Approach to the Patient with Ascites

Differential Diagnosis

Ascites refers to the pathologic accumulation of fluid within the peritoneal cavity. It is important to establish a cause for its development and to initiate a rational treatment regimen to avoid some of the complications of ascites. Most cases of ascites in the United States result from liver disease, although disorders involving other organ systems may produce abdominal fluid accumulation in certain situations (Table 17-1).

Hepatic Disease

Portal hypertension appears to be a prerequisite for ascites formation in patients with liver disease. In general, ascites is a complication of chronic liver diseases (e.g., cirrhosis), but some acute diseases (e.g., acute alcoholic hepatitis or fulminant hepatic failure) may result in ascites. In such cases, ascites also has a high ($\geq$ 1.1 g/dL) serum-ascites albumin gradient indicating acute portal hypertension and a mechanism of formation similar to chronic liver disease. Ascites may complicate Budd-Chiari syndrome because of venous outflow obstruction. Three theories have been proposed to explain fluid accumulation. The underfill theory postulates that an imbalance of Starling forces produces intravascular fluid loss into the peritoneum, with resultant hormonally mediated renal sodium retention. The overfill theory proposes that primary renal sodium retention produces intravascular hypervolemia that overflows into the peritoneum. The more recent peripheral arterial vasodilation theory proposes that portal hypertension leads to vasodilation and reduced effective arterial blood volume, which increases renal sodium retention and promotes fluid accumulation. With the vasodilation theory, the underfill mechanism is

operative in early, compensated cirrhosis, whereas the overflow mechanism operates in advanced disease.

Renal Disease

Nephrotic syndrome is a rare cause of ascites in adults. It results from protein loss in the urine, leading to decreased intravascular volume and increased renal sodium retention. Nephrogenous ascites is a poorly understood condition that develops with hemodialysis; its optimal treatment is undefined and its prognosis is poor. Continuous ambulatory peritoneal dialysis is an iatrogenic form of ascites that takes advantage of the rich vascularity of the parietal peritoneum to promote elimination of endogenous toxins and control fluid balance. Urine may accumulate in the peritoneum in newborns or as a result of trauma or renal transplantation in adults.

Cardiac Disease

Ascites is an uncommon complication of both high- and low-output heart failure. High-output failure is associated with decreased peripheral resistance; low-output disease is defined by reduced cardiac output. Both lead to decreased effective arterial blood volume and thus renal sodium retention. Pericardial disease is a rare cardiac cause of ascites.

Pancreatic Disease

Pancreatic ascites develops as a complication of severe acute pancreatitis, pancreatic duct rupture in acute or chronic pancreatitis, or leakage from a pancreatic pseudocyst. Underlying cirrhosis is present in many patients with pancreatic ascites. Pancreatic ascites may be complicated by infection or left-sided pleural effusion.

Biliary Disease

Most cases of biliary ascites result from gallbladder rupture, which usually is a complication of gangrene of the gallbladder in elderly men. Bile also can accumulate in the peritoneal cavity after biliary surgery or biliary or intestinal perforation.

Malignancy

Malignancy-related ascites signifies advanced disease in most cases and is associated with a dismal prognosis. Exceptions are ovarian carcinoma and lymphoma, which may respond to debulking surgery and chemotherapy, respectively. The mechanism of ascites formation depends on the location of the tumor. Peritoneal carcinomatosis produces exudation of proteinaceous fluid into the peritoneal cavity, whereas liver metastases or primary hepatic malignancy induces ascites likely by producing portal hypertension, either from vascular occlusion by the tumor or arteriovenous fistulae within the tumor. Finally, chylous ascites can result from lymph node involvement with tumor.

Infectious Disease

In the United States, tuberculous peritonitis is a disease of Asian, Mexican, and Central American immigrants, and as a complication of the acquired immunodeficiency syndrome (AIDS). One-half of patients with tuberculous peritonitis have underlying cirrhosis, usually secondary to ethanol abuse. Patients with liver disease tolerate antituberculous drug toxicity less well than patients with normal hepatic function. Exudation of proteinaceous fluid from the tubercles lining the peritoneum induces ascites formation. *Coccidioides* organisms cause infectious ascites formation by similar mechanisms. For sexually active women who have a fever and inflammatory ascites, chlamydia-induced, and now less commonly, gonococcus-induced, Fitz-Hugh–Curtis syndrome should be considered.

