HEPATOLOGY

A clinical textbook

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7. Prophylaxis and vaccination against viral hepatitis

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Abstract

Despite vaccines or effective anti-viral treatment strategies, hepatotropic viruses are still a global problem. In order to prevent fulminant liver failure or chronic liver disease leading to liver cirrhosis and hepatocellular carcinoma, the prophylaxis and vaccination against hepatotropic viruses is fundamental. Effective vaccines against the hepatitis A and B virus are available world-wide. The hepatitis B virus vaccine was the first one being able to prevent cancer development. Nevertheless, chronic hepatitis B virus infections are still a world-wide burden and functional cure can only be achieved in a minority of chronically infected patients. Thus, further research is a necessity to overcome the viral and immunology challenges to improve our treatment strategies. Due to extremely effective direct-antiviral therapy, the hepatitis C virus can be cured in the majority of the patients. Unfortunately, the vaccine development is hampered by the genetic diversity of the virus, escape mutations and the complex immune responses towards the infection. Knowledge about hepatitis E virus is evolving fast. A vaccine is available in some countries. Fulminant liver failure and chronic course of infection in immune-compromised patients are the main challenges. Thus, collectively, prevention of infection with hepatotropic viruses persist as the best option to prevent liver diseases.

Introduction

Understanding of the biology and modes of transmission of hepatitis viruses has significantly improved over the last decades. Even so, prophylactic vaccines are only available for hepatics A (HAV) and B (HBV). Although an enormous amount of basic and clinical research has been performed in trying to develop a vaccine against hepatitis C (HCV), it is unlikely that either a prophylactic or therapeutic HCV vaccine will be available soon. A phase 3 vaccine trial against hepatitis E (HEV) in China resulted in the vaccine being licensed there; it is currently unknown whether or when this vaccine will become available broadly across the globe. Prophylaxis of HCV, HDV (for patients) and HEV infection therefore

involves avoiding the routes of exposure to the respective hepatitis viruses discussed in detail in *Chapters 1–4*.

Prophylaxis of infections with hepatitis viruses

Hepatitis A and E

HAV and HEV are usually transmitted by oral ingestion of contaminated food or water. Acute HEV infection is often asymptomatic in immunocompetent individuals. Nevertheless, some people can develop fulminant liver failure and the risk factors are not yet fully understood. Immune compromised people for example after organ transplantation can progress to chronic HEV infection leading to advanced liver fibrosis (EASL 2018). Thus, caution is warranted when individuals from low endemic areas such as Western Europe and the US travel to countries with a high prevalence of HAV and HEV. Several outbreaks of HEV infection have occurred in different regions of the world and were associated with significant morbidity and mortality, e.g., the recent outbreaks of HEV in refugee camps in Africa.

In addition, HEV (but not HAV) can also be a zoonosis. Consumption of offal and wild boar is associated with a risk for HEV infection. HEV has frequently been detected in the pork and occupational exposure has frequently been identified as a risk factor for being anti-HEV positive (Pischke 2014). Importantly, zoonotic HEV is usually caused by HEV genotype 3 while HEV genotype 1 can be found in travel associated HEV (Wedemeyer 2012, Kamar 2017). *In vitro* experiments have shown that HEV is heat sensitive (> 70°C; > 2 min), but it remains unclear whether heat can be used to sterilise food preparation (Johne 2016). The avoidance of the consumption of certain food is the best prevention strategy especially for people who are immune compromised or at risk for a fulminant acute infection to prevent HEV infection (EASL 2018).

HAV (Hettman 2016) and HEV can also be transmitted by blood transfusion as confirmed in a large study from England screening more than 200.000 blood products (Hewitt 2014). Of note, up to 12% of pooled plasma products can contain HEV RNA in Europe. The overall relevance of HEV transmission by blood products is discussed in more detail in Chapter 4. Distinct genetic polymorphisms may be associated with the risk of becoming infected with HAV (Zhang 2012) and HEV (Wedemeyer 2012). To prevent HEV infection and the complications of chronic liver disease of a very vulnerable cohort, a policy statement of the EASL of 2019 recommends a selective screening of blood products for HEV RNA for immune compromise patients e.g. patients who received an organ transplantation.

