Chronic Viral Hepatitis

9

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Key Points

HBV

- HBV infection acquired in childhood is often a chronic infection.
- Regular monitoring of liver function tests, serological tests and HBV deoxyribonucleic acid level is mandatory to evaluate the possible evolution of the infection.
- The therapies currently available for treatment of chronic HBV infection in children can obtain effective long-term suppression of viral replication but are largely ineffective towards obtaining virological cure and elimination of the infection.

HCV

- Direct-acting antivirals active against HCV can efficiently cure the infection after a short course of treatment (8–12 weeks).
- The fixed-dose combination of ledipasvir/sofosbuvir has been approved by the Food and Drug Administration and the European Medicines Agency for treatment of children older than 12 years of age and infected by HCV genotype 1, 4 and 5.
- The combination of sofosbuvir and ribavirin has been approved by the Food and Drug Administration and the European Medicines Agency for treatment of children older than 12 years of age and infected by HCV genotype 2 and 3.
- Interferon-based treatments are no longer recommended for treatment of children with chronic HCV infection.

Research Needed in the Field

- Up-to-date prevalence of HBsAg and HCV antibodies in children according to different age cohorts and world regions
- Establish a consensus on when to start treatment in HBV-infected children
- Development of new HBV curative treatment strategies to eliminate all replicative forms, including covalently closed circular DNA form in the nucleus
- Evaluation of effectiveness and safety of long-term use of nucleos(t)ide analogues regimens in different paediatric populations
- Development of direct-acting antivirals in children across all paediatric ages

9.1 Hepatitis B Virus

9.1.1 Epidemiology

9.1.1.1 Burden of Hepatitis B Virus Infection

According to the World Health Organization (WHO), globally, in 2015, 257 million people were living with chronic hepatitis B virus (HBV) infection [1, 2]. Prevalence of HBV infection (as measured by HBsAg positivity) in the general population varies by geographical region being highest (>6%) in the WHO Western Pacific and African regions, followed by intermediate prevalence (2–3.5%) in Southeast Asia and East Mediterranean regions and by lower prevalence in Europe and the Americas [2]. Chronic HBV infection (CHB) is associated with significant morbidity and mortality. Around 20–30% of the people with CHB will develop complications such as cirrhosis and hepatocellular carcinoma (HCC). More than half of all liver cancers are the consequence of HBV infection. Worldwide, it is estimated that around 890,000 people die each year from the complications of CHB [2].

To my Family

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L. D'Antiga (ed.), *Pediatric Hepatology and Liver Transplantation*, https://doi.org/10.1007/978-3-319-96400-3_9

The only paediatric estimation of the prevalence of HBV infection is available for children under 5 years of age, and it was about 1.3% in 2015 [2]. Data for older paediatric age cohorts are missing. Geographical distribution for children is similar to adults with the highest prevalence in the African region. In high-income countries where adult seroprevalence is below 2%, HBsAg positivity in patients under 18 years of age is rare [1, 2] due to the widespread use of infant vaccination [2] although in these settings there is experience of an increasing number of infected children migrating from countries with high prevalence of the infection [3, 4].

9.1.1.2 Routes of Transmission

Routes of transmission of HBV infection are summarized in Table 9.1. Worldwide and especially in high prevalence regions, mother-to-child transmission (MTCT) and horizontal transmission during early childhood are the main mechanisms by which HBV is transmitted [1, 5–7]. In countries where prevention of MTCT through infant vaccination has been implemented, the infection is acquired mainly in adulthood. Adults at high risk of acquiring the infection are unvaccinated persons injecting drug use, men who have sex with men, sex workers and unvaccinated persons with multiple sex partners [1, 8–10]. In these countries, only a minority of vaccinated children could get the infection as a consequence of intrauterine transmission or of immunoprophylaxis regimen failure [11]. Since the introduction of donor screening and blood testing for blood-borne pathogens in most countries worldwide, the incidence of post-transfusion hepatitis B is very low (1 in 500,000 per unit exposure) [12]. The extent of horizontal transmission which includes transmissions due to traditional practices and transmission due to poor injection safety during medical and surgical procedures is uncertain.

9.1.1.3 Prevention of MTCT

The risk of vertical transmission, in the absence of any intervention, has been estimated to be 10–40% from HBsAg-positive, HBeAg-negative mothers and 70–90% for HBsAg- and HBeAg-positive mothers [13]. The administration of monovalent hepatitis B vaccine within 24 hours of birth followed by completion of the HBV vaccine series with two more doses within 6–12 months has been demonstrated to be 90–95% effective in preventing the infection [11, 14, 15]. Including a dose of hepatitis B immune globulin (HBIG) at birth to infants can further reduce the risk of transmission to less than 5% [16].

Despite active-passive immunization (vaccine + HBIG), residual transmission may occur from HBV-infected mothers [17] due to transplacental/intrauterine infection or immunoprophylaxis regimen failure [17, 18]. HBeAg-positive mothers with high circulating concentrations of HBV DNA (>10^6 IU/m) are at highest risk of MTCT of HBV [17, 19]. The use of lamivudine, telbivudine or tenofovir [20–22] during third trimester of pregnancy in highly viraemic, HBeAg-positive mothers in combination with standard active-passive immunization to the infant was demonstrated to be effective in further preventing MTCT of HBV with over 70% reductions in the rates of infant HBsAg and HBV deoxyribonucleic acid (DNA) positivity at 6–12 months postpartum [18–22]. In a recent meta-analysis of 26 studies that enrolled 3622 pregnant women, antiviral therapy reduced MTCT when defined as infant HBsAg seropositivity by a risk ratio of 0.3 (95% confidence interval 0.2–0.4) and when defined as infant HBV DNA seropositivity by a risk ratio of 0.3 (95% confidence interval 0.2–0.5) at 6–12 months [22].

Table 9.1 Routes of transmission of hepatitis B virus infection

Vertical
Mother-to-child transmission
Horizontal transmission among unvaccinated persons
Sexual with higher risk for people with multiple sexual partners and men who have sex with men
Unsafe injections
Unscreened or inadequately screened transfusions or dialysis
Traditional practices

9.1.2 Aetiology

HBV is a double-stranded DNA virus, member of the *Hepadnaviridae* family, of the genus *Orthohepadnavirus*. The genetic variability of HBV is very high. There are at least eight major genotypes of HBV labelled A through H. Genotypes are divided into sub-genotypes with distinct virological and epidemiological properties.

9.1.3 Pathophysiology

The pathogenesis and clinical manifestations of HBV infection are due to the interaction of the virus and the host immune system. The immune system attacks HBV and causes liver injury that is the result of an immunologic reaction when activated CD4+ and CD8+ lymphocytes recognize various HBV-derived peptides on the surface of the hepatocytes. Impaired immune reactions (e.g. cytokine release, antibody production) or a relatively tolerant immune status results in chronic hepatitis. Age is a key factor in determining the risk of chronic infection. This is because the immune response to the virus of neonates, infants and children younger than 5 years is physiologically weaker than adults [23]. Young children, being more immune-tolerant, are more likely to develop chronic infection [24–27]. Chronicity rate has been estimated to be 90% for neonates born to HBeAg-positive mothers, 25–30% for children under the age of 5 and less than 5% for adolescents and adults [26–28] (Fig. 9.1).

