Ministry of Defence

Synopsis of Causation

Hepatitis and Liver Injury

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Disclaimer

This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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1. Definition

1.1. Hepatitis is a loosely-applied term used to indicate inflammation of, or damage to the liver, usually accompanied by hepatic cell necrosis. It can arise from a number of causes and may take an acute or chronic form.

1.2. **Acute hepatitis** The term refers to the abrupt onset of signs and symptoms of hepatic inflammation. It may be caused by a number of agents, e.g. viruses and hepatotoxic substances. The clinical features, course and prognosis differ according to the cause.

1.3. **Chronic hepatitis** comprises several diseases which have common clinical manifestations and are all marked by a chronic inflammatory process in the liver that can lead insidiously to cirrhosis and liver-failure. Conventionally, chronic hepatitis is said to be present if there is evidence of ongoing hepatic injury for six months or more, although the strict definition of the condition is based upon histological features of hepatocellular necrosis along with chronic inflammatory cell infiltration.

1.4. A wide variety of agents may cause hepatitis, of which the most important are discussed below.

1.5. **Viral hepatitis** is caused by infection with specific viruses. The nomenclature of these hepatitis viruses is based on the successive discovery of new agents rather than on any consideration of modes of transmission or clinical characteristics. So far, five primary human hepatotropic viruses are recognised; A, B, C, D and E.[1]

1.5.1. **Non-A...E hepatitis** In Western countries serological surveys of cases of acute hepatitis have shown that between 2 and 20% of cases cannot be attributed to any of the five known hepatitis viruses. Acute hepatitis that appears to be viral in aetiology but in which the virus cannot be identified is referred to as acute non-A, non-B, non-C, non-D, non-E hepatitis, or non-A...E hepatitis. A number of candidate viruses have been associated with this condition, but no clear links have emerged.

1.5.2. **Hepatitis G virus and TT virus** Although these two agents were proposed as being responsible for some cases of non-A...E hepatitis, a large body of evidence now suggests that they do not cause liver disease.

1.6. **Alcohol-related hepatitis** This disorder typically evolves from fatty liver. Alcoholic hepatitis may resolve if underlying fibrosis is minimal and the patient ceases to drink alcohol; otherwise the process may advance to cirrhosis.

1.7. **Hepatotoxic syndromes** A large number of drugs and toxins may damage the liver, and the resulting disorders, although histologically disparate, are often included in the loose definition of hepatitis. Adverse drug reactions that affect the liver are difficult to define as the biochemical tests used to detect liver injury may be abnormal merely because they reflect the liver's adaptive response to the drugs. In general, however, liver injury is defined when tests of liver function (serum alanine aminotransferase (ALT), alkaline phosphatase (AP), or bilirubin levels) show an increase to more than twice the upper limit of the normal range.

1.8. **Autoimmune hepatitis** (AIH) is a self-perpetuating hepatocellular inflammation of unknown cause. It is defined by a number of factors, including certain histological characteristics,

manifestations of immunoreactivity and the exclusion of other causes of hepatitis. Classification into the descriptive categories of type 1 or type 2 autoimmune hepatitis is based on the nature of the autoantibodies involved.[2]

1.9. **Miscellaneous** The liver may be affected by a wide variety of infective agents as a component of acute systemic infections. These include bacterial, fungal, parasitic, and viral agents. In a few of these conditions the liver is specifically targeted, but in many the hepatic injury is subsidiary to the overall constitutional effects of the disease.

2. Clinical features

2.1. **Acute viral hepatitis** The clinical characteristics of acute viral hepatitis depend to a large extent on the infecting virus, but four stages are generally recognised:

- **Phase 1** - Viral replication phase. Patients are asymptomatic during this phase, but laboratory studies may demonstrate serological and enzyme markers of hepatitis
- **Phase 2** - Prodromal phase. Patients experience non-specific symptoms such as malaise, fatigue, anorexia, nausea and vomiting, and alterations in taste, painful joints, urticaria, and pruritus are not uncommon
- **Phase 3** - Icteric phase. The urine may become dark in colour and the stools become pale. In addition to the predominant gastrointestinal symptoms and malaise, the patient becomes icteric (jaundiced) and may develop right upper quadrant pain with hepatomegaly
- **Phase 4** - Convalescent phase. Signs and symptoms resolve and liver enzymes return to normal

2.1.1. **Hepatitis A virus (HAV)** The disease is usually mild, and indeed may pass unnoticed in children, only 5% of whom are affected by jaundice compared with around 30% of adults. The incubation period is 15-49 days with an average of 25 days. **It results in acute hepatitis only and does not proceed to a chronic phase**.

