Chronic Viral Hepatitis B and C

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Stefan Wirth

List of Abbreviations

ALT	alanine aminotransferase
Anti-HBc	antibody against HBcAg
Anti-HBc IgG	immune globulin G
Anti-HBc	antibody against HBcAg
Anti-HBe	antibody against HBeAg
Anti-HBs	antibody against HBsAg
Anti-HDV	antibody against delta virus
cccDNA	covalently closed circular DNA
DAA	direct-acting antiviral
DNA	desoxyribonucleic acid
EMA	European Medicines Agency
FDA	Food and Drug Administration
HBcAg	hepatitis B core antigen
HBeAg	hepatitis e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immune deficiency virus
IgG	immune globulin G
IL2	interleukin 2
IL28B	interferon lambda 3 gene
ORF	open reading frame
RNA	ribonucleic acid
SVR	sustained viral response
TNF-α	tumor necrosis factor alpha

S. Wirth (✉)
HELIOS Medical Centre, Department of Pediatrics, Witten/Herdecke University, Heusnerstr. 40, 42283 Wuppertal, Germany
e-mail: stefan.wirth@helios-kliniken.de

Chronic Hepatitis B

Introduction

Hepatitis B virus (HBV) infection remains a global health burden with estimated 300–350 million people chronically infected worldwide. Nevertheless, since HBV vaccine has become available for more than 20 years and many countries introduced vaccination programs as a prevention strategy on a regularly basis for young infants, significant reduction of the incidence of acute hepatitis B in children and adolescents has been observed. Unprotected, approximately 90% of HBV-infected infants and 20–25% of those infected in preschool age will develop chronic infection decreasing to a chronicity rate of around 5% for adolescents and adults [1–3]. Despite of a rather benign spontaneous course of the disease during childhood and adolescence, there is a considerable lifetime risk of progressive liver disease, liver cirrhosis, and the development of a hepatocellular carcinoma (HCC), which may eventually reduce life expectancy. Thus, careful long-term monitoring has to be performed, and appropriate treatment options, which unfortunately are not entirely curative at present, have to be considered.

Pathogenesis of Chronic HBV Infection

HBV belongs to a DNA virus family called hepadna viruses. It contains a partially double-stranded DNA genome with about 3200 nucleotides. The minus strand covers four overlapping open reading frames (ORFs): S, for the surface gene encoding three envelope proteins (hepatitis B surface antigen, HBsAg); C, for the core gene encoding the core protein (hepatitis B core antigen, HBcAg); X, for the regulatory X gene; and P, for the polymerase gene encoding the viral DNA polymerase. By using multiple start codons, HBV is able to encode more than one protein from an ORF. After hepatocyte entry by an unknown receptor, the viral envelope is removed, and the nucleocapsid reaches the nucleus,

S. Guandalini et al. (eds.), *Textbook of Pediatric Gastroenterology, Hepatology and Nutrition,*
DOI 10.1007/978-3-319-17169-2_60

where the double strand will be completed and converted into a covalently closed circular DNA (cccDNA). This is an important step, because the majority of cccDNA is then organized into nucleosomes forming the viral minichromosome, which is serving as template for the synthesis of the viral mRNA. The transcripts are translated into the viral proteins, and simultaneously reverse transcription leads to the synthesis of a complete minus strand of HBV DNA. The plus strand can then be synthesized again, and the molecule circularizes. Thus, the replication of HBV is similar to that of a retrovirus. The proteins are synthesized and assembled at the endoplasmatic reticulum and eventually discharged by vesicular transport as a Dane particle which contains the complete virus. The cccDNA plays a key role in viral persistence, viral reactivation after treatment withdrawal, and drug resistance. It accumulates in the nucleus of the hepatocyte as a stable minichromosome organized by histone and nonhistone viral and cellular proteins [4, 5]. Persistent HBV replication is associated with a high frequency of integration of HBV sequences into the human host liver cell genome. Enhanced DNA replication and DNA damage occurring during chronic inflammation with cycles of cell death and regeneration increase the availability of DNA ends in host genomic DNA and promote the process of viral integration [6]. Furthermore, it is presumed that certain altered cells are susceptible to the development of additional genetic and epigenetic changes that may lead to the development of malignant cell transformation and HCC.

For the understanding of the different phases during the course of the chronic disease, it is important to realize that the virus itself is not primarily pathogenic to the hepatocyte. The mechanism of cell death is generally accepted to be the result of a cytotoxic T-lymphocyte-mediated immune response of the host to the virus. Additionally, it has been shown that some HBV proteins may be able to induce apoptosis. During the transition from the immune tolerant to the immune active phase, a shift from the hepatitis e antigen (HBeAg)-specific Th2 cell tolerance to Th1 cell activation may recognize HBV-related epitopes on hepatocytes resulting in secretion of cytokines such as interleukin (IL)-2 and tumor necrosis factor alpha (TNF-α) and thus activating inflammation [7].