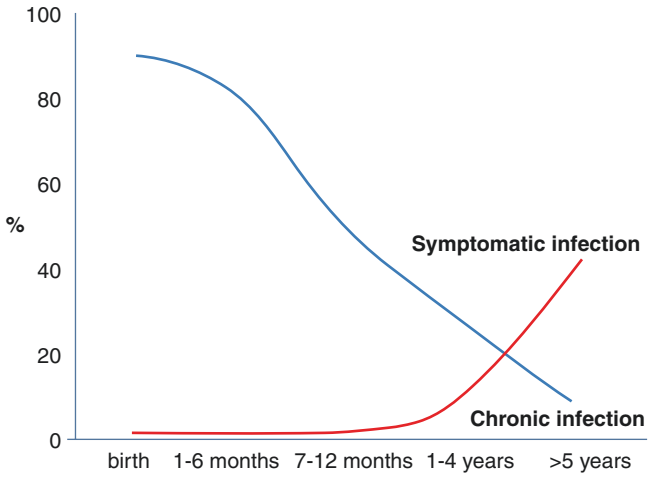

Fig. 9.1 Outcomes of hepatitis B virus infection by age at infection (modified from [71])

Basing on the result of the interplay between the virus and the immune system, HBV can cause acute and chronic infection ranging from asymptomatic infection or mild disease to severe or fulminant hepatitis. The natural history of CHB is dynamic and progresses non-linearly through several recognizable phases of variable duration, which are not necessarily sequential [26, 29]. Historically, the terms "immune-tolerant", "immune-active", "immune-control" and "immune-escape" have been used to describe these different phases, but it is increasingly recognized that these descriptions are not fully supported by immunological data and do not always relate directly to criteria and indications for antiviral therapy. The new accepted nomenclature is now based on the description of infection (characterized by normal aminotransferase) or hepatitis (with raised aminotransferases) and on HBeAg status of the patient. Table 9.2 summarises the revised definitions of the phases of CHB [30].

9.1.3.1 Natural History of Hepatitis B in Children

When hepatitis B is acquired in infancy and childhood, it is likely to lead to chronic asymptomatic infection [25, 31–42]. Only 5–10% of the children develop and resolve acute infection that, although can be associated with severe symptoms in adults [43], is usually asymptomatic in vertically infected children [25, 44]. Children with CHB are expected to be asymptomatic with no clinically detectable sign of liver disease although CHB may lead to progressive liver disease and development of cirrhosis and HCC.

The natural history of CHB in children has been depicted by few large and long-term prospective studies [25, 31–36, 45] with additional data from smaller prospective and retrospective studies [37–42]. Children acquiring HBV infection vertically usually experience a high replicative, low inflammatory phase of long duration. The exact duration of this phase is unpredictable, but it is affected by the route of HBV infection acquisition (it lasts longer in subjects who acquired HBV vertically than in those infected horizontally), by environmental factors such as nutritional status and by viral genotype (HBV genotype C infection is associated with delayed spontaneous seroconversion). In the 29-year longitudinal study from Italy, 89 of the 91 HBeAg-positive children underwent HBeAg seroconversion (i.e. the loss of HBeAg with the appearance of anti-HBe), and the median age of onset of the HBeAg-positive hepatitis phase after vertical infection was 30 years [25]. Overall, across different studies around 90% of children less than 15 years of age are still HBeAg positive, and only a minority of the children infected vertically presents HBeAg seroconversion spontaneously before puberty. In the HBeAg-positive hepatitis phase, aminotransferases are elevated and HBV DNA levels start to decrease. It is noteworthy that in this phase, active inflammation can be found in the liver with necrosis of the parenchyma that can develop into fibrosis over time.

Spontaneous HBeAg/anti-HBe seroconversion leads to the entry in the HBeAg-negative infection phase that is characterized by normalization of aminotransferases, absent or low viral replication, with low (<2000 IU/mL or $<10^4$ copies/mL) or undetectable HBV DNA and inactive liver histology. Regression of liver fibrosis has been described in this phase, and, in the long term, around 15% of the patients in this phase became anti-HBs positive marking the resolution of HBV infection. In these patients the overall prognosis is good if cirrhosis has not developed before anti-e and anti-s seroconversion.

Low-level HBV replication with detectable HBV DNA in the liver may persist in patients who became anti-HBs positive. Few patients (5%) in the HBeAg-negative infection phase can experience the selection of precore mutants leading to HBeAg-negative hepatitis with persistent viral replication and abnormal aminotransferases that is histologically active. The precore mutation, a G3A mutation at codon 1896 that results in the occurrence of a stop codon, makes the virus unable to encode for HBeAg leading to HBV replication uncontrolled by the host's immune system. There is overwhelming evidence from different studies that basal core promoter mutations are independent risk factors for the development of active liver disease and HCC. Finally, in patients in the HBeAg-negative infection phase who undergoes immune-suppression phase reactivations characterized by a rise in HBV DNA, high aminotransferases and hepatic necroinflammatory changes on liver biopsies with or without reverse seroconversion to HBeAg and HBsAg positivity are possible. HBV reactivation may be explained by the persistence of low-level HBV replication in the liver and/or by the presence of covalently closed circular DNA in the nucleus of infected hepatocytes.

Overall, the development of cirrhosis during childhood has been described in 1–5% of HBeAg-positive children

Table 9.2 Phases in natural history of chronic hepatitis B virus infection [30]

Old terminology	New terminology	Characteristics	Notes
Immune-tolerant phase	HBeAg-positive infection	**HBsAg**: high **Aminotransferases**: normal **HBV DNA**: $>10^7$ IU/mL **Liver disease**[a]: none/minimal **Progression to cirrhosis**: none or slow **Treatment**: not generally indicated	Stage seen in most of the children infected at birth (90%) or in the first few 5 years of life (20–60%); young adults infected in the perinatal or early childhood period are in this phase
Immune-active phase	HBeAg-positive hepatitis	**HBsAg**: high **Aminotransferases**: elevated **HBV DNA**: >2000 IU/mL (constantly raised or fluctuating) **Liver disease**: moderate to severe **Progression to cirrhosis**: possible **Treatment**: may be indicated	This phase correlates strictly with treatment in paediatric guidelines; may develop anti-HBe with normalization of ALT leading to "immune-control" phase
Inactive carrier/ immune-control phase	HBeAg-negative infection	**HBsAg**: low **Aminotransferases**: normal **HBV DNA**: <2000 IU/mL **Liver disease**: none **Progression to cirrhosis**: none **Treatment**: not indicated	Anti-HBe positive; risk of cirrhosis and HCC reduced; may develop HBeAg-negative hepatitis; monitoring required for reactivation and HCC; the rate of spontaneous seroconversion to anti-HBe is <2% per year in children younger than 3 years of age and 8% and during puberty; the rate of spontaneous seroconversion to anti-HBe is 12% per year in adults
Immune-escape phase	HBeAg-negative hepatitis	**HBsAg**: intermediate **Aminotransferases**: elevated **HBV DNA**: >2000 IU/mL **Liver disease**: moderate to severe **Progression to cirrhosis**: more rapid than in other phases **Treatment**: may be indicated	HBeAg-negative chronic hepatitis progresses slowly in children. The overall annual incidence of HBeAg-negative hepatitis was 0.37% (95% CI 0.35–0.39) in spontaneous HBeAg seroconverters. HBeAg seroconversion during childhood predicts a lower risk of HBeAg-negative hepatitis in later life [45] According to the old terminology "reactivation" or "acute-on-chronic hepatitis" (characterized by HBeAg-positive or HBeAg-negative hepatitis, moderate to high levels of HBV DNA, seroreversion to HBeAg positivity if HBeAg negative, with high risk of decompensation in presence of cirrhosis) is now classified as HBeAg-positive or HBeAg-negative hepatitis. Reactivation can occur spontaneously or be precipitated by immunosuppression (chemo- or immunosuppressive therapy, human immunodeficiency infection or transplantation), development of antiviral resistance or withdrawal of antiviral therapy
Occult HBV infection	HBsAg-negative infection	**HBV DNA**: undetectable **Aminotransferases**: normal **Liver disease**: none **Progression to cirrhosis**: none **Treatment**: not indicated	Anti-HBc positive, anti-HBs positive or negative

