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| |  | | --- | | ALCOHOLIC LIVER DISEASE |  |  | | --- | | Alcohol remains one of the most common causes of chronic liver disease. |  |  | | --- | | Epidemiology |  |  | | --- | | The risk of alcoholic liver disease is variable and not everyone who drinks heavily will develop liver disease. Only 10% of alcoholics have evidence of cirrhosis at post-mortem. Alcoholic liver disease does not occur below a threshold of 21 units/week in women and 28 units/week in men (unit =8g).Most individuals with liver disease will have drunk heavily for more than 5 years. |  |  | | --- | | Although the average alcohol consumption of an individual with cirrhosis is 160 g/day for an average of 8 years, there is no clear linear relationship between dose and liver damage. |      |  | | --- | | Some of the risk factors for alcoholic liver disease are:   * *Drinking patterns*. Type of beverage drunk does not affect risk, but liver damage is more likely to occur in continuous rather than binge drinkers. * *Gender.* The incidence of alcoholic liver disease is increasing in women, who often conceal alcohol misuse and have higher blood ethanol levels than men after drinking because their body mass is lower. * *Genetics*. Alcoholism is more common in monozygotic than dizygotic twins. However, polymorphisms in the gene-coding enzymes involved in alcohol metabolism, tumour necrosis factor-alpha (TNF-α) and aldehyde dehydrogenase (ALD), have yet to be linked to alcoholic liver disease. * *Nutrition*. Animals given a choline-deficient diet are more likely to develop alcoholic liver disease. |  |  | | --- | | Aetiology |  |  | | --- | | Alcohol is metabolised almost exclusively by the liver. |        |  | | --- | |  |  |  | | --- | | **Acetaldehyde** |  |  | | --- | | Eighty per cent of alcohol is metabolised to acetaldehyde by the mitochondrial enzyme, alcohol dehydrogenase (ADH). Acetaldehyde forms adducts with cellular proteins in hepatocytes which activate the immune system, leading to cell injury. |  |  | | --- | | Acetaldehyde is then metabolised to acetyl coA and acetate by ALD. This generates NADH from NAD (nicotinamide adenine dinucleotide) which changes the redox potential of the cell. |  |  | | --- | | Twenty per cent of alcohol is metabolised by the mixed function oxidase enzymes of the smooth endoplasmic reticulum. Cytochrome CYP2E1 is induced by alcohol, which increases oxygen consumption and lipid peroxidation. Microsomal peroxidation leads to oxygen free radicals which can induce mitochondrial damage. |  |  | | --- | | The mechanisms leading to specific liver lesions of alcoholic liver disease are still poorly understood. |  |  | | --- | | **Cytokines** |  |  | | --- | | Increased endotoxin is released into the blood in alcoholic hepatitis via increased gut permeability. TNF-α production is increased from monocytes. Release of IL-1, 2 and 8 also occurs. These cytokines are also involved in fibrogenesis . |  |  | | --- | | Pathology |  |  |  |  | | --- | --- | --- | | . In about 80% of patients with severe alcoholic hepatitis, cirrhosis will coexist at presentation. Iron deposition is common and does not necessarily indicate haemochromatosis.   |  | | --- | | *PATHOLOGICAL FEATURES OF ALCOHOLIC LIVER DISEASE* |  |  | | --- | | * Alcoholic hepatitis   + Lipogranuloma   + Neutrophil infiltration   + Mallory's hyaline   + Pericellular fibrosis * Macrovesicular steatosis * Fibrosis and cirrhosis * Central hyaline sclerosis | |  |  | | --- | | Clinical features |  |  | | --- | | Alcoholic liver disease manifests itself as a clinical spectrum ranging from incidental abnormal liver biochemistry with few physical signs to advanced cirrhosis. The liver is often enlarged in alcoholic liver disease, even in the presence of cirrhosis. Peripheral stigmata of chronic liver disease, including Dupytren's contractures and palmar erythema, are more common in alcoholic cirrhosis than cirrhosis of other aetiologies. |  |  | | --- | | The spectrum of liver disease is often divided into three syndromes but in reality these overlap considerably, as do the pathological changes seen in the liver. |  |  | | --- | |  |  |  | | --- | | 23.47 CLINICAL SYNDROMES OF ALCOHOLIC LIVER DISEASE  **Fatty liver** |        |  | | --- | | * Asymptomatic abnormal liver biochemistry * Normal/large liver |  |  | | --- | |  | |
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| **Alcoholic hepatitis** |