Epidemiology

There are still high endemic countries in Asia, Africa, and some parts of South America with an HBsAg prevalence of more than 8%. The Arabian region, parts of the Eastern hemisphere, and Greenland show a HBV prevalence of 2–7%, and in the Western countries the rate is below 2% [8]. Global immunization programs have been established in many countries, and the HBV infection rate has declined worldwide. Vertical transmission has become the main route of infection; nevertheless, in some areas, HBV may also be a predominant disease in adolescents and adults due to high-risk sexual behavior and drug abuse [9]. Unfortunately, up to 2–15% of perinatal HBV infection of antibody against HBeAg (anti-HBe)- and HBeAg-positive mothers cannot be prevented by active and passive immunization due to intrauterine infection, vaccine failure, or HBsAg escape mutants [10–12]. Thus, passive and active immunization has to be started immediately after birth in all newborns from HBsAg-positive mothers. HBeAg-positive mothers can be considered to receive treatment with the nucleoside analogues lamivudine or telbivudine in late pregnancy to decrease viral load [13, 14]. After complete immunization, there are no objections against breast feeding. In countries with blood donor screening and serum testing, parenteral transmission does no longer play a significant role. The HBsAg prevalence in children is estimated between 0.02 and 0.03% in Western countries and the USA, in Brazil 0.14% and 0.5% in Taiwan after immunization [1, 15]. Given HBsAg prevalence in pregnant women of 0.4% in Western Europe and an HBV transmission rate of 5–10% despite complete vaccination, 20–40 newborns in 100,000 births may be infected and become a chronic carrier state.

Ten HBV genotypes (A–J) have been documented showing a distinct distribution. Genotypes A and D are predominant in North America, Europe, and India, and genotypes B and C are mostly found in Asian countries. To date, routine determination of genotype is not yet recommended because treatment options are not adjusted to genotypes. Nevertheless, since there is line of evidence that genotypes C and D may be associated with more aggressive liver disease, this might become significant during the long-term follow-up [16].

Diagnostics

Chronic hepatitis B infection is defined as a repeatedly positive HBsAg test result within 6 months. Apart from the aminotransferases, HBeAg, anti-HBe, anti-HBcIgG, and quantitative HBV DNA have to be determined to confirm chronic hepatitis B and to classify the present stage. Additionally, antibody against delta virus (anti-HDV) should be tested to exclude concomitant hepatitis D. It is recommended to perform an ultrasound examination including liver stiffness assessment for baseline findings. Since chronic hepatitis B usually is a mild disease in terms of inflammation in childhood, histological examination by liver biopsy is not mandatory. However, in subjects, who are suspicious of progressive liver disease or cirrhosis or if an impact on therapeutic decisions is identifiable, liver biopsy may be a reasonable completion.

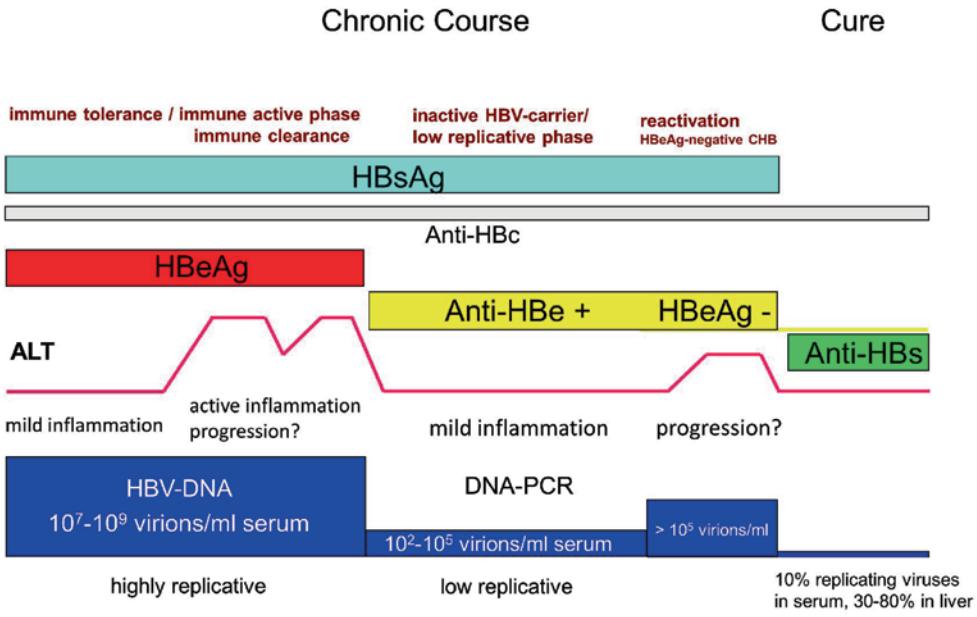

Fig. 60.1 Illustration of the different phases of chronic hepatitis B. *HBV-DNA* hepatitis B virus deoxyribonucleic acid, *DNA-PCR* deoxyribonucleic acid polymerase chain reaction, *HBV* hepatitis B virus, *HBsAg* hepatitis B surface antigen, *Anti-HBc* antibody against HBcAg, *ALT* alanine aminotransferase, *HBeAg* hepatitis e antigen, *Anti-HBs* antibody against HBsAg

Natural History

There are four natural stages of chronic hepatitis B infection: immune tolerance stage, immune reactive or immune clearance stage, inactive HBsAg carrier stage, and reactivation stage. As fifth and last stage, viral elimination with antibody against HBsAg (anti-HBs) seroconversion, which is a rather rare event occurring not more than 0.5 % annually in children, could be denominated [7, 17]. Figure 60.1 illustrates the different phases of chronic hepatitis B.