[a]Necroinflammatory changes

[25, 37, 38] and of HCC in 2–5% [25, 31]. HBeAg seroconversion before the age of 3 years and a longer duration of the HBeAg-positive hepatitis phase [25, 31, 46] have been identified as risk factors for development of cirrhosis in children. HCC is more common in males and cirrhotic children [25, 31, 38]. Long-term risk of HCC is correlated to viral replication and serum HBV DNA levels [47], while seroconversion to anti-HBe reduces the overall risk of developing HCC [48]. Cirrhosis or HCC can occur anytime during childhood or later in adult life. Vertically acquired HBV can cause significant morbidity and mortality beyond the paediatric age. The annual incidence of HCC in HBeAg-negative adults has been estimated to be 0.2% that is 1.6% of asymptomatic HBsAg carriers [48]. In Taiwan, before the start of the universal HBV vaccination program, the estimated incidence of HCC in children with CHB was 0.52–0.60 per 100,000 person-year. HCC incidence in Taiwan was significantly impacted by vaccination and the preventive effect of vaccination extended from childhood to early adulthood confirming that the morbidity related to vertical acquisition of HBV extends beyond the paediatric age [49].

CHB has been associated in children with extrahepatic manifestations such as kidney disease (nephrotic syndrome, non-nephrotic membranous glomerulonephritis, end-stage renal disease and acute kidney injury) [50–52].

9.1.4 Diagnosis

9.1.4.1 Serological Diagnosis

The diagnosis of CHB is usually based on a serological assay to detect HBsAg in two different serum samples taken 6 months apart. In HBsAg-positive children, testing of anti-HBV antibodies and quantification of HBV DNA levels could confirm and define the phase of the infection. Testing of infants born to HBV-infected mothers is problematic because of the presence of maternal antibodies passively transferred during pregnancy. Maternal antibodies usually persist in the child's blood for less than 12 months, but it is generally recommended to test exposed infants for HBsAg and anti-HBV antibodies after 12 months of age to limit the possibility of false positive results [53].

9.1.4.2 Staging of Liver Disease

Staging of liver fibrosis using non-invasive tests (NIT) is the new standard of care in adults. Liver biopsy is no longer used routinely to make treatment decisions in most adults with CHB [7, 29, 30, 54, 55]. Among NIT transient elastography (TE) and serum biomarker-based tests such as fibrosis-4 (FIB-4), aspartate aminotransferase-to-platelet ratio index (APRI) and FibroTest have been validated and are now widely used to assess stage of liver disease and diagnosis of cirrhosis in adults [56–58]. In contrast to adults, only few studies exploring the role of NITs in children with CHB are available [59–65]. The diagnostic and prognostic value of NIT in children with CHB has not yet been well established. Liver biopsy is still the gold standard in children to assess the degree of liver inflammation and stage of fibrosis and indication for treatment [53, 66]. The procedure, although invasive, is associated with a low rate of complications when performed by trained operators [66]. The European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommends liver biopsy in children with CHB presenting elevated serum aminotransferase levels for at least 6 months before considering treatment [53]. In these children, histological assessment of the degree of inflammation and of the stage of fibrosis is crucial [24, 53] as response to treatment with currently available therapies is more likely when at least moderate necroinflammation or moderate fibrosis is present [24, 67].

9.1.4.3 Monitoring

Monitoring of children not yet on antiviral therapy depends on the patient's serological profile (HBeAg positive or negative) and aminotransferases and HBV DNA levels. The evidence base is limited and the optimal timing is not well established. The ESPGHAN guidance to treatment of children with CHB suggested monitoring of aminotransferases and HBV DNA levels every 3–4 months for at least 1 year in HBeAg-positive and HBeAg-negative children with increased aminotransferase levels to evaluate the indication for treatment and to rule out HBeAg-negative active disease [53]. Monitoring every 6 months was recommended in HBeAg-positive children with normal aminotransferase level.

For children receiving treatment, as well after discontinuation of treatment, there are no specific recommendations, and frequency of monitoring for safety, adherence and efficacy should be determined on an individual basis [53].

9.1.5 Treatment

9.1.5.1 Goals of Treatment

The goals of antiviral treatment for patients with CHB are described in Table 9.3 and are usually achieved through effective and sustained suppression of HBV replication [7, 29, 53, 54, 68] that is associated with normalization of serum aminotransferases, loss of HBeAg with or without seroconversion to anti-HBe and improvement in liver histology [69]. Attainment of HBsAg loss and seroconversion to anti-HBs status is achieved in less than 1% of patients using currently available nucleos(t)ide analogues (NA) therapy although the longer is the treatment, the higher are the rates of HBsAg seroconversion [70].

Table 9.3 Goals of antiviral treatment for children with chronic hepatitis B virus infection

Reduce or reverse necroinflammatory change and hepatic fibrosis
Long-term clinical outcomes:
Decrease the risk of disease progression to cirrhosis
Decrease the risk of HCC
Decrease the risk of HBV-related morbidity and mortality
Surrogate measures of long-term treatment outcomes used to assess efficacy
Biochemical measures: normalization of serum aminotransferases as a surrogate measure for the resolution of necroinflammation in the liver
Virological markers: reduction in HBV DNA to undetectable levels by PCR; HBeAg loss or seroconversion to anti-HBe status; HBsAg loss and seroconversion to anti-HBs status

9.1.5.2 Indications for Treatment

According to the guidance to treatment by the ESPGHAN and the American Association for the Study of Liver Disease (AASLD) [53, 54], the decision to start treatment for children with CHB is based on a combined assessment of stage of liver disease, HBV DNA viral load and alanine aminotransferase (ALT) levels, HBeAg, as well as other considerations such as family of history of HCC and/or co-existence of other liver disease [7, 30, 53, 54, 71].

The European paediatric guideline recommends treatment when ALT is persistently elevated for at least 6 months in HBeAg-positive children and for 12 months in HBeAg-negative children. Liver biopsy should demonstrate in these children the presence of moderate to severe inflammation and fibrosis [53]. The AASLD guidelines recommend treatment in HBeAg-positive children with both elevated ALT and measurable HBV DNA levels [54], with no specific duration of ALT elevation (though most studies were based on those with an ALT elevation >1.3 times upper limit of normal for at least 6 months). A family history of HCC was reported as an additional factor to support treatment initiation [53]. AASLD guidelines also recommended deferral of therapy when the HBV DNA level is $<10^4$ IU/mL, until spontaneous HBeAg seroconversion is excluded [54].

9.1.5.3 Antiviral Treatment

Currently, eight HBV antiviral agents are approved and licensed for the treatment of CHB in adults: four nucleoside (entecavir, lamivudine, emtricitabine and telbivudine) and two nucleotide analogues (adefovir dipivoxil, TDF/tenofovir alafenamide [TAF]), of which four are also approved for children with age-specific limitations (Table 9.4), as well as standard interferon (IFN) and pegylated (PEG) IFN α-2b.

IFN and PEG IFN are immune-stimulators and can be administered in non-cirrhotic patients for a predefined duration to inducing an immune-mediated control of HBV infection and to achieve long-lasting suppression of viral replication off-treatment [7, 30, 53, 54, 71]. IFN therapy has been associated with possibly higher rates of HBsAg loss when compared to NA [70] but cannot be used in infants and in pregnant women and is contraindicated in persons with autoimmune disease, uncontrolled psychiatric disease, cytopenia, severe cardiac disease, uncontrolled seizures and decompensated cirrhosis.