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| * Jaundice * Malnutrition * Hepatomegaly * Features of portal hypertension (e.g. ascites, encephalopathy) |

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**Cirrhosis**

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| * Stigmata of chronic liver disease * Large, normal or small liver * Ascites/varices/encephalopathy * Hepatocellular carcinoma |

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| Investigations  Investigations aim to establish alcohol misuse, exclude alternative or coexistent causes of liver disease, such as hepatitis C or haemochromatosis, and assess the severity of liver disease. The clinical history from patient, relatives and friends is most important in establishing alcohol misuse, duration and severity. Biological markers, particularly macrocytosis in the absence of anaemia, may suggest and support a history of alcohol misuse. A raised GGT is not specific for alcohol misuse and will be elevated in the presence of hepatic steatosis and fibrosis. The level may not therefore return to normal with abstinence if chronic liver disease is present. Unexplained rib fractures, particularly bilateral, on a chest X-ray are also suggestive of alcohol misuse. |

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| The presence of jaundice suggests alcoholic hepatitis. Determining the extent of liver damage often requires a liver biopsy. |

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| Prothrombin time and bilirubin can be used to give a 'discriminant function' (DF), also known as the Maddrey's score, which enables the clinician to assess prognosis in alcoholic hepatitis (PT = prothrombin time. Serum bilirubin in μmol/l is divided by 17 to convert to mg/dl): = |

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| A value over 32 implies severe liver disease with a poor prognosis. |

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| Management |

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| Cessation of alcohol consumption is the single most important treatment; without this all other therapies are of limited value. Abstinence is even effective at preventing progression of liver disease and death when cirrhosis is present. Life-long abstinence is the best advice and is essential for those with more severe liver disease. |

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| Treatment for complications of cirrhosis, such as variceal bleeding, encephalopathy and ascites, may also be needed. |

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| Nutrition |

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| Good nutrition is very important and enteral feeding via a fine-bore nasogastric tube may be needed in severely ill patients. |

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| Corticosteroids |

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| 'In severe alcoholic hepatitis corticosteroids improve survival at 28 days from 65% to 85% (NNTB 5).' |

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| These are of value in patients with severe alcoholic hepatitis (Maddrey's discriminative score > 32) and increase survival . Sepsis is the main side-effect of steroids, and existing sepsis and variceal haemorrhage are the main contraindication to their use. If the bilirubin has not fallen 7 days after starting steroids, they are unlikely to reduce mortality and should be stopped. |

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| Pentoxifylline  'In severe alcoholic hepatitis, oral pentoxifylline reduces inpatient mortality, particularly from hepatorenal failure, from 46% to 25% (NNTB 5). |

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| Pentoxifylline, which has a weak anti-TNF action, may be beneficial in severe alcoholic hepatitis. It appears to reduce the incidence of hepatorenal failure and its use is not complicated by sepsis . |

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| Liver transplantation |

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| The role of liver transplantation in the management of alcoholic liver disease remains controversial. In many centres, however, alcoholic liver disease is a common indication for liver transplantation. The challenge is to identify patients with an unacceptable risk of returning to harmful alcohol consumption. Many programmes require a 6-month period of abstinence from alcohol before a patient is considered for transplantation. Although this relates poorly to the incidence of alcohol relapse after transplantation, liver function may improve to the extent that transplantation is no longer necessary. The outcome of transplantation for alcoholic liver disease is good (if the patient remains abstinent) because patients often require minimal immunosuppression and there is no risk of disease recurrence. Transplantation for alcoholic hepatitis has a poorer outcome than for complications of alcoholic cirrhosis. |

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| Prognosis |

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| The most important prognostic factor is the patient's ability to stop drinking alcohol. General health and life expectancy are improved when this occurs, irrespective of the form of alcoholic liver disease. |

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| Alcoholic fatty liver disease |

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| This has a good prognosis and steatosis usually disappears after 3 months of abstinence. |

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| Alcoholic hepatitis |

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| This has a significantly worse prognosis. About one-third of patients die in the acute episode, particularly those with hepatic encephalopathy or a prothrombin time sufficiently prolonged to exclude a percutaneous liver biopsy. Cirrhosis, if not already present, will occur if drinking continues. Patients with acute alcoholic hepatitis often deteriorate during the first 1-3 weeks in hospital. Even if they abstain, it may take up to 6 months for jaundice to resolve. In patients presenting with jaundice who subsequently abstain, the 3- and 5-year survival is 70%. In contrast, those who continue to drink have 3- and 5-year survival rates of 60% and 34% respectively. |