2.1.2. Less than 1% of cases proceed to fulminant liver failure. However the later in life that infection occurs, the greater the clinical severity, and approximately 5% of those over the age of 65 years who are infected will develop fatal acute fulminant hepatitis. Several formalin-inactivated hepatitis A vaccines are available, including a combined preparation with hepatitis B vaccine.

2.1.3. **Hepatitis B virus (HBV)** is the commonest agent causing chronic hepatitis world-wide. In some 90% of children the disease passes unnoticed, but in most adults it pursues a course similar to that described in 2.1 above. The incubation period varies from 30-180 days, with the average approximately 75 days. The condition may resolve rapidly but in some cases it pursues a more prolonged course with slow resolution. Still others may have symptoms that periodically improve, only to worsen later (relapsing hepatitis). A subset of patients (less than 1%) suffers rapid progression of their disease to the point of fulminant hepatic failure. This may occur over days to weeks. **Up to 5% of adult cases of acute HBV hepatitis lead to chronic disease.**

2.1.4. HBV vaccine is now available in most western countries and provides effective immunity in most cases. However it is important that it is administered in the deltoid (upper arm) region, as in a proportion of cases injection into the buttock will fail to confer immunity. In addition, some 2%-10% of adults do not respond adequately to immunisation, and follow-up serological tests are often advised in at-risk occupations to confirm protection. Repeat doses of vaccine can help generate an immunological response in such cases.

2.1.5. **Hepatitis C virus (HCV)** The clinical course depicted in 2.1 above is not typical of HCV infection. It usually causes a mild illness with only 5%-10% of cases showing jaundice. The incubation period ranges from 15 to 120 days, with an average of 50 days. **The importance of hepatitis C is that in 70%-80% of cases it does not resolve, but progresses to chronic hepatitis.**

2.1.6. The virus is highly variable, with a high mutation rate, and the development of antibodies does not protect against re-infection with the same strain of HCV. As a result, there is at present no effective vaccine against HCV infection.

2.1.7. **Hepatitis D virus (HDV)** The hepatitis delta virus is unique in that it requires the hepatitis B virus for replication. This is because it is an incomplete virus, dependent on HBV envelope proteins and the interaction between the two viruses is very complex. Delta hepatitis, as it is conventionally called, therefore can only arise in the presence of hepatitis B infection. It occurs in two clinical patterns; co-infection and superinfection:

- **Delta co-infection** is the simultaneous occurrence of acute delta- and acute hepatitis B virus infections
- **Delta superinfection** represents the occurrence of acute HDV infection in a patient who is already a chronic hepatitis B carrier

2.1.8. Delta hepatitis tends to be more severe than hepatitis B alone and is more likely to lead to fulminant hepatitis. In addition it is more likely to cause severe chronic hepatitis and ultimately cirrhosis. **Most cases of acute co-infection resolve but chronic delta hepatitis will supervene in about 80% of patients with superinfection.**[3] There is no specific vaccine against HDV.

2.1.9. **Hepatitis E Virus (HEV)** The incubation period is about 6 weeks, and faecal excretion of the virus may persist for nearly 2 months after the onset of hepatitis. A striking feature of HEV infection and the main clinical difference from HAV, is the propensity to induce fulminant hepatitis if acquired during mid-trimester pregnancy, and mortality rates of 10% to 40% are recorded amongst pregnant women. **However like HAV, this virus causes acute hepatitis without proceeding to a chronic phase.** An effective vaccine has now been developed but is not yet commercially available.

2.1.10. **Relative infectivity of HBV and HCV** The risk of acquiring HBV infection from a needlestick injury with a needle contaminated with infected blood is in the region of 30%. In comparison the equivalent risk of acquiring HCV infection from a similar injury is 10%, while the risk of infection with human immunodeficiency virus (HIV) in this manner is 0.3%. HBV is readily transmitted during sexual intercourse, while HCV is rarely transmitted by this route.

