INTRODUCTION

Cirrhosis:

DEFINITION:

The word cirrhosis is derived from the Greek word kirrhos, meaning orange or tawny, and osis, meaning condition. World Health Organization definition of cirrhosis is a diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules that lack normal lobular organization.

Structural changes in the liver may cause impairment of hepatic function manifested as:

- Jaundice.
- Portal hypertension and varices.
- Ascites.
- Hepatorenal syndrome.
- Spontaneous bacterial peritonitis.
- Hepatic encephalopathy.
- Progressive hepatic failure.

This definition distinguishes cirrhosis from other types of liver disease that have either nodule formation or fibrosis, but not both. These hepatic disorders may be characterized by portal hypertension in the absence of cirrhosis. Nodular regenerative hyperplasia, for example, is characterized by diffuse nodularity without fibrosis, whereas chronic schistosomiasis is characterized by Symmers' pipestem fibrosis with no nodularity.[(1)]

CLASSIFICATION

1. Morphologic classification is less useful because of considerable overlap:

   a) Micronodular cirrhosis, with uniform nodules less than 3 mm in diameter: causes include alcohol, hemochromatosis, biliary obstruction, hepatic venous outflow obstruction, jejunoileal bypass, and Indian childhood cirrhosis.
   b) Macronodular cirrhosis, with nodular variation greater than 3 mm in diameter: causes include chronic hepatitic C, chronic hepatitis B, alpha-1 antitrypsin deficiency, and primary biliary cirrhosis,
   c) Mixed cirrhosis, a combination of micronodular and macronodular cirrhosis: micronodular cirrhosis frequently evolves into macronodular cirrhosis.

2. Etiologic classification is preferred.
   This method of classification is the most useful clinically; by combining clinical, biochemical, genetic, histologic, and epidemiologic data, the likely etiologic agent can be ascertained.

Table 1 lists the etiologic classification and tests used to determine the cause.

Most cases of cryptogenic cirrhosis may be "burned out" nonalcoholic steatohepatitis (NASH). It is now established that NASH may occur in patients with cryptogenic cirrhosis who undergo liver transplantation, a finding suggesting that NASH is a disease recurrence.

TABLE 1: Etiology and diagnostic workup of the common causes of cirrhosis [(2)]

Etiology	Diagnostic evaluation
Infection :	
Hepatitis B	HBsAg, anti-HBs, anti-HBc, HBV DNA
Hepatitis C	Anti-HCV, HCV RNA
Hepatitis D	Anti-HDV
Toxins :	
Alcohol	History, AST/ALT ratio, liver biopsy
Cholestasis:	
Primary biliary cirrhosis	AMA, IgM, liver biopsy
Secondary biliary cirrhosis	MRCP, ERCP, liver biopsy
Primary sclerosing cholangitis	MRCP, ERCP, liver biopsy
Autoimmune:	
Autoimmune hepatitis	ANA, IgG level, anti smooth muscle antibodies, liver-kidney microsomal antibodies, liver biopsy
Vascular:	
Cardiac cirrhosis	Echocardiogram, liver biopsy
Budd–Chiari syndrome	CT, US, MRI/MRA
Sinusoidal obstruction syndrome	History of offending drug use, liver biopsy
Metabolic:	
Hemochromatosis	Iron studies, *HFE* gene mutation, liver biopsy
Wilson disease	Serum and urinary copper, ceruloplasmin, slit lamp eye examination, liver biopsy
Alpha-1 antitrypsin deficiency	Alpha-1 antitrypsin level, protease inhibitor type, liver biopsy
NASH	Liver biopsy
Cryptogenic	Exclude NASH, drugs

CLINICAL FEATURES

The manifestations of cirrhosis are protean. Patients with cirrhosis may come to clinical attention in numerous ways:

1. Stigmata of chronic liver disease on physical examination (e.g., palmar erythema, spider telangiectasias).
2. Abnormal serum chemistry test results and hematologic indices (e.g., serum aminotransferases, bilirubin, alkaline phosphatase, albumin, prothrombin time, and platelet count).
3. Radiographic abnormalities (e.g., small, shrunken, nodular liver on ultrasound or computed tomographic examination).
4. Complications of decompensated liver disease (e.g., ascites, variceal hemorrhage).
5. Cirrhotic appearance of the liver at the time of laparotomy or laparoscopy.
6. Autopsy.

A patient with cirrhosis may present with none, some, or all of the following findings:

1. General features

Fatigue, Anorexia, Malaise, Weight loss, Muscle wasting and Fever.

2. Gastrointestinal

Parotid enlargement, Diarrhea, Cholelithiasis, Gastrointestinal bleeding

3. Hematologic

- Anemia, Folate deficiency, Spur cell anemia (hemolytic anemia seen in severe alcoholic liver disease), Splenomegaly with resulting pancytopenia.
- Thrombocytopenia, Leukopenia, Impaired coagulation, Disseminated intravascular coagulation, Hemosiderosis.

4. Pulmonary

- Decreased oxygen saturation, Altered ventilation–perfusion relationships, Portopulmonary hypertension, Hyperventilation Reduced pulmonary diffusion capacity and Hepatic hydrothorax.
- Hepatopulmonary syndrome.
- Triad of liver disease, an increased alveolar–arterial gradient while breathing room air, and evidence for intrapulmonary vascular dilatations.

5. Cardiac: hyperdynamic circulation

6. Renal

- Secondary hyperaldosteronism leading to sodium and water retention.
- Renal tubular acidosis (more frequent in alcoholic cirrhosis, Wilson disease, and primary biliary cirrhosis).
- Hepatorenal syndrome

7. Endocrinologic

- **Hypogonadism**
  - *Male patients:* loss of libido, testicular atrophy, impotence, decreased amounts of testosterone, Gynecomastia, Changes in body hair patterns.
  - *Female patients:* infertility, dysmenorrhea, loss of secondary sexual characteristics, Feminization (acquisition of estrogen-induced characteristics).
- **Diabetes mellitus.**

8. Neurologic

- Hepatic encephalopathy
- Variants include spastic paraplegia and acquired non-wilsonian hepatocerebral degeneration
- Peripheral neuropathy
- Asterixis

9. Musculoskeletal

- Reduction in lean muscle mass.
- Hypertrophic osteoarthropathy: synovitis, clubbing, and periostitis.
- Hepatic osteodystrophy.
- Muscle cramps.
- Umbilical herniation.

10. Dermatologic

- Spider telangiectases
- Palmar erythema
- Nail changes.
- Clubbing
- Jaundice
- Paper money skin
- Caput medusa
- Easy bruising.

COMPLICATIONS

- Ascites and Spontaneous bacterial peritonitis.
- Variceal hemorrhage.
- Hepatic encephalopathy.
- Hepatocellular carcinoma.
- Hepatorenal syndrome.[3]

DIAGNOSIS

1. Physical examination

a. Stigmata of chronic liver disease and/or cirrhosis:
Spider telangiectasias, Palmar erythema, Dupuytren's contractures, Gynecomastia Testicular atrophy,

b. Features of portal hypertension
Ascites, Splenomegaly, Caput medusae, Evidence of hyperdynamic circulation (e.g., resting tachycardia), Cruveilhier–Baumgarten murmur: venous hum best auscultated in the epigastrium

c. Features of hepatic encephalopathy:
Confusion, Asterixis, Fetor hepaticus

d. Other:
Jaundice, Bilateral parotid enlargement, Scant chest and axillary hair.

2. Laboratory evaluation

a. Tests of hepatocellular injury:
Aminotransferases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]): most forms of chronic hepatitis other than alcohol have an AST/ALT ratio of less than 1; however, as chronic hepatitis progresses to cirrhosis, the ratio of AST/ALT may reverse.

b. Tests of cholestasis:
Alkaline phosphatase, Serum bilirubin (conjugated and unconjugated), Gamma glutamyl transpeptidase (GGTP), 5′-Nucleotidase.

c. Tests of synthetic function:
Serum albumin, Prothrombin time.

d. Special tests to aid in diagnosis:
- Viral hepatitis serology , PCR techniques for detecting viral RNA or DNA.
- Serum iron, total iron binding capacity (TIBC), ferritin, genetic testing for the HFE.
- Gene mutation (hemochromatosis), Serum Ceruloplasmin, serum and urinary copper (Wilson disease), Alpha-1 antitrypsin level and protease inhibitor type,

Serum immunoglobulins (autoimmune hepatitis), Autoantibodies: antinuclear antibodies (ANA), antimitochondrial antibodies (AMA), anti–liver kidney microsomal antibodies (LKM), anti–smooth muscle antibodies (SMA) (autoimmune hepatitis, primary biliary cirrhosis).

e. Screening test for hepatocellular carcinoma:
Serum alpha fetoprotein.

3. Imaging studies

a. Abdominal Ultrasonography (U/S):
- Noninvasive, relatively inexpensive.
- Can easily detect ascites, biliary dilatation.
- Screening test for primary hepatocellular carcinoma.
- Duplex Doppler ultrasonography can further assess hepatic and portal vein.
- Patency.

b. Computed Tomography (CT):
- Noninvasive, more expensive than ultrasound.
- Findings in cirrhosis are nonspecific.
- May be helpful in the diagnosis of hemochromatosis; increased density of the liver is suggestive.

c. Magnetic resonance imaging (MRI):
- Noninvasive, but expensive.
- Excellent for further evaluation of suspicious liver lesions; can help differentiate focal fat from a possible hepatic malignancy
- Can easily assess hepatic vasculature without the need for nephrotoxic contrast agents; more reliable than Doppler ultrasound.
- May suggest iron overload states (black hypointense liver).
- Magnetic resonance cholangiography (MRC) a noninvasive method to image the biliary tree.

d. Radionuclide studies:
Colloid liver spleen scan using technetium-99m sulfur colloid may aid in detection of cirrhosis; increased uptake of colloid in the bone marrow and spleen, with decreased uptake in the liver.

e. Esophagogastroduodenoscopy (EGD) to screen for gastroesophageal varices.

4. Liver biopsy

a. The gold standard for the diagnosis of cirrhosis.
b. Usually performed percutaneously; occasionally obtained through the transjugular approach or at laparoscopy.
c. Relatively low-risk procedure.
d. Complications: bleeding, infection, pneumothorax, pain, hypotension.

PROGNOSIS

1. This depends on the development of cirrhotic-related complications.
2. A classification scheme proposed to assess survival, Child's classification, has undergone various modifications; the system currently used by many hepatologists is the Child– Turcotte–Pugh (CTP) scoring system (Table 2).

TABLE 2: Modified Child–Turcotte–Pugh scoring system for cirrhosis:[4]

Parameter	Numerical score		
	1	**2**	**3**
Ascites	None	Slight	Moderate/severe
Encephalopathy	None	Slight/moderate	Moderate/severe
Bilirubin (mg/dL)	<2.0	2–3	>3.0
Albumin (mg/L)	>3.5	2.8–3.5	<2.8
Prothrombin time (sec)	1–3	3-6	>6

Total numerical score	Child Pugh class
5-6	A
7-9	B
10-15	C

Portal Hypertension

Definition:

- An increase in portal venous pressure
- Normal portal pressure: 5 to 10 mm Hg
- Portal hypertension: greater than 12 mm Hg
- Normal portal blood flow: 1 to 1.5 L/minute
- Increased resistance to portal blood flow leading to formation of portosystemic collateral vessels that divert portal blood flow to the systemic circulation, thus effectively bypassing the liver.