Children who have HBV infection acquired perinatally or in the first months have an initial tolerance stage which is characterized by the presence of HBsAg, HBeAg, and extremely high HBV DNA levels (10^{7-9} virions/ml) and normal aminotransferases. The duration of the immune tolerant phase is not predictable and may last 1–4 decades. Asian patients seem to have a longer immune tolerant stage. T helper (Th) cell immune tolerance is generated by HBeAg functioning as an immunoregulatory protein mostly already transplacentally transmitted. This kind of induced immune tolerance may explain the high chronicity rate, and the younger the individuals are when they get infected. Usually, only minimal inflammatory activity is detectable in the liver tissue in this phase. Even in adult patients, no severe progression is expected during the immune tolerant stage [18]. Although antiviral therapy is still not recommended for immune tolerant subjects, they should be carefully monitored to duly recognize progression to immune active phase.

With time, a nonspecific increase of inflammatory activity or a decrease of HBeAg serum concentration, which may be due to emerging mutants in the core promotor or precore region resulting in a lower HBeAg production, may activate HBeAg-specific T cell clones. In this immune reactive phase, HBeAg remains positive, and aminotransferases rise. HBV DNA remains high or stays at a little lower level. During this time, progression to liver fibrosis or cirrhosis may occur. However, liver cirrhosis rate is not expected to exceed 3–5 % until reaching adulthood [19–21]. In the immune reactive, phase treatment has to be considered.

A key event in the natural course of chronic hepatitis B is the HBeAg/anti-HBe seroconversion which occurs unpredictably for the single individual during the immune active phase. Anti-HBe seroconversion is associated with a significant decrease of viral replication and normalization of aminotransferases reflecting the biochemical and histological remission of inflammatory activity. In some studies, the annual seroconversion rate depends on the route of infection and the ethnic origin. Whereas the mean seroconversion rate in non-Asian children ranges between 8 and 15 %, seroconversion in Asian children was considerably lower with approximately 5 % per year [7, 20]. Anti-HBe seroconversion is followed by the inactive HBsAg carrier state with persistently normal aminotransferases and a low viral load. Viral replication is considered low when HBV DNA serum concentrations remain below 2000 IU/ml. Some carriers may be lucky and develop anti-HBs antibodies indicating viral elimination and cure of the disease. The estimated incidence of this rare event in children is 0.05–0.8 % per year in endemic areas with predominantly perinatal HBV transmission [7, 15].

Approximately, 20–30 % of inactive HBsAg carriers will experience spontaneous reactivation during long-term follow-up. Those episodes may cause progressive liver damage. The reactivation phase is characterized by the presence of anti-HBe and elevated aminotransferases. HBV DNA levels rise over 2000 IU/ml. This status is also named HBeAg-

negative hepatitis B. However, reactivation rarely occurs during childhood and adolescents.

Another particular condition warrants mention: occult HBV infection. It is defined as the existence of HBV DNA in serum among HBsAg-negative patients and can be classified into seropositive and seronegative with respect to the presence of anti-HBs or antibody against HBcAg (anti-HBc) antibodies. Possible explanations are low levels of viral replication activity or the emergence of HBV variants in the a-determinant of the S-gene. Occult hepatitis B is most common in endemic regions and seems rare with 1.4% [22]. However, prevalence may rise considerably in immunized children from HBsAg-positive mothers. One study reported a prevalence of 28% in this special group [23].

Long-Term Prognosis

Individuals with chronic HBV infection are at risk to develop long-term sequelae such as end-stage liver disease including liver cirrhosis, hepatic failure, and HCC. Progression strongly correlates with the disease activity in terms of viral replication level, inflammatory activity, HBsAg levels, HBV genotypes, and HBeAg/anti-HBe status. Strong risk factors for developing liver cirrhosis and HCC are higher age, male, presence of HBeAg, HBV DNA levels > 10^4 copies/ml, HBsAg serum concentrations > 10^3 IU/ml, and alanine aminotransferase (ALT) > 45 IU/l [24, 25]. Progression to liver cirrhosis in children is under 5% until adulthood and data of the Asian region report 0.01–0.003% of individuals with chronic hepatitis B to be expected developing HCC in childhood [26, 27]. In general, anti-HBe seroconversion significantly reduces the risk of developing HCC. The time at which anti-HBe seroconversion occurs is important. A study in adults investigating the 15-year cumulative incidences of HBeAg-negative hepatitis demonstrated that cirrhosis and HCC increased with increasing age of HBeAg seroconversion [28]. The lowest risk was observed in patients with anti-HBe seroconversion under the age of 30 (cirrhosis 7%, HCC 2.1%) and highest in individuals older than 40 years (cirrhosis 42.9%, HCC 7.7%). The hazard ratio for HBeAg-negative hepatitis, cirrhosis, and HCC was 2.95, 17.6, and 5.22, respectively, in the older compared with the younger group. The authors conclude that patients with HBeAg seroconversion before age 30 have an excellent prognosis, whereas patients with delayed HBeAg seroconversion after age 40 have significantly higher incidences of HBeAg-negative hepatitis, cirrhosis, and HCC. An additional precondition is persistently normal ALT levels [29]. Since children have a high probability to experience anti-HBe seroconversion until adulthood, the overall risk of developing severe liver disease in later life seems limited. Nevertheless, there remain a considerable number of patients with immune tolerance or inflammatory activity that needs careful and professional monitoring.