2.2. **Alcohol-related hepatitis** Milder forms of alcoholic hepatitis are often completely asymptomatic. However in severe cases patients may present with fever, hepatomegaly, leukocytosis, and marked impairment of liver function. Jaundice may be present, along with coagulopathy and signs of portal hypertension (e.g., ascites, hepatic encephalopathy, variceal bleeding). Typical histological changes may be seen on liver biopsy. Alcoholic hepatitis usually progresses to cirrhosis if alcohol abuse continues. If the patient ceases to drink alcohol, alcoholic hepatitis usually resolves slowly over weeks to months, sometimes without permanent sequelae.

2.3. **Liver disease due to drugs and other agents** One striking aspect of liver disease caused by hepatotoxins is the wide variety of clinicopathological syndromes encountered, from altered liver function tests without overt liver injury to acute hepatocellular necrosis or chronic parenchymal liver disease and hepatic tumours, or cholestatic liver disease; indeed some agents may cause more than one type of reaction. Broadly, the clinical picture may be acute or chronic as described below, although this is a considerable oversimplification.

2.3.1. **Acute hepatotoxic hepatitis** At first, patients develop gastrointestinal symptoms such as nausea, vomiting and abdominal pain. After 24-48 hours these symptoms may temporarily resolve but this apparent recovery may be followed by a phase of increasingly severe illness and hepatic failure.

2.3.2. **Chronic hepatotoxic hepatitis** Some drugs are associated with chronic liver disease, usually as a result of prolonged exposure but occasionally short term administration may have this outcome. A condition resembling autoimmune hepatitis may result, or hepatic fibrosis, followed by cirrhosis. There may be general malaise, with anorexia, weight loss, muscle weakness and fatigue. Examination may reveal the characteristic features of palmar erythema, spider naevi, foetor hepaticus and hepatic enlargement.

2.4. **Autoimmune hepatitis** This progressive inflammatory disease of the liver occurs more commonly in young women and girls and may result in chronic hepatitis, eventually leading to fibrosis and cirrhosis. Like chronic viral hepatitis it may progress to primary hepatocellular cancer, although this is uncommon.

2.5. The clinical presentation of autoimmune hepatitis is variable. Typically the onset is insidious with a prodromal phase of many weeks or months, often with a history of one or more episodes of an influenza-like illness. Lethargy is a prominent feature, and other common symptoms include malaise, nausea, anorexia, upper abdominal discomfort and pain, arthralgia or myalgia, skin rashes, and oligomenorrhea in women. In about 30% of patients the onset is acute, with marked jaundice and many of the clinical features of severe viral hepatitis.[4] In about 15% of patients the condition is completely asymptomatic, and it is fortuitously diagnosed in the course of a routine examination.

2.6. **Fulminant hepatic failure** (Synonyms: fulminant hepatitis, acute liver failure). One of the most serious complications of hepatitis and liver injury from all causes is the development of fulminant hepatic failure, which is characterised by coagulopathy, encephalopathy, and cerebral oedema. The case-fatality rate for these patients approaches 80%.[5]

3. Aetiology

3.1. Viral hepatitis

3.1.1. **Hepatitis A virus** (HAV) This virus has a world-wide distribution. It produces outbreaks of infection, usually due to direct faecal-oral contact or contaminated water supplies. Most outbreaks which are traced to a food source are sporadic and due to poor food hygiene. However, contamination of shellfish by sewage is not infrequent and molluscs can retain and concentrate viruses in water. Homosexual men and those working with newly imported non-human primates are high-risk groups for HAV infection. Employment or attendance at a child day care facility is a risk factor, due to exposure to children who may be excreting the virus while not overtly unwell.

3.1.2. A number of investigators have reported an association between certain occupational groups and an increased risk of HAV infection,[6] particularly in relation to sewage workers, but a systematic review of the literature[7] found that there was no difference in seroprevalence between sewage workers and control groups. There does however appear to be an increased risk of contracting hepatitis A among workers whose job involves handling untreated sewage.[6]

3.1.3. Other groups reported to be at risk by reason of their occupation include health care workers, laboratory workers, food handlers, prison staff, armed services personnel and residential- and day care centre staff. However there is no epidemiological evidence of a statistically significant increased risk of HAV infection among these occupations.[6] It is notable that routine vaccination for serving personnel in the British armed forces includes hepatitis A immunisation.

