15.23.1 Hepatitis A to E 3108

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cirrhosis in 5 to 10% after 15 to 25 years, which then predis- poses to hepatocellular cancer; astonishing progress with a range of tailored antiviral agents targeting key viral enzymes has led to viral elimination in over 95% of patients across the spectrum of disease and viral genotype, with little risk of side effects. Hepatitis D virus (HDV): an RNA virus that acts like a cuckoo by replacing the hepatitis B viral core with the hepatitis D viral core and tends to produce more severe liver disease; treatment is as for hepatitis B. Hepatitis E virus (HEV): faecal–oral transmission; incubation about 6 weeks; higher risk of acute liver failure if acquired during midtrimester pregnancy; no specific treatment, although some re- ports suggest ribavirin may be helpful. Introduction Viral infection is the most common cause of hepatitis and remains a clinical problem worldwide, particularly in developing countries. The five major hepatitis viruses (A, B, C, D, and E) account for most cases of viral hepatitis in clinical practice (Table 15.23.1.1). Although these viruses are unrelated, they share tropism for the liver (Table 15.23.1.2). Other viruses that produce systemic infection can also infect the liver and cause hepatitis that is usually asymptom- atic, but occasionally hepatitis can be the dominant manifestation of infection (e.g. cytomegalovirus, Epstein–Barr virus, and herpes 15.23 Hepatitis and autoimmune liver disease

15.23.1 Hepatitis A to E 3109 simplex virus). Many other viruses are known to infect the liver but do not appear to cause clinical disease (e.g. hepatitis G, transfusion- transmitted, and Sen viruses). This chapter describes the clinical and pathological aspects of viral hepatitis including investigation, man- agement, and prophylaxis. Specific virology of hepatitis viruses is covered in Chapters 8.5.21 and 8.5.22. Clinical outcome of hepatitis virus infection The clinical manifestation of viral hepatitis varies according to the severity of inflammation induced in the liver and whether the virus is cleared from the liver or persists in the long term. This variation in clinical picture is influenced by both viral and host factors including lifestyle and the immune response to the virus. In most cases, it is the host immune response to the virus that is responsible for lysis of infected hepatocytes and liver inflammation. Patients who de- velop a strong immune response to the virus may therefore have more severe inflammation and a more symptomatic acute illness, but a greater likelihood of achieving viral clearance. Conversely, those who mount a weaker virus-specific immune response may have a milder or subclinical illness but then develop persistent in- fection, which over many years can lead to cirrhosis predisposing to hepatocellular carcinoma. Acute viral hepatitis is generally a self-limiting illness with low mortality. The preicteric or prodromal phase lasts up to 2 weeks. The patient is viraemic and feels generally unwell with anor- exia, nausea, vomiting, diarrhoea, headaches, myalgia, and arth- ralgia. Fever is usually mild and there may be upper abdominal discomfort. Symptoms usually improve at this point, while jaun- dice may worsen and last several days to several weeks. Ascites and oedema occur rarely in more severe cases. Most cases recover com- pletely, although it may take several weeks or months and residual fatigue is common. The severity of acute hepatitis is best measured by the bilirubin and prothrombin time, with less reliance placed on the alanine aminotransferase (ALT) concentration. Identification of those at risk of liver failure using these parameters is discussed elsewhere, but the onset of hepatic encephalopathy indicates a poor prognosis. There are several variations on the clinical course of acute hepatitis: • Anicteric hepatitis: infection is asymptomatic or characterized by mild flu-like symptoms that resolve within 2 to 3 weeks. Jaundice does not occur, or is not noticed, and the ‘illness’ is often not rec- ognized as viral hepatitis. • Cholestatic hepatitis: jaundice develops accompanied by dark urine and pale stools after an initial viral prodrome character- ized by malaise, anorexia, fever, and upper abdominal pain. The jaundice may be accompanied or followed by pruritus. The ic- teric period last for a few days to a few weeks and

subsides slowly. Residual fatigue may last several months. • Relapsing hepatitis: jaundice worsens transiently after an initial improvement, before eventual recovery. • Acute liver failure: massive hepatocyte necrosis occurs, with liver failure characterized by jaundice and coagulopathy followed by encephalopathy. Fulminant disease is defined by the development of encephalopathy within 2 weeks of the onset of jaundice. • Subacute liver failure: liver failure develops at a slower rate, with encephalopathy appearing more than 2 weeks after the onset of jaundice. Hepatitis A, B, C, and E can all cause an acute self-limiting hepa- titis. Fulminant hepatitis can occur with hepatitis A, B, and E but is very rare with hepatitis C. Hepatitis B and C are the main causes of chronic viral hepatitis, when the virus persists in the liver over years to decades causing varying degrees of inflammation and fibrosis. Hepatitis D infection, which only occurs in patients in- fected with hepatitis B, can contribute to either acute or chronic inflammation. Table 15.23.1.1 Viruses affecting the liver Major hepatotropic viruses Hepatitis A, B, C, D, and E Systemic viruses capable of causing hepatitis Epstein–Barr virus, cytomegalovirus, herpes simplex virus, adenovirus Minor hepatotropic viruses Hepatitis G virus, Sen virus, transfusion-transmitted virus Tropical viruses Yellow fever, dengue fever, haemorrhagic viruses Table 15.23.1.2 Features of hepatitis viruses Hepatitis A Hepatitis B Hepatitis C Hepatitis D Hepatitis E Virus Picornavirus (RNA) Hepadnavirus (DNA) Flavivirus (RNA) Subviral particle (RNA) Hepeviridae (RNA) Spread: Faecal–oral Blood Vertical Sexual Yes Rare No Rare

No Yes Yes Yes

No Yes Occasional Occasional

No Yes Rare Occasional

Yes No No No Incubation Short 2–4 weeks Long 2–6 months Intermediate 2–16 weeks Long Short 4–6 weeks Chronic liver disease Rare case reports only Yes Yes Yes Rare, with immune compromise Liver cancer No Yes Rare Yes No Immunization: Passive Active

