

HEPATOLOGY HANDBOOK

NORFOLK AND NORWICH HOSPITAL

DEPARTMENT OF GASTROENTEROLOGY

This text is designed to give a broad overview of hepatology practice at the at the Norfolk and Norwich Hospital. More detailed guidelines appear on the intranet, and excellent international guidelines may be found on the [EASL](#) and [AASLD](#) websites.

If you have any comments/additions, please do contact me – william.gelson@nnuh.nhs.uk.

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COMMON HEPATOBILIARY PRESENTATIONS

JAUNDICE

History taking should focus on relevant past history, drug history, travel history, sexual contacts and illicit drug taking. Important symptoms to consider are pain and constitutional symptoms. Examination may help in the identification of malignancy and tenderness may suggest gallstone disease.

If jaundice is painless and cancer is not suspected, it may be important to exclude unconjugated hyperbilirubinaemia as the first step. This is achieved by requesting a split bilirubin ("cobi" on ICE). If the unconjugated fraction (indirect bilirubin) is disproportionately elevated then the diagnosis is either haemolysis or a defect of conjugation – namely Gilbert's Syndrome in adults. It is often reasonable to request an ultrasound, split bilirubin and blood count simultaneously.

To investigate conjugated hyperbilirubinaemia, the salient investigation is an ultrasound scan with Doppler studies. This may show lesion/s or features of chronic liver disease, in which case the work up should focus on these diagnoses. If the ultrasound is normal, there is no pain and there is no obvious causative drug (often co-amoxiclav or flucloxacillin taken 4 to 6 weeks before the onset of jaundice), a screen for acute and chronic liver diseases should be undertaken (see below). A biopsy should also be considered in light of the screen for diagnostic and/or prognostic purposes.

In the presence of pain and/or biliary duct dilatation, the following clinical scenarios are common:

Biliary pain with a normal ultrasound scan

The most likely diagnosis in this context is choledocholithiasis as ultrasound has a poor sensitivity. Given that ERCP has a relatively high complication rate, the gold standard approach in this context is to image the biliary tree further with either **radial** endoscopic ultrasound (EUS) or MRI cholangiography (MRCP) before going onto a therapeutic ERCP to remove biliary debris and perform a sphincterotomy to allow the passage of future debris. However, if the level of clinical suspicion is high then pre-ERCP imaging often delays the inevitable ERCP.

Dilated common bile duct (CBD)

CBD stones usually cause pain and may lead to cholangitis. They may be seen at ultrasound, when they will need to be removed at ERCP. If they are not visualised, but choledocholithiasis is strongly suspected, ERCP should be performed, **particularly in the context of deep jaundice or cholangitis**. If there is clinical doubt, further delineation by MRCP or EUS is indicated before undertaking an ERCP.

Once stones have been removed from the CBD, cholecystectomy should be considered.

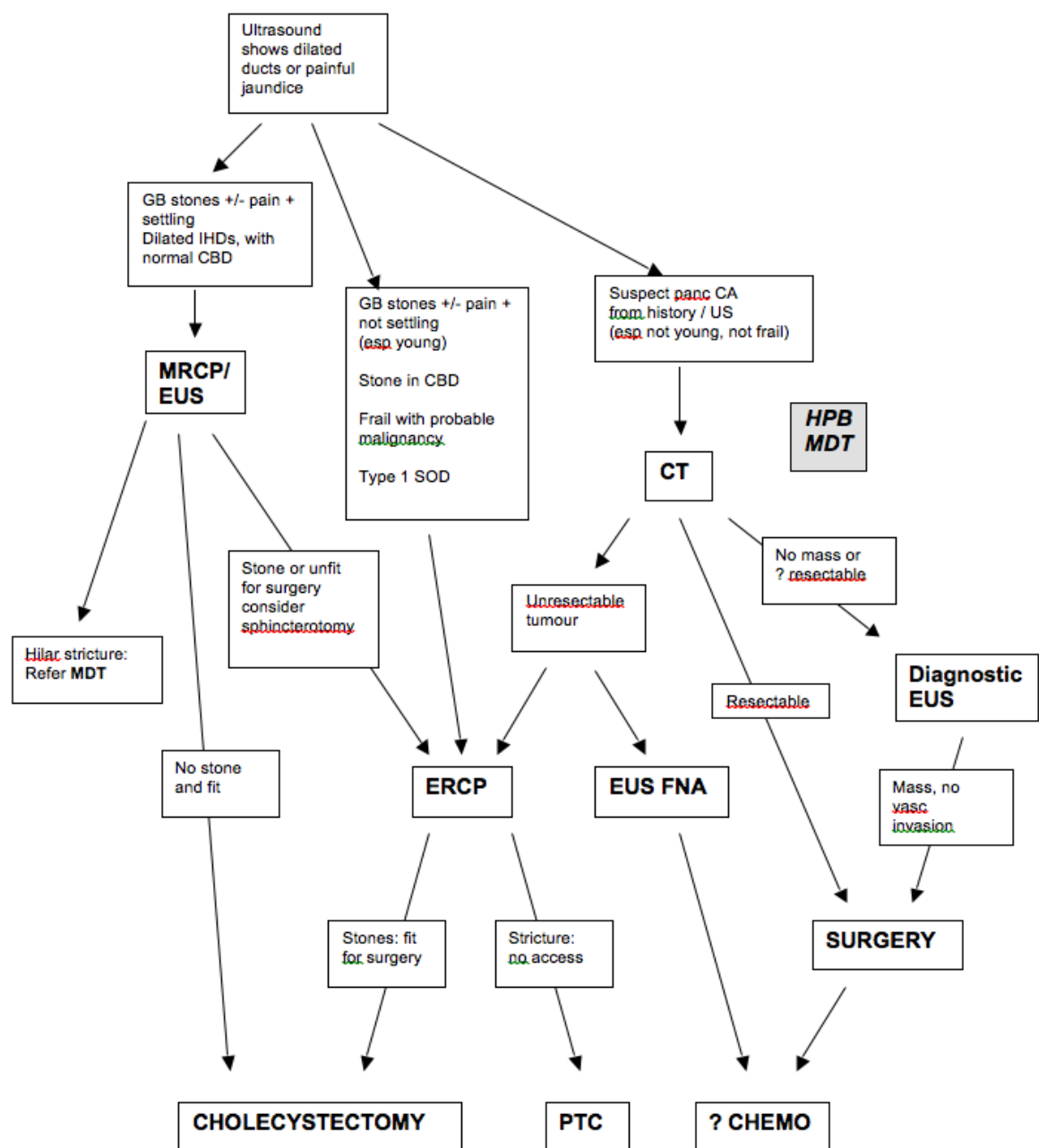
In the absence of pain, the most common diagnosis is pancreatic cancer. The CBD can often be followed to the pancreas at ultrasound and a mass sometimes visualised. The next investigations are a staging CT scan and **linear** EUS with biopsy/FNA to confirm the diagnosis

and further stage the disease. An ERCP with stent insertion to relieve the jaundice is often required whilst awaiting the decision of the MDT regarding definitive management.

Dilated intrahepatic ducts with a normal CBD

The differential diagnosis here is cholangiocarcinoma, inflammation (primary or secondary sclerosing cholangitis), extrinsic compression - often from metastatic disease - and complex gall stone disease. An MRCP with dynamic MRI is usually required to delineate the bile ducts further and assess for mass lesions. Some would advocate CT followed by MRCP. The temptation to reach for the duodenoscope should be avoided before delineating the anatomy, as ERCP is potentially detrimental, particularly if bacteria are introduced into a non-drainable segment. PTC is often preferable as a first line for biliary drainage.

Jaundice Algorithm (LIFTED FROM ADDENBROOKES – TO DISCUSS):



ABNORMAL LIVER ENZYMES

Elevated liver enzymes are a common indication for referral, both in the inpatient and outpatient settings. Investigations are always context specific, making a formulaic approach inadvisable.

In the outpatients, history and examination help to identify the presence of chronic liver disease, features of biliary pathology, potential drug and hereditary causes, risk factors for liver disease and whether the patient is actually unwell. Investigations help to assess disease severity (PT, albumin and bilirubin), identify patients with chronic liver disease (platelets, ultrasound, transient elastography (Fibroscan) and biopsy) and identify a cause (full liver screen, ultrasound with Doppler flows and biopsy).

When there is diagnostic doubt after initial investigations, a biopsy should be considered. This will also stage liver disease in terms of fibrosis. If there is no diagnostic doubt, but staging alone is required then transient elastography is a useful tool in the first instance.

With deranged liver enzymes in the inpatient setting, there are three groups of causes: acute liver disease, underlying chronic liver disease and, as is most common, deranged tests as a secondary phenomenon (inflammation, heart failure, ischaemia, drug-related, malignancy, bone disease and muscle pathology). Relevant liver screens (see below) determine aetiology of acute and chronic liver disease and within these groups it is vital to identify acute liver failure and hepatic decompensation, due to their significant associated morbidity and mortality.

VARICEAL HAEMORRHAGE

The first presentation of portal hypertension may be with a variceal haemorrhage. Treatment of the bleed as discussed below should proceed in tandem with the identification of a cause. This will usually be decompensated cirrhosis or venous thrombosis. Either way, an ultrasound with Doppler studies is an appropriate initial investigation.

ASCITES

Ascites is a common referral to Gastroenterology. An ultrasound is often useful to confirm ascites, which is usually followed by a triple phase CT scan and an ultrasound-guided tap. Fluid should be sent for total protein, albumin, **amylase, lipid profile (if ascites appears chylous)**, cytology, white cell count with differential and microbiology. If these investigations are not diagnostic then a laparoscopy may be helpful.

To guide investigations, it is often useful to divide ascites into exudate or transudate. This is done on the basis of the total protein concentration and serum to ascites albumin gradient (SAAG: serum albumin concentration - ascites albumin concentration), **with values of > 30 g/L for total protein concentration and < 11 g/L for SAAG** being indicative of exudative ascites. Aetiologies according to this classification follow. It is important to note that the classification is not absolute.

Exudate

Peritonitis (including spontaneous bacterial peritonitis [SBP]);

Pancreatitis (check amylase);
Malignancy;
Tuberculosis;
Connective tissue diseases.

Transudate

Portal hypertension (cirrhosis, portal vein thrombosis, hepatic vein thrombosis);
Acute liver failure;
Right heart failure;
Protein losing states (nephrotic syndrome, protein losing enteropathy, malnutrition).

LIVER LESIONS

Liver lesions are usually identified initially by ultrasound. This may be as part of a screening programme or incidentally. Further investigations depend on the clinical context and are predominantly directed by an MDT, but usually involve a combination of tumour markers, triphasic CT, MRI, biopsy and/or interval scanning. Salient investigative features and management of specific lesions are discussed later in the text.

ACUTE LIVER DISEASE

Acute parenchymal liver disease occurs within a short time frame. Decompensation of chronic liver disease - defined as acute on chronic liver disease by some - does not fall within this category.

The principles of management of acute liver disease are to:

- Identify patients with liver impairment (non-vitamin K dependent coagulopathy) or liver failure (coagulopathy and encephalopathy);
- Obtain a diagnosis;
- Offer generic and specific treatments;
- Monitor patients appropriately depending on severity of liver injury. As a guide, monitoring should occur as an inpatient in the presence of liver impairment or significant jaundice and as an outpatient with frequent attendances otherwise.

Whilst the vast majority of patients with acute liver injury will not develop acute liver failure, it is discussed first due to its high associated mortality.

ACUTE LIVER FAILURE

Acute liver failure is subdivided into three distinct entities by the time from the onset of jaundice to the onset of hepatic encephalopathy. This subdivision is useful because each subset has distinct clinical characteristics. Hyperacute liver failure is the development of encephalopathy within seven days of the onset of jaundice; acute liver failure when the onset is from one to five weeks; subacute liver failure when the onset is from five to **twenty-six** weeks.

Acute and hyperacute liver failure lead to similar grades of encephalopathy and derangement of prothrombin time. It is not possible to ascertain the natural mortality of each condition in current practice as most cases are considered for liver transplantation, but hyperacute liver failure has a far better prognosis compared to acute liver failure while mortality is greatest for subacute liver failure, even though the latter carries a low risk of cerebral oedema and less marked derangement of prothrombin time.

In the absence of transplant contra-indication, any patient who may be developing liver failure should be discussed with a transplant centre, and all patients with liver failure transferred urgently. **Ventilation is usually recommended for the transfer of patients with any grade of encephalopathy (definitely grades 3 to 4) as it reduces the risk of exacerbation of cerebral oedema, and ventilation en route is potentially problematic.**

It is useful to document indications for liver transplantation for acute liver failure. These may also be found [here](#). Of course, clinical scenario allowing, patients should always be discussed with a transplant centre before they fulfil these criteria.

Indications for Liver Transplantation

Paracetamol poisoning

- pH < 7.25 more than 24 hours after overdose and after fluid resuscitation;
- Co-existing PT >100 seconds or INR >6.5, and serum creatinine >300 µmol/l or anuria, and grade 3-4 encephalopathy;
- Serum lactate more than 24 hours after overdose > 3.5 mmol/l on admission or >3.0 mmol/l after fluid resuscitation;
- Two of the three criteria from category 2 with clinical evidence of deterioration (eg increased ICP, FiO₂ >50%, increasing inotrope requirements) in the absence of clinical sepsis.

Seronegative hepatitis, hepatitis A or hepatitis B, or an idiosyncratic drug reaction

- PT >100 seconds or INR >6.5, and any grade of encephalopathy.
- Any grade of encephalopathy, and any three from the following: unfavourable aetiology (idiosyncratic drug reaction, seronegative hepatitis), age >40 years, jaundice to encephalopathy time >7 days, serum bilirubin >300 µmol/L, PT >50 seconds or INR >3.5.

Acute presentation of Wilson's disease

A combination of coagulopathy and any grade of encephalopathy.

Investigations for patients with acute liver disease

The following table gives screening investigations for patients presenting with acute liver injury:

Viral	Exposure history, IgM to HAV, IgM anti-HBc, IgM anti-HDV, IgM HEV , EBV serology
Drugs and toxins	Exposure history, drug levels, eosinophil count
Autoimmune	ANA, SMA, LKM and high levels of IgG
Wilson's	Serum copper and caeruloplasmin, evidence of haemolysis, Kaiser-Fleisher rings and a low ALP
Malignancy	Imaging, histology
Pregnancy-related	Fatty liver - ultrasound, uric acid, histology Pre-eclampsia - hypertension, proteinuria and oedema in pregnancy with HELLP (haemolysis, elevated liver enzymes and low platelets)
Ischaemic	History of hypotension/sepsis/risk factors for arterial emboli

Generic management of patients with acute liver failure or significant liver impairment

Generic management involves meticulous correction of metabolic disturbances (especially glucose, potassium, phosphate and sodium), correction of haematological disturbances (clotting should not be corrected unless the patient is bleeding actively, as the PT gives vital prognostic information; thrombocytopenia should be corrected when bleeding is present), prophylaxis against septicaemia (tazocin 4.5 g tds and fluconazole 100 mg daily) and haemodynamic support (vigorous fluid resuscitation, transfusion as required).

Specific management- Paracetamol

Paracetamol overdose is the commonest cause of acute liver failure in general medical practice. When identified early, toxicity is avoided by treatment with N-acetylcysteine. At later stages, even after paracetamol can no longer be detected in plasma, N-acetylcysteine can still beneficially modify the course of acute liver failure.

