Liver cirrhosis and complications

- Objectives:
- To understand Cirrhosis definition, causes and complications
- To know the pathophysiology of Cirrhosis complications
- To know how to approach patients with Cirrhosis and its complications

[Color index : Important | Notes | Extra]

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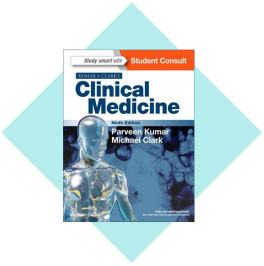
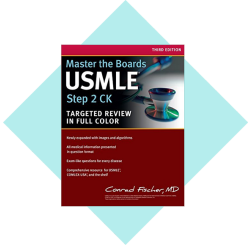
- Resources:
- 435 slides.





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Cirrhosis: Late stage of chronic liver inflammation and fibrosis, in which liver parenchyma is distorted and replaced by fibrous tissue and regenerating nodules (if no nodules present no cirrhosis is there). fibrous tissue replaces damaged or dead hepatocytes

- Chronic liver injury (Chronic hepatitis) → Compensated Cirrhosis → Decompensated Cirrhosis → Death or liver transplantation

Chronic hepatitis is a spectrum depends on how aggressive is the etiology. Some people progress faster to cirrhosis and some remains years and then develop very minimal fibrosis (Genetic predisposition)

Compensated cirrhosis the liver has the ability to regenerate and maintains normal function

Pathophysiology:

The distortion of liver anatomy causes (Cirrhosis):

A- Decreased sinusoidal blood flow through the liver (vasoconstriction) → high resistance in portal circulation (portal hypertension) → this lead widespread manifestations, including (ascites, peripheral edema, splenomegaly, and varicosity of veins).

B- Hepatocellular failure that leads to impairment of biochemical functions, such as decreased albumin synthesis and decreased clotting factor synthesis.

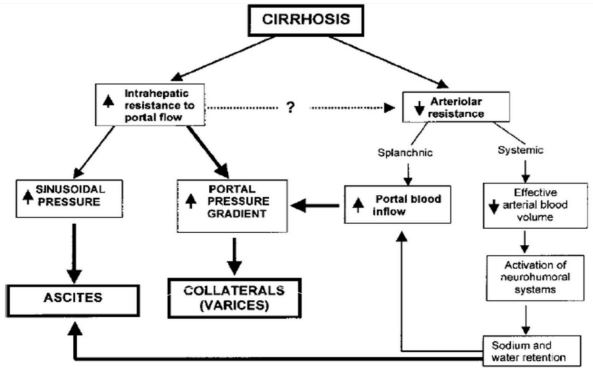


Figure 1. Pathogenesis of portal hypertension and its two main complications: varices and ascites. GASTROENTEROLOGY Vol. 120, No. 3

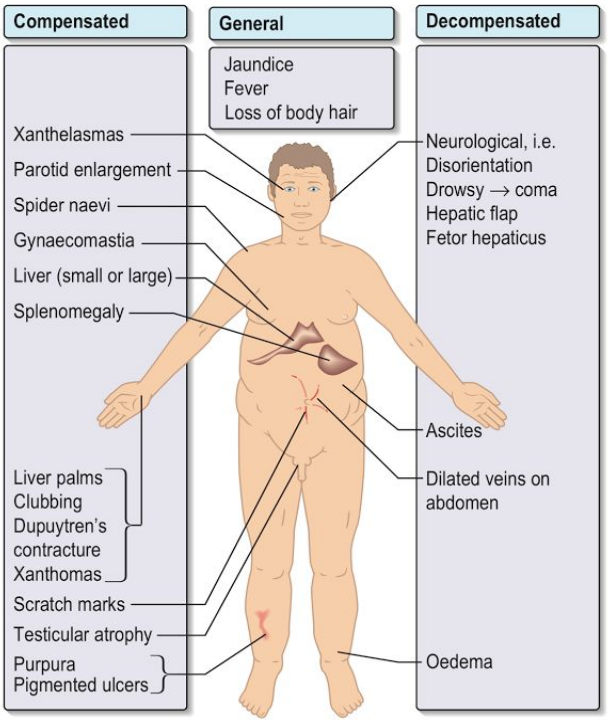
Aetiology:

