

Chapter 7: Prophylaxis and vaccination of viral hepatitis

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Introduction

Understanding the biology and modes of transmission of hepatitis viruses has significantly improved over the last decades. Fortunately, the incidence of hepatitis virus infections has significantly decreased in most areas around the world. Still, prophylactic vaccines are only available against HAV and HBV. Although an enormous amount of basic and clinical research has been performed to develop a vaccine against hepatitis C, it is very unlikely that a prophylactic or therapeutic HCV vaccine will be licensed within the next 5-7 years. A first phase II vaccine trial against hepatitis E has been successful; nevertheless, the completion of this vaccine development will not be in the near future. Prophylaxis for HCV, HDV (for HBV-infected patients) and HEV therefore must happen by avoiding all possible routes of exposure to the respective hepatitis viruses discussed in detail in Chapters 1-4.

Prophylaxis of hepatitis viruses

Hepatitis A and E

The hepatitis A and E viruses are usually transmitted by oral ingestion of contaminated food or water. Thus, particular caution is warranted when individuals from low endemic areas such as Western Europe and the USA travel to countries with a high prevalence of HAV and HEV infections. We must remember that hepatitis E can also be a zoonosis. A recent German case-control study identified 32% of all reported HEV infections as being autochthonous infections, meaning not associated with travelling to endemic countries (Wichmann 2008). In these patients consumption of offal and wild boar meat is independently associated with HEV infection. This may have significant implications for immunosuppressed patients as cases of chronic hepatitis E with the development of advanced fibrosis have been described in patients after organ transplantation (Kamar 2008). HEV has frequently been detected in the meat of pigs; Danish farmers show a higher prevalence of HEV antibodies. Importantly, zoonotic HEV infection is usually caused by HEV genotype 3 while HEV genotype 1 can be found in travelling-associated hepatitis E. HAV and HEV are also transmitted by blood transfusion although cases are extremely rare.

Hepatitis B and D

HBV and HDV were transmitted frequently by blood transfusion before HBsAg testing of all 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 transmissions and thus strict and careful application of standard hygienic precautions for all medical interventions are absolutely mandatory not only in endemic areas but also in Western countries. This

holds true in particular for immunocompromised individuals who are highly susceptible to HBV infection as HBV is characterized by a very high infectivity (Wedemeyer 1998). Moreover, immunosuppressed patients are at risk for reactivation of occult HBV infection after serological recovery from hepatitis B. Treatments with high doses of steroids and rituximab have especially been identified as major risk factors for HBV reactivation (Lalazar 2007). After a new diagnosis of HBV infection, all family members of the patient need to be tested for their immune status against HBV. Immediate active vaccination is recommended for all anti-HBc-negative contact persons. HBsAg-positive individuals should use condoms during sexual intercourse if it is not known if the partner has been vaccinated.

Hepatitis C

Less than 1% of individuals who are exposed to HCV by an injury via contaminated needles develop acute HCV infection. At Hannover Medical School, not a single HCV seroconversion occurred after 166 occupational exposures with anti-HCV positive blood in a period of 6 years (2000-2005). Earlier studies published in the mid-nineties suggested higher rates of HCV transmission by needle stick injury. However, more recent and larger studies have reported significantly lower rates of acute hepatitis C after needle-stick injury. We recently performed a systematic review of the literature identifying 22 studies with a total of 6,956 injuries with HCV contaminated needles. Only 52 individuals (0.75%) became infected. The risk of acute HCV infection 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. Worldwide differences in HCV seroconversion rates may suggest that genetic factors may provide some level of natural resistance against HCV. Factors associated with a higher risk of HCV transmission are likely to be the level of HCV viremia 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 injury are shown in Figure 1.

