein losing enteropathy Malnutrition Ovarian hyperstimulation syndrome	Cirrhosis Right heart failure Alcoholic hepatitis Diffuse hepatic infiltration Nodular regenerative hyperplasia Schistosomiasis Acute liver failure Veno-occlusive disease Budd-Chiari syndrome Acute portal vein obstruction Chronic portal vein obstruction (only in association with liver disease)
Increased neutrophil count	Spontaneous bacterial peritonitis (complicating pre-existing ascites due to the above causes) Pancreatic ascites Biliary ascites Pelvic inflammatory disease	Spontaneous bacterial peritonitis (complicating pre-existing ascites due to the above causes)
Increased lymphocyte count	Peritoneal malignancy Tuberculous peritonitis Connective tissue disorders	Dual pathology (eg. tuberculous peritonitis or peritoneal malignancy in a patient with alcoholic hepatitis or cirrhosis)

* Suggests ascites is not due to portal hypertension. † Suggests ascites is due to portal hypertension. ‡ Normal ascitic white cell count and differential: total count <500/μL, neutrophil count <250/μL, lymphocyte count <500/μL.

ascitic fluid is usually negative as the concentration of infecting bacteria is generally very low.

Since neither the ascitic fluid neutrophil count nor ascitic culture have 100% sensitivity (even in combination), it is appropriate to make a diagnosis of spontaneous bacterial peritonitis in patients with a suggestive clinical picture, even when these tests are negative.

Although a fulminant onset with peritonism and either fever or hypothermia may occasionally occur, patients with spontaneous bacterial peritonitis present more often with nonspecific symptoms such as anorexia and nausea or, in those with cirrhosis, precipitation or exacerbation of hepatic encephalopathy. The serum-to-ascites albumin gradient has no value in identifying patients with spontaneous bacterial peritonitis (see Table 2). This remains ≥11 g/L in patients with underlying portal hypertension-related ascites and <11 g/L in those with spontaneous bacterial peritonitis complicating ascites or another aetiology, such as nephrotic syndrome.

Secondary bacterial peritonitis due to perforation of the gut or an intra-abdominal abscess must be considered in any patient with neutrocytic ascites and a polymicrobial ascitic culture. Gram stain may be positive for multiple organisms, especially in the case of secondary bacterial peritonitis related to gut perforation. A polymicrobial culture in association with a neutrophil count of less than 250/μL (polymicrobial bacterascites) suggests needle perforation of the gut during diagnostic or therapeutic paracentesis.

Chylous ascites

When ascitic fluid appears milky, the triglyceride content should be measured to differentiate between true chylous and pseudochylous ascites. The latter is due to scattering of light by aggregates of cholesterol, phospholipid and protein derived from degenerating malignant or inflammatory cells.

Lymphatic obstruction in association with lymphoproliferative disorders or tuberculosis is a common cause of chylous ascites. This may also occur in patients with nephrotic syndrome and those with uncomplicated cirrhosis, due to rupture of overloaded lymphatics.

Summary

Cirrhosis, peritoneal malignancies and right heart failure account for most cases of ascites in western countries. Nonetheless, there are many possible causes. Broad categorisation into portal hypertension-related and other processes is usually possible based on a relatively simple algorithm focusing on the history, physical examination and analysis of the serum-to-ascites albumin gradient. Such a schema allows a focused approach to further investigation so that the precise cause of ascites can be determined and appropriate management implemented. MT

Further reading

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