Viral Hepatitis

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Abstract

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7.1 Introduction

Hepatitis is a general term, which refers to inflammation of the liver. Hepatitis occurs as a result of infection with various pathogens, exposure to alcohol, medications, chemicals, toxins, as well as immune disorders.

Hepatitis in children is predominantly caused by viruses; and the incidence and etiology of viral hepatitis varies according to the immunization regime and geographical location of different countries. The hepatotrophic viruses, hepatitis A, B, C, D and E account for the majority of cases of viral hepatitis. Other viruses that commonly cause hepatitis include the herpes viruses (cytomegalovirus (CMV), Epstein–Barr virus (EBV) and herpes simplex) and the enteroviruses (coxsackie virus). There are many other viruses that can affect the liver as part of a systemic viral illness (measles, rubella, varicella-zoster virus, parvovirus B19, adenovirus) as well as the mosquito-borne viral infections (yellow fever, dengue haemorrhagic

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R.J. Green (ed.), *Viral Infections in Children, Volume II*,
DOI 10.1007/978-3-319-54093-1_7

fever, Lassa fever, Ebola virus, Marburg virus and Rift valley fever), but they will not be discussed in this chapter.

The clinical symptoms and signs of the different viruses are often indistinguishable, but the epidemiologies are markedly different and clinically this chapter will concentrate on the liver manifestations.

Despite the availability of effective vaccines for hepatitis A, B and E; effective therapy for hepatitis B and herpes simplex infections; and curative therapy for hepatitis C; viral hepatitis remains a significant global health challenge. In May 2016, the World Health Organisation (WHO) adopted a global hepatitis strategy with the goal to eliminate viral hepatitis as a public health threat by 2030. The targets to be achieved by 2030 are ambitious and include: 90% reduction in new cases of chronic hepatitis B and C, 65% reduction in mortality due to hepatitis B and C and 80% of treatment eligible persons with chronic hepatitis B and C infections being treated.

7.2 Hepatotrophic Viruses

7.2.1 Hepatitis A

Hepatitis A (HAV) is endemic in many parts of the world and is transmitted primarily via the fecal-oral route. The prevalence of hepatitis A strongly correlates with socio-economic conditions and access to safe water and adequate sanitation and this has contributed to the endemic nature of hepatitis A.

7.2.2 Virus Structure

Hepatitis A is a small, non-enveloped, single stranded RNA virus and is a member of the family *Picornaviridae* belonging to the genus *Hepatovirus.* Human HAV has only one serotype, but can be grouped into four human genotypes (I, II, III, VII) using RNA sequencing [1–4]. The virus may persist in the environment for prolonged periods even under high levels of environmental stress, but is inactivated by boiling (at >85 °C or 185 °F for 1 min) and on exposure to household bleach (1:100 dilution in tap water) [3].

7.2.3 Epidemiology and Transmission

The global epidemiology of hepatitis A has changed markedly due to improvements in water supply, sanitation and hygiene. In highly industrialized countries, prevalence in blood donors is now <10% and cases are largely imported by individuals visiting endemic areas [3]. As endemicity patterns shift from high to intermediate levels, a larger pool of susceptible older children and adults develops and symptomatic disease with increased morbidity and mortality as well as outbreaks is more frequent [5].

HAV is highly infectious with person-to-person spread being the most common route of transmission, followed by ingestion of fecally contaminated water or food.

7.2.4 Clinical Presentations of Hepatitis A

Hepatitis A infection is usually a self-limiting disease, there is no chronic carrier state and immunity following infection is considered to be life-long. Acute hepatitis A may be a trigger for unmasking autoimmune hepatitis. The incubation period is 15–50 days (average 28 days) and viremia is transient (2–4 weeks). Individuals are most infectious 2 weeks prior to the onset of jaundice. Most individuals will remain infectious for 1–2 weeks following the onset of jaundice [1]. However, prolonged shedding of the virus in stool has been documented, thus increasing the period of infectivity [6]. The clinical presentation in an area is largely influenced by the age at which individuals become infected and the presence of underlying risk factors for severe disease [6, 7]. In areas where socio-economic standards are poor and there is inadequate access to clean water and sanitation, infection occurs early in life and produces mostly mild or asymptomatic disease. In these areas, rates of infection are higher, but morbidity considerably less. Most people in such communities are immune by adolescence and this immunity persists lifelong. In developing countries, most children are infected before the age of 9 years [3].

In areas where exposure to HAV in childhood is less likely due to improved living conditions, infection will occur less frequently, but will present in adolescents and adults and is more likely to be symptomatic. Thus, morbidity associated with disease in this setting is considerably greater.

The overall mortality is 0.3% in icteric cases and 0.1% in children <15 years of age.

The different clinical presentations include:

- ***Asymptomatic infection***: Most children <4 years of age are completely asymptomatic
- ***Symptomatic hepatitis without jaundice***: 90% children aged 4–6 years are anicteric
- ***Symptomatic hepatitis with jaundice***: 40–70% individuals >15 years of age of age, present with jaundice [4]. A prodromal illness usually precedes the jaundice in 85% individuals and includes:
  - Loss of appetite, fatigue and malaise
  - Flu-like symptoms: fever, cough, coryza, pharyngitis, photophobia and headache
  - Arthralgia and myalgia
  - Nausea, vomiting and abdominal discomfort
  - Diarrhea.

The symptoms of the prodrome usually decline with the onset of jaundice.

7.2.5 Complications of Hepatitis A

1. ***Fulminant hepatitis with acute liver failure***: Although there is an increased risk in adults >40 years of age, it can also occur in very young children. The severity of the liver injury is often underestimated in children, as encephalopathy is often

a late and terminal presentation in children <5 years of age. Mortality rates are 70–95% unless liver transplantation is performed, where 65% survival rates have been achieved.
2. ***Cholestatic hepatitis***: An uncommom complication characterized by prolonged jaundice with marked pruritus, more common in adolescents. Steroids should not be used to treat cholestatic hepatitis A.
3. ***Relapsing hepatitis***: This is uncommon, occurring in 3–20% of symptomatic individuals. It may occur 4–15 weeks after the initial symptoms have resolved. Illness manifests with a relapse of symptoms and liver function abnormalities. In addition, HAV is shed in the stool and patients are again infectious. The vast majority will recover fully, but this may take up to 12 months. It tends to occur if individuals return to active sport too early.

7.2.6 Diagnosis of Hepatitis A

Viral hepatitis cannot be distinguished clinically or biochemically but requires a serological diagnosis. Elevated transaminases (ALT and AST usually 10–100 times upper limit of normal) confirm the presence of hepatitis.

- ***Acute hepatitis A***: Positive anti-HAV IgM. Levels decline over 3–6 months following infection
- ***Previous exposure to hepatitis A or post HAV vaccination***: Positive anti-HAV IgG.

7.2.7 Prevention of Hepatitis A

Pre-exposure prevention includes good personal hygiene, adequate sanitation and access to safe food and drinking water. Hepatitis A vaccination (a single dose with a booster at 6–12 months) provides long-term protection. It is not part of the expanded program of immunization (EPI) in many developing countries; but with changing socio-economic demographics and potential transition towards a lower hepatitis A endemicity level in many developing countries; EPI policies may need to be reevaluated. A West African seroprevalence study in urban children has indicated that the midpoint of population immunity has shifted to school-aged children suggesting a transition to lower levels of hepatitis A endemicity, and greater risk of symptomatic disease [8].

Hepatitis A vaccination is recommended in high-risk groups i.e. children with chronic liver disease, immune-compromised children including solid organ transplant recipients and children on immunosuppression. HAV vaccination should be considered in children >2 years of age if affordable.

Vaccination is now the preferred post-exposure approach in children >2 years of age. HAV vaccine must be given early, preferably within 72 hours of exposure, but can be administered up to 14 days post-exposure.

Immune globulin is still recommended as post-exposure prophylaxis for immune-compromised children due to the reduced vaccine immunogenicity and more severe disease.

7.2.8 Treatment of Hepatitis A

There is no specific antiviral treatment for hepatitis A infection and treatment is supportive. Children with severe symptomatic disease (jaundice and associated nausea and vomiting) should be hospitalized and liver transplantation must be considered in patients presenting with fulminant liver failure.