Immunoglobulin Vaccine

Immunoglobulin Vaccine

HBV vaccine

section 15 Gastroenterological disorders 3110 Acute viral hepatitis Particular viruses Hepatitis A virus Hepatitis A virus (HAV) is the most common type of viral hepa- titis worldwide and causes 20 to 40% of clinically apparent hepa- titis; older patients are more likely to be symptomatic. It is an RNA virus, acquired in almost all cases by the faecal–oral route, usually from ingestion of food or water contaminated with human faeces, although transmission via transfusion of blood or blood products or transplantation of organs from viraemic patients has been reported. The virus is endemic and infection is reported worldwide, but occurs primarily in Third World countries with overcrowding and poor sanitation, particularly since the introduction of highly ef- fective vaccination programmes in wealthier countries. In some developing countries, serological evidence of past infection is pre- sent in up to 100% of children, with lifelong immunity. In Western countries, prior infection varies between 5 and 40% depending on age, social class, and other factors. Infection may also be spread through close contact with an infectious person. Promiscuous men

who have sex with men have a higher incidence of infection. Infection with HAV may result in subclinical infection, symp- tomatic clinical infection with or without jaundice, or acute liver failure. It does not cause chronic infection or chronic hepatitis, although prolonged acute infection is reported rarely in immuno- suppressed individuals. Frequently the disease is mild or asymp- tomatic, particularly in the young. The incubation period between infection and symptoms, if they develop, is between 2 and 4 weeks. Viral shedding in the faeces ceases in most people as symptoms de- velop. Symptoms of acute hepatitis, if present, typically last less than 2 months. Severe hepatitis or acute liver failure may occur but is rare and the mortality rate is low (0.4%). Deaths occur more com- monly in the elderly or in people with pre-existing chronic liver disease. During convalescence, 10 to 15% of patients may have a relapse of the hepatitis, but this settles spontaneously. Extrahepatic complications are rare but may include arthritis, vasculitis, myocar- ditis, and renal failure. Hepatitis B virus Hepatitis B virus (HBV) infection is a DNA virus that is common worldwide, with over 1 billion people infected at some point in their lives. Around 300 million people are chronic carriers with the main burden of disease being in South East Asia and sub-Saharan Africa, where prevalence rates reach 10 to 15%. The dominant mode of transmission worldwide is vertical transmission from a mother with chronic infection to an infant, during pregnancy, at birth, or during close family contact in early childhood. Other modes of transmis- sion include transfusion of blood and blood products, reuse of con- taminated needles medically or by drug addicts, exposure in dialysis units, tattooing, and sexual contact (both homosexual and hetero- sexual). The virus is highly infectious (50–100 times more infectious than HIV). Transmission can occur between household contacts by uncertain means, possibly including contact with broken skin or mucous membranes. The incubation period of HBV is 6 to 26 weeks. Those who are infected around the time of birth develop symptoms rarely, but most (90–95%) develop chronic infection. In contrast, 90 to 95% of adults infected with the virus develop a self-limiting acute illness resulting in viral clearance. The acute illness is often not recognized and may be asymptomatic, but if symptoms do occur, there is usually a viral prodrome with nausea, myalgia, arthralgia, and fever, which may then be followed by jaundice. Anicteric infection may occur, in which case the infection may not be recognized as hepatitis. The illness usually lasts a few weeks and then gradually improves in most cases, although acute liver failure may develop and has significant mortality (0.3%). In most cases, HBV is cleared after acute infection and hepatitis B surface antigen (HBsAg) disappears from the blood within weeks. The time to produce a protective hepatitis B surface antibody (anti- HBs) varies greatly and sometimes does not occur, although such patients are not at risk of a further infection. If the patient fails to clear HBsAg within 6 months they are considered chronic carriers. A failure to eradicate hepatitis B e antigen (HBeAg) within 12 weeks is often associated with progression to the carrier state. Extrahepatic symptoms occur in up to 10% of cases and include serum sickness-like immunological syndrome with fever, urticarial rash, membranous glomerulonephritis, and polyarteritis due to immune complex deposition. Other immune-mediated haem- atological disorders such as aplastic anaemia and essential mixed cryoglobulinaemia occur rarely. Hepatitis C virus Hepatitis C virus (HCV) was discovered in 1989 as the dominant cause of non-A, non-B hepatitis. It is an RNA virus spread primarily by blood-to-blood contact associated with intravenous drug use, poorly sterilized medical equipment, and transfusion of blood or blood products. Vertical transmission is well described, while sexual transmission is uncommon but not unknown. The incubation period of the virus typically ranges from 2 to 16 weeks. HCV infection causes acute symptoms in only 15% of cases and thus is often unrecognized. Symptoms, if they develop, are generally mild and nonspecific including fatigue, nausea arthralgia, and myalgia. Jaundice is unusual and fulminant hepatitis is

very rare. About 80% of infected individuals fail to clear the virus and develop chronic hepatitis. HCV infection is therefore usually not recognized until late in the chronic phase. At least six different geno- types are recognized with different epidemiological associations and treatment responsiveness. Hepatitis D virus Hepatitis D virus (HDV), also referred to as hepatitis delta virus, is a small RNA subviral particle enveloped in HBsAg. It is unable to replicate on its own and can only propagate in the presence of HBV. Active HBV protein synthesis, including HBsAg, is reduced by delta infection, while HBV replication is reduced substantially such that patients often become HBV DNA negative. Transmission of HDV can occur simultaneously with HBV (coinfection) or superimposed on chronic hepatitis B (superinfec- tion). Coinfection may result in an otherwise unremarkable acute hepatitis but there is a higher incidence of liver failure than with HBV infection alone. If HBV infection resolves with viral clearance then HDV will also be cleared. Superinfection of a chronic HBV carrier with HDV may result in worsening of liver function. The superinfection may be transient or chronic HDV carriage may de- velop. Chronic infection with HBV and HDV results in more rapid