Classification (Table 3)

1. Portal hypertension has causes other than cirrhosis.
2. The major classification scheme employed is based on the location of the block to portal flow: prehepatic, intrahepatic, and posthepatic; intrahepatic causes are further separated into presinusoidal, sinusoidal, and postsinusoidal.

TABLE 3: Causes of portal hypertension[5]

1. Prehepatic:
• Portal vein thrombosis. • Cavernous transformation of the portal vein. • Splenic vein thrombosis. • Splanchnic arteriovenous fistula. • Idiopathic tropical splenomegaly.
2. Intrahepatic (some overlap exists)
a. **Presinusoidal:** (affects portal venule): • Schistosomiasis (most common cause of portal hypertension worldwide). • Congenital hepatic fibrosis. • Sarcoidosis. • Chronic viral hepatitis. • Primary biliary cirrhosis (early). • Myeloproliferative diseases. • Nodular regenerative hyperplasia. • Hepatoportal sclerosis (idiopathic portal hypertension). • Malignant disease. • Wilson disease. • Hemochromatosis. • Polycystic liver disease. • Amyloidosis. • Toxic agents: copper, arsenic, vinyl chloride, 6-mercaptopurine.
b. **Sinusoidal:** (affects sinusoids): • All causes of cirrhosis. • Acute alcoholic hepatitis. • Severe viral hepatitis. • Acute fatty liver of pregnancy. • Vitamin A intoxication. • Systemic mastocytosis. • Peliosis hepatis. • Cytotoxic drugs.
c. **Postsinusoidal:** (affects central vein): • Sinusoidal obstruction syndrome. • Alcoholic central hyaline sclerosis.
3. Posthepatic
a. Hepatic vein thrombosis: • Budd–Chiari syndrome. • Vascular invasion by tumor.
b. Inferior vena caval obstruction: • Inferior vena cava web. • Vascular invasion by tumor.
c. Cardiac disease: • Constrictive pericarditis. • Severe tricuspid regurgitation.

Clinical Consequences

1. Varices: gastroesophageal, anorectal, retroperitoneal, stomal, other.
2. Portal hypertensive gastropathy, enteropathy, and colopathy.
3. Caput medusae.
4. Ascites and hepatic hydrothorax.
5. Congestive splenomegaly.
6. Hepatic encephalopathy.[6]

Ascites in patients with cirrhosis

Ascites is defined as the pathologic accumulation of fluid in the peritoneal cavity. It is the most common complication of cirrhosis, which is the most common cause of ascites in the United States, accounting for approximately 85 percent of cases.

Within 10 years after the diagnosis of compensated cirrhosis, about 50 percent of patients will have developed ascites.[7]

Pathogenesis:

The development of ascites is the final consequence of a series of anatomic, pathophysiologic, and biochemical abnormalities occurring in patients with cirrhosis. The two older theories of ascites formation, the underfill theory and the overflow theory, appear to be relevant at different stages of the natural history of cirrhosis. However, the most recent theory, the arterial vasodilation hypothesis, appears to match best with the actual hemodynamic data, and has become the most widely accepted theory.[8]

PORTAL HYPERTENSION — The development of portal hypertension (PHT) is the first step toward fluid retention in the setting of cirrhosis. Patients with cirrhosis but without PHT do not develop ascites or edema. A portal pressure >12 mmHg appears to be required for fluid retention; on the other hand, ascites will usually disappear if portal pressure is reduced below 12 mmHg, eg, after a surgical or radiologic portosystemic shunt.[9] Sinusoidal hypertension appears to be required for fluid retention to occur; presinusoidal portal hypertension, as in portal vein thrombosis, does not result in ascites formation in the absence of another predisposing factor.

PHT leads to profound changes in the splanchnic circulation. Although it was formerly thought that PHT was due solely to a mechanical obstruction to portal flow, data from animal models provide evidence for a component of increased portal venous inflow as a consequence of splanchnic arterial vasodilation.[10]

Patients with cirrhosis and clinically significant PHT have several circulatory, vascular, functional, and biochemical abnormalities that contribute to the pathogenesis of fluid retention.[11]

Vasodilation and hyperdynamic circulation — Patients with cirrhosis and ascites usually have a marked reduction in systemic vascular resistance (SVR) and in mean arterial pressure (MAP) plus an increase in cardiac output. These abnormalities result in a hyperdynamic circulation which can be found in patients and experimental animals with cirrhosis before the development of ascites.[12]

The vascular territory where the reduced SVR is most obvious is the arterial splanchnic circulation .The presence of this abnormality in other vascular territories is less obvious and the subject of controversy.[13]

Mechanisms of vasodilation — Considerable effort has been made to elucidate the exact mechanism(s) of arterial vasodilation and the hyperdynamic circulation of cirrhosis. Anatomic and functional liver-related causes have been considered in order to explain the presence of vasodilation.

The opening of portasystemic collaterals, a frequent finding in cirrhosis, helps explain the presence of vasodilation. The performance of portocaval shunts in these patients further decreases SVR.[14]

Although portosystemic collaterals may contribute, most of the studies which have examined the vasodilation in patients with cirrhosis have focused on increased levels of circulating vasodilators. Glucagon has been one of the most widely studied, although its role in the pathogenesis of vasodilation has not been precisely defined. Other vasodilators have been considered, such as vasoactive intestinal peptide, substance P, platelet-activating-factor or prostaglandins.[15]

Increased synthesis of systemic prostacyclin has been observed in patients with cirrhosis even before they develop ascites .The synthesis of renal prostacyclin is increased in these patients and contributes to maintenance of the glomerular filtration rate (as evidenced by reductions in glomerular filtration rate and renal plasma flow following the administration of a nonsteroidal antiinflammatory drug) . Renal prostaglandin synthesis decreases with advanced liver disease and may contribute to the marked renal vasoconstriction in patients with hepatorenal syndrome.[16]

Patients with cirrhosis but without portal hypertension (eg, patients after portasystemic shunt) also show increased levels of systemic prostacyclin . It is possible that this activation is related to the presence of endotoxemia, since selective intestinal decontamination with nonabsorbable antibiotics significantly decreases the synthesis of systemic prostacyclin.[17]

Although the above factors may play a contributory role, much of the recent literature has focused on the possible role of nitric oxide (NO). The following observations suggest that NO is the primary mediator of vasodilation in cirrhosis:

- The activity of endothelial NO synthase (which promotes the synthesis of NO from L-arginine) is increased in the arterial vessels of cirrhotic rats with ascites.[18]

- The serum levels of nitrite and nitrate, an index of in vivo NO synthesis, are significantly higher in patients with cirrhosis than in controls.[19]

- Inhibition of the synthesis of NO in cirrhotic rats significantly increases the arterial pressure and SVR, decreases the cardiac index and reverses the impaired response to vasopressors.[20]

The possible factors responsible for the increased NO synthesis in cirrhosis have been intensively studied. Nitric oxide production may be stimulated by endotoxin or other bacterial products, such as bacterial DNA from the gastrointestinal tract, which are less efficiently cleared due to portal-systemic shunting and decreased reticuloendothelial cell function in cirrhosis. The increased synthesis of NO is mediated by both the endothelial and inducible forms. This hypothesis is supported by the following observations.[21]

- NO concentrations in blood collected from portal vein are higher than those of peripheral veins.[22]
- A significant correlation has been noted between serum nitrite and nitrate levels and endotoxin.[22]

- Oral administration of the antibiotic colistin to patients with cirrhosis significantly reduces plasma endotoxin levels and the serum concentration of nitrite and nitrate , and norfloxacin increases systemic vascular resistance and decreases plasma renin in a subgroup of patients with ascites.[23]

- Fragments of bacterial DNA have been detected in the blood of patients with advanced cirrhosis where they can persist for days.Their presence induces the synthesis of nitric oxide by peritoneal macrophages, suggesting that they may be related to the hemodynamic derangement observed in patients with advanced cirrhosis.[24]

CONSEQUENCES OF VASODILATION — The progressive vasodilation seen in cirrhosis leads to the activation of endogenous vasoconstrictors, sodium and water retention, and increasing renal vasoconstriction.

Activation of endogenous vasoconstrictor agents — The reduction in pressure (or stretch) at the carotid and renal baroreceptors induced by cirrhotic vasodilation results in activation of the sodium-retaining neurohumoral mechanisms in an attempt to restore perfusion pressure to normal. These include the renin-angiotensin-aldosterone system, sympathetic nervous system, and antidiuretic hormone (vasopressin). The secretion of these "hypovolemic" hormones is proportional to the severity of the hemodynamic insufficiency.

The net effect is avid sodium and water retention because the patient is effectively volume depleted even though extracellular sodium stores, the plasma volume, and the cardiac output are increased.[25]

Sodium retention — The retention of sodium and water increases the plasma volume. If this were adequate to refill the intravascular space, the activity of the endogenous vasoconstrictor systems would decrease, with a progressive normalization of the excretion of

sodium and water . However, impaired sodium excretion after a saline load and a reduction in central blood volume have been demonstrated in patients with cirrhosis who have not yet developed ascites. This unstable equilibrium can be affected by infections, drugs, or progressive impairment in liver function. In advanced disease, sodium excretion often falls to less than 10 mEq/day.[26]

Thus, sodium retention is a sensitive marker of the overall status of the patient with cirrhosis. A significant nonlinear relationship has been identified between urinary sodium excretion and the aminopyrine breath test, a measurement of true liver function; the presence of sodium retention was indicative of at least a 50 percent reduction in liver function. Fluid overload is an important landmark in the natural history of these patients, and the degree of sodium retention is inversely related to survival. In one series, for example, patients with ascites and urinary sodium excretion below 10 mEq/day had a mean survival rate as low as five to six months, in comparison to over two years in those with ascites and a higher rate of sodium excretion.[27]

Water retention — Water excretion is usually normal in patients with cirrhosis before the development of ascites and then becomes increasingly impaired as the liver disease progresses. This abnormality is largely related to the increased release of antidiuretic hormone (ADH) described above, since suppression of ADH release is required to excrete a water load. The pathogenetic importance of ADH in water retention in cirrhosis has been demonstrated in rats with cirrhosis in which the administration of an ADH receptor antagonist restores near normal water excretory ability .The inability to excrete water regularly leads to the development of hyponatremia and and hypoosmolality.[28]

Thus, patients with cirrhosis and ascites usually demonstrate urinary sodium retention, increased total body sodium, and dilutional hyponatremia. It can be challenging to explain to patients and their families (and even to some physicians) that the hyponatremia does not indicate a deficiency of sodium.