7.2.9 Hepatitis B

Hepatitis B is an entirely vaccine-preventable disease, but it remains endemic in many regions of the world. In a recent systematic review based on observational studies performed in the general population, amongst blood donors, health-care workers and pregnant women between 1965 and 2013, the number of hepatitis B surface antigen (HBsAg) positive individuals was highest in the Western Pacific (95.3 million, prevalence estimate 5.26%) and Africa (75.6 million, prevalence estimate 8.83%) regions, which together included nearly 70% of the global burden Hepatitis B virus. This is most likely an underestimate due to under-reporting and exclusion of high-risk groups [9]. In endemic countries, hepatitis B virus (HBV) endemicity is established in early childhood with HBsAg seroprevalence studies showing no difference between children aged 5–9 years and adults [10]. Globally, there are ten genotypes (A–J) [11, 12] and the HBV genotypes influence the spectrum of disease, the risk of hepatocellular carcinoma and the response to antiviral treatment.

7.2.10 Virus Structure

HBV is an enveloped partially dsDNA virus and is a member of the *Hepadnaviridae* family. It has a compact genomic structure (±3.2 kb) with four overlapping open reading frames that encode four sets of viral proteins: HBsAg, HB core Ag, viral polymerase and HBx protein.

Ultrastructurally, there are three distinct morphological forms found in the sera of infected patients: small non-infectious spherical particles (17–25 nm), tubular filamentous forms of various lengths and the complex, spherical, double shelled particle (42 nm).

The virus circulates in serum as a 42-nm, double-shelled particle, with an outer envelope component of HBsAg and an inner nucleocapsid component of hepatitis B core antigen (HBcAg). HBV DNA can be detected in serum and is used to monitor viral replication. HBeAg, unlike HBsAg and HBcAg, is not particulate, but rather is detectable as a soluble protein in serum.

HBV is found in blood and all body fluids and survives in dried blood for prolonged periods (weeks) and is stable on environmental surfaces for at least 7 days at 25 °C (77 °F). Hepatitis B virus is stable at temperatures below 60 °C (140 °F): stable at 37 °C (98.6 °F) for 60 min and 56 °C (132.8 °F) for 30 min, and stable for years at −70 °C (−158 °F). HBV is stable at pH 2.4 for up to 6 hours (some infectivity is lost). HBV is susceptible to inactivation by many disinfectants including 1% sodium hypochlorite, 2% alkalinized glutaraldehyde and formaldehyde.

7.2.11 Transmission of Hepatitis B

HBV is a 100 times more infectious than HIV and 10 times more infectious than HCV. HBV is transmissible via perinatal, percutaneous or sexual exposure to HBV-infected body fluids including serum, saliva, semen and vaginal fluids.

All HBsAg positive individuals are infectious; but HBeAg positive individuals are more infectious as they have higher rates of HBV replication.

7.2.11.1 Horizontal Transmission

This is the main route of HBV transmission in sub-Saharan Africa, usually occurring in children between the ages of 6 months and 5 years [13–16], from unapparent percutaneous exposure to infected blood or body fluids. Modes of acquisition include close non-sexual person-person contact over a long period with infected older siblings and playmates; sharing of personal items e.g. toothbrushes, razors, hairclippers and traditional scarification practices.

7.2.11.2 Perinatal Transmission

This occurs mainly at birth and is the main route of transmission in South-East Asia where mothers are usually HBeAg positive in the immune tolerant phase of chronic infection. There is an increased risk of perinatal transmission associated with HBV DNA levels >200,000 IU/mL [17–22]. In-utero transmission is rare and transmission through breast milk is controversial [23]. The risk of chronic HBV infection at 6 months in the absence of any intervention is 70–95% in babies born to HBeAg-positive women and <10% in babies born to HBeAg-negative women.

Risk of transmission from women acutely infected in the first or second trimester is low, but increases to approximately 60%, if acute infection occurs in the third trimester.

Maternal HIV/HBV coinfection increases the risk of perinatal transmission up to 2.5-fold as HIV/HBV coinfected pregnant women are twice as likely to test positive for HBeAg, three times more likely to test positive for HBV DNA and have higher HBV DNA levels, thereby increasing the risk of mother-to-child transmission (MTCT) [10, 24].

7.2.11.3 Sexual Transmission

HBV is efficiently transmitted sexually, but the exact risk of transmission per sexual contact is unknown. Sexually active adolescents who have not been vaccinated are at risk.

7.2.11.4 Percutaneous Transmission: Needle-Stick Injuries [25]

The risk of HBV transmission from needlestick injury is:

- 30–60% from exposure to HBeAg-positive blood
- 10–30% with HBeAg-negative blood
- Injection drug use poses a high risk of HBV transmission.

7.2.12 Clinical Presentations of Hepatitis B

The clinical manifestations of acute and chronic HBV infections are variable.
The risk of chronicity is dependent on the age of acute infection:

- 70–95% for infants exposed perinatally (HBeAg positive mother)
- 25–50% for children aged 1–5 years
- 6–10% for 5–20 years
- 1–3% for adults >20 years.

7.2.13 Acute Hepatitis B

The incubation period ranges between 1 and 4 months and clinical manifestations of acute hepatitis B depend on the age of acquisition:

- Anicteric, asymptomatic infection in about 70% individuals, especially if infected during early childhood
- Symptomatic, icteric illness in 30%
- Fulminant hepatitis occurs in 0.5–1%.

Acute HBV infection in children under the age of 10 is usually asymptomatic, but in adolescents it is usually symptomatic, has various phases and is associated with a full clinical recovery.

7.2.13.1 Early Prodromal Phase

In symptomatic individuals, the illness may be heralded by a serum sickness-like syndrome which precedes jaundice by 14–21 days and disappears with the onset of jaundice. The prodromal symptoms include fever, urticaria, arthralgia and arthritis.

7.2.13.2 Preicteric Phase

The abrupt or insidious onset of non-specific constitutional symptoms or an influenza-like illness may occur and include malaise and fatigue; myalgia; anorexia, nausea and vomiting; epigastric or right upper quadrant discomfort.

Physical examination may be unremarkable or may reveal a tender hepatomegaly and splenomegaly. Hepatosplenomegaly is usually mild (liver palpable 2–3 cm below the costal margin and spleen tipped).

7.2.13.3 Icteric Phase

With the onset of jaundice approximately a week after the preicteric phase; fever and constitutional symptoms subside. Anorexia, nausea and vomiting may transiently worsen. The presence of dark urine and pale stools often raises the clinical concern of obstructive jaundice. Pruritic scratch marks maybe present, if jaundice is severe or prolonged. Weight loss is common.

7.2.13.4 Convalescent Phase

Jaundice tends to wane rapidly over days in adolescents, but tends to persist longer (6 weeks or more) in adults. The preicteric phase symptoms disappear, pruritus abates and the hepatosplenomegaly gradually resolves.

7.2.14 Fulminant Hepatitis B

This syndrome is characterized clinically by jaundice, hepatic encephalopathy and coagulopathy (international normalized ratio (INR) > 1.5), which generally occurs within 8 weeks of the onset of the acute illness. This is the result of massive cellular immune-mediated lysis of infected hepatocytes which explains the frequent lack of detectable viral replication in such patients.

Although the majority of infected infants become chronically infected, infants born to HBsAg positive, HBeAg negative mothers may develop fulminant hepatitis within the first 12 weeks of life [26]. The increased incidence of fulminant hepatitis B at this age is due either to partial immunity (as the mother may have circulating anti-HBe) or due to vaccine failure. However, the majority of cases are associated with the transmission of a pre-core mutant virus from mother to child [27]. Although, fulminant hepatitis B may be effectively prevented by vaccination of all infants of hepatitis BsAg positive mothers, this depends on antenatal screening and effective prevention of MTCT.

7.2.15 Chronic Hepatitis B

Chronic Hepatitis B is defined as the persistence of HBsAg positivity ≥6 months. It is frequently a clinically silent disease and is often identified incidentally.

Physical examination may reveal no or few signs. Peripheral stigmata of chronic liver disease (spider naevi and palmar erythema) and signs of portal hypertension (distended abdominal veins, caput medusa, ascites and splenomegaly) may be present depending on the phase of chronic infection. Weight loss, jaundice and a rapidly enlarging, tender, hard nodular liver together with a systolic bruit raises the concern of a hepatocellular carcinoma (HCC).

7.2.15.1 Natural History

The natural history of chronic infection is determined by the interplay between host immunity, and viral replication. There are five different phases of chronic

infection: Immune tolerant, immune clearance, immune control, immune escape and occult hepatitis B [28, 29].The clinical outcome is determined by the age of acquisition and the phase of the infection at the time of arrest of viral replication by host immunity or antiviral treatment [30]. HBV DNA levels, ALT levels and HBeAg status are important determinants of the risk of cirrhosis [31, 32], whereas HBV DNA >2000 IU/mL, HBeAg status and cirrhosis are key predictors of HCC risk [31–34].