 progression to liver cirrhosis and an increased risk of developing hepatocellular carcinoma. HDV is transmitted by all parenteral routes demonstrated for hepatitis B, including sexual transmission, but appears to be more common in intravenous drug abusers. Eastern Asia, sub-Saharan Africa, and South America are areas of moderate to high incidence. The infection is rare in many developed countries, being most common in Mediterranean regions with a high incidence of intra- venous drug use. Hepatitis E virus Like HAV, hepatitis E virus (HEV) is an RNA virus transmitted via the faecal–oral route. HEV is prevalent in most developing countries where spread is usually due to faecal contamination of food or water; person-to-person transmission is uncommon. In Western countries, HEV cases may be imported or be a zoonosis from infected animals, particularly pigs. The virus has been detected in over 50% of do- mestic pigs in some areas and meat products on sale in developed countries have been found to contain the virus. Some research sug- gests that food must reach 70°C for 20 min to eliminate the risk of infection, a standard not always achieved with barbeques. There are three serotypes with distinct species and geographic distributions. HEV typically causes an acute self-limiting infection but chronic infection is well described in immunocompromised patients (e.g. organ transplant recipients who receive immunosuppressive medi- cation to prevent rejection). The incubation period is about 6 weeks. Viral RNA becomes detectable in the stool and blood during the in- cubation period. Recovery leads to viral clearance from the blood, while faecal excretion may persist for several weeks after the onset of clinical symptoms. The disease is usually mild, but severe liver dis- ease can occur and the overall mortality rate of approximately 2% is higher than that with HAV. Pregnant women, especially those in the third trimester, are particularly susceptible to developing fulminant hepatitis and mortality rates of 20% are seen in this group. Ribavirin has been used with clinical success in patients with prolonged acute infection on a background of immunocompromise. Other viruses Some viruses (e.g. cytomegalovirus, Epstein–Barr virus, and herpes simplex virus) can cause hepatitis as part of a multisystem illness. Hepatitis may be a minor, unrecognized component of the viral illness or the dominant clinical manifestation; the latter is especially true of those with immune compromise or on long-term immune suppression. Hepatitis G virus, Sen virus, and transfusion-transmitted virus are well characterized as viral infections within the liver but they do not cause significant disease, even in those with immune compromise. Cases of unexplained non-A/B/C/D/E hepatitis and fulminant liver failure occur and may be caused by hepatotropic viruses that have not yet been described. Clinical features Symptoms of acute

hepatitis are often nonspecific including nausea, fatigue, arthralgia, and myalgia. Clinical examination may dem- onstrate jaundice, right upper quadrant tenderness, and mild hep- atomegaly. Palpable splenomegaly, as opposed to that detected by liver ultrasonography, is uncommon in classical viral hepatitis and more typical of systemic viral infection with cytomegalovirus or Epstein–Barr virus. Skin manifestations may include urticarial or vasculitic rash, spider naevi, and scratch marks as a result of pruritus. Persistent vomiting in cases of severe hepatitis may result in elec- trolyte disturbance, renal impairment, and hypoglycaemia. Rapid shrinkage of the liver may occur and ascites and peripheral oedema may develop. The onset of encephalopathy indicates hepatic failure and deterioration to coma can be very rapid. Investigation In the prodrome, the serum bilirubin is usually normal, but hepatocellular enzymes (aspartate transferase and ALT) are usually raised and levels may exceed 10 times normal. The serum alkaline phosphatase elevations are more modest, generally two to three times normal. Urine analysis reveals increased urobilinogen. As an episode evolves into the cholestatic phase, the serum transaminase levels fall, alkaline phosphatase and bilirubin levels may rise, and urine analysis demonstrates excess bilirubin. In severe cases, there may be evidence of liver failure, reflected in impairment of synthetic liver function with prolongation of the prothrombin time and a fall in serum albumin. Virological tests that may be used in the investigation of acute hepatitis are outlined in Table 15.23.1.3. An initial virological screen for suspected viral hepatitis includes anti-HAV IgM antibodies, IgM anti-HBc, HBsAg, anti-HCV antibodies, anti-cytomegalovirus IgM antibody, and anti-Epstein–Barr virus IgM antibody. Anti-HEV antibody testing is not available universally, but testing for anti- HEV IgM antibody should be undertaken in any case of suspected acute viral hepatitis or unexplained abnormality of liver blood tests due to the increased prevalence in this infection. Fulminant hep- atic failure secondary to hepatitis B can present occasionally after HBsAg has been cleared from the serum; a positive IgM hepatitis B core antibody (anti-HBc) confirms the diagnosis. Figures 15.23.1.1 to 15.23.1.4 indicate the typical serological evolution of acute viral hepatitis A, B, C, and E. All patients with HBV infection should be tested for HDV infec- tion. The presence of serum IgM anti-δ with IgM anti-HBc suggests acute coinfection with both viruses. Superinfection with HDV is characterized by detection of IgM anti-δ in a patient who is already negative for IgM anti-HBc, but positive for IgG anti-HBc. Hepatic imaging is utilized primarily to exclude other causes of acute hepatic illness, especially biliary obstruction. Liver biopsy is required infrequently unless there is doubt regarding the diagnosis or, more often, if underlying chronic liver disease is suspected. In such cases, biopsy may require correction of clotting factors and a transjugular approach. Differential diagnosis The differential diagnosis is from other causes of acute hepatitis: • Drug-induced jaundice: this is the most common alternative diag- nosis and the clinical course can be very similar. A thorough drug history should be undertaken, including those prescribed as well as those acquired over the counter and herbal medicines. • Autoimmune hepatitis: about one-third of patients with auto- immune hepatitis present with a clinical picture of acute hepatitis, most often middle-aged females. High levels of liver-specific auto- antibodies and elevated IgG levels are found frequently or may develop in the early stages, but the distinction can be difficult since