Causes	Notes
Viral hepatitis (B and C)	The **most common** cause worldwide
Alcoholic Steatohepatitis	The most common cause in the western world Like all drugs causing liver disease gives a **greater elevation in AST compared to ALT**
Non-alcoholic Steatohepatitis	Associated with Obesity, Diabetes, Hyperlipidemia, Corticosteroid use
Autoimmune hepatitis	Circulating auto-antibodies (antinuclear, smooth muscle, soluble liver antigen, Liver/kidney microsomal antibodies) (**ASMA**) **(ANA)** "Hypergammaglobulinemia"
Primary Biliary Cirrhosis (autoimmune)	• Progressive destruction of **intrahepatic bile ducts** causing cholestasis eventually leading to cirrhosis. • Affects women in 40s or 50s • Presents with pruritis with or without jaundice. In advanced disease there is **xanthelasma** (due to secondary hypercholesterolemia) • The most accurate blood test is Antimitochondrial antibody **(AMA)**

Primary Sclerosing Cholangitis (autoimmune)	• Progressive obliterating fibrosis of **intra and extra hepatic ducts eventually leading to fibrosis** • More common in male than female • 75% or more occurs in association with IBD • The **most accurate test is Endoscopic retrograde cholangiopancreatography** not liver biopsy!
Alpha 1 antitrypsin deficiency	Combination of liver disease and emphysema in young patient (under 40) who is non smoker
Wilson's disease	• Disorder of abnormally decreased copper excretion from the body because of a decrease in ceruloplasmin. Copper builds up in the liver, Kidney, Red blood cells and nervous system • Presents with : **Neurological symptoms**, coombs negative hemolytic anemia and renal tubular acidosis
Hemochromatosis	• Genetic disorder leading to **over-absorption of iron** in the duodenum • Presents with : Fatigue and joint pain, Erectile dysfunction in men and Amenorrhea in women, Skin darkening, Diabetes, Restrictive cardiomyopathy
Vascular	Budd-Chiari syndrome, Heart failure, portal vein thrombosis Hypoxic damage and necrosis of hepatocyte
Biliary	Sclerosing Cholangitis
Drugs	methotrexate, acetaminophen toxicity

1. Clinical manifestations (Signs and symptoms)

- No symptoms (Most patients in early cirrhosis)
- Symptoms of cirrhosis (sometimes nonspecific symptoms)
- Symptoms of **decompensations** (when liver start to fail):
    1. Neurological disorientations (Hepatic encephalopathy)
    2. Ascites
    3. Dilated veins on abdomen and Variceal hemorrhage
    4. Hepatocellular carcinoma
    5. Pulmonary (Hepatopulmonary syndrome/Portopulmonary HTN)



2. Investigations

<table>
<tr><th colspan="2">Lab Test</th></tr>
<tr><td colspan="2">LFTs:

● Moderately elevated aminotransferases (often with an AST:ALT ratio >1)
● Elevated ALP (2 to 3 times the ULN[1])</td></tr>
<tr><td colspan="2">CBC:

● Thrombocytopenia (platelets will be low due to hypersplenism)
● Leukopenia/neutropenia
● Anemia</td></tr>
<tr><td colspan="2">Liver function:

Prolonged prothrombin time/elevated INR and Low serum albumin (are the best indicators of liver function * With advanced disease</td></tr>
<tr><td colspan="2">Hyperbilirubinemia / Hyponatremia / Elevated serum creatinine (with severe liver disease)</td></tr>
<tr><th colspan="2">Radiology</th></tr>
<tr><th>Mild to moderate disease</th><th>With advanced disease</th></tr>
<tr><td>1. Surface nodularity
2. Increased echogenicity (ultrasound)
3. Atrophy of the right lobe
4. Hypertrophy of the caudate or the left lobes</td><td>1. Small nodular liver
2. Ascites
3. Hepatocellular carcinoma
4. Portal, splenic, superior, mesentric vein thrombosis
5. Portosystemic collateral</td></tr>
</table>

Confirm the Diagnosis:

- Biopsy (Gold standard)
- Noninvasive tests :

    1- Serum score systems
    2- Elastography (e.g fibroscan) measure liver elasticity and gives you grade

    - Fibroscan : it's the best when there is no cirrhosis at all or a very severe one.

