021

Chapter 3

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 3

Gastroenterology

 Significant alcohol use Hepatitis C (particularly genotype 3) Wilson disease Lipodystrophy Starvation Parenteral nutrition Abetalipoproteinemia Medications Reye syndrome Acute fatty liver of pregnancy HELLP (hemolytic anemia, elevated liver enzymes, low platelet count) syndrome • The confirmatory test for diagnosis is liver biopsy.

Management • Non pharmacological: life style management
 Weight loss: the mainstay of treatment abstinence from alcohol
• Pharmacological there is ongoing research into the role of gastric banding insulin-sensitising drugs (e.g. Metformin) For patients with NASH and diabetes mellitus: Although initial therapy for type 2 diabetes mellitus is typically with metformin, but metformin does not improve liver histology the beneficial impact on liver histology with certain other insulinsensitizing agents could be a consideration when choosing a secondline agent for patients with NASH who cannot take metformin or need additional glucose-lowering therapy. In this setting, pioglitazone and liraglutide are reasonable options. In patients with diabetes mellitus and biopsy-proven NASH, pioglitazone improves fibrosis as well as inflammation and steatosis. use of pioglitazone is limited because it is associated with increased risk of weight gain, heart failure, and fractures. Although less well studied, liraglutide also appears to improve liver biopsy evidence of NASH. Liraglutide is a GLP-1 agonist which results in significant weight loss of up to 7% over 1 year at high dose, (3mg), By driving weight loss it leads to a significant reduction in hepatic fat and may impact on the long-term prognosis of fatty liver disease. Prognosis • Approximately 20% develop cirrhosis

Which liver function test is the best marker of non-alcoholic fatty liver disease in type 2 diabetes mellitus?
→ alanine aminotransferase

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Liver abscess
Pyogenic liver abscess • The most common organisms found in pyogenic liver abscesses are Staphylococcus aureus in children and Escherichia coli in adults. • usually complicates pre-existing biliary and gastrointestinal tract infections. • Management Ideally, a penicillin-based β-lactamase antibiotic combined with metronidazole to provide anaerobic cover would be the treatment of choice. amoxicillin + ciprofloxacin + metronidazole if penicillin allergic: ciprofloxacin + clindamycin

The CT demonstrates a hypodense lesion (A) with surrounding oedema (B).

Amoebic liver abscess
• A solitary abscess in the right lobe of the liver is typical of amoebic liver abscess. The collection is commonly single and confined to the right lobe, but multiple leftsided abscesses may also occur.
• Liver abscesses due to amoebae mainly occur in endemic tropical countries.
• A history of chronic diarrhoea might be elicited in patients with amoebic liver abscess. • Clinical presentation can be indistinguishable from pyogenic abscesses.
• Specific anti-E. histolytica antibodies can be found in 90%
• Management 10-day course of metronidazole. For larger liver abscesses aspiration is the intervention of choice, combined with antibiotic therapy.

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CT showing a pyogenic liver abscess in the right lobe of the liver.

Hydatid cysts Asymptomatic, calcified cystic lesions in the liver are typical of hydatid cysts. • Hydatid cysts are endemic in Mediterranean and Middle Eastern countries.
• Hydatid infection was endemic in sheep farming regions (such as Wales or New Zealand) in the past and sheep dogs were infected by eating infected offal. Humans contract hydatids via faecal/oral spread from dogs. most commonly seen in farming and rural communities • They are caused by the tapeworm parasite Echinococcus granulosus.
• Up to 90% cysts occur in the liver and lungs • An outer fibrous capsule is formed containing multiple small daughter cysts.
• These cysts are allergens which precipitate a type 1 hypersensitivity reaction. Clinical features: • Can be asymtomatic, or symptomatic if cysts > 5cm in diameter The liver cysts are usually asymptomatic, and calcification usually denotes a nonviable cyst. • Morbidity caused by cyst bursting, infection and organ dysfunction (biliary, bronchial, renal and cerebrospinal fluid outflow obstruction) • In biliary rupture there may be the classical triad of; biliary colic, jaundice, and urticaria

Investigations • Ultrasonography is the most helpful initial test since it can usually differentiate a simple cyst from other cystic lesions. It should also be used for follow up studies. • CT scan shows characteristic daughter cysts. • Hydatid serology has a sensitivity of 80-90%.