 low titres of autoantibodies and moderate elevations in IgG also occur in some cases of viral hepatitis. • Alcohol-related hepatitis: this may present acutely with jaundice, but elevations of serum transaminases are generally much less marked and these enzymes are often normal; there may be an as- sociated high leucocyte count and inflammatory response. • Obstructive jaundice: this classically causes less marked rises in

transaminases but higher levels of alkaline phosphatase, al- though the clinical picture may not always be clear cut, especially in the early stages. Obstruction is usually confirmed by abdom- inal imaging with ultrasound examination demonstrating dilated biliary ducts. • Hepatic ischaemia: this can follow episodes of hypotension and present with an acute hepatitis that may cause transient jaundice and coagulopathy. • Wilson's disease: very rare but important to consider as there is a high incidence of acute liver failure with a substantial risk of mortality. • Malignant infiltration of the liver: may mimic acute viral hepatitis. • Pregnancy-associated syndromes: HELLP (haemolysis, elevated liver function tests, low platelets) and acute fatty liver may present with a picture of acute hepatitis, but are rare and less common in pregnancy than acute viral hepatitis. Management Most cases of hepatitis recover spontaneously and management is supportive. There is no proven therapy that enhances recovery. Many cases can be managed at home, but more severe cases may benefit from hospital admission for symptomatic management and to observe for early signs of liver failure. Clinicians should be alert to electrolyte disturbance, renal dysfunction, and hypo- glycaemia that may require intravenous replacement. Alcohol and potentially hepatotoxic drugs should be withdrawn. Pruritus can be difficult to manage but resolves when the cholestatic phase of the illness has passed. Ursodeoxycholic acid, cholestyramine and antihistamines, cool baths, and moisturizing lotion may help. Management of patients with fulminant hepatic failure is covered in Chapter 15.22.5. Hepatitis C infection is recognized occasionally during the acute stage and viral elimination is accelerated with interferon (IFN)-α. Newer agents have not yet been studied in this context. Patients with acute infection who have not cleared the virus within 12 weeks should be considered for a more conventional antiviral approach. The use of antiviral therapy for moderate or severe acute HBV infection has no evidence base but is an approach that has been adopted by some in the field, particularly when there is an elevated prothrombin time, in order to reduce the duration and severity of infection. Table 15.23.1.3 Serological tests used in the assessment of acute hepatitis Test Timing Interpretation IgM anti-HAV Appears around onset of jaundice; persists for around 4 months Acute or recent infection IgG anti-HAV Persists lifelong Indicates acute, recent, or past infection. Also produced following active vaccination HBsAg Appears from about 6–12 weeks after acute infection and then disappears Viral protein in the blood, indicates the patient is infected
with HBV Anti-HBs Develops a few weeks after jaundice and persists lifelong Protective antibody, indicates that viral infection has cleared Also produced after active vaccination HBeAg Rises early and usually declines rapidly by 1 month Infectious phase of HBV infection, high titre of HBV DNA Anti-HBe Appears as HBeAg is cleared, persists Immune response to infectious virus IgM anti-HBc First antibody to appear and persists about 4 months. May be the only marker of recent infection in the window between clearing HBsAg and developing HBsAb Acute HBV infection IgG anti-HBc Persists long term Acute, recent, or past infection HBV DNA Cleared in 2 months in most cases Infectious virus in the blood Anti-HCV Appears several weeks after infection, persists lifelong Acute, recent, or past infection HCV RNA Present at onset of symptoms Active viral replication HDVAg Present at onset of symptoms Presence of viral protein in blood IgM anti-HDV Appears at week 1 and disappears at week 5–6 Acute or chronic infection IgG anti-HDV Appears at onset, persists in chronic carriage Acute, chronic or past infection IgM anti-HEV From onset of symptoms, persists for 4–6 weeks Acute or recent infection IgG anti-HEV From onset of symptoms, persists for several years Acute, recent or past infection Exposure 0 1 2 3 4 Months 1gM anti-HAV Transaminase (ALT) Onset of clinical illness 1gG anti-HAV 5 6 Fig. 15.23.1.1 Typical serology of hepatitis A infection.

15.23.1 Hepatitis A to E 3113 Onset of clinical illness Exposure HCV RNA Transaminase (ALT) Anti-HCV Months 0 1 2 3 4 5 6 7 8 12 Fig. 15.23.1.3 Serological changes during acute hepatitis C with viral clearance. Exposure 0 1 2 3 4 Months 5 6 Transaminases (ALT) HEV RNA in faeces IgG anti-HEV IgM anti-HEV Fig. 15.23.1.4 Typical serological changes of hepatitis E infection. Exposure 0 1 2 3 4 5 6 7 8 Transaminases (ALT) HBV DNA HBs Ag 1gM-anti-HBc anti-HBs 1gG-anti-HBc Onset of clinical illness Fig. 15.23.1.2 Serological changes during acute hepatitis B with viral clearance.