N-acetylcysteine dosing

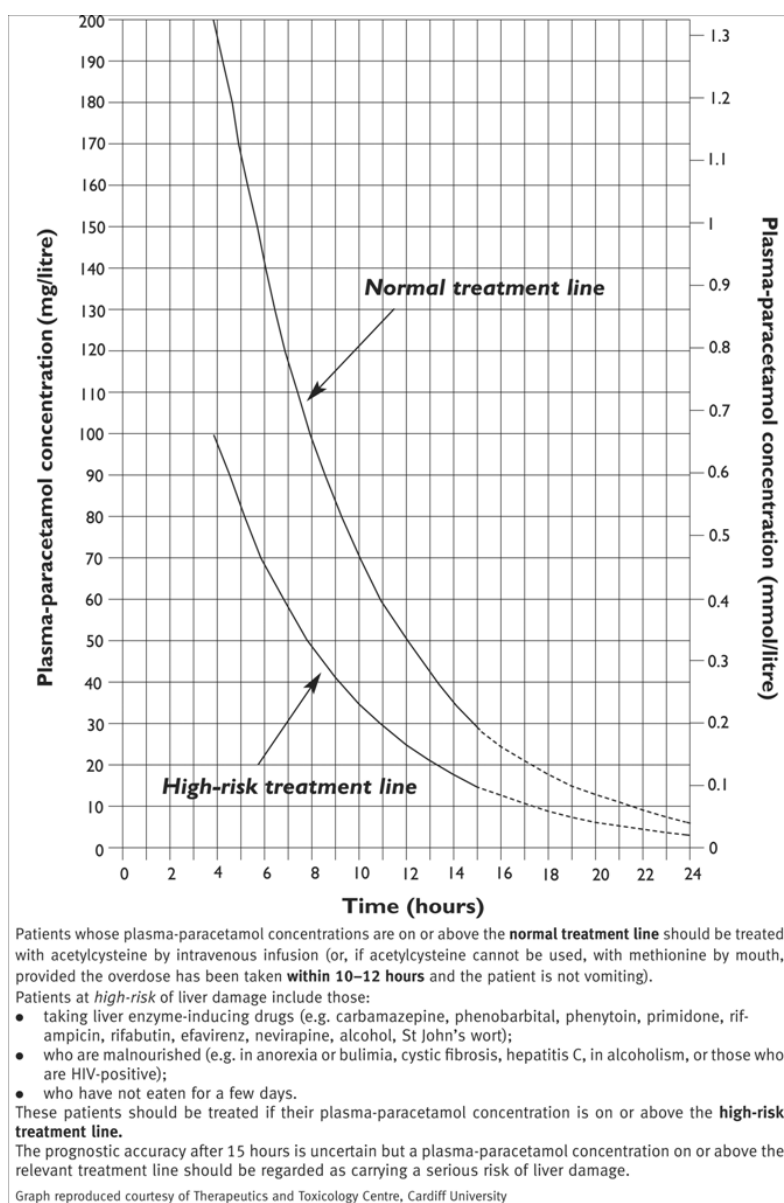
- Initially 150mg/kg in 200mL glucose 5% given over 15 minutes, then
- 50mg/kg in 500mL glucose 5% given over 4 hours, then
- 100mg/kg in 1000mL glucose 5% given over 16 hours

Have a low threshold for giving N-acetylcysteine. The treatment curves for the management of paracetamol poisoning (below) rely completely on the history of the timing of the overdose, which is almost always ascertained from the patient themselves, who may be an unreliable witness for a variety of reasons. If there is any doubt regarding timing to avoid inappropriate non-treatment, either two separate paracetamol levels need to be taken four hours apart or the patient treated empirically, especially if they are known to have ingested a significant amount (> 10 g).

N-acetylcysteine should be given until paracetamol levels are undetectable and the PT is less than **20 seconds**. The minimum duration of treatment is 20 hours. Patients should not be medically discharged until they are asymptomatic, the PT and creatinine are normal and they have an undetectable paracetamol level.

Should adverse features be apparent (renal impairment, acidosis, high lactate or PT > 20), generic management of significant liver impairment (above) should be instigated and the case discussed with a transplant centre. A useful 'rule of thumb' for patients with an isolated PT rise is that if the PT exceeds the time from overdose in hours, then the patient falls within a poor prognostic group and should be transferred to – or at the very least discussed with – a transplant centre.

Treatment curves for the management of paracetamol poisoning



Other drug-induced liver injury

Drug induced liver injury may be predictable and dose-dependent – as with paracetamol – or idiosyncratic. Idiosyncratic drug reactions are either immune mediated or non-immune mediated. The latency for immune mediated liver injury is usually 1 to 6 weeks, whereas for non-immune mediated it is in the region of 1 month to 1 year. If one expects a drug related liver injury, the key to diagnosis is (obviously) a careful drug history. It is often difficult to be definitive about drug injury and, whilst using cut-offs of ALT such as $> 3 \times \text{ULN}$ are sensitive markers, they are not specific.

Common causes of liver injury are clavulanic acid, flucloxacillin, chemotherapeutics, nitrofurantoin, azathioprine, anabolic steroids and isoniazid. A perceived common cause of liver injury are the statins. In fact, whilst they often cause an elevated ALT, significant liver injury is exceedingly rare.

A more extensive list follows and an excellent online tool is at <http://www.livertox.nih.gov>.

Important causes of drug-induced liver injury

Hepatitis - immune mediated (allergic):

Nitrofurantoin, allopurinol, diclofenac, dihydralazine, germander, halothane, methyldopa, minocycline, nevirapine, phenytoin, propylthiouracil, trovafloxacin

Hepatitis - non-immune mediated (non-allergic):

Acarbose, amiodarone, bosentan, dantrolene, diclofenac, disulfiram, felbamate, flutamide, HAART, statins, isoniazid, ketoconazole, labetalol, leflunomide, methotrexate, nefazodone, nevirapine, nicotinic acid, paracetamol, pemoline, pyrazinamide, rifampicin, tacrine, tolcapone, troglitazone, sodium valproate, ximelagatran, zafirlukast, zileutin

Cholestatic - immune mediated (allergic):

ACE inhibitors, amitriptyline, amoxicillin/clavulanic acid, carbamazepine, chlorpromazine, cotrimoxazole, erythromycins, flucloxacillin, phenobarbital, sulfonamides, sulindac, tricyclic antidepressants

Cholestatic - non-immune mediated (non-allergic):

Anabolic steroids, azathioprine, cyclosporine, estrogens, oral contraceptives, terbinafine

Fibrosis

Methotrexate

Granulomas (allergic)

Allopurinol, amoxicillin/clavulanic acid, carbamazepine, hydralazine, methyldopa, penicillamine, phenylbutazone, phenytoin, procainamide, quinidine, sulfonamides

Microvesicular steatosis

NRTIs, sodium valproate

Neoplasms

Adenomas: anabolic steroids, oral contraceptives

Angiosarcoma: anabolic steroids

Cholangiocarcinoma: anabolic steroids

Hepatocellular cancer: danazol, anabolic steroids

Nodular regenerative hyperplasia

Azathioprine, thioguanine, cyclophosphamide, chlorambucil, busulfan, doxyrubicin, cytosine, arabinoside, bleomycin, carmustine, interleukin-2

Non-alcoholic steatohepatitis

Amiodarone, tamoxifen, antipsychotics (insulin resistance)

Vascular lesions

Budd–Chiari: oral contraceptives

Peiliosis hepatis : anabolic steroids, azathioprine, oral contraceptives

Perisinusoidal fibrosis: retinol (vitamin A), methotrexate

Veno-occlusive disease: busulfan, cyclophosphamide

Prognostication

In the case of hepatocellular injury, $\text{bili} > 2 \times \text{ULN}$ and $\text{ALT} > 3 \times$ is associated with mortality in the region of 10 to 15% (Hy's law). In this context, coagulopathy is also an ominous sign. Indications for liver transplantation are given above.

Cholestatic liver injury usually has a good prognosis after the offending drug is removed. Liver biopsy may be helpful to exclude vanishing bile duct syndrome (absence of bile ductules in more than 50% portal tracts), when the prognosis is poor. Overall, mortality is in the region of 4%.

Management

Cessation of the offending drug and monitoring progress are the cornerstones of management. Ursodeoxycholic acid often helps the symptoms of cholestasis and possibly improves outcome. There is no clinical evidence other than by anecdote that steroid therapy is beneficial. In the presence of inflammation on liver biopsy, steroid treatment could be considered.

Viral hepatitis

The hepatitis viruses that cause acute hepatitis are A, B and E. Hepatitis A and E are caught via the faeco-oral route, with hepatitis E having a zoonotic element (deer, pigs and probably other mammals). Hepatitis B is contracted by blood to blood and sexual contact. Other viruses such as CMV and EBV usually cause a transaminitis only. It is likely that there remain many uncharacterised viruses that cause hepatitis.

The mainstay of treatment of viral hepatitis is a swift diagnosis, monitoring for development of liver impairment/failure and supportive care. Rarely, acute liver failure develops that necessitates transplantation. Contact tracing is vital in the case of HBV. Vaccination of those at risk of either contracting hepatitis or having a poor clinical course with it should be undertaken. At the present time there are vaccinations available for HAV and HBV. HEV vaccination is under development.

Incubation periods

HAV: 4 weeks to symptoms, 2 weeks to viraemia, 6 weeks to peak anti-IgM, **infective from 2 weeks pre-symptoms to 4 weeks afterwards**

HBV: 1 to 4 months to symptoms, infectious several weeks before symptoms to clearance of the virus, anti-core IgM develops around the time of symptoms, HBsAg and HBV DNA several weeks before symptoms

HEV: similar to HAV

Natural history

HAV becomes more symptomatic and associated with more complications with increasing age. 75% of adults overall develop symptoms. Mortality is 0.3% overall and 1.8% in the over 50s. Chronic liver disease is a significant risk factor for a poor clinical course.

Acute HBV leads to jaundice in about 30% of adults. Overall 95% adults will clear the virus and have long term immunity, 5% will develop chronic hepatitis (with 15% developing

cirrhosis and 5% developing liver cancer or failure in the future) and < 0.5% will get acute liver failure.

As with HAV, increasingly poor outcomes are seen with increasing age in HEV. Male cirrhotics are particularly at risk, as are pregnant women – at least in the Asian subcontinent – with a reported 20% mortality in this group. More information will be available regarding the natural history of HEV as it becomes increasingly prevalent in the UK.

Autoimmune liver disease

This may present acutely. Specific management includes steroid therapy, which is discussed further below.

Pregnancy-related liver disease

Abnormalities of liver tests are common in pregnancy. Some liver diseases are more common or may present in pregnancy, examples being gallstones, primary biliary cirrhosis and Budd-Chiari Syndrome. Diseases unique to pregnancy include hyperemesis gravidarum, intrahepatic cholestasis of pregnancy, pre-eclampsia and acute fatty liver of pregnancy.

Hyperemesis gravidarum is included because mild elevations in bilirubin and aminotransferases are often associated. It occurs in the first trimester of pregnancy.

Intra-hepatic cholestasis of pregnancy is thought to be secondary to heightened sensitivity to the effects of oestrogen and sulphated progesterones on uptake and the secretion of bilirubin and bile salts, and presents with itch in the third trimester of pregnancy. The condition is diagnosed by the presence of elevated bile salts. It runs a relatively benign course for the mother, but the incidence of pre-term labour and foetal mortality are marginally increased and the pregnancy is not usually allowed to go beyond 37 weeks. Ursodeoxycholic acid (10 to 15 mg/kg) and cholestyramine (8 to 16 g daily) can be safely used therapeutically. The condition recurs in subsequent pregnancies in 60 to 70% of cases and may recur with oral contraceptives with high oestrogen content.

Pre-eclampsia is characterized by the triad of hypertension, proteinuria and oedema. It begins in the late second trimester and affects 7 to 10% of all pregnancies. It is associated with a spectrum of liver injury including the HELLP syndrome, hepatic infarction, haematomas and rupture. The pathogenesis is poorly understood. Endothelial dysfunction is important and leads to vasoconstriction and activation of the coagulation cascade. This causes ischaemic damage to multiple organs including the liver. There is increased mortality in mother and baby and appropriate management (immediate delivery of the baby) is lifesaving. Patients with severe pre-eclampsia have a 25 to 65% recurrence risk.

Acute fatty liver of pregnancy is a serious condition for both mother and foetus, in which hepatocytes are infiltrated by microvesicular fat, leading to profound liver dysfunction. Analogous conditions are Reye's syndrome and some forms of drug toxicity (such as sodium valproate and tetracycline). The condition occurs in approximately 1 in 15000 pregnancies, in the third trimester. Again, the management is delivery of the baby. Mortality and transplant risk both stand at about 2%. Recurrence rates in subsequent pregnancies are unknown, but subsequent pregnancies should be closely monitored.

Budd-Chiari syndrome

This is a condition in which thrombosis of the hepatic vein leads to liver congestion, damage and portal hypertension. The presentation may be acute, sub-acute or chronic. Cardinal features are abdominal pain, hepatomegaly, ascites, deranged liver tests and impaired synthetic function. Risk factors are coagulopathy (either primary or secondary) and local physical factors such as tumours causing venous stasis. Management is non-evidence based, but includes the conventional management of portal hypertension, anti-coagulation, TIPS shunts, angioplasty and if appropriate, transplantation. Hepatic encephalopathy is a poor prognostic sign and usually indicates the need for transplantation. There is usually an underlying coagulation defect which should be addressed: causes include deficiency of protein C, protein S, malignancy and most commonly polycythaemia vera (the latter may not be fully manifest for up to a decade and may not be apparent because of iron deficiency).

Malignant infiltration

Carcinomatous, lymphomatous and amyloid infiltration of the liver can lead to liver failure. Liver biopsy should be considered to guide chemotherapy and avoid inappropriate liver transplantation.

Wilson's disease

Wilson's disease, a chronic liver disorder, can present as an acute liver failure-type syndrome. In the absence of hepatic encephalopathy, patients respond occasionally to high dose D-penicillamine (1.5 g to 2 g daily in divided doses) or trientine (1.2 to 2.4 g daily in divided doses). However, liver transplantation is almost invariably indicated. **Prognostic scores are available to guide the need for liver transplantation.**

Ischaemia

Ischaemic hepatopathy is characterised by a significant elevation in transaminases after an episode of hypoperfusion. If effective circulation is restored transaminases will return to normal in 7 to 10 days. Jaundice may ensue, which takes somewhat longer to resolve. Rarely liver failure may occur. Management is supportive.

CHRONIC LIVER DISEASE

Hepatic decompensation is often a late manifestation of liver disease as the liver displays an extraordinary degree of redundancy, requiring only 20% of hepatocytes to function effectively. Hepatic decompensation can be acute on chronic, or chronic. Acute on chronic decompensation occurs due to a superimposed insult (often sepsis, drugs and toxins, metabolic derangement, constipation, a second liver insult such as alcoholic or viral hepatitis, development of an HCC or development of portal vein thrombosis due to sluggish or reverse flow in the portal vein). Chronic decompensation is directly related to the underlying hepatic pathology.

Decompensation equates with failure of the liver to perform normal physiological function. Normal physiological function can be divided into synthetic, metabolic, immunological and haemodynamic. Whenever a patient decompensates, one should identify and treat the cause of decompensation and run through these physiological parameters and address each one in turn. Of course, it is not usually possible to completely normalize these derangements and eventually with progressive liver disease, death or liver transplantation will ensue.

Each component of physiological function is now reviewed with accompanying treatments to be considered with decompensation.

Synthetic function is assessed by the production of albumin and clotting factors. There is no role for correction of these factors in the chronic setting. If patients present with bleeding complications there may be benefit in giving FFP +/- cryoprecipitate (+/- platelets). With sepsis – certainly with spontaneous bacterial peritonitis (SBP) – albumin support is beneficial.

Metabolic function is assessed by nutritional status, the presence of encephalopathy and serum bilirubin. Nutritional support is important both in the acute and chronic settings, and screening for and treatment of osteoporosis occurs in the chronic setting.

Poor immunological function usually manifests itself as infectious complications, which are very common in liver disease. Indeed, patients with decompensated chronic liver disease should be regarded as being immunosuppressed. The reasons for this are probably multifactorial. Firstly, the liver fails to clear antigen from the portal circulation. Secondly, nutritional and metabolic disturbances lead to immune cellular dysfunction, affecting all aspects of the immune system. Thirdly, the liver fails to produce elements of the humoral immune system such as complement and albumin. When a systemic infection is established, acute hepatic decompensation develops leading to a further decline in immunological function and worsening infection. This vicious cycle must be stopped early by having a low threshold for broad spectrum anti-microbial agents initially until a causative organism is cultured and sensitivities are known.

Haemodynamic decompensation is progressive and probably stepwise. According to the peripheral vasodilatation hypothesis, the important steps are cirrhosis, portal hypertension, splanchnic arterial vasodilatation, reduced effective arterial blood volume, activated vasoconstrictor systems and renal vasoconstriction. This leads to a low systemic vascular resistance, a decrease in central blood volume with increased splanchnic blood volume and activation of the renal angiotension system, sympathetic nervous system and ADH production. In the late stages this leads to an increase of total body sodium and water, with a disproportionate excess of water. The important clinical results are excessive salt and water retention leading to ascites and hyponatraemia, systemic hypotension and the hepatorenal

syndrome (HRS). **Varices are another complication of portal hypertension.** The management of these complications are discussed below.