Table 9.4 Antiviral drugs approved for children with chronic hepatitis B virus infection

Drug	Use in children	Dose	Formulation
Adefovir	≥12 years	10 mg daily	Tablets (10 mg)
Entecavir	≥2 years	10–30 kg: 0.015 mg/kg daily (max 0.5 mg)	Oral solution (0.05 mg/mL) Tablets (0.5 mg and 1 mg)
Interferon-α-2b	≥1 year	6 million IU/m^2 3 times a week	Subcutaneous injections
Lamivudine	≥2 years	3 mg/kg daily (max 100 mg)	Oral solution (5 mg/mL) Tablets (100 mg)
Pegylated-interferon-α-2a	≥3 year	180 μg once a week	Subcutaneous injections
Tenofovir alafenamide[a]	≥12 years	25 mg daily	Tablets (25 mg)
Tenofovir disoproxil fumarate	≥12 years	300 mg daily	Oral powder (40 mg per 1 g) Tablets (150, 200, 250 and 300 mg)

[a]Data available for children with human immunodeficiency virus infection

The NA are used as oral monotherapy for long-term treatment to suppress viral replication or for treatment of finite duration (with or without IFN) to obtain sustained off-treatment virological response [7, 30, 53, 54, 71]. The risk of resistance is the main concern with the use of these drugs. Entecavir and tenofovir are potent HBV inhibitors with high barriers to resistance, while telbivudine, adefovir and lamivudine have lower genetic barrier to resistance.

A recent systematic review and meta-analysis showed that in children with CHB, antivirals compared to no antiviral therapy improved attainment of HBV DNA suppression (124/256, 48.4% and 50/180, 27.7%, respectively; relative risk = 1.4, 95% confidence intervals 1.1–1.8), ALT normalization (106/133, 79.7% and 40/69, 57.9%, respectively; relative risk = 1.4, 95% confidence intervals 1.1–1.7) and HBeAg seroconversion (57/180, 31.7% and 14/110, 12.7%, respectively; relative risk = 2.1, 95% confidence intervals 1.3–3.5) [70].

9.1.5.4 Recommended Drugs

IFN, entecavir and TDF are recommended for treatment of CHB in children by ESPGHAN and AASLD [7, 53, 54]. TDF and adefovir are currently approved by the Food and Drug Administration (FDA) and European Medicines

Agency (EMA) for children 12 and older and entecavir and lamivudine from age 2 and 3 years, respectively. EMA recently approved the use of TAF for children aged 12 years and older and weighing >35 kg. IFN α is approved for use in children older than 1 year, while, only recently, in September 2017, PEG IFN α-2b has been approved by EMA for use in children older than 3 years. Advantages of IFN and PEG IFN for use in children are the absence of viral resistance and the predictable finite duration of treatment [53, 54]. However, use of IFN and PEG IFN is difficult for children as it requires subcutaneous injections three times and once per week, respectively, and is associated with a high risk of adverse events [30, 53, 54]. The AASLD guideline suggests that providers consider use of PEG IFN α-2a as it has the advantage of once weekly administration for children older than 5 years with chronic HBV [54].

Overall, IFN α-2b, lamivudine, adefovir, TDF and entecavir for children with CHB were approved based on the results of five randomized placebo-controlled trials (Table 9.5) [72–76]. A placebo-controlled randomized controlled trial of TDF in adolescents showed a high virological response (89%) and normalization of serum ALT at 72 weeks of treatment, and no observed resistance [72] although HBeAg seroconversion was rare. A placebo-controlled trial of entecavir in children demonstrated the superiority of entecavir at reducing HBV DNA levels to <50 IU/mL (49.2% vs 3.3%; $p < 0.0001$), inducing HBeAg seroconversion (24.2% [29 of 120] vs 10.0% [6 of 60]; $p = 0.0210$) after 48 weeks of treatment (24% vs 2%) and normalizing serum ALT levels (67% vs 23.3%; $p < 0.0001$) [73]. Overall, a good treatment response (defined by the reduction of serum HBV DNA to undetectable levels, by the loss of serum HBeAg and/or by the normalization of aminotransferases) was associated with greater baseline disease activity (i.e. high baseline histology activity index score and aminotransferase levels) and lower baseline HBV DNA levels.

Although for both children and adults in the HBeAg-positive infection phase (the immune-tolerant phase according to the old nomenclature) a conservative approach is warranted, results of two pilot studies in children were highly promising. In the first study, the 23 children enrolled received 8 weeks of lamivudine followed by 44 weeks of combined lamivudine and IFN-α treatment [77]. Seventy-eight percent of the children treated became HBV DNA negative at the end of treatment (62 weeks), five (22%) seroconverted to anti-HBe, and four (17%) of these became persistently HBsAg negative and anti-HBs positive. No YMDD mutation was found [77]. On the basis of this study, two controlled trials in children in the HBeAg-positive infection phase are currently being conducted in the United States (entecavir/PEG IFN-α; NCT01368497) and United Kingdom (lamivudine/PEG IFN-α NCT02263079). A second, recent randomized controlled study have explored the efficacy of IFN-α monotherapy for 12 weeks followed by the combination therapy of IFN-α and lamivudine up to week 72 and subsequently lamivudine alone till week 96 in treatment-naïve chronically HBV-infected Chinese children aged 1–16 years. Of the 46 patients in the treatment group, 73.9% had undetectable serum HBV DNA, 32.6% achieved HBeAg seroconversion and 21.7% lost HBsAg at treatment week 96, confirming the efficacy of the combine therapy in children in the HBeAg-positive infection phase [78]. No lamivudine resistance emerged during the treatment [78].

9.1.5.5 Balancing the Knowledge of the Natural History of CHB with the Effectiveness of the Anti-HBV Drugs That Are Currently Available

HBV infection acquired in infancy or in early childhood is often a chronic infection. In uncomplicated CHB cases, the few and clinically irrelevant symptoms do not represent a

Table 9.5 Main results of therapeutic trials with anti-hepatitis B drugs in children

	Interferon-α-2b [74]	Lamivudine [75]	Adefovir [76]	Tenofovir DF [72]	Entecavir [73]
Virological response (HBeAg negative; HBV DNA negative) (% treated versus placebo)	26% (vs 11%)	23% (vs 13%)	10.6% (vs 0)	21.2% (vs 0)	24.2% (vs 3.3%)
HBsAg negative (% treated versus placebo)	10% (vs 1%)	2% (vs 0)	0.8% (vs 0)	1.9% (vs 0)	5.8% (vs 0)
Number treated	144	191	173	52	120
Duration of treatment (weeks)	24	52	48	72	48
Dose	6 MU/m^2 thrice weekly	3 mg/kg daily (max 100 mg)	2–7 years: 0.3 mg/kg daily >7–12 years: 0.25 mg/kg >12–18 years: 10 mg	300 mg daily	0.015 mg/kg daily (max 0.5 mg)

HBeAg hepatitis B e antigen, *HBV DNA* hepatitis B virus deoxyribonucleic acid, *HBsAg* hepatitis B s antigen

correct and valid indication for starting treatment. Histologically, liver damage (i.e. inflammation and progressive fibrosis) is low in the HBeAg-positive infection phase, while it starts progressing in the HBeAg-positive hepatitis phase. Few children, around 10% of those younger than 15 years, progress to this phase. Continuous monitoring is crucial to identifying children with possible histological progression and treating them according to the indications provided by the major scientific societies described above. In these children, IFN and PEG IFN accelerate spontaneous clearance of the virus but with no major advantage as compared with the natural history of the infection [79]. At the same time, IFN and PEG IFN improve the rate of HBsAg loss that is the current goal of the available therapies. HBsAg loss rate is unsatisfactory as it could be achieved only around 10% of the children treated at the cost of a long therapy with significant side effects. NAs are safe and highly effective in obtaining control of viral replication that results in turn in reduction of the inflammation in the liver, but the duration of treatment is unpredictable and possibly lifelong. Neither IFN nor NA are actually able to cure the infection eradicating the virus and its replicative forms including covalently closed circular DNA form in the nucleus. In the future, the ideal treatment should be aimed at eradicating the virus and preventing the histological progression and therefore should be started in the HBeAg-positive infection phase. The preliminary experience with combined treatments with IFN and NA in HBeAg and highly viraemic patients are promising but far to achieve satisfactory high rates of virological and immunological response and, again, at the cost of significant IFN-based side effects.