Following acute exposure, HBV enters the hepatocyte via binding to the receptor sodium taurocholate cotransporting polypeptide and translocates to nucleus. The partially doubled-stranded DNA is repaired to form a circular extra-chromosomal molecule called the covalently closed circular DNA (cccDNA), which is the transcriptional template for the viral messenger RNAs (mRNAs) [35]. HBV replicates its DNA genome by reverse transcription of an RNA intermediate via the viral reverse transcriptase within the cytoplasm.

Cytoplasmic viral capsids containing mature viral DNA are either transported to the nucleus, thereby replenishing cccDNA, or bind to HBsAg that have accumulated in the endoplasmic reticulum, bud through the cellular membranes and are secreted from the hepatocyte non-cytopathically as virions.

Hence, even if the individual clears HBsAg, the hepatocyte still harbours intranuclear cccDNA and this determines the chronicity and the inability to cure hepatitis B with present day therapies. HBV DNA can also integrate into the hepatocyte genome during chronic infection. This integrated DNA plays no role in viral replication, but plays an important and ill-defined role in the development of HCC.

The natural history of chronic hepatitis B is dynamic and complex, and may progress non-linearly through the five recognizable phases [28, 29, 36]. These phases are of variable duration, are not necessarily sequential and not every individual with chronic hepatitis B will evolve through all the phases. Some individuals will be in a "gray zone" where their ALT and HBV DNA levels fall into different phases and thus longitudinal follow-up of ALT and HBV DNA levels +/− liver histology or fibroscan is necessary to establish the phase of chronic infection [29].

The clearance of HBsAg, whether spontaneous or after antiviral therapy, reduces the risk of hepatic decompensation and improves survival. Approximately 0.5% of individuals in the immune control phase will spontaneously clear HBsAg annually and develop anti-HBs. Most children chronically infected with hepatitis B will be completely asymptomatic and only develop complications when they reach adolescence or adulthood. However, in the setting of immunosuppression, they are at risk of hepatitis flares and decompensation. The risk of HCC increases as children reach adolescence. In untreated adults with chronic hepatitis B, the cumulative 5-year incidence of cirrhosis is 8–20%, and amongst those with cirrhosis, the 5-year cumulative risk of hepatic decompensation is 20%, and the risk of HCC is 2–5% [30, 36, 37].

The cumulative 5-year survival for compensated cirrhosis is 85% and for decompensated cirrhosis is 14–35% [38].

7.2.16 Extrahepatic Manifestations

Extrahepatic manifestations may be the presenting features of both acute and chronic HBV infection [39, 40].

Acute infection: Serum sickness-like syndrome, more common in adolescents.

Chronic infection (10–20% patients): Polyarteritis nodosa, membranous glomerulonephritis and membranoproliferative glomerulonephritis.

7.2.17 HIV/HBV Co-infection

HIV co-infection promotes an accelerated natural history of progression: Increased HBV replication and rates of HBV reactivation; increased rates of acute liver failure, chronicity of newly acquired HBV infections and occult HBV; accelerated progression to fibrosis and cirrhosis with HCC occurring at a younger age and an increased risk of ART hepatotoxicity [41–58].

7.2.18 Diagnosis of Acute and Chronic Hepatitis B

Hepatitis B surface antigen (HBsAg) is the key marker in the diagnosis of HBV infection. Careful interpretation of transaminases, HBV serological markers, HBV DNA levels and liver biopsy or non-invasive markers of fibrosis helps to distinguish between acute infection, resolution of acute infection, fulminant hepatitis, different phases of chronic infection and vaccination status.

Successful vaccination: Positive anti-HBs, protective titre >10 mIU/mL.

Previous exposure to HBV: Positive IgG anti-HBc +/− positive anti-HBs.

Acute Hepatitis B: HBsAg positive, IgM anti-HBc positive, elevated ALT.

Fulminant hepatitis: Maybe HBsAg negative, but IgM anti-HBc positive, HBV DNA detectable, elevated ALT with synthetic dysfunction (elevated ammonia and prolonged INR >1.5).

Chronic Hepatitis B: HBV serology, ALT and HBV DNA levels depend on phase of chronic infection:

- ***Immune tolerant***: HBsAg positive, HBeAg positive, anti-HBe negative, high HBV DNA levels (usually >200,000 IU/mL, typically >1 million IU/mL) and normal ALT
- ***Immune clearance (Chronic Hepatitis B eAg-positive hepatitis)***: HBsAg positive, HBeAg positive, anti-HBe negative, HBV DNA ≥20,000 IU/mL, elevated ALT
- ***Immune control***: HBsAg positive, HBeAg negative, anti-HBe positive, HBV DNA <2000 IU/mL, normal ALT
- ***Immune escape (Chronic Hepatitis B eAg-negative hepatitis)***: HBsAg positive, HBeAg negative, anti-HBe positive, HBV DNA ≥2000 IU/mL, fluctuating elevated ALT levels. Hepatitis B IgM core antibody maybe low positive with a flare
- ***Occult HBV infection***: HBsAg negative, anti-HBs negative, IgG anti-HBc positive, HBV DNA <200 IU/mL, normal ALT.

7.3 Management of Hepatitis B Infection

7.3.1 Acute Hepatitis B [28, 29, 59]

Treatment is largely supportive as more than 95% immunocompetent adolescents will spontaneously recover, clear HBV and seroconvert to anti-HBs. Interferon therapy is contraindicated as this exacerbates hepatic necro-inflammation and can precipitate acute liver failure, particularly in individuals with synthetic dysfunction. The use of nucleoside/tide analogues (lamivudine, tenofovir and entecavir) is not routinely advised.

Nucleoside/tide analogues (NUC) therapy is currently recommended in acute liver failure (jaundice, encephalopathy and INR > 1.5) as patients can stabilise and NUCs prevent reinfection of the liver graft. NUC therapy (lamivudine, tenofovir or entecavir) should be continued for at least 3 months after seroconversion to anti-HBs; 12 months after anti-HBe seroconversion without HBsAg loss and indefinitely, if the individual undergoes liver transplantation.

7.3.2 Chronic Hepatitis B

It is important to establish the phase of chronic hepatitis B and the need for therapy depending on disease activity, the presence of cirrhosis or the use of immunosuppressive therapy.

Assessment of liver disease and need for therapy:

- Establish phase of chronic infection
- Detailed clinical history and physical examination
- Assessment of the severity of the liver disease
  - Liver profile: total bilirubin, conjugated bilirubin, ALT, AST, ALP, gamma-glutamyltransferase (GGT)
  - Full blood count (FBC) including a differential count
  - Albumin and INR to assess synthetic function
- Look for other co-factors
  - Viral co-infection: HIV, HCV
  - Alcohol
  - Non-alcoholic fatty liver disease
  - Iron overload
  - Drug/toxin-induced liver injury
- Serological assessment
  - HBsAg, anti-HBs, HBeAg and anti-HBe ± IgM anti-HBc (low positive with a flare)
  - Hepatitis B IgG core antibody positive (if assessing for occult HBV or previous cleared infection)
  - Anti-HAV IgG to assess need for HAV vaccination
- Virological assessment
  - Serum HBV DNA quantification
  - HBV genotype is useful when deciding on potential efficacy of interferon therapy

  - Precore and basal core promoter mutations help predict risk of HCC
  - Previous exposure to Lamivudine and concerns regarding resistance: YMDD mutations can be measured
- Alpha-fetoprotein
- Ultrasound of the liver and dopplers
- Endoscopy to assess for varices in cirrhotic individuals
- Liver biopsy:
  - Determining the severity of liver disease (necro-inflammation and fibrosis)
  - Excluding other contributing factors to the development of acute or chronic liver disease
- Non-invasive markers of fibrosis
  - APRI Score = (AST/ULN) × 100)/platelet count (10^9/L)

An ***APRI Score > 2 identifies patients with cirrhosis (F4) and in need of antiviral therapy***

  - Fibroscan.

7.3.3 Goals of Therapy

1. ***Prevention of long-term complications of chronic hepatitis B:***
   - Cirrhosis
   - Liver failure
   - Hepatocellular carcinoma.
2. ***Prevention of reactivation in the setting of immunosuppression/biologicals/chemotherapy***
3. ***Ensure HBV viral suppression in acute liver failure***

A virological cure defined as viral eradication with elimination of cccDNA is not yet possible with the presently available treatment options. At present, the ideal endpoint of treatment is a functional immunological cure with sustained HBV DNA suppression and sustained HBsAg loss, with/without seroconversion to anti-HBs, as HBsAg is a surrogate marker for transcriptionally active cccDNA.