Chylous Ascites

Chylous ascites is a result of the obstruction of or damage to chyle-containing lymphatic channels. The most common causes are lymphatic malignancies (e.g., lymphomas, other malignancies), surgical tears, and infectious causes.

Other Causes of Ascites Formation

Serositis with ascites formation may complicate systemic lupus erythematosus. Meigs' syndrome, ascites and pleural effusion due to benign ovarian neoplasms is a rare cause of ascites with most cases of ascites due to ovarian disease being the result of peritoneal carcinomatosis. Ascites with myxedema appears to be secondary to hypothyroidism-related cardiac failure. Mixed ascites occurs in ~5% of cases when the patient has two or more separate causes of ascites formation, usually due to cirrhosis and infection or malignancy. A clue is frequently an inappropriately high white cell count in otherwise transudative ascites.

Workup

History

The history can help to elucidate the cause of ascites formation. Increasing abdominal girth as a result of ascites may be part of the initial presentation of patients with alcoholic liver disease; however, the laxity of the abdominal wall and the severity of underlying liver disease suggest that the condition can be present for some time before it is recognized. Patients who consume ethanol only intermittently may report cyclic ascites, whereas patients with nonalcoholic disease usually have persistent ascites. Other risk factors for viral liver disease should be ascertained (i.e., drug abuse, sexual exposure, blood transfusions, and tattoos). A positive family history of liver disease raises the possibility of a heritable condition (e.g., Wilson's disease, hemochromatosis, or α_1-antitrypsin deficiency) that might also present with symptoms referable to other organ systems (diabetes, cardiac disease, joint problems, and hyperpigmentation with

hemochromatosis; neurologic disease with Wilson's disease; pulmonary complaints with α_1-antitrypsin deficiency). Patients with cirrhotic ascites may report other complications of liver disease including jaundice, pedal edema, gastrointestinal hemorrhage, or encephalopathy. The patient with long-standing stable cirrhosis who abruptly develops ascites should be evaluated for possible hepatocellular carcinoma.

Information concerning possible nonhepatic disease should be obtained. Weight loss or a prior history of cancer suggests possible malignant ascites, which may be painful and produce rapid increases in abdominal girth. A history of heart disease raises the possibility of cardiac causes of ascites. Some alcoholics with ascites have alcoholic cardiomyopathy rather than liver dysfunction. Obesity, diabetes, and hyperlipidemia are all risk factors for non-alcoholic fatty liver disease (NAFLD), which can cause cirrhosis on its own or act synergistically with other insults (e.g., alcohol, Hepatitis C). Tuberculous peritonitis usually presents with fever and abdominal discomfort. Patients with nephrotic syndrome usually have anasarca. Patients with rheumatologic disease may have serositis. Patients with ascites associated with lethargy, cold intolerance, and voice and skin changes should be evaluated for hypothyroidism.

Physical Examination

Ascites should be distinguished from panniculus, massive hepatomegaly, gaseous overdistention, intra-abdominal masses, and pregnancy. Percussion of the flanks can be used to rapidly determine if the patient has ascites. The absence of flank dullness excludes ascites with 90% accuracy. If dullness is found, the patient should be rolled into a partial decubitus position to test if the air-fluid interface determined by percussion shifts (shifting dullness). The fluid wave has less value in the detection of ascites. The puddle sign detects as little as 120 ml of ascitic fluid,

but mandates that the patient assume a hands-knees position for several minutes, and is also less useful than flank dullness.

The physical examination can help in determining the cause of ascites. Palmar erythema, abdominal wall collateral veins, spider angiomas, splenomegaly, and jaundice are consistent with liver disease. Large veins on the flanks and back indicate blockage of the inferior vena cava that is caused by webs or malignancy. Masses or lymphadenopathy (e.g. Sister Mary Joseph's nodule, Virchow's node for upper abdominal malignancies) suggest underlying malignancy. Distended neck veins, cardiomegaly, and auscultation of an S_3 or pericardial rub suggest cardiac causes of ascites, whereas anasarca may be observed with nephrotic syndrome.

