HEPATOLOGY

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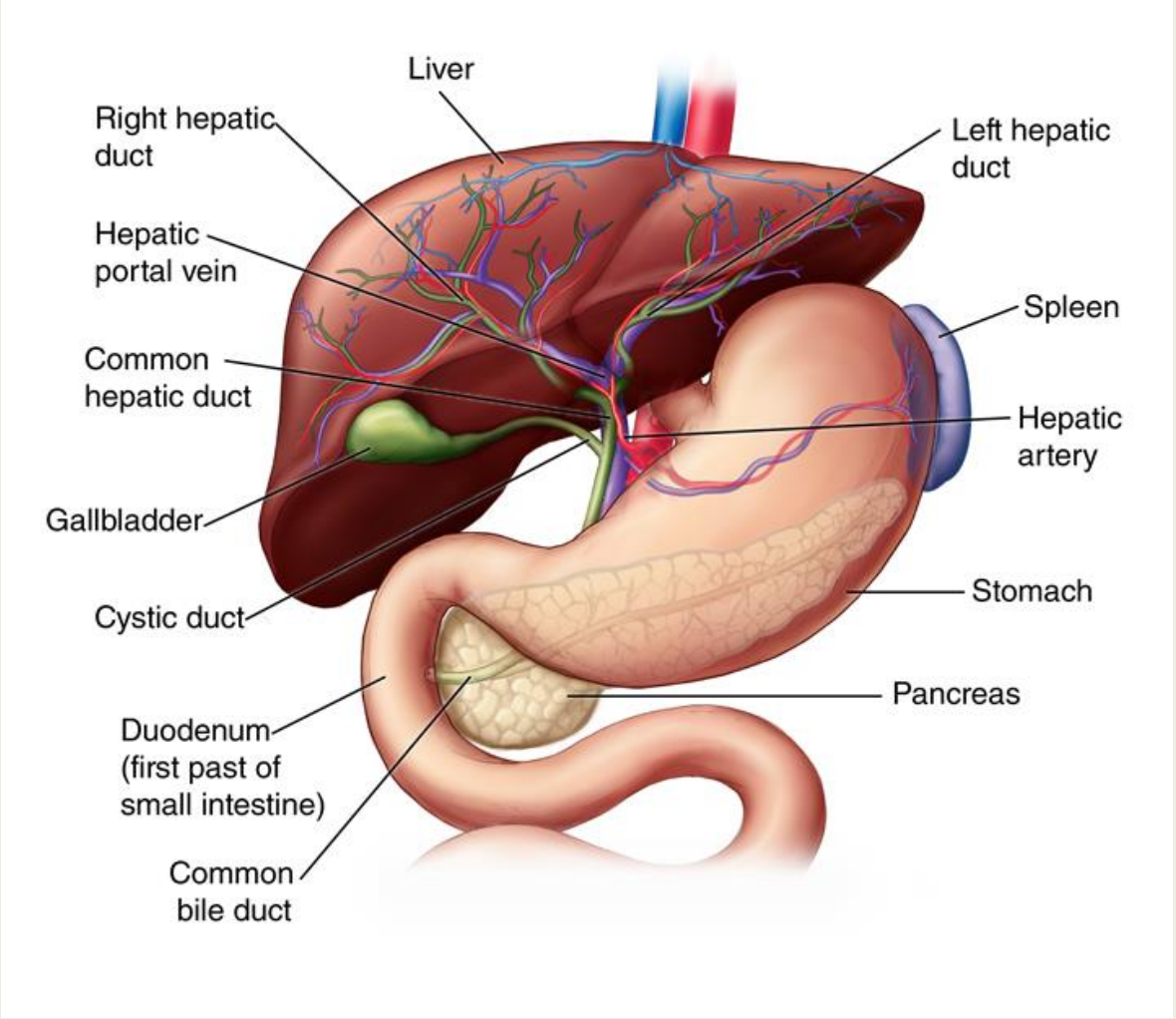
Content to Cover