• If hydatid serology is negative, then further imaging (CT/MRI) +/- aspiration may be required to make a diagnosis. • CT is the best investigation to differentiate hydatid cysts from amoebic and pyogenic cysts. Treatment • Surgery is the mainstay of treatment (the cyst walls must not be ruptured during removal and the contents sterilised first). • benzimidazoles

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Drug-induced liver disease

Hepatocellular Picture Cholestasis (+/- Hepatitis) Liver Cirrhosis • Alcohol • Amiodarone • Anti-tuberculosis:

isoniazid, rifampicin, pyrazinamide • Ketoconazole
• Halothane • MAOIs • Methyldopa • Paracetamol • Sodium valproate, phenytoin • Statins • Nitrofurantoin chronic active hepatitis. • Anabolic steroids, testosterones • Antibiotics: flucloxacillin, coamoxiclav*, erythromycin**, nitrofurantoin • Fibrates • Oral contraceptive pill • Phenothiazines: chlorpromazine, prochlorperazine • Rarely: nifedipine • Sulphonylureas • Amiodarone • Methotrexate • Methyldopa

Notes • with co-amoxiclav, a four-week delay in symptoms and signs is not unusual.
• ** with erythromycin risk may be reduced with erythromycin stearate

Epidemiology • commoner in women Features • jaundice (elevated bilirubin) • hepatomegaly,
• deranged transaminases
• associated with anti-LKM2 autoantibodies. Differential diagnosis • autoimmune hepatitis
 may also be associated with anti-LKM positivity,
 short history and drug exposure make drug-induced hepatitis more likely .
Prognosis • Liver function can improve after drug withdrawal, but relapses are possible.

Budd-Chiari syndrome Triad of abdominal pain, ascites and liver enlargement. Definition
• obstruction of the main hepatic veins by thrombus. • Budd-Chiari syndrome, or hepatic vein thrombosis, is usually seen in the context of underlying haematological disease or another procoagulant condition

Causes • polycythaemia rubra vera

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• thrombophilia: activated protein C resistance, antithrombin III deficiency, protein C & S deficiencies • pregnancy • oral contraceptive pill Features • abdominal pain: sudden onset, severe • ascites • tender hepatomegaly

• Signs of portal hypertension are present and patients may develop acute variceal haemorrhage as a complication.
Diagnosis • Ultrasound Doppler or contrast CT scan is often used to make the diagnosis.
 Hypertrophy of the caudate lobe on imaging is a characteristic sign but is seen in only 50% of cases.
• Ascitic tap usually demonstrates a high SAAG (>11 g/L). Management • Thrombolysis and subsequent anticoagulation Prognosis • Three-year survival in patients with chronic Budd-Chiari syndrome has been reported as 50%.

Gilbert's syndrome • Gilbert's syndrome is an autosomal recessive condition of defective bilirubin conjugation due to a deficiency of UDP glucuronyl transferase.
• The prevalence is approximately 1-2% in the general population Features • unconjugated hyperbilinaemia (i.e. not in urine) • normal dipstix urinalysis excludes Dubin-Johnson and Rotor syndrome as these both produce a conjugated bilirubinaemia. • jaundice may only be seen during an intercurrent illness Investigation • rise in bilirubin following prolonged fasting or IV nicotinic acid Management
• no treatment required

Crigler-Najjar syndrome • Crigler-Najjar syndrome refers to a condition of absent UDP-glucuronyl transferase.
• This condition presents early in life with jaundice, increased unconjugated bilirubin and kernicterus.
• This disease is life threatening and the only cure is liver transplant.

Dubin-Johnson syndrome • benign autosomal recessive disorder • Resulting in hyperbilirubinaemia (conjugated, therefore present in urine). • It is due to a defect in the canillicular multispecific organic anion transporter (cMOAT) protein. This causes defective hepatic bilirubin excretion • patients have a black liver on gross examination of the tissue.
• On microscopic examination, patients have epinephrine metabolite accumulations in their hepatocytes.
• No treatment is necessary.

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Autoimmune hepatitis The combination of deranged LFTs combined with secondary amenorrhoea in a young female strongly suggest autoimmune hepatitis • Autoimmune hepatitis is condition of unknown aetiology which is most commonly seen in young females.
• more common in females. Pathophysiology
• T-cell mediated progressive necro-inflammatory process resulting in fibrosis and cirrhosis.
Associations • Other autoimmune disorders including:
 coeliac disease,
 pernicious anaemia,
 thyroiditis

 type 1 diabetes mellitus. • IgG hypergammaglobulinaemia • sicca syndrome (xerostomia/dry eyes, keratoconjunctivitis sicca) may occur. • HLA B8, DR3 and Dw3.

Types • Three types of autoimmune hepatitis have been characterised according to the types of circulating antibodies present Type I Type II Type III Anti-nuclear antibodies (ANA) and/or anti-smooth muscle antibodies (SMA). Affects both adults and children Anti-liver/kidney microsomal type 1 antibodies (LKM1) Affects children only Soluble liver-kidney antigen

Affects adults in middle-age Features • may present with signs of chronic liver disease • acute hepatitis: fever, jaundice etc (only 25% present in this way) • amenorrhoea (common) Investigations • ANA/SMA/LKM1 antibodies,
• raised IgG levels • liver biopsy:
 The gold standard for diagnosis
 inflammation extending beyond limiting plate 'piecemeal necrosis', bridging necrosis Management
• steroids, other immunosuppressants e.g. azathioprine Prednisolone (with or without azathioprine) is better than azathioprine alone.