However, even if HEV RNA screening is performed by HEV RNA testing, this is usually performed in pooled samples resulting in a remaining risk for HEV transmission if high volume plasma products are transfused (Cordes 2022). Thus, the risk of transfusion-transmitted hepatitis E in these patients may not be sufficiently controlled by mini-pool HEV RNA screening. Single donor screening should therefore be considered to improve the safety of blood products.

Sexual transmission of HEV is poorly studied. Some studies highlight a sexual transmission in men who have sex with men (Montella 1994, Payne 2013). HEV can be detected in ejaculate of chronically infected men (Horvatits 2021). The use of condoms could be an effective strategy to prevent infection (EASL 2019).

HEV is excreted in the stool and thereby extremely infectious. In many patients, HEV is also detectable in urine (Stahl 2023). Though, the relevance on the transmission is not fully understood yet (Geng 2016).

Hepatitis B and D

HBV and HDV were frequently transmitted by blood transfusion before HBsAg testing of blood products was introduced in the 1970s. Since then, vertical transmission and sexual exposure have become the most frequent routes of HBV infection. Medical procedures still represent a potential source for HBV and thus strict and careful application of standard hygienic precautions for all medical interventions are mandatory, and not only in endemic areas.

Immune compromised individuals are particularly susceptible to HBV infection as HBV is characterised by very high infectivity. Moreover, immunosuppressed patients are at risk for reactivation of occult HBV after serological recovery from HBV. Treatments with high doses of steroids and rituximab have especially been identified as major risk factors for HBV reactivation. The FDA and all scientific associations highlight attention to the potential risk for fatal HBV reactivations in patients receiving B cell depleting therapies (EASL 2017). However, also other immunosuppressive drugs may lead to increased HBV replication. Thus, immune compromised individuals would benefit most from effective HBV prevention. All patients receiving immune modulating agents should be screened for HBsAg and anti-HBc. The need for pre-emptive antiviral differs according to the HBV serostatus (anti-HBs positive or negative, HBsAg positive or negative) and the level of immunomodulation induced by the respective drug (Perillo 2015). The reactivation in HBsAg positive patients differs depending on the therapy and it is up to 75% after bone marrow transplantation. Among the complications of HBV reactivation, fulminant courses with liver failure and

death are the most severe (Cornberg 2021).

To prevent infection after a positive test of a family member or sexual partner, the patients need to be tested for their immune status against HBV. Immediate active vaccination is recommended for contacts who are anti-HBc negative. HBsAg positive individuals should use condoms during sexual intercourse if it is not known whether the partner has been vaccinated. Non-immune individuals who have experienced an injury and were exposed to HBsAg positive fluids should undergo passive immunisation with anti-HBs as soon as possible, preferentially within 2–12 hours (Cornberg 2021).

Infant HBV infections develop to a chronic stage in 90% of the cases. Thus, it is tremendously important to prevent perinatal infection and HBV infection during early childhood. To prevent vertical infection during pregnancy, an HBV screening should be performed in the first trimester. Women with high HBV viraemia of 200.000 IU/mL or more, should receive antiviral therapy with a potent HBV polymerase inhibitor during their pregnancy (EASL 2017, Pan 2025, Li 2018). Randomised trials showed that both tenofovir (Pan 2016) and telbivudine (Han 2011, Wu 2015) can reduce the risk for vertical HBV transmission when antiviral treatment is started during the third trimester of pregnancy. Tenofovir and telbivudine have been classified as category B drugs by the FDA and can therefore be given during pregnancy. HBV positive pregnant women should continue their anti-viral medication, but it might be necessary to exchange the medication to tenofovir or telbivudine (EASL 2017). A caesarean section is not recommended for women with low viral load or under anti-viral therapy but could be beneficial to prevent transmission if the viral load exceeds 200 000 IU/mL (Cornberg 2021, Pan 2013). Recent guidelines also recommend that breat-feeding can be continued if antiviral therapy is administered (EASL 2025, in press).

Hepatitis C

An important factor in preventing HCV infection is screening the population to prevent further transmission. HCV infection can be asymptomatic for a long period of time so that many people are not aware of their infection. Screening should be performed regarding local epidemiology and risk factors of the individuals (Cooke 2019, EASL guidelines 2020). The treatment of HCV positive patients is one important strategy to prevent onward infection ("treatment as prevention"), this is particularly important for individuals with risk factors of infection (EASL 2020). Several studies confirmed the efficacy and safety of direct acting antivirals also in patients with acute ore recent HCV infection (Deterding 2017, Cornberg 2025).

