عوارض کبدی هپاتیت B

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HBV

- **Acute HEPATITIS**
- **Chronic HEPATITIS**

عوارض هپاتیت حاد

- Fulminant hepatic failure
- chronic hepatitis

ACUTE HEPATITIS

- Approximately 70 percent of patients with acute hepatitis B have subclinical or anicteric hepatitis.
- while 30 percent develop icteric hepatitis.
- The disease may be more **severe** in patients **coinfected** with other hepatitis viruses or with underlying liver disease .
- Fulminant hepatic failure is unusual, occurring in approximately 0.1 to 0.5 percent of patients.

- The incubation period lasts one to four months.
- A serum sickness-like syndrome may develop during the prodromal period, followed by constitutional symptoms, anorexia, nausea, jaundice, and right upper quadrant discomfort.
- The symptoms and jaundice generally **disappear** after **one to three months**, but some patients have prolonged fatigue even after normalization of serum aminotransferase concentrations.

- **Laboratory testing** during the acute phase reveals elevations in the concentration of alanine and aspartate aminotransferase levels (ALT and AST); values up **to 1000 to 2000 int.** unit/L are typically seen during the acute phase with *ALT being higher than AST*.
- The serum **bilirubin** concentration may be normal in patients with anicteric hepatitis.
- The prothrombin time is the best indicator of prognosis.
- **In patients who recover**, the normalization of serum aminotransferases usually occurs within one to four months.
- A persistent elevation of serum ALT for more than six months indicates a progression to chronic hepatitis.

- The **rate of progression from acute to chronic** hepatitis B is determined primarily by the age at infection.
- The rate is approximately 90 percent for a perinatally acquired infection
- 20 to 50 percent for infections between the age of one and five years
- and less than 5 percent for an adult-acquired infection.

- **For most patients, treatment is mainly supportive**.
- **The likelihood of liver failure from acute HBV is less than 1 percent**

- There are known subgroups of patients whose **prognosis** is relatively **worse**
- (eg, patients who are immunocompromised
- have concomitant infection with hepatitis C virus [HCV]
- have pre-existing liver disease
- or are older adults

CHRONIC HEPATITIS B

- The diagnosis of chronic HBV infection is :

(HBsAg) for greater than six months

- Many patients with chronic hepatitis B are asymptomatic (unless they progress to decompensated cirrhosis or have extrahepatic manifestations), while others have nonspecific symptoms such as fatigue.

- **Physical examination** may be normal, or there may be stigmata of chronic liver disease. Jaundice, splenomegaly, ascites, peripheral edema, and encephalopathy may be present in patients with **decompensated cirrhosis**.
- **Laboratory tests** may be normal, but most patients have a mild to moderate elevation in serum AST and ALT.
- During exacerbations, the serum ALT concentration may be as high as 50 times the upper limit of normal, and alfa-fetoprotein (AFP) concentrations as high as 1000 ng/mL may be seen.

A progression to cirrhosis is suspected when :

- there is evidence of hypersplenism (decreased white blood cell and platelet counts) or
- impaired hepatic synthetic function (hypoalbuminemia, prolonged prothrombin time, hyperbilirubinemia).

- Patients with severe exacerbations should be referred to specialized centers for liver transplantation or treatment with nucleos/tide analogues.

- Not all exacerbations lead to HBeAg seroconversion and clearance of HBV DNA from the serum, a phenomenon termed **abortive** immune clearance .
- These patients may develop recurrent exacerbations with an intermittent disappearance of serum HBV DNA with or without a transient loss of HBeAg .
- Such repeated episodes of hepatitis may increase the risk of developing **cirrhosis** and hepatocellular carcinoma **(HCC).**

SEQUELAE AND PROGNOSIS OF CHRONIC HBV INFECTION

- The **sequelae of chronic HBV infection** vary from an inactive carrier state to the development of cirrhosis, hepatic decompensation, hepatocellular carcinoma (HCC), extrahepatic manifestations, and death.
- majority remain asymptomatic with a very low risk of cirrhosis or HCC .

complications of cirrhosis

- Cirrhosis is generally considered to be irreversible in its advanced stages, at which point the only option may be liver transplantation.

- In earlier stages, specific treatments aimed at the underlying cause of liver disease may **improve** or even **reverse cirrhosis**.