CIRRHOSIS/CLD SURVEILLANCE

HCC surveillance

The following patients are at risk of HCC and should be surveyed with six monthly ultrasound and assay of serum AFP:

- All cirrhotic patients;
- HBV sAg positive male patients > 40 yrs old;
- HBV sAg positive female patients > 50 yrs old;
- **HBV sAg positive African patients**

If a liver lesion > 1 cm is detected at ultrasound and/or the AFP is significantly elevated, cross sectional imaging (usually MRI) should be requested and the imaging discussed at an MDT. With a normal AFP, lesions < 1 cm should be investigated with a further ultrasound scan in 3 months to ensure that the nodule is not increasing in size. With increasing size, cross sectional imaging is required. If the size is stable, reversion to six monthly scanning is a reasonable approach. A guide to the management of HCC is given [below](#).

Variceal surveillance

All patients with cirrhosis should be entered into a variceal screening programme. Management algorithms after index endoscopy follow.

Findings at index endoscopy	Management
No varices and Child A cirrhosis	3 year f/u endoscopy
No varices and Child B/C cirrhosis	1 year f/u endoscopy
Small, low risk* varices	2 year f/u endoscopy
Small, high risk* varices	Consider beta blockade
Medium/large varices without high risk features*	Consider beta blockers or endoscopic variceal band ligation (EVL) if intolerant or have tense ascites
Medium/large varices with high risk features	Beta blockers or EVL

* High risk varices are those with stigmata of bleeding risk (red wales, "nipples" and cherry red spots) or any varix in a patient with Child B/C cirrhosis.

If a banding programme is embarked upon, EVL should occur every 2 to 3 weeks until eradication and every 6 to 12 months thereafter. The technique is summarised as follows:

Endoscopic variceal band ligation

1. Do full endoscopy first noting PHG, gastric varices and their site, and position of the GOJ;
2. Apply band at the GOJ and then spiral up for 5 cms. Ensure 'red-out' before firing band.
3. Hold suction on for a few secs after band fired;
4. Start PPI and sucralfate 1g qds;
5. Fluids and soft diet until mane.

There is no consensus on primary prophylaxis of gastric varices and each case should be considered on an individual basis.

Osteoporosis surveillance

For patients with cirrhosis, PBC, PSC or long term steroid use, calcium and vitamin D supplementation should be considered and DEXA scanning at 3 to 5 yearly intervals to assess for osteopaenia/osteoporosis. With a T score < -2.5, other secondary causes should be investigated for with TSH, Ca and Pi and oestradiol/FSH/LH. Hypogonadal females should be treated with HRT and eugonadal/male patients given a bisphosphonate. DEXA reassessment should occur at 3 years in the context of osteopaenia and 5 years if normal (DISCUSS).

Immunization protocols

In the absence of prior exposure, patients with chronic HCV of any stage or cirrhosis of any aetiology should be immunized against HAV and HBV. Patients with chronic HBV and no prior exposure should be vaccinated against HAV. Pneumococcal and annual influenza vaccinations are recommended for patients with cirrhosis.

COMPLICATIONS

Encephalopathy

Diagnosis of encephalopathy is not always straightforward. It involves a combination of clinical assessment, serum ammonia testing and occasionally EEG assessment (although neither of these tests are sensitive or specific).

Encephalopathy is graded as follows:

Grade 1 - Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction; reversal of the sleep wake cycle; slight flap

Grade 2 - Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behaviour; liver flap

Grade 3 - Somnolence to semi-stupor, but responsive to verbal stimuli; confusion; gross disorientation

Grade 4 - Coma (unresponsive to verbal or noxious stimuli)

Acute encephalopathy

Management of acute encephalopathy is crude and involves:

1. Ensuring a regular bowel habit with lactulose and enemas;
2. Perfusing the liver by providing an optimal intravascular volume;
3. Avoiding sedative drugs that are metabolised by the liver such as opiates and benzodiazepines;
4. Identifying and treating the cause of decompensation, with common causes being sepsis, metabolic derangement, constipation, dehydration, GI haemorrhage, sedatives, alcohol and PV/HV occlusion. Clinical assessment, a full set of blood tests, a septic screen (including ascitic tap in the presence of ascites) and a liver ultrasound with Doppler studies is an appropriate screen.

Chronic encephalopathy

Chronic encephalopathy is managed initially with lactulose +/- enemas. If these measures are ineffective or a patient does not tolerate them, rifaximin 550 mg bd should be considered. The latter has been demonstrated to reduce hospital admissions over a six month period in

patients with chronic encephalopathy. Chronic encephalopathy is a variant indication for liver transplantation.

Malnutrition

Decompensated cirrhosis is almost invariably associated with malnutrition. In the outpatient setting, patients with Child B/C cirrhosis should be encouraged to eat little and often. Nutritional supplements are frequently required and early referral to the dietetic team should be considered.

In the inpatient setting, decompensation is often associated with severe malnutrition and a low threshold for nutritional supplementation should be adopted. Nasogastric feeding is often required.

Variceal haemorrhage

The following management approach for variceal haemorrhage should be adopted:

Resuscitation and correction of anaemia, thrombocytopenia and coagulopathy (vitamin K +/- FFP). Aim for Hb > 8, Plts > 50 and INR < 1.5.

At least 48 hours and up to 5 days of empirical broad spectrum anti-microbials – tazocin 4.5 g iv tds

Splanchnic vasoconstriction for 5 days. This should only be used before endoscopy if there is a strong clinical suspicion of variceal haemorrhage **after discussion with the on call consultant**. Terlipressin 2 mg iv qds in the absence of contraindication (IHD, PVD); octreotide 50 µg bolus and 50 µg/hr (500 µg in 50 ml normal saline at 5ml/hr) otherwise.

Endoscopy (**ideally within 4 hours**) to confirm the diagnosis and treat the varices ([see below](#));

Sengstaken tube insertion if the bleeding is uncontrollable with the above measures ([see below](#));

Referral to a tertiary unit for rescue transjugular intrahepatic portosystemic shunt (TIPS shunt) or surgical shunt if bleeding cannot be controlled. For bleeding gastric varices due to splenic vein thrombosis, splenectomy should be considered.

As for encephalopathy management, risk factors for variceal haemorrhage should be screened for and treated, the most important being mesenteric vein thrombosis, HCC and sepsis. Portal vein patency is required for TIPS shunt placement.

Mortality after a herald variceal bleed stands at 15 to 20% at six weeks.

Endoscopic management

EVL is the preferred management strategy for the treatment of bleeding oesophageal and cardiac varices. Failing this, injection sclerotherapy is often effective.

Non-cardiac gastric varices should initially be managed with tissue adhesives (e.g. histoacryl glue).

Variceal haemorrhage is often accompanied by hepatic encephalopathy and frequently occurs in patients who are dependent on alcohol. This combination may make sedation problematic and a low threshold for anaesthetic input should be adopted. Given the risk of aspiration, pre-endoscopy ventilation should be considered for patients with grade 2 encephalopathy and above. **Any unstable patient should be endoscoped in theatre or ITU.**

Endoscopic variceal band ligation

The technique for this is given [above](#).

Following successful therapy, EVL should be repeated every **2 to 3 weeks** until eradication and every 6 to 12 months thereafter. Beta blockade **with propranolol** in addition to EVL is indicated for secondary prevention.

Injection sclerotherapy

Do full endoscopy first noting PHG, gastric varices and their site, and position of the GOJ.

Inject ethanolamine intravariceal in aliquots of 0.5 mls up to a maximum of 2 mls per varix

Injections spiral up oesophagus for 5 cms or very rarely if seen to be bleeding higher then up to that point.

Start PPI and sucralfate 1 g qds

Repeat OGD at **1 to 2 weeks** and consider further sclerotherapy

Histoacryl glue injection

Protective goggles should be worn.

1. Prime injection needle with 1 ml lipiodol
2. When in position, mix 1 ml histoacryl with 1 ml lipiodol in 2 ml syringe
3. Inject varix with glue/lipiodol mix and chase with injection needle volume + 0.5 ml saline or lipiodol
4. Repeat OGD 1 week and repeat procedure until varix is firm

Insertion of Sengstaken Tube

This should be performed for bleeding oesophageal, oesophago-gastric or fundal gastric varices if endoscopic therapy is unsuccessful. A tube should only be passed after sedation and endotracheal intubation. A Sengstaken tube stabilises bleeding before definitive endoscopic management or TIPS shunt insertion. It should not remain in place for more than 24 hours. Insertion technique follows.

1. Sengstaken tubes should be kept in the fridge to maintain stiffness
2. Once removed from the fridge, the gastric and oesophageal balloons should be suctioned and clamped
3. The tube should be inserted into the oesophagus via the mouth and passed to **70 cm**

4. 250 mls (Simon says 400 mls – what do you reckon Martin?) saline should be injected into the gastric balloon, the gastric balloon port clamped and the tube pulled back and kept under tension by taping the tube to the cheek
5. The gastric and oesophageal aspiration ports should be aspirated then remain on free drainage

Never inflate the oesophageal balloon as this may lead to oesophageal necrosis.

Ascites

When a patient with chronic liver disease presents with ascites/worsening ascites, a fluid sample should always be sent. The procedure for this follows:

Ascitic tap procedure

1. Ensure that the patient has ascites – request/perform an ultrasound scan if there is any doubt and ask for a spot to be marked if the patient is having a departmental scan.
2. If a spot has not been marked, choose a site two finger breadths above and medial to superior anterior ileac spine, thus selecting a site relatively devoid of subcutaneous fat and away from the inferior epigastric arteries. The left side may be preferable as it avoids the caecum. Do not place a needle through an operative (for example appendicectomy) scar.
3. With appropriate aseptic technique, clean the area, infiltrate lignocaine (not mandatory) and take at least 20 mls fluid, noting its colour and translucency.
4. Send sample for total protein, albumin, cytology and microbiology (cell count, Gram stain and culture). Universal containers are used for biochemical and cytological specimens. The microbiology department should receive universal container and blood culture bottle samples.

Management of ascites related to portal hypertension

Strategies include diuresis, salt restriction and paracentesis. Diuresis and salt restriction address salt overload. Diuretics should always be used with extremely close monitoring of renal function. They should rarely be used in the acute setting, as fluid balance is often on a knife-edge in this context and diuretics may precipitate life-threatening renal failure. With progressive liver disease, ascites becomes refractory to diuresis and fluid restriction. The presence of ascites is a poor prognostic sign, carrying a 2-year survival of just 50%. When tense, it is managed by paracentesis and albumin replacement pending a definitive management plan (transplantation or a TIPS shunt) where appropriate.

When the ascitic total protein is < 15 g/L, if patients have ascites as part of Child Pugh C liver disease and/or after an episode of SBP, SBP prophylaxis has been shown to reduce mortality. Current first line is ciprofloxacin 500 mg od; second line **septrin 960 mg od**.

Diuretic prescribing protocol

A reasonable strategy for most patients follows:

1. Spironolactone 100 mg daily;
2. If unresponsive, add in frusemide 40 mg daily;
3. If unresponsive, double the dose of both and gradually increase until symptoms resolve, a complication occurs (often renal impairment/hypovolaemia) or a maximum of 200 mg bd spironolactone/80 mg bd frusemide is reached.
4. At each dose change, kidney tests should be taken within the first week and tests monitored 4 to 8 weekly thereafter. **Hyponatraemia (Na < 130 mmol/L) or renal impairment (20% increase in creatinine or creatinine > 120 umol/L) necessitate consideration of cessation or reduction of diuretic therapy.** Urinary sodium assessment can be helpful as failure of diuretics to produce a naturesis makes their use futile.

Ascitic drainage procedure

Paracentesis should be reserved for patients with large volume ascites. Unless the ascites is loculated, ultrasound guided drain placement is not usually required.

1. If a spot has not been marked, choose a site two finger breadths above and medial to superior anterior ileac spine, thus selecting a site relatively devoid of subcutaneous fat and away from the inferior epigastric arteries. The left side may be preferable as it avoids the caecum. Do not place a needle through an operative (for example appendicectomy) scar.
2. With appropriate aseptic technique, clean the area, infiltrate lignocaine and ensure that your position is correct by aspirating fluid with the anaesthetic needle.
3. Site the drain and take a sample of fluid for cell count and Gram stain from it.
4. Place the drain on free drainage and leave in for 6 hours.
5. Replace every 2.5 L ascites with 100 mls 20% human albumin starting at time 0.

Sepsis/spontaneous bacterial peritonitis

A common complication of ascites is spontaneous bacterial peritonitis (SBP), when ascites becomes infected by enteric organisms, presumably due to bacterial transit from the bowel into a rich ascitic fluid culture medium at an optimal temperature in an immunocompromised host. The diagnosis should always be entertained when a patient with ascites becomes acutely unwell.

An ascitic fluid sample should be sent for microscopy and culture in blood culture bottles. A white cell count > 500/ml or a neutrophil count of > 250/ml is diagnostic and necessitates the use of broad-spectrum antibiotics (e.g. tazocin 4.5 g tds **or cefotaxime 2 g bd**) before the sensitivities of the causative organism are known. **There is also evidence for a reduction in mortality and development of type 1 HRS** by giving 1.5 g/kg human albumin at the time of diagnosis, followed by 1 g/kg on day 3, the efficacy of which may in part be due to the antibiotic effects of albumin.

If a patient's clinical condition has returned to baseline after a 5-day course of antibiotics, there is no evidence that a second tap is required before transferring patients onto ciprofloxacin prophylaxis prior to discharge.

Secondary bacterial peritonitis should be considered when multiple organisms are grown or when patients fail to respond to a 5-day course of therapy. When treatment failure occurs, a second tap may help to identify resistant organisms **and a CT scan considered**.

SBP is associated with poor outcome – a mortality of 40% at one year.

Renal impairment/fluid management

The most common causes of renal failure in patients with cirrhosis are hypovolaemia and sepsis. In any context, these should be considered and treated first before a diagnosis of hepatorenal syndrome can be entertained.

Hepatorenal syndrome

Type 1 HRS is characterized by rapidly progressive renal impairment, most commonly precipitated by SBP. Without treatment it has a very poor prognosis with a median survival of less than two weeks, with almost 100% mortality at 10 weeks. Type 2 HRS is characterized by a slowly progressive reduction in glomerular filtration rate (GFR). These patients often have diuretic-resistant ascites and have a median survival of 3 to 6 months.

HRS is a diagnostic label that is commonly used inappropriately. It is a diagnosis of exclusion, with the key being reduced GFR in the absence of other causes of renal failure in a patient with decompensated cirrhosis. The International Ascites Club has produced the following guidelines to help make the diagnosis.

Criteria for the diagnosis of HRS

1. Presence of cirrhosis and ascites
2. Serum creatinine > 133 $\mu\text{mol/L}$
3. No improvement of serum creatinine (decrease to < 133 $\mu\text{mol/L}$) after at least 48 hours of diuretic withdrawal and volume expansion with albumin (recommended dose: 1 g/kg per day up to a maximum of 100 g of albumin/day)
4. Absence of shock
5. No current or recent treatment with nephrotoxic drugs
6. Absence of parenchymal kidney disease as indicated by proteinuria > 500 mg/day, microhematuria (> 50 RBCs/high power field), and/or abnormal renal ultrasound scanning

Definition of type-1 HRS:

Type-1 HRS is characterized by a rapidly progressive renal failure defined by a doubling of the initial serum creatinine to a level greater than 220 $\mu\text{mol/L}$ in less than 2 weeks.

Although it may appear spontaneously, type-1 HRS often develops with a precipitating event, particularly SBP.

Type-1 HRS occurs in the setting of an acute deterioration of circulatory function (arterial hypotension and activation of the endogenous vasoconstrictor systems) and is frequently associated to rapid impairment in liver function and encephalopathy. **Once diagnosed, treatment is with terlipressin (0.5 mg qds with daily titration upwards depending on response) and intravenous 20% HAS 100 mls bd.**

Definition of type-2 hepatorenal syndrome:

Type-2 HRS is characterized by a moderate renal failure (serum $> 133 \mu\text{mol/l}$), which follows a steady or slowly progressive course. It appears spontaneously in most cases.

Type-2 HRS is frequently associated with refractory ascites. Survival of patients with type-2 HRS is shorter than that of patients with ascites without renal failure.

