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 small intestinal bacterial overgrowth Ileal resection
 drugs:
 Biguanides (metformin) ,
 Colchicine, used for treating gout in patients where (NSAIDs) are contraindicated Investigation • the test of choice is SeHCAT nuclear medicine test using a gamma-emitting selenium molecule in selenium homocholic acid taurine or tauroselcholic acid (SeHCAT) (75Selenium HomotauroCholic Acid Test) scans are done 7 days apart to assess the retention/loss of radiolabelled75SeHCAT Retention values of less than 15% have been considered abnormal and indicative of bile acid malabsorption. retention values of 10–15% (mild bile acid malabsorption)
 retention values of 5–10% (moderate bile acid malabsorption)
 retention values of 0–5% (severe bile acid malabsorption). Management • bile acid sequestrants e.g. cholestyramine

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Primary biliary cirrhosis

Primary biliary cirrhosis - the M rule • IgM • anti-Mitochondrial antibodies, M2 subtype • Middle aged females

Aetiology • autoimmune condition.
Mechanism
• chronic inflammatory process damage to interlobular bile ducts cholestasis & cirrhosis.
Epidemiology • female: male ratio 9:1

Associations • Sjogren's syndrome (seen in up to 80% of patients) • rheumatoid arthritis • systemic sclerosis • thyroid disease Clinical features The two main conditions causing pigmentation and chronic liver disease are:

1. primary biliary cirrhosis (PBC) and
2. Haemochromatosis.

• early: may be asymptomatic (e.g. raised ALP on routine LFTs) or fatigue, pruritus classic presentation itching in a middle-aged woman • cholestatic jaundice • hyperpigmentation, especially over pressure points • xanthelasmas, xanthomata • also: clubbing, hepatosplenomegaly • Fat malabsorption leading to deficiency of the vitamins A, D, E, K (hence osteomalacia and also bruising). • Back pain

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 due to osteomalacia resulting from malabsorption or osteoporosis - hepatic osteodystrophy. • late: may progress to liver failure

Diagnosis • anti-mitochondrial antibodies (AMA) M2 subtype are present in 98% of patients and are highly specific
 (AMAs) targeted against pyruvate dehydrogenase. Pyruvate dehydrogenase (PD) is found in the mitochondria. required for the generation of acetyl-CoA from pyruvate for entry into the tricarboxylic acid (TCA) cycle. • smooth muscle antibodies in 30% of patients • raised serum IgM • Liver function tests LFT correlate poorly with histology in PBC – the disease may progress insidiously with normal or near-normal LFTs.
Complications • malabsorption: osteomalacia, coagulopathy • Osteoporosis is a common complication, possibly due to vitamin D malabsorption and/or premature ovarian failure. All patients with PBC should be screened for the condition The patient should undergo bone mineral densitometry. • sicca syndrome occurs in 70% of cases • portal hypertension: ascites, variceal haemorrhage • hepatocellular cancer (20-fold increased risk) Management • pruritus: cholestyramine • fat-soluble vitamin supplementation • ursodeoxycholic acid (UDCA) UDCA delays the need for liver transplantation improves liver biochemistry and may slow disease progression. The effectiveness of UDCA is monitored by improvements in ALP and GGT, but ALP is more widely used than GGT. • liver transplantation
 e.g. if bilirubin > 100 (PBC is a major indication)
 Liver transplantation has a good prognosis (90–95% survival) recurrence in graft can occur but is not usually a problem occur in 10% to 40% of patients
 but recurrent PBC does not affect either graft or patient survival rates. contraindication to liver transplantation: Psychological factors that may impair compliance with immunosuppression

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Primary sclerosing cholangitis (PSC)

Definition • Primary sclerosing cholangitis is a biliary disease of unknown aetiology characterised by inflammation and fibrosis of intra and extra-hepatic bile ducts Epidemiology • Sex: ♂ > ♀ (2:1) • Age: The median age at diagnosis is ~ 40.
• primarily seen in middle-aged men with inflammatory bowel disease.

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Associations • ulcerative colitis: 4% of patients with UC have PSC, 80% of patients with PSC have UC • Crohn's (much less common association than UC) • HIV If a patient with pre-existing chronic inflammatory bowel disease displays increased ALP, GGT, and conjugated bilirubin, always consider PSC

Features • asymptomatic
 50 % of patients
• cholestasis: (alkaline phosphatase greater than transaminases) jaundice and pruritus conjugated hyperbilirubinemia. • right upper quadrant pain • fatigue • intermittent diarrhoea.
Investigation • MRCP (Magnetic resonance cholangiopancreatography)
 Non-invasive , often performed initially. the initial diagnostic investigation of choice
• ERCP the standard diagnostic tool,
 More invasive but also more accurate than MRCP
 Good alternative for patients who cannot undergo MRI testing (e.g., patients with pacemaker)
 showing multiple biliary strictures giving a 'beaded' appearance • Antibodies:
 ANCA may be positive (pANCA 84%, aCL 66%, , and ANA 53%) • IgM increased (hypergammaglobulinaemia) • Liver biopsy
 there is a limited role for liver biopsy,
 may show fibrous, obliterative cholangitis often described as 'onion skin' Complications • cholangiocarcinoma (in 10%) • increased risk of colorectal cancer • PSC ↓ secretion of bile acids; steatorrhea ↓ fat-soluble vitamins Night blindness
Treatment • Liver transplant is the definitive treatment
Prognosis • The median time to liver failure around 12 years.