Because the increase in ADH secretion (and therefore the degree of water retention) is roughly proportional to the severity of the cirrhosis, the degree of hyponatremia parallels the severity of the liver disease and is, along with the degree of sodium retention, of prognostic value. The severity of hyponatremia correlates with worsening survival.[29]

Renal vasoconstriction — The activation of vasoconstrictor systems tends to reduce renal blood flow. Renal perfusion may initially be maintained due to vasodilators such as prostaglandins and perhaps nitric oxide. However, the natural progression of liver disease overcomes these protective mechanisms, leading to progressive renal hypoperfusion, a gradual decline in the glomerular filtration rate, and, in some patients, the hepatorenal syndrome.[30]

The importance of splanchnic vasodilation in the genesis of renal ischemia has been indirectly illustrated by the response to ornipressin and terlipressin, analogs of antidiuretic hormone (arginine vasopressin) that are preferential splanchnic vasoconstrictors. In patients with advanced cirrhosis, the administration of ornipressin or terlipressin raised the mean

arterial pressure, increased renal blood flow, glomerular filtration rate, and urinary sodium excretion and volume.[31]

The reduction in glomerular filtration rate in patients with liver disease is often masked clinically. Both urea and creatinine production may be substantially reduced in this setting, due to the liver disease and to decreased muscle mass. The net effect is that a serum creatinine concentration that appears to be within the normal range (1 to 1.3 mg/dL or 88 to 115 µmol/L) may, depending primarily upon muscle mass, be associated with a glomerular filtration rate that ranges from as low as 20 to 60 mL/min to a clearly normal value above 100 mL/min.[32]

Diagnosis and evaluation of patients with ascites

Successful treatment of ascites depends upon an accurate diagnosis of its cause (table 4).[33]

Table 4 : Causes of ascites

Cirrhosis	81%
Cancer	10%
Heart Failure	3%
Tuberculosis	2%
Dialysis	1%
Pancreatic disease	1%
Others	2%

The most common cause in the United States is cirrhosis, which accounts for approximately 80 percent of cases . Ascites is the most common complication of cirrhosis.[34] Such patients usually respond to diuretics and sodium restriction in contrast to those with some other causes of ascites (such as peritoneal carcinomatosis) in whom sodium restriction and diuretics usually cause intravascular volume depletion without loss of ascitic fluid.[35]

The initial approach to the patient with ascites include:

History — In the current obesity epidemic an obese abdomen can masquerade as ascites, potentially leading to inappropriate treatment with diuretics. The description of the onset of symptoms may be helpful for distinguishing fat from ascites. Patients frequently seek medical attention within a few weeks of ascites development. The fluid usually accumulates rapidly, and patients are intolerant of the distension and the associated early satiety and shortness of breath. In contrast, the thickening abdominal wall and enlarging omentum associated with obesity develop over months or years.[3]

Liver disease — Patients should be questioned extensively regarding risk factors for liver disease since cirrhosis is the most common cause of ascites.

Viral hepatitis — Risk factors for hepatitis C include transfusions before 1990, needle sharing, substance use including cocaine snorting, tattoos, and acupuncture. Patients

at increased risk for hepatitis B include those who received a transfusion before 1971, persons born in hyperendemic areas (these include Africa, Southeast Asia including China, Korea, Indonesia and the Philippines, the Middle East except Israel, South and Western Pacific islands, the interior Amazon River basin, and certain parts of the Caribbean (Haiti and the Dominican Republic), men who have sex with men, injection drug users, those on dialysis, HIV infection, family, household, and sexual contacts of HBV-infected persons.

Nonalcoholic steatohepatitis — Patients suspected of having cirrhosis without an obvious cause should be questioned about risk factors for nonalcoholic steatohepatitis (NASH). NASH accounts for most patients previously thought to have cryptogenic cirrhosis . Risk factors include obesity, diabetes, and hyperlipidemia. It is useful to inquire about lifetime maximum body weight. Calculating the current body mass index and determining how many years it has been >30 kg/m2 may be helpful in assessing the risk of NASH.[(36)]

Miscellaneous causes — Patients with ascites who lack risk factors for or evidence of cirrhosis (based upon history, physical findings, and laboratory and imaging tests) should be questioned about cancer, heart failure, tuberculosis, hemodialysis (called nephrogenic ascites), and pancreatitis.[(37)]

Physical examination — Almost all patients with cirrhosis severe enough to lead to ascites formation have stigmata of cirrhosis on physical examination. An exception to this rule is the darkly-pigmented patient in whom reddish skin findings (vascular spiders and palmar erythema) are not readily apparent. Stigmata that are useful in increasing suspicion of the presence of cirrhosis are vascular spiders, palmar erythema, and abdominal wall collaterals. Spiders are most apparent on the face, neck, shoulders, and upper chest, and are unusual below the umbilicus. The palmar erythema of cirrhosis is "blotchy" and most prominent on the hypothenar eminence and next most prominent on the thenar eminence, with sparing of the center of the palm. The collaterals are most noticeable from the umbilicus extending cephalad.

Many patients with advanced liver disease also have jaundice, muscle wasting, and leukonychia (white nails). Parotid enlargement may be present but is probably due to alcohol, not cirrhosis per se. The liver and spleen may be palpable. The most helpful physical finding in confirming the presence of ascites is flank dullness . When flank dullness is detected, it is useful to see if it shifts with rotation of the patient (ie, "shifting dullness").[(38)]

DIAGNOSIS — The diagnosis of ascites is established with a combination of a physical examination and an imaging test (usually ultrasonography).

Ascites is frequently suspected based upon the history and physical examination. However, the accuracy of physical findings is variable depending in part upon the amount of fluid present, the technique used to examine the patient, and the clinical setting (eg, detection may be more difficult in patients who are obese). The sensitivity and specificity of the physical examination ranged from 50 to 94 percent and 29 to 82 percent in a study comparing various physical findings to ultrasound as the gold standard.[(39)]

The absence of flank dullness was the most accurate predictor against the presence of ascites; the probability of ascites being present was less than 10 percent in such patients. However, approximately 1500 mL of fluid had to be present for flank dullness to be detected; thus, lesser degrees of ascites can be missed. Ultrasonography can be helpful when the physical examination is not definitive.[40]

Grading — A grading system for ascites has been proposed by the International Ascites Club:[41]

- Grade 1: mild ascites detectable only by ultrasound examination.
- Grade 2: moderate ascites manifested by moderate symmetrical distension of the abdomen.
- Grade 3: large or gross ascites with marked abdominal distension.

Imaging tests — Patients with ascites should be "imaged" to confirm or refute the presence of ascites, cirrhosis, or malignancy. Ultrasound is probably the most cost-effective modality. Another advantage of ultrasound is that it involves no radiation or intravenous access, and no risk of contrast allergy or nephropathy. These features contrast dramatically with computerized tomographic scanning, although ascites can be seen easily on CT.[42]

ABDOMINAL PARACENTESIS — Abdominal paracentesis with appropriate ascitic fluid analysis is the most efficient way to confirm the presence of ascites, diagnose its cause, and determine if the fluid is infected . The technique of paracentesis has been described in detail elsewhere . An ultrasound study demonstrated that a left lower quadrant tap site is superior to a midline site; the abdominal wall is relatively thinner in the left lower quadrant while the depth of fluid is greater . The EDTA "purple-top" tube is used for the cell count; a red-top tube is used for the "chemistries;" and blood culture bottles are used for the bacterial cultures.[43]

ASCITIC FLUID TESTS — Many ascitic fluid tests have been proposed as useful in the past, while some of the newer tests have been found to be more confusing than helpful and have been abandoned. The tests that are ordered are determined by the clinical setting. The two main issues that arise regarding ascites are:

- Is the fluid infected?
- Is portal hypertension (PHT) present?

Cell count and differential — The cell count with differential is the single most helpful test performed on ascitic fluid to evaluate for infection and should be ordered on every specimen, including therapeutic paracentesis specimens. Ascitic fluid infection is a reversible cause of deterioration and a preventable cause of death in patients with cirrhosis and ascites. The key to survival is early detection and treatment. The cell count should be available within one hour while the culture takes several hours to days . Antibiotic treatment should be considered in any patient with a polymorphonuclear count ≥250/mm3.[44]

Serum-to-ascites albumin gradient — The serum-to-ascites albumin gradient (SAAG) accurately identifies the presence of portal hypertension and is more useful than the protein-based exudate/transudate concept . The SAAG is easily calculated by subtracting the ascitic fluid albumin value from the serum albumin value, which is obtained on the same day.

•The presence of a gradient ≥1.1 g/dL (11 g/L) indicates that the patient has portal hypertension with 97 percent accuracy .

•A gradient <1.1 g/dL (<11 g/L) indicates that the patient does not have portal hypertension .The SAAG need not be repeated after the initial measurement.[45]

Cultures — Bacterial cultures of ascitic fluid should be obtained on specimens from patients with new onset ascites, those who are being admitted with ascites, and those who deteriorate with fever, abdominal pain, azotemia, acidosis, or confusion . In comparison, therapeutic paracentesis samples in patients without symptoms of infection do not need to be cultured.[46]

Protein — Ascitic fluid had been classified as an exudate if the total protein concentration is ≥2.5 or 3 g/dL and a transudate if it is below this cut-off. However, the exudate/transudate system of ascitic fluid classification has been replaced by the SAAG, which, as described above, is a more useful measure for determining whether portal hypertension is present.

Despite its problems, the ascitic fluid total protein concentration remains of some value. This parameter does not change with development of spontaneous bacterial peritonitis (SBP); patients with a value less than 1 g/dL have a high risk of SBP. Selective intestinal decontamination may help prevent SBP in patients with low protein ascites.[47]

Tests for tuberculous peritonitis — A variety of tests have been used for the detection of tuberculous peritonitis.

- Direct smear — The direct smear of ascitic fluid has only 0 to 2 percent sensitivity in detecting Mycobacteria . We have not encountered a single true positive ascitic fluid Mycobacterial smear.

- Culture — When one liter of fluid is cultured, sensitivity for Mycobacteria supposedly reaches 62 to 83 percent . However, most laboratories can only process 50 mL of ascitic fluid for Mycobacterial culture.

- Peritoneoscopy — Peritoneoscopy with culture of a biopsy specimen has a sensitivity for detecting tuberculous peritonitis that approaches 100 percent .