3.1.4. Due to improved sanitary conditions in childhood, immunity to HAV has fallen over the past twenty years, and people travelling from low-risk to high-risk areas are at substantial risk of acquiring HAV infection. There is a particular risk in travelling to highly endemic areas with poor conditions of sanitation and a contaminated water supply, and in many countries infection rates are as high as 95% by the age of 16 years.[8]

3.1.5. **Hepatitis A immunisation** The Health Protection Agency advise that HAV vaccination should be offered to all individuals travelling to countries where they may be at risk of HAV. It should also be considered for those individuals with special needs whose capacity to maintain good standards of hygiene is limited and for their carers. Occupational vaccination should be offered to laboratory workers working directly with HAV or with non-human primates and to sewage workers who are at high likelihood of regular direct contact with raw sewage. In addition, individuals with haemophilia, hepatitis B or C virus infection or liver cirrhosis, and injecting drug users should be offered HAV vaccination as a preventive measure.[9]

3.1.6. **Hepatitis B virus (HBV)** It is estimated that there may be as many as 400 million people in the world chronically infected with hepatitis B virus.[1] Hepatitis B virus infection is relatively rare in developed countries. Even in the UK however, where acute infection is relatively uncommon, almost 2% of the population show evidence of previous infection. In sub-Saharan Africa and South East Asia this figure may be as high as 95%.

3.1.7. The infection is highly transmissible, and carriers, i.e. individuals who already harbour the virus, form the major reservoir of infection. In this group, those with hepatitis B e antigen (HBeAg) in their serum tend to have higher viral titres and thus greater infectivity. It is transmitted parenterally, i.e. by penetration of the skin, for example by a shared needlestick used in injection drug abuse, and through sexual contact. Saliva, serum, and semen all have been confirmed as potential sources of infection. High-risk groups for infection with HBV include children born to HBV-infected mothers, intravenous drug users, people born in endemic areas, and men who are homosexually active. Less commonly, tattooing and acupuncture have been implicated.[10]

3.1.8. Other vulnerable groups include health care workers who may be exposed to infected blood or bodily fluids, patients undergoing haemodialysis, recipients of multiple blood transfusions, e.g. haemophiliacs, and heterosexual individuals with multiple partners or those with a history of sexually transmitted disease. People living in institutions, including prisoners, people who are developmentally disabled, and household contacts or sexual partners of HBV carriers are also at particular risk.

3.1.9. Immigrants or refugees from areas of high HBV endemicity (Asia, Sub-Saharan Africa, Amazon Basin, Eastern Europe, Middle East) as well as children born in the United Kingdom to individuals from these areas are also at high risk.

3.1.10. Perinatal infection is another significant mode of transmission. At greatest risk are the newborn infants of HBeAg-positive women, whose risk of infection is in the region of 95%. By the age of six months, 90% of these children will themselves have the serological markers of HBV infection, and 90% will go on to develop chronic infection with HBV.

3.1.11. Epidemiological data indicate that transmission of HBV requires direct contact with or parenteral inoculation of blood and blood products, semen, or tissues. The mere presence of, or casual contact with, an infected person cannot be construed as exposure to HBV. Although the theoretical possibility of rare or low-risk alternative modes of transmission cannot be totally ruled out, the only documented occupational risks of HBV infection are associated with parenteral (including open wound) and mucous membrane exposure to blood and tissues.

3.1.12. **Immunisation** It is recommended that all healthcare workers who may be in contact with infected blood and body fluids should be immunised against hepatitis B infection and should be shown to have had a serological response to the vaccine. In other occupational groups, such as embalmers and morticians there is also an established risk of HBV infection and immunisation is recommended.

3.1.13. **Hepatitis C virus (HCV)** In contrast with HBV, this infection is very common in the developed world, and some 0.3–0.7% of the UK population are infected. It is estimated that there are 170 million people in the world with chronic hepatitis C.

3.1.14. The virus is spread almost exclusively by contact with infected blood, but since the introduction of screening of blood products for HCV in 1990 or 1991, the risk of acquiring hepatitis C from blood transfusion is now less than 1%. Since then, intravenous drug abuse has emerged as the almost exclusive mode of hepatitis C transmission in northern Europe and North America. Sexual transmission is unusual, with less than 5% of long-term sexual partners becoming infected.

3.1.15. Transmission from mother to child is also unusual and the frequency of infection in children of viraemic mothers is less than 5%. The mode of delivery of the infant does not affect infection rates and breast-feeding is safe. The rate of infection in children of infected parents does rise in the first 10 years of life but it seems relatively unusual to acquire the infection from close household contact.