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| Alcoholic cirrhosis |

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| This often presents with a serious complication such as variceal haemorrhage or ascites, and only half of such patients will survive 5 years from presentation. However, most who survive the initial illness and who become abstinent will survive beyond 5 years.   |  | | --- | | NON-ALCOHOLIC FATTY LIVER DISEASE |  |  | | --- | | Non-alcoholic fatty liver disease (NAFLD) is a disease of affluent societies and its prevalence is increasing in proportion to the rise in obesity. It has become the most common cause of chronic liver disease after hepatitis B, hepatitis C and alcohol. It can be classified into simple fatty liver disease (or non-alcoholic fatty liver, NAFL) and non-alcoholic steatohepatitis (NASH). The former has a benign prognosis but the latter is associated with fibrosis and progression to cirrhosis. |  |  | | --- | | Epidemiology |  |  | | --- | | NAFLD affects about 3% of the population in the USA. The prevalence is higher in those with diabetes and those with the metabolic syndrome. Rare causes of NAFLD include tamoxifen, amiodarone and exposure to certain petrochemicals. NAFLD has also been reported following weight-reducing jejenal bypass surgery. Many cases of cirrhosis that were previously labelled crypto-genic (i.e. cause unknown) are now thought to be due to NAFLD. |  |  | | --- | | Aetiology and pathogenesis |  |  | | --- | | Most individuals with NAFLD have insulin resistance but not necessarily overt glucose intolerance. The current two-hit hypothesis explains why not everyone with fatty liver disease develops hepatic fibrosis. The 'first hit' results in steatosis (fatty liver), which is only complicated by inflammation if a 'second hit occurs'. Leptin is probably then needed to cause hepatic fibrosis. |  |  | | --- | | Clinical features |  |  | | --- | | Most patients present with asymptomatic abnormal LFTs, particularly elevation of the transaminases or isolated elevation of the GGT. Occasionally, the condition presents with a complication of cirrhosis such as variceal haemorrhage or hepatocellular carcinoma. In contrast to alcoholic liver disease, jaundice only occurs when cirrhosis is established. NAFLD is the most likely diagnosis in a patient with elevated serum transaminases, no history of alcohol abuse and a negative chronic liver disease screen. |  |  | | --- | |  | |  | |  |  |  | | --- | |  |  |  | | --- | | Investigations |  |  | | --- | | Liver function tests |  |  | | --- | | Unfortunately, there is no single diagnostic blood test; however, in contrast to alcoholic liver disease, the ALT is normally higher than the AST. Elevated alkaline phosphatase levels are seen in about 30% of cases. It is important to differentiate simple fatty liver disease (NAFL), which does not require follow-up, from NASH. Elevated serum transaminases greater than twice the upper limit of normal and the presence of the metabolic syndrome (hypertriglyceridaemia, hypertension, diabetes mellitus, an elevated BMI > 25 and especially truncal obesity) are useful predictors of NASH. |  |  | | --- | | Ultrasound |  |  | | --- | | Ultrasound cannot differentiate simple fatty liver disease without fibrosis (NAFL) from NASH; in both cases the liver will appear bright on ultrasound. |  |  | | --- | | Liver biopsy |  |  | | --- | | Individuals with serum transaminases greater than twice the upper limit of normal and features of the metabolic syndrome should be offered a liver biopsy to determine whether inflammation and fibrosis are present. Histologically, fat deposition is usually macrovesicular , in contrast to the microvesicular fat seen in acute fatty liver disease of pregnancy. NASH is characterised by fat, Mallory bodies, neutrophil infiltration and pericellular fibrosis. These features are indistinguishable histologically from alcoholic hepatitis, so a diagnosis of NASH relies on excluding alcohol misuse, the absence of jaundice, and the presence of risk factors such as obesity and diabetes. Fat often disappears by the time cirrhosis develops. |  |  | | --- | | Management |  |  | | --- | |  | |  | |  |  |  | | --- | | Current treatments are aimed at reducing BMI and insulin resistance. Metformin has been shown to improve LFTs and should be the first-line treatment in type 2 diabetes with NAFLD. Thiazolidinediones such as pioglitazone also improve LFTs in NAFLD and early data suggest they may improve inflammation and fibrosis. Weight loss will also reduce serum transaminase levels, improve liver fibrosis and reduce insulin resistance. Antioxidants such as vitamin E are not effective. There is no rationale for using HMG CoA reductase inhibitors (statins) in the treatment of NAFLD but they are not contraindicated for treatment of coexistent hyperlipidaemia. |  |  | | --- | | Prognosis |  |  | | --- | | Once cirrhosis has occurred, survival is similar to that in hepatitis C cirrhosis with 5- and 10-year survival rates of 90% and 84% respectively. Hepatocellular carcinoma frequently complicates NAFLD cirrhosis. Although less than 5% of liver transplants are currently performed for NAFLD, this is likely to increase. Unfortunately, the condition may recur in the graft. | |
| DRUGS, TOXINS AND THE LIVER |