Less than 1% of individuals who are exposed to HCV by an injury with contaminated needles develop an acute HCV infection. For example, in the early 2000s 166 occupational HCV exposures have been reported over a period of 6 years at Hannover Medical School and for none of the cases a seroconversion has been observed during a 6 year follow-up. A systematic literature review identified 22 studies including a total of 6956 injuries with HCV contaminated needles. Only 52 individuals (0.75%) became infected. The risk of acute HCV was lower in Europe at 0.42% compared to eastern Asia at 1.5% (Kubitschke 2007). Thus, the risk of acquiring HCV infection after a needle-stick injury is lower than frequently reported. Global differences in HCV seroconversion rates may suggest that genetic factors provide some level of natural protection. Indeed, distinct polymorphisms have been identified that are associated either with protection from HCV or with a higher likelihood of recovering spontaneously from acute HCV (Schaefer 2011). Factors associated with a higher risk of HCV transmission are likely to be HCV viraemia in the index patient, the amount of transmitted fluid and the duration between contamination of the respective needle and injury. Suggested follow-up procedures after needle stick episode include:

- Testing for HCV RNA immediately and an ALT testing.
- If possible, HCV RNA quantification in the serum of index patient.
- There is no need for prophylactic treatment with IFN and ribavirin or direct acting antivirals.
- HCV RNA testing should be performed after 2 and 4 weeks; if the results are negative, HCV RNA testing should be repeated at weeks 6 and 8.
- After 12 and 24 weeks, anti-HCV and ALT levels should be determined; if the results are out of range or positive, HCV RNA testing should be performed.

On the other hand, individuals who consume intravenous drugs have a high risk of HCV infection if they share their equipment e.g. syringes, needles etc. (Simmons 2016, Hahn 2002). Long term strategies should be implemented to avoid HCV transmission by reducing frequency of injections, using new sterile needles (e.g. in needle syringe service programmes), avoiding re-use of materials, disposing materials safely, opioid substitution programmes, medical support and counseling of possible re-infection (Tsui 2014, Hagan 2011, Platt 2017, Grady 2013).

Sexual transmission has clearly been identified as a risk for HCV, as about 10–20% of patients with acute HCV report this as having been a potential risk factor (Deterding 2009). However, there is also evidence that the risk of acquiring HCV sexually is extremely low in individuals in stable partnerships who avoid injuries: Cohort studies including more than 500 HCV positive patients followed over periods of more than four years could not identify any cases of confirmed HCV transmission. The risk for HCV

transmission has recently been estimated to be about 1 per 190,000 sexual contacts in monogamous relationships (Terrault 2013). Having multiple sexual partners increases the risk of HCV infection (Tohme 2010). There was no association between specific sexual practices and HCV infection in monogamous heterosexual couples. Thus, current guidelines do not recommend the use of condoms in monogamous heterosexual relationships (EASL 2020). Risk of sexual transmission of HCV is increased in men who have sex with men. Several outbreaks of acute HCV have been described in this population (Boesecke 2012, Bradshaw 2013). Transmission of HCV was associated with more sexual partners, increased levels of high-risk sexual behavior (in particular fisting) and were more likely to have shared drugs via a nasal or anal route than controls (Newson 2020). The CDC recommends certain prevention strategies (CDC 1998). In long-term monogamous relationship regular testing should be performed but the sexual behavior does not need to be altered. In other settings use of latex condoms plus reduction of injuries and bleeding is highly effective to avoid HCV transmission. Besides to "treatment as prevention", education to increase the awareness of risk factors is extremely important.