Sexual intercourse with HCV-infected persons has clearly been identified as a risk for HCV infection, as about 10-20% of patients with acute hepatitis C report this as a potential risk factor (Table 1). However, there is also large evidence that the risk of acquiring HCV sexually is extremely low in individuals with stable partnerships who avoid injuries. Cohort studies including >500 HCV-infected patients followed over periods of more than 4 years could not identify any cases of confirmed HCV transmission. Thus, guidelines generally do not recommend the use of condoms in monogamous relationships. However, this statement does not hold true for HIV-positive homosexual men. Recently, several outbreaks of acute hepatitis C have been described in this scenario (Fox 2008; Low 2008). Transmitted cases had more sexual partners, increased levels of high-risk sexual behaviour (in particular, fisting) and were more likely to have shared drugs via a nasal or anal route than controls (Turner 2006).

Due to the low HCV prevalence in most European countries and due to a relatively low vertical transmission rate of 1-6%, general screening of pregnant women for anti-HCV is not recommended. Interestingly, transmission may be higher for girls than for boys (European Pediatric Hepatitis C Virus Network 2005). Transmission

rates may be higher in HIV-infected women so pregnant women should be tested for hepatitis C. Other factors possibly being associated with high transmission rates are the level of HCV viremia, maternal intravenous drug use, and specific HLA types of the children. Caesarean sections are not recommended for HCV RNA positive mothers as there is no clear evidence that Caesarean sections reduce transmission rates. Children of HCV-infected mothers should be tested for HCV RNA after 1 month as maternal anti-HCV antibodies can be detected for several months after birth. Mothers with chronic hepatitis C can breast-feed their children as long as they are HIV-negative and do not use intravenous drugs (European Pediatric Hepatitis C Virus Network 2001).

The Spanish Acute HCV study group has recently identified hospital admission as a significant risk factor for acquiring HCV infection in Spain (Martinez-Bauer 2008). The data are in line with other reports from Italy (Santantonio 2006) and the USA (Corey 2006). We have recently reported data from the German Hep-Net Acute HCV studies and found 38 cases (15% of the entire cohort) of acute HCV patients who reported a medical procedure as the most likely risk factor for having acquired HCV (Deterding 2008). The majority of those were hospital admissions with surgery in 30 cases; other invasive procedures including dental treatment were present in only 4 cases. Medical procedures were significantly more often the probable cause of infection in patients older than 30 years of age ($p=0.002$) but not associated with disease severity or time from exposure to onset of symptoms. Thus, medical treatment per se represents a significant risk factor for HCV infection – even in developed countries. Strict adherence to universal precaution guidelines is urgently warranted.

Vaccination against hepatitis A

The first active vaccine against HAV was licensed in 1995. 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 basically all vaccinated healthy persons develop protective anti-HAV antibodies. Similar vaccine responses are obtained in 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, 2 months schedule (Hammitt 2008). Patients with chronic liver disease do respond to vaccination but may display lower anti-HAV titers (Keefe 1998). Since 1996 a combined vaccine against HAV and HBV is available that needs to be administered three times, on a 0, 1, 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 are 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 different groups of individuals including non-immune individuals who plan to travel to endemic countries, medical health professionals, homosexual men, persons in contact with hepatitis A patients, and individuals with chronic liver diseases. Some studies have suggested that patients with chronic hepatitis C have a higher risk to develop fulminant hepatitis A (Vento 1998), however this finding has not been confirmed by several other investigators (Deterding 2006). The implementation of childhood vaccination programs has led to a significant and impressive declines of HAV infections in several countries, justifying further efforts aiming to control the spread of HAV in endemic countries (Hendrickx 2008). It is important to highlight that most studies have also shown that HAV vaccination is cost-effective (Rein 2008; Hollinger 2007).

Recently, long-term follow-up studies after complete HAV vaccination have been published. Interestingly, anti-HAV titers sharply decline during the first year after vaccination but remain detectable in almost all individuals for at least 10 years after vaccination. Based on these studies it was estimated that protective anti-HAV antibodies should persist for at least 27 years after successful vaccination of children or young adults (Hammit 2008).

Vaccination against hepatitis B

The hepatitis B vaccine is the first vaccine able to reduce the incidence of cancer. In Taiwan, a significant decline in cases of childhood hepatocellular carcinoma has been observed after the implementation of programs to vaccinate all infants against HBV (Chang 1997). This landmark study impressively highlighted the usefulness of universal vaccination against HBV in endemic countries. 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 hepatitis B everywhere. In the long run, hepatitis B can be eradicated by worldwide implementation of this recommendation, because humans are the only epidemiologically relevant virus host. 164 countries have introduced a hepatitis B vaccine in their national infant immunization schedules by the end of 2006 (www.who.int; accessed Nov 12th 2008).