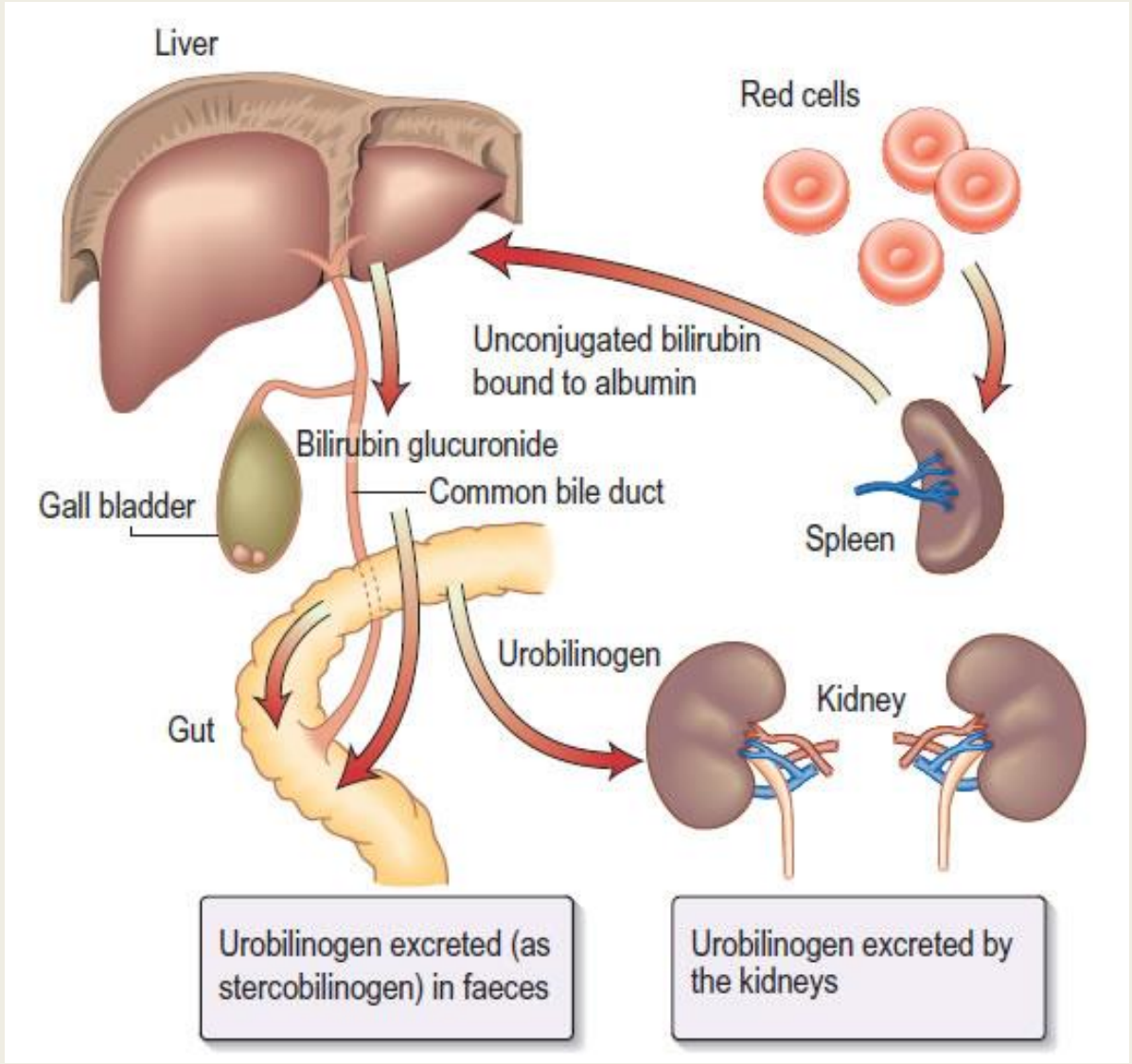
- Jaundice
- Hepatitis
- Hepatic Failure
- Chronic Liver Disease – Alcoholic & Non-Alcoholic Liver Disease, Cirrhosis, HCC
- Complications – Ascites, Portal HTN, SBP, Encephalopathy
- Pancreatic Disease
- PSC, PBC + Cholangiocarcinoma

Basic Hepatic Anatomy



JAUNDICE

- Yellowing of the skin, sclera, mucous membranes due to raised serum bilirubin (>19umol/l)
- May not be clinically apparent until levels >51umol/l
- Pre-Hepatic, Hepatic, Post-Hepatic



PRE-HEPATIC JAUNDICE

- Excessive haemolysis exhausts liver's capacity to conjugate extra load so bilirubin builds up in the ECF → jaundice
- Causes → Haemolytic Anaemias (Homozygous SCD, Thalassaemia Major, Hereditary Spherocytosis, G6PD Deficiency), Drugs (Methyldopa, Sulfasalazine), Malaria
- Px = Jaundice, Anaemia sx, abdominal mass (splenomegaly), FHx, recent travel, autoimmune disease
- Ix = FBC, Blood film, LFTs (normal), Bilirubin (normal/raised)
- Mx = Depends on underlying cause

HEPATIC JAUNDICE

- Hepatic Unconjugated Hyperbilirubinaemia = Failure of **transport** of unconjugated bilirubin into hepatocyte, Failure of **enzyme activity** (Gilbert's Syndrome, Crigler-Najjar)
- Hepatic Conjugated Hyperbilirubinaemia = Infection, Drugs/Alcohol
- Mixed conjugated + unconjugated
- Causes → Viral Infection (Hepatitis, EBV, HIV), Alcohol, Fatty liver disease, Autoimmune, Malignancy, Drugs (Paracetamol overdose, RIPE)
- Px = Jaundice, pruitus, abdominal pain, malaise, alcohol abuse, Hepatomegaly, signs of CLD O/E, RFx for hepatitis (recent travel, sexual history, IVDU)
- Ix = LFTs (raised ALT/AST), Bilirubin (Raised)
- Mx = Depends on underlying cause

POST-HEPATIC JAUNDICE

- Obstruction to the flow of bile
- Causes = Gallstones, surgical strictures, malignancy (pancreatic, cholangiocarcinoma), pancreatitis, PSC, PBC, parasitic infection
- Px = Jaundice, pruitus, **pale stools, dark urine**, Hepatomegaly
- Ix = LFTs (moderately raised ALT/AST, **raised ALP**), Bilirubin (raised)