Choice of intravenous fluid in patients with decompensated cirrhosis

The choice of fluid in patients with chronic liver failure is a matter of constant debate. In the acutely ill patient, albumin is probably the best choice (combination of 4.5% and 20%). It has beneficial oncotic properties, antibiotic properties and is a free radical scavenger and transporter. It also avoids additional salt and water loading. 5% dextrose is likely to be the best maintenance fluid in a less acute setting given the salt overload of chronic liver failure.

Hyponatraemia

Hyponatraemia is a worrying development in patients with chronic liver disease and, in the absence of a reversible cause (**such as adrenal insufficiency**), is associated with death in several studies. For moderate hyponatraemia ($\text{Na} > 125$), avoidance of diuretics where possible is effective. For more severe hyponatraemia, initial management involves stopping diuretics and increasing intravascular volume and thus free water clearance with albumin. Failure of this approach, or when hyponatraemia is unrelated to diuresis, necessitates fluid restriction. This should start at 1.5 L and progress to 750 mL if required.

PROGNOSTICATION

The following figures provide important prognostic information for patients with cirrhosis. They are taken from D'Amico et al J Hep 2006.

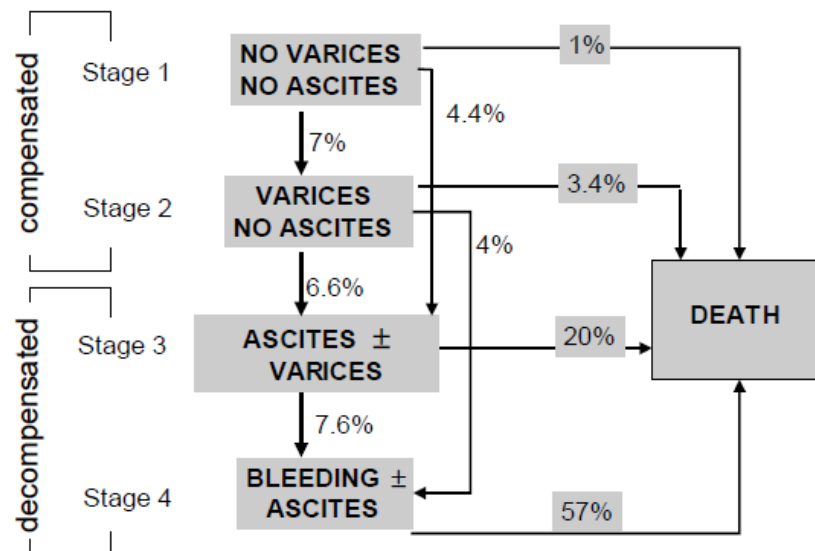
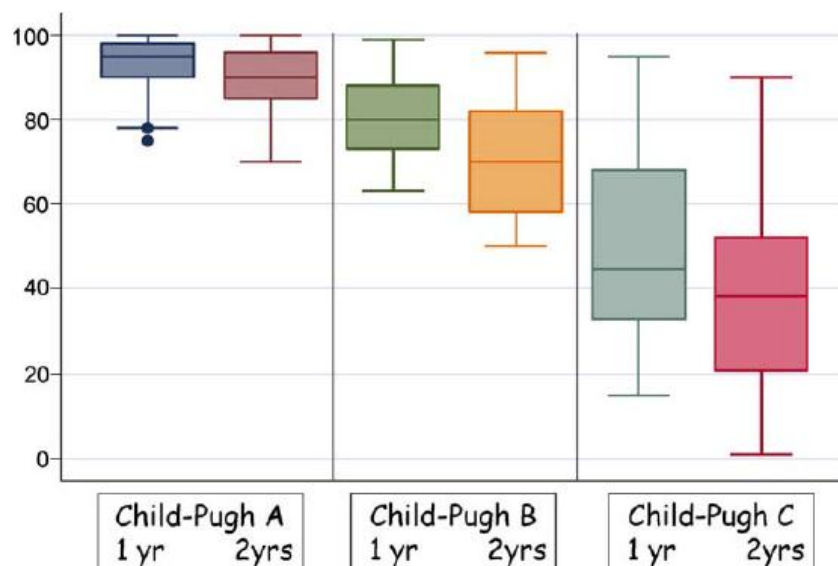


Fig. 4. Clinical course of cirrhosis: 1-year outcome probabilities according to clinical stages.



Child-Pugh Calculation

Measure	1 point	2 points	3 points
Bilirubin ($\mu\text{mol/l}$)	<34	34-50	>50
Albumin (g/l)	>35	28-35	<28
INR	<1.7	1.71-2.30	> 2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade 1-2/ suppressed with Rx	Grade 3-4/ Refractory to Rx

Child Pugh class A 5-6 points; B 7-9; C 10-15

Model of End-stage Liver Disease Score (MELD)

MELD is calculated as follows:

$$\text{MELD} = 3.78[\text{Ln serum bilirubin (mg/dL)}] + 11.2[\text{Ln INR}] + 9.57[\text{Ln serum creatinine (mg/dL)}] + 6.43$$

Interpretation

MELD score	3-month mortality
≥ 40	71%
30 to 40	53%
20 to 30	20%
10 to 20	6%
< 10	2%

UK End-stage Liver Disease Score (UKELD)

See [below](#).

Miscellaneous points

- The development of ascites is associated with 50% mortality at 5 years
- SBP carries a 40% survival at 1 year
- A variceal haemorrhage has 15% to 20% mortality at 6 weeks
- Without treatment, median survival of patients with type 1 HRS is less than 2 weeks, and most patients (> 90%) die within 10 weeks after the onset of renal failure
- Patients with type 2 HRS are often diuretic-resistant with a median survival of 3-6 months

LIVER TRANSPLANTATION FOR CHRONIC LIVER DISEASE

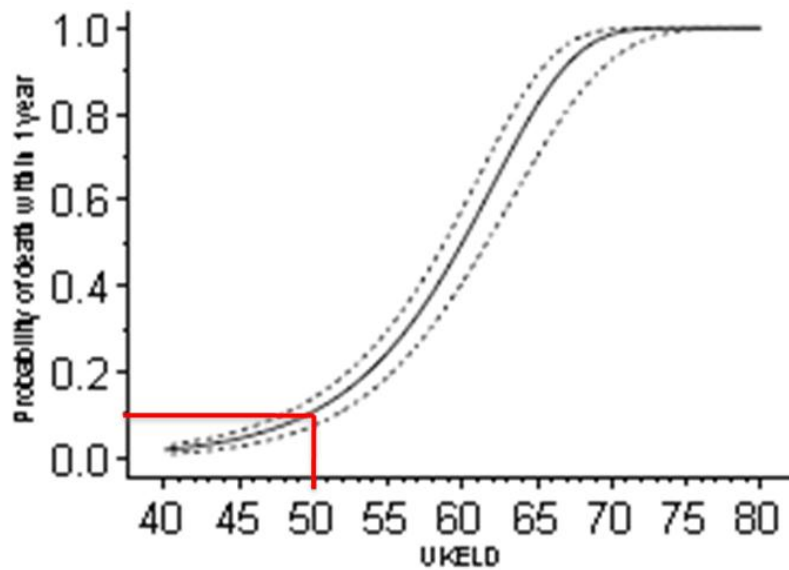
Indications

Indications fall into three categories:

Decompensated cirrhosis

The principle of selecting patients with decompensated cirrhosis is that a patient has a better survival with than without a liver graft. In the UK, this is ascertained by calculating the UK End-stage Liver Disease Score (UKELD). To calculate this, follow [this link](#) to an Excel spreadsheet from the UK Blood and Transplant website. Required blood test parameters are Na, cr, bili and INR.

With the following graph, mortality at one year can be calculated for patients with cirrhosis. Given that mortality at one year after transplantation is 9%, a UKELD cut-off of 49 is used as a criterion for listing patients with decompensated cirrhosis.



Hepatocellular

carcinoma

This indication is covered in the section on liver lesions.

Variant indications

These are for patients with decompensated cirrhosis with a UKELD < 49, who may benefit symptomatically or prognostically from transplantation.

- Diuretic resistant ascites: ascites non-responsive to TIPS shunt or when TIPS shunt is contraindicated
- Hepatopulmonary syndrome: arterial pO₂ < 7.8 kPa, A-a gradient < 20 mmHg, shunt fraction > 8%
- Chronic hepatic encephalopathy: confirmed on EEG with at least two admissions in 1 year due to exacerbations of encephalopathy that has not been manageable by standard therapy
- Persistent and intractable pruritis: in the context of cholestatic liver disease and refractory to cholestyramine, ursodeoxycholic acid, rifampicin, naltrexone and after exclusion of psychiatric morbidity contributing to the itch
- Familial amyloidosis
- Primary hyperlipidaemias
- Polycystic liver disease: intractable symptoms or portal hypertensive complications

Other considerations

Operative suitability

Anaesthetic and surgical assessments will be made in the transplant centre. To do this, an echocardiogram, lung function tests and a CT scan are required.

Prognosis with a graft

An arbitrary survival estimate of > 50% at 5 years from transplantation is required to list a patient for transplantation. This is not an exact science, but involves an assessment of co-morbidities by appropriate experts.

CAUSES OF CHRONIC LIVER DISEASE

In the UK, the three most common causes of chronic liver disease are alcohol-related (ALD), non-alcohol related steatohepatitis (NASH) and hepatitis C (HCV). For diagnostic purposes, it is important for all patients with chronic liver disease to have a complete liver screen. Many patients have more than one cause of liver damage and many carry an incorrect label, which could compromise active treatment and eligibility for liver transplantation. The most common scenario is the under-investigated patient who consumes alcohol to excess. A screening panel is available on ICE.

A liver panel to screen for chronic liver disease

Alcohol-related	Record of units consumed per week - with a collateral history, MCV, IgA level
Chronic viral hepatitis	HBsAg (if positive, HBeAg/HBeAb and HBV DNA), anti-HCV antibody (if positive HCV RNA and genotype)
PBC	Anti-mitochondrial antibody, anti-PDH if AMA positive, IgM level
Autoimmune hepatitis	Anti-nuclear, anti-smooth muscle and anti-liver/kidney microsome antibody, IgG level
Haemochromatosis	Ferritin/transferrin saturation and if abnormal C282Y and H63D mutation analysis
Wilson's	Caeruloplasmin and if abnormal a slit lamp assessment, serum copper, urinary copper pre- and post-D-penicillamine and liver copper
α -1 antitrypsin deficiency	α -1 antitrypsin level and if low phenotype
PSC	pANCA and consider MRCP and liver biopsy
Other	Ultrasound scan to assess for portal hypertension, Budd-Chiari syndrome, liver lesions and infiltrative disorders

ALCOHOL RELATED LIVER DISEASE

Alcoholic liver disease (ALD) is the most common liver disease encountered in clinical practice. Alcohol abuse is a major public health problem in the UK with far-reaching medical, social and psychological effects on the individual and others around them. Although it is well known that the amount of alcohol consumed is related to the development of ALD, there is large variability in susceptibility. Research into this area is sparse perhaps because of the

stigma attached to alcohol. Of the few risk factors that are known, being overweight, female and having co-existent HCV are important. **Genetic factors are clearly also important, but these are not yet characterised.** The diagnosis of ALD relies on a compatible history, compatible blood results and an exclusion of other causes of liver disease. Any diagnostic doubt necessitates liver biopsy.

Alcohol can lead to four hepatic entities: fatty liver, alcoholic hepatitis and chronic liver disease with cirrhosis, sometimes with superimposed HCC. The fatty liver can be an acute phenomenon, after a drinking binge, or can persist chronically with ongoing alcoholic insult, leading to chronic liver disease.

General treatments for chronic liver disease are discussed above. The most important specific treatment for ALD is abstinence, which is absolutely vital and achievable. 30% of patients who enter a liver service with chronic ALD stop consuming alcohol and can experience marked improvement in liver function for up to 2 years after stopping. Support is the most important component and the Norwich Recovery Partnership (NRP) and other local support groups provide an excellent service. Some efficacy may be achieved with acamprosate or baclofen.

Alcoholic hepatitis

Alcoholic hepatitis presents with jaundice and relatively normal liver enzymes. It occurs on a background of alcohol-related liver damage. It is characterised histologically by a neutrophil-rich infiltrate, **steatohepatitis and cholestasis**. The clinical syndrome can be mistaken easily for sepsis and encompasses weakness, anorexia, confusion, abdominal pain, jaundice, elevated inflammatory markers, renal impairment and variable features of hepatic decompensation and chronic underlying liver disease. A biopsy is often helpful in confirming the diagnosis.

Prognosis is determined by the Maddrey Discriminant Function (DF), defined as serum total bilirubin (in $\mu\text{mol/L}$)/17 + 4.6 x (patient prothrombin time in seconds – control prothrombin time). Untreated patients with a DF > 32 have a 30-day mortality rate of 33% and a six-month mortality rate of 50%. Patients with a DF < 32 have a > 90% chance of surviving six months.

The mainstay of treatment for alcoholic hepatitis is supportive with fluid resuscitation, careful use/avoidance of diuretics, avoidance of both alcohol and an alcohol withdrawal syndrome, nutritional support and vitamin replacement. Complications such as renal failure and sepsis should be addressed appropriately. Specific treatments are with prednisolone or pentoxiphylline.

Prednisolone 40 mg daily is beneficial in terms of short-term mortality, but should be used with caution and only once sepsis has been excluded/controlled. It should be prescribed for one month then stopped. If there is no reduction in bilirubin after one week of therapy, it should be stopped as benefits are probably outweighed by risks.

Pentoxiphylline 400 mg tds is sometimes used in preference to prednisolone, but only in the absence of renal impairment as the main beneficial effect seems to be preventing the development of HRS.

VIRAL HEPATITIS

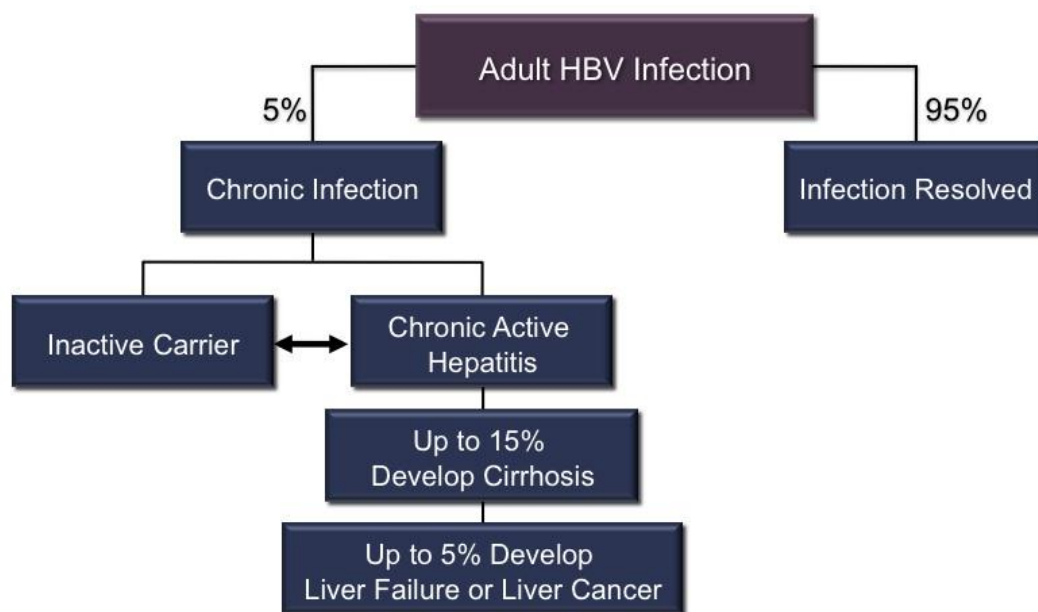
Hepatitis B

HBV is contracted either sexually or by blood to blood transmission. The combined prevalence of HBV and HCV is just over 2%.