Additional Testing

Blood and Urine Studies

Laboratory blood studies can provide clues to the cause of ascites (Fig. 17-1). Abnormal levels of aminotransferases, alkaline phosphatase, and bilirubin are seen with liver disease. Prothrombin time prolongation or hypoalbuminemia is also observed with hepatic synthetic dysfunction, although low albumin levels are noted with renal disease, protein-losing enteropathy, and malnutrition. Hematologic abnormalities, especially thrombocytopenia, suggest liver disease. Renal disease may be suggested by electrolyte abnormalities or elevations in blood urea nitrogen and creatinine. Urinalysis may reveal protein loss with nephrotic syndrome or bilirubinuria with jaundice. Specific tests (e.g., □-fetoprotein) or serologic tests (e.g., antinuclear antibody) may be ordered for suspected hepatocellular carcinoma or immune-mediated disease, respectively.

Ascitic Fluid Analysis

Abdominal paracentesis is the most important means of diagnosing the cause of ascites formation. It is appropriate to sample ascitic fluid in all patients with new-onset ascites as well as in all those admitted to the hospital with ascites, as there is a 10% to 27% prevalence of ascitic fluid infection in the latter group. Paracentesis is performed in an area of dullness either in the midline between the umbilicus and symphysis pubis, as this area is avascular, or in one of the lower quadrants. Needles should not be inserted close to abdominal wall scars with either approach because of the high risk of bowel perforation; puncture sites too near the liver or spleen should be avoided as well. In 3% of cases, ultrasound guidance may be needed. The needle is inserted using a Z-track insertion technique to minimize postprocedure leakage, and 25 ml or more of ascitic fluid is removed for analysis.

Analysis of ascitic fluid should begin with gross inspection. Most ascitic fluid resulting from portal hypertension is yellow and clear. Cloudiness raises the possibility of infectious processes, whereas a milky appearance is seen with chylous ascites. A minimum density of 10,000 erythrocytes per µl is required to provide a red tint to the fluid, which raises the possibility of malignancy if the paracentesis is atraumatic. Pancreatic ascitic fluid is tea colored or black. The ascitic fluid cell count is the most useful test. The upper limit of the neutrophil cell count is 250 cells per µl, even in patients who have undergone diuresis. If paracentesis is traumatic, only 1 neutrophil per 250 erythrocytes and 1 lymphocyte per 750 erythrocytes can be attributed to blood contamination. With spontaneous bacterial peritonitis (SBP), the neutrophil count exceeds 250 cells per µl and represents >50% of the total white cell count in the ascitic fluid. Chylous ascites may produce increases in ascitic lymphocyte counts. If infection is suspected, ascitic fluid should be inoculated into blood culture bottles at the bedside and sent for bacterial culture. Gram stain is insensitive for the detection of bacterial infection, and results

should not be considered reliable if negative, as 10,000 organisms per milliliter are needed for Gram stain positivity, whereas spontaneous peritonitis may occur with only 1 organism per milliliter. Similarly, the direct smear has only 0% to 2% sensitivity for the detection of tuberculosis. Ascites fluid culture for tuberculosis is only 40% sensitive and the sensitivity of peritoneal biopsy is 64% to 83%. If tuberculosis is strongly suspected, peritoneal biopsy is indicated using direct visualization of the peritoneal surface with a laparoscope, which has almost 100% sensitivity, rather than blind biopsy. Certain infections can reduce ascitic fluid glucose levels (usually related to GI tract perforation), but because glucose concentrations usually are normal with SBP, this measure has limited utility. Similarly, testing of ascitic fluid pH and lactate levels has been proposed to evaluate for infected fluid; however, their sensitivities are low.