[1] Upper limit of normal

3. Assess Severity and Prognosis of Liver Disease :

This is variable and depends on the etiology and presence of complications

1-Child-Turcotte-Pugh score or Child Criteria (CPT score) (The best)

Table 3-1 Child–Pugh Classification to Assess Severity of Liver Disease			
POINTS	**1**	**2**	**3**
Ascites	Absent	Slight	Moderate
Bilirubin	<2.0 mg/dL (<34.2 micromol/L)	2.0–3.0 mg/dL (34.2-51.3 micromol/L)	>3.0 mg/dL (>51.3 micromol/L)
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4
PT (seconds over control)or **INR** ratio	<4	4 to 6	>6
	<1.7	1.7–2.3	>2.3
Albumin	>3.5 g/dL (>35 g/L)	2.8–3.5 g/dL (28-35 g/L)	<2.8 g/dL (<28 g/L)

- **Class A—5 to 6 points total** (least severe liver disease), 100-85% 2-year survival
- **Class B—7 to 9 points total** (moderate severe liver disease), 80-60% 2-year survival
- **Class C—10 to 15 points total** (severe liver disease), 45-35% 2-year survival

2- MELD score (model for end-stage liver disease) (Calculation basically)

- MELD = 3.8 [serum bilirubin (mg/dL)] + 11.2 [lNR] + 9.6 [serum creatinine (mg/dL)] + 6.4 (constant)

(Bilirubin+INR+Serum Creatinine) أهم شي تعرفون يعتمد على ايش

Complications of liver failure
(note the mnemonic **AC, 9H**)
- Ascites
- Coagulopathy
- Hypoalbuminemia
- Portal Hypertension
- Hyperammonemia
- Hepaticencephalopathy
- Hepatorenal syndrome
- Hypoglycemia
- Hyperbilirubinemia/jaundice
- Hyperestrinism
- Hepatocellularcarcinoma

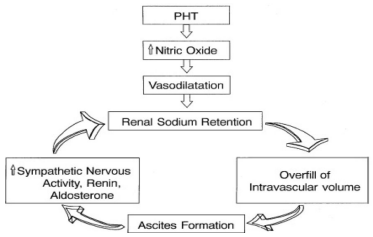
4. Management:

Cirrhosis is irreversible and frequently progress. Management is that of complications seen in decompensated cirrhosis. Correcting the underlying cause, venesection for haemochromatosis, abstinence from alcohol for alcoholic cirrhosis, may halt the progression of liver disease

Complications of liver cirrhosis :

1. Ascites important

Accumulation of fluid in the peritoneal cavity. First step in development of ascites is the presence of significant portal HPN (increased hydrostatic pressure) and hypoalbuminemia (reduced oncotic pressure). In cirrhosis peripheral arterial vasodilation leads to reduction in effective blood volume with activation of the sympathetic nervous system and renin-angiotensin system > Promoting salt and water retention



Causes (DDx):	**Transudate**	**Exudate**
	• Portal hypertension (most common) • Cardiac failure	• Cancer • Infections • Nephrotic syndrome • Pancreatitis • Lymphatic obstruction
Examination	• **1.5 L of fluid must be present before flank dullness is detected** • **Shifting dullness** • **If no Flank dullness is present less likely ascites**	
Investigation	**Diagnostic aspiration of ascitic fluid should be carried out in an new ascites** **Routine:** 1. Cell count and differential 2. Albumin and total protein **"To measure SAAG"** **Optional** (when there is suspicion of infection)**:** 1. Gram stain and culture 2. Glucose 3. Lactate dehydrogenase 4. Amylase to exclude pancreatic ascitis **Unusual:** 1. AFB smear (Not sensitive) and culture (higher sensitivity) 2. Cytology 3. Triglyceride 4. Bilirubin	
Management **Depends on the cause!** **So the most important thing is to treat underlying cause**	Management of ascites due to portal HTN	**Treatment of refractory ascites ~10%**
	Stepwise approach: 1. Salt restriction(<2000 mg/d) 2. Diuretics (Combination of Spironolactone and Furosemide) Monitor electrolytes and kidney function • An advantage with this diuretic combination is to avoid abnormalities in serum potassium.	Ascites that : Unresponsive to sodium restricted diet and high dose diuretic treatment / Development of clinically significant complications of diuretics 1. Serial therapeutic paracenteses + intravenous infusion of albumin if draining > 5L fluid 2. Transjugular intrahepatic portosystemic shunt 3. Liver transplantation 4. Peritoneovenous shunt