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 Steroid therapy produce symptomatic, biochemical and histological improvement, with improvement in survival.
 It does not, however, prevent progression to frank cirrhosis. • liver transplantation Prognosis • The prognosis with long-term immunosuppression is excellent even in the presence of cirrhosis and few patients subsequently develop liver failure.

Ischaemic hepatitis • Ischaemic hepatitis is a diffuse hepatic injury resulting from acute hypoperfusion (sometimes known as 'shock liver').
• It is diagnosed in the presence of an inciting event (eg: cardiac arrest) and marked increases in aminotransferase levels (exceeding 1000 international unit/L or 50 times the upper limit of normal).
• Often, it will occur in conjunction with acute kidney injury (tubular necrosis) or other end organ dysfunction.

Pregnancy: jaundice

Physiological liver changes during pregnancy • albumin level decreases earlier in 1st trimester due to hemodilution • ALT& AST aminotransferase remains normal. Thus, serum aminotransferase levels is the most useful test for the routine diagnosis of liver diseases during pregnancy.
• total and free bilirubin decreases during all three trimesters. Conjugated bilirubin ↓↓in 2nd & 3rd trimesters.
• ALP ↑↑ in late pregnancy, due both to the production of the placental isoenzyme and to the

increase in bone isoenzyme. (Thus ALP levels is not a suitable test for the diagnosis of cholestasis during pregnancy).
• Serum gamma-glutamyl transferase ↓↓ in 2nd & 3rd trimesters,
• serum 5'nucleotidase slightly ↑↑ in 2nd & 3rd trimesters.
• Serum total bile acid concentrations not changed during pregnancy. Measurement of serum bile acids may be useful for the diagnosis of cholestasis, especially when serum aminotransferase levels are within normal limits. • Intrahepatic cholestasis of pregnancy would not occur in the first trimester.

Gilbert's & Dubin-Johnson syndrome, • may be exacerbated during pregnancy

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HELLP syndrome • HELLP syndrome is a mnemonic that stands for Hemolysis, Elevated Liver enzymes, and Low Platelets in a patient with severe preeclampsia.
• HELLP syndrome is a manifestation of severe preeclampsia that can lead to hepatic subcapsular hematoma formation. • Schistocytes are an erythrocyte variant that may be seen in HELLP syndrome. • Immediate delivery is the only definitive treatment

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Obstetric cholestasis Epidemiology • Obstetric cholestasis affects around 0.7% of pregnancies in the UK • most common in the third trimester
Pathophysiology • Caused by a bile acid transporter defect
Features • pruritus - may be intense - typical worse palms, soles and abdomen • Jaundice occurs in less than 10% of patients. Diagnosis (cholestatic picture of (LFTs) with a high ALP and, with a lesser rise in ALT.) • ↑ Total Serum bile acid levels (cholic acid and chenodeoxycholic acid) >10 micromol/L • ↑↑ GGT
• ↑ ALT, AST • ↑ direct bilirubin bilirubin < 100 only slightly elevated in about 10% • ↑ ALP ALP is not useful as it is normally raised in late pregnancy anyway. • prothrombin time may be prolonged in any cholestatic process due to vit k deficiency
Complications • increased risk of prematurity and still birth.
Differential diagnosis:
• Viral hepatitis is the commonest cause of jaundice in pregnancy but the elevated bile acids make this unlikely Management • ursodeoxycholic acid
 First-line medication widely used but evidence base not clear early therapy with ursodeoxycholic acid reduces the risk of preterm birth and stillbirth. • Cholestyramine SE: may cause a deficiency in fat-soluble vitamins Rarely, there are cases of cerebral hemorrhage associated with vitamin K shortage under cholestyramine therapy. • induction of labour at 37 weeks is common practice but may not be evidence based • vitamin K supplementation • phenobarbital Prognosis • fully reversible postpartum • Recurrence in following pregnancies (40–60%)

Cardiac output and blood volume increase in pregnancy but hepatic blood flow does not.

Acute fatty liver of pregnancy (AFLP) Definition • a rare disease most common in the third trimester characterized by extensive fatty infiltration of the liver, which can result in acute liver failure
Risk factors • older maternal age,
• primiparity,

• multiple pregnancies,
• pre-eclampsia,
• male foetus
• previous AFLP. Pathophysiology • dysfunction of fatty acid β-oxidation microvesicular fat deposition.
Features • abdominal pain • nausea & vomiting • headache • jaundice • hypoglycaemia • severe disease may result in pre-eclampsia • Coagulopathy with an increased risk of disseminated intravascular coagulation (DIC)
• Hypoalbuminemia → ascites
• encephalopathy later. Investigations • ALT is typically elevated e.g. 500 u/l • ↑ WBC, ↓ platelets Management • support care • once stabilised delivery is the definitive management