7.3.4 Indications for Treatment

1. **Patients who must be treated:**
   - Acute liver failure
   - Compensated or decompensated regardless of ALT levels, HBeAg status or HBV DNA levels
   - Patients receiving chemotherapy, rituximab or immunosuppressive therapy (all phases of chronic infection).
2. **Patients who should be considered for therapy and the appropriate therapy and timing of therapy discussed:**
   - Chronic HBeAg-positive hepatitis B (Immune clearance phase)
   - Chronic HBeAg-negative hepatitis B (Immune escape phase).

3. **Patients who do not require immediate therapy, but should be monitored:**
   - Patients in the immune tolerant phase
   - Patients in the immune control phase.

Chronic hepatitis B in children is typically benign, as children are usually in the immune tolerant phase. Liver biopsy is helpful in guiding the need for therapy in children with abnormal liver profiles. Treatment is recommended in HBeAg positive children with persistently elevated ALT (>30 IU/mL). As the HBV DNA is usually $>10^6$ IU/mL, there is no recommended HBV DNA threshold for treatment in children. If HBV DNA $<10^4$ IU/mL, defer therapy until other causes of liver disease, or spontaneous HBeAg seroconversion are excluded.

7.3.5 Treatment Options

- ***Lamivudine and Entecavir*** are approved for children ≥2 years of age, but long-term use of lamivudine is associated with the development of resistance (70% at 5 years)
- ***Lamivudine***: The recommended dosage for children is 3 mg/kg/day with a maximum dosage of 100 mg/day. A liquid formulation is available for children
- ***Tenofovir is*** approved for children ≥12 years of age
- ***Standard interferon alpha-2b*** is approved for children ≥1 year of age and the duration of treatment is 24 weeks. The recommended dosage for children is 6 MU/m^2 3 times a week with a maximum dosage of 10 MU 3 times a week
- ***Pegylated interferon-alpha-2a*** (180 μg/1.73 m^2 body surface area, maximum 180 μg weekly) is not approved for children with Hepatitis B, but has been approved for children ≥5 years of age with chronic hepatitis C.

7.3.5.1 Treatment Recommendations [60]

- Entecavir in children ≥2 years of age and weighing at least 10 kg. The oral solution should be given to children with a body weight up to 30 kg and is dosed according to body weight. Children who are treatment naïve with a body weight of ≥30 kg should receive 0.5 mg or 10 mL entecavir daily
- Tenofovir 300 mg daily in children ≥12 years of age and weighing at least 35 kg
- Treatment with NUCs is continued until HBeAg seroconversion followed by an additional 12 months of consolidation therapy [29]
- On stopping therapy, need to monitor every 3 months for at least 1 year for hepatitis B flares and clinical decompensation.

7.3.6 Prevention of Hepatitis B

The WHO recommended the incorporation of the HBV vaccine into the Expanded Program of Immunization (EPI) in 1991 as the most effective way to reduce the global burden of HBV. To date 194 countries worldwide and 45 in WHO Africa region have incorporated hepatitis B vaccination into the EPI.

A systemic review from 1990 to 2005 confirmed that HBV seroprevalence has decreased in many regions of the world as a result of universal HBV vaccination and it is estimated to have prevented more than 1.3 million deaths [61].

In 2009, WHO recommended a Hepatitis B birth dose (HepB-BD) vaccine for all countries, even those with a low HBV prevalence [62]. A monovalent HBV vaccine should be administered within 24 hours of delivery and preferably within 12 hours. However, in 2014, only 96 of 194 countries (49%) reported offering HepB-BD vaccine as part of their national immunization programs and <38% of babies born worldwide received HepB-BD within 24 hours after birth [63, 64].

7.3.6.1 The Efficacy of Universal HBV Vaccination

This has proved exemplary in Taiwan, where universal vaccination, introduced in 1984, together with a catch-up vaccination programme and improved maternal screening, resulted in a decrease in the prevalence of HBsAg positivity in children aged <15 years from 9.8% in 1984 to 0.3% in 2009 [65–67]. The infection rate (antiHBc seropositive rate) deceased from 38% in 1984 to 4.6% in 2009 [68]. Furthermore, the average annual incidence of HCC in children aged 6–14 years decreased from 0.7 per 10,000 children in 1981–1986 to 0.36 per 100,000 children in 1990–1994 [69, 70]. Incomplete vaccination has been shown to be an important risk predictor of HCC with a hazard ratio (HR) of 2.52 ($p = 0.0094$) [71].

A similar decline in HBsAg seroprevalence rate and in the incidence of HCC has been seen in other hepatitis B endemic countries that have implemented universal HBV vaccination [72].

7.3.6.2 Prevention of Mother to Child Transmission

It is essential that all pregnant women be screened for HBsAg. Neonates born to HBsAg positive mothers should receive 0.5 mL (200 IU) HBIG and HBV monovalent vaccine within the first 24 hours, but preferably within 12 hours of delivery at different injection sites (anterolateral thigh). Thereafter, the same immunization schedule is followed as for other infants. Combined immunoprophylaxis with HBIG and HepB-BD vaccine fails in 10–30% of infants born to mothers with HBV DNA levels >6$\log_{10}$ copies/mL [21, 73–78]. In addition, HBIG is expensive and is not easily accessible in many developing countries.

A number of studies have suggested that antiviral therapy with lamivudine or telbivudine or tenofovir during the third trimester of pregnancy could be clinically and cost effective in reducing the vertical transmission of hepatitis B infection when compared to no treatment or placebo.

AASLD recommends the initiation of tenofovir 300 mg daily at 28–32 weeks of pregnancy if HBV DNA >200,000 IU/mL to further reduce risk of perinatal transmission and EASL suggests antiviral therapy in third trimester if HBV DNA >10^{6-7} IU/mL [28, 29].

Infants born to HBsAg positive mothers should be offered post-vaccination testing for HBsAg and anti-HBs at 9–18 months of age. Children with anti-HBs ≥10 mIU/mL are protected and need no further management. Those who have

anti-HBs <10 mIU/mL should be given a second course of vaccination as they may be at risk of exposure in the household. Children who are HBsAg positive should be referred for clinical management.

7.3.6.3 Post-exposure Prophylaxis (PEP)

PEP is indicated following exposure to blood or body fluids of a known or potential HBsAg positive source if the exposed individual does not have protective anti-HBs ≥10 mIU/mL or if anti-HBs status is unknown and testing will delay administration of HBV vaccination or HBIG.

Exposures in which HBV post-exposure prophylaxis should be given include:

- Percutaneous (e.g. bite or needlestick) or mucosal exposure to blood or body fluids of a known or potential HBsAg positive source
- Neonates born to HBV infected women
- Sex or needle sharing contact of a HBsAg positive person or a person of unknown HBsAg status
- Victims of sexual assault/abuse by a perpetrator who is HBsAg positive or of unknown HBsAg status.

7.3.6.4 Effectiveness of PEP

- A combination of HBIG and active HBV vaccination is highly effective in preventing transmission after exposure to HBV
- HBIG provides passively acquired anti-HBs which is immediately protective and lasts for 3–6 months
- HBIG is approximately 75% effective in preventing clinical HBV infection if administered soon after HBV exposure
- PEP effectiveness decreases with increasing delay in administration following exposure and is unlikely to be effective >7 days after perinatal and needle stick exposures and >14 days after sexual exposure
- HBIG alone does not confer long-lasting protection against HBV
- HBIG is the primary means of protection of non-responders to vaccination.

7.4 Hepatitis C

Prior to the discovery of Hepatitis C (HCV) and the use of anti-HCV in the early 1990s as a marker of exposure to exclude infected blood and organ donors; most HCV infections were acquired through transfusions or inadequately sterilized needles or instruments. Children were frequently affected following repeated administration of blood and blood products for hemoglobinopathies, hemophilia or cancer therapy. Perinatal mother-to-child transmission accounts for 95% of all cases of hepatitis C in children born after 1990 in developed countries. Unfortunately in many regions of the world, post-transfusional hepatitis C remains a hazard as does unsafe injection practices.

7.4.1 Virus Structure

HCV is an enveloped, ribonucleic acid (RNA) virus that was identified and sequenced in 1989 [79]. It is classified as a separate genus (*Hepacivirus*) within the *Flaviviridae* family. Approximately 10^{12} viruses are produced daily and given the lack of an RNA proofreading polymerase, many mutations develop with the formation of so-called viral quasispecies in a single host [80].

There are six clinically relevant HCV genotypes and >80 subtypes. Genotype prevalence varies according to geographic region and route of acquisition [79].