Major complications of cirrhosis include :

- Variceal hemorrhage
- Ascites
- Spontaneous bacterial peritonitis
- Hepatic encephalopathy
- Hepatocellular carcinoma
- Hepatorenal syndrome
- Hepatopulmonary syndrome

- Once these complications develop, patients are considered to have decompensated cirrhosis.
- Multiple factors can predispose to decompensation in a patient with cirrhosis. Risk factors for decompensation include **bleeding**, **infection, alcohol intake**, **medications**, **dehydration**, and **constipation**.
- In addition, patients with **obesity** are at increased risk for decompensation .
- **Once decompensation has developed, patients should be considered for liver transplantation.**

Other major complications of cirrhosis include

- portal vein thrombosis
- and cardiomyopathy.

- However, patients with these complications alone are not considered to have decompensated cirrhosis.

Complications of portal hypertension

- Many of the complications of cirrhosis are the result of portal hypertension (increased pressure within the portal venous system).
- This can lead to the **formation of venous collaterals (varices)** as well as circulatory, vascular, functional, and biochemical abnormalities that contribute to the **pathogenesis of ascites and other complications.**

Complications of portal hypertension include:

- ● Ascites
- ● Hepatic encephalopathy
- ● Variceal hemorrhage
- ● Spontaneous bacterial peritonitis
- ● Hepatorenal syndrome
- ● Portal hypertensive gastropathy
- ● Hepatic hydrothorax
- ● Hepatopulmonary syndrome
- ● Portopulmonary hypertension
- ● Cirrhotic cardiomyopathy

Variceal hemorrhage

- **Patients with variceal hemorrhage typically present with hematemesis and/or melena. It is typically treated with endoscopic variceal band ligation.**
- Other treatments include endoscopic sclerotherapy and placement of a transjugular intrahepatic portosystemic shunt (TIPS).
- Variceal hemorrhage is associated with high mortality rates.

Portal hypertensive gastropathy

- Portal hypertensive gastropathy (congestive gastropathy), while extremely common in patients with portal hypertension, is an uncommon cause of significant bleeding in these patients.
- When portal hypertensive gastropathy is the sole cause of bleeding, there is diffuse mucosal oozing with no other lesions, such as varices, to account for the GI bleeding and anemia.
- The mucosa is friable, and **bleeding presumably occurs when the ectatic vessels rupture.**

Ascites

- Ascites is the **accumulation of fluid within the peritoneal cavity**.
- It is the most common complication of cirrhosis.
- The first step leading to fluid retention and ultimately ascites in patients with cirrhosis is the development of portal hypertension. **Patients without portal hypertension do not develop ascites or edema.**
- ***Ascites is typically treated*** with a combination of diuretics and sodium restriction, though some patients require repeated therapeutic paracenteses or TIPS placement.
- Among patients with ***refractory ascites*** or ***spontaneous bacterial peritonitis***, the use of nonselective beta blockers may be associated with increased mortality .
- This may occur because failure to maintain an adequate mean arterial blood pressure is strongly correlated with survival in patients with advanced cirrhosis.

Spontaneous bacterial peritonitis

- Spontaneous bacterial peritonitis (SBP) is an infection of preexisting ascitic fluid without evidence for an intra-abdominal secondary source, such as a perforated viscus.
- SBP is almost always seen in the setting of end-stage liver disease.
- **Clinical manifestations of SBP** include fever, abdominal pain, abdominal tenderness, and altered mental status.
- Some patients are asymptomatic and present with only mild laboratory abnormalities.
- The index of suspicion for SBP must be high with a low threshold for diagnostic paracentesis. The **diagnosis** is established by **a positive ascitic fluid bacterial culture** and/or **an elevated ascitic fluid absolute polymorphonuclear leukocyte count (≥250 cells/mm^3).**
- Without early antibiotic treatment, mortality is high.

Hepatorenal syndrome

- Hepatorenal syndrome refers to the **development of renal failure in a patient who has advanced liver disease due to cirrhosis, severe alcoholic hepatitis, acute liver failure, or less often, a metastatic tumor**.
- Rather than being a new disease, hepatorenal syndrome usually represents the end-stage of a sequence of reductions in renal perfusion induced by increasingly severe hepatic injury. **Arterial vasodilatation in the splanchnic circulation, which is triggered by portal hypertension, appears to play a central role in the hemodynamic changes and the decline in renal function in hepatorenal syndrome.**
- The initial **reductions in glomerular** filtration rate are often masked clinically since associated decreases in muscle mass and hepatic urea production minimize elevations in the plasma creatinine concentration and blood urea nitrogen.
- **Hepatorenal syndrome is characterized** by a generally benign urine sediment, a very low rate of sodium excretion, and **a progressive rise in the plasma creatinine concentration**. There is some confusion regarding the presence or absence of oliguria.
- The diagnosis is one of exclusion, being made when other causes of renal dysfunction have been excluded.
- **In particular, volume depletion (as with overly rapid diuresis) can mimic all of the findings of hepatorenal syndrome.**
- **The prognosis is poor unless hepatic function improves or a liver transplantation is performed.**