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Haemochromatosis

• Haemochromatosis is an autosomal recessive disorder of iron absorption and metabolism resulting in iron accumulation.
Aetiology • It is caused by inheritance of mutations in the HFE gene on both copies of chromosome 6*.
 *there are rare cases of families with classic features of genetic haemochromatosis but no mutation in the HFE gene • 90 % of cases are caused by the substitution of tyrosine for cysteine at position 282 of the HFE gene found on chromosome 6. • HLA-A3 is associated with haemochromatosis Epidemiology • 1 in 10 people of European descent carry a mutation genes affecting iron metabolism, mainly HFE • prevalence in people of European descent = 1 in 200 • Haemochromatosis is the most prevalent genetic condition in Caucasian population, with a carrier rate of 1 in 10 and is present in about 1 in 200-400 people • Males and females are affected equally but females are often 'protected' from the clinical features by menstrual blood loss.
Pathophysiology • Iron absorption is regulated in the duodenal crypts. • HFE is a protein that regulates iron absorption,
• HFE forms a complex at the basolateral membrane that if bound to transferrin + iron at the basolateral membrane of the duodenal crypt cells prevents maturation and consequently absorption of iron in the bowel.
• mutation in the HFE gene failure of complex formation and constant maturation of duodenal crypt cells subsequent unregulated uptake of iron.

Presenting features • often asymptomatic in early disease • early symptoms include
 fatigue, erectile dysfunction
 arthralgia (often of the hands) Joint x-rays characteristically show chondrocalcinosis • 'bronze' skin pigmentation • diabetes mellitus • liver: stigmata of chronic liver disease, hepatomegaly, cirrhosis, hepatocellular deposition) • cardiac failure (2nd to dilated cardiomyopathy) • hypogonadism (2nd to cirrhosis and pituitary dysfunction - hypogonadotrophic hypogonadism) • arthritis (especially of the hands). Joint x-rays characteristically show chondrocalcinosis Questions have previously been asked regarding which features are reversible with treatment: Reversible complications

• Cardiomyopathy • Skin pigmentation

Irreversible complications

• Liver cirrhosis** • Diabetes mellitus • Hypogonadotrophic hypogonadism • Arthropathy

**whilst elevated liver function tests and hepatomegaly may be reversible, cirrhosis is not
Investigation

The best investigation to screen for haemochromatosis • General population: transferrin saturation is considered the most useful marker.
 Ferritin should also be measured but is not usually abnormal in the early stages of iron accumulation.
• testing family members: genetic testing for HFE mutation These guidelines may change as HFE gene analysis become less expensive Diagnostic tests • liver biopsy: Perl's stain the gold standard investigation (as it quantifies iron deposition and also stages the amount of fibrosis) • molecular genetic testing for the C282Y and H63D mutations found in 90% there is substitution of tyrosine for cysteine at position 282 of the HFE gene on chromosome 6.
 However, there is low penetrance of clinical disease and haemochromatosis also occurs in patients who are negative for this mutation. genetic testing for HFE gene mutations is indicated for an individuals meeting one of the following criteria: Elevated serum ferritin (> 300 microgram / L in males; > 200 microgram / L in females) Elevated transferrin saturation (> 45 %) First degree relative with haemochromatosis • MRI has high specificity but low sensitivity for demonstrating iron overload in the liver - it has not replaced the need for biopsy in the majority of cases.

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Typical iron study profile in patient with haemochromatosis • transferrin saturation > 55% in men or > 50% in women • raised ferritin (e.g. > 500 ug/l).
 Ferritin is measured to help guide further investigation and treatment:

 if more than 1000 a liver biopsy should be performed, and treatment initiated. • low TIBC

0BDiabetes and impotence associated with high ferritin → haemochromatosis • The combination of DM and hypogonadotrophic hypogonadism (HH) (low testosterone & FSH)) is compatible with a diagnosis of haemochromatosis and measuring ferritin would be a reasonable investigation. • The next investigation would be measurement of transferrin saturation

Treatment • Venesections
 survival and morbidity are improved if phlebotomy is initiated prior to the development of cirrhosis. weekly or twice weekly (if tolerated) venesections of 500 cm3 until the serum ferritin is less than 50 ng/mL & transferrin saturation less than 50% • Chelation with desferrioxamine
 When iron overload and anaemia are present concomitantly. may be utilised where venesection cannot be continued and there is still evidence of iron overload.
 It is more commonly used in other conditions associated with iron overload such as thalassaemia major.
• Avoid vitamin C supplementation
 as this can enhance iron toxicity. • liver transplantation
 End stage liver disease, portal hypertension and hepatocellular carcinoma (which is increased up to 200-fold) may necessitate liver transplantation. Monitoring adequacy of venesection • BSCH recommend 'transferrin saturation should be kept below 50% and the serum ferritin concentration below 50 ug/l'

MRCPUK-part-1-May 2005 exam: Which feature of haemochromatosis may be reversible with treatment?
 Cardiomyopathy

MRCPUK-part-1-May 2014 exam: H/O fatigue and arthralgia. The joint pain is worse around his metacarpophalangeal joints and knees. polyuria and polydipsia. An x-ray of his knees reveals chondrocalcinosis. What is the mode of inheritance of the likely underlying diagnosis?
 Autosomal recessive
 (This patient has typical symptoms of haemochromatosis: 1/ Lethargy. 2/arthralgia, with evidence of chrondrocalcinosis. 3/diabetes mellitus (polyuria and polydipsia)

MRCPUK-part-2-march-2018: abnormal liver function, low testosterone level, diabetes mellitus and elevated serum ferritin level. What is the most effective intervention to treat

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iron overload?
 Venesection Δ haemochromatosis.