7.4.2 Transmission of Hepatitis C

HCV remains viable on environmental surfaces at room temperature for at least 16 hours, but typically no longer than 4 days [81] and transmission occurs via parenteral and non-parenteral routes. The major route of HCV infection in the pediatric age group is vertical, with infection occurring in up to 5% of infants born to mothers positive for HCV-RNA.

7.4.2.1 Parenteral Transmission

HCV is most efficiently transmitted through parenteral inoculation. The predominant risk is in people who inject drugs (PWID) through the sharing of syringes and needles. The risk is as high as 90% after 5 years in PWID. Other parenteral transmission routes include tattooing, body piercing and needle-stick injuries.

7.4.2.2 Non-parenteral Transmission

This is less well defined and includes:

- **Mother-to-child transmission**: This only occurs in 1–5% of infants born to HCV infected women. Risk factors shown to increase the possibility of HCV vertical transmission include coinfections with human immunodeficiency virus (HIV), intravenous drug use and elevated maternal HCV viral load. Vertical transmission risk increases to ~20% in HIV/HCV coinfected mothers [82]
- **Sexual transmission** especially in the setting of high risk sexual practices and in men who have sex with men (MSM).

7.4.2.3 Household Transmission

- Percutaneous/mucosal exposure to blood, and sharing of contaminated personal items such as razors, toothbrushes and nail-grooming equipment is described, but is uncommon.

7.4.3 Clinical Presentations of Hepatitis C

Variation in disease progression is characteristic of HCV infection and contributing factors include environmental, host genetic and immunological factors.

Hepatitis C usually has an incubation period of 4–16 weeks and most individuals who develop acute hepatitis C are completely asymptomatic. Jaundice is uncommon and fulminant liver failure complicating acute HCV infection is rare. Anti-HCV antibodies can take 12–16 weeks, from the time of first infection to develop. However, HCV RNA is detectable in serum as early as 1–3 weeks after exposure. The persistence of HCV RNA beyond 24 weeks after acute infection marks the onset of chronic infection [83].

The natural course of HCV infection in children is characterized by a high rate of spontaneous clearance, an asymptomatic clinical course, and normal or mild histologic changes. Cirrhosis is reported in 1–2% of children, and progression to severe chronic liver disease and HCC occurs 20–30 years after infection. Only a few cases of HCC have been reported in adolescents.

Approximately 25–40% children with vertically acquired HCV, will undergo ALT normalization and loss of HCV-RNA by the age of 2–3 years [84–86]. Spontaneous resolution can be achieved in up to 6–12% of infected children, as late as 7 years of age [84–87].

High ALT levels are associated with increased chance of biochemical remission and viral clearance [85, 88]. HCV clearance is also significantly higher in infants infected with HCV genotype 3 [89].

In children infected via the parenteral route, HCV-RNA clearance is highly variable. In long-term follow-up studies of 25–30 years, clearance ranged from 11% in a cohort of infants infected by an HCV-RNA-positive blood donor [90] to 30–45% in cohorts similarly infected in early infancy via contaminated blood products during surgery [91, 92]. Eighty percent children who do not clear HCV spontaneously will be asymptomatic with normal or mildly elevated transaminases. Ten to twenty percent of HCV-infected children will have persistent elevation of transaminases and may manifest clinical signs of liver disease.

Histology reveals that most children have no or only mild fibrosis, but there is evidence of insidious progression of liver disease on follow-up liver biopsies.

Risk factors for more severe disease include obesity, alcohol consumption and intravenous drug use, childhood cancer, immunosuppression and liver transplantation, congenital anemia requiring chronic transfusions, and co-infection with HIV/hepatitis B virus [93–97].

7.4.4 Extrahepatic Manifestations of Hepatitis C

Hepatitis C has been associated with several extra-hepatic manifestations:

- Autoimmune (e.g. Sjögren's syndrome, cryoglobulinemia, polyarteritis nodosa)
- Porphyria cutanea tarda
- Lymphoproliferative diseases (e.g. B-cell non-Hodgkin's lymphoma)

- Insulin resistance: Progressive insulin resistance, impaired fasting glucose (IFG) and/or type 2 diabetes mellitus (DM) is higher in chronic HCV patients (50%) than in the general population (14.5%) [98].

7.4.5 HIV/HCV Co-infection

HIV coinfection significantly alters the natural history of hepatitis C and is regarded as a priority for HCV treatment given that there is:

- Accelerated fibrosis and progression to cirrhosis
- Increased HCC risk
- Increased HCV infectivity risk, especially MTCT of HCV
- Increased risk of ART and TB drug induced liver injuries
- Reduced response to interferon-based therapy.

7.4.6 Diagnosis of Hepatitis C

- ***Anti-HCV***: Detects anti-HCV in 80% infected individuals within 6 weeks of primary infection and has >95% sensitivity
- ***Quantitative HCV PCR (Viral load quantification)***: Confirms active viraemia
- ***Genotype testing***: This is required to choose correct treatment.

7.4.7 Pretreatment Clinical Evaluation

Medical evaluation includes:

- Clinical history and physical examination
- Assessment of the liver disease
  - Liver profile: Total bilirubin, conjugated bilirubin, albumin, ALT, AST, ALP, GGT
  - FBC and differential count
  - INR to assess synthetic function
  - Fibrosis assessment: Liver histology or non-invasive methods
- HBV and HAV serology to assess need for vaccination
  - Anti-HAV IgG negative: Needs HAV vaccination - HBsAg and anti-HBs negative - vaccinate against HBV
- HCC screening: Alpha-fetoprotein and ultrasound of the liver (6–12 monthly).

7.4.8 Prevention

There is no immunoglobulin and no vaccine available.

7.4.9 Treatment of Hepatitis C

As there is a high spontaneous clearance rate in infancy and early childhood and most children have no or only mild fibrosis, it is recommended that children not be treated before the age of 5–6 years [99].

The aim of treatment is to achieve a sustained virological response (SVR) that results in:

- Reduced necro-inflammation and progression to fibrosis, cirrhosis and end stage liver disease
- Reduction in risk of HCC
- Improved liver-related morbidity and mortality
- Improved all-cause mortality.

Treatment prioritization i.e. patients who need to be treated first:

- Significant fibrosis (F3) or F4/cirrhosis (including compensated cirrhosis)
- HIV or HBV coinfection
- Liver transplant
- Extra-hepatic manifestations.

Treatment with pegylated interferon (Peg-IFN) and ribavirin for 24 weeks results in 90–100% SVR12 in children with HCV genotypes 2 or 3, but only 45–55% SVR12 in those infected with genotypes 1 or 4 treated for 48 weeks [100–102]. Treatment is associated with adverse effects ranging from flu-like symptoms, myalgia, anemia and thrombocytopenia, to less commonly observed thyroid-related symptoms, alopecia, neuropsychiatric manifestations and possible long-term effects on growth.

No all-oral, direct-acting antiviral regimens have been approved as yet for children with chronic hepatitis C. A phase 2, multi-centre, open-label study evaluating the efficacy and safety of ledipasvir-sofosbuvir in adolescents with chronic HCV genotype 1 infection has been performed. One hundred adolescents aged 12–17 years (median age 15 years) received a combination tablet of 90 mg ledipasvir and 400 mg sofosbuvir once daily for 12 weeks. Eighty percent were HCV treatment naïve, and 84% were infected through perinatal transmission. One patient had cirrhosis and 42 did not; in 57 patients the degree of fibrosis was unknown. Overall, 98% (98/100; 95% CI, 93–100%) of patients reached SVR12. No patient had virological failure. The two patients who did not achieve SVR12 were lost to follow-up either during or after treatment. The three most commonly reported adverse events were headache (27% of patients), diarrhea (14%), and fatigue (13%) [103].

As the natural history of Hepatitis C is mild and the side-effects of pegylated interferon and ribavirin are significant, the decision to treat should be based on evidence of active disease progression. Most children with chronic hepatitis C will be able to wait for the availability of all-oral, direct-acting antiviral regimens and preferably a pangenotypic regimen. Such new therapies are under investigation and new agents are being registered and used in some countries.

7.5 Hepatitis D

HDV is a unique RNA virus that is dependent on hepatitis B for survival. HDV does not encode its own replicase and is dependent on HBV providing HBsAg to coat its virion in order to replicate. Thus, there are no viral replicative enzymes for drugs to target.