9.2 Hepatitis C Virus

9.2.1 Epidemiology

9.2.1.1 Burden of Hepatitis C Virus Infection

The exact prevalence of HCV infection in children is unknown. According to the latest WHO estimation, in 2015, about 71 million persons (1% of the world population) were living with HCV infection in the world with the highest prevalence in the Eastern Mediterranean Region followed by the European and African Regions (1%) [2]. Paediatric epidemiological global data are limited. Based on studies from 102 countries approximately 3.5 million children younger than 19 years of age were estimated to be infected with HCV worldwide [80]. Higher rates of infection have been reported in special groups such as children treated in hospital for renal failure and malignancy or those who had undergone surgical procedures or haemodialysis [81].

9.2.1.2 Routes of Transmission

Vertical transmission of HCV from the mother to the child is actually the main route of acquisition of the infection worldwide [82]. Before the introduction in the early nineties of universal blood supply screening for HCV, parenteral transmission through unscreened or inadequately screened blood transfusions was the major route of transmission of HCV in children [83].

The rate of vertical transmission from mothers positive for anti-HCV antibodies irrespective of HCV ribonucleic acid (RNA) status is <2% [84]. The risk is higher (10.8%; 95% confidence intervals, 7.6–15.2%) when the mother is HCV RNA positive and co-infected with human immunodeficiency virus and is 5.8% (95% confidence intervals, 4.2–7.8%) from HCV RNA positive, human immunodeficiency virus-negative women [85]. Vertical transmission from the HCV-infected mother to the foetus or to the child can occur during pregnancy or in the perinatal period [86] although its exact timing is unknown. Only few children who acquire the infection vertically are HCV RNA positive in the first days of life [87, 88] suggesting early intrauterine infection. The majority (more than two third) of the children who are vertically infected presents detectable HCV RNA levels several weeks after delivery, suggesting late intrauterine or intrapartum transmission [88–90]. Maternal viraemia, independently of HCV genotype, is the major risk factor and the limiting condition for vertical transmission of HCV [91]. A higher concentration of maternal serum HCV RNA has been associated with a higher risk of vertical transmission in few studies although significant overlap of viraemia levels between transmitting and non-transmitting mothers has been reported [92, 93]. All the conditions favouring the contact between maternal infected blood and the child can theoretically increase the risk of vertical transmission. Some reports showed an increased risk of transmission related to invasive internal foetal monitoring [94, 95] and to prolonged (>6 hours) duration of the rupture of membranes [94]. On the other side, large studies comparing vaginal delivery, which exposes the child to the contact with maternal blood, with elective or emergent caesarean section did not find any difference in the risk of vertical transmission of the virus [96]. Breastfeeding was not associated with an increased risk of vertical transmission of HCV [89, 97]. Table 9.6 summarizes the factors that have not been associated with an increased risk of vertical transmission of HCV.

Table 9.6 Factors not associated with vertical transmission of HCV

Mode of delivery
Breastfeeding
HCV genotype
Previous delivering of a child infected perinatally with HCV
Mother–child HLA class I concordance
Single nucleotide polymorphisms of *interferon λ3*

In high-income countries, horizontal transmission through injection drug use has been described as an emerging and concerning route of acquisition of HCV in adolescents [98]. On the other side, in low-income countries, iatrogenic transmission and transmission through traditional practices such as scarification and circumcision are still relevant and could account for the higher prevalence of the infection in these settings [99].

9.2.1.3 Prevention of Mother-to-child transmission (MTCT)

A hepatitis C vaccine, capable of protecting against hepatitis C, is not available. Most vaccines work through inducing an antibody response that targets the outer surfaces of viruses. However, the HCV is highly variable among strains and rapidly mutating, making an effective vaccine very difficult to develop. The major preventive measures for HCV infection therefore stand on improvement of injection safety, with adoption of nonreusable syringes and on policies to reduce unnecessary injections [100, 101]. With regard to MTCT, caesarean section is not recommended to reduce the risk of vertical transmission of HCV [96], and breastfeeding from HCV-infected mothers is not contraindicated.

The parents of the HCV-infected child should be informed of the possibility of transmission of the infection to others. Household contacts should avoid sharing toothbrush, shaving, equipment, nail clippers, tweezers, glucometers or other personal items that may be contaminated with blood [102]. Parents should not be forced to disclose the child's infection status, and restriction from any routine childhood activity is not recommended [102]. HCV is not transmitted by casual contact (e.g. kissing, hugging, holding hands), and the infected child does not pose a risk to other children [102]. He can participate in all regular childhood activities (school, sports and athletic activities) without restrictions [102]. Parents should be informed that universal precautions should be followed at school and at any place as well as at home. Moreover, the child should be educated to minimize the risk of HCV transmission and avoid any blood exposure by using gloves and dilute bleach to clean up blood [102]. Adolescents with HCV infection should be aware that the risk of sexual transmission is low, but barrier precautions are nevertheless recommended [102].

9.2.2 Aetiology

HCV is a small (55–65 nm in size), enveloped, positive-sense single-stranded RNA virus, member of the *Flaviviridae* family, of the genus *Hepacivirus* [103]. Seven major viral genotypes of the virus have been identified in different regions of the world [104], and each genotype comprehends several subtypes. Among the different genotypes, genotype 1 is the most prevalent. Genotypes and subtypes have different geographic distribution.

HCV virions consist of a core of genetic material (RNA), surrounded by an icosahedral protective shell of protein, and further enveloped in a lipid bilayer in which two glycoproteins (E1 and E2) are anchored. HCV has a positive sense single-stranded RNA genome of approximately 9.6 kb with a single open reading frame translated in a single polyprotein of approximately 3000 amino acids [105]. The polyprotein is processed by host signal peptidases encoding structural proteins (E1 and E2) and nonstructural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A and NS5B) [105, 106]. Viral replication is mediated by HCV RNA polymerase together with nonstructural proteins. New direct-acting antivirals (DAA) active against HCV inhibit viral replication targeting nonstructural proteins of the virus.

9.2.3 Pathophysiology

HCV is a non-cytopathic virus that enters the liver cell and undergoes replication simultaneously causing cell necrosis by several mechanisms including immune-mediated cytolysis. Innate immunity presents a first-line defence for the control of HCV infection as it does for several other viral infections, while successful clearance of HCV during acute HCV infection depends on the rise, strength and persistence of the adaptive, Th1-mediated immune response. Following HCV infection around one third of the infected adults and children present viral clearance and a self-limited disease course, while the remaining develop chronic infection.

9.2.3.1 Natural History of Hepatitis C in Children

Following MTCT of HCV, spontaneous clearance of the virus has been described in approximately 20% of the infected children usually in the first 4 years of life. Spontaneous clearance is an unpredictable phenomenon. Children with HCV genotype 3 infection and raised aminotransferase levels in the first year of life are more likely to present spontaneous clearance [107]. Recently, the single nucleotide polymorphism rs12979860 of the *interferon λ3* gene and altered natural killer cells number and phenotypes were associated with spontaneous clearance of HCV in children, suggesting a primary role of the innate immunity [108–110].