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| The liver is the primary site of drug metabolism. Liver disease may affect the capacity of the liver to metabolise drugs and unexpected toxicity may occur when patients with liver disease are given drugs in normal doses .   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | |  | | --- | | HEPATOTOXIC DRUG REACTIONS |  |  | | --- | | Drug toxicity should be high in the differential diagnosis of acute liver failure, jaundice and abnormal liver biochemistry. Some typical patterns of drug toxicity are listed in [Box 23.50](mk:@MSITStore:C:\Davidson's%20Principles%20&%20Practice%20of%20Medicine%2020th.2007.Ed.CHM::/www.studentconsult.com/content/bookcontent.cfm@xrefid=b023050#B023050); the most common picture is a mixed cholestatic hepatitis. The presence of jaundice indicates more severe liver damage. Although acute liver failure can occur, most drug reactions are acute and self-limiting; chronic liver damage is rare. LFTs often take weeks to return to normal following a drug-induced hepatitis and it may take months for them to normalise following a cholestatic hepatitis. Occasionally permanent bile duct loss (ductopenia) follows a cholestatic drug reaction, such as that due to co-amoxiclav, resulting in chronic cholestasis with persistent symptoms such as itching. |  |  | | --- | | 23.50 EXAMPLES OF COMMON CAUSES OF DRUG-INDUCED HEPATOTOXICITY |      |  |  | | --- | --- | | **Pattern** | **Drug** | | **Cholestasis** | Chlorpromazine High-dose oestrogens | | **Cholestatic hepatitis** | NSAIDs Co-amoxiclav Statins | | | **Acute hepatitis** | Rifampicin Isoniazid | | **Non-alcoholic steatohepatitis** | Amiodarone | | **Venous outflow obstruction** | Busulfan Azathioprine | | **Fibrosis** | Methotrexate |  |  | | --- | |  |  |  | | --- | | 23.51 THE DIAGNOSIS OF ACUTE DRUG-INDUCED LIVER DISEASE |      |  | | --- | |  |  |  | | --- | | * Tabulate drugs taken   + Prescribed   + Self-administered * Establish if reported hepatoxicity in the literature * Relate time drugs taken to onset of illness 4 days-8 weeks (usual) * Effect of stopping drugs on normalisation of liver biochemistry   + Hepatitic LFTs (2 months)   + Cholestatic/mixed LFTs (6 months) * Exclude other causes   + Viral hepatitis   + Biliary disease * Consider liver biopsy |  |  | | --- | |  | | |  | | **N.B.** Challenge tests with drugs should be avoided. |  |  | | --- | |  |  |  | | --- | | The key to diagnosing acute drug-induced liver disease is always to take a detailed drug history ([Box 23.51](mk:@MSITStore:C:\Davidson's%20Principles%20&%20Practice%20of%20Medicine%2020th.2007.Ed.CHM::/www.studentconsult.com/content/bookcontent.cfm@xrefid=b023051#B023051)). A liver biopsy should be considered if there is suspicion of pre-existing liver disease or if blood tests fail to improve when the suspect drug is withdrawn. |  |  | | --- | | TYPES OF LIVER INJURY |  |  | | --- | | Different histological patterns of liver injury may occur. |  |  | | --- | | Cholestasis |  |  | | --- | | Pure cholestasis (selective interference with bile flow in the absence of liver injury) can occur with oestrogens; this was seen quite frequently when higher concentrations of oestrogens (50 μg/day) were used as contraceptives. Both the current oral contraceptive pill and hormone replacement therapy can be safely used in chronic liver disease. |  |  | | --- | | Chlorpromazine and antibiotics such as flucloxacillin are examples of drugs that cause cholestatic hepatitis, which is characterised by inflammation and canalicular injury. Co-amoxiclav is the most common antibiotic to cause abnormal LFTs but, unlike other antibiotics, it may not produce symptoms until 10-42 days after it is stopped. Anabolic steroids used by body-builders may also