- **Classification of ascites by the serum albumin-ascites gradient :**

High albumin gradient (SAAG>=1.1g\dL) Transudate	Low albumin gradient (SAAG<1.1g\dL) Exudate
• **Cirrhosis** • Heart failure / Constrictive pericarditis • Alcoholic hepatitis • Budd chiari • Massive hepatic metastases In case of Portal HTN and Heart disease	• Peritoneal carcinomatosis • Peritoneal tuberculosis • Pancreatitis • Serositis • Nephrotic syndrome

Complications of ascites:

Spontaneous bacterial peritonitis (important): Infection of ascitic fluid (spontaneous means without perforation = idiopathic cause). Usually gram negative (**E.Coli**), **klebsiella**, **s.pneumoniae**.

- ➔ **Presentation:** variable (Fever, abdominal pain, abdominal tenderness , altered mental status) maybe all, some or none present.
- ➔ **Diagnosis:** PMN count (>250 cells/mm3) and positive ascitic fluid bacterial culture
- ➔ **Treatment:**
  - ◆ Cefotaxime or a similar third generation cephalosporin IV covers 95% of flora including common organism.
  - ◆ Albumin when: severe cases to reduce mortality and renal failure in the first and third day.**Creatinine** >1 mg/dL **BUN** > 30 mg/dL total **bilirubin** >4 mg/dL

2. Hepatic encephalopathy important

- Hepatic encephalopathy is a reversible brain dysfunction caused by liver insufficiency and portosystemic shunts Because the portal blood contains toxins which are then shunted to the systemic circulation even with normal liver!
- Occurs with advanced hepatocellular disease either chronic (Cirrhosis) or acute (Fulminant) it is also present in patient following surgical or TIPS shunts
- **Pathophysiology Different mechanisms :**

1. Neurotoxin (ammonia) The liver degrades ammonia. If the liver is abnormal Ammonia Accumulates and Affects the brain.
2. Blood-to-brain transport of neurotransmitter
3. Activation of inhibitory (gamma-aminobutyric acid, serotonin) neurotransmitter systems
4. Impairment of excitatory (glutamate, catecholamines) neurotransmitter systems
5. Enhanced neural inhibition

- **Clinical features:**

Flapping tremor +

Grading system for hepatic encephalopathy

Grade	Mental status	Asterixis	EEG
I	Euphoria/depression	Yes/no	Usually normal
	Mild confusion		
	Slurred speech		
	Disordered sleep		
II	Lethargy	Yes	Abnormal
	Moderate confusion		
III	Marked confusion	Yes	Abnormal
	Incoherent		
	Sleeping but arousable		
IV	Coma	No	Abnormal

Precipitants of hepatic encephalopathy caused by: Go through the headlines	Treatment
1. Drugs eg. Benzodiazepine, narcotics, alchohol 2. Increased ammonia production, absorption or entry into the brain 3. Dehydration 4. Portosystemic shunts 5. Vascular occlusion 6. HCC	**The aims of management is to identify and treat any precipitating factors and to minimize absorption of ammonia:** 1. Lactulose First line of treatment (reduces colonic pH and limits ammonia absorption) 2. Antibiotics to reduce the number of bowel organisms and hence production of ammonia (Rifaximin or metronidazole) 3. Maintenance of nutrition with adequate calories and protein is initially restricted

3. Hepatorenal syndrome

Development of [2]functional acute kidney injury in a patient who usually **has advanced liver disease** either cirrhosis or alcoholic hepatitis. Marked peripheral vasodilatation leads to fall in systemic vascular resistance and effective hypovolemia. This in turn results in vasoconstriction of the renal circulation with markedly reduced renal perfusion. Poor prognosis.