Relevance of Genotypes and Mutants

During the replication cycle, HBV polymerase is acting as a reverse transcriptase without proof-reading function. Therefore, mutant viral genomes are regularly emerging in a considerable number particularly during the high replicative status. Peculiar requirements such as replication modalities, selection pressure, and changing immunological conditions may select variants and strongly influence the predominant HBV quasispecies in an infected individual. Generally, a change of the primarily determined genotype is possible during long-term course and ranges between 2.8 and 19% usually associated with anti-HBe seroconversion [26, 30]. It is not yet known, if there is any clinical impact at all. In adults, genotype C infection is rather than genotype B associated with a delayed anti-HBe seroconversion and a higher risk of developing HCC. Genotype D trends to proceed more severely and shows delayed anti-HBe seroconversion compared with genotype A. Precore and basic core promotor (BCP) mutants are frequently associated with HBeAg-negative hepatitis, and HBsAg escape mutants are now increasingly observed in association with primarily vaccinated children. The typical precore point mutant is the G1896A stop codon preventing the production of HBeAg. It emerges typically around the time of anti-HBe seroconversion and may be associated with a decreased risk of developing HCC compared with the wild type. But it can also be found in patients with HBeAg-negative hepatitis. Depending on European or Asian regions, precore mutants have been detected between 8 and 50% in HBeAg-negative children. The BCP mutants A1762T/G1764A prevail to be associated with an increased risk for HCC. But finally, the data remain controversial [7, 16, 31, 32].

Treatment

Since there is no definitely curative medical treatment available to date, it has to be defined what the aim of antiviral treatment should be in dependence on age group and phase of chronic hepatitis B. There is no doubt that one major goal is to reduce the risk of progressive liver disease and long-term sequelae such as liver cirrhosis, hepatic decompensation, and HCC and eventually to achieve the same life expectancy compared with healthy individuals of the same age. Unfortunately, anti-HBs seroconversion can only be reached in 5–10% at the most under current medical treatment strategies. Thus, the most important task in the treatment of children and adolescents is to achieve anti-HBe seroconversion at the earliest possible time associated with suppressed viral replication and decreased liver inflammation followed by persistent presence of anti-HBe, undetectable HBV DNA, and preferably aminotransferases values less than half of the upper limit of normal. Children with HBeAg-positive

hepatitis should be monitored every 6 months with physical examination, measurement of laboratory parameters such as aminotransferases, hepatitis B serology, alpha-fetoprotein, and ultrasound of the liver. After anti-HBe seroconversion follow-up visits can be performed for lifetime on an annual basis [15, 17, 33].

The decision to treat should be based on age, phase of HBV infection determined by ALT level, HBeAg/anti-HBe status, liver histology, coexisting diseases, and expectable compliance. The response rate in patients in the immune tolerant phase is very low. Thus, treatment of children with normal aminotransferases has not been recommended to date. At present, clinical trials in immune tolerant children combining a nucleoside analogue and peg-alpha-interferon are being performed. Treatment should be considered when aminotransferases rise and transition to the immune active phase is recognized. Children and adolescents who have persistently elevated ALT levels for more than 6 months should be offered treatment. Currently, seven treatment options are approved for hepatitis B in adults, including two formulations of conventional and pegylated interferon as an immunmodulatory therapy and five nucleos(t)ide analogues (lamivudine, adefovir dipivoxil, entecavir, telbivudine, and tenofovir disoproxil) with strong reduction of viral replication. Approval for children and adolescents depends on the region. Large trials have been performed in children for lamivudine, adefovir, entecavir, and tenofovir. Entecavir has been authorized from 6 years onwards, and Adefovir and tenofovir have been approved for subjects older than 12 years of age in the USA and Europe [34–36]. Predictors of response may be increased ALT levels, relatively low HBV DNA levels, and infection with genotype A or B. The main problem of all clinical trials with nucleos(t)ide analogues is the duration of medical treatment of not more than 96 weeks. Although a high proportion of treated patients will experience a significant decrease of viral load, the anti-HBe seroconversion rate cannot be expected to exceed 25%. After ceasing treatment, a reactivation of viral replication to baseline levels can be observed. A 24-week course of alpha interferon yields an approximately 10% higher anti-HBe seroconversion rate. Anti-HBs seroconversion rate is limited to single cases with nucleos(t)ide analogues and may range between 6 and 10% in patients with alpha interferon. There is no doubt that these results are dissatisfying with respect to our primary goal of anti-HBe seroconversion. Another interesting fact is that alpha interferon treatment only accelerates anti-HBe seroconversion in successfully treated individuals, but does not enhance the absolute number of responders [37]. Extending the treatment with nucleos(t)ide analogues for several years will result in an anti-HBe seroconversion rate of 40–50% [33]. However, there are no long-term data in children with regard to side effects. In the case of anti-HBe seroconversion, treatment should be maintained for 12 months, because the treatment-induced anti-HBe-positive status may be instable and reactivation may occur [38, 39].