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Cholangiocarcinoma • The vast majority of cholangiocarcinomas (70%) are sporadic. • Risk factors:
 Primary sclerosing cholangitis (PSC) is the most common risk factor Others diabetes fatty liver disease, and inflammatory bowel disease without PSC. Alcohol Smoking Chronic hepatitis B obesity • The imaging characteristics of a cholangiocarcinoma are hypovascularity with scarring and calcification. CT contrast is delivered in early (hepatic arterial) phase and delayed (portal venous) phase.
 80% of normal liver tissue derives its blood supply from the portal vein, but tumours generally derive their blood supply from the hepatic artery and are therefore hypervascular. Cholangiocarcinomas are an exception as hypovascular lesions.
• The Bismuth-Corlette classification is as follows: Type I - below confluence of left and right hepatic ducts Type II - reaching confluence but not involving left or right hepatic ducts Type III - occluding common hepatic duct and either right (IIIa) or left (IIIb) hepatic duct

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Liver conditions

Hepatomegaly Common causes of hepatomegaly • Cirrhosis: if early disease, later liver decreases in size. Associated with a non-tender, firm liver • Malignancy: metastatic spread or primary hepatoma. Associated with a hard, irregular. liver edge • Right heart failure: firm, smooth, tender liver edge. May be pulsatile Other causes • viral hepatitis • glandular fever • malaria • abscess: pyogenic, amoebic • hydatid disease • haematological malignancies • haemochromatosis • primary biliary cirrhosis • sarcoidosis, amyloidosis

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Hepatosplenomegaly Causes of hepatosplenomegaly • chronic liver disease* with portal hypertension • infections: glandular fever, malaria, hepatitis • lymphoproliferative disorders • myeloproliferative disorders e.g. CML • amyloidosis *the latter stages of cirrhosis are associated with a small liver

Gaucher's disease is a lysosomal storage disease, due to deficiency of the lysosomal hydrolase beta-glucosidase. most commonly seen in Ashkenazi Jews. Its features include hepatosplenomegaly, haematological abnormalities and skeletal involvement.

Liver function test • Gamma-glutamyl-transferase (GGT)
 ↑↑ by drugs such as phenytoin and alcohol. Mild raises in GGT can occur with any alcohol intake, and a rise does not always indicate liver pathology. ↑↑ in fatty liver • Transaminase
 differential diagnosis for elevated serum aminotransferases: viral hepatitis,
 hepatotoxicity from drugs or toxins,
 alcoholic liver disease,
 hepatic ischemia, and
 malignant infiltration
 Only ischaemic hepatitis and paracetamol overdose tend to produce transaminase levels that are raised to very high degree (more than 100 times the upper limit of normal). hypotension (particularly in an individual who is normally hypertensive) is the usual precipitant for ischaemic hepatitis.

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 Remember that the level to which transaminases are elevated cannot be used to judge the degree of liver damage and impairment of hepatic function. Patients with a hepatocellular process generally have a disproportionate elevation in the serum aminotransferases compared with the alkaline phosphatase, while those with a cholestatic process have the opposite findings.
 AST/ALT ratio:
 fatty liver: AST/ALT usually <1 alcohol abuse: AST/ALT ratio >2:1 • Alkaline phosphatase (ALP) Causes of raised (ALP): liver: cholestasis, hepatitis, fatty liver, neoplasia In cholestasis, ALP is typically elevated to at least four times the upper limit of normal.
 Lesser degrees of elevation are nonspecific and may be seen in other liver diseases Paget's osteomalacia bone metastases hyperparathyroidism renal failure physiological:

pregnancy, growing children, healing fractures

The table below splits the causes according to the calcium level Raised ALP and raised calcium Raised ALP and low calcium • Bone metastases • Hyperparathyroidism • Osteomalacia • Renal failure

↑ALP do ultrasonography: • presence of biliary dilatation extrahepatic cholestasis (gallstones, strictures, or malignancy).
• absence of biliary dilatation intrahepatic cholestasis (drug toxicity, primary biliary cholangitis, primary sclerosing cholangitis, viral hepatitis, cholestasis of pregnancy, benign postoperative cholestasis, infiltrative diseases, and total parenteral nutrition).

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Evaluation of elevated serum alkaline phosphatase (2019 UpToDate) AMA: antimitochondrial antibodies; ERCP: endoscopic retrograde cholangiopancreatography; MRCP: magnetic resonance cholangiopancreatography; ULN: upper limit of normal.

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Liver biopsy Contraindications to percutaneous liver biopsy • deranged clotting (e.g. INR > 1.4) Percutaneous liver biopsy should be avoided if the INR is greater than 1.3 (prothrombin time greater than three seconds above normal).
 If the INR is >1.4, fresh frozen plasma (FFP) may be administered and liver biopsy then carried out if the INR is less than 1.4. • low platelets (e.g. < 60 * 109/l) The minimum safe lower limit of platelets is 60.
 Where the platelet count is 40-60 biopsy can be performed immediately after platelet transfusion provided there has been an increment to the recommended level. • Anti-platelet medication
 should be stopped for at least one week prior to liver biopsy. • anaemia • extrahepatic biliary obstruction • hydatid cyst • haemoangioma • uncooperative patient • ascites Significant volume ascites is a contraindication to percutaneous liver biopsy but a trans-jugular biopsy can be performed as an alternative.

Acute liver failure Acute liver failure describes the rapid onset of hepatocellular dysfunction leading to a variety of systemic complications. Causes • paracetamol overdose • alcohol • viral hepatitis (usually A or B) • acute fatty liver of pregnancy Features* • jaundice • coagulopathy: raised prothrombin time • hypoalbuminaemia • hepatic encephalopathy • renal failure is common ('hepatorenal syndrome') Note: • *remember that 'liver function tests' do not always accurately reflect the synthetic function of the liver. This is best assessed by looking at the prothrombin time and albumin level.