3.1.16. Needlestick accidents are a potential source of HCV infection, and the incidence in health care workers with a history of needlestick exposure to infected blood is almost 10%. However the prevalence of HCV infection among health care workers is no greater than that found in the general population.[11] Contamination and inadequate sterilization of re-useable needles and syringes, and sharing straws during intranasal cocaine use are also risk factors.

3.1.17. Researchers in the United States have found that HCV infection risk among serving military forces is lower than in veterans and lower than in the general civilian population aged <40 years. The authors conclude that low level of HCV infection may be attributed to the low prevalence of injection drug abuse in the military due to mandatory testing for illicit drugs prior to induction and throughout military service.[12] In contrast, a study of 8,588 veterans in the United States found that 35% were positive for HCV, with a mean age of 48.4 yr. Risk factors for HCV infection in this study group were intravenous drug abuse (81%), unknown (11%), blood transfusion (3%), sexual/household contact (2%), transfusion and intravenous drug use (2%), and tattooing (1%).[13] In a smaller series of 1032 veterans, the authors concluded that infection with HCV among veterans is strongly associated with the traditional risk factors for this infection and less strongly associated with combat-related risk, e.g. as a combat medical worker.[14]

3.1.18. However, it is noteworthy that these studies relate to US personnel and no equivalent studies are available for UK troops. Although of considerable interest the findings cannot be directly extrapolated to UK.

3.1.19. **Hepatitis D virus (HDV)** Hepatitis D is commonest in areas of the world with a high prevalence of HBV infection, particularly Italy and other countries bordering the Mediterranean. It is also common in eastern Europe, the Middle East, South America, and parts of Africa, particularly western Africa. Antibody to HDV has been found in most countries, commonly among intravenous drug abusers. It has been estimated that 5% of HBV carriers worldwide (approximately 18 million people) are infected with HDV. Along with HBV, HDV is declining rapidly almost certainly due to the success of HBV vaccination.

3.1.20. HDV infection is strongly associated with intravenous drug abuse, although it may affect all those individuals who are at risk from HBV. It may affect health care workers, recipients of blood and blood products e.g. haemophiliacs, and the developmentally disabled.

3.1.21. **Hepatitis E virus (HEV)** Epidemiologically, hepatitis E resembles hepatitis A, and outbreaks have occurred in the Indian subcontinent, Russia, China, Africa, and South America. Usually these outbreaks have been linked to faecal contamination of drinking water. No outbreaks of the disease have been described in the United States or Western Europe but cases have occurred among people returning from endemic areas. Like HAV it is transmitted by the faecal-oral route, usually by sewage-contamination of drinking water, and the disease tends to occur both in epidemics and sporadically. Recently, HEV strains have been isolated from pigs in industrialised countries, and it has been suggested

that hepatitis E is a zoonotic disease.[15]

3.1.22. **Prevention of viral hepatitis** Patient education strategies can do much to address the problem. Strict personal hygiene and hand washing help to prevent transmission of HAV, and those travelling to endemic areas are advised not drink untreated water, ingest raw seafood or shellfish, or eat fruit and vegetables unless cooked or peeled. HAV immunization is effective. Similarly, avoidance of risk-taking behaviour will prevent the great majority of infections with HBV, HCV and HDV. Workers occupationally exposed to blood, body fluids, or tissues can be protected from the recognized risks of HBV infection by imposing barriers in the form of protective equipment and safe work practices, that are readily available, commonly used, and minimally intrusive. HBV immunization prior to travel to endemic areas is also advised, and in occupations at high risk of the disease.

3.2. **Other virus infections** A number of other virus infections may involve the liver, including yellow fever, infectious mononucleosis, cytomegalovirus, herpes simplex, coxsackie B virus, varicella and varicella-zoster, measles (in the older age-group), rubella and paramyxoma virus.

3.3. **Exotic viruses** Hepatitis may be associated with infection with exotic viruses. They include:

3.3.1. **Lassa fever** Lassa fever is an acute viral haemorrhagic illness in which the virus is transmitted to humans from contact with food or household items contaminated with rodent excreta. The disease is endemic in the rodent population in parts of West Africa. Person-to-person infections and laboratory transmission can also occur, particularly in the hospital environment in the absence of adequate infection control measures. The case fatality is 36-67%.