- Cell count — Tuberculous peritonitis can mimic the culture-negative variant of SBP, but mononuclear cells usually predominate in tuberculosis.[48]

- Adenosine deaminase — Adenosine deaminase is a purine-degrading enzyme that is necessary for the maturation and differentiation of lymphoid cells. Adenosine

deaminase activity of ascitic fluid has been proposed as a useful non-culture method of detecting tuberculous peritonitis; however, patients with cirrhosis and tuberculous peritonitis usually have falsely low values .This test is useful in countries such as India, but of very limited utility in the United States because most patients in the United States with tuberculous peritonitis also have cirrhosis.[49]

Management of ascites in cirrhosis:

The effective treatment of ascites in cirrhosis involves correcting one or more of the pathophysiological processes that lead to ascites formation (Fig. 1). In short, the presence of cirrhosis and portal hypertension leads to vasodilatation in the systemic and splanchnic circulations, but vasoconstriction in the renal circulation. Together with alterations in renal auto-regulation, a reduction in functional liver cell mass, and the development of cirrhotic cardiomyopathy, these processes result in a gradual increase in renal sodium and water retention. The presence of portal hypertension then preferentially localizes the excess fluid in the peritoneal cavity as ascites.[50]

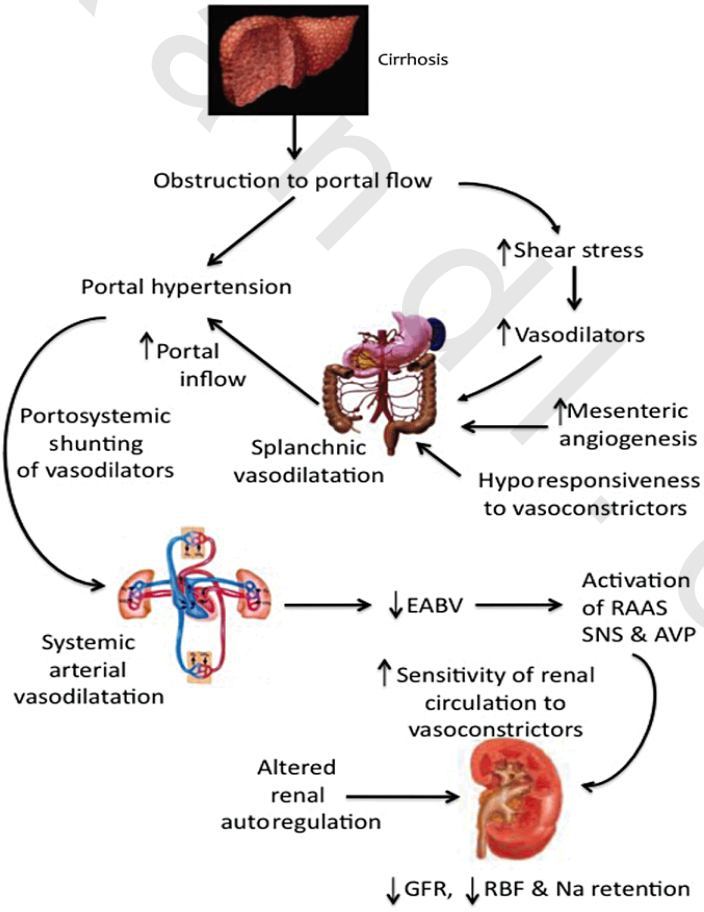

Figure 1: Pathogenesis of ascites formation. EABV, effective arterial blood volume; GFR, glomerular filtration rate; Na, sodium; RAAS, rennin–angiotensin–aldosterone system; RBF, renal blood flow; SNS, sympathetic nervous system.

The management of ascites requires a stepwise approach, beginning with dietary sodium restriction and diuretic therapy, followed by second-line treatments once refractory ascites sets in.[51]

Dietary sodium restriction

The underlying pathophysiology that leads to ascites formation in cirrhosis is renal sodium retention; therefore, the mainstay of treatment of ascites is to induce a negative sodium balance. This can be achieved by reducing the dietary sodium intake, as well as increasing the renal sodium output using a combination of diuretics.[51]

It is not uncommon for patients with ascites who are not on diuretics to have renal sodium excretion of < 20 mmol/day. Such a patient on a no-added-salt diet containing 130–150 mmol of sodium will retain at least 100 mmol of sodium/day, equivalent to the accumulation of 10 L of ascitic fluid in 2 weeks (100 mmol/day × 14 days ÷ 140 mmol/L = 10 L). The International Ascites Club has recommended a sodium intake of 88 mmol/day. This will require the use of special, low-sodium food items, and consultation with a dietician is usually required. Patients are more likely to adhere to a low-sodium diet if there is family support.[41]

In patients who normally consume a high-salt diet, the use of sodium restriction alone can lead to the reduction of ascites, especially if the urinary sodium excretion is > 78 mmol/day. If a patient who admits to adhering to a low-sodium diet and is still gaining weight rapidly, calculating the sodium balance can often bring the message home. Salt substitutes usually contain high potassium contents, and can lead to hyperkalemia if patients are also on potassium-sparing diuretics. In the majority of cirrhotic patients with ascites, diuretics are usually required to induce a natriuresis.[52]

Diuretic therapy

Diuretics block sodium reabsorption along the various nephron sites, thereby increasing renal sodium excretion. Water excretion then follows passively. It is customary to start diuretic therapy with an aldosterone antagonist, such as spironolactone, otherwise all the renal sodium that is not absorbed at the loop of Henle with the use of a loop diuretic alone will be reabsorbed at the distal tubule under the unopposed action of the high aldosterone levels. Spironolactone is usually administered at a start-up dose of 100 mg/day, and gradually increased up to 400 mg/day. The diuretic effect can be seen within 48 h, but the peak onset of action is 2 weeks, due to impaired metabolism in cirrhotics and a very long half-life of up to 5 days.[53]

Amiloride can be used instead of spironolactone, starting at 5 mg/day, and gradually increased to 20 mg/day. It has a shorter half-life, and therefore, a quicker onset of action, but is less effective than spironolactone, as shown in a randomized, controlled trial.[54] Potassium canrenoate, another aldosterone antagonist, is popular in Europe, and has been shown to reduce the 1-year cumulative occurrence of ascites in cirrhosis.[55]

If the use of a distal diuretic is not producing the desired response, a loop diuretic, such as furosemide, can be added, starting at a dose of 40 mg/day, and gradually increased to 160 mg/day. The dose response curve of furosemide is sigmoidal. Therefore, once a maximum diuretic response is reached, further increases in furosemide dose will not increase the diuretic response. The most successful therapeutic regimen is the combination of a distal diuretic, such as spironolactone, and a loop diuretic, such as furosemide, beginning with 100 mg and 40 mg respectively, and increased in a step-wise fashion, preferably maintaining the same ratio of dosages, in order to maintain normal potassium levels.[52]

There have been discussions as to whether the simultaneous or sequential use of an aldosterone antagonist and a loop diuretic is more efficacious in the treatment of ascites. Santos *et al*. reported that both the sequential or combined use of diuretics was similar in terms of the diuretic response and diuretic-induced complications.[53] However, Angeli *et al*. demonstrated in a randomized, controlled trial that treatment with combined diuretics could mobilize moderate ascites more rapidly than sequential diuretics, and was associated with less side-effects, including renal failure.[56]

The explanation for the difference in the findings could be that the patients in the study of Santos *et al*. were at a much earlier stage of ascites, with 60% of the patients enrolled at their first presentation of ascites, and at least 40% of them had normal supine levels of aldosterone.[53] In the study of Angeli *et al*., at least 70% of patients had recurrent ascites that required repeat paracenteses. Most had hyperaldosteronism, and many had reduced renal function. Therefore, it is reasonable to use sequential diuretics in patients with ascites at first appearance, and they will likely respond with a satisfactory natriuresis with ascites reduction. However, patients with recurrent ascites will be better served with combination diuretic therapy in order to reduce the time required to achieve a satisfactory diuretic response and to reduce the risk of hyperkalemia.[56]

Patients on diuretic therapy need to be monitored regularly for electrolyte abnormalities, over-diuresis, and renal failure. As the volume of ascites that can be resorbed into the systemic circulation is approximately 400 mL/day, weight loss in excess of 0.5 kg/day means that there is reduction of the intravascular volume, thereby placing these patients at risk of the development of renal failure from over-diuresis. Patients with peripheral edema can tolerate more rapid fluid loss until the edema has resolved. Compliance with and response to sodium restriction and diuretics can be evaluated regularly by 24-h urine collection for sodium excretion.[57]

In situations where this is not feasible, a random urine sodium to a potassium ratio of > 1 predicts a > 78 mmol/day sodium excretion in 90% of patients. Non-compliance with a low-sodium diet is reflected by an adequate renal sodium excretion, but without any weight loss. A low renal sodium excretion necessitates increasing the diuretics doses as tolerated, up to the maximum recommended levels. When the combination of sodium restriction and diuretics is given to carefully-monitored patients, 90% of them can reduce or even eliminate their ascites with significant improvement in their quality of life.[58]

Albumin

Albumin is a plasma protein that is most responsible for plasma colloid oncotic pressure. It is a negatively-charged molecule that attracts sodium and water, and therefore, it is a very good volume expander. In addition, it has many other functions, such as ligand binding, and antioxidant and endothelial stabilizing properties. Therefore, albumin seems the ideal solution to manage conditions where there is intravascular volume reduction, inflammation, or circulatory dysfunction.(59)

Albumin has been advocated as a treatment for many complications of cirrhosis and ascites, such as spontaneous bacterial peritonitis and HRS. As the basic pathophysiological process that leads to the development of ascites is a reduction of the effective arterial blood volume, it makes physiological sense to use albumin in the management of ascites, although this has been controversial.(60)

In one randomized, controlled trial in cirrhotic patients with ascites, weekly infusions of 25 g of albumin added to standard diuretics was shown to produce a significantly better diuretic response compared to diuretics alone, including shorter hospital stay, lower probability of ascites reaccumulation, and a lower likelihood of readmission to hospital, but no effect on survival.(61) In a later study by the same investigators, the use of 25 g/week albumin for 1 year, and thereafter, 25 g every 2 weeks for up to 120 months in patients with first-onset ascites, resulted in a significant increase in survival of 16 months and a significantly lower probability of ascites recurrence. The major drawback of chronic albumin use is its cost. For this reason, there is currently no standard recommendation to use albumin as an adjunct therapy to diuretics in the treatment of uncomplicated ascites.(62)

Refractory Ascites

Ascites is occasionally refractory despite salt restriction and the use of diuretics. Defining refractory ascites accurately is critical because ascites is often deemed refractory before truly fitting criteria. Ascites may be suboptimally treated or more aggressive interventions prematurely implemented. The importance of taking a history regarding concomitant medication use and compliance cannot be overstated. The clinical impact of refractory ascites is that it is associated with increased mortality. For instance, 2-year survival in patients with diuretic-resistant ascites is approximately 25%.[(63)]

The International Ascites Club Definition

Refractory ascites is defined as either: (1) diuretic-resistant ascites-ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of a lack of response to dietary sodium restriction and intensive diuretic treatment; or (2) diuretic intractable ascites-ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of the development of diuretic-induced complications that preclude the use of an effective diuretic dosage.[(64)]

Diuretic-resistant ascites in patients with cirrhosis is considered to be present when one or both of the following two criteria is present in the absence of therapy with a nonsteroidal antiinflammatory drug (NSAID), which can induce renal vasoconstriction and diminish diuretic responsiveness:

- An inability to mobilize ascites despite compliance with dietary sodium restriction (as confirmed by a 24-hour urine collection containing less than 78 meq of sodium or urine sodium less than the urine potassium on a random sample) and the administration of maximum tolerable doses of oral diuretics (400 mg/day of spironolactone and 160 mg/day of furosemide) . The 78 meq of sodium represents the recommended 88 meq intake minus 10 meq in nonurinary losses. Patients who gain weight despite excreting more than 78 meq of sodium per day (or urine sodium > urine potassium on a random sample) are not compliant with the diet.
- The development of prohibitive diuretic-related complications, such as progressive azotemia, hepatic encephalopathy or progressive electrolyte imbalance.[(65)]

Differential diagnosis — Resistant ascites in patients with cirrhosis must be differentiated from malignant ascites due to peritoneal carcinomatosis or from chylous malignant ascites. These disorders are typically refractory to diuretic therapy because of an inability to mobilize the ascitic fluid . In contrast, massive hepatic metastases, another cause of malignant ascites, is due to intrahepatic hypertension and can be treated in a similar fashion to patients with cirrhosis.[(66)]

Another form of diuretic-resistant ascites, called nephrogenic ascites, occurs in patients with end-stage renal disease who are usually being treated with maintenance dialysis. The pathogenesis of this disorder, which is usually not due to liver disease or portal hypertension, may be related to an increase in peritoneal capillary permeability induced in

part by inadequate dialysis . The serum-ascites albumin gradient is <1.1 g/dL, consistent with the absence of portal hypertension unless the patient has cirrhosis or heart failure in addition to their renal failure. Some patients respond to more intensive dialysis but definitive therapy is renal transplantation.[67]

Patients with Budd-Chiari syndrome (hepatic vein thrombosis) may be unusually diuretic-resistant. Doppler ultrasound frequently provides information about hepatic venous patency.

