8.5.22 Hepatitis C virus 896

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896 section 8 Infectious diseases Lok AS, et al. (2017). Hepatitis B: from discovery to regulatory approval. J Hepatol 67, 847–61. Rehermann B (2013). Pathogenesis of chronic viral hepatitis: differential roles of T cells and NK cells. Nat Med, 19, 859–68. Rehermann B, Nascimbeni M (2005). Immunology of hepatitis B virus and hepatitis C virus infection. Nat Rev Immunol, 5, 215–29. Rizzetto M (2016). The adventure of delta. Liver Int, 36 Suppl 1, 135–40. Taylor JM (2006). Structure and replication of hepatitis delta virus RNA. Curr Top Microbiol Immunol, 307, 1–23. 8.5.22 Hepatitis C virus Paul Klenerman, Katie J.M. Jeffery, Ellie J. Barnes,
and Jane Collier ESSENTIALS Hepatitis C virus is a major cause of liver disease worldwide. It is estimated that globally 170 million people are affected. Infection is parenteral. In many countries most recent acquisition is in people who inject drugs, but transmission worldwide also occurs in in healthcare settings due to the reuse or inadequate sterilization of medical equipment and the transfusion of unscreened blood and blood products. Sexual transmission also occurs, particularly in men who have sex with men. The virus has a tendency to be- come persistent in most of those infected. However, a substantial minority (around 25%) do clear the virus as a result of effective innate and adaptive immune responses at the time of acute infec- tion. In those with persistent infection, the clinical course is quite variable. Most individuals will develop some degree of hepatic in- flammation and fibrotic liver disease, of whom a fraction will go on over time do develop cirrhosis, with an excess risk of hepatocellular carcinoma. Cofactors that predispose to increased progression in- clude coinfection with HIV and alcohol use. Historically therapy was a combination of Interferon-α, delivered weekly as a pegylated compound, and ribavirin. Cure rates were 50–80% dependent on viral genotype, with significant side effects. Recently, oral therapies targeted against viral gene products such as protease, and NS5A and NS5B polymerases given for 2–3 months are much better tol- erated and have increased cure rates to greater than 90% across a range of viral genotypes. Introduction Hepatitis C virus (HCV) is a major global pathogen. The only known natural host is man, although it has been possible to in- fect chimpanzees experimentally. The origin of the virus in human populations is not well established, but the huge genetic diversity and global distribution, together with analyses of the viral mo- lecular clock, suggest that it has coevolved with human populations for centuries. However, recent spread through changes in med- ical practice and intravenous drug use have created an emerging health problem, recognized since the 1990s. The capacity of the virus to persist in the face of host innate and adaptive immune responses has made it difficult to develop vaccines. Recently there have been major improvements in the efficacy of treatment regi- mens, but these are still expensive, and some are associated with major side effects. A key task is to identify those who are infected, and those most likely to benefit from the available therapies, taking into account the observed progression and the likely response

to treatment. Historical perspective The presence of HCV as an infectious entity, previously known as non-A, non-B hepatitis, had been recognized for many years before its discovery by Kuo and Houghton in 1988. It was quickly appreciated that HCV was a major infectious agent and the development of antibody-based assays allowed an assessment of its prevalence to be made, as well as allowing the development of screening tools for blood products. Molecular techniques for detection of viral RNA in blood identified most of those infected as chronic viral carriers, while sequencing and bioinformatics approaches led to the description of diverse viral genotypes. The inability to culture the virus proved a major obstacle to be over- come, but the development of a replicon system by Bartenschlager in 1999 proved a significant breakthrough, allowing a dissection of viral replication in vitro. However, no infectious virus system was available until 2005, when several groups took advantage of an unusual Japanese strain (JFH-1), to develop cell culture infectious systems. Aetiology, genetics, pathogenesis, and pathology HCV is a positive-sense, single stranded RNA virus. It is classed in- dividually as a Hepacivirus and genetically related to flaviviruses, such as dengue. Related hepaciviruses have been found in dogs, horses and mice, and a human virus that is closely related to both hepaciviruses and human pegiviruses (human hepegivirus 1) has re- cently been identified in blood transfusion recipients. The viral RNA genome is approximately 10 kb in length and comprises a long single open reading frame. The genome is typ- ically divided into structural and nonstructural proteins. The structural proteins–contained within virions—comprise core and envelope (E1 and E2). The latter are glycosylated, form a heterodimer, and are important targets for antibodies. They are also highly variable and contain sites known as hypervariable re- gions (HVR 1 and 2), which evolve rapidly under antibody selection pressure. The non-structural proteins contain enzymes with defined protease and helicase activity, as well as a viral polymerase. Viral replication is initiated using an internal ribosomal entry site in the 5’ untranslated region (5’UTR). The latter is a highly conserved area, which varies slightly between genotypes and thus has become an important target for molecular diagnostics. The