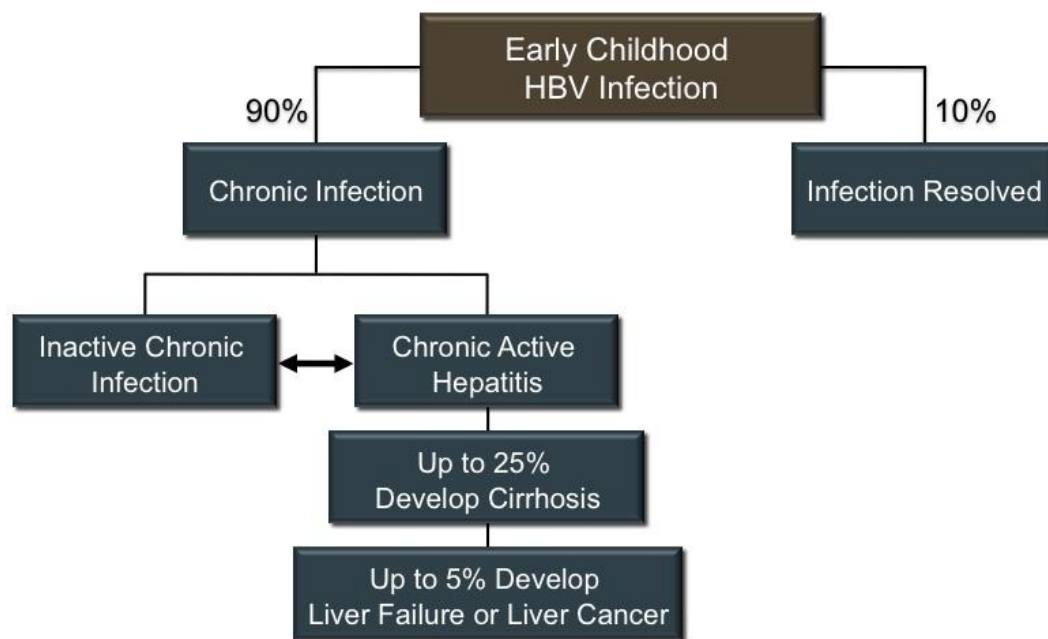
Natural history of HBV

More than 95% of immune competent patients clear HBV **following infection** (loss of HBsAg with development of anti-HBs and anti-HBc), unless the disease is contracted in childhood, when 10% or less clear HBV. The patients who do not clear the virus develop a protracted relapsing/remitting chronic hepatitis. Untreated, up to 15% of adults with chronic HBV (CHB) develop cirrhosis and of those up to 1/3 develop HCC or decompensated cirrhosis; up to 25% of children with CHB eventually become cirrhotic and up to 20% of those develop HCC or decompensated cirrhosis.

Adult HBV



Childhood HBV



Natural history of CHB

Patients with CHB go through the following disease states. Characterising where patients fall within these groupings guides management.

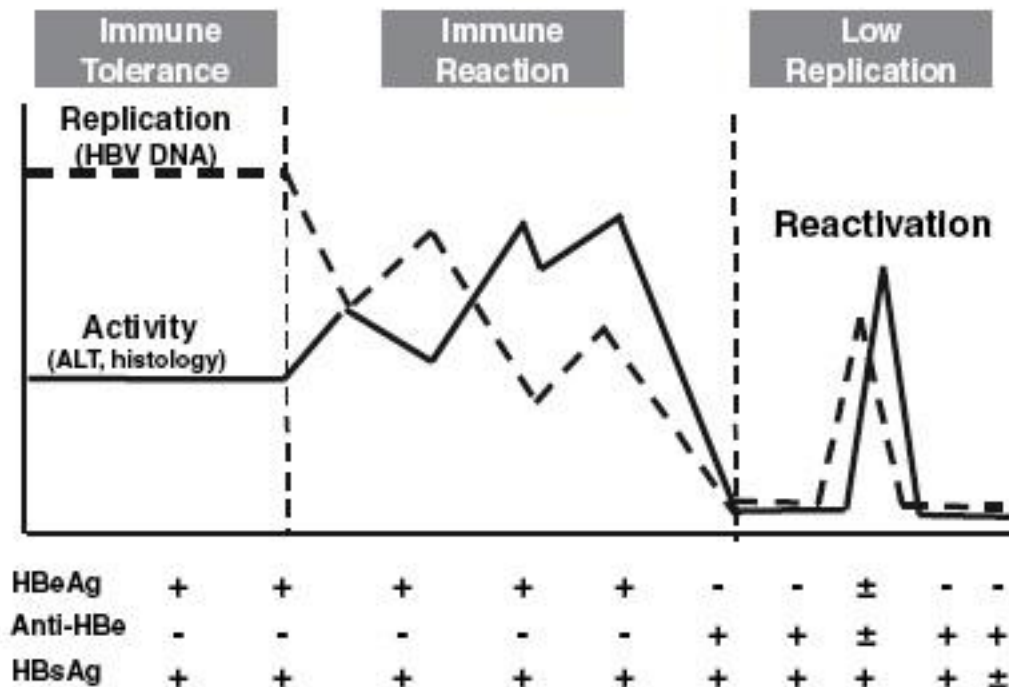
Immune tolerance. Viral replication is undetected by the immune system. Patients are highly infectious, but do not develop liver damage. This usually lasts until the age of between 20 and 40 for childhood CHB, but is not usually prolonged for adults who develop CHB.

Immune reactive. During this phase, which lasts for between several weeks and several years, the immune system becomes active as detected by the development of anti-HBe. Significant liver damage may occur and close monitoring of patients with *immune tolerant* disease should occur by means of 3 monthly ALT and 6 monthly HBV DNA levels to detect entry into the *immune reactive* phase. An increased ALT > 2 x ULN (normal being 19 for females and 30 for males) or HBV DNA > 2000 IU/ml usually indicates liver biopsy with liver damage necessitating treatment with either pegylated IFN or oral anti-viral agents. The aim of IFN treatment is to expedite eAg seroconversion, with success favoured by a low ALT, significant interface hepatitis, female gender and lower HBV DNA levels. IFN treatment is finite (usually one year) whereas oral anti-virals (current first line being tenofovir 245 mg daily) may be life long.

Low replication/inactive carrier state. This is sometimes referred to as low risk CHB. However, immune escape may occur in this phase and at least six monthly ALT and HBV DNA assessments should be made with flares of either necessitating further assessment by means of a biopsy. Interval elastography may be useful in monitoring for development of fibrosis in this phase, with an elevated score being investigated with liver biopsy. This approach allows the detection of eAg negative CHB (reactivation) that is usually treated with oral anti-viral agents.

HBsAg negative phase. This is characterised by development of anti-HBsAg and loss of HBsAg. The disease has 'burnt out'. *What follow up do you think that we should offer HBsAg neg patients?*

Representation of the natural history of HBV



Common clinical issues

Decision to biopsy. It is reasonable to have a low threshold for liver biopsy for patients with CHB. If the ALT is elevated > 2X normal in the presumed immune tolerant state, or the ALT is elevated > 2X normal and/or HBV DNA > 2000 IU/ml in the eAg neg state and the patient has not been biopsied before, then discuss biopsy, which would be performed to ascertain whether there is significant liver disease requiring treatment. In practice, an ALT above the normal range would be argued by some to be > 2X upper limit of normal.

Follow up interval. *Immune tolerant disease:* 3 monthly blood tests (LFT most important) and 6 monthly clinic/blood test visits. *Immune reactive disease* will depend on management strategy, but should be documented at the head of each clinic letter. *Low replication/inactive carrier state:* 3 monthly blood tests (LFT and HBV DNA) and 6 monthly clinic/blood test visits for one year. 6 monthly blood tests and annual clinic/blood test visits unless HCC surveillance is required. HBsAg/anti-HBs every two years. Patients on *oral anti-viral therapy:* 3 monthly clinic/blood test (LFT, UE, HBV DNA 6 monthly when established)/prescription visits.

Use of elastography. Liver biopsy gives information regarding grade and stage of liver disease whereas elastography informs stage only. *Information regarding stage alone is sometimes useful – for example when following up patients with eAg negative disease and normal liver tests, or for patients with bland biopsies but continually abnormal ALT or high viral load.*

HCC surveillance. This should be offered to cirrhotic patients, male patients > 40 yrs and female patients > 50 yrs with childhood acquisition of CHB, **African patients** and patients with CHB and a family history of HCC. Surveillance should be by six monthly ultrasound and AFP measurements.

Immunization. Patients with CHB who contract HAV are at risk of following a fulminant course. Vaccination of anti-HAV IgG negative patients should therefore be undertaken.

Screening and immunization of partners and children should be ensured. Immunization of newborns should be arranged by the obstetricians/paediatricians and there is a protocol on the intranet (CA2017). Essentially, babies to eAg pos mothers receive HBIG and active immunization, whereas those to eAg **neg** mothers receive a course of active immunization only, unless the HBV DNA is > 10^6 IU/mL, which should be rare given the pregnancy advice documented below.

Oral antiviral agents. Current first line is tenofovir 245 mg daily (with normal eGFR). Once the decision to instigate oral therapy is made, patients should be counselled concerning side effects (usually asymptomatic, but the more common ones are GI disturbance and musculoskeletal pain; worrying ones are renal failure, lactic acidosis and pancreatitis). Kidney tests should be taken pre-treatment and at two weeks. Follow up at 4 weeks (UE) then 3 monthly UE and LFT thereafter with HBV DNA levels until suppression has been achieved **with UE , LFT and HBV DNA 6 monthly thereafter**. Use of other anti-viral agents should be discussed on a case by case basis.

Pregnancy. Interferon therapy is contra-indicated with pregnancy. If a patient's liver disease is significant enough to require oral anti-viral agents then they should be prescribed as the benefits outweigh the risks. No cases of teratogenicity secondary to tenofovir have been reported. Significant liver disease is associated with miscarriage. Suppressing HBV DNA reduces the risk of vertical transmission. Indeed, pregnant women with CHB and an HBV DNA > 10^6 IU/ml carry a vertical transmission risk of about 10% despite passive and active vaccination of newborn infants and should therefore have their viral DNA temporarily suppressed pre-delivery. Tenofovir is a reasonable choice for this. See immunization of newborns above. Breastfeeding is not contra-indicated.

Immune suppression. HBsAg positive patients should have HBV DNA suppressed before receiving immunosuppressive therapy or chemotherapy. HbsAg neg, anti-HBc pos patients should have an HBV DNA performed and if this is positive they should be treated. If HBV DNA is negative in this context then 3-monthly monitoring of ALT and HBV DNA should be performed and treatment instigated if HBV DNA becomes positive. The exception to this is when rituximab and/or combined regimens for haematological malignancies are used in which case oral anti-virals should be considered. Tenofovir is a reasonable choice in all of these contexts and should be given until 12 months after cessation of immune suppression. Pre-emptive vaccination for HBV is recommended pre-immune suppression for those who have not been exposed to HBV.

Healthcare workers. Guidelines for vaccination of non-infected healthcare workers and healthcare workers with CHB are given on the intranet (CA2070).

Hepatitis D

HDV is a defective virus that requires the presence of HBV to replicate. If HDV is contracted with HBV then the course of the virus follows that of HBV (co-infection). If HDV is contracted

on top of CHB then it follows an aggressive course (super infection). HDV is treated with pegylated IFN for one year, but clearance only occurs in about 25% patients.

Hepatitis C

HCV is contracted by blood to blood contact. Sexual transmission is reported but is rare and probably by anal intercourse. Between 5 and 10% of patients develop an acute hepatitis, usually unnoticed, about six weeks from HCV exposure. Around 20% remain HCV RNA negative after exposure and are considered to have recovered, but there is no clear serological profile to indicate acquired immunity. 80% evolve to a chronic hepatitis, which is progressive rather than relapsing and remitting. 20% of the patients with chronic HCV develop cirrhosis within 1 to 3 decades. Risk factors for rapid progression are smoking, older age at the time of infection, high BMI, concomitant alcohol abuse and being male. Cirrhotic patients have a 25% risk of death in 5 to 10 years. The annual risk of HCC in HCV with cirrhosis is 3 to 5% and is rare in the absence of cirrhosis.

The presence of serum HCV RNA confirms chronic HCV infection. Staging of HCV is either performed with a combination of ultrasound, elastography and/or biopsy.

Treatment of genotypes 2 to 6 is by a combination of pegylated IFN and ribavirin. For genotype 1 the addition of a protease inhibitor (telaprevir or beceprevir) is recommended. Treatment algorithms are complex (see regional guidelines) and the decision to treat involves a careful evaluation of contra-indications, benefits and risks.

Pregnancy. It is preferable to render patients HCV RNA negative before pregnancy to avoid vertical transmission. When patients are HCV RNA positive, the transmission rate is in the order of 5%.

NAFLD

On the basis of epidemiological and longitudinal studies, it is now well recognized that cryptogenic cirrhosis is predominantly caused by non-alcoholic fatty liver disease (NAFLD). NAFLD is a spectrum of liver disease characterised by insulin resistance that begins with fat accumulation (hepatic steatosis) and progresses through steatohepatitis (NASH) and fibrosis to cirrhosis. The degree of inflammation and fibrosis on biopsy is important. Hepatic steatosis is relatively benign: indeed, 25% of Americans have it. However, of patients with steatohepatitis 10% will go on to get cirrhosis and 30% of patients with fibrosis develop cirrhosis in ten years.

Risk factors for NAFLD are central obesity, type 2 diabetes and **hyperlipidaemia**. NAFLD can also be secondary to some drugs (anti-psychotics for example), hereditary metabolic defects and malnutrition. Risk factors for severe fibrosis include age > 45, male sex, type 2 DM and an AST:ALT > 0.8.

Many patients with NAFLD die with, rather than of their liver disease. In one series of 420 patients diagnosed with NAFLD between 1980 and 2000, 13% had died at follow up in 2005. The relative risk of death was 1.32, but liver disease was only third on the list of cause of death behind malignancy and ischaemic heart disease.

Management involves weight loss, exercise and optimal management of all features of the metabolic syndrome. Metformin, glitazones and statins may be beneficial.

Elastography can be used to stage liver disease in the absence of any indication of another pathology (positive liver screen or an unusual pattern of liver test).

AUTOIMMUNE HEPATITIS

Autoimmune hepatitis (AIH) has a female preponderance. It is divided into types 1, 2 and 3. Characteristics of these groups follow.

Clinical Features	Type 1	Type 2	Type 3
Diagnostic autoantibodies	ASA ANA	Anti-LKM	Soluble liver-kidney antigen
Age	10 y-elderly	Pediatric (2-14 y) Rare in adults	Adults (30-50 y)
Women (%)	78	89	90
Concurrent immune disease (%)	41	34	58
Gamma globulin elevation	+++	+	++
Low IgA*	No	Occasional	No
HLA association	B8, DR3, DR4	B14, Dr3, C4AQO	Uncertain
Steroid response	+++	++	+++
Progression to cirrhosis without Rx (%)	45	82	75

Diagnosis

Diagnosis of AIH is straightforward for patients with an ALT of more than five times normal, an IgG of more than double normal or a positive smooth muscle antibody and compatible liver histology. When there is diagnostic doubt then a combination of clinical instinct and the following scoring system should be employed.

- Autoantibodies: assign one point if the ANA or SMA are 1:40 OR assign two points if the ANA or SMA are $\geq 1:80$ (OR if the LKM $\geq 1:40$ OR if the SLA is positive).
- IgG: assign one point if the IgG is > the upper limit of normal OR assign two points if the IgG is >1.10 times the upper limit of normal.
- Liver histology (evidence of hepatitis is a mandatory condition): assign one point if the histological features are compatible with autoimmune hepatitis OR two points if the histological features are typical of autoimmune hepatitis. Typical histologic features were defined as the presence of interface hepatitis, lymphocytic/lymphoplasmacytic infiltrates in the portal tracts and extending into the lobule, emperipolesis (active penetration of one cell into and through a large cell), and hepatic rosette formation. Compatible features were defined as a picture of chronic hepatitis with lymphocytic infiltration without all the features considered typical.
- Absence of viral hepatitis: assign two points if viral hepatitis has been excluded. In the validation study, patients were mainly tested for hepatitis B and C. However, other forms of hepatitis should be considered depending upon the clinical setting.

A probable diagnosis of autoimmune hepatitis is made if the total points are six, while a definite diagnosis is made if the total points are \geq seven.

Treatment

AIH is usually steroid responsive. The decision to treat is straightforward in the presence of a severe hepatitis (ALT > 10 x ULN, ALT > 5 x ULN and IgG 2 x ULN or histology showing bridging necrosis or multiacinar collapse). However, with less florid disease, a careful evaluation of the risks and benefits of treatment should be made.

An appropriate prednisolone-based treatment regimen follows *(need to discuss)*:

1. Prednisolone 20 mg for 3 months, with a tapering off to 5 to 10 mg by one year in (5 mg every 3 months). Careful review initially (2 to 4 weekly follow up) until steroid responsiveness is confirmed on blood tests (LFT, globulins and IgG). Prescribe a bisphosphonate and PPI with treatment.
2. Azathioprine 1 to 1.5 mg/kg when bilirubin has normalized. Ensure normal TPMT. Weekly FBC for 1 month. 3 monthly thereafter.
3. At 1 year to 18 months re-biopsy. The absence of interface hepatitis indicates the potential for steroid withdrawal. Check a short synacthen test first.