7.5.1 Epidemiology and Transmission

HDV is found worldwide, but the prevalence varies in different geographical areas. It is commonly encountered in the Mediterranean basin, the Far East, certain regions in South America and in Africa [104]. Eight HDV genotypes have been identified and are associated with variable clinical courses: Genotype 1 is found worldwide (range of liver disease severity); Genotype 2 occurs in Japan, Taiwan, Russia (milder disease); Genotype 3 occurs in the northern countries of South America (more severe disease including fulminant presentations) and Genotype 4 occurs in Japan and Taiwan (milder disease). Genotypes 5–8 have been identified in African patients and are associated with HBV genotypes A–E, but little is known about the clinical course of the liver disease. In Africa, where HBV is endemic, documented HDV seroprevalence rates vary geographically from low rates in countries south of the Equator (0–0.6%) to high rates north of the Equator (3–67%). Transmission is parenteral, but risk of perinatal transmission is low [104].

7.5.2 Clinical Presentations [105]

- ***Acute HBV/HDV coinfection*** (including fulminant hepatitis)
- ***Acute HDV super-infection of an individual with chronic HBV infection***: This can present as an acute hepatitis in a previously asymptomatic HBsAg carrier or result in further clinical deterioration in individuals with established HBV disease
- ***Chronic HDV infection***: HBV replication is usually suppressed (low or undetectable HBV DNA) and HBeAg is negative. Hepatitis D becomes chronic in 70–90% individuals with superinfection and there is more rapid progression to cirrhosis and decompensation, especially in injecting drug users where end-stage liver disease can occur in <2 years. There is also an increased risk of HCC.

7.5.3 Diagnosis

- ***Acute HBV/HDV co-infection***: Positive anti-HDV IgM and HDV RNA; HBsAg positive and Hepatitis B IgM core antibody positive
- ***Acute HDV super-infection of patient with chronic HBV infection***: Positive anti-HDV IgM and HDV RNA; HBsAg positive
- ***Chronic HDV infection***: Positive anti-HDV IgG and HDV RNA; HBsAg positive.

7.5.4 Prevention and Treatment

There is no immunoglobulin available and no specific HDV vaccine. HBV vaccination is effective prophylaxis against HDV. The currently recommended treatment is Peginterferon alfa given weekly for 48 weeks, leading to HDV RNA clearance in 17–47% of infected individuals [106].

7.6 Hepatitis E

Hepatitis E virus (HEV) is a major etiologic agent of enterically transmitted non-A, non-B, non-C hepatitis worldwide [107–111].

7.6.1 Virus Structure

HEV is a spherical, non-enveloped, small single stranded, positive-sense RNA virus that measures approximately 27–34 nm. HEV is classified as the sole member of the genus *Hepevirus* under the family *Hepeviridae*. Four genotypes (1–4), but only one serotype have been identified [112, 113] and there are clear differences in the epidemic potential of the various genotypes [110].

7.6.2 Epidemiology and Transmission

Hepatitis E is a food-borne and water-borne disease. Compared to hepatitis A, HEV is less resistant to environmental conditions such as temperature; and prolonged excretion of HEV in stool following symptomatic/asymptomatic infections is rare.

The modes of transmission vary dependent on the HEV genotype. Genotypes 1 and 2 have fecal-oral and waterborne transmission and are associated with epidemics. Epidemics of hepatitis E have been reported in Central and South-East Asia; North, West and Central Africa; Mexico and in sub-Saharan Africa. Genotypes 3 and 4 have food-borne transmission. Parenteral transmission has also been described via blood transfusions and perinatal transmission.

7.6.3 Clinical Presentations

The incubation period following exposure to HEV ranges from 15 to 60 days, with a mean of 40 days. The period of infectivity following acute infection has not been determined. HEV-RNA can be detected in stool from 1 week prior to the onset of symptoms and virus excretion in stools has been demonstrated up to 14 days after onset of illness [114]. The clinical presentation is modulated by the underlying epidemiological pattern of a particular region, by genotype; and the immune status and age of the individual. Symptoms tend to increase with age. The overall mortality is

0.5–4% with increased mortality in certain groups: 5–8% in children <3 years [115, 116], 25% in pregnant women in the third trimester [117, 118] and 75% in individuals with chronic liver disease [119].

The different clinical presentations include:

1. ***Mild subclinical illness***: Asymptomatic infections tend to be more common in children and the symptomatic to asymptomatic ratio for children is 1:12 compared with 1:3 for adults [120].
2. ***Self-limiting acute hepatitis resembling hepatitis A***: Attack rate is highest in men aged 15–40 years (10–30%). Symptomatic acute hepatitis occurs in up to 15% during an outbreak.
3. ***Severe disease*** occurs in pregnant women in the third trimester and individuals with chronic liver disease.

Chronic hepatitis defined as HEV RNA positivity in stool or serum persisting for >6 months. This occurs in solid organ transplant recipients, HIV patients and haematological malignancies and has only been documented with Genotype 3 infections [121–125]. The transaminitis is usually mild in the range of 100–300 U/L, and patients are usually not jaundiced. Progression to chronicity occurs in approximately 60% immunosuppressed solid organ transplant recipients as a result of impaired specific T-cell responses. Rapid progression to cirrhosis can occur. Tacrolimus therapy is the main predictive factor for the development of chronic hepatitis.

7.6.4 Diagnosis

Acute Hepatitis E: Positive anti-HEV IgM (Wantai ELISA).
Previous exposure to hepatitis E: Positive anti-HEV IgG (Wantai ELISA).
Chronic Hepatitis E: Positive anti-HEV IgG and a positive HEV PCR for >6 months.

7.6.5 Prevention and Treatment

Hepatitis E prevention and control strategies are generally as for hepatitis A, but also need to consider zoonotic transmission. In endemic areas, improving sanitation, ensuring safe water supplies and maintaining good hygienic practices e.g. washing hands with soap can prevent spread. In non-endemic areas, avoid intake of raw uncooked meat to prevent zoonotic transmission. An effective vaccine is available, but this has not been tested in children or pregnant women. There is no protective immunoglobulin currently available.

Clinical management of hepatitis E is supportive. Ribavirin therapy for 3 months can be considered in children presenting with acute hepatitis and impaired synthetic function; and in immune-compromised children with chronic hepatitis.

7.7 Herpes Viruses

The herpesvirus family contains five important human pathogens: herpes simplex virus types 1, 2 and varicella-zoster virus, cytomegalovirus, and Epstein–Barr virus.

Herpesviruses are noted for their ability to cause latent infections where the acute infection is followed by an asymptomatic period during which the virus remains in a quiescent or latent state. On exposure to a trigger event such as immunosuppression, reactivation occurs and clinical symptoms may be similar to the initial infective episode or different as in varicella-zoster infections.

7.7.1 Herpes Virus Structure

All herpesviruses are structurally similar with an icosahedral core surrounded by a lipoprotein envelope. They are large, linear double-stranded DNA viruses ranging from 120 to 200 nm in diameter. The virion does not contain a polymerase and replication occurs in the nucleus. They are the only viruses that obtain their envelopes by budding from the nuclear membrane.

7.8 Herpes Simplex Viruses (HSV) 1 and 2

Herpes simplex viruses (HSV-1 and HSV-2) are endemic worldwide, can cause disease at any age and result in lifelong infection. HSV-1 and HSV-2 are structurally and morphologically indistinguishable, but can be differentiated by the restriction endonuclease patterns of their genome DNA and by type-specific monoclonal antisera. Humans are the natural hosts of both HSV-1 and HSV-2.

After entry into the cell, the virion is uncoated and the genome DNA enters the nucleus. Early virus messenger RNA is transcribed by host cell RNA polymerase and then translated into early, non-structural proteins in the cytoplasm. Two of these early proteins, thymidine kinase and DNA polymerase, are important because they are targets for antiviral drugs e.g. acyclovir. As the initial containment of HSV infection requires intact cellular immunity, immunocompromised patients are at risk for more frequent and severe/disseminated HSV infections.

7.8.1 Epidemiology and Transmission

HSV-1 is transmitted primarily by saliva, whereas HSV-2 is transmitted by sexual contact. Most primary HSV-1 infections are asymptomatic. Only 20–25% patients with HSV-1 antibodies and 10–20% of those with HSV-2 antibodies have a history of oral-labial or genital infections. Viral shedding can lead to unsuspected transmission to others via contact with secretions or mucous membranes.

7.8.2 Clinical Presentations

HSV-1 typically causes acute gingivostomatitis, herpes labialis, keratoconjunctivitis, and encephalitis, whereas HSV-2 causes genital herpes, neonatal herpes and aseptic meningitis. Both HSV-1 and HSV-2 can cause hepatitis [126].