Ascites Causes
• The serum ascites albumin gradient (SAAG) is the most sensitive and specific method of categorising ascites.
 To calculate the ascitic fluid albumin should be subtracted from the serum albumin.
 A value that is ≥11 g/L (high SAAG) indicates a transudate (e.g. cirrhosis, cardiac failure), <11 g/L (low SAAG) indicates an exudate (e.g. malignancy, pancreatitis). • The causes of ascites can be grouped into those with a serum-ascites albumin gradient (SAAG) <11 g/L or a gradient >11g/L as per the table below:

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SAAG > 11g/L SAAG <11g/L Cirrhosis Alcoholic hepatitis Cardiac ascites Mixed ascites Massive liver metastases Fulminant hepatic failure Budd-Chiari syndrome Portal vein thrombosis Veno-occlusive disease Myxoedema Fatty liver of pregnancy Peritoneal carcinomatosis Tuberculous peritonitis Pancreatic ascites Bowel obstruction Biliary ascites Post operative lymphatic leak Serositis in connective tissue diseases Characteristics of ascitic fluid • Causes of a transudate (protein < 30 g/l, assuming a normal albumin level): Hepatic cirrhosis Right-sided cardiac failure Hypoalbuminaemia (nephrotic syndrome) Acute nephritis Budd-Chiari syndrome • Causes of an exudate (protein > 30 g/l): Infection (tuberculosis, peritonitis) Inflammation (vasculitis) Malignancy inhaler. Treatment
• Large, symptomatic ascites therapeutic paracentesis. Several large randomised, controlled trials have shown that repeated large volume paracentesis (4-6 L) is safer and more effective for the treatment of tense ascites compared with larger than usual doses of diuretics. Paracentesis is relatively contraindicated if the patient is encephalopathic,
 Paracentesis is less likely to be successful if the patient has peripheral oedema Whilst therapeutic paracentesis will be necessary in light of the large volume tense ascites it would be advisable to consider doing this with FFP cover. • Not large, asymptomatic ascites dietary salt restriction (to no more than 90 mmol/day) + spironolactone. The initial management would be spironolactone Initial dose of spironolactone is 100 mg/day and may be titrated up to 400 mg/day.
 Once the maximum dose of spironolactone has been reached furosemide can be added if there is still significant ascites accumulation and the renal function and electrolytes will tolerate further diuresis.
 Doses of furosemide are advised start at 40 mg/day titrating up to 160 mg/day as tolerated or needed. Furosemide alone has poor efficacy in cirrhosis. A major reason for so-called diuretic-resistant ascites is an excess sodium intake,
 no-added salt diet is recommended for all patients with ascites secondary to chronic liver disease. Spironolactone is more effective than furosemide because the site of sodium retention in cirrhosis is the distal nephron The ideal weight loss is 0.5 kg/day, as any more than this may cause cardiovascular strain.

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Gastroenterology • transcutaneous liver biopsy is contraindicated with ascites (use transjugular biopsy if absolutely necessary). • Management of hyponatraemia in patients with chronic liver disease and ascites: serum sodium is 126-135 mmol/L No specific intervention other than monitoring serum sodium is 121-125 mmol/L + normal creatinine Reduce diuretics serum sodium is 121-125 mmol/L + high creatinine Stop diuretics + give volume expansion serum sodium is ≤120 mmol/L Stop diuretics + give volume expansion with colloid or normal saline. • Management of hypoproteinemia in patients with chronic liver disease Cirrhotic ascites has significantly lower protein and complement levels than noncirrhotic ascites. This can result in less opsonic activity of the peritoneal fluid predisposing to spontaneous bacterial peritonitis. indications for the use of albumin in cirrhosis: post-paracentesis circulatory dysfunction, spontaneous bacterial peritonitis, and hepatorenal syndrome. Albumin replacement treatment is warranted in this diagnosis and can also decrease the development of the hepatorenal syndrome. 20% salt poor albumin (human albumin solution) The salt-poor preparation of albumin is particularly important in this scenario as high salt load will encourage fluid to shift into the extravascular compartment resulting in fluid overload. What is the most characteristic physiological activity that retains sodium in the face of salt and water overload? Arterial underfilling In liver cirrhosis, arterial vasodilatation due to nitric oxide overactivity, coupled with hypoalbuminemia, which drives low colloid osmotic pressure, leads to arterial underfilling. Meig's syndrome ovarian fibroma associated with a pleural effusion and ascites

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Summary table of the current uses of albumin in hepatology, according to the main international guidelines and looking at future perspectives (PPCD: post-paracentesis circulatory dysfunction; SBP: spontaneous bacterial peritonitis; HRS: hepatorenal syndrome; HE: hepatic encephalopathy; ACLF: acute-on-chronic liver failure).

Liver cirrhosis

Pathophysiology • which hepatic cells are central to the process of fibrosis? The hepatic stellate cells are central to the process of fibrosis within the liver. • What is the pro-inflammatory factor in fibrotic liver injury which activate the stellate cells? Tumour necrosis factor-a is a pro-inflammatory effector in fibrotic liver injury, through activation of the stellate cells. These cells then secrete the fibrillar collagen constituting the defining features of hepatic fibrosis. Interleukin-10 is thought to exert anti-inflammatory effects on the stellate cell. • Which mediator is released by stellate cells that causes fibrosis seen in cirrhosis?.
 Transforming growth factor-beta is the mediator released by stellate cells that causes fibrosis • Which factor that causing contraction of the hepatic stellate cells?
 Endothelin is a vasoconstrictor in the hepatic sinusoids (similarly in the endothelium of the systemic circulation) and functions by causing contraction of the hepatic stellate cells thus increasing intrahepatic sinusoidal resistance and promoting portal hypertension. Nitric oxide antagonises the effects of endothelin in the liver. • Pathogenesis includes the replacement of type IV collagen in the perisinusoidal space (space of Disse) with type I and III collagen. Features
• Cardiac

 Cardiac output is often elevated The cardiomyopathy of alcoholism is a dilated or congestive form.