PATHOGENESIS — True diuretic-resistant ascites is usually associated with advanced cirrhosis, marked neurohumoral activation (of the sympathetic and renin-angiotensin-aldosterone systems), and very low urinary excretion of sodium, frequently less than 10 meq/day despite maximal tolerated doses of diuretics. Neurohumoral activation results in renal vasoconstriction and enhanced sodium reabsorption in the proximal tubule (under the influence of angiotensin II and norepinephrine) and collecting tubules (under the influence of aldosterone). Even among patients with nonazotemic cirrhosis, those with a greater degree of neurohumoral activation show diminished diuretic responsiveness.[68]

The development of true diuretic resistance in a previously diuretic-sensitive patient is most often due to progression of the liver disease . However, it can also be due to two other complications of cirrhosis: hepatocellular carcinoma and/or portal vein thrombosis. A liver and spleen ultrasound with Doppler or CT scan and measurement of serum alpha fetoprotein can help diagnose or exclude these complications.[69]

Progression to diuretic-resistance is generally an irreversible process unless there is a reversible component to the liver disease (eg, alcoholic hepatitis) or the patient undergoes a successful liver transplant, transjugular intrahepatic portosystemic stent shunt (TIPS), or peritoneovenous shunt. As urinary sodium excretion dwindles despite diuretics, progressive azotemia and electrolyte imbalance (eg, hyponatremia) are expected. Diuretics are generally discontinued in such patients.

Diuretics do not cause the hepatorenal syndrome. This association is inappropriately suggested because most patients are taking diuretics when the hepatorenal syndrome is diagnosed. However, diuretics can cause azotemia, particularly if fluid is removed too rapidly in patients without peripheral edema. Diuretic-induced azotemia improves with the cessation of therapy and fluid repletion. In comparison, the hepatorenal syndrome typically worsens inexorably, even after diuretics are stopped. Vasoconstrictor treatment of hepatorenal syndrome can be successful.[70]

Management Strategies

Ascites becomes refractory in between 5% and 10% of patients with ascites.

Patients with diuretic-resistant ascites have pre-hepatorenal syndrome and a very poor prognosis . The two-year survival rate of all patients with cirrhosis after the development of ascites is approximately 50 percent.[71] In comparison, survival in patients with diuretic-

resistant ascites is 50 percent at six months and 25 percent at one year . Similar prognostic stratification can be achieved using baseline urinary sodium excretion. In one series, for example, patients with ascites and urinary sodium excretion below 10 meq/day had a mean survival rate of five to six months compared to over two years in those with ascites and a higher rate of sodium excretion.[72]

There are three major therapeutic options in patients with diuretic-resistant cirrhotic ascites:

- Liver transplantation.
- Serial therapeutic paracentesis approximately every two weeks.
- Transjugular intrahepatic portosystemic stent shunt (TIPS).

Other modalities such as a peritoneovenous (LeVeen or Denver) shunt have very limited indications. Oral midodrine has shown some promise in the treatment of refractory ascites, especially in unusually hypotensive patients.[73]

Liver transplantation — The development of ascites in a previously compensated cirrhotic patient is an accepted indication for listing for liver transplantation, provided that there are no contraindications, such as active alcohol use. Patients usually progress from diuretic-sensitive to diuretic-resistant ascites over a period of months to years if they do not die from other complications of cirrhosis . Patients developing diuretic-resistant ascites should ideally already be listed for and awaiting liver transplantation.[69]

Therapeutic paracentesis — Contrary to old dogma based upon anecdotal observations of hemodynamic deterioration after therapeutic paracentesis, the safety of this approach in patients with cirrhosis and tense ascites has been proven in randomized controlled trials.[74]

Large-volume paracentesis (LVP) ameliorates the shortness of breath and early satiety that these patients experience. It also may be associated with collateral advantages, such as reductions in the hepatic venous pressure gradient , intravariceal pressure, and variceal wall tension . These parameters are considered important predictors of variceal bleeding and the improvement after LVP may decrease the risk of bleeding.[75]

Retrospective studies have suggested a risk of deterioration in hospitalized patients following LVP. However, the risk attributable to the paracentesis is unclear given the difficulty in adjusting for underlying severity of illness and comorbidities in these patients, and understanding whether they were truly diuretic-resistant.[76]

The real issue is not the proven value of a single LVP for tense ascites but the role of serial LVP for recurrent tense ascites. Most of these patients, in our experience, are noncompliant with their sodium-restricted diet and/or medications and are masquerading as diuretic-resistant. Many feel so much better after an LVP that they prefer to come to the clinic frequently to have their ascites removed rather than follow the diet and take their medications. The problem with this approach is that repeated LVPs cause protein and

complement depletion compared to diet/diuretic therapy, and this may in theory indirectly predispose to ascitic fluid infection .Thus, it seems more reasonable to treat diuretic-sensitive patients with diet and diuretics and to reserve serial LVPs for patients who are truly diuretic-resistant . The paracentesis volume generally consists of as much fluid as can be removed without excessive manipulation of the patient.[77]

The frequency with which LVP is required and the volume of fluid removed provide insight into patients' compliance. Patients who are consuming 88 meq (2000 mg) of sodium per day and are excreting no sodium in the urine should require paracentesis of approximately 8.4 liters every two weeks. Scheduling two-week returns to the clinic works well in our experience, and the typically flaccid, compliant abdomens in these patients permit the accumulation of 8 liters of fluid without the development of "tenseness." Patients with some sodium excretion in the urine should require the removal of less fluid, while those requiring the removal of a total of more than 8.4 liters every two weeks are not complying with their diet and should receive more diet education rather than rapid repeat LVPs.[78]

Need for routine testing of ascites — The prevalence of occult ascitic fluid infection in asymptomatic outpatients undergoing large volume paracentesis for resistant ascites is low . As a result, the routine culture of fluid during paracentesis in such patients is probably not warranted. Our policy is to obtain a cell count and differential on all samples of ascitic fluid in the paracentesis clinic setting while obtaining cultures only in symptomatic patients or if the fluid is cloudy.[79]

Colloid replacement — The need for colloid replacement after LVPs remains controversial . In a widely quoted study, 105 patients with tense ascites undergoing LVP were randomly assigned to receive albumin (10 g/L of ascites removed) or no albumin .Patients not receiving albumin were more likely to show signs of hemodynamic deterioration including an increase in the plasma renin activity; these patients were also much more likely to develop worsening renal function and/or severe hyponatremia (20.8 versus 3.8 percent in those receiving albumin). One concern with these results is that almost one-third of patients had not received diuretics prior to entry into the study, and cannot be considered diuretic-resistant.[80]

Patient selection is crucial for the evaluation of the changes in intravascular volume after large volume paracentesis . An increase in plasma renin activity after paracentesis has been considered as evidence of effective hypovolemia and labeled postparacentesis circulatory dysfunction (PCD).[81]

In a controlled trial, total paracentesis was performed in cirrhotic patients who were randomized to receive replacement with albumin, dextran 70, or polygeline. PCD was much less common with albumin administration (19 versus 34 and 38 percent, respectively). This benefit, which may reflect the longer half-life of albumin, was limited to patients in whom at least 5 liters of ascitic fluid were removed. However, the need for diuretic treatment after discharge was higher in patients who had already developed PCD than in patients who did not, suggesting that many patients were not diuretic-resistant. Patient survival was significantly shorter in patients who developed PCD but there were no differences in survival

among the three treatment groups.[81] Postparacentesis plasma volume expansion does help prevent asymptomatic laboratory abnormalities, and some of these abnormalities are associated with shortened survival. However, no study has shown a direct survival advantage of one expander over another or compared to no expander More studies with careful selection of truly diuretic-resistant patients are needed. Meanwhile, it seems reasonable to forego albumin after paracenteses of <5 liters. For larger paracenteses, albumin (6 to 8 g/L of fluid removed) can be administered.[80]

It has been suggested that reducing the flow rate of ascites extraction may help prevent postparacentesis circulatory dysfunction . Prophylactic use of midodrine (an oral alpha-adrenergic agonist) has also been suggested as a less expensive alternative to albumin . More studies are needed before considering the therapeutic utility of either of these approaches.[82]

Transjugular intrahepatic portosystemic stent-shunt — The prerequisite for the development of ascites is portal hypertension. Thus, measures directed at the reductionof portal pressure could theoretically eliminate the cause for ascites formation.

TIPS is a side-to-side portacaval shunt, usually placed through the right internal jugular vein under local anesthesia by an interventional radiologist. In two uncontrolled studies of 75 patients, TIPS led to an increase in urine output, a marked or complete reduction in ascites, and cessation of diuretic therapy or the use of much lower diuretic doses in approximately 75 percent of patients.[83] There may also be a delayed improvement in renal function, including a lower plasma creatinine concentration and improved sodium excretion . In one study, for example, the average plasma creatinine concentration was 1.5 mg/dL (132 micromol/L) at baseline, was unchanged at one week, and fell to 0.9 mg/dL (80 micromol/L) by six months . Other potential benefits include improvements in the nutritional status of the patient and quality of life.[84]

Several randomized controlled trials have compared TIPS to large volume paracentesis , and at least three meta-analyses have been published.[84]

- A meta-analysis of four randomized trials (with a total of 264 patients) found no difference in 30-day or 24-month mortality . TIPS was associated with a significantly reduction in ascites re-accumulation at three months (OR .07, 95%CI 03-.18) and 12 months (OR .14, 95% CI .06-.28). Hepatic encephalopathy occurred significantly more often after TIPS.[85]

- A later meta-analysis included five trials with a total of 330 patients . The authors evaluated characteristics of the individual trials that might have a bearing on the likelihood of mortality. The differences in mortality among trials were explained mostly by baseline levels of serum bilirubin and the proportion of patients in each trial in whom TIPS was successful (ranging from 77 to 100 percent). The analysis identified one trial that was an outlier. After excluding this trial, TIPS was significantly more effective than LVP in reducing the likelihood of recurrent ascites (OR 0.14, 95% CI 0.07-0.27) but was more likely to be associated with encephalopathy (OR 2.26, 95% CI 1.35-3.76).