section 15 Gastroenterological disorders 3114 Prevention The frequency of enteric infections with HAV or HEV can be re- duced by improved sanitation, better hygiene, and decreasing overcrowding. Active immunization against HAV with formalin- inactivated viral preparations is a safe, rapid, and effective means of protection and is advisable for Western individuals prior to travel to highly endemic areas. Early postexposure vaccination may also be of benefit. Patients with established chronic liver dis- ease should also be offered the vaccine to prevent HAV-related decompensation of underlying liver disease. Vaccines are being developed for HEV. Passive protection against hepatitis B is available soon after ex- posure (sexual contact or needlestick injury) using specific high- titre immunoglobulins against HBV (HBIg). Active immunization to HBV initially involved a vaccine derived from viral proteins in infected blood, but now uses recombinant viral envelope (HBsAg) proteins. The vaccine is safe and the conventional programme of three doses over a 6-month period leads to protective immunity in 90% of individuals. Early postexposure vaccination may also be of benefit. Nonresponders may responder to further vaccine boosting or may be candidates for newer vaccines containing additional viral antigens. Vaccination strategies vary from country to country, from universal vaccination in infancy to vaccination restricted to high-risk individuals. Universal vaccine practice has been shown in Taiwan to reduce the incidence of chronic viral carriage, chronic liver disease, and hepatocellular carcinoma within a few years of initiation. Active immunization is recommended immediately after birth for children born to infected mothers. Those born to highly infectious mothers, as judged by the presence of HBeAg and high circulating HBV DNA levels, should also be offered passive HBIg within hours of birth. In some infants in some parts of the world, vaccination may fail with evolution to chronic in- fection with a mutated HBsAg ‘escape’ virus selected by the vac- cine programme, especially with viraemic mothers who also receive HBIg. There is no vaccine currently available for HCV, although clin- ical trials are underway. The major difficulty is the rapid evolu- tion of changes in the composition of HCV structural proteins as the virus mutates rapidly, producing many quasispecies. Passive immunization with gammaglobulin containing antibodies to HCV is not protective. For similar reasons, patients treated suc- cessfully with effective antiviral agents may remain susceptible to reinfection Chronic viral hepatitis Chronic hepatitis B Chronic HBV infection is defined as the persistence of HBsAg in blood for more than 6 months. After infection up to 10% of adults and more than 90% of infected infants become chronic HBV car- riers. Failure to clear the virus is associated with infection as a neo- nate or infant, those infected late in life, male sex, and those with a weaker immune response, either naturally or as a result of disease or medication. Around 1% of chronic carriers clear the virus spon- taneously each year. There is geographical variation in the carriage rates with notably high levels in East Asia and sub-Saharan Africa (10–20%) and lower prevalence in Northern Europe and North America (<1%). Phases of chronic hepatitis B virus infection The clinical outcome of chronic HBV carriage is varied and influ- enced by the strength of the immune response mounted by the host, the duration of infection, and alterations in viral replication with time. The natural history of chronic infection is characterized by dif- ferent phases (Table 15.23.1.4). In the early phase of infection (‘tol- erant’ or ‘replicative’ phase) the virus

replicates avidly, expressing HBeAg and producing high levels of infectious viral particles (HBV DNA levels usually >106 IU/ml). ALT levels are usually normal and, if undertaken, liver biopsy often shows little inflammation or scar- ring. This stage is variable in length but may be prolonged over many decades, especially if infection is acquired as an infant. Later in infection the host immune response increases associ- ated with hepatic inflammation. During this ‘inflammatory phase’, HBeAg seroconversion may occur, with loss of HBeAg and devel- opment of antibody to HBeAg (anti-HBe). The amount of inflam- mation and necrosis, measured biochemically or with histology, influences the prognosis of chronic HBV infection. Some patients pass through this phase easily and sustain little in the way of liver disease. In others, viral replication persists, often without symptoms, and repeated cycles of inflammation and repair lead to progressive scarring of the liver. Following HBeAg seroconversion, many patients retain con- trol of the virus and have undetectable levels of HBV DNA in the blood (‘nonreplicative’ phase). The virus remains quiescent in the liver without causing further inflammation. Viral sequences may be- come integrated into the host genome and HBsAg production may continue. A significant number, however, develop mutants in the precore and basal core promoter regions of the viral genome leading Table 15.23.1.4 Serological tests in chronic HBV infection Phase HBsAg Anti-HBs IgM anti-HBc IgG anti-HBc HBeAg Anti-HBe HBV DNA Early months + − + + + − +++ Tolerant + − − + + − +++ Inflammatory + − −a + +/− +/− ++ Nonreplicative + − − + − + Or minimal Reactivation (precore mutant) + − − + − + ++ a IgM anti-HBc persists at low titre in the long term but is usually not detected by commercial tests that have been set to be positive only at high titre and thus detect acute infection. During acute flares, levels may rise and be detected as weak positive results.

 to continued viral replication with rising HBV DNA levels in the presence of anti-HBe antibody. Chronic HBeAg-negative HBV can follow an aggressive course, may lead to the rapid development of cirrhosis and hepatocellular carcinoma, and requires long-term or even indefinite treatment. Investigation After establishing the diagnosis of chronic HBV infection, it is ne- cessary to define the virological status of the patient with respect to infectivity and viral replication, and the hepatic status with respect to the presence of inflammation and liver damage. Interpretation of viral status may be complicated by the emergence of viral mutants, particularly the precore mutant that results in absent HBeAg expres- sion, but which nonetheless is associated with active inflammation and circulating HBV DNA. Serological markers of chronic HBV in- fection and their relevance to the phases of chronic HBV infection are outlined in Fig. 15.23.1.5. Chronic hepatitis B causes a spectrum of histological patterns and liver biopsy may be useful in assessing the severity of liver disease. During the tolerant phase, the inflammatory response to the virus may be minimal such that the histological appearances are virtually normal. Virally infected hepatocytes can be seen as ‘ground-glass’ cells on routine staining or by immunohistochemical staining for viral antigens. Biopsies undertaken during the replicative phase demonstrate chronic lymphocytic infiltration of portal tracts with varying extent of periportal and/or lobular inflammation. Fibrosis spreads from the portal tracts and in some cases spurs of fibrosis de- velop and progress into cirrhosis. These histological appearances can be categorized in terms of inflammatory activity and stage of fibrosis. In general, the replicative phase of HBV infection with HBeAg posi- tivity, particularly in its later phase, is associated with more marked inflammation than the subsequent anti-HBe-positive stage. Noninvasive methods of assessing liver fibrosis have been intro- duced and are supplementing (and, in some clinical practices, replacing) liver biopsy. Direct biomarkers of fibrosis, such as hya- luronic acid and procollagen III N-peptide, have been measured in serum and combined in various algorithms. These have validated accuracy against liver biopsy in assessing