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 Dilated cardiomyopathy
 hyperdynamic circulation systemic vasodilatation ↓↓ vascular resistance, increased plasma volume low serum sodium. Most patients have sodium and water retention. Secondary hyperaldosteronism will result in total body sodium overload but not necessarily hypernatraemia.
 Remember that the sodium level is a concentration, therefore if the amount of solvent (water) is increased then it will not necessarily rise. • Abdominal symptoms Hepatomegaly (possibly causing RUQ pain)
 Splenomegaly
 Ascites
• Portal hypertension
 Hepatic intrasinusoidal pressure is elevated Which features is most indicative of decompensated portal hypertension? Caput medusae • Which sign is a direct result of decreased hepatic oncotic function in cirrhotic patients? Lower limb swelling • Hormone disorders Hyperestrogenism
 Gynecomastia, decreased body hair (e.g., chest hair) Gynaecomastia
 What is the cause of gynaecomastia in cirrhosis? Altered oestrogen metabolism (an aldosterone antagonist). Hypogonadism (testicular atrophy) Reduced libido, erectile dysfunction, infertility
 Amenorrhea

Classifications
Why do patients get oedema in liver disease?

1. Low albumin
2. Stimulation of RAAS leads to fluid retention • Child-Pugh classification of liver cirrhosis The Child-Pugh classification is a scoring system to assess the severity of liver cirrhosis Score

Bilirubin (m mol/l) <34 34-50

> 50 Albumin (g/l) 35 28-35 <28 Prothrombin <4 4-6 6 Notes & Notes for MRCP By Dr. Yousif Abdallah Hamad

∗ ↓↓ metabolism of sex steroids ↑↑ oestrogen level.
∗ there is associated testicular atrophy and loss of body hair. ∗ May occur as a result of spironolactone therapy

Score

time, prolonged by (s) Encephalopathy None mild marked Ascites None mild marked Summation of the scores allows the severity to be graded either A, B or C: < 7 = A 7- 9 = B 9 = C • Cirrhosis can be micro- or macronodular in type.

1. micronodular form: the nodules are less than 3 mm across with uniform liver involvement - seen in alcohol or biliary disease.
2. macronodular form: there are larger nodules, classically seen in chronic viral hepatitis. Investigations • ALT is more specific than other liver enzymes in diagnosing hepatic injury. • the most important immediate investigation for patient with hepatic cirrhosis presented in a confused and drowsy state Blood glucose (hepatic gluconeogenesis can be significantly down-regulated) • ↑↑ plasma volume
   • ↓↓ serum sodium
    Patients with cirrhosis are frequently hyponatraemic.
    This is a function of an inability to excrete free water (increased ADH levels and systemic vasodilation contribute, but the underlying mechanism is complex and not entirely understood). • Urinary sodium concentration is usually less than 10 mmol/l
    Reduced urinary sodium excretion
    Patients with cirrhosis are frequently hyponatraemic. This is a function of an inability to excrete free water (increased ADH levels and systemic vasodilation contribute, but the underlying mechanism is complex and not entirely understood).

Thrombocytopenia is a common finding in chronic liver disease.

Sex hormones in liver cirrhosis • Clinical features of male cirrhotic subjects are feminization(gynecomastia etc) and hypogonadism(testicular atrophy, reduced fertility, loss of libido, impotence etc).
• sex hormones
 decrease in serum testosterone levels
 increase in serum estrogen levels
 increase in ratio of estrogen to testosterone
 Hyperestrogenization may be related with feminization of male cirrhotic subjects, whereas hypogonadism is the result of alcohol abuse per se, rather than the indirect consequence of liver cirrhosis.

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Prognosis • Five-year survival after liver transplantation is now 75%.

Liver transplant
Guidelines for referral to a liver unit following paracetamol overdose include • Metabolic acidosis (pH <7.3 or bicarbonate <18 mmol/L). • INR >3 (or prothrombin time >50 seconds) INR >2.0 at or before 48 hours or >3.5 at or before 72 hours should prompt referral to a specialist unit.
 Peak elevation occurs around 72-96 hours. • Oliguria • Creatinine >200 µmol/L, (use haemodialysis if >400 µmol/L) • Hypoglycaemia. • Systolic BP <80 mm Hg despite adequate fluid resuscitation • Any degree of encephalopathy 48 hours after ingestion. • raised intracranial pressure (ICP)
 signs of CNS oedema include: BP >160/90 mmHg (sustained) or brief rises (systolic >200 mmHg),
 bradycardia,
 decerebrate posture,
 extensor spasms, and
 poor pupil responses Criteria for liver transplant in fulminant failure in cases of paracetamol overdose include: • arterial pH lower than 7.3 or
• all of the following: Prothrombin time greater than 100 seconds Creatinine greater than 300 µmol/L, and Grade 3-4 encephalopathy. Criteria for liver transplant in fulminant failure in non-paracetamol cases include: • INR greater than 6.7 or
• prothrombin time greater than 100 seconds, or
• any three of the following: Aetiology that is not due to hepatitis A, hepatitis B or a drug reaction Age less than 10 years or more than 40 years Jaundice more than seven days before encephalopathy INR greater than 4 or prothrombin time greater than 50 seconds, and Bilirubin greater than 300 µmol/L.