If no improvement with steroids or there is a flare of ALT, reconsider the diagnosis (review case) and consider a repeat biopsy.

Alternative therapies

Alternatives to azathioprine are 6-mercaptopurine (1.5 mg/kg) and mycophenolate mofetil (MMF - 1 g BD starting at 500 mg bd).

Budesonide may be used in favour of prednisolone (9 mg initially down to a maintenance of 3 mg), but it may not be efficacious in patients with poor hepatic reserve and the evidence base for it is limited.

Tacrolimus (10 - 15 mg/kg initially starting at 5 mg bd) may be used for AIH that is difficult to control. MMF may be a good alternative to azathioprine in this setting.

Prognosis

There is a 90% survival at 10 years and 70% survival at 20 years from diagnosis. The SMR is 1.63 for all-cause mortality, 1.86 for liver-related mortality and 0.91 for non-liver-related mortality.

Broadly speaking, prognosis is excellent if ALT normalises with therapy. Most patients (nearly 100%) relapse if immune suppression is stopped.

PRIMARY BILIARY CIRRHOSIS

Primary biliary cirrhosis (PBC) is a disease that usually presents in middle age and affects women nearly ten times more commonly than men. The diagnosis can be made serologically in most cases. Characteristically, the alkaline phosphatase and γ -glutamyl transpeptidase are more than two times the upper limit of normal and the patient is anti-mitochondrial antibody positive and anti-PDH positive (pyruvate dehydrogenase, the major mitochondrial auto-antigen). These antibodies have in excess of 95% specificity and 98% sensitivity, obviating

the need for biopsy except in unusual circumstances. If the disease is still suspected you can send for AMA negative PBC antibodies through the Cambridge immunology laboratories.

Whilst a proportion of patients are asymptomatic, common symptoms are of malaise, pruritus and lethargy. Hyperlipidaemia, which probably does not accelerate atherosclerosis, is a feature, as is osteoporosis, which must be screened for and treated accordingly and co-existent autoimmune disorders. PBC has a variable course, with some patients never developing symptoms and others progressive jaundice and chronic liver failure. Younger age at presentation is a poor prognostic sign, as is failure to reduce bili to within 1 x ULN, ALT 2 x and ALP 3 x after one year of treatment with ursodeoxycholic acid (Paris 2 Criteria). In the presence of jaundice, the Mayo PBC Score provides prognostic modelling.

HCC is rare with PBC and it is a matter of debate whether the cost of screening for HCC is warranted in this group, but we recommend it. Screening for HCC and varices begins when there is ultrasound or blood test evidence of portal hypertension. Portal hypertension occurs early in PBC and is partly pre-sinusoidal due to extensive portal fibrosis. Biannual staging ultrasounds assess for features of portal hypertension.

Ursodeoxycholic acid (12 - 15 mg/kg) is first line therapy for pruritus and probably slows disease progression. Those patients who do not satisfy the Paris 2 Criteria may benefit from alternative agents and a liver biopsy should be considered for them, with budesonide trialled in the presence of significant interface hepatitis or, perhaps, fenofibrate if not. Alternatives for itch include cholestyramine (4 g to max 16 g avoiding taking with drugs that it binds), rifampicin (150mg od for 1 week then bd increasing up to 300mg bd if necessary with LFT monitoring throughout), ondansetron 4 - 8 mg bd, naltrexone (25mg increasing to 50mg daily), MARS (extra-corporal albumin dialysis) and UV light.

Before the onset of jaundice, accurate prognostication is not possible. Once bilirubin begins to increase, the Mayo risk score may be used. All patients with a bilirubin greater than 50 umol/L should be considered for liver transplantation assessment.

PRIMARY SCLEROSING CHOLANGITIS

Primary sclerosing cholangitis (PSC) is strongly associated with inflammatory bowel disease and negatively associated with smoking. Whereas PBC is a disease of solely the intrahepatic bile ductules, PSC predominantly affects the larger intrahepatic and extra-hepatic ducts. pANCA positivity has 70% sensitivity and 90% specificity. Biliary imaging is vital diagnostically. This must be by MRCP unless a biliary procedure is indicated, when ERCP can be utilized. Liver biopsy stages the disease. There is little data on the use of transient elastography in PSC.

Management of PSC involves detection and management of complications until transplantation becomes necessary. If patients do not have inflammatory bowel disease (IBD) then colonoscopy is required at initial assessment to exclude it and perhaps then at 5 years also. Patients with IBD and PSC should have annual colonoscopic screening for neoplasia.

Screening and treatment for osteoporosis is important. Ursodeoxycholic acid (15-18 mg/kg) may help pruritus and decrease the risk of cholangiocarcinoma, but if there is no therapeutic response at one year (ALP < 1.5 x ULN) then it should probably be stopped. Episodes of

cholangitis are treated with antibiotics and in jaundiced patients, the dilatation or stenting of dominant strictures can be considered.

The risk of cholangiocarcinoma in PSC is high. Screening can be carried out by measurement of CA 19-9, which has low specificity. Annual imaging should be undertaken to restage the disease and assess for gallbladder polyps that indicate cholecystectomy and features suspicious of cholangiocarcinoma. This will often be with alternate ultrasound and MRCP scans.

It is increasingly becoming apparent that there are different phenotypes of PSC. Patients with intrahepatic PSC only tend to run a more benign course (this probably particularly applies to those with a “subtle intrahepatic cholangiopathy” at MRCP). Women have a better prognosis than men. Overall, median time to death or transplantation from diagnosis was given as 12 years in older studies, but probably stands at between 20 and 25 years.

GRANULOMATOUS HEPATITIS

Three main causes are PBC, sarcoidosis and drug reactions. The following investigations may be indicated, depending on the clinical context.

Diagnosis	Possible investigations
PBC	AMA, anti-PDH, IgM; common in early stages
PSC	pANCA, MRCP/ERCP rare 7%
Sarcoidosis	CXR, CT, PFTs, ACE, urine Ca, trans-bronchial biopsy
Drugs	Long list - take a careful history and search literature on each prescription
TB	Culture; mycobacterial PCR; consider atypical mycobacteria
Brucellosis	Blood cultures and rising titre agglutin antibody Rx doxycycline
Melioidosis	Blood culture, liver culture
<i>Treponema pallidum</i>	TPHA+ve, FTA-ABS +ve
Q fever	As a PUO, or hepatitis like picture ; thrombocytosis; phase 1 and 2 antibody
Rarely CMV, EBV	CMV PCR
Rarely schistoma, leishmania	Biopsy
Rarely <i>Borrelia</i> , leprosy	
HIV	HIV serology
SLE	ANA, anti-DNA Abs
Hypogammaglobulinaemia	Igs
Chemical; beryllium	History
Hodgkins lymphoma	CT abdomen
Chronic granulomatous disease	Refer to Clinical Immunology
Idiopathic	Most are variants of Sarcoidosis

Management of Sarcoidosis

Therapy is indicated for pain, extra-hepatic disease and if there is significant or progressive fibrosis. An interval biopsy (e.g. at 3 years) may be required to ascertain whether there is

progressive fibrosis. To assess for extra-hepatic disease a high resolution chest CT scan and pulmonary function tests should be performed and patients referred onwards as necessary.

When therapy is indicated, initiate prednisolone 30 to 40 mg given as a single daily dose and then gradually taper to a maintenance dose of 10 to 15 mg daily, over a period of approximately six months. The proper length of therapy for those who respond to treatment is not known. We usually aim for a duration of therapy of at least one year. A steroid sparing agent such as azathioprine or mycophenolate may be required.

Approximately 1/3 patients respond to a course of steroids and remain in remission afterwards; 1/3 require long term immune suppression and 1/3 are non-responsive.

HAEMOCHROMATOSIS

Genetic haemochromatosis is common, with a recessive HFE gene mutation frequency of 10% and an incidence of approximately 1 in 400. The clinical syndrome of diabetes, hypogonadism, bronze skin, arthralgia and liver disease is caused by iron deposition in the pancreas, pituitary, skin, joints and liver respectively. Not all homozygous patients with HFE gene mutations develop haemochromatosis and this is explained by the contributions of other proteins involved in the metabolism of iron. In those that do, clinical features can vary. Women are protected from iron overload between menarche and menopause.

A ferritin of greater than 200 µg/L and transferrin saturation of greater than 50% is seen in 90% of patients with genetic haemochromatosis. Transferrin saturation is particularly important as, being an acute phase protein, ferritin is elevated in many clinical contexts including most chronic liver diseases. Assessment of HFE genotype by testing for the common mutations (C282Y and H63D) is the next step.

Liver biopsy is indicated if there is diagnostic doubt or to identify cirrhotic patients so that they can have appropriate screening. Homozygotes with the C282Y mutation who have normal LFTs, no hepatomegaly and a ferritin of less than 1000 µg/L will not have cirrhosis (100% negative predictive value) and do not require biopsy. If patients are without these criteria, biopsy is indicated.

Management of haemochromatosis is by venesection. A unit of blood is taken weekly until ferritin and transferrin saturation starts to fall. Once this occurs, venesection can be progressively spaced until the ferritin normalises (< 50 µg/L and transferrin saturation < 50%). Patients then require maintenance venesection, which usually occurs with a frequency of between 2 and 4 monthly. The Haematology Department co-ordinate venesection in this trust.

First degree relatives should be screened with a ferritin and genetic mutation analysis.

ALPHA 1 ANTITRYPSIN DEFICIENCY (A1ATD)

There are three common allelic variants of A1AT. These are M (wild type), Z and S. MZ frequency is 3%; ZZ 0.09%. Homozygous ZZ A1ATD leads to cirrhosis or HCC in 10 to 15%. MZ A1ATD rarely causes significant liver disease in the absence of another risk factor. A1ATD may cause emphysema.

Patients with suspected chronic liver disease should be screened for A1ATD with a level. If < 1g/L a phenotype should be requested. A phenotype should also be requested if abnormal accumulation of A1AT is seen on liver biopsy.

Whilst there is no treatment for A1ATD, it is a risk factor for liver disease and its presence should prompt aggressive risk reduction of co-factors such as obesity, heavy alcohol intake and smoking.

First degree relatives should be screened with phenotypic analysis.

WILSON'S DISEASE

Wilson's disease is an autosomal recessive disorder caused by mutations of the ATP7B gene on chromosome 13, which results in failure to excrete copper into bile and a failure of copper to be incorporated into apocaeuloplasmin. This leads to a reduction in the generation of caeuloplasmin and an excess of free serum copper and toxic tissue deposition. Estimated prevalence is 13 per million.

Clinical presentations

Hepatic: abnormal LFTs, steatosis, NASH, autoimmune hepatitis mimic, cirrhosis and acute liver failure

Neurological: chorea, dystonia and Parkinsonism

Eyes: cataracts, Keiser Fleischer rings (present in 40-60% of adults, rare in children)

Bones: osteoporosis

Psychiatric presentations: depression, neurosis, psychosis and personality changes

Endocrine: hypoparathyroidism and infertility

Rheumatology: pseudogout

Heamatology: haemolysis (11% present with this)

Cardiomyopathy

Pancreatitis

Proximal Renal Tubular Acidosis

Diagnostic pathways

If Wilson's disease is suspected, slit lamp examination and 24 hour urinary copper excretion should be performed in addition to caeuloplasmin level.

1) If KF rings +ve, caeuloplasmin < 20 mg/dL, urine copper > 0.6 µmol/day – diagnostic

2) If KF rings +ve, caeruloplasmin > 20 mg/dL, urine copper > 0.6 µmol/day – biopsy to determine hepatic copper content. If > 250 µg/g of liver then Wilson's Disease is confirmed. If < 250 µg/g, for molecular analysis (Sheffield).

3) If KF rings -ve, caeruloplasmin < 20 mg/dL, urine copper < 0.6 µmol/day – biopsy to determine hepatic copper content. If > 250 µg/g of liver then Wilson's Disease is confirmed. If 50-250 µg/g, for molecular analysis (Sheffield). If < 50 µg/g – Wilson's excluded.

4) If KF rings -ve, caeruloplasmin < 20 mg/dL, urine copper > 0.6 µmol/day – biopsy to determine hepatic copper content. If > 250 µg/g of liver this is confirmatory of Wilson's. If 50-250 µg/g resort to molecular analysis (Sheffield). If < 50 µg/g – Wilson's excluded.

Treatment

Dietary Advice

High copper containing foods (shellfish, nuts, chocolate, mushrooms, and organ meats) should be avoided, at least in the first year of treatment.

Family Screening

Molecular testing for ATP7B mutations or haplotype studies should be used for all first degree relatives greater than 3 years old.

Pharmacotherapy

Penicillamine: maximum 20 mg/kg daily in divided doses 1 hour before or 2 hours after food with pyridoxine 25 mg; max 2 g daily for 1 year; multiple side effects.

Start at 500 mg and increase by 250 mg weekly until 20 mg/kg is reached. Monitor UE, LFT, FBC and clotting at 1, 2 and 4 weeks, and 2 and 3 months then 6 monthly.

Check 24 hour urinary copper at 1 month then 3 monthly until stable then 6 monthly. Aim for 3-8 µmol/L. When stable reduce penicillamine dose by 25%.

Trientine: maximum 20 mg/kg daily in 2 to 4 divided doses 1 hour before or 2 hours after food; few side effects. Reduce by 25% when stable (as for penicillamine).

Doses of penicillamine and trientine should be reduced for surgery and wound healing.

Alternative therapies are zinc and tetrathiomolybdate.

Transplantation

As discussed above, Wilson's Disease can present with a syndrome akin to liver failure. Liver transplantation may be indicated in this context, or for decompensated liver disease.

LIVER LESIONS

HEPATOCELLULAR CARCINOMA (HCC)

HCC usually occurs in the context of cirrhosis. If a patient presents with HCC, cirrhosis should be excluded.

Diagnosis

If a new nodule is found during surveillance ultrasound that is ≤ 1 cm, further imaging is recommended at 3 months to ensure that this is a cirrhotic nodule and not an HCC. For lesions > 1 cm, classical imaging features are enough to confirm a diagnosis. These features comprise arterial enhancement and portal venous washout – characteristics that are attributable to hypervascularity, but lack of portal venous blood supply. In the absence of these classical features, a second cross sectional imaging modality is employed. If findings are equivocal then the next step is usually biopsy, which is avoided where possible due to the small risk of tumour seeding. AFP measurement is a useful adjunct.

Staging and Management

With the exception of transplantation for which the criteria for suitability have been extended (see below), the Barcelona Clinic liver cancer (BCLC) staging system is used to categorize and manage HCC. This uses a combination of tumour stage, liver disease severity and WHO performance status to guide management. A table demonstrating this stratification follows:

Stage	Tumour	Liver disease	PS ¹	Treatment
0	1 < 2 cm	CP A with nx HVPG	0	Resection/RFA
		CP A with raised HVPG	0	OLT/RFA
A1	1 < 5 cm	CP A-B with nx HVPG	0	Resection/RFA
A2		CP A-B with raised HVPG and nx bili	0	Resection/RFA/OLT
A3		CP A-B with raised HVPG and bili	0	RFA/OLT
A4	3 < 3 cm	N/A	0	OLT/TACE
B	Multifocal	CP A-B	0	TACE
C	Vascular invasion/mets	CP A-B	1-2	Sorafenib
D	Any	CP C	3-4	Supportive care

CP – Child Pugh; HVPG – hepatic venous pressure gradient; RFA – radiofrequency ablation; TACE – transarterial chemoembolization; OLT – orthotopic liver transplant; PS – performance status

Essentially, if a patient is fit, has a normal liver or very well compensated cirrhosis and a resectable lesion then surgery is a good option. Otherwise, if a patient is fit and falls within transplant criteria then they should be transplanted with RFA/TACE whilst they wait on the list. If they are without these criteria then TACE and failing this sorafenib are the only options without the trial setting. CP C and PS > 0 contra-indicate RFA and TACE. CP C and PS > 2

¹ WHO Performance Status

0 – Asymptomatic

1 – Symptomatic but completely ambulatory

2 – Symptomatic, $<50\%$ in bed during the day

3 – Symptomatic, $>50\%$ in bed, but not bedbound

4 – Bedbound

5 – Death

contra-indicate sorafenib. Guidelines for TAE, TACE and RFA are found here (clerking sheet).