Due to the low HCV prevalence in most European countries and a relatively low vertical transmission rate of 1–6%, general screening of pregnant women for anti-HCV is not recommended. The German guidelines only recommend screening for individuals with a high risk of HCV infection. The U.S. Preventive Services Task Force and CDC recommends universal HCV screening of all adults, including all pregnant women (CDC 2018). Interestingly, vertical transmission may be higher for girls than for boys (European Paediatric Hepatitis C Virus Network 2005). Transmission rates are higher in HIV positive women, so these women should be tested for HCV. Other factors possibly associated with high transmission rates are the level of HCV viraemia, maternal intravenous drug use, and the specific HLA types of the children. Immunoregulatory changes during pregnancy reduce the pressure by cytotoxic T cells which may select viruses with optimised replication fitness and thereby facilitate vertical transmission (Honegger 2013, Coss 2020). Cesarean sections are not recommended for HCV RNA positive mothers as there is no clear evidence that these reduce transmission rates. It is not clear yet whether direct-acting antivirals (DAAs) against HCV can reduce transmission rates of HCV when given during the last trimester of pregnancy. HCV therapy should be considered in all HCV positive women who want to become pregnant (EASL 2020). Children of HCV positive mothers should be tested for HCV RNA after one month as maternal anti-HCV antibodies can be detected for several months after birth. Mothers with chronic HCV can breastfeed their children if they are HIV negative, do not have any breast injuries and do not use intravenous drugs (European Paediatric Hepatitis C Virus Network 2001, EASL 2020). This clinical recommendation is supported by experimental data showing inactivation of HCV by human breast milk in a dose dependent manner. Of note this effect is specific to human breast milk and the mechanism is destruction of the lipid envelope but not of viral RNA or capsids (Pfaender 2013).

Vaccination against HAV

The first active HAV vaccine was licensed in 1995 and currently there are multiple inactivated and live-attenuated vaccines available (Martin 2006).

The currently available inactive vaccines are manufactured from cell culture adapted HAV, grown either in human fibroblasts or diploid cells (Nothdurft 2008). Two doses of the vaccine are recommended. The second dose should be given between 6 and 18 months after the first dose. All vaccines are highly immunogenic and all vaccinated healthy persons develop protective anti-HAV antibodies. Similar vaccine responses are obtained in both children and adults and no relevant regional differences in response to HAV vaccination have been observed. The weakest vaccine responses have been described for young children receiving a 0, 1 and 2 month schedule (Hammitt 2008). Of note, maternal anti-HAV positive children vaccinated at age 6 months have lower vaccine responses and are less likely to maintain HAV antibodies through age 10 years (Spradling 2016). Patients with chronic liver disease do respond to vaccination but may display lower anti-HAV titres (Keeffe 1998). HAV vaccination in HIV positive people is more effective if HIV replication is already suppressed by antiretroviral therapy and patients have higher CD4+ T-cell counts (Tseng 2013).

A combined vaccine against HAV and HBV is available that needs to be administered three times, on a 0, 1, and 6 months schedule. More than 80% of healthy individuals have detectable HAV antibodies by day 21 applying an accelerated vaccine schedule of 0, 7 and 21 days using the combined HAV/HBV vaccine, and all study subjects were immune against HAV by 2 months (Kallinowski 2003). HAV vaccines are very well tolerated, and no serious adverse events have been linked with the administration of HAV vaccines (Nothdurft 2008). The vaccine can safely be given together with other vaccines or immunoglobulins without compromising the development of protective antibodies. Vaccination is recommended for non-immune individuals who plan to travel to endemic countries, medical health professionals, men who have sex with men, people in contact with patients with HAV, and individuals with chronic liver diseases. Some studies have suggested that patients with chronic HCV have a higher risk of developing fulminant HAV (Vento 1998), although this finding has not been confirmed by other investigators (Deterding 2006). The recommendation to vaccinate all patients with HCV against HAV has recently been challenged. A meta-analysis including

studies on mortality from HAV in people with HCV revealed a number-needed-to-vaccinate to prevent one death of more than 800,000 (Rowe 2012), thus questioning the use of routine HAV vaccination in HCV positive people. The implementation of childhood vaccination programmes has led to significant and impressive declines of HAV infections in several countries, justifying further efforts aiming at controlling the spread of HAV in endemic countries (Hendrickx 2008). It is important to highlight that most studies have confirmed that HAV vaccination is cost-effective (Rein 2008, Hollinger 2007). Several long-term follow-up studies after complete HAV vaccinations have been published in recent years (Stuurman 2016). Anti-HAV titres usually decline during the first year after vaccination but remain detectable in almost all individuals for at least 10–15 years after vaccination (Van Herck 2011) which also has been confirmed by systematic reviews (Ott 2012). Based on these studies it was estimated that protective anti-HAV antibodies should persist for ≥30 years after successful vaccination (Hammitt 2008, Bovier 2010, Spradling 2016).