What are the causes of decompensation in liver disease • Infection • Spontaneous bacterial peritonitis • GI bleeding • Sedatives • HCC

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Portal hypertension Basics • The liver receives approximately 1500 ml of blood each minute, two-thirds of which is provided by the portal vein.

Definition:
• abnormally high pressure in the hepatic portal vein (hepatic venous pressure gradient of 10 mm Hg or more). • Portal hypertension is present when the wedged hepatic vein pressure is more than 5 mmHg higher than the inferior vena cava pressure. Mechanism of porto-systemic collaterals
• Because the veins in the portal system lack valves, increased resistance to flow at any point between the splanchnic venules and the heart will increase the pressure in all vessels on the intestine site of the obstruction.
• This is manifest clinically by the development of porto-systemic collaterals (oesophageal varices), splenomegaly and/or ascites. Site of Anastomosis Clinical Sign Portal ↔ Systemic Esophagus Esophageal varices Left gastric ↔ esophageal Umbilicus Caput medusae Paraumbilical ↔ superficial and inferior epigastric Rectum Anorectal varices (sometimes referred to as internal hemorrhoids though they are different) Superior rectal ↔ middle and inferior rectal

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Causes : (Vascular resistance and blood flow are 2 important factors in its development). • Pre-hepatic - (pre-sinusoidal) blockage of the portal vein before the liver Congenital atresia or stenosis. Portal vein thrombosis (idiopathic, umbilical and portal sepsis, malignancy, hypercoagulable states, pancreatitis). Longstanding portal vein thrombosis is a well recognised complication in premature neonates due to cannulation of the umbilical vein during neonatal intensive care. the best initial investigation is Ultrasound with Doppler Splenic vein thrombosis. Extrinsic compression - eg, tumours. • Hepatic (sinusoidal) Cirrhosis. (the most common cause) Chronic hepatitis. Schistosomiasis. Myeloproliferative diseases. Idiopathic portal hypertension. Granulomata - eg, sarcoid. Nodular (nodular regenerative hyperplasia, partial nodular transformation). Toxins (arsenic, vinyl chloride). Fibropolycystic disease (including congenital hepatic fibrosis). • Post-hepatic - (post-sinusoidal) blockage of hepatic veins or venules Budd-Chiari syndrome (hepatic vein obstruction). Constrictive pericarditis. Right heart failure. Veno-occlusive disease of the smaller hepatic veins/venules (due to ingestion of pyrrolizidine alkaloids; antileukaemic drugs, radiation). Sclerosing hyaline necrosis. Portal hypertension measurement: • Portal pressure is indirectly measured in clinical practice by the hepatic venous pressure gradient (HVPG). • The HVPG is calculated by subtracting the free hepatic venous pressure (which reflects intraabdominal pressure) from the wedged hepatic venous pressure (which reflects portal venous pressure). These values are obtained by hepatic venous catheterization. • Normal HVPG values are <5 mm Hg. • HVPG >10 mm Hg predicts the development of oesophageal varices. • However, HVPG is moderately invasive and its clinical role is uncertain. • The normal hepatic venous pressure gradient (normal HVPG = 1-5 mmHg) means that the portal hypertension is not related to post-sinusoidal intrinsic liver disease such as cirrhosis

(caused in children by metabolic disorders such as A1ATD) or post-hepatic venous obstruction (HV thrombosis). • The haemodynamic goal of treatment is reduce the HVPG by 20% or to less than 12 mmHg, using a non-selective beta blocker. If this is not achievable despite titrating the beta-blocker dose, then endoscopic variceal ligation must be considered. • Wedged hepatic venous pressure the pressure recorded by a catheter wedged in a hepatic vein. It reflects the portal venous pressure in the hepatic sinusoids.
 ↑↑ in sinusoidal and post-sinusoidal portal hypertension,
 remains normal in pre-sinusoidal portal hypertension.

Complications of portal hypertension: • Haematemesis or melaena - suggest bleeding varices. • Lethargy, irritability and changes in sleep pattern - suggest encephalopathy. • Increased abdominal girth, weight gain - suggest ascites. • Abdominal pain and fever - suggest spontaneous bacterial peritonitis. • Pulmonary involvement is common in patients with portal hypertension

Trans-jugular intrahepatic porto-systemic shunt (TIPSS) • Indications are: Diuretic resistant ascites (Intractable ascites) Intractable portal hypertensive bleeding and Hepato-renal failure. • contraindications to shunting: Severe hepatic encephalopathy Severe heart failure Septicaemia

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Hepatic encephalopathy • Hepatic encephalopathy may be seen in liver disease of any cause. • The aetiology is not fully understood but is thought to include excess absorption of ammonia from bacterial breakdown of proteins in the gut Features • confusion, altered GCS (see below) • hepatic flap Asterixis (also called the flapping tremor, or liver flap) is a tremor of the hand when the wrist is extended, sometimes said to resemble a bird flapping its wings. hepatic encephalopathy is unlikely to be present if a liver flap (asterixis) cannot be detected. • constructional apraxia: inability to draw a 5-pointed star • triphasic slow waves on EEG • raised ammonia level (not commonly measured anymore) Grading of hepatic encephalopathy • Grade I: mood changes like depression or irritability, and sleep abnormalities (typically sleep inversion) • Grade II: Confusion, inappropriate behaviour • Grade III: Incoherent, restless