In patients who do not clear the virus (about 80% of the vertically infected), chronic HCV infection (CHC) persists into adulthood. CHC is usually asymptomatic in children [83, 111]. Only few cases of severe hepatitis have been described [112, 113]. According to the results of a multicentre, European, prospective study on 266 children born to HCV-infected mothers, hepatomegaly was the only clinical finding reported in 10% of the children, usually in the first

year of life [114]. In the same study, persistently raised alanine aminotransferase levels were described in almost half of the children during follow-up [83, 114]. There is limited amount of information concerning liver disease progression in children with CHC [115]. Liver fibrosis usually progresses slowly [111, 116–125]. The majority of children presents minimal changes at liver histology after more than two decades of CHC [116, 117, 119, 125], although very young children with advanced liver disease have been described [83, 116]. Liver fibrosis increases with the patient's age [111, 117, 118, 122], the duration of the infection [117–119] and the severity of histological necroinflammation [116, 122–124]. Overall, in large cohorts of selected children afferent to highly specialized centres, cirrhosis has been described in 1–4% of children with chronic hepatitis C, while bridging fibrosis and severe inflammation is reported in about 15% of them [83, 111, 114, 116]. Comorbidities such as obesity, alcohol consumption, malignancy, haematological diseases with iron overload and viral co-infections (human immunodeficiency virus and HBV) accelerate the development of liver disease [116, 117]. Only few cases of hepatocellular carcinoma in children with HCV infection have been described [126, 127].

HCV infection is not confined to hepatocytes, but it involves also other cells such as thyrocytes [128], lymphocytes [129] and endothelial cells of the blood–brain barrier [130]. The direct and the indirect involvement of organs other than liver is thought to contribute to the development of extrahepatic manifestations of CHC. Extrahepatic manifestations of the infection are common and potentially severe in adults [131] and are considered rare in children [132]. The most common extrahepatic manifestation of the infection in children is the appearance of non-organ-specific autoantibodies (NOSA) which include smooth muscle autoantibody (SMA), antinuclear antibody (ANA) and liver kidney microsomal type-1 (LKM-1) [133–136]. The production of NOSA is probably due to the interaction between HCV and B lymphocytes and to the ability of HCV to trigger an autoimmune response via a molecular mimicry mechanism [136]. HCV can induce cellular injury allowing the exposure of "self" antigens, which are normally protected from the immune system and eliciting an autoimmune response [137, 138]. The clinical significance of NOSA production is still not well defined. NOSAs production could be considered a simple consequence of hepatocellular damage without pathogenic significance. Children presenting with NOSA generally do not show increased transaminases and other features of autoimmunity such as increased IgG levels [133–135]. On the other hand, some studies reported that LKM-1-positive HCV-infected children seem to have a more advanced liver disease when compared with LKM-1-negative peers, suggesting that NOSA may have a possible negative impact on the course of the chronic infection [137].

Subclinical hypothyroidism and autoimmune thyroiditis have been described in 11% and 5.6% of HCV-infected children, respectively [139]. Membranoproliferative glomerulonephritis, the most frequently observed HCV-related renal disease in adults [140], is extremely rare in children with only few cases described [141–143]. Other extrahepatic manifestations such as inflammatory myopathy and opsoclonus-myoclonus syndrome are anecdotal [136].

9.2.4 Diagnosis

9.2.4.1 Serological Diagnosis

Diagnosis of HCV infection is based on the detection of anti-HCV antibodies and on the identification of HCV RNA by polymerase chain reaction (PCR) assays [144]. The detection of immunoglobulin (Ig) M against HCV is not useful to discriminate between acute and chronic infection, because some patients with chronic infection produce specific IgM intermittently and not all patients respond to acute HCV infection by producing specific IgM [145]. When vertical transmission of HCV is suspected, testing the child for HCV-specific antibodies is not informative up to 18 months of age, due to the persistence of maternal antibodies in the child's blood. Before 18 months of age, PCR for HCV RNA is the only useful test for identification of the infection. Different criteria are available to diagnose vertical transmission of HCV. A practical and widely acceptable recommendation is to consider children born to anti-HCV-positive mothers infected as with HCV when HCV RNA is detected in at least two serum samples at least 3 months apart during the first year of life and/or when testing of antibodies against HCV is positive after 18 months of age [146]. A practical diagnostic algorithm for diagnosis and management of children born to HCV-infected mothers is provided in Fig. 9.2.

9.2.4.2 Staging of Liver Disease

NITs using serological markers (APRI, FIB-4, FibroTest) and TE have now replaced in adults with CHC liver biopsy as reference methods for grading the necroinflammatory activity and staging of fibrosis [147]. So far, there has been limited evaluation and validation of these non-invasive methods for staging of liver fibrosis in children. Only few studies have evaluated the role of TE in children with CHC [63, 132, 148, 149], and only in a minority of cases, the results of TE have been compared with liver biopsy results [63, 149]. The use of non-invasive methods in routine clinical practice in children is not yet recommended [66] but can be considered while the performance characteristics are being evaluated.

9.2.4.3 Monitoring

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition suggests annual monitoring of

serum aminotransferases, bilirubin, albumin, HCV RNA levels, complete blood count and prothrombin time/international normalized ratio in children with CHC not receiving antiviral therapy [102]. A proposed algorithm for monitoring of children undergoing treatment with DAA is summarized in Fig. 9.3 [150]. Following treatment, a single viral load measurement at 12 weeks following discontinuation of treatment is recommended, i.e. in both adults and children, to document treatment success. Continued follow-up of those with cirrhosis is recommended, since complications can occur even after successful HCV eradication.

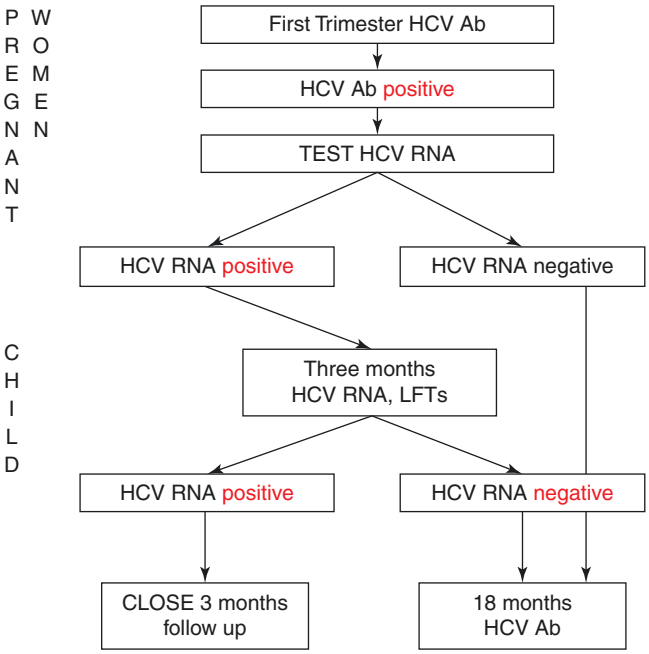

Fig. 9.2 Diagnostic algorithm for children born to hepatitis C virus-infected mothers