 polymerase replicates the virus through a double stranded intermediate, which is a substantial trigger for host innate responses. However, the virus can disable triggering of one of these pathways (RIG-I) through the action of the protease, which cleaves a cellular target (CARDIF). One further important feature of replication is that it is highly error-prone, thus within any one individual the virus exists as a swarm of closely related variants, sometimes de- scribed as ‘quasispecies’. HCV replicates largely in hepatocytes. The existence of virus in other cell types, including lymphocytes and dendritic cells, and within the central nervous system, has been described. However, the contribution of such sites to disease pathogenesis has not been defined. Several cellular receptors for HCV have been described. These include CD81 (a member of the tetraspanin family with signalling properties on lymphocytes), Claudin 1, Occludin, the low-density lipoprotein receptor, DC-Sign, and a macrophage scav- enger receptor. After natural or experimental infection, there is a substantial period, lasting weeks to months, where virus may be detect- able, without any apparent clinical, biochemical, or immuno- logical disturbance. During this time, virus may replicate to high levels in blood and within the liver, indicating that the direct cytopathic effects of the virus, in the absence of host immune responses, are minimal. This silent phase is followed by the onset of acute hepatitis, which may or may not be clinically apparent. Detailed intrahepatic studies in animal models (not possible in man), reveal that the first responses at this stage of infection are mediated by innate immune mediators (interferons, NK cells). Polymorphisms in the region of interferon-lambda 3 (IL28B) have a major impact on spontaneous

resolution, suggesting a critical role for this cytokine in early viral control. This innate response is followed by an influx of T cells (both CD4 + and CD8 +). In studies of human acute hepatitis C, the emergence of highly activated virus-specific CD8 + T cells correlates quantitatively and temporally with the peak of the alanine transaminase (ALT). This suggests that at this stage the tissue damage is largely a result of the host T-cell response. The subsequent events vary substantially between different pa- tients, but three clinical patterns are observed—clearance of virus below the level of detection in blood, persistence of virus without host control, or an intermediate state, where virus is transiently controlled, with relapse (Fig. 8.5.22.1). The immunological events that determine these different outcomes are not fully understood, but the association of specific HLA genes both Class II (such as HLA DR11/DQ3) and Class I (such as HLA A3, B27 and B57) with spontaneous resolution point to the importance of host T-cell re- sponses. It is generally considered that T-cell responses that are broader and more sustained in number and function are most likely to be successful in viral control. B-cell responses are also likely to be involved. However, the rapid emergence of viral escape mutants in the hypervariable envelope regions may limit the efficacy of neu- tralizing antibody responses in containing viral replication. Viral mutation within T-cell epitopes is also a major cause of persistence in the face of T-cell responses, although other phenomena such as T-cell exhaustion and the emergence of regulatory T-cell subsets also contribute to T-cell failure. In those where virus is cleared below the level of detection long term, around 25% overall, antibody and T-cell responses may be HCV Load HCV detection threshold Weeks Weeks Weeks ALT HCV Load ALT HCV Load ALT Upper limit of normal (ALT) Acute-resolving Acute-persistent Acute-transient Control-persistent Fig. 8.5.22.1 Distinct clinical outcomes following acute hepatitis C virus (HCV) infection. Some patients are able to eliminate virus following infection (upper panel) but the majority develop persistent infection (middle panel). A subgroup have a period of transient control but ultimately develop long-term carriage (lower panel).