In view of the present data and experience, there is a remarkable counseling conflict between the choice of drug and the duration of treatment, given that anti-HBe seroconversion remains the essential goal. Antiviral drug resistance is a major limitation to the long-term success of antiviral treatment. For this reason, lamivudine with a 5-year resistance rate of 70% has been considered obsolete just as adefovir which does often not sufficiently suppress viral replication. Nevertheless, at least for smaller children, lamivudine can be used as an approved drug for a limited time. Telbivudine has also a considerable resistance risk. Entecavir and tenofovir do not show significant resistances after years of treatment. Tenofovir may be associated with an increase in serum creatinine levels after 3–5 years of therapy. Decrease of bone mineral density has also been reported. Oral treatment with nucleos(t)ide analogues is quite comfortable but needs a real true commitment to the treatment, and alpha interferon may have sometimes restrictive side effects but with the advantage of a defined duration.

Thus, the decision which treatment option to choose is not that easy and has to be achieved in agreement with the patient and the parents. Alpha interferon is particularly appropriate for those children and adolescents who are reluctant to commit to a long duration of treatment and are not in the pubertal growth spurt. Nowadays, peg-alpha-interferon should be recommended for 48 weeks. Nucleos(t)ide analogues are most appropriate for patients with contraindications to interferon, after liver transplantation with an anti-HBc-positive donor or under immune suppressive treatment. It is most important that they are willing to commit to a treatment for several, probably 3–5 years, may be longer. Entecavir and tenofovir have the best profile in terms of safety, efficacy, and drug resistance. For younger patients, entecavir seems actually the preferable option.

Children and adolescents with a HBeAg-negative hepatitis should be treated with a nucleos(t)ide analogue if ALT levels are elevated and HBV DNA concentration is above 20,000 IU/ml to prevent progressive liver disease [40]. During long-term treatment with nucleos(t)ide analogues, HBV DNA, HBeAg/anti-HBe status, and aminotransferase levels should be monitored every 3 months. Very low or negative HBV DNA concentrations are important preconditions to avoid drug resistance.

Prevention

Vaccination is the most effective procedure in order to prevent infection with the HBV. Active and passive immunization is well established in newborns of HBsAg-positive mothers. The first injections have to be administered within 12–24 h after birth to achieve a seroprotective response in

90–95 % when two monthly follow-up active vaccinations are completed. Very low birth weight preterm infants should receive a total of four doses. HBeAg-positive mothers can be treated with a nucleoside analogue (lamivudine, telbivudine) during the last trimester of pregnancy to reduce the risk of vertical transmission.

In many countries, routine active HBV vaccination is implemented in the vaccination schedule of all infants. Post-vaccination testing for a protective anti-HBs concentration (> 100 IU/l) is not routinely recommended. If indicated, the best time would be approximately 2–3 months after the last vaccination. Revaccination is indicated in subjects with an anti-HBs titer < 10 IU/l. In the majority of nonresponders, three more vaccinations will induce protective response. According to present experiences, protective anti-HBs response will be maintained for more than 15 years [13, 39].

Chronic Hepatitis C

Introduction

Hepatitis C virus (HCV) infection is a frequent course of chronic liver disease, and approximately 150–200 million people are estimated to be chronically infected worldwide. Unfortunately, to date, no preventive vaccination could be developed. Despite of a normally benign course of the disease during childhood and adolescence, there is a considerable lifetime risk of progressive liver disease, liver cirrhosis, and the development of a HCC, which may eventually reduce life expectancy. Remarkable advances have been made in therapeutic approaches during the last 10 years, and considerable rates of cure have been yielded with the current standard of care. Nevertheless, careful long-term monitoring has to be performed, and appropriate improved treatment options have to be discussed, always considering that the development of novel treatment regimen is going fast and may continuously further improve the response rate [41].

Pathogenesis of Chronic Hepatitis C Infection

HCV is a positive-stranded RNA virus within the Flaviviridiae family. It forms its own genus Hepacivirus, and there are six main genotypes. The viral genome encodes nine proteins including its own RNA polymerase. Because of the high error rate of the virus-specific RNA polymerase, many variants may be produced. So-called quasispecies represent the high variability of the virus which allows a survival advantage to the virus. Replication of HCV starts with the binding to hepatocytes and entry which is a rather complex procedure. RNA is released into the cytoplasma and translated in the rough endoplasmatic reticulum. A 3000-amino-acid-long polypeptide arises and is then cleaved into ten different products. Membranous replication vesicles are induced, and HCV assembly is accomplished and released with the help of very low density lipoprotein (VLDL) synthesis. Chronic hepatitis C in children is associated with a variety of histological patterns, mostly considered as mild and slow progressive. Nevertheless, significant fibrosis or cirrhosis may occur, but is not expected to exceed 4 % until reaching adulthood. Need for liver transplantation is very rare as is the development of HCC [42]. Little information is available about the host responds to the virus. Cluster of differentiation 4 (CD4) + lymphocytes seem to be involved. Infants with the rs 12979860 CC genotype for the IL28B polymorphism trend to experience a higher spontaneous viral elimination [43–45].