7.8.2.1 Hepatitis

Herpes simples virus (HSV) hepatitis is a rare complication of both HSV-1 and HSV-2 infection and usually occurs in immunocompromised patients. Those at risk include neonates, patients taking steroids, HIV-infected patients, liver transplant recipients and oncology patients, but HSV-related hepatitis can also occur in immunocompetent young individuals. HSV hepatitis frequently presents as a fulminant disease with a high mortality (>80%), if left untreated. HSV accounts for 0.8% of acute liver failure and 2–4% of acute viral hepatitis cases. Mucocutaneous lesions occur in less than 40% of patients and clinical symptoms are often non-specific and include fever (82%), headache (80%), anorexia with nausea and/or vomiting (18%), abdominal pain (33%), leukopenia (43%), and coagulopathy (20%). Jaundice is frequently absent. Patients with HSV hepatitis are moderately ill for 3–10 days, and then deteriorate rapidly with hepatic necrosis resulting death within 1 week. HSV hepatitis is a difficult diagnosis to establish. It should be considered in the differential diagnosis of any case of severe hepatitis with or without jaundice. It is important to recognize the entity and start specific treatment early in the course of the illness.

7.8.3 HSV Diagnosis

Early diagnosis may be difficult as the characteristic vesicular rash is absent in up to 40% of the neonates who acquire the infection. Early symptoms are often non-specific and the majority of their mothers lack a history of genital herpes infection.

The diagnosis of HSV infection can be made by a variety of techniques including liver biopsy, PCR assays or serology.

Liver biopsy: This was historically the "gold standard" investigation for HSV hepatitis. Histology may reveal HSV-type intranuclear inclusions and immunostaining for HSV can be performed.

Serology: Serological testing for HSV-1 and 2 (IgG and IgM) is limited by a high rate of false-positive and false-negative tests. IgM antibodies may be useful in diagnosing neonatal infections, which appear during the first 4 weeks of infection and persist for months. In immunocompromised children, there is often a delay in the development of IgM antibodies leading to a delay in diagnosis and treatment of acute HSV hepatitis.

Polymerase chain reaction: HSV serum PCR is both a highly sensitive and specific test, can be quantitative and allows for a rapid diagnosis and earlier initiation of therapy.

7.8.4 Treatment and Prevention

The high mortality (80%) of untreated HSV hepatitis is greatly reduced to 33% with early treatment with intravenous acyclovir (10 mg/kg 8 hourly for 14–21 days) which inhibits viral replication. Immunocompromised patients may have a more severe and protracted course and may require longer therapy [127]. If the diagnosis is suspected, treatment with intravenous acyclovir should be started immediately, whilst awaiting confirmation of the diagnosis with HSV PCR.

Liver transplantation has been carried out successfully in a few reported neonates with fulminant hepatic failure associated with disseminated neonatal HSV disease [128, 129].

There is no currently licensed, effective vaccine or immunoglobulin against HSV-1 or HSV-2 infection.

7.9 Cytomegalovirus (CMV)

CMV is a ubiquitous human herpes virus that causes a lifelong persistent infection. CMV is a well-recognized cause of hepatitis. It occurs more commonly in immunocompromised children, particularly in organ transplant recipients and HIV-infected children. CMV hepatitis can occur during a primary infection or following reactivation of latent CMV infection especially in the setting of immunosuppression. Symptomatic CMV infection in immunocompetent children typically has a benign, self-limited course, but there are numerous reports of severe clinical CMV disease in immunocompetent patients.

7.9.1 Virus Structure

CMV is an icosahedral shaped, encapsulated, double-stranded DNA β-herpes virus about 200 nm in diameter. The complete virion consists of an inner core of DNA genome, surrounded by capsid, which in turn is surrounded by a proteinaceous tegument and an outer lipid envelope. During infection, the virus replicates in hepatocytes and cholangiocytes. It is uncertain whether the pathogenesis of hepatic disease is related to the direct cytopathic effect of the virus or to the immune response of the host.

7.9.2 Epidemiology and Transmission

Social and environmental factors are determinants in the age of acquiring CMV infection. Most children in resource-poor settings are infected with CMV during infancy and early childhood and that is in contrast to resource-rich countries where the primary CMV infection occurs later at an older age. Transmission can occur

perinatally or with close contact of infected blood and tissues or sexually. The incubation period is 4–6 weeks. The natural immune response of the host to primary CMV infection does not clear the virus completely and it persists in a latent or non-lytic state.

7.9.3 Clinical Presentation [130]

The clinical presentation of acute CMV hepatitis usually includes jaundice and vague abdominal pain, but may be non-specific and present with vomiting and prolonged unexplained fever and headaches. Liver function test abnormalities are characterized by a transaminitis and an elevated lactate dehydrogenase. The bilirubin is often only mild-to-moderately elevated, but can be entirely normal. Portal vein thrombosis has also been described as a rare complication of acute CMV-associated hepatitis.

7.9.4 CMV Diagnosis

There are several diagnostic investigations to determine CMV infection.

Viral Culture: CMV can be cultured in secretions (saliva, urine, breast milk) and blood. This is a direct culture system with human fetal lung fibroblasts used to prove CMV infection by visualizing typical cytopathic effects of the virus. It can take up to 21 days to visualize these changes. This technique lacks sensitivity and is rarely used.

Histopathological diagnosis of CMV: The gold standard of diagnosing CMV disease is to detect cytomegalic cells on histology. Typical CMV-infected cells increase in size and contain cytomegalic inclusion bodies with a halo, which gives the cell an owl's eye appearance. The sensitivity of CMV detection in tissue specimens has been improved with immunoperoxidase or immunofluorescence staining for CMV antigens using monoclonal antibodies and/or in situ DNA hybridization.

Serology: CMV infection is diagnosed by comparing the IgG antibody titre at the acute stage with the titre of the recovery stage. Paired serum samples obtained at least 2–4 weeks apart are necessary. It is not sensitive and CMV-specific IgG does not distinguish CMV reactivation from CMV carriers so is not useful in the diagnosis of CMV hepatitis. CMC IgM antibodies can also be measured, but there can be a delay in detection in immunocompromisd individuals.

CMV antigenemia: The CMV antigenemia method has a sensitivity of 60–100% and a specificity of 83–100%. The detection of antigen (pp65)-positive cells in peripheral blood cells reflects reactivation of CMV; however, the positive finding of CMV antigenemia does not necessarily reflect CMV disease and is not useful in the diagnosis of CMV hepatitis.

CMV polymerase chain reaction (PCR) analysis: Standardized commercial qualitative and quantitative PCR assays are available to detect CMV-DNA in the urine, stool, blood, and tissues. The PCR analysis is sensitive for diagnosing CMV

infection and monitoring the viral load. However, the high sensitivity of the PCR assay may result in low specificity for diagnosing active CMV infection because very few copies of CMV-DNA can be detected, which may have no clinical significance but only point towards a local low level reactivation.

Quantitative CMV PCR is useful in monitoring the response to therapy.

7.9.5 Treatment and Prevention

Antiviral treatment is indicated in CMV hepatitis in all immunocompromised patients, but in an immunocompetent patient, treatment will depend on the clinical course and the viral load level. Treatment is with either intravenous ganciclovir (5 mg/kg 12 hourly) or oral valganciclovir for a minimum of 3 weeks.

There is as yet no effective vaccine against CMV.

7.10 Epstein–Barr Virus (EBV)

EBV or human herpesvirus 4 is a gamma herpesvirus that infects more than 95% of the general population by the age of 20 years [131]. EBV is structurally and morphologically identical to other herpesviruses, but is antigenically different. There are two strains of EBV (EBV-1 and EBV-2) and they can simultaneously infect individuals causing identical acute illnesses. Human are the natural hosts and EBV infects mainly lymphoid cells, primarily the B lymphocytes. EBV infection is associated with the development of B-cell lymphomas, T-cell lymphomas, Hodgkins lymphoma and nasopharyngeal carcinoma in certain individuals [132].

7.10.1 Epidemiology and Transmission

Epstein–Barr virus is present in oropharyngeal secretions and is most commonly transmitted through saliva. Early asymptomatic infection tends to occur in children in lower socio-economic groups. Clinically apparent infectious mononucleosis, however, is more common in individuals who are exposed to the virus later in life.

After initial inoculation, the virus replicates in nasopharyngeal epithelial cells. Cell lysis is associated with a release of virions, with viral spread to adjacent structures, including salivary glands and oropharyngeal lymphoid tissues. EBV viremia leads to infection of the lymphoreticular system, including the liver, spleen, and peripheral B lymphocytes. The host immune response to the viral infection includes CD8+ T lymphocytes with suppressor and cytotoxic functions, the characteristic atypical lymphocytes found in the peripheral blood. The T lymphocytes are cytotoxic to the Epstein–Barr virus-infected B cells and eventually reduce the number of Epstein–Barr virus-infected B lymphocytes to less than 1 per 10^6 circulating B cells.