 detected for many years. In most individuals, virus persists after acute hepatitis, in the presence of antibody responses. T-cell re- sponses in blood during chronic disease are weak but within the liver, infiltrates of T cells may be found. The pathology of HCV is highly variable between patients, and there is no diagnostic staining pattern, but it is typified by portal tract infiltrates of T and B cells, with the emergence in some cases of lymphoid follicles within liver tissue. Histologic scores (Ishak’s, Metavir) have been developed to quantify the degree of liver damage. These comprise a measure of the degree of hepatic inflammation (typically portal tract infiltration, ‘interface’ hepa- titis, lobular infiltration, and necrosis), together with the degree of hepatic fibrosis. The viral genotype is thought to have some influence on the pathogenesis, with genotype 3 associated with the development of hepatic steatosis, increased inflammation and fibrosis, and more rapid progression to cirrhosis. Epidemiology HCV is thought to infect around 170 million individuals world- wide. Spread is parenteral, and largely associated with needle use and exposure to infected blood products. Mother to child spread does occur but at relatively low rates (around 3–5%) (2–3-fold higher in the context of HIV coinfection), and sexual spread is documented but rates are also low (see next). Thus, the risk groups are those exposed to infected blood products (recipients of un- screened blood/plasma fractions, haemophiliacs) and contam- inated needles (people who inject drugs (PWID), participants in parenteral therapy programmes, nosocomial spread). Of these, in the west, PWID groups have particularly high rates of acquisi- tion and represent the main current focus of the infection. In some countries, most notably Egypt, medical programmes have been re- sponsible for spread of HCV in specific groups, and the prevalence of HCV in Egypt is the highest worldwide, up to 20–30% in some communities. In the

last decade, epidemic spread of HCV infec- tion among HIV + men who have sex with men has been observed in many countries globally. HCV has evolved into multiple genotypes (1–6) and subtypes. Molecular typing techniques can trace the spread of individual strains within populations (including infections from a single source). Thus the Egyptian outbreak is genotype 4a, the older cir- culating western strains were typically genotype 1a and 1b, and the more recent strains acquired in Western PWID populations are 3a. Genotype 3 strains were originally linked to Southeast Asia, where genotype 6 is still largely found. Genotype 2 and Genotype 5 have remained localized strains, in West Africa and South Africa, respectively, but all strains are to some extent found globally. Prevention Primary prevention There are no licensed vaccines to prevent HCV infection although some are in development. Primary prevention of HCV worldwide depends on ensuring a safe blood supply and scrupulous atten- tion to the provision of sterile injection devices for all necessary healthcare interventions. The provision of sterile injection equip- ment has been shown to reduce the prevalence of HCV in people who inject drugs. HCV is not transmitted by typical household ex- posures but household contacts of HCV-positive individuals are advised to avoid sharing razors and toothbrushes. Sexual trans- mission of HCV is inefficient, and studies show a low prevalence (average: 1.5%) of HCV infection in long-term spouses of patients with chronic HCV infection who had no other risk factors for in- fection. No intervention has been clearly shown to decrease the risk of mother to child transmission of HCV, and breastfeeding is not discouraged. In healthcare settings, equipment, facilities, and policies should be in place to reduce the risk of percutaneous injury to staff. Postexposure prophylaxis Immune globulin is not effective in preventing HCV infection postexposure. Individuals exposed to the virus (e.g. via a percutan- eous injury), or perinatally, should be offered follow-up testing for HCV. The average risk of infection following a percutaneous injury is 1.8% (range 0–7%) and those who become infected should be offered early antiviral therapy. Clinical features Acute hepatitis C Acute HCV infection is clinically indistinguishable from other causes of acute viral hepatitis, and may therefore present with a pro- drome of fever, myalgia, and malaise. However, the acute phase is usually asymptomatic, and compared with hepatitis A or B it is un- common to develop the classical symptoms of jaundice, pruritus, pale stools, and dark urine. Serum levels of transaminases can be markedly elevated, although levels of up to 10 times the upper limit of normal would be more usual. Fulminant hepatic failure in acute HCV is rare. There is evidence that patients with symptomatic acute HCV in- fection have a higher rate of spontaneous viral clearance than those with asymptomatic infection. Overall approximately one in four patients will clear the virus spontaneously. Serum transaminases usually remain elevated at around twice the upper limit of normal in those who fail to clear the virus, although may normalize completely. Chronic infection Chronic infection with HCV is defined as the persistence of HCV RNA in blood for greater than six months. Most patients with chronic HCV infection will be unaware of their diagnosis, and many will have been tested following an incidental finding of abnormal liver function tests or have tested positive on rou- tine screening (e.g. for blood donation), or having given a his- tory of potential HCV exposure, such as intravenous drug use. Such patients will either be asymptomatic or have nonspecific symptoms such as fatigue. Symptoms suggestive of liver dis- ease are unlikely to be present unless cirrhosis has developed. Hypoalbuminaeamia, thrombocytopaenia, and coagulopathy are