Epidemiology

The prevalence of HCV infection in children in developed countries ranges between 0.1 and 0.4 %. For adults, prevalence rates are 0.4–3 % in North America and Western Europe and higher in Eastern Europe and Middle East. Egypt has the highest prevalence with 9 %, almost exclusively genotype 4 [41, 46, 47]. Central and East Asia and North Africa are estimated to have a prevalence between 3.6 and 3.8 % [48]. During the last 15 years, the predominant route of viral hepatitis C transmission has become vertical infection. Contamination through blood products is exceedingly rare in developed countries, but may remain an issue in developing countries. The rate of perinatal transmission from an HCV-RNA-positive mother ranges from 2 to 5 %. Out of this group, a considerable number of infants received the infection probably already in utero [49]. Concomitant HIV infection may increase the risk of HCV transmission. Breast feeding does not promote viral transmission and is allowed. The HCV prevalence in pregnant women from North America and Central Europe was reported between 0.16 and 0.53 %. Assumed a perinatal transmission rate of 2–4 %, 8–10 newborns in 100,000 births per year may be infected and become chronically infected during the first year of life. Viral clearance in vertically infected children seems to be dependent on the genotype and was reported to range from 2.4 to 25 %. In contrast, children infected with genotype 3 had a higher spontaneous clearance rate compared to individuals with genotype 1. Beyond the age of 5 years, spontaneous viral elimination becomes less likely [50, 51].

Diagnosis

Serologic testing for anti-HCV antibodies is the appropriate screening test for HCV. The next diagnostic step is the determination of quantitative HCV RNA and the genotype. The most prevalent genotype in pediatric trials performed in Western countries was genotype 1 (ca. 74 %) followed by

genotype 3 (ca. 14%) and 2 (ca. 9%). Genotype 4 had the lowest prevalence (ca. 3%) [52]. It is useful to perform an ultrasound examination including liver stiffness assessment for the baseline report. As chronic hepatitis C usually is a histologically mild disease with low inflammatory activity in childhood, liver biopsy is not mandatory. However, in subjects, who are suspicious of progressive liver disease or cirrhosis or if there is an impact on therapeutic decisions, liver biopsy may be a reasonable measure [41, 52].

Several studies have demonstrated that certain host polymorphisms (e.g., CC) located upstream of the IL28B (interferon lambda 3) gene are associated with a higher sustained viral response rate to combination treatment with peg-alpha-interferon and ribavirin. There is also an association with spontaneous clearance of HCV. To date, determination of IL28B polymorphisms is not routinely used, but might be of interest to identify the individual patients' likelihood of response particularly in future therapy options [41].

Natural History

Normally, HCV infection is asymptomatic. Histological findings are usually mild, and the risk of severe complications until the infected individuals are reaching adulthood is low. Not more than 5% of children and adolescents will have evidence of advanced liver fibrosis or cirrhosis. Liver transplantation units from the USA have reported on 133 transplanted children due to chronic hepatitis C during a time span of 13 years. In a lifetime, the risk of developing liver cirrhosis is about 20%, and the risk of HCC based on liver cirrhosis is estimated 2–5% [44]. These data are from adults, and there are no long-term follow-up studies in vertically infected patients. Natural history is also affected by other medical and social factors. Overweight children with liver steatosis are at greater risk for progressive liver disease. Risky behaviors and alcohol misuse worsen the long-term prognosis. Similar course and progression of hepatitis C were reported in former pediatric patients with successfully treated malignant disease after three decades of observation with about 20% spontaneous clearance and up to 5% liver cirrhosis. During the chronic course, ALT levels may be normal or intermittently elevated. Only few patients show persistent markedly elevated aminotransferases. Also the HCV RNA serum concentration may considerably fluctuate, but without immediate prognostic relevance. Spontaneous resolution beyond the preschool age is quite rare and may occur in up to 10% of adolescents [44, 47, 53]. Some extrahepatic manifestations may be associated with chronic hepatitis C such as glomerulonephritis and possibly cognitive deficits or developmental delay [54]. However, in adult patients, the clinical effects of reported symptoms such as fatigue, depression, or marginal poorer learning efficiency were rather limited [55]. In conclusion, early acquired chronic hepatitis C is a clinically and histologically silent and hidden condition. Nevertheless, it may become insidious. Although the rate developing liver cirrhosis until adulthood is low, activation beyond the second decade of life is likely. A large Danish study in adults revealed that in patients with chronic HCV infection, the 8-year risk of liver-related death was 5.5% compared with 2.0% in individuals who cleared the infection [56]. However, patients who have eventually proceeded to compensated liver cirrhosis have a dubious prognosis. In a follow-up study of cirrhotic patients over more than 10 years, HCC developed in 32% and the annual mortality rate was 4% [57]. Thus, the literal aim of therapeutic interventions in children and adolescents is not the treatment of an ongoing liver disease, but the prevention of a future one by early eradication of the infection.