A single dose administration of an inactivated HAV vaccine can induce protective antibody levels which can persist for more than 10 years (Ott 2012). Argentina, Brazil and Russia, as countries with a high incidence of hepatitis A infection in children causing liver failure and being the leading cause of liver transplantation, implemented a single dose vaccine programme. In these countries a single dose vaccine seems to be an effective method to reduce liver failure, but effectiveness of this approach needs to be closely monitored which would be cost saving and increase overall vaccine coverage (Brito 2020, Mikhailov 2020, Vizzotti 2014).

Live-attenuated hepatitis A vaccines are approved in China, India and a few other countries (Fangcheng 2012). Studies showing the efficacy and longevity of these vaccines were only performed in China and demonstrated a 93% effectiveness to prevent HAV infection and IgG antibodies in 72-88 % of the participants 15 years after the single dose vaccine (Irving 2012, Zhao 2000).

Vaccination against HBV

The HBV vaccine was the first vaccine able to reduce the incidence of cancer. In Taiwan, a significant decline in cases of childhood hepatocellular carcinoma (HCC) has been observed since the implementation of programmes to vaccinate all infants against HBV (Chang 1997). This landmark study impressively highlighted the usefulness of universal vaccination against HBV in endemic countries. The findings were confirmed in various additional studies and a reduced incidence of HCC not only in infants but also in young adults has been shown in a 30 year follow-up of a randomised neonatal vaccination study (Qu 2014). Controversial discussions are ongoing regarding to what extent universal vaccination against HBV may be cost-effective in low-endemic places such as the UK, the Netherlands or Scandinavia (Zuckerman 2007). In 1992 the World Health Organization recommended general vaccination against HBV. It should be possible to eradicate HBV by worldwide implementation of this recommendation, because humans are the only epidemiologically relevant host for HBV. The first plasma-derived HBV vaccine was approved by FDA in 1981. Recombinant vaccines consisting of HBsAg produced in yeast became available in 1986. In the US, two recombinant vaccines have been licensed (Recombivax and Engerix-B) while additional vaccines are used in other countries. The vaccines are administered three times, on a 0, 1, and 6 month timetable. The third-generation vaccines Heplisav-B and PreHevbrio/PreHevbri have been approved by FDA and EMA and show higher vaccine efficacy, especially in subgroups that respond sub-optimally to conventional hepatitis B vaccines.

Who should be vaccinated? This list is based on the German Guidelines for Hepatitis B and can be considered as a recommendation for most countries (Cornberg 2021).

- HBV high-risk persons working in health care settings including trainees, students, cleaning personnel;
- Personnel in psychiatric facilities or comparable welfare institutions for cerebrally damaged or disturbed patients; other people who are at risk because of blood contact with people who are possibly infected depending on the risk evaluation, e.g., persons giving first aid professionally or voluntarily, employees of ambulance services, police officers, social workers, and prison staff who have contact with drug addicts;
- People with chronic kidney disease, dialysis patients, patients with frequent blood or blood component transfusions (e.g., haemophiliacs), patients prior to extensive surgery (e.g., before operations using heart-lung machine. The urgency of the operation and the patient's wish for vaccination protection are of primary importance);
- People with chronic liver disease including chronic diseases with liver involvement as well as HIV positive people without HBV markers;
- People at risk of contact with HBsAg carriers in the family or shared housing, sexual partners of HBsAg carriers;
- Patients in psychiatric facilities or residents of comparable welfare institutions for cerebrally damaged or disturbed persons as well as persons in sheltered workshops;
- Special high-risk groups, e.g., men who have sex with men, people who inject drugs (PWID), sex workers, prisoners serving extended sentences;

- People at risk of being in contact with HBsAg carriers in facilities (kindergarten, children's homes, nursing homes, school classes, day care groups);
- People travelling to regions with high HBV prevalence for an extended period of time or with expected close contact with the local population;
- People who have been injured by possibly contaminated items, e.g., needle puncture (see post-exposition prophylaxis);
- Infants of HBsAg positive mothers or of mothers with unknown HBsAg status (independent of weight at birth) (see post-exposition prophylaxis);
- Routine testing for previous contact with HBV is not necessary before vaccination unless the person belongs to a risk group and may have acquired immunity against HBV before. Pre-vaccine testing is usually not cost-effective in populations with an anti-HBc prevalence below 20%. Vaccination of HBsAg positive individuals can be performed without any danger – however, it is ineffective.