 suggestive of cirrhosis, although this can only be diagnosed de- finitively with a liver biopsy. HCV is associated with several extrahepatic manifestations, the best documented of which are HCV related lymphoproliferative dis- orders, most commonly characterized by mixed cryoglobulinaemia. Although studies suggest a high prevalence of serum

cryoglobulins in HCV-positive patients, they are generally present at low levels with absent or only mild symptoms. Occasionally patients will pre- sent with neuropathies, arthralgias, and purpura and more severe cases may involve the kidney. B-cell non-Hodgkin's lymphomas, porphyria cutanea tarda, Sjogren's syndrome, and lichen planus have been found more commonly in association with HCV infec- tion than in HCV negative control groups in some studies, and other studies suggest autoimmune thyroiditis and type II diabetes mellitus are found with a higher frequency than expected in HCV-positive individuals. Prognosis The rate of progression of HCV is highly variable. Risk factors for progression include older age at acquisition of infection, male gender, presence of immunosuppression including coinfection with HIV and concurrent heavy alcohol consumption. It is estimated that between 7 to 20% will develop cirrhosis within 20 years of infec- tion. Progression is higher in transfusion associated hepatitis than in community acquired HCV (i.e. people who inject drugs). However, some patient groups, such as a cohort of Irish women infected in 1977 through contaminated blood products, show rates very much lower than this with only 3% developing cirrhosis within 20 years of infection. Once cirrhosis develops, 80% will develop complications such as ascites and variceal bleeding within 10 years, and once complica- tions have developed, 50% will develop liver failure within a further 5 years. Hepatocellular carcinoma only occurs in the presence of cir- rhosis with an incidence of 1–5% per year. HIV coinfected patients progress more rapidly to liver failure once complications of cirrhosis have occurred. Liver transplantation is indicated for decompensated HCV cirrhosis and in cirrhotics who develop small hepatocellular carcinomas despite good liver function. In the absence of therapy, infection universally recurs in the transplanted liver and pro- gression to cirrhosis occurs in about 10% of transplant recipients within 5 years. Diagnosis Serology Initial diagnosis of HCV infection is usually made by detecting HCV-antibodies directed against recombinant HCV proteins in highly sensitive screening immunoassays. In low prevalence popu- lations, the probability of a false positive antibody test is high, and supplementary confirmatory tests should be performed. The de- velopment of an antibody response can take up to 2 months in im- munocompetent individuals, and can be delayed or not occur at all in immunocompromised individuals such as those with HIV infection or on haemodialysis. By six months, 97% of those infected will have developed an antibody response. It is good practice to confirm HCV-antibody positivity with a second antibody test and a test for active infection, such as viral RNA or hepatitis C antigen, and also to test a second independent sample. Hepatitis C antigen detection is becoming a widely available immunoassay and correl- ates highly with the detection of HCV RNA, although it may lack some sensitivity at low HCV viral loads (<1000 IU/ml). Hepatitis C antigen testing can be used to rapidly confirm active hepatitis C infection in the context of a newly detected HCV-antibody. As it re- duces the 'window period' when compared with antibody only tests, the antigen test is particularly useful for screening blood donations in resource poor settings. Specialist laboratories may be able to pro- vide further immunoassays which examine responses to different antigens, or line/strip immunoblots which have individual synthetic or recombinant antigens applied as separate lines to a solid phase; serologic responses to different HCV antigens can be distinguished. However, the diagnosis of HCV positivity can be established with a high degree of specificity with a combination of antibody and antigen/RNA assays. HCV RNA testing Nucleic acid-based tests are the gold standard for the diagnosis of acute and ongoing chronic HCV infection. HCV RNA can be detected by polymerase chain reaction (PCR) as early as 2 weeks postinfection before the development of antibody responses. Commercial assays now produce quantitative results with in- creasingly sensitive limits of detection. Methods used to detect HCV RNA include reverse transcription PCR (RT-PCR), and transcription-mediated amplification. Although quantitative re- sults may be