Mortality in the TIPS group was reduced by a statistically nonsignificant amount (OR 0.74, 95% CI 0.40-1.37); this does not exclude a clinically important reduction or increase in mortality with TIPS.[86]

- A third meta-analysis of individual patient data (149 allocated to TIPS and 156 to large volume paracentesis) found that TIPS was significantly more effective in preventing recurrent tense ascites . In addition, transplant-free survival was significantly better in the TIPS group. The average number of hepatic encephalopathy episodes was greater in the TIPS groups, although the probability of developing a first episode of hepatic encephalopathy was similar.[87]

Unfortunately, the primary studies included in these meta-analyses were started (and many were completed) before many of the improvements were achieved in the technical aspects of TIPS and in the selection of appropriate patients. No study, for example, incorporated the MELD score for patient selection; MELD was developed to predict 90-day TIPS mortality . In addition, none used a coated stent .Thus, we probably cannot use these studies to predict outcomes of TIPS in the current era.[88]

The following illustrate the findings in individual studies:

- One trial that included a total of 60 patients found that patients randomized to TIPS were more likely to be free of ascites at three months (61 versus 18 percent) and had higher survival without the need for transplantation . The frequency of new hepatic encephalopathy was not significantly different between the two groups.[89]

- Another controlled trial that included 70 patients found that TIPS was associated with a lower rate of ascites recurrence and decreased risk of hepatorenal syndrome , although TIPS did not improve survival and was associated with an increased frequency of severe hepatic encephalopathy and higher costs. However, the cost data were not at all representative of costs in the United States (eg, $216 per tap including albumin) and diuretic use appears to have been minimal in the TIPS group. It is my observation that the main function of TIPS for ascites is to convert diuretic-resistant patients to di uretic-sensitive. Poor results can be expected if no diuretics are used.[90]

- A large United States multicenter randomized trial found that ascites was much better controlled in the TIPS group, but there was no survival advantage.[91]

- In contrast, a multicenter European trial found that TIPS was associated with significantly better survival without liver transplantation .Most deaths were due to progressive liver dysfunction. In the multivariate analysis, treatment with paracentesis and higher MELD score independently predicted death.[92]

Although the results are heterogeneous, increasing evidence suggests that TIPS is more effective than LVP in controlling ascites in carefully selected patients and may possibly be associated with a survival advantage. However, complications of TIPS must also be considered. Hepatic encephalopathy occurs in approximately 30 percent of patients .In a

subset of patients, encephalopathy can become incapacitating, and may be associated with progressive liver failure.The encephalopathy can usually be managed by lactulose therapy; in resistant cases, the stent blood flow can be reduced by a "wasp waist" constrictor or the shunt can be occluded.[93]

Another significant problem after TIPS placement is the development of early thrombosis or delayed shunt stenosis. These problems occurred in 22 to 50 percent of patients, leading to the need for redilatation of the shunt in the pre-polytetrafluoroethylene (Goretex)-covered stents era. New stents show excellent patency rates in a randomized trial; this may be a breakthrough in technology that may substantially reduce the need for redilatation of the stent.[94]

A more detailed understanding of the best candidates for TIPS may improve outcomes with TIPS. The model for end-stage liver disease (MELD) score, for example, was developed to predict 90-day survival after TIPS. Newer trials will screen patients better than prior trials and should probably incorporate MELD score and exclude patients with a high score. In addition, echocardiograms are now usually performed to screen for subtle heart failure. Patients with cirrhosis and ascites usually have ejection fractions of 70 to 75 percent . Cardiac function can deteriorate after TIPS; a baseline ejection fraction of >60 percent may be the minimum for candidates for TIPS.[95]

Peritoneovenous shunt — A peritoneovenous shunt, which drains into the internal jugular vein, reinfuses ascites into the vascular space. This technique was popularized as a "physiologic" treatment of resistant ascites (and of the hepatorenal syndrome). However, this procedure has been virtually abandoned due to an excessive rate of complications.[96]

The only remaining indication for peritoneovenous shunt is the rare patient with diuretic-resistant ascites, who is not a candidate for transplantation or TIPS, and is too obese or has too many abdominal surgical scars to permit safe, successful paracentesis.[97]

Surgical portasystemic shunts — As with TIPS placement, surgical portasystemic shunts significantly reduce the hepatic venous pressure gradient, the development of ascites, and the frequency of spontaneous bacterial peritonitis . Shunt surgery has traditionally been associated with a high morbidity and mortality, and its use in the treatment of ascites is only of historical interest.[98]

Oral **midodrine** is effective in combination with parenteral **octreotide** in reversing type I hepatorenal syndrome. There is also accumulating evidence that midodrine may be useful in treatment of refractory ascites without use of octreotide . Midodrine is an oral vasopressor that will usually increase blood pressure in advanced cirrhosis resulting in improved renal perfusion. Some of these patients are severely hypotensive, with systolic pressures in the 70s and 80s. Nurses and sometimes physicians may be reluctant to give diuretics to these patients. Midodrine at a dose of 10 mg orally three times daily (with titration of the dose to achieve the desired increase in blood pressure) can improve renal perfusion and increase renal sodium excretion.[73]

Splenic artery embolization — Case reports have described splenic artery embolization for management of bleeding gastric varices or cytopenias associated with portal hypertension . The resulting decrease in splenic blood inflow reduces flow through the splenic vein and subsequently decreases portal pressure. A case report described resolution of tense ascites in a patient who had undergone liver transplantation for Budd-Chiari syndrome . The patient was ineligible for TIPS because of extensive thrombosis of the portal vein. The use of this procedure for treatment of refractory ascites awaits more data.[(99)]

Hypertonic saline plus loop diuretic — The potential efficacy of hypertonic saline in combination with loop diuretics was evaluated in a study involving 84 patients with cirrhosis and refractory ascites who were randomly assigned to either high dose intravenous furosemide plus small volume hypertonic saline or to repeated paracentesis plus a standard diuretic regimen . Those randomized to hypertonic saline had significantly better control of ascites, pleural effusions, and leg edema.

The extent to which patients were compliant with a diuretic regimen and sodium restriction (and hence truly diuretic-resistant) was unclear. Furthermore, why hypertonic saline should cause patients to become more responsive to diuretics is uncertain. Thus, more studies are needed before this approach should be considered.[(100)]

Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP) is the most frequent and life-threatening infection in patients with liver cirrhosis requiring prompt recognition and treatment. It is defined by the presence of >250 polymorphonuclear cells (PMN)/mm^3 in ascites in the absence of an intra-abdominal source of infection or malignancy.[(101)]

SBP is the most frequent bacterial infection in cirrhosis, accounting for 10-30% of all reported bacterial infections in hospitalised patients.[(102)]

In outpatients without symptoms the prevalence is low (3.5% or lower), but the prevalence increases in the nosocomial setting, ranging from 8% to 36%.[(103)]

Bacterascites, defined as positive culture results but no increase in the PMN count in the ascitic fluid, occurs with a prevalence of 1 -3% in outpatients and in up to 11% in hospitalised patients.[(104)]

In-hospital mortality for the first episode of SBP ranges from 10% to 50%, depending on various risk factors. One-year mortality after a first episode of SBP has been reported to be 31% and 93%.[(105)]

In fact, the occurrence of SBP or other severe bacterial infections markedly worsens the prognosis in patients with cirrhosis and it has been proposed that a new prognostic stage of cirrhosis not reflected in current staging systems should be defined, the so-called 'critically ill cirrhotic'. Patients at this late stage have to be evaluated for the possibility of liver transplantation.[(106)]

Predictive factors reported for a poor prognosis in various cohorts of patients with SBP include age, Child score, intensive care, nosocomial origin, hepatic encephalopathy, elevated serum creatinine and bilirubin, lack of infection resolution/need to escalate treatment and culture positivity as well as the presence of bacteraemia and CARD15/NOD2 variants as a genetic risk factor.[107]

Bacterial Translocation (BT) and Pathophysiology

Bacterial translocation (BT) is the most common cause of SBP. However, particularly in nosocomial SBP, other sources such as transient bacteraemia due to invasive procedures can lead to SBP. Limited BT to mesenteric lymph nodes (MLN) is a physiological phenomenon, whereas any increase in the rate and severity of BT may be deleterious for the patient and thus should be termed 'pathological BT'. [108]

Only a few intestinal bacteria are able to translocate into MLN, including *Escherichia coli*, *Klebsiella pneumoniae* and other Enterobacteriaceae. Interestingly, these species most frequently cause SBP, and DNA sequencing studies reveal genotypic identity of bacteria in MLN and ascites in the vast majority of cases.[109] This suggests that pathological BT is the underlying cause and source of SBP in cirrhosis and supports the view that the route of pathological BT leading to SBP is largely lymphatic. Three factors have been implicated in the development of pathological BT in liver cirrhosis: (1) alterations in gut microbiota; (2) increased intestinal permeability; and (3) impaired immunity.[110]

Microbiota Liver cirrhosis is associated with distinct changes in faecal microbial composition including an increased prevalence of potentially pathogenic bacteria such as Enterobacteriaceae. Moreover, small intestinal bacterial overgrowth (SIBO), defined as $>10^5$ colony forming units/ml jejunal aspirate and/or colonic-type species, is frequently present in advanced stages of liver cirrhosis and has been linked with pathological BT, SBP and endotoxinaemia.[111]

In cirrhosis, factors promoting these changes may include deficiencies in paneth cell defensins, reduced intestinal motility, decreased pancreatobiliary secretions and portal-hypertensive enteropathy. In experimental cirrhosis, in the absence of SIBO, BT occurs rarely (0-11%) and at rates comparable to healthy conditions. However, BT does not occur in up to half of the animals with SIBO and, thus, SIBO is necessary but not sufficient for BT to occur.[112]

Intestinal Permeability Cirrhosis is associated with structural and functional alterations in the intestinal mucosa that increase permeability to bacteria and bacterial products. In particular, changes in enterocyte mitochondrial function and increased oxidative stress of the intestinal mucosa have been identified.[113]

Local Ascitic-peritoneal Host Defence in Peritonitis

The peritoneal cavity probably has the most severe lack of host defence compared with other compartments in decompensated cirrhosis. In fact, ascites per se may be considered a risk factor for the development of peritonitis. In healthy conditions, peritoneal

host defence mechanisms are very efficient and intraperitoneal injection of various numbers of single organisms does not cause peritonitis unless adjuvant substances or ascites are present. In cirrhosis, deficiencies in local defence mechanisms against bacteria, including dysfunction of cellular and humoral immunity, limit peritoneal bacterial clearance.(114)