The serum-ascites albumin gradient provides important information about the cause of the ascites. Calculating the gradient involves subtracting the albumin concentration in the ascitic fluid from the serum value. If the serum albumin minus ascitic albumin concentration is 1.1 g per dl or higher, the patient can be diagnosed with portal hypertension with 97% accuracy. Causes of high-gradient ascites include cirrhosis, alcoholic hepatitis, cardiac ascites, massive liver metastases, Budd-Chiari syndrome, portal vein thrombosis, veno-occlusive disease, acute fatty liver of pregnancy, myxedema, and some mixed ascites. Conversely, a gradient of <1.1 g per dl signifies ascites that is not caused by portal hypertension. Low albumin gradient ascites may result from peritoneal carcinomatosis, tuberculosis, pancreatic or biliary disease, nephrotic syndrome, or connective tissue disease. Previous means of assessing the cause included measurement of total ascitic fluid protein and ascitic fluid-to-serum lactate dehydrogenase ratios.

Although sometimes still used to distinguish “exudative” from “transudative,” the accuracy of these measures is only 55% to 60%.

The detection of malignancy in ascitic fluid can be a diagnostic challenge. Although nearly 100% of patients with peritoneal carcinomatosis have positive results on cytologic analysis of the peritoneal fluid, patients with liver metastases, lymphoma, and hepatocellular carcinoma usually give negative cytology results. Peritoneal biopsy is rarely needed for peritoneal carcinomatosis. The value of ascitic fluid levels of carcinoembryonic antigen and humoral tests of malignancy in detection of malignant ascites is undefined.

Other ascitic fluid tests may be ordered depending on the clinical scenario. In uncomplicated cirrhotic ascites, the ascitic fluid amylase level is low with an ascitic fluid-to-serum ratio of 0.4. With pancreatic ascites, the levels may exceed 2000 IU per liter and amylase ratios may increase to 6. With milky ascitic fluid, a triglyceride level is obtained. Chylous ascites triglyceride levels exceed 200 mg per dl versus 20 mg per dl in cirrhotic ascites. If patients have brown ascitic fluid, bilirubin levels in the ascites that are greater than the serum level suggests biliary or bowel perforation.

Structural Testing

Radiographic, endoscopic, and scintigraphic means can be used to assess the cause of ascites. Computed tomography or ultrasound with Doppler may show findings suggestive of cirrhosis, detect mass lesions of the liver, pancreas, or ovaries, and evaluate for portal or hepatic vein thrombosis. Upper endoscopy may show varices or portal gastropathy, indicative of portal hypertension. Liver-spleen scintigraphy may show colloid shifting in cirrhosis. Chest radiography may show apical disease consistent with tuberculosis. Abdominal radiography also is useful in assessing complications of ascites. Plain abdominal radiographs can be assessed for

free subdiaphragmatic air followed by water-soluble gut contrast studies in patients with peritonitis to exclude bowel perforation as a cause.

Principles of Management

Ascites Unrelated to Portal Hypertension

In patients with peritoneal carcinomatosis, peripheral edema will respond to diuretic administration but the ascites does not. The mainstay of management of these patients is periodic therapeutic paracentesis. Peritoneovenous shunts may be performed in selected cases; however, in most instances, the short life expectancy does not warrant this aggressive intervention. Nephrotic ascites will respond to sodium restriction and diuretics. Tuberculous peritonitis requires specific antituberculosis agents. Pancreatic ascites may resolve spontaneously, respond to octreotide therapy, or require endoscopic stenting or surgery if a ductal leak is present. Postoperative lymphatic leaks may require surgical intervention or peritoneovenous shunting. Nephrogenous ascites may respond to vigorous dialysis.

Portal Hypertension–Related Ascites

For patients with ascites secondary to portal hypertension, dietary sodium restriction to a daily level of 2 g is essential. Fluids do not need to be restricted unless the serum sodium is <120 mEq per liter. If single-agent diuretic therapy is planned, spironolactone at a daily dose of 100 mg is the best choice. For patients who experience spironolactone side effects (e.g., painful gynecomastia), amiloride may be given at 10 mg per day. The physician should expect a slow response to spironolactone because of its long half-life; weight loss may not be evident for 2 weeks. It is often reasonable to add a loop diuretic (e.g., furosemide) at 40 mg per day to maximize natriuresis. Doses may slowly be increased to maximums of 400 mg per day of spironolactone and 160 mg per day of furosemide. If diuresis is still suboptimal, metolazone or