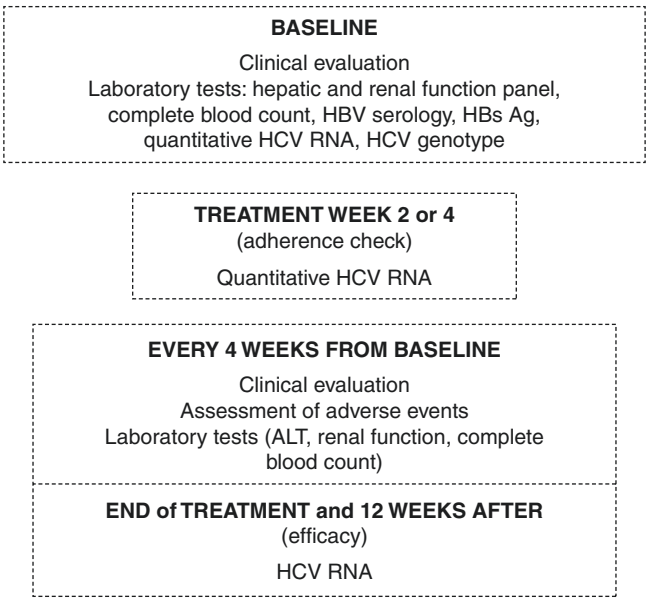

Fig. 9.3 Proposed algorithm for monitoring of children undergoing treatment with direct-acting antivirals (modified from [150])

9.2.5 Treatment

Treatment of CHC for adults and children has changed radically with the discovery of new highly effective DAA drugs active against HCV. Since 2011, ten different oral regimens have been licensed by the EMA and the US FDA for treatment of adults with CHC. Each of these regimens has been demonstrated to be highly effective and safe, independently of viral genotype, staging of liver disease and co-infection with human immunodeficiency virus. Between April and July 2017, the first two DAA regimens have been licensed for adolescents with age- and weight-specific limitations (Table 9.7).

9.2.5.1 Goals of Treatment

The main goal of treatment of CHC in children is to cure the infection aiming to prevent the progression of liver disease and its possible complications. Although the risk of HCV-related hepatic and extrahepatic complications such as liver

Table 9.7 Direct-acting antiviral regimens approved by the Food and Drug Administration and European Medicines Agency for children with chronic hepatitis C virus infection with age- and weight-specific limitations

Ledipasvir/sofosbuvir	
Hepatitis C Virus Genotypes	1, 4, 5, 6
Age of the patient	12–18 years (only for the Food and Drug Administration, independently of age, if weight >35 kg)
Dose	– 12–17 years: fixed-dose combination sofosbuvir 400 mg/ledipasvir 90 mg
Treatment duration	– 12 weeks: treatment-naïve or -experienced with or without cirrhosis – 24 weeks: treatment-experienced patients (pegylated-interferon + ribavirin ± protease inhibitor) with genotype 1 infection and cirrhosis
Sofosbuvir and ribavirin	
Hepatitis C Virus genotypes	2, 3
Age of the patient	12–18 years (only for the Food and Drug Administration, independently of age, if weight > 35 kg)
Dose	– 12–17 years: sofosbuvir 400 mg; ribavirin 15 mg/kg in two doses (maximum <75 kg = 1000 mg and ≥75 kg = 1200 mg; with food)
Treatment duration	– Genotype 2: 12 weeks – Genotype 3: 24 weeks

fibrosis, cirrhosis and hepatocellular carcinoma in children is low and lower than for adults [120], the clinical course of CHC in childhood is unpredictable, and the long-term outcome of vertically infected children into adulthood is uncertain [83, 111, 116, 124]. The endpoint of anti-HCV therapy is sustained virological response (SVR). SVR is obtained when HCV RNA is undetectable in the blood of patients by using sensitive molecular method with a lower limit of detection (<15 IU/mL). SVR at 12 weeks (SVR12) and/or 24 weeks (SVR24) after the end of treatment are conventionally used as endpoints in studies on CHC therapy.

9.2.5.2 Indications for Treatment

Treatment is recommended for all adults with CHC independently of treatment history (both for treatment-naïve and -experienced) and of liver disease severity (compensated or decompensated HCV-related chronic liver disease) [68, 147, 151, 152]. The rationale for treatment in adults is valid also for children [151, 153].

IFN-based treatments were generally deferred in children with CHC because of the burdensome safety profile and the low efficacy of PEG IFN and ribavirin together with the overall benign course of the infection [154, 155]. However, the clinical course of CHC in children and the progression to advanced liver disease sometimes are rapid and unpredictable [117, 124, 126]. The availability of the new effective, safe, all-oral, DAA therapies changes the treatment perspective. Early treatment, i.e. treatment of children older than 4 years (the threshold age up to the child can still present spontaneous clearance of the infection), can prevent the unlikely but unpredictable progression of the infection and all its indirect consequences. Studies assessing the physical and psychosocial health and cognitive functioning of asymptomatic children with CHC, for example, showed a significant reduction in performances compared to children without HCV [156, 157]. From another point of view, the medical costs of the management of infected children in the long term could be significant, and therapy, despite the costs of drugs, could have a positive economic impact [158]. Moreover, the treatment of young children could reduce the possibility as adolescents and young adults of vertical and horizontal transmission of the infection by injecting drug use and sexual transmission.

9.2.5.3 IFN-Based Therapies

Up to December 2018, the combination of PEG IFN and ribavirin is the only treatment option available for children aged less than 12 years. Basing on the results of registration trials [115, 159–162], the combination of PEG IFN α-2a and ribavirin has been approved by EMA in December 2009 and by FDA in December 2008. PEG IFN α-2b and ribavirin have been approved by EMA in March 2013 and by FDA in December 2009. The standard duration of treatment with PEG IFN and ribavirin is 48 weeks for children with HCV genotypes 1 or 4 infection and 24 weeks for children with genotype 2 or 3 [115, 159–162]. Less than 50% of the children with genotype 1 or 4 infection and 90% of those with genotype 2 or 3 achieve SVR24 when treated with PEG IFN and ribavirin [161, 162]. Although the efficacy of PEG IFN and ribavirin is good for HCV genotype 2 and 3, the safety of this combination is poor. The more common adverse effects related to PEG IFN and ribavirin include flu-like symptoms, myalgia and neutropoenia [163]. Anaemia, thrombocytopenia, thyroid disease and alopecia are less frequently observed [163, 164]. PEG IFN therapy is also associated with neuropsychiatric manifestations ranging from mood alterations, irritability and agitation to aggressive behaviour, depression, anxiety and suicidal ideation [154, 165]. Weight loss and decrease in growth velocity are other two major issues in children with CHC treated with PEG IFN and ribavirin. While compensatory weight gain generally occurs following the end of therapy [160, 162], growth velocity does not appear to be fully compensatory. The long-term evaluation of height in children treated led to controversial results with some studies showing the complete recovery of height growth velocity [161] and others, the failure to return to the baseline height-for-age scores after 2 years of observation [162, 166].

Given the low efficacy of IFN-based therapy for HCV genotype 1 and 4 infection, the burdensome safety profile and the availability of new highly effective all-oral, DAA therapies, the updated ESPGHAN [153] and the AASLD [151] guidance for treatment of CHC in children no longer recommend PEG IFN and ribavirin for treatment of children younger (and older) than 12 years [153]. In age cohorts and countries where PEG IFN and ribavirin are the only treatment available, therapy can be generally postponed until the expected extension to the existing age indication for DAAs is granted [151, 153]. Therapy with PEG IFN plus ribavirin may be warranted in the rare situation in which liver biopsy shows significant fibrosis and DAAs are not available. In this case, the decision to administer PEG IFN and ribavirin should take in consideration HCV genotype, severity of the disease, potential side effects, presence of comorbidities and the likelihood of response [153] and should be balanced against the possible risk of deferring treatment or with the possible off-label use of DAAs.