3.3.2. **Ebola virus infection** Ebola hemorrhagic fever is a severe illness probably transmitted to humans from infected primates. It causes a severe haemorrhagic fever which is highly infectious and mortality approaches 90%.

3.3.3. **Marburg virus infection** This disease is due to a virus transmitted by vervet monkeys, producing a haemorrhagic fever. Droplets of body fluids, or direct contact with persons, equipment, or other objects contaminated with infectious blood or tissues are all possible sources of transmission of the infection.

3.4. **Alcohol-related hepatitis** Because liver disease is not inevitable in individuals who abuse alcohol, it is probable that additional factors play a role in its pathogenesis. So far, research has failed to identify with certainty the genetic mechanisms responsible for this observation and susceptibility to liver damage is probably caused not by a single gene defect but by the cumulative interaction of a number of genes. Women are more susceptible to alcohol-related liver disease, and obesity is now well recognized as an independent risk factor.[16] When excessive alcohol consumption is superimposed on obesity, the risk of liver disease rises almost sixfold, and alcohol intake accelerates the progression of chronic hepatitis C.

3.5. **Hepatitis due to drugs and other hepatotoxic agents**

3.5.1. Many authors have emphasised the comparative infrequency of hepatotoxin- and drug induced liver disease, and one survey found that liver injury from this cause was only about one fifth as common as viral hepatitis as a cause for admission to hospital.[17] Although rare, some reactions may be severe and their potential reversibility makes

early recognition important.

3.5.2. **Hepatitis and cholestasis due to drugs** The drugs most commonly implicated include paracetamol, tetracycline, methotrexate, halothane, erythromycin, diclofenac, co-amoxiclav, isoniazid, flucloxacillin and chlorpromazine. Herbal remedies may also cause liver damage, and drugs of abuse which may cause hepatic injury include cocaine, phencyclidine, methylenedioxymethamphetamine ("ecstasy"), toluene, and trichloroethylene.

3.5.3. **Hepatitis due to other hepatotoxic agents** Liver damage can result from a single exposure to certain substances which may be ingested, inhaled as toxic fumes, or absorbed through the skin. More than 20,000 substances which may be encountered in industry and elsewhere have been noted to possess toxic properties and may cause liver injury. Examples include **bromobenzene**, used as a heavy liquid solvent and as an intermediate to manufacture organic chemicals and pharmaceuticals, and **carbon tetrachloride**, once used in the production of refrigeration fluid and propellants for aerosol cans, as a pesticide, and as a cleaning fluid and degreasing agent. However because of its harmful effects, these uses are now banned and carbon tetrachloride is only used in a few industrial applications under strict control. **Organic arsenicals**, once widely used as herbicides and pesticides, the fungus *Amanita phalloides*, and yellow phosphorus, a rodenticide whose use is now discontinued in the UK, may also cause hepatic injury.[18]

3.5.4. Potentially hepatotoxic agents are conventionally divided into two categories based on the way in which they produce liver disease:

- intrinsic or predictable hepatotoxins and
- idiosyncratic hepatotoxins.

3.5.5. **Intrinsic hepatotoxins** typically produce acute liver damage in a predictable, dose-dependent fashion. Paracetamol overdose is the prototype example of this class. In most instances, toxic metabolites formed from the parent compound are responsible for producing liver damage.

3.5.6. **Idiosyncratic hepatotoxins** on the other hand produce liver disease in an infrequent, unpredictable fashion after a variable latent period, often only after several months of administration of a drug or exposure to some other hepatotoxin. A large number of drugs are capable of producing idiosyncratic hepatotoxic reactions in a small proportion of patients who receive them (e.g., halothane, phenytoin, isoniazid, and chlorpromazine). These reactions are independent of dose, and are therefore unexpected reactions to therapeutic doses of the responsible agent. The mechanism may either be due to a metabolic idiosyncrasy or to a hypersensitivity to the agent.[19]

3.6. **Autoimmune hepatitis** The aetiology of autoimmune hepatitis is not known. It is probable however that some agent incites an autoimmune response directed against the liver in an individual who is genetically predisposed to the condition.[2,20] Many diverse triggering factors have been proposed, including infectious agents, drugs, and toxins. Other autoimmune disorders are frequently found in patients with AIH and in their first-degree relatives and it is significant that individual immune responses, age, sex, and genetic factors especially influence susceptibility to AIH, its clinical manifestations and the treatment outcome.