Hepatic hydrothorax

- Hepatic hydrothorax is defined as the presence of a pleural effusion in a patient with cirrhosis and no evidence of underlying cardiopulmonary disease.
- It results from the movement of ascitic fluid into the pleural space through defects in the diaphragm, and it is usually right-sided.
- The **treatment** for hepatic hydrothorax includes **diuretics** and **sodium restriction**. Patients who do not respond to conservative therapy may require **repeated therapeutic thoracenteses or TIPS**.
- The most important aspect of management is evaluation for **liver transplantation** .
- **Chest tubes should not be placed in patients with hepatic hydrothorax**. Placement of chest tubes in this setting can result in massive protein and electrolyte depletion, infection, renal failure, and bleeding.

Hepatopulmonary syndrome

Hepatopulmonary syndrome (HPS) is defined by the following triad:

- ●Liver disease
- ●Increased alveolar-arterial gradient while breathing room air
- ●Evidence for intrapulmonary vascular abnormalities, referred to as intrapulmonary vascular dilatations

- Estimates of the prevalence of HPS among patients with chronic liver disease range from 4 to 47 percent, depending on the diagnostic criteria and methods used.
- Even in those without HPS, **mild hypoxemia is common** and is presumably caused by ascites, with resulting diaphragmatic elevation and ventilation/perfusionmismatch.

- There are no effective medical therapies for HPS. Liver transplantation offers the most promise for successful treatment.

Portopulmonary hypertension

- Portal hypertension-associated pulmonary hypertension (portopulmonary hypertension) refers to the presence of pulmonary hypertension in patients with portal hypertension.

- The prevalence in patients with cirrhosis is approximately 2 percent.
- Neither the prevalence nor the severity of portopulmonary hypertension appears to correlate with the degree of portal hypertension .

- Patients with ***portopulmonary hypertension*** may present with **fatigue, dyspnea, peripheral edema**, **chest pain**, and **syncope.**

- The diagnosis may be suggested by **echocardiography** and confirmed by **right heart catheterization.**

- Patients with moderate to severe portopulmonary hypertension are difficult to treat with medical therapy, and the perioperative mortality with liver transplantation is high.

Cirrhotic cardiomyopathy

- Up to 50 percent of patients with advanced cirrhosis have features of cardiac dysfunction.
- The term "cirrhotic cardiomyopathy" has been used to describe such patients, who are characterized as having normal to increased cardiac output and contractility at rest, but a blunted response to pharmacologic, physiologic, or pathologic stress.
- Cardiomyopathy can occur from any cause of cirrhosis, although patients with **alcoholism** or **hemochromatosis** may have additional contributing causes to cardiac dysfunction.

Hepatic encephalopathy

- Hepatic encephalopathy describes the spectrum of potentially reversible neuropsychiatric abnormalities seen in patients with liver dysfunction.
- Disturbance in the diurnal sleep pattern (**insomnia and hypersomnia)** is a common early feature that typically precedes overt neurologic signs .
- **More advanced neurologic features** include the presence of asterixis, hyperactive deep tendon reflexes, and, **less commonly**, transient decerebrate posturing.
- **Treatments for hepatic encephalopathy** include addressing any predisposing conditions (eg, infection or gastrointestinal bleeding), synthetic disaccharideseg, lactulose), and nonabsorbable antibiotics (eg, rifaximin).

Hepatocellular carcinoma

- Patients with **cirrhosis** have a markedly increased risk of developing hepatocellular carcinoma (HCC).
- Patients with most forms of chronic hepatitis are not at an increased risk until cirrhosis develops. Exceptions to this rule are patients with chronic hepatitis B virus infection, who can develop HCC in the absence of cirrhosis.