The first plasma-derived hepatitis B vaccine was approved by the FDA in 1981. Recombinant vaccines consisting of HBsAg produced in yeast became available in 1986. In the USA, two recombinant vaccines are 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 months schedule.

Who should be vaccinated? (The German Guidelines (Cornberg 2007))

- Hepatitis B 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 persons who are at risk because of blood contact with possibly infected persons dependent on the risk evaluation, e.g., persons giving first aid professionally or voluntarily, employees of ambu-

lance services, police officers, social workers, and prison staff who have contact with drug-dependent people;

- Patients with chronic kidney disease, dialysis patients, patients with frequent blood or blood component transfusions (e.g., hemophiliacs), 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);
- Persons with chronic liver disease including chronic diseases with liver involvement as well as HIV-positive persons without HBV markers;
- Persons 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., homosexually active men, regular drug users, sex workers, prisoners serving extended sentences;
- Persons at risk of contacting HBsAg carriers in facilities (kindergarten, children's homes, nursing homes, school classes, day care groups);
- Persons travelling to regions with high hepatitis B prevalence for an extended period of time or with expected close contact with the local population;
- Persons 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 hepatitis B is not necessary before vaccination unless the person belongs to a risk group and may have acquired hepatitis B before. Pre-vaccine testing is usually not cost-effective in populations with anti-HBc prevalence below 20%. Vaccination of an HBsAg-positive individual can be performed without any danger – however, it is ineffective.

Efficacy of vaccination against hepatitis B

A response to HBV vaccination is determined by the development of anti-HBs antibodies which is detectable in 90-95% of individuals one month after a complete vaccination schedule (Wedemeyer 2007; Coates 2001). Responses are lower in elderly people and much weaker in immunocompromised persons such as organ transplant recipients, patients receiving haemodialysis and HIV-infected individuals. In case of vaccine non-response, 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 2007). The response to vaccination should be controlled in high-risk individuals such as medical health professionals and immune-compromised persons. Some guidelines also recommend to test elderly persons after vaccinations as vaccine response does decline more rapidly in the elderly (Wolters 2003).

Post-exposure prophylaxis

Non-immune persons who have been in contact with HBV-contaminated materials (e.g., needles) or who have had sexual intercourse with an HBV-infected person should undergo active-passive immunization (active immunization plus hepatitis B immunoglobulin) as soon as possible – preferentially within the first 48 hours of exposure to HBV. Individuals previously vaccinated but who have an anti-HBs titer of <10 IU/L should also be vaccinated both actively and passively. No action is required if an anti-HBs titer of >100 IU/l is documented; active vaccination alone is sufficient for persons with intermediate anti-HBs titers between 10 and 100 IU/L (Cornberg 2007).

Safety of HBV vaccines

Several hundred million individuals have been vaccinated against hepatitis B. The vaccine is very well tolerated. Injection site reactions in the first 1-3 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 seldomly-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 hepatitis B vaccination causes and induces acute episodes of multiple sclerosis or other demyelating diseases is repeatedly discussed (Geier 2001; Hernan 2004; Girard 2005). However, there are no scientific facts proving 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; Institute of Medicine Report 2002; CDC 2004; Schattner 2005).

What is the long-term immunogenicity of the hepatitis B vaccination?

Several studies have been published in recent years investigating the long-term efficacy of HBV vaccination. After 10-15 years, between one third and two thirds of vaccinated individuals have completely lost anti-HBs antibodies and only a minority maintain titers 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 B- and 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 infants develop anti-HBc indicating active HBV infection (18%) and some children develop chronic hepatitis B (van der Sande 2007). Thus, persons at risk should receive booster immunization if HBs antibodies have been lost.