fibrosis in patients with chronic hepatitis B. Readily available indirect markers of altered hepatic function such as platelet count, coagulation studies, and the levels of ALT and aspartate transferase, have also been utilized. Such tests have some utility in clinical practice but are not liver specific and can be influenced by comorbid conditions. Transient elastography is a rapid and objective technique for staging liver fi- brosis by measuring the stiffness of the liver, expressed in units of kilopascals. It has proven utility in defining minimal and advanced hepatic fibrosis, particularly when the disease is stable. Caution should be observed, however, during suspected inflammatory phases of chronic HBV infection when these tests may be less re- liable since none of these parameters is an accurate measure of in- flammation and inflammatory activity precedes fibrosis. Clinical features Chronic HBV infection is frequently asymptomatic and often clinic- ally silent for many years. There may be nonspecific symptoms such as fatigue or upper abdominal discomfort. Progression to cirrhosis is not inevitable and, where it does occur, it usually takes many years, although the rate varies. The condition may be detected coinci- dentally through investigation of abnormal liver function tests or hepatomegaly, or recognized on screening (e.g. during pregnancy or via contact tracing of family members or other at-risk individ- uals). Some patients present at a late stage with established cirrhosis. Episodes of enhanced inflammation (‘flares’) may give rise to tran- sient worsening of liver function tests, particularly elevations of transaminases and occasionally jaundice at any stage of the disease. Physical examination is frequently normal, or there may be stigmata of chronic liver disease (e.g. jaundice, splenomegaly, ascites, oedema, and encephalopathy). Chronic HBV infection may also give rise to a number of extrahepatic manifestations. These include glomerulonephritis, polyarteritis nodosa, and cryoglobulinaemia. The incidence of hepatocellular carcinoma in chronic HBV is high, probably increased over 100-fold over noninfected controls. In those with HBV cirrhosis, repeated cycles of damage followed by repair can lead to errors during DNA repair, which in turn Replicative phase IgG anti-HBc HBs Ag HBe Ag+ HBV DNA ALT levels Up to 20–40 years Non-replicative phase Reactivation Pre-core mutant HBeAb+ eAg to eAb conversion Inflammatory phase Fig. 15.23.1.5 Serological markers during chronic hepatitis B.

 lead to hepatocarcinogenesis. The virus is also capable of causing hepatocellular carcinoma in the absence of cirrhosis by integrating viral genomic sequences into infected cells. Management The ultimate goals of treatment in chronic HBV infection are to prevent progression to cirrhosis and development of hepatocellular carcinoma. The prospects of an individual patient clearing the virus spontaneously or with therapy are relatively low, but suppression of HBV replication (clearance of HBeAg and undetectable HBV DNA) can induce remission of liver disease (normalization of ALT and reduced intensity of hepatic inflammation). The two current approaches are the use of IFN-α or inhibitors of viral replication, nucleotide and nucleoside analogues. Patient selection is important. For IFN therapy, those with active inflammation have the greatest potential for benefit. Most such patients have circulating HBeAg, an elevated ALT (two to five times normal) and lower levels of serum HBV DNA (<1000 IU/ml). In the absence of elevated transaminases, the response to treatment is very poor. Interferons IFNs have antiviral, antiproliferative, and immunomodulatory effects. They increase host T-cell-mediated viral clearance by processes including enhancement of hepatocyte class I HLA ex- pression. The main theoretical advantage of IFN-α treatment is the absence of induction of viral mutations to drive resistance and the potential that the host develops immune-mediated control of HBV infection when therapy ceases. Treatment involves subcutaneous injections of IFN-α administered weekly in pegylated form (long acting, conjugated to polyethylene glycol) for 6 to 12

months. Side effects include fever, malaise (particularly in the first few weeks of treatment), anaemia, alopecia, and depression. HBeAg to anti-HBe seroconversion or loss of HBV DNA occurs in 30 to 40% of cases and may be associated with an inflammatory flare during the second or third month. HBsAg clearance occurs in less than 10% of cases. Women, those with a shorter duration of carriage, Westerners, and those without an additional immuno- suppressed background (such as HIV infection) respond more favourably. Most responders have a sustained response although 10 to 20% of patients who clear HBeAg experience reactivation of HBV replication, usually within the first year after completing therapy. Successful treatment with sustained suppression of HBV replication is associated with improved histological progression and reduced liver-related mortality due to decompensation or hepatocellular carcinoma. Antiviral drugs Nucleoside and nucleotide analogues inhibit both viral reverse transcriptase and DNA polymerase resulting in inhibition of viral replication. Agents used in the treatment of HBV are shown in Table 15.23.1.5. These drugs have the advantage of oral bioavail- ability and minimal side effects but the disadvantage that their ef- fects are suppressive rather than curative, hence treatment has to be given long term. Discontinuation of therapy has to be undertaken with caution and careful monitoring as it may be followed by re- lapse with flares of inflammatory activity. Table 15.23.1.5 Nucleoside and nucleotide analogues used for treating chronic HBV Drug Dose Notes Lamivudine 100 mg daily Inexpensive Potent, rapid decline in HBV DNA HBeAg seroconversion <20% after 12 months Rapid emergence of resistant strains (YMDD mutants) 20% after 1 year, 80% after 4 years In developed countries, use now replaced by newer agents Adefovir dipivoxil 10 mg daily Weak activity, slow decline in HBV DNA HBeAg seroconversion <15% after 12 months Capable of suppressing wild type and YMDD mutant Effective in combination with lamivudine Nephrotoxicity limits clinical usefulness Telbivudine 600 mg daily Weakly acting agent High tendency for resistant virus (YMDD mutant) Not recommended in international guidelines Tenofovir disoproxil fumarate 245 mg daily Potent nucleotide analogue Structurally similar to adefovir but less nephrotoxic Requires monitoring of renal function, can cause proximal renal tubulopathy with hypophosphataemia and osteomalacia High barrier to resistance Active against YMDD mutant 76% virological response after 12 months 74% histological response after 12 months 21% HBeAg seroconversion after 12 months Entecavir 0.5–1 mg daily Potent nucleoside analogue High barrier to resistance 70% histological response after 12 months 70% virological response after 12 months HBeAg seroconversion = 20% after 12 months Weak activity against YMDD mutant Emtricitabine 200mg daily Potent inhibitor of HBV and HIV Selects for YMDD mutant virus Used in combination with tenofovir for HIV/HBV coinfection