Extended transplant criteria

Currently, these are the criteria for transplantation for HCC in the UK:

1. A single tumour ≤ 5 cms diameter or
2. Up to 5 tumours all ≤ 3 cms or
3. Single tumour >5 cms and ≤ 7 cms diameter where there has been no evidence of tumour progression (volume increase by $<20\%$) and no extrahepatic spread and no new nodule formation over a 6 month period

No vascular invasion or extra-hepatic spread and AFP $< 100,000$.

ADENOMA

These are benign liver tumours that are usually solitary (80%). They are often found incidentally and are either sporadic or associated with the combined oral contraceptive pill (COCP), anabolic steroids, glycogen storage disorders (GSD) or MODY type 3. For patients who have not used the COCP the incidence is 1/1,000,000; 30-40/1,000,000 otherwise.

Diagnosis

Adenomas are usually first seen at ultrasound where they are hyperechoic. At CT, they tend to be well demarcated, isodense (or hyperdense in a fatty liver) in the pre-contrast phase, arterially enhancing and isodense in the portal phase. At MRI, adenomas usually have a high signal on T2 weighted images and enhance early after gadolinium administration. Isointensity is then seen in the portal phase. A lesional biopsy is sometimes required to make the diagnosis.

In the presence of multiple adenomas, it is important to investigate for MODY3 and GSD 1/3.

Management

Management principles follow:

1. Stop COCP and anabolic steroids
2. If greater than 5cm consider resection due to malignant potential
3. Monitor annually with US/MRI and AFP if not surgically resected
4. Carefully monitor in pregnancy – 4 and 8 month US scan.

HAEMANGIOMA

Hepatic haemangiomas are the most common benign mesenchymal liver tumour. They may be multiple in up to 40% patients and range in size from a few millimeters to over 20 cm. The majority are small (< 5 cm). Peak presentation is between 30 and 50 years old (60 to 80% cases) and there is a 3:1 female to male ratio. Growth can occur in response to the COCP and pregnancy, but haemangiomas do not contraindicate COCP usage. Large and complex haemangiomas can occur in patients with HHT.

Haemangiomas are rarely symptomatic. If large, they may cause pressure symptoms, high output cardiac failure, consumptive coagulopathy and can occasionally rupture. There is an association with hypothyroidism.

Radiological features

A hyper-reflective lesion at ultrasound scan. There is variation at CT scan, but classic features are of a well demarcated hypodense mass with peripheral nodular enhancement in the early arterial phase, followed by a centripetal pattern of "filling in" during the late phase to isodensity on the delayed phases.

MRI is the most accurate imaging modality for the diagnosis of haemangiomas. The typical MRI appearance is a smooth, well-demarcated homogeneous mass that has low signal intensity on T1-weighted images and is hyperintense on T2-weighted images. There is early peripheral discontinuous nodular or globular enhancement on arterial phase imaging with gadolinium and progressive centripetal enhancement ("filling-in") on delayed scans similar to that seen at CT.

Management

If < 2cm and seen at ultrasound in a non-cirrhotic liver, no more investigations are required. Otherwise, cross sectional imaging is required. In the absence of symptoms, management is conservative. Resection is sometimes necessary for symptomatic patients.

FOCAL NODULAR HYPERPLASIA (FNH)

FNH is relatively common. The highest incidence is in females (8:1 predominance) between the ages of 20 and 50 years old. FNH is generally accepted to be due to a hyperplastic (regenerative) response to hyperperfusion secondary to anomalous arterial perfusion. FNH is usually an incidental finding.

Radiological features

Ultrasound appearances are highly variable. A central scar, which is characteristic, is only seen in 20% cases by ultrasound. At CT, lesions are hypodense or isodense on non-contrast imaging with the central scar identified in 33%. The lesion becomes hyperdense during the hepatic arterial phase with isodensity during the portal venous phase. The central scar may become hyperdense as contrast diffuses into it. Remember that a central scar may be present in the fibrolamellar variant of HCC.

At MRI there may be little to distinguish FNH from normal liver on standard MRI. When present, the scar typically shows high signal intensity on T2-weighted images due to vessels

or oedema within. Gadolinium/Primovist infusion produces rapid enhancement of the FNH mass due to its arterial blood supply. On delayed images it becomes more isointense with respect to normal liver. The central scar enhances on delayed imaging as contrast gradually diffuses into the fibrous centre of the mass.

Management

If imaging is characteristic then FNH should be managed conservatively. In the presence of diagnostic doubt, a lesional biopsy should be considered. Very rarely pain can be reasonably attributed to FNH and resection should be considered in these instances.

LIVER METASTASES

Liver metastases are usually multiple and hypoechoic at ultrasound. On cross sectional imaging, metastases may be hypodense during the arterial phase (colon, stomach and pancreas) or hyperintense if vascular (neuroendocrine tumors, renal cell carcinoma, breast carcinoma, melanoma and thyroid carcinoma).

Management is usually a game of “hunt the primary” and proceed along specific lines of management for that cancer. Primary lesions may be identified according to symptomatology or seen on cross sectional imaging. When a primary lesion is not identified, liver biopsy is usually diagnostic.

LIVER ABSCESES

Liver abscesses often present with pain and fever. Causative organisms usually originate from the biliary tree or bowel and colonoscopy +/- MRCP are required at some point in the management pathway.

Management of pyogenic liver abscesses follows:

1. Blood cultures and antibiotics (iv tazocin first line if septic and as guided by sensitivities thereafter).
2. Consider iv antibiotics alone for abscesses < 3 cm diameter with weekly imaging until resolution is seen – aiming for 2 weeks iv antibiotics and 2 weeks oral.
3. For abscesses of 3 to 5 cm, aspiration (which may need to be serial) should be considered and management otherwise as per 2.
4. If an abscess is > 5 cm drain insertion is probably optimal. The drain can be removed once imaging demonstrates effective resolution. At least 2 weeks iv and 2 weeks oral antibiotics will be required.

For complex pyogenic liver abscesses, surgical resection is sometimes required.

Amoebic liver abscesses should be considered in travellers returning from endemic areas. The diagnosis can usually be made by a combination of serology, stool antigen testing and characteristic imaging features. Aspiration is occasionally required to make the diagnosis, but

pharmacological management is usually all that is necessary therapeutically (oral metronidazole 500 mg to 750 mg tds for 7 to 10 days).

LIVER CYSTS

Simple Cysts

These are usually asymptomatic and are found in about 1% adults. Imaging features are characteristic with a well demarcated, thin walled, bland fluid filled cavity confirming the diagnosis. For large simple cysts, interval imaging for perhaps one year should be considered to exclude a more worrying pathology.

Simple cysts can bleed, become infected or occasionally burst. This leads to pain and fever (in the context of infection). It also causes diagnostic doubt as the classical imaging features will be clouded by septation or wall thickening.

Management

In the absence of symptoms, small to moderate sized cysts should be managed expectantly and reassurance provided. Surgical management of complicated cysts should be considered. Options include deroofing and resection. Procedures such as aspiration are ineffective, as failure to remove the epithelial cyst lining will lead to rapid cyst reformation.

Polycystic Liver Disease and Congenital Hepatic Fibrosis

Polycystic liver disease and congenital hepatic fibrosis are two manifestations of ductal plate malformation. They are congenital disorders that can occur in isolation or in association with polycystic kidney disease.

Polycystic liver disease is usually asymptomatic. The most common symptom is the feeling of an abdominal mass and pain. As with simple cysts, complications of bleeding, infection and rupture may occur. Management comprises analgesia, reassurance and acute care of complications. Large cysts can be removed surgically, but symptomatic relief from this is often short lived with the accumulation of more cysts to replace the one that has been removed. Transplantation is reserved for patients with intractable symptoms, but does not improve mortality and is problematic in terms of organ allocation, as patients with polycystic liver disease are often relatively low priority.

Congenital hepatic fibrosis causes portal hypertension, but not the other complications of chronic liver disease outlined [above](#). This usually manifests with variceal complications. Management is similar, but variceal band ligation is favoured over beta blockade for primary prophylaxis. Transplantation is rarely required.

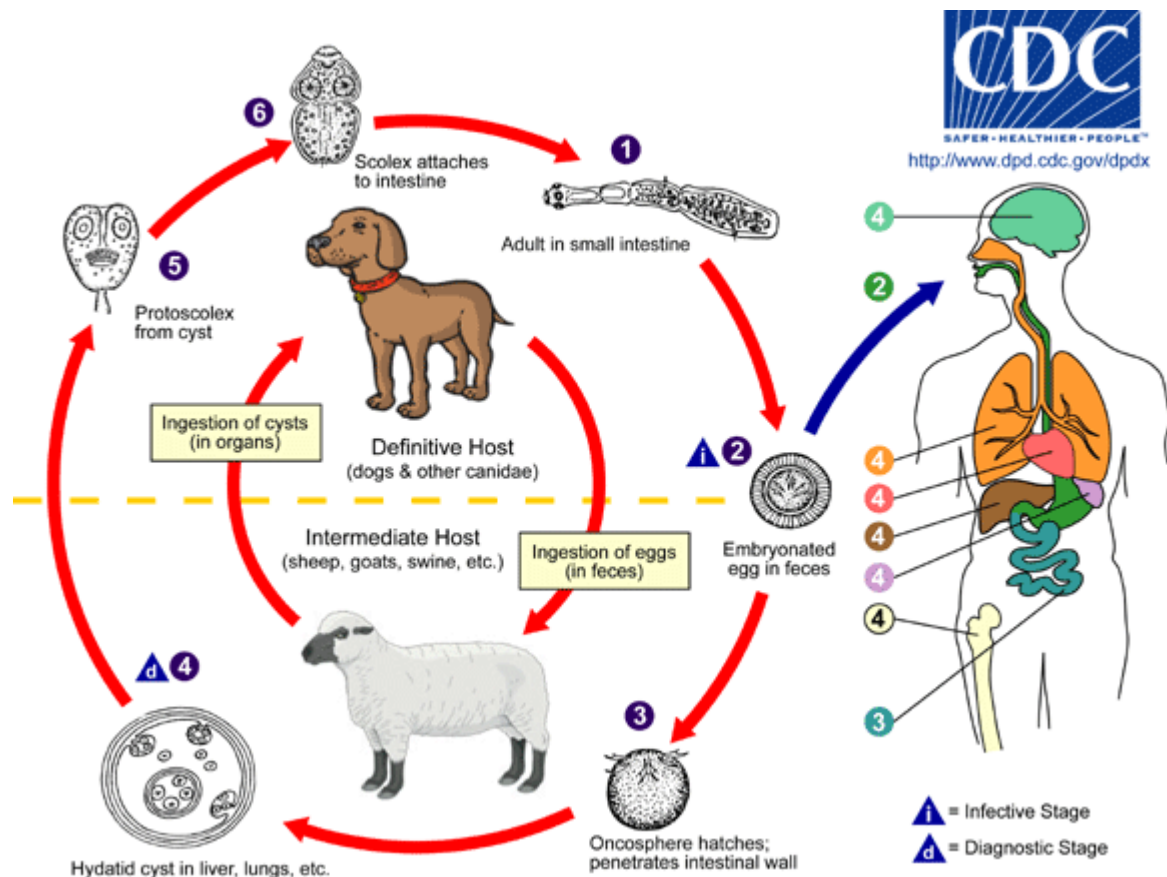
Hepatic cystadenoma and cystadenocarcinoma

Hepatic cystadenomas are rare liver lesions that commonly presents with pain or mass effect. The cysts often grow to a large size and usually require resection, especially given that they have malignant potential. Thickening and septation are usually seen on imaging, but cyst fluid or cyst wall biopsy are required to make a definitive diagnosis.

Hepatic cystadenocarcinomas probably occur from malignant transformation of cystadenomas. Patients are often elderly at presentation. In a fit patient, resection is the management strategy of choice.

Echinococcal (hydatid) cyst

Hydatid cysts are caused by the larval form of *Echinococcus granulosus*. The cyst membrane is derived from the organism. The condition is usually contracted from infected dogs (see lifecycle below). Patients may be asymptomatic or have pain, mass effect or rare complications such as cyst rupture into the biliary tree, peritoneum or lungs.



On human image: 2, ingestion of egg from host (usually dog) faeces; 3, oncosphere hatches in intestine; 4, potential cyst sites.

Diagnosis and management

Diagnosis usually relies on a combination of imaging and serology. Diagnostic aspiration carries a risk of anaphylaxis. This can be minimised by giving albendazole beforehand.

Management should be dictated by a specialist centre such as the London School of Hygiene and Tropical Medicine. WHO Guidelines also exist for characterising and managing the cysts, which go through active, inactive and transitional stages.

BILIARY DISEASES

PRIMARY SCLEROING CHOLANGITIS

See [above](#).

CHRONIC PANCREATITIS

Chronic pancreatitis is a condition in which a chronic inflammatory stimulus leads to architectural distortion, fibrosis and calcification. Common presenting features include abdominal pain, diarrhoea, weight loss and the symptoms of diabetes mellitus. Some patients present with complications. Diagnosis of chronic pancreatitis is based on imaging and identification of complications (often exocrine deficiency with low faecal elastase).

Risk factors for pancreatitis are toxic/metabolic (alcohol, tobacco, hypocalcaemia, chronic renal failure, medications and toxins), genetic (mutations in cationic trypsinogen gene (PRSS1 – autosomal dominant), CFTR and SPINK1 (both autosomal recessive)), autoimmune (see [below](#)), recurrent acute and obstructive (pancreatic divisum, tumours (intrinsic and extrinsic) and blockage (stones)).

A screen for chronic pancreatitis should include history (alcohol, tobacco, drug/toxin history), blood tests (UE, FBC, bone profile, lipids and immunoglobulin subclasses), genetic testing (in the absence of a definite alternative cause), imaging (CT scan in the first instance and often MRCP) and occasionally biopsy/FNA (often EUS driven).

Complications of chronic pancreatitis include pancreatic failure (exocrine and endocrine), pain, pseudocyst formation, ductal strictures and stones, biliary obstruction, duodenal obstruction, splenic vein thrombosis, splenic artery pseudoaneurysm, pancreatic ascites and malignancy (5% risk of pancreatic adenocarcinoma).

Management of chronic pancreatitis includes removal of the cause where possible and dealing with complications. Some common complications and their management follow.

Pancreatic exocrine deficiency is diagnosed on clinical grounds (steatorrhoea and weight loss) and biochemically (low faecal elastase). Treatment is with pancreatic supplementation (Creon 40,000 units before main meals and 25,000 units before snacks is a reasonable starting regimen).

Pancreatic endocrine deficiency manifests with glucose intolerance or diabetes mellitus and should be screened for and treated with insulin replacement as necessary.

Pain from chronic pancreatitis can be difficult to manage. The first step is to identify and treat any secondary cause (e.g. PD stricture/stone, biliary stricture, pseudocyst, duodenal obstruction), which may require referral to a specialist centre such as UCLH. Otherwise, analgesia is the mainstay of management. An appropriate analgesic ladder is given below, which addresses visceral and neuropathic pain. Other options for pain are coeliac plexus neurolysis under EUS guidance or pancreatic resection.

Approaches to PD strictures and stones are endoscopic or surgical. Pseudocysts can be drained intermittently or continuously (via cyst gastrostomy) or excised surgically.

Analgesia ladder for chronic pancreatitis

Jamie to advise

AUTOIMMUNE PANCREATITIS AND IGG4 ASSOCIATED CHOLANGITIS

Autoimmune pancreatitis usually presents with pain or jaundice. Imaging may demonstrate mass lesion/s, pancreatic duct stricturing or diffuse enlargement ("sausage pancreas"). The following three categories that originate from the Mayo guidelines are useful diagnostically:

1. Pancreatic core biopsy or surgical specimen that shows characteristic histological features
2. Characteristic imaging features and IgG4 level > twice upper limit of normal
3. IgG4 level > twice upper limit of normal without characteristic imaging features, but with a good response to steroid therapy

No big studies exist to guide steroid prescription, but a common strategy is to give prednisolone 30 - 40 mg for 2 to 4 weeks followed by a reducing course by 5 mg per week thereafter. Steroid failure (relapse or failed remission) necessitates the use of azathioprine at 2 mg/kg. Poor prognostic features include a high IgG4 level at baseline and presentation with biliary strictures, and should prompt consideration of early azathioprine use. Failure of immune suppression necessitates reconsideration of the diagnosis and then use of poorly evidenced based therapies such as adalimumab and cyclophosphamide.