Test	Pre-hepatic	Hepato-cellular	Obstructive
Total Bilirubin	↑	↑	↑
Conjugated to Total Bilirubin ratio	<20%	20-40%	>50%
Urine bilirubin (Only conjugated is filtrated)	Absent	Present	Increased
Urine urobilinogen	Increased	Present	Absent
Stool	Polycholic	Polycholic	Pale/acholic

JAUNDICE SUMMARY

- Work through each category and ask the relevant questions
- Jaundice duration, previous episodes
- Additional sx → Pruitus, anaemia sx, urine/stool colour, B-symptoms, Social History (Alcohol, Travel), PMH
- Ix → Bloods (FBC, LFTs, Clotting screen, amylase, hepatitis screen), Imaging (Abdo US/CT, ERCP/MRCP), Liver Biopsy
- If obstructive picture → refer to upper GI surgeons
- If non-obstructive picture → screen for other causes (hepatitis, autoimmune)

HEPATITIS

- ACUTE → x2 raised ALT/AST, often asx, jaundice, GI sx, RUQ pain, Hepatomegaly, fatigue, jaundice, sx of underlying disease
- CHRONIC → sustained infection for >6 months (CLD, Cirrhosis, HCC)
- Infection
- Autoimmune
- Metabolic (NASH)
- Drugs (Paracetamol, TB Drugs)
- Alcohol
- Malignancy
- Genetics (Wilson's, Haemochromatosis, Alpha-1 Antitrypsin deficiency)

HEPATITIS A

- ssRNA picornavirus
- Benign, self-limiting – No CLD
- Faeco-oral transmission, 2-6 weeks incubation period
- RFx: Living in endemic area, contact with affected individual
- Px: Flu-like prodrome, RUQ pain, tender hepatomegaly, jaundice, cholestatic picture (check Nice CKS for more detail)
- Ix: **PCR (Hep A RNA)**, HAV-IgM + IgG, LFTs, Bilirubin, PT (prolonged), FBC, U+E, CRP
- Mx: **Vaccination** for high risks individuals, **Supportive** (analgesia, rest, hydration), **Lifestyle** advice (good hygiene/avoid tap water or street food/safe sex)
- Notify Acute infections to Health Protection Unit

HEPATITIS A

- HAV-IgM detectable >5 days post-onset and remains positive for **up to 6 months**
- HAV-IgG detectable 5-10 days post-onset and **persists**
- Positive IgM + Positive IgG → Acute Infection
- Negative IgM + Positive IgG → Past Infection/Immunity from vaccination
- Moderately raised IgM + Significantly raised IgG → Recent Infection
- Positive IgM + Negative IgG → False positive

HEPATITIS B

- Ds-DNA hepadnavirus
- Transmission via **blood/body fluids**, 1-5 months incubation period
- ACUTE: Self-limiting transient infection; prodromal fever, rash, arthralgia → jaundice, Bsx, RUQ pain

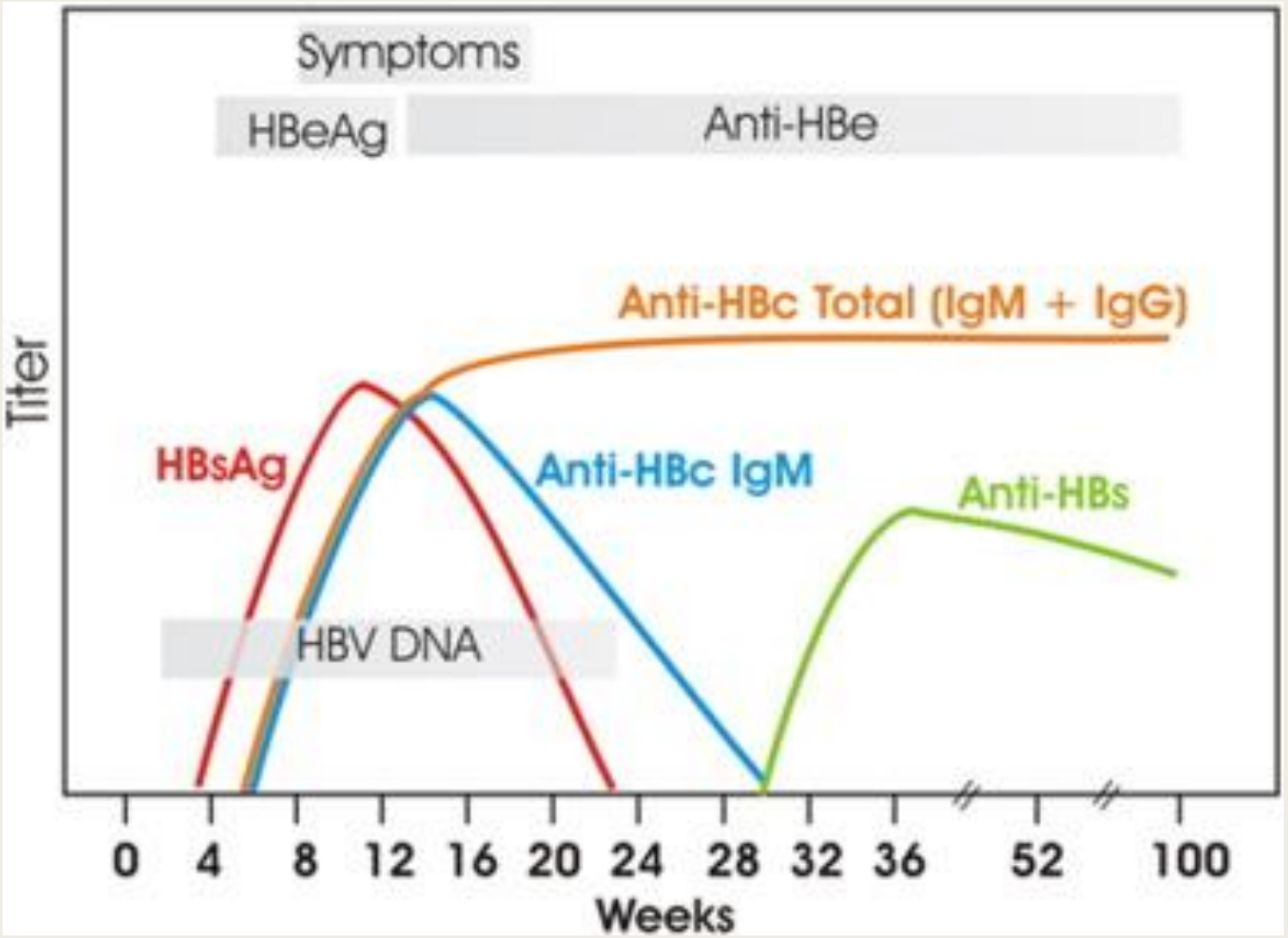
  → Extra-hepatic sx = Glomerulonephritis, Vasculitis, Polyarteritis Nodosa
- CHRONIC: persistence of HepBsAg for >6 months; no physical sx, may show signs of CLD
- Ix = FBC, U+E, LFTs, Bilirubin, PT, **Hep B serology**
- Mx = Hep B Vaccination, Pegylated Interferon Alpha, Antiretrovirals (Tenofovir, Entecavir), IM Hep B Immunoglobulins (<48hrs) if no immunity + potential contact