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• Grade IV: Coma Precipitating factors • infection e.g. spontaneous bacterial peritonitis • GI bleed • constipation • drugs: sedatives, diuretics • hypokalaemia • renal failure • increased dietary protein (uncommon) Treatment • Treat precipitating cause (e.g., give K+ if hypokalemic)
• Lactulose
 metabolized to lactic acid by colonic flora, converts NH3 to NH4+ which can be absorbed • Neomycin
 replaced with rifamixin, neomycin no longer routinely used antibiotics kill colonic flora leading to decreased NH3 production

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Hepatorenal syndrome (HRS)

Pathophysiology
• vasoactive mediators cause splanchnic vasodilation ↓↓ systemic vascular resistance 'underfilling' of the kidneys activation of the renin-angiotensin-aldosterone system by the juxtaglomerular apparatus renal vasoconstriction which is not enough to counterbalance the effects of the splanchnic vasodilation. Types • Hepatorenal syndrome has been categorized into two types: Type 1 HRS Type 2 HRS • Rapidly progressive • Doubling of serum creatinine to > 221 mmol/L or a halving of the creatinine clearance to less than 20 ml/min over a period of less than 2 weeks • Very poor prognosis Management • The ideal treatment is liver transplantation, but patients are often too unwell to have surgery and there is a shortage of donors • Other Management options agonists of vasopressin V1 receptors such as terlipressin vasoconstriction of the splanchnic circulation volume expansion with 20% albumin transjugular intrahepatic portosystemic shunt

• Slowly progressive • characterised by a moderate and stable reduction in renal function, hypotension and diuretic resistance. • Prognosis poor, but patients may live for longer

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Wilson's disease Wilson's disease - serum caeruloplasmin is decreased

Wilson's disease is an autosomal recessive

Definition • Wilson's disease is an autosomal recessive disorder characterised by impaired copper transport via caeruloplasmin results in excessive copper deposition in the tissues. • Wilson disease is a disorder resulting from impaired copper excretion into bile. Copper overload and deposition in tissues leads to predominantly hepatic and neuropsychiatric symptoms. • Metabolic abnormalities include increased copper absorption from the small intestine and decreased hepatic copper excretion. Aetiology and pathophysiology • autosomal recessive
• caused by a defect in the ATP7B gene located on chromosome 13. • Mutations within the ATP7B gene result in disruption of an ATPase within hepatocytes which is responsible for the movement of copper across intracellular membranes. This results in hepatic retention of copper, and low serum levels.
• The mechanism of tissue damage in Wilson disease is copper-mediated hydroxyl free radical tissue damage. Features
• The onset of symptoms is usually between 10 - 25 years. • Children usually present with liver disease whereas the first sign of disease in young adults is often neurological disease • liver: hepatitis, cirrhosis • neurological:
 basal ganglia degeneration, speech and behavioural problems are often the first manifestations.
 The most common early neurological sign is an asymmetrical tremor,
 Also: the initial sign is usually increased clumsiness. parkinsonism,
 dystonia. asterixis,
 chorea,
 dementia • Kayser-Fleischer rings
 Golden corneal rings in the posterior surface of the retina, within its Descemet’s membrane.
 Detected by Slit lamp examination Present in up to 90% of symptomatic patients but is not pathognomonic. • renal tubular acidosis (esp. Fanconi syndrome) • haemolysis • blue nails Diagnosis • Reduced serum caeruloplasmin Ceruloplasmin is normal in approximately 5% of cases • Slit lamp examination

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 slit lamp examination will detect Kayser-Fleischer corneal rings in approximately 98% of untreated cases and the sunflower cataract will be more obvious. • ↓ Total serum copper • increased 24hr urinary copper excretion greater than 1.6 µmol/day • Liver biopsy
 The most reliable investigation to confirm the diagnosis Shows:
 increased hepatic parenchymal copper concentration steatosis, glycogenated nuclei, focal hepatocellular necrosis, fibrosis and cirrhosis.
• MRI of the brain commonly shows increased density in the basal ganglia. • Genetic testing for ATP7B mutation
 usually reserved for patients where the diagnosis is in doubt, or for screening of siblings.
Complications • higher risk of hepatocellular carcinoma.
Management • General management Low-copper diet: avoid foods such as organs, shellfish, nuts, and chocolate Hepatotoxic drugs, alcohol and foods high in copper (liver, chocolate, shellfish etc.) should be avoided.
 Regular check-ups: liver biochemical tests every 6 months if disease is stable[9] Liver transplantation in cases of fulminant liver failure • Medical therapy Initial therapy: chelating agents
 Penicillamine:
 first-line treatment
 side effects in ~ 30% of cases
 (e.g., sensitivity reactions) bone marrow suppression Alternatives: trientine or zinc salts Trientine may become first-line treatment in the future better tolerated than penicillamine, and is therefore used as an alternative where side effects are seen when penicillamine is initiated.
 Maintenance therapy: zinc salts or low dose chelating agents

• Zinc acetate is the intervention of choice for patients with asymptomatic Wilson’s disease (i.e. those who present with elevated transaminases without evidence of cirrhosis or neurological dysfunction). • screening of first degree relatives
 Once a diagnosis of Wilson's disease is made, screening of first degree relatives (with genetic testing) should be done.
Treatment with a chelating agent should be administered gradually over the course of 3 to 6 months, as mobilizing the copper stored in tissues too rapidly may exacerbate neurological symptoms