Efficacy of vaccination against HBV

A response to HBV vaccination is determined by the development of anti-HBs antibodies, detectable in 90–95% of individuals one month after a complete vaccination schedule (Coates 2001). Responses are lower in elderly people and much weaker in immunocompromised persons such as organ transplant recipients, patients receiving haemodialysis and HIV positive individuals who have low CD4 counts. In case of vaccine nonresponse, another three courses of vaccine should be administered, and the dose of the vaccine should be increased. Other possibilities to increase the immunogenicity of HBV vaccines include intradermal application and co-administration of adjuvants and cytokines (Cornberg 2021). The response to vaccination should be monitored in high-risk individuals such as medical health professionals and immunocompromised persons. Some guidelines also recommend testing elderly persons after vaccinations as vaccine response does decline more rapidly in the elderly (Wolters 2003).

Post-exposure prophylaxis

People who are not immune who have been in contact with HBV contaminated materials (e.g., needles) or who have had recent sex with an HBV positive person should undergo active-passive immunisation (active immunisation plus HBV immunoglobulin) as soon as possible – preferentially within the first 48 hours of exposure to HBV. Individuals previously vaccinated but who have an anti-HBs titre of <10 IU/L should also be vaccinated both active and passive. No action is required if an anti-HBs titre of 100 IU/L is documented; active vaccination alone is sufficient for persons with intermediate anti-HBs titres between 10 and 100 IU/L (Cornberg 2021).

Safety of HBV vaccines

Several hundred million individuals have been vaccinated against HBV. The vaccine is very well tolerated. Injection site reactions in the first 1 to 3 days and mild general reactions are common, although they are usually not long lasting. Whether there is a causal relationship between the vaccination and the seldom observed neurological disorders occurring around the time of vaccination is not clear. In the majority of these case reports the concomitant events most likely occurred coincidentally and are independent and not causally related. That HBV vaccination causes and induces acute episodes of multiple sclerosis or other demyelinating diseases have been repeatedly discussed 10 to 15 years ago (Geier 2001, Hernan 2004, Girard 2005). However, there is no scientific proof of such a relationship. Numerous studies have not been able to find a causal relationship between the postulated disease and the vaccination (Sadovnick 2000, Monteyne 2000, Ascherio 2001, Confavreux 2001, Schattner 2005).

Long-term immunogenicity of HBV vaccination

Numerous studies have been published in recent years investigating the long-term efficacy of HBV vaccination. After 10 to 30 years, between one third and two thirds of vaccinated individuals have completely lost antiHBs antibodies and only a minority maintain titres of >100 IU/L. However, in low/intermediate endemic countries such as Italy, this loss in protective humoral immunity did not lead to many cases of acute or even chronic HBV infection (Zanetti 2005). To what extent memory T cell responses contribute to a relative protection against HBV in the absence of anti-HBs remains to be determined. Nevertheless, in high-endemic countries such as Gambia, a significant proportion of vaccinated infants still seroconvert to antiHBc indicating active HBV infection (18%) and some children even develop chronic HBV (van der Sande 2007). A very high efficacy of a single booster vaccine after 15 to 30 years has been shown in several studies (e.g. Su 2013, Bruce 2016) suggesting that immune memory is maintained in the majority of initial vaccine responders. However, protective titres are frequently lost

again a few years after booster vaccination. Overall, these data indicate that no regular HBV booster doses are recommended in vaccine responders. Still, booster vaccinations should be considered in persons at risk including medical health professionals.

Prevention of vertical HBV transmission

Infants of HBsAg positive mothers should receive an active and passive immunisation within 12 hours of birth. Thereby, vertical HBV transmission rate can be reduced from 95% to 5% (Ranger-Rogez 2004). If active/passive immunisation can be performed, there is no need to recommend cesarean section (Wong 2014). Mothers of vaccinated infants can breastfeed even if antiviral medications against HBV are being taken by the mother (EASL 2025 HBV Clinical Practice Guidelines).

New HBV vaccines

Although available vaccines are already very effective, new vaccine strategies have been shown to improve the vaccine response of elderly people or individuals with a low antibody reaction towards the available mono-antigenic vaccines. A detailed summary of currently available and recently approved vaccines against HBV is given in the current version of the EASL HBV Clinical Practice Guidelines (EASL 2025, in press).

Vaccination against HCV

Despite the vastly improved anti-viral treatment strategies against HCV, there are no prophylactic or therapeutic vaccines against HCV available at the moment. HCV elimination will be very unlikely with HCV treatments alone (Razavi 2025) – thus an effective and safe HCV vaccination is highly warranted to prevent HCV spreading in high-risk groups.