Interpreting Hepatitis B Serology

- HepBsAg = Active acute OR chronic infection
- HepBeAg = High Infectivity
- Anti-HepBs = Recovery/**Immunity** from Hep B, appears late (positive in vaccinated/previously infected individuals)
- Anti-HepBc (first antibody to appear)
    - → IgG = Previous/current infection (persists in circulation)
    - → IgM = Recent (<6m) infection – only seen in acute infection
- Anti-HepBe = Clearance of Hep BeAg (low infectivity)

HBsAg **anti-HBc** **anti-HBs**	negative negative negative	Susceptible
HBsAg **anti-HBc** **anti-HBs**	negative positive positive	Immune due to natural infection
HBsAg **anti-HBc** **anti-HBs**	negative negative positive	Immune due to hepatitis B vaccination
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive positive negative	Acutely infected
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive negative negative	Chronically infected
HBsAg **anti-HBc** **anti-HBs**	negative positive negative	Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. “Low level” chronic infection 4. Resolving acute infection

https://www.cdc.gov/hepatitis/hbv/pdfs/serologicchartv8.pdf


Symptoms
HBeAg
Anti-HBe
Anti-HBc Total (IgM + IgG)
Titer
HBsAg
Anti-HBc IgM
Anti-HBs
HBV DNA
0
4
8
12
16
20
24
28
32
36
52
100
Weeks

HEPATITIS D

- ssRNA, requires activation by HBV
- Transmission, Incubation, RFx and Px same as HBV
- Co-infection → HBV + HDV occur simultaneously
- Super-infection → HDV occurs in an already infected HBV individual
- Ix = Liver Profile, Hep D RNA PCR +/- Hep B serology
- Mx = Hep B Vaccine, Interferon

HEPATITIS C

- RNA Flavavirus
- Transmission via **blood products**, 6-9 weeks incubation period
- RFx: Sharing needles, blood transfusions, tattoos/body piercings, household contacts, perinatal transmission, sexual transmission
- Px: Mainly asx, may have flu-like sx
- Ix: Liver Profile, HCV Antibody Test, HCV RNA PCR
- Mx: Antivirals (Pegylated IF-alpha + Oral Ribavirin), Lifestyle Advice (good hygiene, avoid sharing needles, safe sex)