Hepatocellular carcinoma (HCC)

• Hepatocellular carcinoma (HCC) is the third most common cause of cancer worldwide.
• Chronic hepatitis B is the most common cause of HCC worldwide with chronic hepatitis C being

the most common cause in Europe. Risk factors
• The main risk factor for developing HCC is
 Liver cirrhosis, for example secondary* to hepatitis B & C, alcohol, haemochromatosis and primary biliary cirrhosis.
 *Wilson's disease is an exception 75% to 90% of patients with HCC have cirrhosis.
 HCC develops in 4% of cirrhotics per year. Patients with chronic hepatitis B have 100-fold higher risk of developing HCC.

• Other risk factors include: alpha-1 antitrypsin deficiency hereditary tyrosinosis glycogen storage disease aflatoxin drugs: oral contraceptive pill, anabolic steroids porphyria cutanea tarda male sex diabetes mellitus, metabolic syndrome Features • tends to present late • features of liver cirrhosis or failure may be seen: jaundice, ascites, RUQ pain, hepatomegaly, pruritus, splenomegaly • possible presentation is decompensation in a patient with chronic liver disease Screening with ultrasound (+/- alpha-fetoprotein) should be considered for high risk groups such as: • patients liver cirrhosis secondary to hepatitis B & C or haemochromatosis • men with liver cirrhosis secondary to alcohol Management options • early disease: surgical resection • liver transplantation • radiofrequency ablation • transarterial chemoembolisation • sorafenib: a multikinase inhibitor Management of liver capsule pain • Stretching of the liver capsule by a primary hepatoma or metastases within the liver can cause chronic cancer pain. • This commonly presents as dull, right-sided subcostal pain. • Referred pain at the top of the ipsilateral shoulder occurs due to diaphragmatic irritation if the superior aspect of the capsule is involved.

• Corticosteroids can be used in the management of liver capsule pain and dexamethasone is usually the choice of steroid. • Which analgesics would be most suitable for the management of liver capsule pain? Dexamethasone

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Carcinoid syndrome

Which biochemical markers is most likely depleted in carcinoid syndrome? Biosynthesis of serotonin begins with tryptophan, so tryptophan depletion is most likely.

• usually occurs when metastases are present in the liver and release serotonin into the systemic circulation • may also occur with lung carcinoid as mediators are not 'cleared' by the liver Features • flushing (often earliest symptom) • diarrhoea • bronchospasm • hypotension • right heart valvular stenosis (left heart can be affected in bronchial carcinoid) (mostly tricuspid insufficiency) and pulmonary stenosis, Endocardial fibrosis is due to constant exposure of the right heart to serotonin.
• other molecules such as ACTH and GHRH may also be secreted resulting in, for example, Cushing's syndrome • pellagra can rarely develop as dietary tryptophan is diverted to serotonin by the tumour Investigation • urinary 5-hydroxy-indole-acetic acid (5-HIAA) (specificity 100% , sensitivity 70%) • plasma chromogranin A y (The most sensitive marker 100%) Management •

somatostatin analogues e.g. Octreotide (Side effects of octreotide therapy include increased risk of gallstones) The best treatment for symptoms of carcinoid is the somatostatin analogue, octreotide, which improves symptoms and prognosis • Other potential treatments following resistance or failure of octreotide include hepatic artery embolisation.
• diarrhoea: cyproheptadine may help the treatment for the diarrhoea will be through treating the underlying diagnosis, which is carcinoid octreotide Cyproheptadine is not a first line treatment for diarrhoea and in fact may cause diarrnoea as a side effect. Telotristat inhibits tryptophan hydroxylase, which mediates serotonin biosynthesis. It is indicated for carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy. Telostristat approved by (FDA) in 2017 for carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by an SSA.

Which vitamin deficiency may be associated with carcinoid syndrome?

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 Vitamin B3 Vitamin B3, niacin, is used to make NAD and is derived from tryptophan.
 In carcinoid syndrome, the increased synthesis of serotonin would deplete the supply of tryptophan needed to make niacin.
 A deficiency of niacin would result in pellagra, which is characterized by diarrhea, dermatitis, and dementia

MRCPUK-part-1-May 2007 exam: If the patient develops carcinoid syndrome, which one of the following symptoms is most likely to occur first?
 Facial flushing

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hepatic metastases

The abdominal CT demonstrates a number of ill-defined low-density deposits in the liver consistent with hepatic metastases (A) along with significant intrahepatic biliary duct dilatation (B). The likely diagnosis is metastatic pancreatic cancer causing biliary obstruction with a concomitant cholangitis.