hydrochlorothiazide may be added, although the hyponatremic and hypovolemic effects of such triple drug regimens mandate close physician follow-up, often on an inpatient basis. There should be no limit to the amount of weight that can be diuresed daily if pedal edema is present. Once the dependent edema has resolved, diuretics should be adjusted to achieve a daily weight loss of 0.5 kg. Urine sodium levels may be used to direct diuretic therapy. Patients with urine sodium excretion < potassium excretion likely require higher diuretic doses and sodium excretion exceeds sodium the total daily sodium excretion is likely adequate (i.e. > 78 mmol/d) in 95% of circumstances. Development of encephalopathy, a serum sodium level of <120 mEq per liter that does not respond to fluid restriction, or serum creatinine of >2 mg per dl are relative indicators for discontinuation of diuretic therapy. Because concurrent use of NSAIDs promotes renal failure, inhibits the efficacy of diuretics, and may cause gastrointestinal hemorrhage, their use is discouraged.

Various nonmedical means to treat refractory ascites are available. Large-volume paracentesis, with removal of 5 liters of fluid, can be performed in as little as 20 minutes. Total paracentesis, with withdrawal of 20 liters or more of fluid, is now known to be safe. The issue of concurrent administration of intravenous albumin is controversial. Some clinicians advocate albumin infusion as a means to prevent paracentesis-induced changes in electrolytes and creatinine. Other physicians avoid albumin infusion in view of its cost, particularly because differences in long-term survival have not been demonstrated with such measures. Transjugular intrahepatic portosystemic shunts (TIPSs) are effective in many patients with diuretic-resistant ascites. Peritoneovenous shunts (e.g., Denver and LeVeen) drain ascitic fluid into the central venous circulation; however, they have not achieved widespread use because of a lack of efficacy, shunt occlusion, and side effects (e.g., pulmonary edema, variceal hemorrhage, diffuse

intravascular coagulation, and thromboembolism). Surgical portocaval shunt procedures were used in the past, but frequent postoperative complications (e.g., encephalopathy) have tempered enthusiasm for the techniques. Liver transplantation will be curative treatment for both refractory ascites and underlying cirrhosis and should be considered in patients without contraindications.

Complications

Infection

SBP is defined as ascitic fluid infection with pure growth of a single organism and an ascitic fluid neutrophil count of >250 cells per μl without evidence of a surgically remediable intra-abdominal cause. SBP occurs only in the setting of liver disease, for all practical purposes, although it has been reported with nephrotic syndrome. Ascites is a prerequisite for SBP; however, it may not be detectable on physical examination. Infection usually occurs with maximal fluid accumulation. *Escherichia coli*, *Klebsiella pneumoniae*, and *Pneumococcus* organisms are the most common isolates in SBP, with anaerobes being the causative organism in 1% of cases. Eighty-seven percent of SBP patients present with symptoms, most commonly fever, abdominal pain, and changes in mental status, although the clinical manifestations may be quite subtle. Antibiotics should be initiated when an ascitic fluid neutrophil count of >250 cells per μl is documented before obtaining formal culture results. The most well-accepted antibiotic for SBP is the third-generation cephalosporin cefotaxime, to which 98% of offending bacteria are sensitive, though ceftriaxone, amoxicillin-clavulanic acid, and fluoroquinolones have been used in trials with seemingly equivalent results. When susceptibility testing is available, a drug with a narrower-spectrum may be substituted. A randomized trial comparing 5 to 10 days of therapy showed no difference, supporting a shorter antibiotic course, and treatment course is generally 5-7 days. A repeat paracentesis that demonstrates a reduction in neutrophil counts 48 hours after

initiating antibiotic treatment indicates that the antibiotic choice was appropriate. If the correct antibiotics are given in a timely manner, the mortality rate of SBP should not exceed 5%; however, many patients succumb to other complications of the underlying liver disease. Oral quinolones or trimethoprim-sulfamethoxazole is given as prophylactic agents after an initial episode of SBP because of a reported 1-year recurrence rate of 69% in the absence of prophylaxis.