HEPATITIS E

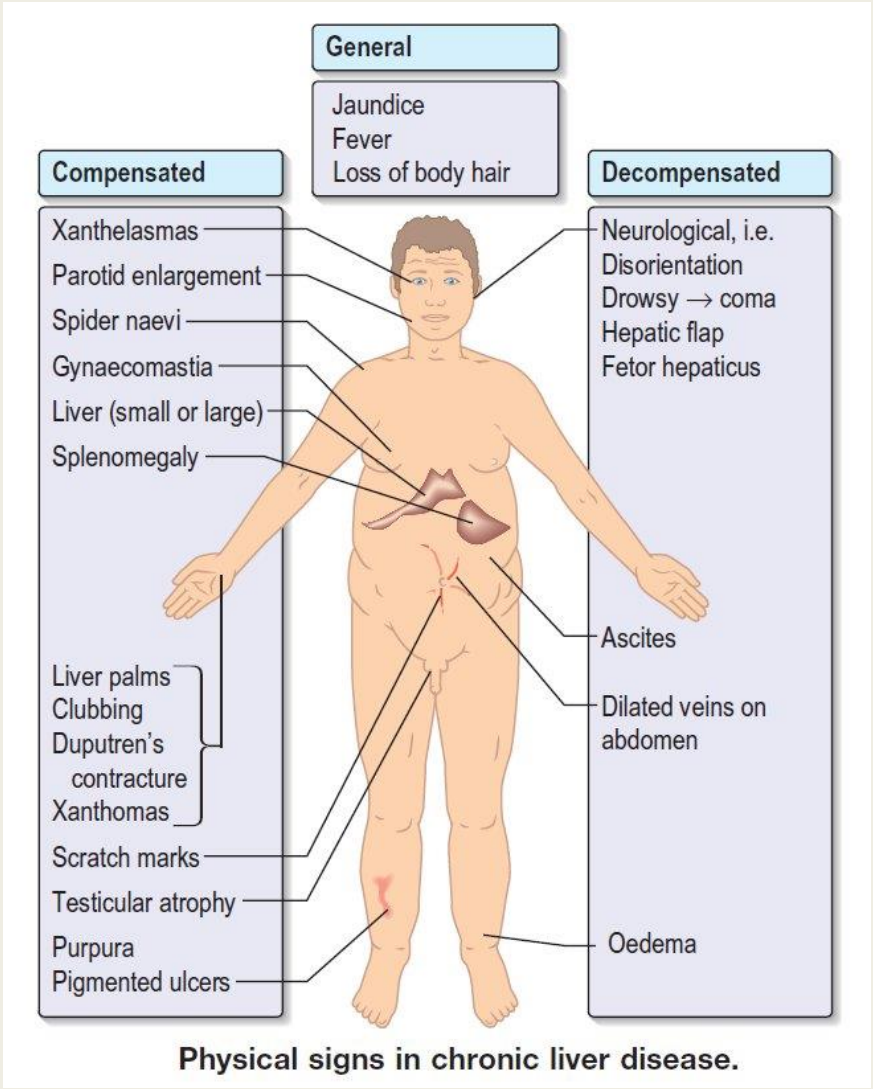
- ssRNA Hepevirus
- Faeco-oral transmission, 3-8 weeks incubation period - No CLD
- RFx: Shellfish and pork
- Px: Same as HAV; flu like prodrome, followed by RUQ pain and systemic sx
- Ix: Liver Profile, HEV Antibody Test +/- HAV-IgG/IgM
- Mx: Vaccine currently under development

AUTOIMMUNE HEPATITIS

- Defective suppressor T-cells with autoantibodies directed against hepatocyte surface antigens.
- Px = Usually young females, sx of CLD, acute hepatitis, amenorrhoea
- Type I → ANA/Anti-SMA
- Type II → Anti-liver/kidney microsomal 1 Ab (only affects children)
- Type III → Soluble liver/kidney Ag (affects middle aged)
- Ix = FBC, U+E, LFTs, Bilirubin, PT, ANA/SMA/LKM1 Abs (raised IgG), Liver Biopsy, Hepatitis Serology
- Mx = Steroids, Immunosuppressants, Liver Transplant

CHRONIC LIVER DISEASE

- Progressive destruction of the liver for >6 months → fibrosis, cirrhosis, and reduced liver function
- Includes chronic hepatitis, cirrhosis and HCC
- <u>Causes:</u> Infection, Drugs (Amiodarone, Methotrexate, Nitrofurantoin), Chronic Alcohol Abuse, NASH/NAFLD, Haemochromatosis, Wilson's, CF, A1AT deficiency, Autoimmune (PBC, PSC, Autoimmune Hepatitis)
- <u>Px:</u> Jaundice, Fever, Bsx, RUQ pain
- Compensated → Liver can still function, no complications
- Decompensation → Liver function impaired → Complications (ascites, variceal haemorrhage, encephalopathy, peripheral oedema)



Physical signs in chronic liver disease.

CIRRHOSIS

- Necrosis of liver cells → fibrosis + nodule formation → liver cell impairment + gross distortion of structure → portal hypertension
- Causes same as CLD but mainly **Hep B + C, Alcohol, NAFLD**
- Px same as in CLD, depends on cause
- Ix: FBC, U+E, LFTs, Bilirubin, **PT, Albumin**, Hepatitis Serology, AFP, US Abdomen, CT Abdomen, Ascitic Tap (MC+S)
- **Transient Elastography:** Assess degress of fibrosis/stiffness (HCV, alcohol abuse, dx with alcohol related liver disease)
- Monitoring: OGD to check for varices on dx, Liver US every 6 months
- Mx = Correcting underlying cause/complications, Lifestyle advice (limit alcohol intake, diet, avoid hepatotoxic drugs, fluid restriction), Symptomatic treatment, Liver Transplant

ALCOHOLIC LIVER DISEASE

1) Alcoholic Fatty Liver Disease - Triglycerides accumulate in liver tissue (steatosis) due to increased fat input and reduced fat export