cause a cholestatic hepatitis. In some cases (e.g. NSAIDs and COX-2 inhibitors) there is overlap with acute hepatocellular injury. |  |  | | --- | | Hepatocyte necrosis |  |  | | --- | | Many drugs cause an acute hepatocellular necrosis with high serum transaminase concentrations; paracetamol ([p. 208](mk:@MSITStore:C:\Davidson's%20Principles%20&%20Practice%20of%20Medicine%2020th.2007.Ed.CHM::/www.studentconsult.com/content/bookcontent.cfm@xrefid=p0208#P0208)) is the best known. Inflammation is not always present but does accompany necrosis in liver injury due to diclofenac (an NSAID) and isoniazid (an anti-tuberculous drug). Granuloma may be seen in liver injury following the use of allopurinol. Acute hepatocellular necrosis has also been described following the use of several herbal remedies including germander, comfrey and jin bu huan. Recreational drugs, including cocaine and ecstasy, can also cause severe acute hepatitis. |  |  | | --- | | Steatosis |  |  | | --- | |  | |  | |  |  |  | | --- | | Microvesicular hepatocyte fat deposition, due to direct effects on mitochondrial beta-oxidation, can follow exposure to tetracyclines and sodium valproate ([Box 23.63](mk:@MSITStore:C:\Davidson's%20Principles%20&%20Practice%20of%20Medicine%2020th.2007.Ed.CHM::/www.studentconsult.com/content/bookcontent.cfm@xrefid=b023063#B023063), [p. 988](mk:@MSITStore:C:\Davidson's%20Principles%20&%20Practice%20of%20Medicine%2020th.2007.Ed.CHM::/www.studentconsult.com/content/bookcontent.cfm@xrefid=p0988#P0988)). Macrovesicular hepatocyte fat deposition has been described with tamoxifen, and amiodarone toxicity can produce a similar histological picture to NASH ([p. 971](mk:@MSITStore:C:\Davidson's%20Principles%20&%20Practice%20of%20Medicine%2020th.2007.Ed.CHM::/www.studentconsult.com/content/bookcontent.cfm@xrefid=p0971#P0971)). |  |  | | --- | | Vascular/sinusoidal lesions |  |  | | --- | | Drugs such as alkylating agents used in oncology can damage the vascular endothelium and lead to hepatic venous outflow obstruction. Chronic overdose of vitamin A will also damage the sinusoids and trigger local fibrosis that can result in portal hypertension. |  |  | | --- | | Hepatic fibrosis |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | Most drugs cause reversible liver injury and hepatic fibrosis is very uncommon. Methotrexate, however, as well as causing acute liver injury when it is started, can lead to cirrhosis when used in high doses over a long period of time. Risk factors for drug-induced hepatic fibrosis include pre-existing liver disease and a high alcohol intake   |  | | --- | | DRUGS TO AVOID IN CIRRHOSIS |  |  | | --- | | Most analgesics can precipitate complications and need to be used cautiously in cirrhosis ([Box 23.52](mk:@MSITStore:C:\Davidson's%20Principles%20&%20Practice%20of%20Medicine%2020th.2007.Ed.CHM::/www.studentconsult.com/content/bookcontent.cfm@xrefid=b023052#B023052)). NSAIDs are hepatotoxic and can potentiate hepatorenal failure; they should therefore be avoided in cirrhosis. Paracetamol up to a dose of 3 g/day can be used safely in chronic liver disease but higher doses may result in acute hepatic necrosis, particularly in patients with alcoholic liver disease. |  |  | | --- | | 23.52 DRUGS TO BE AVOIDED IN CIRRHOSIS |      |  |  |  | | --- | --- | --- | | **Drug** | **Problem** | **Toxicity** | | **NSAIDs** | Reduced renal blood flow Ulceration | Hepatorenal failure Bleeding varices | | **ACE inhibitors** | Reduced renal blood flow | Hepatorenal failure | | **Codeine** | Constipation | Hepatic encephalopathy | | **Narcotics** | Constipation Drug accumulation | Hepatic encephalopathy | | **Anxiolytics** | Drug accumulation | Hepatic encephalopathy | | |

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