3.7. HIV and infective hepatitis Because of shared risk factors, concomitant HCV and HBV are both common in individuals with HIV. A recent study conducted in the USA estimated an overall prevalence of 16% HCV, rising to 73% in higher risk populations such as haemophiliacs and injection drug users. Similarly, up to 90% of patients infected with HIV have markers of past HBV infection and 10% to 15% are chronically infected with HBV (HBsAg positive).[21]

4. Prognosis

4.1. **Viral hepatitis** The severity and prognosis of infective hepatitis depends on a number of factors, including the age of the patient and the presence of any coexistent factors, e.g. concurrent alcohol abuse.

4.1.1. **Hepatitis A** is usually mild and self-limiting, and the infection confers life-long immunity. The case fatality rate is 0.1%-2.7%. Complications are rare, but relapsing hepatitis, cholestatic hepatitis, and fulminant hepatic failure do occasionally occur.

4.1.2. **Hepatitis B** The risk of chronic HBV infection depends on the age of infection; it is some 95% in neonates and 5% in adults. Fulminant hepatic failure develops in 0.5-1% of patients infected with HBV; in this group the fatality rate is 80%. Patients with chronic HBV infection are at risk of cirrhosis and hepatocellular cancer.

4.1.3. **Hepatitis C** Chronic infection develops in 70%-80% of patients with HCV, and these patients are at risk of chronic hepatitis, cirrhosis and hepatocellular cancer. Antiviral treatment reduces the risk of these complications. Almost all studies have concluded that they have a considerably increased risk of hepatocellular cancer, although the reported odds ratios and incidence rates vary considerably. However, in one large prospective population-based study of the risk of hepatocellular cancer in patients with hepatitis C, 12,008 men were followed up and the authors concluded that being anti–HCV-positive conferred a 20 fold increased risk of hepatocellular cancer compared with anti-HCV-negative.[22] Over 50% of patients with chronic infection can be cured by anti-viral therapy. Advances in knowledge of the mechanisms of viral persistence and pathogenesis, the development of a vaccine and the introduction of new therapies are the major aims for future hepatitis C research.

4.1.4. **Hepatitis D** Simultaneous infection with HBV and HDV (co-infection) may result in fulminant liver failure in 1% of patients. Complete clinical recovery and clearance of HBV and HDV co-infection is the most common outcome. Chronic infection with HBV and HDV occurs in less than 5% of these patients.

4.1.5. Infection with HDV in a patient already HBsAg-positive (superinfection) may result in fulminant liver failure in 5% of patients. Approximately 70-80% develop chronic HDV infection. These patients progress more rapidly to develop cirrhosis and may develop hepatocellular cancer.

4.1.6. **Hepatitis E** Although the condition is usually mild and self-limiting, the fatality rate reaches 15-20% in pregnant women. HEV does not result in chronic disease. A vaccine will soon be generally available.

4.2. **Alcohol-related hepatitis** Alcohol-related hepatitis carries a high risk of mortality. In studies which examined the natural history of alcoholic liver disease on the basis of histological characteristics at diagnosis, it has been found that patients with alcohol-related hepatitis have a 50% to 75% survival rate at 4 to 5 years. However in those with cirrhosis combined with alcoholic hepatitis, the prognosis is much poorer, with a 30% to 50% survival rate at 4 to 5 years.[23]

4.2.1. While fatty liver resolves completely within 4 to 6 weeks after alcohol ingestion is

discontinued, the prognosis of alcoholic hepatitis is dependent on at least four factors:

- **Cessation of alcohol ingestion** Progressive liver disease and accelerated mortality are inevitable in the patient with alcoholic hepatitis who continues to drink alcohol. However in some two thirds of patients who stop drinking, normal function will be restored provided there is little underlying fibrosis

- **Degree of inflammation** 10% to 20% of cases with persistent leukocytosis progress to hepatic failure despite withdrawal of alcohol

- **Perivenular fibrosis** If present, and alcohol abuse continues, this localised fibrosis is likely to progress to cirrhosis

- **Signs of liver failure**. Poor prognostic signs include:

    - coagulopathy,

    - ascites,

    - hepatorenal syndrome

    - encephalopathy

4.2.2. Alcohol-related cirrhosis also confers an increased risk of hepatocellular cancer. Alcohol alone is an independent risk factor for hepatocellular cancer, although to a lesser extent than viral hepatitis. When combined with viral hepatitis, alcohol-related liver disease poses a high risk of hepatocellular cancer, particularly in men older than 50 years of age.