Diagnosis By exclusion	Type l: rapid, aggressive Type Il : slow, less aggressive ➔ **present as:** azotemia, oliguria, hyponatremia, hypotension,low urine sodium < 10 mEq/L.
Treatment	• Correct underlying cause • Albumin • Vasoconstrictors of splanchnic vessels (Terlipressin, octreotide, midodrine, epinephrine) • HD (Hemodialysis) • Liver Transplantation

4. Portopulmonary Syndrome

- Refers to the presence of **pulmonary hypertension** in the coexistent **portal hypertension**
- Prevalence in cirrhotic patients is approximately 2%
- Diagnosis:
  - Suggested by echocardiography
  - Confirmed right heart catheterization

[2] i.e. in the presence of normal kidneys

5. Hepatic Hydrothorax

- **Pleural effusion** in a patient with cirrhosis and no evidence of underlying cardiopulmonary disease.
- 5-10% of cirrhosis patients.
- **Cause:** movement of ascitic fluid into the pleural space through defects in the diaphragm.
- Commonly Rt side
- Reveals a **transudative fluid**
- Serum to fluid albumin gradient greater than 1.1
- Management similar to ascites

6. Hepatopulmonary syndrome

Triad:

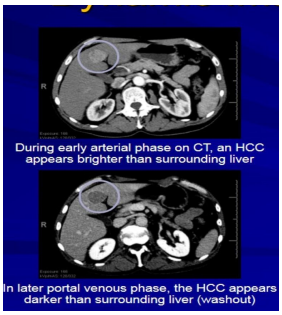
1. Liver disease (liver disease, portal hypertension, or portosystemic shunts)
2. Increased alveolar-arterial gradient while breathing room air
3. Evidence for intrapulmonary vascular abnormalities, referred to as intrapulmonary vascular dilatations (shunting)

➔ Mild hypoxemia is common

➔ In severe disease patients are breathless on standing

7. Hepatocellular carcinoma (Hepatoma) important

- Patients with chronic liver disease or cirrhosis have a markedly increased risk of developing hepatocellular carcinoma
- Other aetiological factors include **aflatoxin, androgenic steroids and contraceptive pills**
- Poor prognosis (median survival is only 6-20 months)

Investigations	• **Blood tests** (Alpha Fetoprotein AFP) • **Radiology** (most important) Dynamic CT and MRI (See tumor density with time after IV bolus contrast. Requires both arterial enhancement and washout). HCC are Hypervascular. the tumor Receives blood 100% from the Hepatic artery. After the contrast **reaches the hepatic artery**, only the tumor will light up with the contrast on arterial pulse while the rest of the liver will not. • Biopsy only performed when there is diagnostic doubt as there is risk of tumor seeding in the percutaneous needle biopsy tract. 
Treatment	**depends on several factors, including:** • The stage of the tumor + stage of liver disease • Different scoring systems, Famous system(Barcelona Clinic Liver Cancer Staging Classification (BCLC) 1. Liver Transplantation

	2. Surgical resection 3. Ablation (alcohol, RFA, Microwave) 4. Transarterial chemoembolization or Radioembolization (injection of a chemotherapeutic agent and lipiodol into the hepatic artery) 5. Systemic therapy (very limited role)

Liver Transplantation

- Liver transplantation is the definitive treatment for patients with decompensated cirrhosis
- Depends upon the severity of disease, quality of life and the absence of contraindications

General Recommendations for all cirrhotic patients

- **HCC Surveillance:** US for HCC surveillance Q6 months for all cirrhosis patients
- **Endoscopy screening for varices:** Upper Gl endoscopy every 2 years and then less if varices develop
- **Avoidance of Superimposed Insults**
    1. Alcohol
    2. Acetaminophen
    3. Herbal medications
- **Vaccinations**

1. Hepatitis A and B
2. Pneumococcal vaccine
3. Influenza vaccination

1. A 67-year-old man presents feeling unwell and complaining of general malaise. He mentions a long history of alcohol abuse and his past medical history shows deranged liver function tests. Which of the following clinical signs does not form part of chronic liver disease?