→ Px = Fatigue, malaise, abdominal pain, anorexia, N+V

→ Ix = LFTs, **GGT**, Bilirubin, Albumin (low), PT, Liver US/CT

→ Mx = Alcohol abstinence, weight loss, Hep A+B vaccinations, high protein diet

2) Alcoholic Hepatitis – Combined liver steatosis, **inflammation** and focal regions of **necrosis**

→ Px = Rapid onset jaundice, RUQ pain, Bsx, signs of CLD

→ Ix = LFTs (**2-3x AST>ALT**), GGT, Bilirubin, PT, Albumin, Clotting, Liver US/Biopsy

→ Mx = Same as 1), refer for further tests (elastography/AFP/ELF blood test), Glucocorticoids

3) Alcoholic Cirrhosis – Destruction of liver structure + fibrosis from alcohol abuse

→ Px = may be asx, sx of CLD, complication of cirrhosis

→ Ix = Same as above

→ Mx – Same as above, consider Liver Transplant

NON-ALCOHOLIC LIVER DISEASE

1) Non-Alcoholic Fatty Liver Disease (NAFLD) – Steatosis in the absence of excessive alcohol consumption (<2.5U/day for women, <3.75U/day for men)
2) Non-Alcoholic Steato-Hepatitis (NASH) – Fat + inflammation + hepatocellular injury

- **Most common cause** of liver disease
- RFx = Obesity, T2DM, Hyperlipidaemia, Jejunoileal bypass, sudden weight loss/starvation
- Px = Usually asx (detected incidentally), Hepatomegaly
- Ix = Liver Profile (LFTs: **ALT>AST**), US Abdomen (Raised echogenicity; consistent with fatty liver changes), Assess for fibrosis (ELF, NAFLD fibrosis score, FIB4), assess CVD risk
- Mx = Lifestyle (Diet, Exercise, limit Alcohol), manage co-morbitidies

HEPATIC FAILURE

- ACUTE = Rapid onset of hepatocellular dysfunction → systemic complications, occurring in individuals with no evidence of prior liver disease
- FULMINANT = Development of severe liver injury + **encephalopathy**
- Causes = Infection, Drugs, Alcohol, Wilson's, Haemochromatosis, A1AT deficiency
- Px = Jaundice, RUQ pain, N+V, Bsx, Hepatomegaly, coagulopathy, cerebral oedema, hypoglycaemia, severe bacterial + fungal infections, renal failure
- Ix = FBC, U+E, LFTs, Bilirubin, Clotting/PT, Albumin, Glucose, Paracetamol levels, Hepatitis Serology, Ferritin, A1At, AutoAbs, Blood/Urine cultures, CXR, Abdo US, Doppler flow studies of portal vein

HEPATIC ENCEPHALOPATHY

- Decline in cerebral function as a result of severe liver disease → build up of ammonia/toxins in the circulation which can cross the BBB
- Px = Confusion/altered GCS, Asterix/liver flap, constructional apraxia
- Grade I → Irritability
- Grade II → Confusion, Inappropriate behaviour
- Grade III → Incoherent, Restless
- Grade IV → Coma
- Precipitating Factors = Infection, GI Bleed, post-TIPSS, Constipation, Drugs (sedatives, diuretics), Hypokalaemia, Renal failure

HEPATIC FAILURE - Management

- ICU → Head elevation (reduce cerebral oedema), A-E assessment, Supportive Mx (Fluids, Analgesia, Oxygen)
- Coagulopathy → only correct if significant bleeding
- Infection → Treat as it comes
- Renal Replacement Therapy
- Treat any metabolic disturbance (consider Hartmann's)
- Encephalopathy → Lactulose + Rifaximin (secondary prophylaxis), Liver transplant assessment, Neuro status monitoring, Monitor bloods (glucose + electrolytes)

COMPLICATIONS OF LIVER DISEASE

- Portal Hypertension → Obstruction of inflow of portal blood to the liver causing diversion of blood into portosystemic collaterals → Varices/GI Bleeds
- Ascites → Peripheral arterial vasodilation in cirrhosis causes activation of RAAS allowing salt/water retention + hypoalbuminaemia
- SBP → Seen in cirrhosis, usually caused by E. coli; ascites, abdominal pain, fever