Since the absolute number of PMN per mm^3 ascitic fluid defines SBP, the mechanisms of chemotaxis mediating PMN influx into the peritoneal cavity are important. The degree of PMN migration and accumulation in the peritoneal cavity combating invading bacteria depends on a number of factors. Resident macrophages are the first to phagocytose bacteria, they further help to attract PMN by release of chemotactic factors and activate complement. For instance, monocyte chemotactic protein 1 is one of the most potent chemokines, and a functional polymorphism has been proposed as a risk factor for SBP in alcoholic cirrhosis.(115) A chemotactic gradient is necessary to achieve appropriate neutrophil recruitment into the peritoneal cavity. In fact, PMN chemoattractants such as zymosan are very effective in preventing the death of animals with *E coli*-induced peritonitis when administered locally but not systemically. Unfortunately, little is known about the influx, efflux and kinetics of neutrophils in ascitic fluid in cirrhosis and its dependency on type, extent and duration of bacterial stimulus as well as host factors.(116)

Besides influx of PMN, bacterial clearance is determined by the overall killing capacity which is dependent on opsonisation, burst activity and inflammatory response. A marked reduction in opsonic and bactericidial activity is well-known in cirrhosis. In particular, low C3 levels in cirrhotic ascites correlate strongly with opsonic activity and have been shown to predispose to SBP. However, the total protein content aslo mirrors opsonic activity and has been shown to be predictive of the development of SBP. (117) At a protein level of >1.5 g/dl ascitic fluid, the incidence rates of SBP have been consistently reported to be lower than 1%. In contrast, at protein levels <1.5 g/dl ascitic fluid, the risk of SBP increases, parallelling the decrease in protein content and reaching incidence rates of 27-41% at levels <1.0 g/dl. (118)

Other factors that may contribute but have not been addressed thoroughly include compartmentalisation via activation of coagulatory systems or the omentum (called the 'abdominal policeman') and visceral fat. The latter is a relevant source of adipokines known to modulate the inflammatory response. In fact, significant levels of, for example, adiponectin, visfatin and resistin are observed in ascites and the latter is increased in the presence of SBP. (119)

Liver Dysfunction and Systemic Risk Factors

Cirrhosis is accompanied by deficits in innate and adaptive intrahepatic, intestinal and systemic immunity. Patients with cirrhosis with decreased reticuloendothelial system (RES) activity develop SBP at a higher rate than those with close to normal RES activity.(120) Accordingly, markers of advanced liver dysfunction have been identified as independent risk factors for a first episode of SBP. A bilirubin level of >3.2 mg/dl and platelet count of <98 000/mm^3 significantly increase the likelihood of SBP, and each model for end-stage liver

disease (MELD) point increases the risk of SBP by about 11%. However, circulating mononuclear cells also present with alterations in Toll-like receptor (TLR) and HLA expression as well as reduced chemotactic, opsonic, phagocytic and killing capacity. (121)

Furthermore, genetic variants influencing host defence mechanisms such as CARD15/NOD2 and TLR2 have been reported to be associated with an enhanced probability of acquiring SBP. TLR2 polymorphisms and NOD2 variants seem to represent supplementary risk factors since the simultaneous presence of both unfavourable polymorphisms markedly increases the risk of SBP. This underlines the known interaction of NOD2 and TLRs, in particular the modulation of TLR2-dependent cytokine responses by NOD2. (122)

Medication can also affect the chances of developing SBP. The use of proton pump inhibitors (PPI) has been proposed to facilitate SIBO and thus to contribute to pathological BT. In fact, retrospective case-control studies reveal a potential association between the use of PPI and development of SBP. Considering the frequently inadequate overuse of PPI in patients with cirrhosis, we therefore recommend restricting their use to indications of proven benefit. (123)

In contrast, non-selective beta blockers (NSBB) may prevent SBP. It is tempting to speculate that this benefit relates to an improvement in chemotaxis, proinflammatory cytokine release and killing capacity reported for beta-adrenergic antagonists in various experimental settings. Since the sympathetic nervous system affects PMN chemotaxis, the question arises as to how treatment with NSBB affects the validity of diagnosing SBP based on PMN count in the ascitic fluid. (124)

Diagnosis of SBP

Symptoms and signs are frequently absent in patients with SBP, so a diagnostic paracentesis should be performed in all patients with ascites admitted to hospital regardless of whether or not there is clinical suspicion. Diagnosis should be prompt and treatment must not be delayed until the microbiology results are available. Thus, in all the available guidelines, diagnosis is based on a fixed defined cut-off PMN count in the ascitic fluid.(125) In patients with haemorrhagic ascites (ie, red blood cell count >10 000/mm^3), subtraction of one PMN per 250 red blood cells should be made to adjust for the presence of blood in ascites. Owing to the short lifespan of PMN, their ascitic count is independent of diuretics and/or other modulations of ascites volume. In contrast, lymphocytes which have a long lifespan increase in concentration during diuresis.(126) Moreover, differential diagnoses of predominant lymphocytosis in ascitic fluid include tuberculous peritonitis, neoplasms, congestive heart failure, pancreatitis and myxedema, but not usually SBP. PMN are therefore used to define SBP, and the greatest sensitivity is reached at a cut-off value of 250 PMN/mm^3, although the best specificity has been reported with a cut-off of 500 PMN/mm. (127)

Interestingly, bacterial DNA from Gram-negative bacteria in ascitic fluid is associated with a higher ascitic PMN count than bactDNA from Gram-positive bacteria, underscoring the differences in stimulatory capacity for PMN migration depending on the type of bacteria.(128)

Detection of bacterial DNA (bactDNA) using various approaches has recently been proposed in the ascitic fluid of patients with cirrhosis. The advantage of such a system would be the immediate identification of the causative bacteria, thus enabling more accurately targeted antibiotic treatment. BactDNA is found in the ascitic fluid of about 40% of patients with cirrhosis, being derived mainly from Gram-negative bacteria. However, detection of bactDNA in ascites or serum was not associated with an enhanced incidence of SBP and does not appear to predict the development of bacterial infections. (129)

Gram staining of peritoneal fluid is rarely helpful and is not recommended. In contrast, culture is the recommended procedure. Although only a few species and genera are found to cause SBP, more than 70 different microbial species have been isolated from the ascitic fluid of patients with bacteriologically-confirmed SBP. Classical culture techniques fail to grow bacteria in up to 65% of neutrocytic ascites. Bedside inoculation of ascites into blood culture bottles has been shown to increase the sensitivity to nearly 80%. In this regard, non-radiometric (eg, colorimetric BacTec) systems in particular have improved the time to diagnosis since they are faster than conventional blood culture bottles. Handling processes influence culture results and delay in transport increases false negative results. Separate and simultaneous blood cultures should be collected since 30-58% of SBP cases are associated with bacteraemia. (130)

Other markers found to be indicative of SBP include ascitic pH, lactate dehydrogenase, lactate (and corresponding arterial-ascitic gradients), but none of these is sufficiently predictive or discriminative and may be increased in malignancy-related ascites. Proteins such as granulocyte elastase and lactoferrin released by PMN upon activation have likewise been shown to be increased in SBP. Lactoferrin was reported to give rates of sensitivity and specificity of 95.5% and 97%, respectively, using a cut-off value of 242 ng/ml and to decrease to below the cut-off value in patients responding to treatment. However, because of the small number of SBP cases in this investigation, confirmation is required in multicentre trials including assessment of its accuracy in haemorrhagic and coexisting malignant ascites. (131)

Differentiation of SBP from secondary peritonitis due to perforation or inflammation of an intra-abdominal organ is clinically very relevant as the associated mortality is exceedingly high. In fact, all patients with perforated secondary peritonitis not undergoing timely surgery have been reported to die during hospitalisation and, thus, delayed diagnostic investigation is fatal. However, the proposed criteria to suspect secondary peritonitis (eg, inadequate response to therapy, multiple organisms) are identified too late and therefore rapid and accurate 'chemical' parameters available at the time of paracentesis are needed. Parameters proposed by Runyon *et al* are neutrocytic ascites with at least two of the following three criteria: ascitic fluid total protein >1 g/dl (in contrast to SBP), glucose <50 mg/dl (due to bacterial glucose utilisation) or lactate dehydrogenase >225 mU/ml. The

sensitivity of these criteria can be less than 68% and thus can be optimised. (132) In addition, Wu *et al* reported that ascitic fluid with either alkaline phosphatase >240 U/l or carcinoembryonic antigen >5 ng/ml in 80% of cases reflects peritonitis of secondary origin.[133]

Treatment of SBP

Treatment has to be started immediately after diagnosis of SBP and therefore is empirical since culture results are not available at this time point. The strain of bacteria causing SBP mainly depends on the site of acquisition. However, none of the international guidelines to date differentiates between nosocomial and community-acquired SBP with regard to the type of antibiotic regimen to use. This may be deleterious since nosocomial infections are associated with high rates of bacterial multiresistance and mortality . Patients with cirrhosis are also at increased risk of healthcare-associated infections, but studies are needed to determine the associated risk for multiresistant bacteria causing SBP. [134]

Historically, Gram-negative bacteria-almost exclusively Enterobacteriaceae-have been isolated in the overwhelming majority of SBP cases. More recently, several studies have found an increasing rate of infections with Gram-positive bacteria and resistant microorganisms . However, in patients with no previous hospitalisation and no prior antibiotic treatment, the causative bacteria still usually belong to the easily treatable Enterobacteriaceae family of bacteria. [135] Several antibiotics have been recommended for the initial treatment of SBP in these cases including cefotaxime or other third-generation cephalosporins, amoxicillin-clavulanic acid or quinolones. Although earlier trials have shown comparable efficacy of intravenous amoxicillin/clavulanic acid (1/0.2 g every 8 h) and intravenous cefotaxime in the treatment of SBP, recent increases in resistance to aminopenicillin/beta-lactamase inhibitors may limit their usefulness.[136] In patients presenting without complicating factors that may worsen therapeutic efficacy, oral treatment with quinolones appears sufficient in countries with a relatively low rate of quinolone-resistant strains of *E coli*. Possible complicating factors include shock, ileus, gastrointestinal bleeding, severe hepatic encephalopathy or renal dysfunction (serum creatinine >3 mg/dl).[137]

