HEPATIC DISORDERS

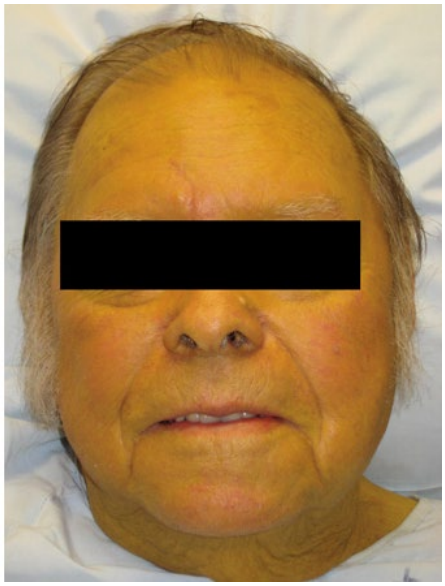
PATHOPHYSIOLOGY:

- ACUTE HEPATITIS:
  - Caused by an infectious, toxic or metabolic injury to hepatocytes
    - Initial injury leads to cellular death and potential scarring
  - In chronic disease, liver parenchyma is replaced by fibrous tissue, which separates the functioning hepatocytes into isolated nodules
- Disruption can become severe and lead to central characteristics:
  - At cellular level→loss of metabolic and synthetic function
  - Gross level→progressive development of portal hypertension and portal-systemic shunting
- SYNTHETIC DYSFUNCTION:
  - Production of coagulation and anticoagulation factors
    - Clotting→ factors II, Vii, Ix and X
    - Protein C and S
  - Inadequate function leads to coagulopathy observed in cirrhosis and liver failure
- ASCITES:
  - Due to portal hypertension, hypoalbuminaemia and poor renal management of sodium and water
  - Excess fluid in peritoneum can cause respiratory compromise
  - Can cause SBP
    - Normal flora translocate across the bowel wall into peritoneum
    - Facilitated by bowel wall oedema and poor production of immunologic proteins by the diseased liver
- PORTAL HYPERTENSION:
  - Due to increased resistance through liver and thus increased hydrostatic pressure in portal vein and feeder vessels
  - Eventually leads to oesophageal and gastric varices and portal-systemic shunting
    - Catastrophic GI bleeding can result
  - Also contributes to hepatic encephalopathy due to hepatocytes deprivation of substrates of ammonia metabolism
- ENCEPHALOPATHY:
  - Poorly understood
  - ??AMMONIA as culprit, but not properly understood
  - Large protein loads (including GI bleeding) can worsen encephalopathy
  - In fulminant hepatic failure, cerebral oedema and increased ICP can develop with loss of autoregulation
- JAUNDICE:
  - Can be present in acute, chronic and fulminant liver disease
  - Due to elevated levels of BILIRUBIN leading to deposition in skin, sclerae and mucous membranes
  - Increased bilirubin due to:

- PREHEPATIC CAUSES e.g. haemolysis
- INTRAHEPATIC:
    - Inadequate cellular processing
- POST-HEPATIC:
    - Decreased excretion
        - Choledocholithiasis
        - Pancreatic tumour

CLINICAL FEATURES:

- At presentation, multiple chief complaints should raise prospect of liver disease:
    - Jaundice
    - N + V
    - RUQ pain
    - Pruritus
    - Inappropriate bleeding/bruising
    - Altered mental status
- PHYSICAL EXAMINATION:
    - Hepatomegaly
    - Jaundice
    - Extremity muscle wasting
    - Dupuytren contracture
    - Palmar erythema
    - Cutaneous spider nevi
    - Distended abdomen with fluid wave
    - Caput medusae
    - Asterixis



ACUTE HEPATITIS – VIRAL:

- HAV, HBV and HCV are most prevalent forms of viral hepatitis

- HAV:
    - Faecal oral transmission
    - Incubation 15-50 days
    - No chronic component
    - Death from hepatic failure is rare
- HBV:
    - Transmitted sexually, blood transfusion and by contaminated needles
    - Incubation 1-3 months
    - In those who develop chronic infection will remain infectious indefinitely
    - Chronic disease in only 6-10% cases
- HCV:
    - Transmission primarily via exposure to contaminanted blood or blood products
    - Most often asymptomatic at presentation
    - >75% progress to chronic disease
    - Progression to liver failure depends on cofactors (alcohol and HIV)
- HDV:
    - Uncommon
    - Seen in those with pre-existing HBV
    - Can result in a rapidly progressive or fulminant form of liver disease with high mortality rates

ACUTE HEPATITIS – TOXIC:

- A toxic insult to the liver can cause acute hepatitis and/or fulminant liver failure
- MOST COMMON IS PARACETAMOL OVERDOSE
    - 40% of liver failure attributed
    - One third toxicology related deaths
    - Likelihood depends on time from ingestion to presentation
- ALCOHOLIC LIVER DISEASE → wide spectrum
    - 35% mortality rate over 5 years
    - If acute alcoholic hepatitis develops and drinking continues, mortality much higher
- AMANITA PHALLOIDES → mushroom poisoning