Viral hepatitis Hepatitis A (HAV)

The classic story of (HAV) is initial GIT symptoms then improved condition followed by jaundice and very high alanine aminotransferase (ALT) .

Diagnosis • Anti-hepatitis A IgM antibody will confirm the diagnosis
• IgG antibody would suggest: a previous hepatitis A infection or
 another underlying cause such as cytomegalovirus. Indicator of poor prognosis

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• Hepatitis A infection on a background of hepatitis C (but not B) has very poor prognosis.

Hepatitis B

• Hepatitis B is a double-stranded DNA hepadnavirus
Spread through
• vertical transmission from mother to child.
 Perinatal transmission is the most common route of hepatitis B infection worldwide
 the infection rate is 90% in infants born to HBeAg (hepatitis B envelope antigen) positive mothers. • exposure to infected blood or body fluids,
 Sexual transmission comprises 30% of hepatitis B infections in developed countries.
Incubation period
• 6-20 weeks. Features:
• fever,
• jaundice
• elevated liver transaminases. (ALT) will be elevated more than (AST).

• Symptoms of decompensated liver disease include: ascites,
 encephalopathy and
 gastrointestinal haemorrhage.

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Complications
• chronic hepatitis (5-10%) • fulminant liver failure (1%) • hepatocellular carcinoma • polyarteritis nodosa the vascular extrahepatic manifestation of hepatitis B. There is a hepatitis B seropositivity in 30% of patients with polyarteritis nodosa. • cryoglobulinaemia • hematologic extrahepatic manifestation of hepatitis B Aplastic anemia
• renal extrahepatic manifestations of hepatitis B
 Membranous glomerulonephritis (more common)
 membranoproliferative glomerulonephritis (less common) are.

Prognosis • Most adults with hepatitis B will progress to full resolution.

Immunisation against hepatitis B • contains what?: HBsAg adsorbed onto aluminium hydroxide adjuvant
• prepared from what? prepared from yeast cells using recombinant DNA technology • schedule? give 3 doses of the vaccine + one-off booster 5 years following the initial primary vaccination • At risk groups who should be vaccinated include:
 healthcare workers,
 intravenous drug users,
 sex workers,

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 close family contacts of an individual with hepatitis B,
 individuals receiving blood transfusions regularly,
 chronic kidney disease patients who may soon require renal replacement therapy,
 prisoners,
 chronic liver disease patients • failure to respond or respond poorly to 3 doses of the vaccine
 occur in 10-15% of adults.
 Risk factors include: age over 40 years,
 obesity,
 smoking, alcohol excess and
 immunosuppression how to check response? testing for anti-HBs levels testing for anti-HBs is only recommended for: those at risk of occupational exposure (i.e. Healthcare workers) and patients with chronic kidney disease.
 In these patients anti-HBs should be checked 1-4 months after primary immunisation how to interpret anti-HBs levels? the table below shows

Anti-HBs level (mIU/ml) Response

> 100 Indicates adequate response, no further testing required. Should still receive booster at 5 years 10 - 100 Suboptimal response - one additional vaccine dose should be given.
> If immunocompetent no further testing is required < 10 Non-responder. Test for current or past infection. Give further vaccine course (i.e. 3 doses again) with testing following. If still fails to respond then HBIG would be required for protection if exposed to the virus

Hepatitis B serology Interpreting hepatitis B serology: It is important to remember a few key facts: • surface antigen (HBsAg) is the first marker to appear and causes the production of anti-HBs appears in the serum 1 to 10 weeks following acute exposure, even before symptoms or (ALT) rise.
 normally implies acute disease (present for 1-6 months) if present for > 6 months then this implies chronic disease (i.e. Infective) In those who recover HBsAg will usually become undetectable after 4 to 6 months. • Anti-HBs

 implies immunity (either exposure or immunisation).
 It is negative in chronic disease • Anti-HBc
 implies previous (or current) infection.
 IgM anti-HBc appears during acute or recent hepatitis B infection and is present for about 6 months.
 Anti-HBc IgM is detectable between 6 and 32 weeks after exposure
 IgG anti-HBc persists • HbeAg

 results from breakdown of core antigen from infected liver cells as is therefore a marker of infectivity HBeAg is a marker of infectivity in all patients except those who have Hepatitis B virus (HBV) pre-core mutant or the core promoter mutant, because they do not synthesise HbeAg,
 this is most commonly due to a stop-codon mutation at nucleotide 1896.
 So the learning here is that although the e antigen is negative, the patient may still be infective.
• previous immunisation: anti-HBs positive, all others negative • previous hepatitis B (> 6 months ago), not a carrier: anti-HBc positive, HBsAg negative • previous hepatitis B, now a carrier: anti-HBc positive, HBsAg positive

IgM anti-HBc jointing HBV-DNA is most effective and most practicable in distinguishing Acute Hepatitis B from Chronic Hepatitis B With Acute Flare.