  → Paracentesis

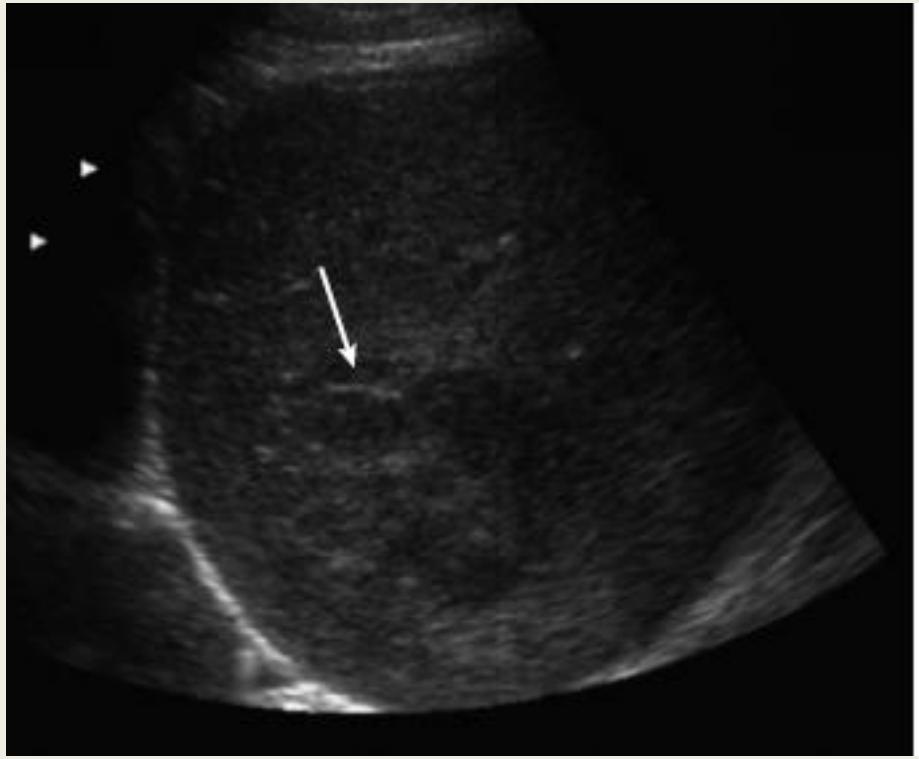
  → Mx = IV Cefotaxime

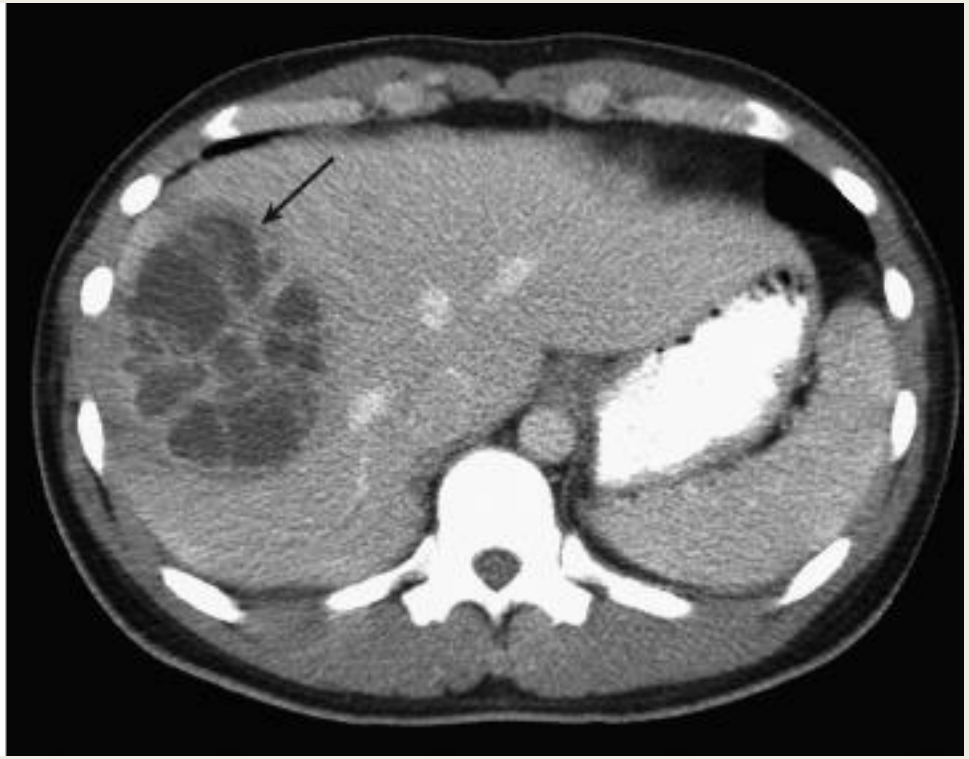
- *'Offer prophylactic oral ciprofloxacin or norfloxacin for people with cirrhosis and ascites with an ascitic protein of 15 g/litre or less until the ascites has resolved'* (NICE)

HEPATIC ABSCESS

- Pus-filled mass in the liver resulting from liver damage, biliary sepsis or intra-abdominal infection spreading to liver via portal circulation
- Causes = E coli, Staph aureus
- Px = Fever, RUQ pain, jaundice
- Imaging (US) = Fluid-filled cavity, hyper-echoic walls in chronic abscesses
- Mx = Drainage, Antibiotics (Amoxicillin + Ciprofloxacin + Metronidazole) – usually required long-term

HEPATIC ABSCESS





HEPATOCELLULAR CARCINOMA (HCC)

- Malignant tumour of the hepatocytes
- RFx = Chronic Hep B, cirrhosis, chronic alcohol abuse, diabetes, obesity, FHx
- Px = Bsx, RUQ pain, abdominal distension/early satiety, weight loss/cachexia, decompensation
- O/E = Hepatomegaly, Jaundice, sx of CLD
- Ix = Baseline bloods + AFP, Abdo CT/MRI, Biopsy
- Staging by Liver MRI + CT-TAP
- Examine testes
- Mx = Surgical resection of tumour, if small primary disease consider whole liver resection + transplant, ablation, chemo/radiotherapy, embolization