A. Finger clubbing
B. Palmer erythema
C. Spider naevia
D. Koilonychia
E. Jaundice

2. You see a 56-year-old man in your clinic with suspected alcoholic liver disease. Liver function tests reveal a bilirubin of 36iu/L, AST of 150iu/L, ALT 75iu/L and ALP 100iu/L. Which of the following blood test parameters would support a diagnosis of alcoholic-related liver disease?

A. Normal mean cell volume (MCV)
B. Low MCV
C. Normal mean cell haemoglobin (MCH)
D. Low MCH
E. Raised MCV

3. A 47-year-old man presents complaining of weight gain, on examination there is an abdominal distension with a fluid thrill. Which of following is not a cause of ascites secondary to venous hypertension?

A. Congestive heart failure
B. Cirrhosis
C. Constrictive pericarditis
D. Budd–Chiari syndrome
E. Nephrotic syndrome

4. A 56-year-old man, diagnosed with emphysema, presents with a one-month history of jaundice and ascites. Your registrar suspects that this patient may have liver disease secondary to α1-antitrypsin deficiency. Select the most likely mode of inheritance from the list below:

A. Autosomal dominant
B. X-linked dominant
C. Autosomal recessive
D. Polygenic
E. None of the above

5. You see a 56-year-old woman who presents with a two-month history of jaundice. Associated symptoms include lethargy and polyarthralgia. Her LFTs reveal a bilirubin of 46iu/L, AST 200, ALT 175, ALP 104. On examination, the patient is jaundiced and has finger clubbing. There are several spider naevi on the front and back of the trunk. Her abdomen is soft and there is a smooth hepatomegaly. Prior to her onset of symptoms, the patient has been fit and well. Viral serology is normal and anti-soluble liver antigen (SLA) is detected. You decide to start this patient on treatment. The most appropriate treatment is:

A. Liver transplantation
B. Methotrexate
C. Prednisolone
D. Cyclosporin
E. Antivirals

6. During a ward round, you are questioned about tumours that may arise from the liver parenchyma. Which of the following liver tumours is considered to be benign?

A. Angiosarcoma
B. Fibrosarcoma
C. Adenoma
D. Hepatoblastoma
E. Leiyomyosarcoma

7. A patient on your ward is diagnosed with hepatocellular carcinoma. You are asked to perform a tumour marker level on this patient. Which of the following tumour markers are elevated in hepatocellular carcinoma?

A. α-fetoprotein
B. Carcinoembryonic antigen (CEA)
C. CA15-3
D. HcG
E. CA125

Answers

1. **D.** Finger clubbing (A), palmer erythema (B), spider naevi (C) and jaundice (E) are all known clinical signs of chronic liver disease. Others include bruising and liver flap (secondary to hepatic encephalopathy). Koilonychia (D) refers to spooning of the nails and occurs in iron deficiency anaemia. It is leuconychia (whitening of the nails due to hypoalbuminaemia which can occur due to chronic liver disease, nephrotic syndrome, malnutrition) that is seen in chronic liver disease.

2. **E.** Macrocytosis, i.e. an elevated MCV (>96fL) of which the causes can be seen in:

- megaloblastic anaemia secondary to vitamin B12 and folic acid deficiency;
- chronic alcoholism and/or alcoholic liver disease (most common causes of all causes of macrocytosis), pregnancy, hypothyroidism, reticulocytosis, aplastic anaemia, myelodysplastic syndromes and can also be caused by drugs that inhibit DNA synthesis (e.g. azathioprine);
- an elevated MCV would suggest, along with the deranged LFTs, and support a diagnosis of alcoholic liver disease.

Therefore answers A–D are incorrect.