- Certain causes of cirrhosis appear to have a relatively increased risk for HCC. Patients with cirrhosis from hepatitis B, hepatitis C, nonalcoholic steatohepatitis, and hemochromatosis are at the **highest risk,** while those with cirrhosis from autoimmune hepatitis and Wilson disease appear to have a **lower risk**.
- Because of the large functional reserve of the liver, patients with HCC are frequently asymptomatic early in its course, and the diagnosis is often delayed.
- **Decompensation** in a patient with **previously compensated** cirrhosis should raise the clinical suspicion that HCC has developed.
- **Other common signs and symptoms** of HCC are usually **related to mass effect** from the tumor and include pain, early satiety, obstructive jaundice, and a palpable mass.
- HCCs can rupture, causing **hemoperitoneum**.
- **Paraneoplastic manifestations** include erythrocytosis, hypercalcemia, hypoglycemia, and diarrhea.

- The **diagnosis of HCC** may be suggested by marked elevations of serum alpha-fetoprotein (AFP) or by characteristic radiographic findings.
- Elevated AFP is **not specific** for HCC since it can also be seen in patients with acute or chronic hepatitis, gonadal tumors, and pregnancy.
- However, rising serum AFP levels in a patient with cirrhosis should raise clinical suspicion for HCC.
- However, a significant proportion of patients with HCC have normal AFP levels, especially when the tumor is small.
- ***As a result, a normal AFP does not preclude a diagnosis.***

Portal vein thrombosis

- Portal vein thrombosis can develop in patients with cirrhosis and contribute to the development of portal hypertension.
- In patients with cirrhosis, the **pathogenesis** is likely related to unbalanced hemostasis and slowing of portal flow.
- **Treatment** often involves anticoagulation, though the decision to anticoagulate must take into account the patient's risk for bleeding, particularly if esophageal varices are present.

GENERAL MANAGEMENT

- The major goals of managing patients with cirrhosis include:
- ●Slowing or reversing the progression of liver disease
- ●Preventing superimposed insults to the liver
- ●Identifying medications that require dose adjustments or should be avoided entirely
- ●Managing symptoms and laboratory abnormalities
- ●Preventing, identifying, and treating the complications of cirrhosis
- ●Determining the appropriateness and optimal timing for liver transplantation

Slowing or reversing the progression of liver disease

- Although cirrhosis is generally considered to be irreversible in its advanced stages, the exact point at which it becomes irreversible is unclear .
- **Some chronic liver diseases respond to treatment even when the liver disease has progressed to cirrhosis.**
- Thus, specific therapies directed against the underlying cause of the cirrhosis should be instituted.

As examples:

- Patients with hepatitis C and advanced fibrosis or cirrhosis who achieve a sustained virologic response (SVR) with antiviral treatment have a **lower risk of liver-related mortality** compared with patients who do not achieve an SVR.
- Abstinence from alcohol substantially **improves survival in alcoholic cirrhosis**.
- Successful treatment of chronic viral hepatitis can **improve long-term outcomes and may affect fibrosis**.
- In a study of 91 patients with chronic hepatitis C and significant fibrosis based on liver elastography, patients who achieved a sustained virologic response had a significant decrease in liver stiffness (and thus presumably fibrosis) 24 weeks after the end of treatment .

Preventing superimposed insults to the liver

- **Vaccinations** — Vaccination against hepatitis A and B for those who are not already immune can help prevent superimposed insults to the liver. Other vaccinations, such a yearly influenza vaccination, are also recommended .
- **Avoidance of hepatotoxins** — Patients with cirrhosis should avoid medications, supplements, and other substances that are commonly associated with liver injury. This includes abused substances, such as alcohol, over-the-counter medications (such as nonsteroidal anti-inflammatory drugs), prescribed drugs with hepatotoxic side effects, and certain herbal remedies.
- **Medication adjustments** — Patients with cirrhosis are at increased risk of adverse events with many medications because of impaired hepatic metabolism or renal excretion. ***Many medications require dose adjustments or should be avoided entirely.***

Preventing and identifying complications

- Patients should be **monitored for the development of complications**, and when possible, steps should be taken to **prevent their development**. In particular, patients should be screened for esophageal varices and hepatocellular carcinoma.
- If **varices** are present, prophylactic treatment with **beta blockers** or **esophageal variceal ligation** is indicated.