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Prognosis • Early treatment allows a normal length of life, • however without treatment Wilson's disease is usually fatal by the age of 40 years. MRCPUK-part-1-September 2014 exam: A 23-year-old woman developed unilateral hand tremor at rest, behaviour & mood changes, speech problems & bradykinesia. Dark circular marks noted around the iris. her uncle died of liver cirrhosis at the age of 40 years. Given the likely diagnosis, what is the mode of inheritance?
 Autosomal recessive

Hyponatraemia in Patients with chronic liver disease • Patients with chronic liver disease and ascites often develop hyponatraemia, the management of which can be difficult. • Diuretic therapy

for the management of ascites often contributes to the hyponatraemia. • The British Society of Gastroenterology guidelines suggest that: serum sodium is ≤120 mmol/L normal saline + stop diuretic
 serum sodium is 126-135 mmol/L No intervention other than careful monitoring. serum sodium is 121-125 mmol/L + normal serum creatinine reduce diuretics or stop it if necessary
 serum sodium is 121-125 mmol/L +↑↑ serum creatinine volume expansion + stop diuretics
 fluid restriction should only be used in patients who are clinically euvolaemic, not on diuretics and have severe hyponatraemia with a normal serum creatinine.

Alcohol
After drinking excessive amounts alcohol
• Mechanism of polyuria Ethanol inhibits ADH secretion
• Mechanism of nausea vagal stimulation to the vomiting centre.
• Mechanism of tremors increase glutamate production by neurones to compensate for the previous inhibition by ethanol. • Mechanism of hypoglycemia hepatic sequestration of Reduced nicotinamide adenine dinucleotide (NADH) In the liver alcohol dehydrogenase converts ethanol to acetaldehyde but to do so requires the reduction of oxidized nicotinamide adenine dinucleotide (NAD+) to reduced nicotinamide adenine dinucleotide (NADH).
 Acetaldehyde is then further oxidized to acetate to aldehyde dehydrogenase, which requires the reduction of another NAD+ to NADH.
 When excess alcohol is consumed then the system becomes overwhelmed and NADH accumulates in hepatocytes. This sequestration of NADH reduces the amount of NAD+ available to oxidize gluconeogenic precursors hypoglycemia

Alcohol induced hypoglycemia • Alcohol metabolized to acetyl-CoA. • NADH produced during alcohol metabolism interferes with gluconeogenesis. • NADH causes production of: lactate, malate, and glycerol 3-phosphate. • Thus, glycerol 3-phosphate causes lipid accumulation in liver alcoholic disease.
• NAD, required for lactate metabolism (and lactate is used for gluconeogenesis), is being used for alcohol metabolism.

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Gastroenterology

The large anion gap and hypoglycemia in alcoholic patients can be explained by which mechanism?
 Inhibition of dehydrogenase enzymes by NADH Excess alcohol intake leads to accumulation of NADH that decreases gluconeogenesis as well as impairs fatty acid oxidation. (Key gluconeogenic dehydrogenases are inhibited by the elevated levels of NADH, including: lactate dehydrogenase,
 glycerol 3-phosphate dehydrogenase, and
 malate dehydrogenase).

Alcohol - drinking problems: management Nutritional support • SIGN recommends alcoholic patients should receive oral thiamine if their 'diet may be deficient'

Drugs used • benzodiazepines for acute withdrawal • disulfram: promotes abstinence - alcohol intake causes severe reaction due to inhibition of acetaldehyde dehydrogenase. Patients should be aware that even small amounts of alcohol (e.g. In perfumes, foods, mouthwashes) can produce severe symptoms. Contraindications include ischaemic heart disease and psychosis • acamprosate: reduces craving, known to be a weak antagonist of NMDA receptors, improves abstinence in placebo-controlled trials Disulfiram
• Indication: used as an aid to stop alcohol abuse. • Mode of action: irreversible inhibitor of aldehyde dehydrogenase, therefore if alcohol is ingested, aldehyde accumulates causing unpleasant reactions including vomiting, palpitations and breathlessness.
• The reaction with alcohol only occurs at least 12 hours after the start of disulfiram therapy and may occur up to 10 days after stopping disulfiram therapy.
• Disulfiram is active against scabies, although other treatments are usually preferred.

Alcoholic liver disease
The recommended maximum alcohol intake per week is 21 units for men and 14 units for women. Governmental guidelines suggest that women should not have more than 2-3 units per day and men should not have more than 3-4 units per day Alcoholic liver disease includes fatty liver, alcoholic hepatitis and cirrhosis. • fatty liver (hepatic steatosis) accumulation of fat within the hepatocytes.
 Mechanism: increased generation of NADH reduces the activity of the TCA cycle, the acetyl-Co A is diverted to fatty acid synthesis. reduction in cytosolic NAD+ leads to reduced activity of glycerol-3-phosphate dehydrogenase resulting in increased levels of glycerol 3-phosphate which is the backbone for the synthesis of the triglycerides, lead to fatty acid deposition in the liver leading to fatty liver syndrome. asymptomatic and detected incidentally. Elevated transaminases and a background of alcoholism are clues to the diagnosis.
 macrovesicular fatty changes.
 Microvesicular fatty changes are not found in hepatic steatosis. An ultrasound demonstrates hyper-echogenicity and a bright liver. This is reversible with abstention from alcohol.