important in predicting the response to interferon- based therapies, they are not useful for predicting disease severity or long-term progression in contrast to HIV infection. Some coun- tries have successfully introduced nucleic acid-based testing of pools of samples for blood donation screening. Pretreatment evaluation HCV virus genotyping is essential prior to treatment as it predicts duration of treatment and response (see next). HCV genotyping can be performed by line probe assays utilizing reverse hybridization and nucleic acid probes, or by viral sequencing which has the ad- vantage of identifying rare intergenotypic recombinant strains. In the era of directly acting antiviral agents (DAAs), next-generation sequencing that can provide full viral sequences can be used to track specific mutations linked to drug resistance. Resistance testing pretreatment is not in common clinical use (except in the case of simeprevir) but the detection of specific resistance patterns will be under close review as the DAA drugs become more com- monly used. Noninvasive methods of assessing the degree of liver fibrosis using serum markers of fibrosis, assessment of liver stiffness using an ultrasound probe or newer magnetic resonance techniques (e.g. Fibroscan™, FibroTest™, and MRI) are good negative predictors of significant fibrosis. Liver biopsy is usually reserved for those indi- viduals where noninvasive markers suggest scarring to exclude cir- rhosis, where hepatocellular carcinoma surveillance may be needed, or those who may have dual liver pathology such as associated

 non-alcoholic fatty liver disease. Polymorphisms in IL28B are as- sociated not only with spontaneous clearance but also clearance associated with interferon-based treatment regimens. IL28B also impacts on highly effective directly acting antiviral agent regimens but its effect is less evident. Treatment The aim of treatment of HCV is to eradicate HCV RNA from serum. Although loss of viraemia is associated with improvement in liver histology, if cirrhosis is present, the risk of hepatocellular carcinoma remains after successful treatment with antiviral therapy, although the risk is reduced. Screening for hepatocellular carcinoma should, therefore, continue in patients with cirrhosis during and after treatment. HCV viraemia can re-emerge within 3 months of stopping treatment (relapse) but individuals who remain HCV RNA nega- tive 3 months after completing therapy are considered to be cured (sustained response) and will remain HCV RNA negative, unless reinfected. Chronic hepatitis C Interferon-α and ribavirin have been the mainstay of treatment for over a decade with historical cure rates of 45–70% but have now largely been replaced by better tolerated and more effective direct acting antiviral drugs (DAAs) for most genotypes. Interferon-α induces the expression of multiple genes that have antiviral and antiproliferative action including those encoding RNAases, 2’-5’ oligo-adenylate synthase, and pro- tein kinase R. It is administered as pegylated interferon which has the advantage of being given once weekly. There are two pegylated interferons, 2a and 2b, which are modified interferon- α molecules with different side chains which lengthen their half-life. Ribavirin is a guanosine analogue which, when used alone, does not reduce HCV RNA levels but, when combined with interferon-α, improves the sustained virological response compared to interferon-α monotherapy and might also improve cure rates in cirrhotic patients when used with the direct acting antiviral therapies. The oral directly acting antiviral agents are inhibitors of the hepatitis C viral gene proteins such as the NS3 protease, NS5A and NS5B polymerases (Fig. 8.5.22.2). They are typically given in 2 or 3 drug combinations for 8 to 12 weeks. In genotype 1 the overall sustained response rate is more than 90% even in the presence of cirrhosis. Cure rates are probably slightly lower, at 70% in decom- pensated more advanced cirrhosis, but historically this patient group could not be treated because interferon treatment is asso- ciated with worsening liver failure. Drug combinations in current clinical practice include e.g. ledipasvir plus sofosbuvir, sofosbuvir with