Other measures to decrease the risk of complications include :

- judicious diuresis and avoiding proton pump inhibitors in patients without clear indications for their use (spontaneous bacterial peritonitis);
- treating infections (spontaneous bacterial peritonitis, hepatic encephalopathy);
- avoiding sedatives and treating hypokalemia and hyponatremia (hepatic encephalopathy);
- avoiding nephrotoxic agents and aggressive diuresis (hepatorenal syndrome);
- and only using urinary catheters, mechanical ventilation, and central lines when clearly indicated (secondary infections).

Variceal bleeding

- All patients with cirrhosis should undergo screening for esophageal varices with upper endoscopy so that prophylactic therapy can be given to those with varices that are at increased risk for bleeding and to determine the risk of variceal hemorrhage.
- Prophylactic therapy most commonly involves treatment with a nonselective beta blocker or endoscopic variceal ligation, which reduces the risk of variceal bleeding.

Hepatocellular carcinoma

- **Patients with cirrhosis should undergo surveillance with ultrasonography every six months.**

Spontaneous bacterial peritonitis

- The risk of spontaneous bacterial peritonitis (SBP) can be reduced by efforts to diurese patients since diuresis concentrates ascitic fluid, thereby raising ascitic fluid opsonic activity.
- Early recognition and aggressive treatment of localized infections (eg, **cystitis, cellulitis**) can also help to prevent bacteremia and SBP.
- Proton pump inhibitor use has been associated with an increased risk of SBP, so proton pump inhibitors should only be given to patients who have clear indications for their use.
- Finally, prophylactic antibiotics aimed at decontaminating the gut have a role in specific clinical settings.

Hepatic encephalopathy

- Patients with cirrhosis should be evaluated regularly for hepatic encephalopathy, the earliest features of which can be subtle.

- Events that can precipitate hepatic encephalopathy include the development of variceal bleeding, infection (such as SBP), the administration of sedatives, hypokalemia, and hyponatremia, all of which should be corrected/avoided whenever possible .

Portal vein thrombosis

- Enoxaparin may be effective for preventing portal vein thrombosis (PVT) in patients with cirrhosis, though it is not used routinely.

- If it is to be used, we suggest eradication of varices (if present) prior to initiation of anticoagulation when possible.

Hepatorenal syndrome

- Nephrotoxic agents (such as aminoglycosides) and vigorous diuresis should be avoided in patients with cirrhosis since they can precipitate renal failure.

Secondary infections

- Patients with **cirrhosis who are hospitalized** often **acquire infections** while in the hospital. Factors that have been associated with hospital-acquired econdary infections in patients with cirrhosis include the use of urinary catheters, mechanical ventilation, and the placement of central lines .

- Many of these interventions are performed routinely (such as placement of urinary catheters to measure urine output).
- However, **avoiding these interventions unless they are absolutely necessary** may decrease the risk of acquiring an infection while in the hospital, and it is our practice to only use these interventions when clearly indicated.

Liver transplantation

- Liver transplantation is the definitive treatment for patients with decompensated cirrhosis.
- It is important to determine whether patients may be eligible for transplantation and to refer them to a transplant center for evaluation.
- Several guidelines are available which help determine when referral for liver transplantation may be beneficial.
- The decision to proceed to liver transplantation (either cadaveric or live donor) **depends upon the severity of disease, quality of life, and the absence of contraindications.**

PROGNOSIS

- The prognosis of cirrhosis is highly **variable** since it is influenced by a number of factors, including etiology, severity, presence of complications, and comorbid diseases.
- Once **decompensation** occurs (eg, the patient develops variceal bleeding, hepatic encephalopathy, or spontaneous bacterial peritonitis), **mortality rates are high**.

- **Compensated cirrhosis —** Patients with cirrhosis who have not developed major complications are classified as having compensated cirrhosis.

- The ***median survival*** of patients with compensated cirrhosis is >12 years .
- Patients with varices but who have not developed variceal bleeding are considered to have compensated cirrhosis, though their prognosis is worse than that of patients who have compensated cirrhosis without varices .

- **Decompensated cirrhosis —** Patients who have developed complications of cirrhosis, such as variceal hemorrhage, ascites, spontaneous bacterial peritonitis, hepatocellular carcinoma, hepatorenal syndrome, or hepatopulmonary syndrome, are considered to have decompensated cirrhosis and have a worse prognosis than those with compensated cirrhosis.
- ***median survival*** was ≤6 months in patients with decompensated cirrhosis and a Child-Pugh score ≥12 or a Model for End-stage Liver Disease
- (MELD) score ≥21 .