In nosocomial SBP, use of the antibiotics recommended above (third-generation cephalosporins, amoxicillin/clavulanic acid or quinolones) has recently led to disappointing and unacceptably low rates of resolution . Resistance to third-generation cephalosporins and quinolones has been reported to increase continuously and to reach levels of 23-44% and 38-50%, respectively, in some institutions and countries. [138] In addition, the incidence of extended-spectrum beta- lactamase (ESBL)-producing bacteria as well as multiresistant Gram-positive bacteria such as *Enterococcus faecium* or methicillin-resistant *Staphylococcus aureus* (MRSA) causing nosocomial SBP is alarming . MRSA has been found in 24-27% of cases of SBP, with detection of *S aureus* in ascites several years ago. [139] Nosocomial SBP due to ESBL strains or to multiresistant bacteria is often associated with a failure of first-line empirical antibiotic treatment. Indeed, the need for escalation of treatment associated with poor survival is predictive of in-hospital mortality and therefore must be avoided. The use of carbapenems and glycopeptides would be safest and easiest since no resistance has so far

been reported in cases of SBP, but this is not practical and the choice of antibiotics needs to be stratified for parameters defining the risk of resistant bacteria. This includes host factors as well as validated knowledge of the resistance profile of bacteria acting in the setting in which the patient is diagnosed and treated. (140)

Reported independent risk factors for bacterial multiresistance are previous hospitalisation (particularly within 3 months and intensive care treatment) and prior prophylactic or therapeutic antibiotic treatment . It is therefore suggested that, in patients with cirrhosis who develop nosocomial SBP and present with such risk factors, a more effective first-line empirical antibiotic therapy with a broader spectrum should be used, namely carbapenems. (141)

It is controversial whether culture-positive results in the absence of an increased PMN count in the ascitic fluid require immediate initiation of antibiotic therapy. Some guidelines recommend antibiotic treatment only in patients with signs of infection or inflammation. Otherwise, a follow-up paracentesis should establish whether SBP is present (PMN count >250/mm^3) and thus whether treatment is indicated. However, this is based on a single-centre observational cohort study and has not been addressed prospectively. Until then we think that considering the lack of symptoms in a large number of cirrhotic patients even in presence of severe bacterial infection antibiotic treatment should be used in case of bacterascites. (142)

In patients with cirrhosis with SBP, a prospective randomised comparative study reported that adjuvant administration of high-dose albumin (1.5 g/kg on day 1 and 1 g/kg on day 3) with antibiotic treatment prevented worsening of renal function with a concomitant improvement in in-hospital and 3-month survival. However, this regimen is mainly effective in high-risk patients characterised by serum bilirubin >4 mg/dl. In addition, in unselected patients with SBP, even low-dose albumin (10 g/day on days 1-3) has been shown to reduce tumour necrosis factor and interleukin 6 levels in serum and ascites and to prevent increases in serum NO_x induced by SBP. Therefore, future trials need to determine whether other patients with cirrhosis could also benefit and to establish the dose and timing of albumin needed to give most benefit to the individual patient. (143)

Antibiotic treatment can safely be discontinued after the ascites PMN count has decreased to <250/mm^3. In a comparative study, extension of treatment duration to 10 days was not superior to treatment for 5 days, and it is therefore recommended that antibiotic therapy should be given for 5 days only. Moreover, current guidelines recommend changing treatment if the PMN count does not decrease by at least 25% compared with the pretreatment level after 2 days of antibiotic treatment. However, this has not been established in a prospective manner and/or treatment algorithm. In fact, this is based on a retrospective analysis of the half-life of PMN in ascites after initiation of antibiotic treatment and the observation that the reduction in the ascites PMN count 48 h after initiation of antibiotic treatment is greater in survivors than in non-survivors. (144)

Hepatorenal syndrome

Hepatorenal syndrome (HRS) is a functional renal failure that often occurs in patients with cirrhosis and ascites. HRS develops as a consequence of a severe reduction of effective circulating volume due to both extreme splanchnic arterial vasodilatation and a reduction of cardiac output. [145]

There are two different types of HRS. Type 1 HRS, which is often precipitated by a bacterial infection, especially spontaneous bacterial peritonitis, is characterized by a rapidly progressive impairment of renal function. Despite its functional origin, the prognosis of type 1 HRS is very poor. Type 2 HRS is characterized by a stable or slowly progressive renal failure so that its main clinical consequence is not acute renal failure, but refractory ascites and its impact on prognosis is less negative. [146]

Pathophysiology of HRS

Type 1 HRS can be precipitated by hypovolemia, gastrointestinal bleeding, spontaneous bacterial peritonitis, sepsis, large-volume paracentesis, or receipt of nephrotoxic agents such as nonsteroidal anti-inflammatory drugs or radiographic contrast. Underlying kidney disease and ATN may also result in azotemia in patients with liver disease. [147]

Although the mechanism leading to HRS is unclear, patients develop renovascular vasoconstriction and alteration of intrarenal blood flow. These changes may be consequences of the increased splanchnic vasodilation, reduced systemic vascular resistance, and elevated cardiac output characteristic of patients with cirrhosis. Splanchnic vasodilation occurs in response to elevated levels of splanchnic nitric oxide with portal hypertension. [148] The result is an effective reduction of circulating vascular volume and renal perfusion. To compensate for the lower effective intravascular volume, activation of the renin-angiotensin system and sympathetic nervous system plus secretion of antidiuretic hormone result in sodium and water retention coupled with renal vasoconstriction, reduced renal blood flow, and ultimately renal hypoperfusion. [149]

As cirrhosis progresses, the continuing decline in systemic vascular resistance cannot be compensated by the increase in cardiac output, leading to a further deterioration of arterial blood flow. Activation of the sympathetic nervous system results in renal vasoconstriction and reduced renal blood flow, leading to progressive renal failure, reduced glomerular filtration, and even ATN.[150]

Patient Evaluation

Patients with suspected HRS need a careful evaluation for precipitating factors, a review of potentially nephrotoxic medications, a careful history for underlying renal disease, and an evaluation of the severity of associated liver disease. The criteria for the diagnosis of HRS were established by the International Ascites Club in 1996[151] and subsequently revised in 2007 [152] (Table 4).

Table 5: International Ascites Club Criteria of Hepatorenal Syndrome [152]

Cirrhosis and ascites
Serum creatinine > 1.5 mg/dL
No improvement in serum creatinine following albumin administration (albumin 1 g/kg up to 100 g total/day)
Absence of significant hypotension
No current nephrotoxic drugs
Absence of underlying kidney disease (proteinuria < 500 mg/day, < 50 red blood cells/hpf,[a] renal ultrasound normal)

A complete metabolic panel, liver tests, blood count, urinalysis, and estimation of urine protein, sodium, and potassium on a spot urine specimen should be obtained. Ultrasound of the kidney and liver is helpful to rule out obstructive uropathy and verify the presence of acute or chronic liver disease. [153]

Differential Diagnosis

The diagnosis of HRS is typically established in part by exclusion. Prerenal azotemia should be excluded by initial albumin and crystalloid infusion. A fractional excretion of sodium of < 1% favors a diagnosis of HRS. The presence of bland urinary sediment coupled with low urine sodium can be seen in both hypovolemic renal failure and HRS. However, in patients with HRS these urinary indices will not improve following adequate volume resuscitation. ATN can develop in patients with cirrhosis, making the diagnosis of HRS more difficult. Granular casts can be present in both ATN and HRS, although the presence of tubular epithelial cells suggests ATN. Postrenal disease, such as obstructive uropathy, should be excluded by ultrasound of the kidney, ureters, and bladder. [152]

Management

The diagnosis of HRS should be quickly established so that treatment is promptly implemented. Response to therapy is an independent predictor of survival, and patients most likely to respond to vasoconstrictor therapy plus albumin infusion generally have a pretreatment creatinine level < 3 mg/dL. [154]

Patients with HRS should be managed in an intensive care setting with an initial search for precipitating events followed by treatment or correction of identified risk factors. For example, early correction of hypovolemia that is a consequence of gastrointestinal bleeding may prevent progression to HRS. Monitoring of central venous pressures can reduce the risk for intravascular volume overload during resuscitation. Diuretics should be limited, and potential nephrotoxic drugs such as nonsteroidal anti-inflammatory drugs discontinued. If the patient has evidence of significant central volume overload, cautious use of furosemide may be helpful. [155]

A search for infection with cultures of blood, urine, and ascites plus a routine chest radiograph should be obtained. If no precipitating event is identified, broad-spectrum antibiotics can be administered until cultures are available. Patients with sepsis may also have relative adrenocortical insufficiency, and administration of hydrocortisone can be beneficial.(156)

In patients with massive ascites and possible compartment syndrome of the abdomen, large-volume paracentesis accompanied by intravenous (IV) albumin (8 g/L of ascites fluid removed) may help. The authors generally use 25% albumin for both volume expansion and replacement of large-volume paracentesis. (157)

The treatment goal for type 1 HRS is to improve renal perfusion. A sustained increase in mean arterial pressure is associated with improved outcome. Initial volume expansion with up to 100 g of 25% albumin and/or administration of up to 1.5 L of normal saline can be considered. (158)

Current evidence suggests that the administration of vasoconstricting agents coupled with IV albumin can improve renal function. The combination of terlipressin and IV albumin has been evaluated in patients with HRS. Terlipressin is a vasopressin analogue and an agonist for the V1 vasopressin receptor with a longer half-life than vasopressin. It is effective in up to 50% of patients with type 1 HRS. (159) A minimum of 3 days of terlipressin therapy is needed to produce a positive effect in HRS. The therapeutic response seems best in those who have a serum bilirubin < 10 mg/dL and achieve at least a 5 mm Hg increase in mean arterial pressure by the third day of therapy. In addition, patients with a creatinine level < 3 mg/dL also tend to have better outcomes following terlipressin with albumin infusion. (160)

Treatment of HRS reduces short-term mortality whereas long-term outcomes are related to the severity of the underlying liver disease. A meta-analysis of 223 patients with type 1 HRS who received at least 3 days of terlipressin and IV albumin had a 52% response rate with a recurrence of HRS in 8% following cessation of therapy. (161) Approximately 7% of patients had adverse effects requiring discontinuance of therapy. However, because of the severity of the associated liver disease, the use of terlipressin plus albumin should be considered only as a bridge to liver transplantation rather than a long-term treatment. Risks of vasoconstrictor therapy include ischemic events in up to 12% of patients. (162)

Midodrine and octreotide have also been studied. These agents also are not approved for treatment of HRS in the United States. Midodrine is an alpha-adrenergic agent, and octreotide is a long-acting somatostatin analogue. Midodrine 7.5-12.5 mg 3 times daily with subcutaneous octreotide 100-200 µg 3 times daily with or without IV albumin have reduced mortality and improved renal function in both type 1 and type 2 HRS. The dose of midodrine can be titrated to increase mean arterial pressure. (163)

Hemodialysis is not indicated in the treatment of patients with HRS unless it is being used as a short-term bridge to liver transplantation. Complications such as hypotension and gastrointestinal bleeding are common. (164)

The role of transvenous intrahepatic portosystemic shunt (TIPS) has not been established in HRS, although this technique has been successful in small series. Some patients will not be candidates for TIPS because of the severity of their liver disease and encephalopathy. Patients with type 2 HRS often have severe ascites, and treatment of the ascites may improve renal function. The use of TIPS can decrease ascites, increase venous return, and improve renal perfusion and function. [165]

Liver transplantation is the definitive therapy for HRS. If renal function can be improved prior to liver transplantation, post-transplant mortality and morbidity are improved. Pretransplant creatinine is a predictor of post-transplant survival. [166]