Vaccine development is hampered by the genetic diversity of the virus, escape mutations and the complex immune responses towards the infection. The host-virus interaction including cellular and humoral immunity determines the outcome of infection. HCV leads to a chronic course of infection in the majority of individuals, although 25-40% of infected individuals can clear the infection spontaneously (Mosley 2008). Spontaneous viral clearance is much higher after re-infection with HCV (Sacks-Davis 2013). HCV specific T cell responses play an important role in the natural course of HCV infection. The adaptive T cell response is mediated by both CD4+ helper T cells and CD8+ killer T cells. As CD8+ T cells have effector functions and destroy the target cells, CD4+ T cells are important to establish a long-lasting T cell memory pool and contribute to the longevity of the humoral immune response (Laidlaw 2016, Zhang 2019). Several studies have consistently found an association between a strong, multispecific and maintained HCV specific CD4+ and CD8+ T cell response and the resolution of acute HCV infection (Rehermann 2013). While CD4+ T cells seem to be present for several years after recovery, there is conflicting data whether HCV specific CD8+ T cell responses persist or decline over time (Wiegand 2007). Studies in chimpanzees have demonstrated that CD4+ and CD8+ specific T cells are mandatory for spontaneous viral clearance, as the absence of one of the subpopulations lead to persistent infection (Grakoui 2003, Shoukry 2003).

However, several studies have observed durable HCV specific T cells in HCV negative individuals who were exposed to HCV by occupational exposure or as household members of HCV positive partners, but who never became HCV RNA positive. A 10-year longitudinal study involving 72 healthcare workers demonstrated that about half of the individuals developed HCV specific T cell responses, detectable most frequently four weeks after exposure (Heller 2013). These observations suggest that HCV specific T cells may be induced upon subclinical exposure and may contribute to protection against clinically apparent HCV infection. However, it could be possible that repeated subinfectious exposure to HCV may not protect from HCV but rather increase susceptibility by expansion of regulatory T cells which suppress effector T cell responses in case of an infection (Park 2013). Virus specific T cells are usually detected at a lower frequency during chronic HCV infection and have an impaired functionality in comparison virus specific T cells during acute HCV infection. Different mechanisms contribute to the impaired T cell effector function, including higher frequencies of regulatory T cells, altered dendritic cell activity, upregulation of inhibitory molecules such as PD-1, CTLA-4 or 2B4 on T cells and escape mutations. In addition, HCV peptides can directly or indirectly contribute to altered functions of different immune cells (Rehermann 2013, Owusu Sekyere 2015).

The contribution of the humoral immune response to spontaneous clearance of HCV infection has not yet been clearly clarified. Higher levels of neutralising antibodies early during the infection are associated with viral clearance (Pestka 2007). These early neutralising antibodies detect a narrow epitope variety against the original virus without covering escape mutations (Walker 2019, Gu 2018). Broadly neutralisation antibodies develop with a delay in chronic HCV infection which might contribute to ineffective or delayed viral clearance (Dowd 2009, Law 2008). Although, cross-reactive neutralising antibodies are detectable in chronic infection they are not potent to clear the virus but are associated with less severe

liver fibrosis (Swann 2016). The understanding of development of broadly neutralising antibodies against HCV has improved in recent years e.g. by studying antibodies from HCV elite neutralisers (Weber 2022). This opens the idea of creating *de novo* highly potent neutralising antibodies which may also be generated *in vivo* as an alternative vaccination strategy.

A large HCV vaccine trial based on recombinant viruses expressing HCV proteins has been conducted in 548 individuals at risk for HCV infection with the aim to prevent chronicity of HDV infection by induction of HCV-specific T cell responses (Page 2021). This trial was negative regarding the primary endpoint, which was defined as HCV viraemia for 6 months. Still, peak viraemia was significantly lower in vaccinated individuals in whom HCV-specific T cell responses were detected in more than three quarter of vaccinated persons. Future vaccine development against HCV may be accelerated with controllend human infection models which are currently being explored in different settings (Liang 2021, Barnes 2023, Feld 2023).