Table 83-2 Common Herbal Remedies Known to Cause Hepatic Toxicity

Common Name	Botanical Name	Potential Toxic Constituents	Recommended Use
Skullcap	*Scutellaria lateriflora*	Crystalline glycoside	Tension, epilepsy, hysteria
Chaparral	*Larrea tridentata*	Nordihydroguaiaretic acid	Anti-aging, skin disorders, arthritis
Germander	*Teucrium chamaedrys*	Furano neoclerodane flavonoids	Obesity, antipyretic, asthma, diuretic
Mistletoe	*Viscum album*	Flavonoids, acetylcholine	Infertility, hypertension, asthma, epilepsy
Valerian	*Valeriana officinalis*	Alkaloids	Tension, headache, intestinal cramps
Comfrey	*Symphytum officinale*	Pyrrolizidine-type alkaloids	Gastric and duodenal ulcers
Senna	*Cassia angustifolia*	Sennosides	Constipation
Coltsfoot	*Tussilago farfara*	Pyrrolizidine-type alkaloids	Colds, flu, asthma, abortifacient
Green tea extract	*Camellia sinensis*	Unclear	Weight loss, anti-aging, anti-inflammatory
Black cohosh	*Cimicifuga racemosa*	Quinolizidine-type alkaloid	Menopause

Table 83-3 Hepatotoxic Medications, Listed by Type of Hepatic Injury

Acute Injury	Acute Injury	Chronic Injury	Chronic Injury
Hepatocellular	Amoxicillin/clavulanate	Steatohepatitis	Autoimmune hepatitis
Acarbose	Anabolic steroids	Amiodarone	Nitrofurantoin
Acetaminophen	Azathioprine	Ethanol	Minocycline
Allopurinol	Chlorpromazine	Tamoxifen	Statins
Aspirin	Clopidogrel	Valproic acid	Chronic hepatitis
Bupropion	Cytarabine	Microvesicular steatosis	Diclofenac
Bromfenac	Erythromycins	Ethanol	Methyldopa
Diclofenac	Estrogens	Methotrexate	Minocycline
Ethanol	Ethanol	Nucleoside analog reverse transcriptase inhibitors	Nitrofurantoin
Fluoxetine	Irbesartan		Trazodone
Halothane	Phenothiazines	Tetracycline	Neoplasm
Isoniazid	Sulindac	Valproic acid	Anabolic steroids
Ketoconazole	Terbinafine	Granulomatous hepatitis	Oral contraceptives
Lisinopril	Tricyclics	Allopurinol	Vinyl chloride
Losartan	Mixed	Carbamazepine	Ischemic necrosis
Methyldopa	Amitriptyline	Diltiazem	Ergot
Nefazodone	Azathioprine	Hydralazine	
Nevirapine	Captopril	Penicillamine	
Paroxetine	Carbamazepine	Phenytoin	
Phenytoin	Clindamycin	Procainamide	
Pyrazinamide	Cyproheptadine	Quinidine	
Rifampin	Enalapril	Rosiglitazone	
Risperidone	Flutamide	Sulfonamides	
Ritonavir	Ibuprofen	Sinusoidal obstruction syndrome	
Sertraline	Nitrofurantoin	Busulfan	
Statins	Phenobarbital	Cyclophosphamide	
Tetracycline	Phenothiazines	Imuran	
Trazodone	Phenytoin	Fibrosis	
Thiazolidinediones	Sulfonamides	Ethanol	
Trovafloxacin	Trazodone	Methotrexate	
Valproate	Verapamil	Methyldopa	
Cholestasis		Peliosis hepatis	
Angiotensin-converting enzyme inhibitors		Anabolic steroids	
		Vinyl chloride	

CHRONIC HEPATITIS AND CIRRHOSIS:

- Chronic hepatitis manifests as cirrhosis and resultant complications
- HBV, HCV both progress to chronic liver disease
- Cirrhosis can present as abdo pain, ascites or SBP
- Large volume ascites can displace the diaphragm up and producte sympathetic pleural effusion
- SBP can be subtle but has high mortality rates:
    - First episode→ survival at one month 68%, 6 months 30%
    - Roughly 30% of ascitic patients will develop SBP in a given year
    - Subtle, hence low threshold for paracentesis
        - GI bleeding puts patient at higher risk for SBP
- HEPATORENAL SYNDROME:
    - Development of ARF in a patient with histologically normal kidneys in the presence of pre-existing chronic or acute hepatic failure
    - Cause is unknown
- HEPATIC ENCEPHALOPATHY:
    - DIAGNOSIS OF EXCLUSION
        - CONSIDER THE FOLLOWING:
            - Hypoglycaemia (common in liver disease)
            - ICH (coagulopathy common)
            - Wernicke-Korsakoff
            - Hyponatraemia
            - Decreased hepatic clearance of sedative agents
            - Sepsis
    - Suggests that liver is no longer able to metabolise the usual supply of nitrogenous wast or that the supply of such waste has increased
    - Common after TIPS
    - Adding or removing antibiotics can also precipitate encephalopathy by changing the intestinal flora
    - Changes in personality, worsening dementia, decreased LOC, declining neuromuscular function