Prevention of vertical HBV transmission

Infants of HBsAg positive mothers should be immunized actively and passively within 12 hours of birth. This is very important as the vertical HBV transmission rate can be reduced from 95% to <5% (Ranger-Rogez 2004). Mothers with very high HBV viremia, of >50 million IU/ml, should receive in addition antiviral therapy with a potent HBV polymerase inhibitor (European Association For The Study Of The Liver 2008).

If active/passive immunization has been performed, there is no need to recommend Caesarean section. Mothers of vaccinated infants can breast feed unless oral antiviral medications are being taken by the mother, which can be detected in the breast milk.

Vaccination against hepatitis C

No prophylactic or therapeutic vaccine against hepatitis C is available. As re-infections after spontaneous or treatment-induced recovery from hepatitis C virus infection have frequently been reported, the aim of a vaccine will very likely be not to prevent completely an infection with HCV but rather to modulate immune responses in such a way that the frequency of evolution to a chronic state can be reduced.

HCV specific T-cell responses play an important role in the natural course of HCV infection. The adaptive T-cell response is mediated both by CD4⁺ helper T-cells and CD8⁺ killer T-cells. Several groups 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. While CD4⁺ T-cells seem to be present for several years after recovery, there are conflicting data whether HCV-specific CD8⁺ T-cells responses persist or decline over time. However, several studies have observed durable HCV-specific T-cells in HCV-seronegative individuals who were exposed to HCV by occupational exposure or as household members of HCV-positive partners, but who never became HCV RNA positive. These observations suggest that HCV-specific T-cells may be induced upon sub-clinical exposure and may contribute to protection against clinically apparent HCV infection. T-cell responses are usually much weaker in chronic hepatitis C. The frequency of specific cells is low but also effector function of HCV-specific T-cells is impaired. Different mechanisms are discussed as being responsible for this impaired T-cell function, including higher frequencies of regulatory T-cells (T-regs), altered dendritic cell activity, upregulation of the inhibitory molecules PD-1 on T-cells and many others. HCV proteins can directly or indirectly contribute to altered functions of different immune cells.

To what extent humoral immune responses against HCV contribute to spontaneous clearance of acute hepatitis C is less clear. Higher levels of neutralizing antibodies early during the infection are associated with viral clearance (Pestka 2007). However, antibodies with neutralizing properties occur at high levels during chronic infection. Yet, no completely sterilizing humoral anti-HCV immunity exists in the long-term after recovery (Rehermann 2005).

Few phase I vaccine studies based either on vaccination with HCV peptides, HCV proteins or recombinant vectors expressing HCV proteins have been completed. HCV-specific T-cells or antibodies against HCV can be induced by these vaccines in healthy individuals. However, it will be difficult to prove vaccine efficacy and vaccine effectiveness. Studies in chimpanzees have shown that it is very unlikely that a vaccine will be completely protective against heterologous HCV infections. However, a reasonable approach might be the development of a vaccine that does not confer 100% protection against acute infection but prevents progression of acute hepatitis C to chronic infection. This approach has, however, to compete with antiviral treatment of acute hepatitis C. It is very unlikely that a vaccine against hepatitis C will be licensed within the next 5-7 years.

Some studies regarding therapeutic vaccination have taken place (Wedemeyer 2006; Klade 2008). These studies show that induction of HCV-specific humoral or cellular immune responses is possible even in chronically infected individuals. However, so far neither therapeutic vaccination nor other immunomodulatory attempts such as treatment with cytokines (interferon gamma; IL-2; IL-10; IL-12) or toll-like receptor agonists have shown significant clinical benefits in patients with chronic hepatitis C.

Vaccination against hepatitis E

A phase II vaccine trial performed in Nepal showed a vaccine efficacy of 95% for an HEV recombinant protein (Shrestha 2007). 2000 soldiers received three vaccines on a 0, 1, 6 months schedule or placebo and subjects were followed for a median of 800 days. Except injection site reactions side effects were similar in both groups. Importantly, of the 69 subjects who developed hepatitis E, 66 were in the placebo group. However, and unfortunately, no phase III study to complete the vaccine's development has yet started to our knowledge. Thus, no HEV vaccine will be available in the next few years. Until then, preventive hygienic measures remain the only option to avoid HEV infection.

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