Vaccination against HEV

A phase 2 vaccine trial performed in Nepal with 2000 soldiers showed a 95% efficacy for an HEV recombinant protein (Shrestha 2007). However, the development of this vaccine was stopped. In September 2010, data from a very large phase 3 trial were reported involving about 110,000 individuals in China (Zhu 2010). The vaccine efficacy of HEV-239 was 100% after three doses to prevent cases of symptomatic acute HEV. Further observation confirmed the ability of the vaccine to prevent clinical hepatitis. However, the induction of HEV antibodies does not induce sterilising immunity and thus does not completely protect from HEV infection. Still, vaccination largely reduces infection rates with a RR of 0.15 during further follow-up of the Chinese vaccine trial (Huang 2014). Similarly, naturally acquired immunity against HEV does not provide complete protection (Huang 2014). A 10 year follow-up of the phase 3 vaccine study was published in 2024 confirming long-lasting protection from symptomatic hepatitis E infections (Huang 2024). It remains to be formally determined if the HEV genotype 1-derived vaccine also prevents against zoonotic HEV genotype 3, while the vaccine was effective in China against HEV genotype 4. HEV-specific T cell immunity has been shown to be cross-HEV genotype-specific in patients with acute HEV (Gisa 2016). One can therefore assume that the vaccine should induce pan-genotypic immunity. Still, preclinical studies in pig models with other vaccine candidates suggested that cross-genotype induced complete protection from infection may be difficult to achieve (Dähnert 2024). Moreover, vaccine efficacy in special risk groups such patients with end-stage liver disease, immunocompromised individuals or elderly persons are unknown. Finally, the duration of protection needs to be determined as antibody titres have been shown to decline after vaccination (Shrestha 2007, Zhu 2010). To what extent cellular immunity against HEV is important in the context of HEV vaccination is also unknown but HEV specific T cell response has been associated with the control of chronic (Suneetha 2012) and acute (Gisa 2016, Brown 2016) HEV infection. It is currently unknown if and when the vaccine HEV-239 will become available in other countries. Until then, preventive hygienic measures remain the only option to avoid HEV infection. There are currently many efforts from the Word Health Organization to reach the “emergency prequalification” for the vaccine in order to prevent outbreaks in high-risk areas such as refugees camps.

Recently, broadly neutralising antibodies have been identified conferring protection against HEV infection *in vitro* against different HEV genotypes and also against enveloped virions. The antibodies also prevented durable HEV infection in a chimeric mouse model. The clinical development of these antibodies could be an option both to treat chronic HEV infection as well as a strategy to protect individuals at risk for acute severe infection by passive immunisation (Ssebyatika 2025). HEV-induce acute-on-chronic liver failure is an emerging threat considering the increasing prevalence of liver cirrhosis due to metabolic dysfunction-associated steatotic liver disease in regions with very frequent HEV exposures.

Outlook

Hepatitis A virus: Effective vaccine strategies are available. Though, current vaccines require a three-dose regimen which is rather unpractical in most parts of the world with highest incidences. Current efforts are on the way to investigate the efficiency and the longevity of a one dose regimen, which would reduce cost and could dramatically increase vaccine acceptance and availability. Furthermore, a greater understanding of the routes of infection may lead to improved prevention campaigns.

Hepatitis B virus: Although the vaccination is very effective for most individuals, around 5 % of all vaccinees do not develop a measurable humoral response to current vaccines. The development of novel vaccines with different antigens and adjuvants offers the opportunity to improve the protection of a very vulnerable cohort. More data on requirements for booster vaccinations are needed both for individuals after infant or childhood vaccination as well as for persons who have been vaccinated as adults.

Hepatitis C virus: The complex immune response and viral strategies to evade the immune system e.g. by viral mutations, impedes the development of a vaccine. First promising preclinical and clinical trials were performed.

Novel vaccine strategies are currently in pre-clinical development. Until vaccines become available, access to antiviral treatment both for chronically as well as recently infected individuals is critical to prevent further spreading of the virus.

Hepatitis E virus: As the virus can be detected urine and in blood, a better understanding of spreading of the virus within families and close contact persons is needed. Correlates of protection are also not well understood as well as duration of immune responses after exposure and infection or vaccination. As the solitary vaccine with phase 3 data is available in China and few other countries only, additional efforts are needed to develop vaccines against HEV. The development of neutralising antibodies would be valuable that could be used in a passive vaccination strategy for high-risk groups such as immunocompromised individuals. The protection of active or passive vaccination strategies across against different HEV genotypes will be another challenge.

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