Table 83-4 Stages of Clinical Hepatic Encephalopathy

Stage	Features
I	General apathy
II	Lethargy, drowsiness, variable orientation, asterixis
III	Stupor with hyperreflexia, extensor plantar reflexes
IV	Coma

- LIVER FAILURE:

- Final common pathway
- Very poor prognosis

LABORATORY EVALUATION:

- FOUR CATEGORIES:
  - MARKERS OF ACUTE INJURY
  - MEASURES OF SYNTHETIC FUNCTION
  - INDICATORS OF CATABOLIC ACTIVITY
  - DIAGNOSTIC TESTS FOR SPECIFIC ENTITIES
- BILIRUBIN:
  - A metabolite of haem proteins
    - An increased total and indirect bilirubin signifies either an overwhelming supply (haemolysis) or an injury to the hepatocytes themselves that damages their capacity to conjugate a normal supply of bilirubin
  - Direct and total bilirubin are increased when there is some obsturciton preventing the secretion of conjugated bilirubin by normally functioning hepatocytes
- TRANSAMINASES:
  - Hepatocyte injury or necrosis releases these into the circulation
  - ALT is more specific for hepatocyte injury as AST is present also in heart, smooth muscle, kidney and brain
- ALP:
  - Associatd with biliary obstruction and cholestastis especially when elevated >4 times normal
- GGT produced by alcohol consumption and in conjunction with drugs that activate hepatic microsomal enzyme activity
- AMMONIA:
  - Elevated in liver disease but do not reliably correlate with acute worsening of hepatic function but rather demonstrate a general decline
- PROTHROMBIN TIME:
  - CAN BE ELEVATED WITH NORMAL LIVER FUNCTION:
    - Fat malabsorption syndromes
- ALBUMIN:
  - Reflects liver's synthetic function
  - Three week half life, therefore less useful in acute assessment of liver function
- ASCITIC FLUID:
  - Test for:
    - Cell count
    - Glucose
    - Protein
    - Culture

TREATMENT:

- With the exception of paracetamol poisoning, treatment for acute hepatitis is SUPPORTIVE
    - Pay attention to:
        - Hyponatraemia
        - Withdrawal states
        - Alcoholic ketoacidosis
        - Hypoglycaemia
- In management of chronic hepatitis means taking care of its many sequelae:
    - Ascites
    - Encephalopathy
    - Coagulopathy
    - Variceal bleeding
- Mild-moderate ascites:
    - Salt-restriction
    - Diuretics → creating negative sodium balance
        - Spironolactone, amiloride
        - Frusemide can be problematic can lead to overdiuresis
- Large volume:
    - Paracentesis with albumin cover
- SBP:
    - Most common life threatening complication of ascites
    - Classically present with fever and diffuse abdominal pain
    - Diagnosed by ascitic fluid with PMN >250 or WCC >1000 or bacteria on gram stain
    - Treat with cefotaxime, timentin, tazocin or ceftriaxone
- Hepatic encephalopathy:
    - LACTULOSE is the mainstay of treatment
    - Given PO or PR
    - It is converted to lactic acid in the colon and the acidified environment traps ammonia and thus aids its excretion
- Coagulopathy:
    - Needs to be treated if the patient has uncontrolled bleeding or is scheduled to undergo a procedure with potential bleeding complications
        - Vitamin K, FFP and platelets as appropriate
- Liver failure in the ED:

Table 83-6 Fulminant Liver Failure

Presentation	Causes/Associations	Complications
Acute hepatocellular necrosis with rapid development of encephalopathy and liver failure developing in <8 wk	Hepatitis B, C, D	Encephalopathy
	Hepatitis A (rare)	Hypoglycemia
	Hepatotoxins	Hyponatremia
	Acetaminophen	Hypokalemia
	Isoniazid	GI hemorrhage
	Halothane	Renal failure
	Valproic acid	Cerebral edema
	Mushrooms	Sepsis
	Carbon tetrachloride	Spontaneous bacterial peritonitis

- Care of respiratory failure common → compromised due to pleural effusions/ascites → intubation may be needed
- Blood pressure → LOW due to malnutrition, vomiting, bleeding, third spacing → treat with judicious fluids
- Encephalopathy
- Identification of cerebral oedema or ICH
  - Mannitol as temporising measure for raised ICP
  - Haematoma evacuation