The humoral immune response involves the development of IgM antibody to the viral capsid antigen (VCA), followed by the IgG antibody to VCA and this persists for life. In addition to the EBV-specific antibodies, nonspecific heterophile antibodies that are directed against cell membrane constituents also occur. These heterophile antibodies are not specific for the EBV infection and usually disappear after 6 weeks. After acute EBV infection, latently infected B lymphocytes and epithelial cells persist and are immortalized as EBV DNA is integrated into the cell genome.

7.10.2 Clinical Presentations

The incubation period in adolescents is 30–50 days, but tends to be shorter in young children. EBV infection is usually subclinical during early childhood. Symptomatic acute infectious mononucleosis is more common in adolescents and is characterized primarily by fever, sore throat, lymphadenopathy, and splenomegaly. Anorexia and lethargy are prominent. Hepatitis is frequent with 80–90% patients demonstrating a moderate, but transitory elevation of liver enzymes [132]. Encephalitis occurs in some patients. Spontaneous recovery usually occurs within 2–3 weeks in immunocompetant individuals. Splenic rupture is a rare complication. In the setting of immunosuppression, chronic EBV infection or a severe, often fatal EBV infection may occur.

EBV Hepatitis: A mild, self-limiting cholestatic hepatitis is seen in immunocompetant children with liver involvement during acute EBV infections. A severe hepatitis is uncommon in immunocompetant individuals [133]. ALP, AST, and bilirubin levels peak 5–14 days after onset, and GGT levels peak at 1–3 weeks after onset.

Occasionally, GGT levels remain mildly elevated for as long as 12 months, but most liver enzymes are normal within 3 months. Lactic acid dehydrogenase (LDH) levels are increased in approximately 95% patients. Serum ferritin can also be increased.

The cholestasis may be functional due to impaired activity of sinusoidal and canalicular transporting systems associated with the production of systemic and intrahepatic pro-inflammatory cytokines or due to direct infection of biliary epithelial cells. Chronic hepatitis is rare [134]. Fifty percent of fatal infectious mononucleosis cases are due to liver failure [135].

7.10.3 Diagnosis

The diagnosis of infectious mononucleosis is based on three criteria: Lymphocytosis, ≥10% atypical lymphocytes and positive EBV serology.

Full blood count and differential: An absolute lymphocytosis occurs and usually 20–40% of the lymphocytes are atypical. These “atypical lymphs” are larger with a lobulated less dense nucleus, a lower nuclear-to-cytoplasmic ratio and a

vacuolated, basophilic cytoplasm. Most of these atypical lymphocytes are polyclonal-activated CD8 cytotoxic-suppressor T lymphocytes, although CD4 helper T cells and CD11 natural killer cells are also present.

Serology: The heterophile antibody test is useful for the early diagnosis of infectious mononucleosis as it is usually positive by week 2 of the illness. The heterophile antibody tests are recommended as screening tests in adolescents and adults, but not in children. The antibody titre declines after recovery and so is not useful for detection of prior infection. These heterophile antibodies agglutinate cells from other species and are not directed against Epstein–Barr virus. These antibodies are the basis of the Paul-Bunnell and the Monospot test. The Monospot test is more sensitive, more specific, and cheaper than the tube agglutination test.

The EBV-specific antibody test is used primarily in diagnostically difficult cases, atypical presentations or the immunocompromised. Early antigen (EA) are expressed early in the lytic cycle, whereas VCA and membrane antigens are structural viral proteins expressed late in the lytic cycle. Ebstein–Barr virus nuclear antigen (EBNA) is expressed in latently infected cells.

The IgM VCA antibody response can be used to detect early illness and the IgG VCA antibody response detects prior infection. Antibodies to EA and EBNA can be useful diagnostically. Antibody to EBNA appears 3–4 weeks after infection and persists for life.

Primary acute Epstein–Barr virus infection is associated with positive VCA-IgM, and VCA-IgG antibodies; and absent EBNA antibodies.

Recent EBV infection (3–12 months): positive VCA-IgG and EBNA antibodies, negative VCA-IgM antibodies, and, usually, positive EA antibodies. After 12 months EA antibodies are negative.

EBV polymerase chain reaction (PCR) analysis: Quantitative PCR is useful in investigating EBV-associated disease in the context of immunosuppressed or immunodeficient patients where acute serology is often negative. Quantitative PCR can be used to measure EBV DNA in plasma during acute infectious mononucleosis. Levels decline during convalescence and are rarely measurable in latently infected individuals. EBV DNA in serum is detectable with PCR during EBV reactivation.

Histology: Viral inclusions may be detectable. Certain EBV-associated tumors have characteristic histology (eg, Reed Sternberg Cells). In situ testing with DNA probes or immunohistochemistry for viral proteins can be done to further demonstrate infection.

7.10.4 Treatment

The mainstay of treatment for individuals with infectious mononucleosis and other manifestations of primary EBV disease is supportive care. Acetaminophen or non-steroidal anti-inflammatory drugs are recommended for the treatment of fever, throat discomfort, and malaise. Provision of adequate fluids and nutrition is also recommended.

Antiviral therapy including acyclovir, gangciclovir and foscarnet, have not been shown to be of proven efficacy for treatment of EBV infections, but are frequently used in imunocompromised patients and in the setting of severe disease in immunocompetant individuals [136, 137]. Foscarnet, a pyrophosphate analog, has been reported to be active against acyclovir- or ganciclovir-resistant herpes family viruses including EBV. Corticosteroids are not recommended for uncomplicated cases. Corticosteroids are reserved for severe complications of mononucleosis such as impending airway obstruction, acute hemolytic anaemia, severe thrombocytopenia, and severe clinical disease. Intravenous immunoglobulin is used to modulate immune function in the presence of autoantibodies and has been used successfully in the treatment of immune thrombocytopenia associated with infectious mononucleosis [138]. Avoidance of contact sports for at least 1 month is recommended in individuals with enlarged spleens to decrease the risk of splenic rupture.

7.10.5 Prevention

Currently, there is no commercially available vaccine for EBV-related disease and no immunoglobulin directed against EBV.

7.11 Coxsackie Virus

Coxsackie viruses belong to the family *Picornaviridae* and the genus Enterovirus. Coxsackie virus infections occur throughout the world [139].

7.11.1 Virus Structure

Coxsackie viruses are nonenveloped viruses with linear single-stranded RNA. Coxsackie viruses are divided into two groups: group A and group B viruses. At least 23 serotypes (1–22, 24) of group A and 6 serotypes (1–6) of group B are recognised.

In general, group A coxsackie viruses tend to infect the skin and mucous membranes and group B coxsackie viruses tend to infect the heart, pleura, pancreas, and liver, causing pleurodynia, myocarditis, pericarditis, and hepatitis.

7.11.2 Epidemiology and Transmission

Coxsackie virus infections occur in all age groups, but are more common in young children and infants. Children are at higher risk of infection during the first year of life. The rate of illness decreases greatly following the first decade of life.

Coxsackie viruses are transmitted primarily via the fecal-oral route, respiratory droplets and less commonly via fomites. The viruses replicate in the upper respiratory tract and in the distal small bowel. They have been found to persist in the respiratory tract for up to 3 weeks after initial infection and in feces up to 8 weeks after initial infection. Spread to target organs occurs following a secondary viremia. Immunity is thought to be predominantly humoral.

7.11.3 Clinical Presentation

In general, group A coxsackie viruses tend to infect the skin and mucous membranes and group B coxsackie viruses tend to infect the heart, pleura, pancreas, and liver, causing pleurodynia, myocarditis, pericarditis, and hepatitis. Coxsackie B is a rare cause of isolated hepatitis in an immunocompetent person. The hepatitis is clinically indistinguishable from other causes of viral hepatitis.

7.11.4 Laboratory Diagnosis

Serology: Antibody testing is available for coxsackie virus group B. A fourfold increase in the IgG titre in acute and convalescent serum or a single titre greater than 1:320 is diagnostic of a recent infection.

7.11.5 Prevention and Treatment

There is no specific treatment for coxsackie virus group B hepatitis and no immunoglobulin or vaccine available against coxsackie infections.

7.12 Conclusions

Viral hepatitis remains a global health problem with significant associated morbidity and mortality. It is not possible to distinguish biochemically between the different forms of viral hepatitis and diagnosis is dependent on appropriate serological and virological testing in order to implement therapeutic and preventative measures.

Development and implementation of National Guidelines for the Prevention and Treatment of Viral Hepatitis will be important to combat this increasing global health problem. It is essential to ensure access to affordable diagnostics, preventative vaccines and therapeutics. This will enable early identification and linkage to appropriate care.

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