 Antiviral use can induce viral mutations and development of resistant viruses able to cause hepatic flares. This was a particular problem with earlier drugs such as lamivudine, but the newer potent HBV inhibitors tenofovir and entecavir have a higher barrier to re- sistance and viral mutations are seen rarely, even after several years of therapy. Monitoring of HBV DNA levels is a key part of effective management of antiviral therapy and suppression of levels to un- detectable or minimal levels is regarded as the aim of therapy. Antiviral agents are used in additional specific situations. Reactivation of HBV replication in chronic HBV carriers under- going immunosuppressive or cancer chemotherapy can have serious consequences, including icteric flares and even decompensation and death. The use of prophylactic lamivudine during immunosup- pressive therapy in HBV DNA-negative patients and for 6 months afterwards can reduce the rate of HBV reactivation, the severity of hepatic flares, and mortality. Highly viraemic HBeAg mothers carry approximately a 10% risk of vertical HBV transmission des- pite a combination of active and passive vaccination of the neonate. Lamivudine and more recently tenofovir therapy in the last tri-

mester of pregnancy have been shown to be safe (although the num- bers studied are much smaller for the latter) and to reduce the risk of intrauterine and perinatal transmission of HBV and thus may be considered for this indication. If used only for this indication it may be discontinued within 3 months after delivery with close moni- toring. This approach is not an alternative to vaccination and does carry the risk of an inflammatory flare after treatment withdrawal, and not all physicians are convinced that this is the correct approach. Chronic hepatitis C Approximately 200 million people worldwide are infected with hepa- titis C. Prevalence rates vary geographically from around 0.5% in the United Kingdom to greater than 20% in some parts of Africa and Asia. Within developed countries, there are marked variations in preva- lence from 0.04% in healthy blood donors, 1% in patients attending genitourinary clinics, to up to 50% in people who inject drugs. In developed countries, recreational drug use is the dominant mode of HCV transmission from sharing needles as well as the paraphernalia used to prepare drugs, hence participants of needle- exchange programmes are still at risk. Prior to the 1990s, blood transfusion and treatment of clotting disorders with plasma concen- trates were important modes of transmission. This has been reduced almost to zero with the advent of effective screening of blood prod- ucts. In developing countries, poorly sterilized medical and dental equipment, including vaccination programmes, tattooing, dentistry, and communal shaving practices, as well as infected blood products, are the primary sources of infection. Sexual transmission of HCV is infrequent and those in long-term monogamous relationships are generally at very low risk of trans- mitting the virus. Those with multiple partners are at higher risk and outbreaks of HCV have been reported in HIV-positive and HIV- negative homosexual men in several cities in Europe. Perinatal transmission occurs in approximately 5% of infants born to HCV infected women. Breastfeeding and close household contact do not appear to transmit the virus. Clinical features Acute HCV infection is usually asymptomatic and thus unrecog- nized. Most patients (60–85%) who become infected with HCV fail to clear the virus and become chronic carriers. Chronic infection induces a persistent necroinflammatory response in the liver and 20 to 30% of patients develop cirrhosis over a 20-year period. Once cirrhosis has developed, the risk of developing liver failure is 2 to 5% per year, while that for hepatocellular carcinoma is 1 to 4% per year. Factors associated with disease progression include excessive alcohol consumption, obesity, diabetes, male sex, older age at infec- tion, and coinfection with HIV or HBV. In addition to its effects on the liver, HCV is associated with extrahepatic manifestations. These are thought to reflect either antigen–antibody complex formation or the induction of cross-reacting autoimmunity and can themselves carry significant morbidity and risks of mortality (Table 15.23.1.6). Patients may be diagnosed incidentally during investigation of fatigue or abnormal liver function tests, with manifestations of chronic liver disease, or when investigated for symptoms or signs of an associated extrahepatic manifestation of HCV. In addition, screening programmes are being developed for high-risk individ- uals including prisoners and intravenous drug users. Investigation As in HBV, assessment of a patient with HCV involves both the viro- logical and the hepatic status. The initial screening test for HCV is detection of circulating anti-HCV antibodies. Screening is recom- mended in those with risk factors for disease and patients found to have abnormal liver biochemistry. Anti-HCV antibodies stay posi- tive for life, regardless of therapy. False-negative results may be seen in acute infection, immunocompromised patients, or those with end-stage renal disease. Active infection is diagnosed by detection of HCV RNA in the blood by polymerase chain reaction assays. Highly sensitive quantitative commercial assays are available for detecting virus and for monitoring responses during and after treatment. Viral genotyping (types 1–6) and subtyping (a and b) is important as re- sponse to treatment varies between genotypes. Unless reinfected, genotypes do not change during

the course of infection and repeat testing is not required. The severity of inflammation in the liver correlates poorly with serum ALT and viral load. Histological assessment may reveal both significant inflammation and progressive fibrosis despite normal serum ALT. The histological changes in the liver are similar to those in HBV, with portal inflammation of varying degrees, periportal hepatocyte necrosis, and progressive fibrosis leading to cirrhosis. The presence of lymphoid follicles in portal tracts and parenchymal Table 15.23.1.6 Extrahepatic manifestations of HCV infection Autoimmune Thyroid disease Sialadenitis Immune thrombocytopenic purpura Haematological Cryoglobulinaemia Monoclonal gammopathy Lymphoma Ocular Dry eyes Pulmonary Fibrosis Renal Membranoproliferative glomerulonephritis Skin Porphyria cutanea tarda Lichen planus Leucocytoclastic vasculitis Bone Osteosclerosis