Type 1 autoimmune pancreatitis is associated with high IgG4 levels and in 40-90% is part of a systemic autoimmune disorder. Associated conditions are:

- Inflammatory bowel disease
- IgG4 associated cholangitis
- Lung nodules, adenopathy and infiltrates
- Sjögren's syndrome
- Retroperitoneal fibrosis
- Tubulointerstitial nephritis
- Autoimmune thyroiditis

A normal IgG4 level usually accompanies type 2 autoimmune pancreatitis, which is often associated with inflammatory bowel disease. It often remits with a single course of steroids.

IgG4 associated cholangiopathy usually presents with jaundice or abnormal liver biochemistry. MRCP demonstrates a diffuse stricturing disease, which has similar appearances to PSC. Diagnosis is confirmed by an elevated IgG4 and steroid responsiveness. 10% cases of PSC are in fact mis-characterised and so an IgG4 level is mandatory when working up a patient for PSC as the prognosis for treated IgG4 associated cholangitis is probably superior to that for PSC.

PANCREATIC ADENOCARCINOMA

Pancreatic adenocarcinoma usually presents with painless jaundice if in the head of the gland and pain and weight loss otherwise. It is diagnosed by a combination of imaging (usually ultrasound followed by CT scan) and histological confirmation. Histology comes from either biliary brushings, EUS guided FNA or biopsy of metastases (usually hepatic). Other lesions such as neuroendocrine tumours, lymphomas and focal pancreatitis can masquerade as adenocarcinoma so these diagnoses should always be considered.

Pancreatic adenocarcinoma has a poor prognosis with a median survival of < 6 months and a 5-year survival < 5%. It is staged as follows, with staging requiring a CT chest, abdomen and pelvis:

Primary tumour (T)

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

Tis Carcinoma in situ*

T1 Tumour limited to the pancreas, 2 cm or less in greatest dimension

T2 Tumour limited to the pancreas, more than 2 cm in greatest dimension

T3 Tumour extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery

T4 Tumour involves the celiac axis or the superior mesenteric artery (unresectable primary tumour)

Regional lymph nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Regional lymph node metastasis

Distant metastasis (M)

M0 No distant metastasis

M1 Distant metastasis

Treatment options

1. **Surgery.** If a patient is fit enough to undergo major biliary surgery, the following unresectability criteria should be considered. These are formally discussed at the regional SMDT:
 - a. Head of pancreas lesions
 - Greater than 180 degrees superior mesenteric artery (SMA) encasement, any celiac abutment
 - Unreconstructable superior mesenteric vein (SMV)/portal vein occlusion
 - Aortic invasion or encasement
 - b. Body
 - SMA or celiac encasement greater than 180 degrees
 - Unreconstructable SMV/portal vein occlusion
 - Aortic invasion

- c. Tail
 - SMA or celiac encasement greater than 180 degrees
 - d. For all sites
 - Distant metastases
 - Metastases to lymph nodes beyond the field of resection
2. *Chemotherapy.* This may be used alone or in combination with surgery. Its use is directed by Oncology.
 3. *Radiotherapy.* This is sometimes appropriate for small unresectable lesions, but there is no good evidence of a survival benefit for this patient group.
 4. *Palliation.* A liaison with palliative care is useful. Medical management strategies include chemoradiotherapy, biliary stent placement, analgesia and coeliac plexus neurolysis (CPN). Psychosocial issues are also important to consider.

CHOLANGIOCARCINOMA

Cholangiocarcinoma may be intrahepatic and present as a liver mass or ductal when jaundice is a common presenting feature. Diagnosis is made by a combination of imaging and usually histology (brushings or biopsy). Imaging generally involves a combination of CT scan and MRI with MRCP. If decompression is deemed necessary (for an unresectable tumour or if the surgical team request it), an MRCP is vital to obtain a “roadmap” for drainage. Broadly speaking, drainage of a post hilar stricture is achieved by ERCP and stenting, whereas pre-hilar and hilar strictures are best decompressed percutaneously (either by drain insertion or drain and stent insertion depending on the clinical context). Cannulating an undrainable biliary segment at ERCP often introduces sepsis that is often fatal: an indisputably sub-optimal outcome.

For resectable tumours, 5-year survival stands at between 10% and 40%. Overall, 5 year survival is in the region of 5% to 10%. There is little evidence of significant efficacy of chemoradiotherapy, but it is worthwhile considering on a case by case basis.

Criteria for resectability

The traditional guidelines for resectability of cholangiocarcinoma are:

- Absence of retropancreatic and paracoeliac nodal metastases or distant liver metastases
- Absence of invasion of the portal vein or main hepatic artery (although some centres support *en bloc* resection with vascular reconstruction)
- Absence of extrahepatic adjacent organ invasion
- Absence of disseminated disease

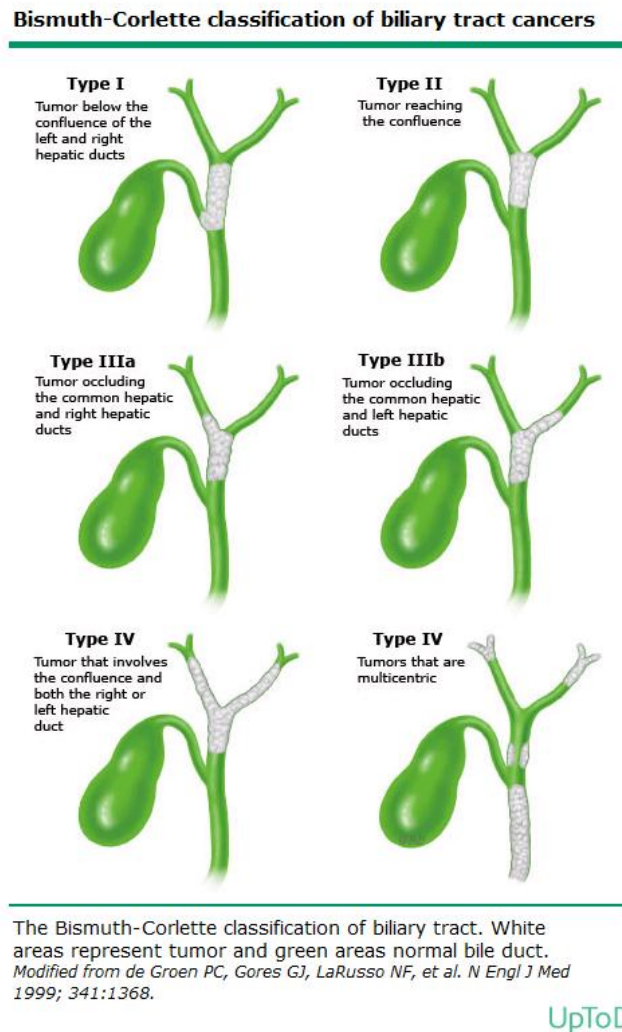
Additional criteria are specific to tumour location and all cases should be discussed with the pancreaticobiliary regional SMDT. Resection of distal cholangiocarcinomas is usually by a Whipple's procedure, hilar lesions are often resected with a partial liver resection and

formation of a hepaticojejunostomy, and intrahepatic lesions are treated with hepatic resection.

Staging

Staging of cholangiocarcinoma is complex. Staging systems for reference follow.

Bismuth staging system for hilar cholangiocarcinoma



TNM staging for intrahepatic cholangiocarcinoma

Primary tumor (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis Carcinoma in situ (intraductal tumor)

T1 Solitary tumor without vascular invasion

T2a Solitary tumor with vascular invasion

T2b Multiple tumors, with or without vascular invasion

T3 Tumor perforating the visceral peritoneum or involving the local extra hepatic structures by direct invasion

T4 Tumor with periductal invasion

Regional lymph nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Regional lymph node metastasis present

Distant metastasis (M)

M0 No distant metastasis

M1 Distant metastasis present

Anatomic stage/prognostic groups

Stage 0 Tis N0 M0

Stage I T1 N0 M0

Stage II T2 N0 M0

Stage III T3 N0 M0

Stage IVA T4 N0 M0

Any T N1 M0

Stage IVB Any T Any N M1

TNM staging system for perihilar cholangiocarcinoma

Primary tumor (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis Carcinoma in situ

T1 Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue

T2a Tumor invades beyond the wall of the bile duct to surrounding adipose tissue

T2b Tumor invades adjacent hepatic parenchyma

T3 Tumor invades unilateral branches of the portal vein or hepatic artery

T4 Tumor invades main portal vein or its branches bilaterally; or the common hepatic artery; or the second-order biliary radicals bilaterally; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement

Regional lymph nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Regional lymph node metastasis (including nodes along the cystic duct, common bile duct, hepatic artery, and portal vein)

N2 Metastasis to periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes

Distant metastasis (M)

M0 No distant metastasis

M1 Distant metastasis

Anatomic stage/prognostic groups

Stage 0 Tis N0 M0

Stage I T1 N0 M0

Stage II T2a-b N0 M0
Stage IIIA T3 N0 M0
Stage IIIB T1-3 N1 M0
Stage IVA T4 N0-1 M0
Stage IVB Any T N2 M0
Any T Any N M1

TNM staging system for distal cholangiocarcinoma

Primary tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ
T1 Tumor confined to the bile duct histologically
T2 Tumor invades beyond the wall of the bile duct
T3 Tumor invades the gallbladder, pancreas, duodenum, or other adjacent organs without involvement of the celiac axis, or the superior mesenteric artery
T4 Tumor involves the celiac axis, or the superior mesenteric artery

Regional lymph nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis
Distant metastasis (M)
M0 No distant metastasis
M1 Distant metastasis

Anatomic stage/prognostic groups

Stage 0 Tis N0 M0
Stage IA T1 N0 M0
Stage IB T2 N0 M0
Stage IIA T3 N0 M0
Stage IIB T1 N1 M0, T2 N1 M0, T3 N1 M0
Stage III T4 Any N M0
Stage IV Any T Any N M1

CYSTIC PANCREATIC LESIONS

The more common types of pancreatic cystic lesions are given below.

Serous cystadenomas

These are benign lesions that do not require follow up. They have bland imaging features and a low CEA (< 192 ng/mL) and normal cytology at aspiration.

Mucinous cystadenomas and cystadenocarcinomas

These are pre-malignant and malignant lesions respectively that require excision. They have a high CEA (> 192 ng/mL), and may have abnormal cytology and worrying imaging features such as thickened or irregular cyst walls and solid components.

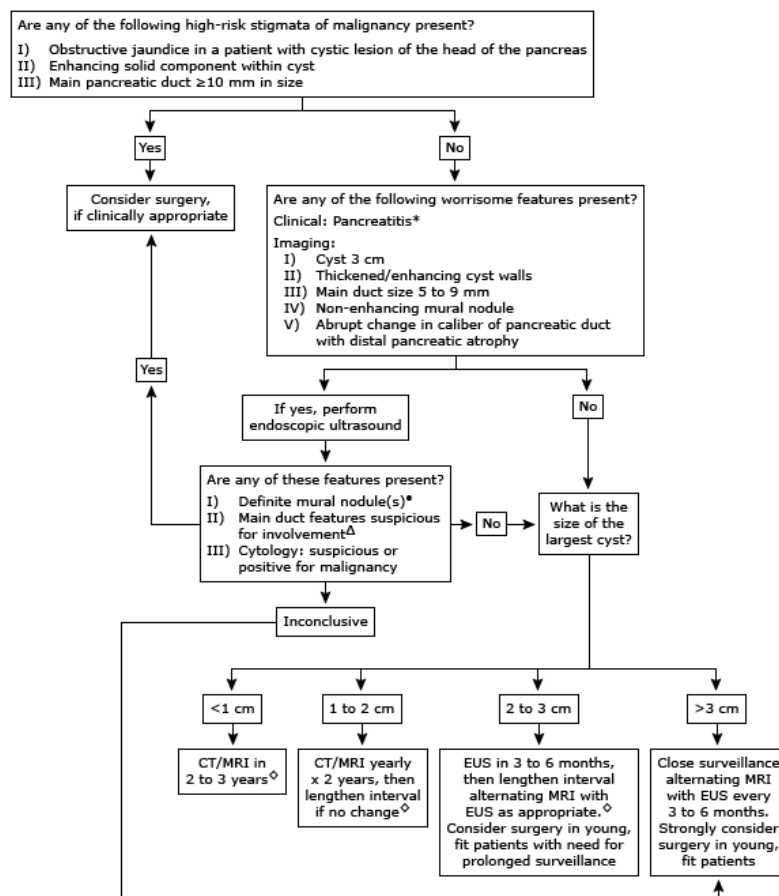
Intraductal papillary mucinous neoplasms (IPMNs)

These cysts form due to papillary proliferation of mucous producing cells. They have malignant potential. Risk factors for malignant transformation and therefore consideration of resection are determined by international consensus guidelines from 2012. These separated into main duct and branch duct IPMNs.

Main duct IPMN

- Main duct is ≥ 10 mm in diameter
- Main duct is 5 to 9 mm in diameter and at EUS any of:
 - Thickened walls
 - Intraductal mucin
 - Mural nodules on EUS
 - Suspicious cytology

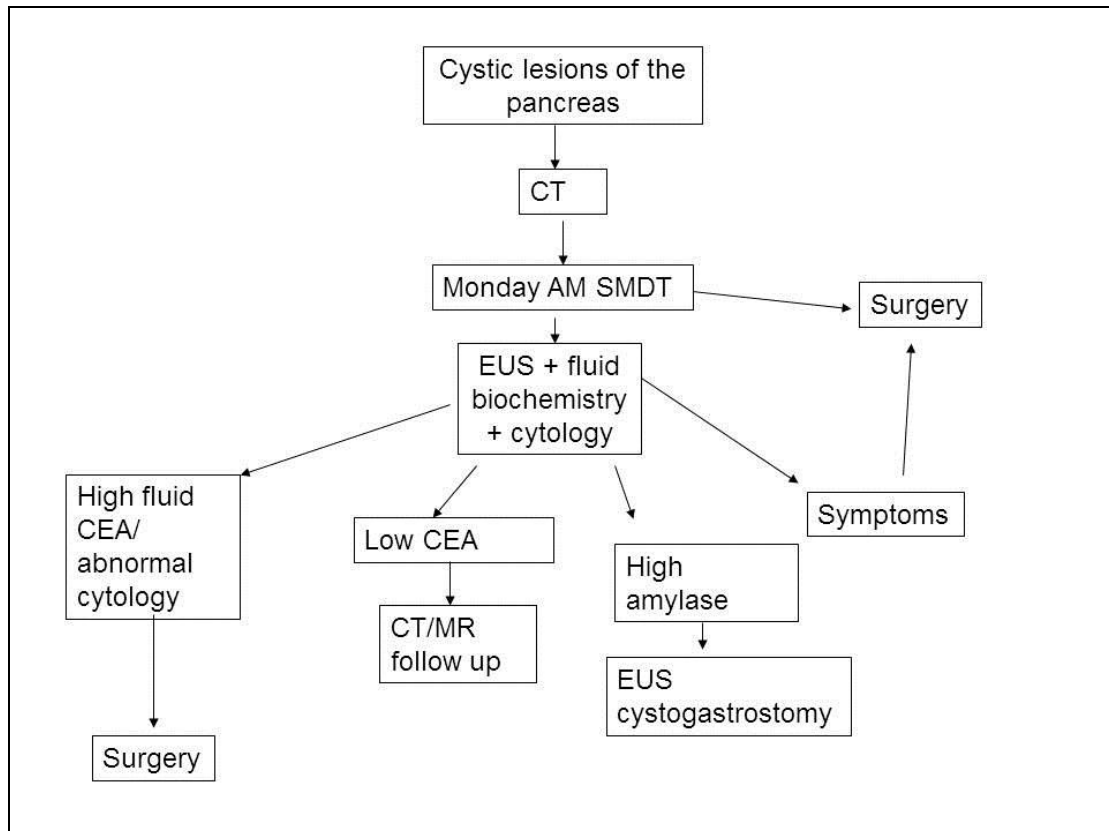
Branch duct IPMN



Pseudocysts

These are a complication of pancreatitis, are usually diagnosed on imaging grounds and have a high amylase if aspirated. Management involves either aspiration and dealing with the underlying cause of pancreatitis or cystogastrostomy drainage by EUS.

An overall management strategy for cystic pancreatic lesions as recommended by the Addenbrooke's SMDT follows.



VASCULAR LIVER DISEASES AND NON-CIRRHOTIC PORTAL HYPERTENSION