3. **E.** Ascites can be described as the pathological accumulation of fluid in the abdominal cavity. Ascites occur secondary to:

- conditions leading to venous hypertension (e.g. cirrhosis, congestive heart failure, constrictive pericarditis, Budd–Chiari syndrome, portal vein thrombosis)
- hypoalbuminaemia (e.g. nephrotic syndrome, malnutrition)
- malignant disease (e.g. secondary metastases of carcinomas of breast, ovary, colon);
- infections (e.g. tuberculosis)
- others (e.g. pancreatic disease, ovarian disease, myxoedema).
  Answers A–D are all known causes of ascites that occur secondary to venous hypertension. Nephrotic syndrome (E), however, leads to ascites secondary to hypoalbuminaemia.

4. **C.** α 1-antitrypsin deficiency is an autosomal recessive disorder (C), which results from single amino acid substitutions at positions 264 and 342 on chromosome 14. α 1-antitrypsin is a serine protease, synthesized in the liver, required in controlling inflammatory cascades. The lack of this serine protease results in emphysema (75 per cent), chronic liver disease and hepatocellular carcinoma, asthma, pancreatitis, gallstones, Wegener's granulomatosis. Patients with liver disease secondary to α 1-antitrypsin deficiency usually present with dyspnoea (from emphysema), liver cirrhosis, cholestatic jaundice. Investigations include: serum α 1-antitrypsin levels, liver biopsy, genetic phenotyping and DNA analysis at prenatal diagnosis. Management involves quitting smoking, augmentation therapy with α 1-antitrypsin pooled from human plasma and liver transplantation is the treatment of choice in decompensated cirrhosis.

5. **C.** This patient has symptoms of chronic liver disease secondary to auto- immune hepatitis (AIH) which is indicated from the history (no history of excessive alcohol consumption), negative viral serology and positive SLA autoantibody. AIH is an inflammatory liver disease of unknown cause which is characterized by suppressor T-cell defects which are directed against hepatocyte surface antigens. Three types of AIH have been identified according to the various autoantibodies detected (e.g. Type-1: anti-smooth muscle antibodies, antinuclear antibodies; type-2: anti-liver/kidney microsomal type 1 antibodies; and type-3: antibodies against soluble liver antigen or liver–pancreas antigen). AIH is known to affect women (young and middle-aged) with 25 per cent presenting with acute hepatitis and signs of autoimmune disease (e.g. polyarthralgia, glomerulonephritis, pernicious anaemia, PSC). The remaining patients are asymptomatic and are diagnosed when signs of chronic liver disease develop. Investigations include: (1) Blood: LFTs, immunoglobulins (e.g. IgG), auto-antibodies (see above) and FBC (may show low WCC and platelets); (2) liver biopsy may reveal mononuclear infiltration, fibrosis or cirrhosis; and (3) MRCP to exclude PSC. Management involves: (1) Symptomatic treatment for chronic liver disease; (2) immunosuppressant therapy: Corticosteroid therapy (e.g. prednisolone) or steroid-sparing agent such as azathioprine can be used; and (3) liver transplantation is indicated for decompensated liver cirrhosis or failure to respond to medical treatment.

6. **C**

Benign primary liver tumours include:

- haemangiomas (most common);
- adenomas (C);
- cysts;
- focal nodular hyperplasia;
- fibromas;
- leiyomyomas.

The malignant primary liver tumours include:

- hepatocellular carcinoma (accounts for 90 per cent of primary liver tumours);
- cholangiocarcinoma;
- angiosarcoma (**A**);
- hepatoblastoma (**D**);
- fibrosarcoma (**B**);
- leiyomyosarcoma (**E**).

7.**A** Fifty to 80 per cent of hepatocellular carcinomas are associated with high serum levels of α-fetoprotein (AFP), a tumour marker, which is also linked to, and elevated in, testicular carcinomas. Serum levels of AFP can be monitored either post-surgical resection (if the tumour is solitary) or post chemotherapy; falling or rising levels post treatment could be indicative of disease remission or progression, respectively. CEA (**B**) is primarily linked with colorectal carcinoma. CA 15-3 (**C**) is linked with breast carcinoma. HcG(**D**) and CA 125 (**E**) are usually associated with ovarian carcinoma.