section 15 Gastroenterological disorders 3118 steatosis are more characteristic of HCV. As with chronic HBV in- fection, noninvasive methods of assessing liver fibrosis and moni- toring progression in patients with HCV are increasingly being used in clinical practice. Management The main goal of treatment of chronic HCV infection is to clear the virus. Sustained loss of viral RNA is associated with a 70% reduc- tion in the risk of liver cancer, a 90% reduced risk of mortality re- lated to liver disease, as well as resolution of symptoms and reduced risk of transmission to the wider community. All patients should be considered for treatment, but the cost of therapy means that some healthcare providers prioritize those with more advanced liver dis- ease for newer, expensive treatment regimens. Those with mild dis- ease may have to choose whether to have treatments with greater side effects and lower success rates or to wait until better therapies are available for them. Interferon and ribavirin Until 2011, the standard of care was combination therapy with pegylated IFN-α-2a or IFN-α-2b (weekly injection) plus oral ribavirin. The mode of action of IFN-α has been discussed previ- ously under HBV treatment. Ribavirin is a guanosine analogue that inhibits viral RNA synthesis. It has no direct action against HCV but augments the response to IFN by unknown mechanism(s). Genotypes 2 and 3 respond well to 6 months of treatment with IFN- α plus ribavirin, with clearance rates of up to 80%. For genotypes 1 and 4, treatment for 12 months produced sustained loss of viral RNA in 40 to 50% of patients, though prolonged therapy (up to 72 months) increased viral clearance rates further. Older patients respond less well. Polymorphisms in IFN-λ-3 determine both spon- taneous elimination of HCV as well as the efficacy of IFN-based treatments. Use of serial and quantitative RNA analysis can define nonresponders in whom therapy can be abandoned after 3 months as well as rapid responders who may have sustained remission and substantially shorten duration therapy. Therapy is associated with side effects that affect treatment up- take, compliance, and accessibility. Thrombocytopenia, leucopenia, and anaemia may limit the ability to sustain IFN therapy, though the use of growth factors may help. Psychiatric side effects or pre- existing diagnoses may contraindicate or limit IFN use, and it is contraindicated in decompensated cirrhosis, reflecting both a lack of efficacy and a high incidence of side effects. Ribavirin induces cough, rash, dyspnoea, and insomnia in about 25% of patients and there is predictably a dose-dependent haemolytic anaemia. The drug is contraindicated in renal failure as it accumulates and then causes severe haemolysis. Both pregnancy and fathering children need to be avoided while taking ribavirin. Newer agents A major breakthrough in the management of HCV came with the development of cell culture systems that support complete HCV replication. This improved the basic understanding and led to the identification of specific viral targets and antiviral compounds. In 2011, first-generation protease inhibitors telaprevir and boceprevir were approved as add-on therapy to IFN and ribavirin in treatment- naïve and treatment-experienced genotype 1 patients. Addition of these directly acting antiviral agents boosted response rates to 70 to 80%. These agents have significant limitations

however, including a low barrier to resistance, limited genotypic activity, clinically signifi- cant side effects, worsening liver function in patients with cirrhosis, significant drug interactions, and multiple daily dosing. The development of new directly acting antiviral agents with different modes of action has broadened treatment options con- siderably. These all-oral, IFN-free regimens are a radical change to clinical practice and provide the opportunity for cure in patients who previously could not be treated. Combinations of these agents can eradiate viral infection with treatment durations of 12 weeks or less in many patients, and with few or no side effects. Treatment ap- pears to be well tolerated even in those with liver decompensation, a group who were previously ineligible for treatment with IFN-based regimens. The HCV RNA polymerase inhibitor sofosbuvir has been shown to be extremely effective in most genotypes in combination with ribavirin, often without IFN. These new drugs are expensive, however, and current accessibility is under tight control by regulatory bodies in many countries. In the United Kingdom in 2015, those with the most severe disease were pri- oritized for treatment with the NS5B polymerase inhibitor sofosbuvir with or without ribavirin in combination with NS5A inhibitors daclatasvir and ledipasvir. Many other IFN-free regimens are now available and many more are in development, hence this field is al- tering rapidly. Guidelines are being updated regularly at http://www. hcvguidelines.org/. Choice of agents should take into account drug– drug interactions, which are regularly updated on the University of Liverpool’s website (http://www.hep-druginteractions.org). Coinfection with HIV Treatment of HIV–HCV coinfected patients is a growing practice. HIV–HCV coinfected patients suffer more liver-related morbidity and mortality, and overall mortality, than HCV monoinfected pa- tients, and they benefit greatly from eradication of HCV. Uptake of HCV therapy was lower in coinfected patients due to historically lower response rates, patient comorbidity, and adverse effects of IFN-based therapy. With the advent of HCV directly acting antiviral agents, more coinfected patients can be treated, but this requires close monitoring and awareness of complex drug interactions be- tween antihepatitis and antiretroviral medication. Other patients, previously identified as difficult to treat, including those with post- transplant HCV and those with renal impairment, may now be con-sidered for treatment with directly acting antiviral agents, but such patients require meticulous monitoring. Chronic hepatitis D Chronic HDV generally follows superinfection of a chronic HBV carrier. HBV–HDV chronic infection tends to cause more severe liver disease, and 10–15% of chronic HDV carriers progress rapidly (within 1–2 years) to cirrhosis. In most patients, HDV acts to sup- press HBV replication so that markers of HBV activity, such as HBV DNA, in the serum may be low and occasionally undetectable. Liver damage in these patients is essentially due to HDV alone. High-titre anti-HDV IgG is present and correlates with HDV replication. Anti- HDV IgM may also persist in chronic infection and HDV RNA is usually positive on polymerase chain reaction assays. The main goal of treatment is to eradicate both HBV and HDV. IFN-α is the only approved treatment for chronic HDV. Treatment frequently suppresses HDV replication with normalization of ALT

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