simeprevir, ombitasvir with ritonavir boosted paritaprevir and dasabuvir. It is currently unclear whether shorter courses of 4–6 weeks of therapy will be effective in some patient groups. In genotype 2 treatment with one DAA, sofosbuvir, with ribavirin for 12 weeks is associated with an 87% cure rate. Genotype 4 has a cure rate of 90% with two oral directly acting antiviral agents—ombitasvir and paritaprevir—boosted with ritonavir for 12 weeks in noncirrhotics, and 24 weeks in presence of cirrhosis. Genotype 3 has proven the more difficult virus to eradicate with the newer DAAs. A shorter 3-month course of pegylated α-interferon given with sofosbuvir and ribavirin has a cure rate of greater than 85% even in the presence of cirrhosis. Daclatasvir also has genotype 3 efficacy when given with sosfosbuvir and ribavirin. Newer NS5A inhibitors with pan-genotypic activity (such as Velpatasvir) show good clinical efficacy against genotype 3 in combination with other DAAs. Cure rates in the presence of HIV coinfection and in the presence of immunosuppression ap- pear similar to noninfected immunocompetent patients with the new DAAs. With interferon-based regimens, side effects of treatment were common and quality of life was universally affected, although many individuals were able to continue working during therapy. Treatment with the α-interferons is associated with fatigue, depres- sion, and mood swings. Other side effects include rashes and thy- roid abnormalities. Bone marrow suppression was common with such regimens and led to the need for dose reductions. This was a particular problem in patients with cirrhosis who were already pancytopaenic before the start of treatment. Interferon-α is also contraindicated in renal and cardiac transplant recipients because of the risk of inducing acute cellular rejection. Ribavirin causes haemolysis and frequently leads to a 2–3 gram drop in haemoglobin during treatment and, because of its renal ex- cretion, it is contraindicated in renal failure. In contrast, the new directly acting antiviral agents have few side effects, mainly limited to headache and nausea. However, drug interactions are common and a careful history of prescribed and over the counter medication is needed pretreatment. Potential drug interactions can be checked at https://www.hep-druginteractions.org. Acute hepatitis C The results of treating acute HCV are much better than chronic infec- tion. Although as many as 50% of patients with acute symptomatic C E1 E2 NS2 NS5A NS3 NS4A NS5B NS3/4A Protease inhibitor Paritaprevir (ritonavir boosted) Grazoprevir Voxilaprevir Glecaprevir Simeprevir NS5A Polymerase inhibitor Ombitsavir Elbasvir Ledipasvir Velpatasvir Pibrentasvir Daclatasvir (Odalasivir)* NS5B Polymerase inhibitor Dasabuvir Sofosbuvir (AL-335)*

- Phase II only in combination Fig. 8.5.22.2 Directly acting antiviral (DAA) therapy for hepatitis
  C virus infection. The figure shows the proteins encoded by the virus and the drugs used to target protease (‘previrs’), NS5A (‘asvirs’) and NS5B polymerase (‘buvirs’). These drugs need to be used in combination; drugs used together are grouped by colour. All drugs shown are approved by the FDA/EMA for clinical use, except those in brackets which are in development in combination (Phase-II).

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