SBP is not the only infectious complication of ascites. *Monomicrobial bacterascites* is defined as the presence of a positive result on ascitic fluid culture for a single organism with a concurrent fluid neutrophil count of <250 cells per µl. One series of patients with bacterascites demonstrated a predominance of gram-positive organisms, whereas another showed flora similar to SBP. Because of the high mortality rate of untreated bacterascites (22% to 43%), antibiotic treatment is warranted for many patients. Alternatively, paracentesis may be repeated for cell count and culture. *Culture-negative neutrocytic ascites* (CNNA) is defined as ascitic fluid with a neutrophil count of ≥250 cells per µl with negative fluid culture results in patients who have received no prior antibiotics. Patients with CNNA usually have spontaneously resolving SBP, but empirical antibiotics usually are given. A decline in ascitic neutrophil counts on repeat paracentesis indicates an appropriate response to therapy. If there is no response to antibiotics, cytologic analysis and culture of the ascitic fluid for tuberculosis may be indicated. *Secondary bacterial peritonitis* manifests as a polymicrobial infection with a very high ascitic fluid neutrophil count with an identified intra-abdominal source such as appendicitis, diverticulitis, or intra-abdominal abscess. In contrast to SBP, secondary peritonitis usually requires surgical intervention. Gut perforation is suspected with two of the following three criteria: ascitic protein concentration of >1 g per dl, glucose level of <50 mg per dl, and lactate dehydrogenase level of

>225 mU per ml. Water-soluble contrast enemas are used in older patients to exclude a perforated colonic diverticulum, whereas young patients should have an upper gastrointestinal study using water-soluble dye because of the probability of a perforated ulcer. In patients with secondary peritonitis but no perforation, repeat paracentesis 48 hours after initiating antibiotic treatment will usually demonstrate increasing neutrophil counts. *Polymicrobial bacterascites* with an ascitic neutrophil count of <250 cells per μl is diagnostic of inadvertent gut perforation by the paracentesis needle. It is usually treated with broad-spectrum antibiotics that include coverage for anaerobes. Alternatively, the decision to treat may be deferred until the results of a repeat paracentesis are obtained.

Tense Ascites

Some patients develop tense ascites with abdominal discomfort or dyspnea with as little as 2 liters of ascitic fluid, whereas others may accumulate 20 liters or more before becoming tense. Therapy for tense ascites relies on large-volume paracentesis, which may have the added benefit of increasing the venous return to the heart with resultant improvement in cardiac output and stroke volume.

Abdominal Wall Hernias

Umbilical and inguinal hernias are common in patients with ascites. These hernias may produce skin ulceration or rupture (Flood's syndrome), or they may become incarcerated. More than one-half of these patients will need surgery, but if possible it should be delayed until the time of liver transplantation. A more aggressive surgical approach is needed for ulceration, rupture, or incarceration because of the risks of systemic infection but should be performed after preoperative paracentesis or TIPS to control ascites. The mortality of rupture is significant (11% to 43%), and it increases in patients with jaundice or coagulopathy.

Hepatic Hydrothorax

Pleural effusions (usually right-sided) are prevalent in cirrhotic ascites. Left-sided effusions are more common with tuberculosis or pancreatic disease. Hepatic hydrothorax is postulated to result from a defect in the diaphragm, which preferentially permits fluid passage into the thorax during the negative pressures generated by normal inspiration. Infection of this fluid is unusual, except in a patient with concurrent SBP. Therapy of hepatic hydrothorax is often challenging because it often does not respond to diuretics. Pleurodesis and peritoneovenous shunts have been tried, but complications are very common. TIPS has been used successfully for hepatic hydrothorax.

Hepatorenal syndrome

Hepatorenal syndrome is the final stage of functional renal impairment in patients with cirrhosis and portal hypertension, occurring almost exclusively in patients with refractory ascites. It is characterized by peripheral vasodilatation and a creatinine clearance < 40 mL/min (or creatinine > 1.5 mg/dL) with normal intravascular volume and the absence of intrinsic renal disease or other renal insults. Urine sodium is not necessarily < 10 mmol/L. Treatment initially is withdrawal of diuretics and nephrotoxins, followed by saline and/or albumin infusion. Vasoactive agents, octreotide, midodrine, and vasopressin, as well as TIPS have been used with some encouraging results in largely uncontrolled studies and liver transplantation is the only definitive cure and should be undertaken in all appropriate candidates.