Acute Infection Chronic Carrier HBs

+ +

-

Anti-HBs

-
-

Anti-HBc + (IgM)

- (IgG)
- (IgG)

-

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Window Complete Recovery Immunized Period

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Distinguish between acute HBV and a flare of chronic disease • originates from an area of the world with a high prevalence of HBV infection In areas of low HBV prevalence, such as the United

Kingdom, a combination of HBsAg positivity and features of acute hepatitis usually indicates acute self-limiting hepatitis B infection. In countries with high prevalence of hepatitis B the majority of infection is acquired vertically during childhood and leads to chronicity rather than acute infection.

• Anti-HBc-IgM is typically found in acute HBV infection; however it can be found in10-15% of patients with chronic HBV. This is especially true when considering acute flares of chronic hepatitis.
 The sensitivity and specificity for HBc-IgM to distinguish between acute HBV and a chronic flare has been reported as low as 77% and 70% respectively.
 Using high titres to determine cut-offs (1:10,000 or greater) does improve this significantly however. • Flares of chronic HBV are typically associated with higher levels of HBV DNA and AFP than acute self-limiting disease.
 The alpha-fetoprotein is commonly elevated during acute hepatitis due to hepatic regeneration.
• flares of chronic HBV tend to be associated with less necroinflammation, and thus ALT tends to be as raised as in acute HBV, but hepatic synthetic dysfunction is more common. Distinguish between patients who have recovered from hepatitis B and those immunized for it • Although both patients who have recovered from hepatitis B and those immunized for it will test positive for antibody to hepatitis B surface antigen, only patients who have recovered from hepatitis B will be positive for IgG antibody to hepatitis B core antigen.

Assessment of liver disease in secondary specialist care for adults with chronic hepatitis B • The initial test for liver disease in adults newly referred for assessment is transient elastography Transient elastography (FibroScan) is a new, non-invasive, rapid method allowing evaluation of liver fibrosis by measurement of liver stiffness. Interpretation of transient elastography score ≥ 11 kPa antiviral treatment without a liver biopsy between 6 and 10 kPa liver biopsy to confirm the level of fibrosis < 6 kPa liver biopsy, if the: Age < 30 years and HBV DNA > 2000 IU/ml and abnormal ALT (≥30 IU/L for males and ≥ 19 IU/L for females) on 2 consecutive tests conducted 3 months apart. < 6 kPa NO liver biopsy, if the:
 HBV DNA < 2000 IU/ml and normal ALT. Offer annual reassessment of liver disease using transient elastography to adults who are not taking antiviral treatment.

Management • Acute HBV
 the majority of patients will resolve spontaneously,
 treatment with an oral anti-HBV agent is not necessary. Patients who are positive for HBsAg for more than six months but are HBeAg negative, HBV DNA negative and have normal ALT do not require liver biopsy nor do they require antiviral therapy, but hepatitis B serology and ALT should be monitored annually. • Chronic HBV Indications of antiviral treatment in adults with chronic hepatitis B (NICE 2013) age ≥ 30 years + HBV DNA > 2000 IU/ml + abnormal ALT (≥30 IU/L in males ≥19 IU/L in females) on 2 consecutive tests conducted 3 months apart. Age < 30 years +

HBV DNA > 2000 IU/ml + abnormal ALT if there is: evidence of necro-inflammation or fibrosis on liver biopsy
 or a transient elastography score > 6 kPa. HBV DNA > 20,000 IU/ml + abnormal ALT regardless of age or the extent of liver disease. (on 2 consecutive tests conducted 3 months apart)
 cirrhosis + detectable HBV DNA, regardless of HBeAg status, HBV DNA and ALT levels. HBV DNA > 2000 IU/ml + evidence of necro-inflammation or fibrosis on liver biopsy. with compensated liver disease First-line 48-week course of pegylated interferon-alpha
  ↓↓ viral replication in up to 30% of chronic carriers.
 better response is predicted by being female, < 50 years old, low HBV DNA levels, non-Asian, HIV negative, high degree of inflammation on liver biopsy Interferon alfa is usually given short term and is not very effective in patients without an elevated ALT.
 stopping peginterferon alfa-2a 24 weeks after starting treatment if HBV DNA level has decreased by less than 2 log10 IU/ml and/or if HBsAg is greater than 20,000 IU/ml 2nd line second-line tenofovir disoproxil (nucleotide analogue, reverse transcriptase inhibitor (NRTI)

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 to people who do not undergo HBeAg seroconversion or who relapse (revert to being HBeAg positive following seroconversion) after firstline treatment with peginterferon alfa-2a. would be of most value for long-term treatment of HBV Offer entecavir (nucleoside analogue, reverse transcriptase inhibitor) as an alternative second-line treatment to people who cannot tolerate tenofovir disoproxil or if it is contraindicated. Entecavir is a pro-drug and requires phosphorylation to the triphosphate form before it becomes active. Nucleoside = Sugar + Base Nucleotide = Sugar + Base + Phosphate

 Lamivudine would be an alternative, although resistance develops commonly.