ACUTE PANCREATITIS

- Autodigestion of pancreatic tissue by its enzymes → necrosis
- RFx (GET SMASHED) = Gallstones, Alcohol, Trauma, Steroids, Mumps/EBV, Autoimmune, Scorpion Venom, Hyperlipidaemia/Hypothermia/Hypercalcaemia, ERCP, Drugs (Thiazides, Azathioprine, Tetracyclines, Mesalazine, Oestrogen, Valproic Acid, Gliptins)
- Px = Sudden onset epigastric pain +/- radiation to back, relief on foetal position, N+V, low-grade fever, anorexia
- O/E = Abdominal tenderness, distension, Cullen's Sign + Grey Turner's sign, Tachycardia + Hypotension (shock)
- Complications = Hyperglycaemia, Hypocalcaemia, Hypoalbuminaemia, Pancreatic necrosis, pseudocyst, pancreatic abscess, fistulae, portal HTN, AKI, Sepsis, ARDS, DIC

ACUTE PANCREATITIS – Glasgow Scoring System

Glasgow Imrie Criteria for Acute Pancreatitis	
3 or more of the below in first 48hrs indicates a severe attack	
PaO2	<8KPa
Age	>55 years
Neutrophils	>15x10^9/L
Calcium	<2mmol/L
Renal Function	Urea >16mmol/L
Enzymes	LDH >600iU/L / AST >2000iU/L
Albumin	<32g/L
Sugar	Glucose >10mmol/L

Score of 3 or more → refer to ITU

ACUTE PANCREATITIS

- Ix = FBC, U+E, LFTs, Amylase (x3 ULN)/Lipase (more sensitive + specific), CRP, Glucose, Calcium, ABG, Urine Dip, ECG, CXR, CT Abdomen
- Mx = A-E, Fluid resuscitation, monitor urine output (aim >30ml/hr), keep NBM if severe vomiting, Analgesia, Anti-emetic, correct electrolyte imbalance
- If proven gallstones → ERCP
- Infected necrosis → Endoscopic drainage/aspiration/necrosectomy

CHRONIC PANCREATITIS

- Chronic, irreversible inflammation/fibrosis of the pancreas → progressive endocrine and exocrine dysfunction
- Recurrent episodes of acute pancreatitis → fibrosis, dilation + calcification of pancreatic duct/branches
- RFx = Alcohol, Idiopathic, Smoking, Autoimmune (Sjogren's, IBD, PBC), Genetics, Drugs, Obstruction (gallstones/strictures)
- Px = Chronic deep/dull epigastric pain; post-prandial, steatorrhoea (bloating, cramps, wind), N+V, jaundice, weight loss, DM/IGT sx (late sign)
- Ix = Bloods (same as in acute), CT Abdomen (more sensitive in showing calcification), **faecal elastase**, secretin stimulation test (once Ix suggestive of dx)
- Mx = Lifestyle (reduce alcohol intake, low fat diet), Analgesia (coeliac axis block/splanchnicectomy if uncontrolled), Pancreatic enzyme replacement
- Monitoring → HbA1c, exocrine function/malnutrition, pancreatic cancer

PANCREATIC CANCER

- >80% ductal adenocarcinomas affecting head of pancreas
- RFx = Age, Smoking, Diabetes, Chronic pancreatitis, Lynch Syndrome, MEN Syndrome, BRCA-2 gene
- Px = Painless jaundice, palpable gallbladder, weight loss, epigastric pain, back pain, steatorrhoea (loss of exocrine function), DM (loss of endocrine function)
- O/E = Hepatosplenomegaly, Lymphadenopathy, Ascites
- Ix = FBC, U+E, LFTs, Bilirubin + other liver tests, CA199, MRCP, High Resolution CT (staging)
- Mx = Surgical resection (Whipple's procedure), Stenting, Chemotherapy, Coeliac Plexus Block, Pancreatin enzyme replacement

PSC + PBC

Primary Sclerosing Cholangitis → Inflammation intra + extra-hepatic bile ducts eventually causing **fibrosis**

→ Px = Cholestasis (jaundice, pale stools, dark urine), RUQ pain, Fatigue

→ Associations = UC>Crohn's, HIV

→ Ix = LFTs, ERCP (multiple biliary strictures – beaded appearance), ANCA

→ Mx = Cholestyramine (pruitus), Ursodeoxycholic acid, treating complications

Primary Biliary Cirrhosis/Cholangitis → **Chronic** inflammation + progressive cholestasis of the bile ducts leading to **cirrhosis**

→ RFx = Middle aged females, Sjogren's, RA, Systemic sclerosis, Thyroid Disease

→ Px = **Pruitus**, Jaundice, Fatigue, Xanthelasma, Steatorrhea (advanced px), Asx

→ Ix = LFTs (cholestasis), **Anti-mitochrondial Abs** (AMA) M2 Subtype, Anti-smooth muscle antibodies (30%), Raised serum IgM

→ Mx = Cholestyramine, Ursodeoxycholic Acid, Liver transplant

CHOLANGIOCARCINOMA

- Malignant tumour of the bile ducts – 80% arise in the extra-hepatic biliary tree
- RFx = PSC, Typhoid, Liver flukes
- Px = Jaundice (end-stage), Bsx
- Ix = LFTs, CA199, CEA, CA125 (often elevated), CT/MRI, MRCP
- Mx = Surgical Resection

THANK YOU - Any Questions?

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