Treatment

The primary goal of HCV therapy is to cure the infection which is reflected by persistently negative HCV RNA in serum and normalized aminotransferases. Sustained viral response (SVR) is defined as an undetectable HCV RNA level 24 weeks after cessation of treatment. The combination of pegylated alpha interferon with ribavirin and a protease inhibitor, either telaprevir or boceprevir for the treatment of genotype-1-infected patients for 48 weeks was the approved and established standard of care in adults. Non-genotype 1 patients are treated with peg-alpha-interferon in combination with ribavirin, for example, genotype 2 and 3 for 24 weeks. With these regimens, considerable sustained viral response rates can be achieved ranging from more than 65% for genotype 1 to over 80% for genotype 2 and 3 patients [58]. Two pegylated alpha-interferon molecules can be used, that is, alpha-interferon-2a and alpha-interferon-2b. The pharmacokinetics of these drugs differ, but there is currently no conclusive evidence that one peg-alpha-interferon should be preferred to the other one. Currently, approved interferon-free treatment options and more protease inhibitors such as sofosbuvir and ledipasvir are changing the treatment regimen.

Treatment management of children with chronic hepatitis C infection is formed by the attitude of the medical attendant regarding the need of therapeutic intervention with respect to a generally slow progressive disease. Thus, delay of treatment seems common with barely a quarter of patients being treated [51]. Adverse events during treatment are frequent, and due to age, adolescents may have a lack of compliance. On the other side, mostly treatment is better tolerated in younger patients, and in case of success, the benefit of socio-economic aspects is not to disregard. Under the aspect of health prevention for a long lifetime, all children with a measureable level of HCV RNA should be considered for treatment. Neither the level of aminotransferases nor of

HCV RNA predicts the long-term outcome of the disease. Also liver histology is not a helpful entry criterion for indicating treatment, because children generally do not have severe lesions. Nevertheless, new direct-acting antivirals (DAA) against the HCV have been developed, and interferon-free oral treatment regimen is an important goal for the next years. Toward this aim, several clinical trials combining only oral antiviral compounds have begun to show promising results in some subgroups. It will take a couple of years to have approved substances available for children. However, with the present knowledge, well-balanced counseling is particularly important for the individual patient and his parents when indicating treatment or advising deferral.

Experiences with the treatment of children with chronic hepatitis C started in the early 1990s. Nineteen studies using recombinant alpha interferon were published between 1992 and 2003. A meta-analysis of trials with alpha-interferon mono-therapy showed a wide range of viral response (0–76 %). Based on an increasing number of trials in adults, ribavirin was also added to alpha-interferon treatment trials for children. Between the years 2000 and 2005, six studies were published showing a sustained viral response rate from 27 to 64 % [52]. It became clear that genotype-2- and genotype-3-infected individuals responded much better. Alpha-interferon-2b in combination with ribavirin was then approved by the FDA. Interestingly, the only controlled randomized trial, comparing a pegylated alpha interferon (-2a) with and without ribavirin, was only published in 2011, definitely showing that the addition of ribavirin was necessary to obtain significantly better treatment results than without [52, 59]. Trials with peg-alpha-interferon and ribavirin followed in the next years and both peg-alpha-interferon-2b and peg-alpha-interferon-2a have been approved by FDA and EMA 2008/2009 and 2011/2012 in combination with ribavirin for children. Peg-alpha-interferon-2b can be used in children from 3 years and peg-alpha-interferon-2a from 5 years onwards. A meta-analysis with eight trials to examine the efficacy and safety of peg-alpha-interferon treatment in combination with ribavirin was recently published, confirming that combination therapy is effective and safe in this age group [60]. Most subjects who achieved an early viral response (70 %) also achieved a sustained viral response (58 %). Relapse rate was rare with only 7 %, as were discontinuations due to adverse events (4 %). Two trials stratified the results in genotype 1 patients according to the baseline viral load. In both studies, patients with a lower viral load before treatment (< 600,000 IU/ml and < 500,000 IU/ml, respectively) had a better sustained viral response rate (73 and 62 %) [61, 62]. Mode of infection and baseline levels of aminotransferases do not significantly correlate with the outcome. Representative trials with peg-alpha-interferon and ribavirin with more than 20 treated patients are summarized in Table 60.1 [59, 61–65].

Most adverse events are mild to moderate. Apart from flue like symptoms, which are very common, the most frequent side effects were in 32 % neutropenia and in 52 % leukopenia, whereas anemia and thrombocytopenia were documented in only 11 and 5 %, respectively. Injection site erythema, pruritus, alopecia, and growth inhibition, which was reversible in the majority of patients, were also observed. Severe psychiatric side effects were rare in prepubertal individuals. Up to 20 % of patients with 48-week treatment may have abnormal thyroid-stimulating hormone levels or other signs of thyroid dysfunction [52].