4.3. **Hepatotoxic syndromes** The prognosis in hepatotoxic syndromes depends on a number of factors, including:

- The nature of the harmful agent

- The duration of exposure to the agent

- Any concomitant hepatic dysfunction

- Any idiosyncratic susceptibility of the individual

- Recovery occurs when the agent is withdrawn

4.4. **Autoimmune hepatitis** The prognosis depends on the stage of advancement of the disease at the time of first diagnosis and the initiation of treatment. Typically, the condition responds rapidly to corticosteroid therapy, in terms of both resolution of clinical symptoms and improvement in tests of liver function. Prednisone alone or in combination with azathioprine induces a clinical, biochemical, and histological remission in 65% of patients but the majority (more than 80%) of patients will relapse if therapy is stopped; treatment is therefore required long-term. Liver transplantation may sometimes be required.[2]

5. Summary

5.1. Hepatitis is a term which is loosely employed to indicate inflammation of the liver. It may assume an acute or chronic form.

5.2. Hepatitis may be due to specific hepatitis viruses. HAV and HEV are spread by faecal contamination of food or water and do not lead to chronic disease. Some forms of acute viral hepatitis (HBV, HCV and HDV) are contracted parenterally; e.g. by injection of the virus as a result of injectable drug abuse, or (rarely) the administration of contaminated blood products, and may progress to a chronic condition which renders the patient susceptible to cirrhosis and hepatic cancer.

5.3. The course of the disease caused by hepatitis B virus infection can be slowed by antiviral therapy and in hepatitis C over 50% are cured.

5.4. Hepatitis may also be caused by drugs or toxic substances, including alcohol. Drug-induced hepatitis often also has a cholestatic component. One variety of hepatitis is caused by an autoimmune process; the cause is unknown but it is controlled by immunosuppressant therapy.

5.5. The clinical features and prognosis of hepatitis vary, depending on the causative agent, the age of the patient and the presence of any pre-existing liver disease.

6. Related Synopses

HIV Infection and Acquired Immune Deficiency Syndrome.

Cirrhosis

7. Glossary

arthralgia	Joint pain.
ascites	Abnormal accumulation of fluid in the abdominal cavity.
autoantibody	A substance (immunoglobulin) formed in response to, and reacting against, one of the individual's own normal body constituents.
cerebral oedema	Abnormal accumulation of fluid in the brain.
cholestatic	Referring to an arrest of the normal flow of bile due to a blockage of the bile ducts.
cirrhosis	A disorder of the liver, often irreversible, characterised by diffuse hepatic fibrosis and the conversion of normal liver architecture into abnormal nodules.
coagulopathy	Abnormality in clotting of the blood.
encephalopathy	Involvement of the brain in a disease process.
erythema	Redness.
fibrosis	The replacement of normal cells by fibrous tissue.
foetor hepaticus	Characteristic odour of the breath in patients with advanced liver disease.
HBeAg	One of the HBV antigens; a good marker of HBV replication.
HBsAg	An HBV antigen produced on the surface of the hepatitis B virus.
hepatic	Pertaining to the liver; hence, *hepatitis*, *hepatotoxic*, *hepatocellular* etc.
hepatomegaly	Enlargement of the liver.
hepatorenal syndrome	Acute renal failure occurring in a patient with liver failure.
immunoreactivity	Immunological reaction between antigen and antibody.

inflammatory cells	Cells of the body which are concerned with inflammation.
leukocytosis	An abnormal elevation in the white blood cell count.
myalgia	Muscle pain.
necrosis	Cell death.
oligomenorrhea	Scanty menstrual periods.
prodromal phase	Early or premonitory stage of a disease.
pruritus	Itching.
spider naevus	A non-malignant skin abnormality, whose appearance consists of localised prominence of a few tiny, radiating blood vessels.
urticaria	An allergic skin reaction, characterised by irregular, elevated patches and itching.
variceal	Relating to abnormally dilated veins.
zoonotic	Pertaining to a disease whose natural reservoir species is non-human.

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