 If HBV DNA remains detectable at 96 weeks: If No history of lamivudine resistance add lamivudine to tenofovir disoproxil. With a history of lamivudine resistance add entecavir to tenofovir disoproxil. with decompensated liver disease (portal hypertension, bleeding varices, ascites and encephalopathy) Do not offer peginterferon alfa-2a worsen hepatic decompensation First-line entecavir (if there is no history of lamivudine resistance). people with a history of lamivudine resistance tenofovir disoproxil

• When to consider stopping nucleoside or nucleotide analogue treatment? without cirrhosis 12 months after HBeAg seroconversion with cirrhosis do not stop • Co-infection with chronic hepatitis B and C peginterferon alfa + ribavirin

Notes & Notes for MRCP
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Hepatitis B and pregnancy Risk of vertical transmission
• Without intervention the vertical transmission rate is around 20%,

• increases to 90% if the woman is positive for HBeAg. • there is little evidence to suggest caesarean section reduces vertical transmission rates Treatment • Treatment of the baby: babies born to mothers who are chronically infected with hepatitis B or to mothers who've had acute hepatitis B during pregnancy should receive a complete course of vaccination + hepatitis B immunoglobulin Breastfeeding
 hepatitis B cannot be transmitted via breastfeeding (in contrast to HIV) they may continue antiviral treatment while they are breastfeeding. • Treatment of the woman: all pregnant women are offered screening for hepatitis B Interferon is contraindicated
 Offer tenofovir disoproxil to women with HBV DNA > 107 IU/ml in the third trimester to reduce the risk of transmission of HBV to the baby. Monitor quantitative HBV DNA 2 months after starting tenofovir disoproxil and ALT monthly after the birth to detect postnatal HBV flares in the woman. Stop tenofovir disoproxil 4 to 12 weeks after the birth unless the mother meets criteria for long-term treatment

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Hepatitis C

• Hepatitis C is likely to become a significant public health problem in the UK in the next decade. • It is thought around 200,000 people are chronically infected with the virus.
• The most common route of transmission of hepatitis C in the United States is intravenous drug use.
• Zone I of the liver is the zone first affected by hepatitis C infection. • Hepatitis C virus genotypes
 There are 6 genotypes and more than 50 subtypes.
 In England and Wales genotypes 1 and 3 account for more than 90% of all diagnosed infections.
 In Japan, North America, and western Europe, the majority of infections are with genotypes 1, 2, and 3.
 Subtype 1a is the most predominant genotype in the US,
 subtype 1b predominates in Asia and Europe.

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 Genotype 4 is more prevalent in the middle east and in northern and central Africa.
 Genotypes 5 and 6 have been identified in South Africa and southeast Asia, respectively.
 Differences in subtype can result in subtle differences in response to antiviral therapies. Hepatitis C genotype 3 is associated with insulin resistance and hepatic steatosis Genotype 3a is most strongly associated with a positive response to therapy Genotypes 2 and 3 respond reasonably well to polyethylene glycol (PEG) interferon and ribavirin; genotypes 1and 4 less well. Risk factors • intravenous drug users
• patients who received a blood transfusion prior to 1991 (e.g. haemophiliacs). Pathophysiology • hepatitis C is a RNA flavivirus • incubation period: 6-9 weeks The risk of Transmission: • vertical transmission rate from mother to child is about 6%.
• sexual intercourse is probably less than 5% (in contrast to hepatitis B, sexual transmission is uncommon). • needle stick injury is about 2% The risk is higher if there is coexistent HIV •

breast feeding is not contraindicated in mothers with hepatitis C

Features • after exposure to the hepatitis C virus less than 20% of patients develop an acute hepatitis • Chronic hepatitis C is a very common cause of minor elevations in serum transaminases. Other liver function tests can be entirely normal
Diagnosis • first Arrange an anti-HCV antibody test • HCV RNA tests are normally only ordered following a positive antibody test.
Associations • chronic hepatitis C associated with insulin resistance
• insulin sensitising drugs may improve response to anti-viral therapy Extrahepatic association of hepatitis C • Sjögren's syndrome • dermatologic
 Porphyria cutanea tarda Lichen planus • hematologic
 Cryoglobulinaemia (mixed essential type)
 myeloma and monoclonal gammopathies non-Hodgkin lymphoma,
 immune thrombocytopenia,
 autoimmune hemolytic anemia • renal
 membranoproliferative glomerulonephritis (more common)
 Membranous glomerulonephritis (less common)

Complications • chronic infection (80-85%)
• cirrhosis (20-30% of those with chronic disease) • hepatocellular cancer • cryoglobulinaemia

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