In summary, there is sufficient evidence to recommend antiviral therapy in chronic hepatitis C [66]. Peg-alpha-interferon and ribavirin therapies in treatment naïve children and adolescents yield a sustained viral response rate in approximately 50 % of adequately treated genotype-1-infected patients. Thus, this option can be offered to all interested individuals. In patients infected with genotype 2 or 3, treatment for 24 weeks should absolutely be performed because the response rate is more than 90 %. According to the approvals of the drugs, treatment start is possible beyond the age of 3 and 5 years, respectively. However, since spontaneous viral elimination in vertically infected subjects may occur within the first years until preschool age, watchful waiting is a justified alternative to an early treatment start. Additionally, various individual and family variables may influence the appropriate time to initiate treatment. Mid-childhood age before pubertal growth spurt is preferable. Re-therapy in previously treated genotype-1- and genotype-4-infected individuals produces sustained viral response in roughly one third, so deferral until availability of better treatment options seems reasonable [63].

In adults, triple therapy is still an approved current standard of care. However, oral interferon-free treatment regimens have been started. It could be expected that triple therapy would also increase the sustained viral response rate in children. Therefore, clinical trials in combination with boceprevir and telaprevir have been launched for children and adolescents. Most interestingly, the FDA stopped the boceprevir study for ethical reasons. One essential was the rapidly upcoming of numerous DAA with the perspective of interferon-free oral treatment options in the foreseeable future also for children [58]. For example, sofosbuvir is a new promising nucleotide analogue which has been tried with good results in combination with ribavirin in genotypes 2 and 3 infected and combined with peg-alpha-interferon in genotype-1-infected adults [67, 68]. The protease inhibitor faldaprevir was tested in combination with the polymerase inhibitor Deleobuvir as interferon-free regimen in genotype 1 patients [69]. This new way with a couple of upcoming further compounds will allow a shortened and more individual response-guided therapy. As of the beginning of the year 2015, a panel of new substances has been licensed

Table 60.1 Representative trials with peg-alpha-interferon and ribavirin in children and adolescents with chronic hepatitis C (wk: week)

	Wirth 2005[a] [64]	Jara 2008[a] [65]	Pawlowska 2010 [63]	Wirth 2010[a] [62]	Total PEG-IFN-a2b trials	Schwarz 2011[b] [59]	Sokal 2010[b] [61]	Total all trials
Dosage	1.5 µg/kg/wk	1.0 µg/kg/wk	1.0 µg/kg/wk	60 µg/m²/wk		180 µg/1.73 m²/wk	100 µg/m²	
Total	36/61 (59%)	15/30 (50%)	18/29 (62.1%)	70/107 (65.4%)	*139/227 (61.2%)*	29/55 (53%)	43/65 (66.1%)	*211/347 (60.8%)*
Genotype								
1	22/46 (48%)	12/26 (46%)	10/16 (62%)	38/72 (53%)	*82/160 (51.3%)*	21/45 (47%)	27/47 (59%)	*130/252 (51.6%)*
2/3	13/13 (100%)	3/3 (100%)		28/30 (93%)	*44/46 (96%)*	8/10 (80%)	16/17 (94%)	*68/73 (93%)*
4	1/2	0/1	8/11 (72%)	4/5 (80%)	*13/19 (68.4%)*		Included in G1	
ALT levels								
Elevated	12/25 (48%)			27/44 (61%)			19/33 (58%)	*58/102 (57%)*
Normal	24/36 (67%)			42/63 (67%)			24/30 (80%)	*90/129 (70%)*
Mode of infection								
Parenteral	19/27 (70%)	7/9 (78%)		5/5 (100%)	*31/41 (76%)*			
Genotype 1	13/21 (62%)		10/16 (62%)	1/1				
Vertical	12/25 (48%)	8/21 (38%)		46/75 (61%)	*66/121 (55%)*			
Genotype 1	7/20 (35%)			26/52 (50%)	*33/72 (46%)*			
Break through	9.8%		6 (20%)			6/41 (15%)		
Relapse	7.7%		1 (3.4%)	8%		6/35 (17%)		

PEG-IFN-a2b pegylated interferon alpha-2b, ALT alanine aminotransferase

for adults: sofosbuvir, simeprevir, daclatasvir, ledispavir in combination with sofosbuvir and the combination of paritaprevir, ritonavir, ombitasvir, dasabuvir, and ribavirin. Thus, it is clearly conceivable that the current adult triple therapy will never routinely be used in children even with a pediatric approval, because the rapid development of new treatment options significantly accelerates the timeline. DAA trial in children have now been started. Therefore, we have to consider well balanced, if it would be better for the individual patient, to wait some time until oral treatment options for children, particularly infected with genotype 1, are available. Another issue is the question, if we actually have enough patients to perform appropriate trials for approval for the best drug combination. Thus, experts should carefully discuss, if waivers for pediatric investigation plans for some substances would be useful, when it becomes foreseeable that advanced concepts will get ahead of previous one.

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