• Alcoholic hepatitis presents as: acute right upper quadrant (RUQ) pain
 Tender hepatosplenomegaly jaundice
 fever
 frequently occurs on a background of cirrhosis marked derangement of LFTs LFT typically show an AST elevated greater than the ALT with at least a 2:1 ratio AST:ALT ratio can be useful in diagnosing alcoholic liver disease, because more than two-thirds of patients will have a ratio greater than 2. transaminases are typically only slightly elevated rarely over 300 and virtually never over 500.
 The alkaline phosphatase may well be significantly elevated giving the liver profile an 'obstructive' appearance. High IgA levels are seen in alcoholic liver disease. At a microscopic level there is inflammation of the liver. • liver cirrhosis,
 the hepatocytes are damaged so much that they are replaced by scar tissue which is permanent.
 Alcoholic hepatitis and cirrhosis may co-exist. Alcoholic hepatitis and cirrhosis may lead to

encephalopathy, portal vein hypertension and hepato-renal syndrome, increase risk of infections and they are usually malnourished. There is no specific therapy for alcohol-related hepatitis and cirrhosis. • Cardiomyopathy of alcoholism is a dilated or congestive form. • Gout
 Gout is a common finding in chronic alcoholics. Mechanism: Lactate accumulate in alcoholics causes lactic acidosis (Metabolic acidosis). Lactate competes with uric acid for excretion, decreasing its excretion and thus aggravating gout.

Chronic alcohol abuse is typically associated with
Increased carbohydrate deficient transferrin (CDT)

Which feature would suggest a diagnosis of hepatic steatosis rather than non-alcoholic fatty liver disease? Reversible hepatic damage after discontinuing alcohol consumption

The common abnormalities in chronic alcohol dependence • Macrocytosis • Hypertriglyceridaemia - can contribute to pancreatitis • Hyperuricaemia - can cause gout • Hypoglycaemia - can contribute to seizures and coma • Increased carbohydrate deficient transferrin - considered a marker of chronic abuse and sometimes checked to ensure abstinence, for example, while awaiting liver transplantation • Hypogonadism • Thiamine deficiency • Abnormal iron
 Iron levels are variable in alcohol dependence: hepatitis causes increased serum iron while poor diet can result in iron deficiency Ferritin can be elevated in the acute phase response, but reduced in advanced liver disease due to possible reduced synthesis rates

• Abnormal electrolytes Hyponatraemia and hypokalaemia are often seen in established liver disease Hypomagnesaemia hypocalcaemia which may be linked to alcohol-related hypomagnesaemia and poor dietary intake of calcium and vitamin D;
• Elevated liver enzymes
 Elevated GGT - this is due to enzyme induction but does not necessarily indicate that there is liver damage ALT is elevated in liver disease and hepatocellular damage AST is elevated (but can also be increased in cardiac or muscular damage). AST:ALT ratio can be elevated due to the mitochondrial effects of alcohol causing a disproportionate increase in AST. However, this is not specific.

Patients with alcoholic liver disease are often surprisingly sensitive to opiate analgesia which should only be used with caution. (eg: a patient prescribed dihydrocodeine regularly for abdominal pain associated with chronic pancreatitis, became drowsy with deterioration in his Glasgow coma scale. What is the agent should be administered initially? Naloxone)

Alcoholic ketoacidosis Definition • Alcoholic ketoacidosis is a non-diabetic euglycaemic form of ketoacidosis. Features • Metabolic acidosis • Elevated anion gap • Elevated serum ketone levels • Normal or low glucose concentration Treatment • The most appropriate treatment is an infusion of saline & thiamine.
 Thiamine is required to avoid Wernicke encephalopathy or Korsakoff psychosis.

Non-alcoholic fatty liver disease (NAFLD) (Non-alcoholic steatohepatitis (NASH)

Definition • liver changes similar to those seen in alcoholic hepatitis in the absence of a history of alcohol abuse.
• NAFLD is subdivided into: nonalcoholic fatty liver (NAFL): hepatic steatosis without inflammation nonalcoholic steatohepatitis (NASH): hepatic steatosis with hepatic inflammation that may be histologically indistinguishable from alcoholic steatohepatitis • the diagnosis is made only by histology of liver biopsy which shows lesions suggestive of ethanol intake in a patient known to consume less than 40 g of alcohol per week.

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Epidemiology • Non-alcoholic fatty liver disease (NAFLD) is now the most common cause of liver disease in the developed world. • relatively common and though to affect around 3-4% of the general population. • It is projected to become a leading indication for liver transplantation, superseding hepatitis C. Mechanism
• NAFLD is thought to represent the hepatic manifestation of the metabolic syndrome and hence insulin resistance is thought to be the key mechanism leading to steatosis

Associated risk factors • Obesity • Hyperlipidaemia • Type 2 diabetes mellitus • Jejuno-ileal bypass • Sudden weight loss/starvation

Complications • Liver cirrhosis
• NASH is associated with insulin resistance and diabetes.

Features • Usually asymptomatic • Hepatomegaly • Some patients with NASH may complain of fatigue, malaise, and vague right upper abdominal discomfort.

Investigations • LFT ALT is typically greater than AST (ALT > AST = Lipids) normal aminotransferase levels do not exclude NAFLD

• Radiographic finding: U/S → increased echogenicity on ultrasound CT → decreased hepatic attenuation MRI → an increased fat signal
• Liver biopsy The hallmark of the condition on liver biopsy is the association of inflammation with fatty infiltration of the liver. This can progress to fibrotic change and eventually to cirrhosis. fatty infiltration of hepatocytes causing cellular “ballooning” and eventual necrosis.

Diagnosis • A definitive diagnosis of NAFLD requires all of the following:

1. Demonstration of hepatic steatosis by imaging or biopsy
2. exclusion of common liver disorders like viral hepatitis, alcoholic liver disease, drug induced and autoimmune liver disease (e.g. primary biliary cirrhosis). Exclusion of other causes of hepatic steatosis: e.g:

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