9.2.5.4 DAA

The discovery of DAA changed the history of treatment of CHC. DAAs target viral enzymes responsible for crucial steps of the life cycle of HCV [167] and have different molecular targets: HCV NS5B polymerase inhibitors, HCV NS3/4A protease inhibitors and HCV NS5A inhibitors [167]. Up to December 2018, EMA and FDA have approved two different IFN-free treatment regimens based on DAA combi-

nations in children: the fixed-dose combination of ledipasvir/sofosbuvir and sofosbuvir and ribavirin. Thus far, both regimens can be administered to children older than 12 years or, according to FDA, with a body weight of at least of 35 kg. Ledipasvir, a NS5A inhibitor, in the fixed-dose combination with sofosbuvir (90 and 400 mg daily in a single dose) is approved for treatment of children infected with HCV genotype 1 or 4. Treatment duration for sofosbuvir/ledipasvir is 12 weeks for all children except for those treatment-experienced with HCV genotype 1 infection who should receive 24 weeks of treatment. Sofosbuvir (400 mg daily in a single dose), a NS5B polymerase inhibitor, used with ribavirin (15 mg/kg per day in two divided doses) is approved for treatment of children infected with HCV genotype 2 for 12 weeks and genotype 3 for 24 weeks. The approval of the new treatment regimens has been based on the results of the registration trials [168, 169]. The efficacy and safety of the combination of sofosbuvir/ledipasvir have been evaluated in 100 adolescents with HCV genotype 1 infection [168]. The efficacy of the combination was high (SVR12 98%, intention to treat analysis). Of the 100 patients who started the treatment, 99 completed and 1 discontinued the treatment, while 1 did not attend the post-treatment follow-up visits after having achieved end of treatment response. No patients had virologic non-response, breakthrough or relapse. The efficacy was similar among treatment-naïve (78/80, SVR12 98%; 95% CI 91–100%) and treatment-experienced patients (20/20, SVR12 100%; 95% CI 83–99%). The only patient with cirrhosis was treatment-naïve, received 12 weeks of therapy and achieved SVR12 [168]. The efficacy and safety of the association sofosbuvir and ribavirin have been evaluated in 52 adolescents (75% genotype 3 and 25% genotype 2). Fifty-one of them (95% CI 90–100%, intention to treat analysis) achieved SVR12 (100% for genotype 2, 95% CI 75–100%, and 97% for genotype 3, 95% CI 87–100%). Nine children were treatment-experienced and achieved SVR12 (100%; 95% CI 66–100%). The single patient, who did not achieve SVR12, achieved end of treatment response and SVR4 (HCV RNA negative 4 weeks after the end of treatment) and then was lost to follow up. No patients had virologic non-response, breakthrough or relapse [169]. The two regimens showed an excellent safety profile. No treatment discontinuation due to adverse events has been reported [168, 169]. The most commonly reported adverse events during treatment with ledipasvir/sofosbuvir have been headache (27%), diarrhoea (14%) and fatigue (13%) [168], nausea (27%) and headache (23%) with the association of sofosbuvir plus ribavirin [169].

IFN-free regimens are the recommended options for treatment of adolescents older than 12 years of age or weighing more than 35 kg. According to the recent ESPGHAN and AASLD-ISDA guidance for treatment of CHC in children, PEG IFN plus ribavirin are no longer recommended [151, 153]. Indications for treatment in patient with co-infections (human immunodeficiency virus and HBV), comorbidities and patients who did not achieve SVR with DAA are still lacking, but also in these special groups of patients, IFN-free therapies will be the best option, since new regimens based on DAA will be available soon.

9.2.5.5 Other DAA Regimens

Preliminary results of new combinations of DAA already approved for treatment of CHC in adults are available for children. The ZIRCON trial is an open-label, multicentre study exploring the safety and efficacy of the combination of ombitasvir (NS5A inhibitor)/paritaprevir (NS3/4A protease inhibitor)/ritonavir with or without dasabuvir (NS5B polymerase inhibitor), with or without ribavirin in treatment-naïve and treatment-experienced children, aged 3–17 years, with HCV genotype 1 or 4 infection and with or without compensated cirrhosis [170]. In this study the fixed-dose combination of ombitasvir/paritaprevir/ritonavir has been used with dasabuvir for patients with genotype 1 infection and with ribavirin for those with genotype 1a and 4 infection. The duration of treatment has been 12 weeks for all the patients enrolled except for those with genotype 1a infection or with compensated cirrhosis who have been treated for 24 weeks. Preliminary results have been recently presented for the 12–17 age cohort [170]. Thirty-eight adolescents have been enrolled, and the combination showed excellent efficacy and a good safety profile. SVR12 was 100%, independently of genotype, treatment history and stage of liver disease [170]. Moreover, no adverse event led to discontinuation of the study drugs [170].

The preliminary results of a trial on the efficacy and safety of the combination of sofosbuvir plus daclatasvir with or without ribavirin have been recently presented [171]. Thirteen adolescents aged between 15 and 17 years with HCV genotype 4 infection received 24 weeks of treatment [171]. Ribavirin was added for four patients with cirrhosis [171]. SVR12 was 100% [171]. No serious adverse event has been reported, but mild adverse events were noted in the form of mild headache, dizziness, itching and ribavirin-induced haemoglobin reduction [171]. Interestingly, a recent pilot study explored the efficacy of a shortened 8-week duration of sofosbuvir and daclatasvir in a cohort of ten consecutive adolescents. All patients (10/10; 100% CI, 72.25–100%) achieved sustained virologic response at week 12 post-treatment (SVR12) with good tolerability and no serious adverse events [172].

New treatment perspectives will be offered in the near future by the pangenotypic combinations glecaprevir (NS3/4A protease inhibitor)/pibrentasvir (NS5A inhibitor) and sofosbuvir/velpatasvir (NS5A inhibitor) which have become recently available for adults and are being studied in children. The pangenotypic efficacy will make genotype

identification no more necessary, and these DAA regimens will be a reliable option for treatment of CHC also in low-income countries, where HCV genotyping is often not available. Furthermore, these new-generation DAA regimens have the advantage of a shorter treatment duration (8 weeks).

9.2.6 Implications for Liver Transplantation

HBV and HCV infections in children without any comorbidity lead only in a minority of cases to end-stage liver disease and liver transplantation. For children with CHB who present decompensated cirrhosis as a consequence of HBV infection or due to the co-existence of other chronic liver disease, adults' guidelines suggest the use of NA with high barrier to resistance (i.e. entecavir or tenofovir) irrespective of the level of HBV replication while being assessed for liver transplantation. PEG IFN is contraindicated in patients with decompensated cirrhosis. Antiviral therapy could modify the natural history of decompensated cirrhosis, improving liver function and increasing survival. In patients with CHB who undergo liver transplantation, the combination of HBIG and NA is recommended after liver transplantation for the prevention of HBV recurrence. The same approach should be used for noninfected recipients (HBsAg negative) receiving livers from donors with evidence of past HBV infection (anti-HBc positive) who are at risk of HBV recurrence and should receive antiviral prophylaxis with a NA [30].

For children with CHC, isolated experiences with young children undergoing liver transplantation or with cirrhosis who were treated with DAA are available [173, 174]. In adults with CHC and decompensated cirrhosis without HCC, awaiting liver transplantation, the suggested approach is to initiate treatment with DAA as soon as possible in order to complete a full treatment course before transplantation [68, 151]. The positive effect of viral clearance on liver function may lead to delisting selected cases. When the patient is listed for liver transplantation and the expected waiting time is shorter than the duration of the full DAA treatment course, there is indication to make the transplant first and treat for HCV promptly after transplantation [68, 151]. In adults with HCV, recurrence after liver transplantation treatment with DAA is considered without delay [68, 151]. Similar approaches seem reasonable for children with decompensated cirrhosis without HCC awaiting or having undergone liver transplantation.

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