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Guidelines on the diagnosis and management of chronic liver disease in haemophilia

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Virtually all haemophiliacs treated with clotting-factor concentrates before 1985 have been exposed to the hepatitis C virus (HCV) and almost 100% of these are HCV-antibody positive. A major problem of HCV infection is its propensity to cause chronic liver disease and it is generally acknowledged that this will occur in at least 50–75% of infected subjects [1]. Hepatocellular carcinoma is now emerging as a complication of chronic HCV infection, but this is usually a development of cirrhosis and hepatitis C [2].

Fluctuating abnormalities of liver enzymes are a chararacteristic feature of HCV-related chronic liver disease but it should be stressed that there is no definite relationship between the degree of abnormality of enzyme levels and liver histology. To date, interferon is the only drug of proven value for the treatment of chronic liver disease but sustained responses are limited to no more than 25% of most treated patients. Factors associated with poor response include HCV genotype 1 [3], high HCV viral titre, cirrhosis and increasing age [4].

The Working Party wish to stress that wherever possible, close collaboration should be established between the Haemophilia Centre Director and a consultant hepatologist, and that the latter should play an important role in the management of haemophiliacs with chronic liver disease.

The patient should be kept fully informed of the results of all laboratory tests, including antibody status. The clinical implications of the findings should also be discussed.

Diagnosis of HCV infection

All patients who have been treated with blood products should be tested by a second/third-generation HCV antibody test. It is recommended that, for those individuals who are HIV-antibody positive and HCV-antibody negative, a diagnosis of HCV infection should be sought by detection of HCV RNA by polymerase chain reaction (PCR). For this group of patients in particular, decisions with respect to treatment with interferon should be made through consultation with a hepatologist.

Sexual transmission of HCV

Sexual transmission of hepatitis C is possible. Currently the risk is estimated at < 3%, although the possibility of higher transmission risks under some circumstances cannot be excluded.

The current data on the rate of sexual transmission and the advantages of barrier contraception should be discussed. Patients should be encouraged to take a joint decision with their sexual partners.

HCV testing of sexual partners

Anti-HCV antibody testing should be offered to all sexual partners of HCV-antibody-positive patients. Although there is little evidence of vertical HCV transmission, HCV testing of children of HCV-positive mothers should be offered, but the interpretation of this may be difficult.

Follow-up of HCV-infected patients

1 HCV-infected patients known to have abnormal aspartate aminotransferase/alanine transaminase (AST/ALT) levels should attend for review at approximately 4-monthly intervals.

2 For those HCV-antibody-positive patients without documented liver biochemistry results, ALT/AST levels should be determined on three occasions over a period of 6 months. If all three determinations are normal then, wherever possible, PCR should be performed for HCV RNA. This is to establish whether the patient has detectable viraemia, despite normal serum ALT. If HCV RNA is detected, the results and therapeutic implications should be discussed with a hepatologist. Patients with abnormal AST/ALT levels should attend for review at approximately 4-monthly intervals.

It is important to stress that no definite relationship exists between liver enzymes (ALT/AST) levels and liver histology.

Treatment with interferon alpha

Although interferon is of proven value in chronic HCV-

related liver disease, sustained remissions are achieved in only approximately 20% of patients treated with this drug. Recently a number of factors have been identified which influence this response rate. Of particular importance are HCV genotype, HCV viral titre, and the presence or absence of cirrhosis. Poor sustained responses, i.e. less than 1:4, can be anticipated in subjects infected with HCV genotype 1, in those with high levels of circulating virus and in subjects with cirrhosis. With respect to viral titres, it has been suggested that a virus level of 10^6 copies/ml might represent a threshold above which conventional treatment with interferon may be unsuccessful.

With this background, the Working Party on Chronic Liver Disease in Haemophilia wish to make the following recommendations.

Patients with biochemical and serological evidence of chronic HCV-related liver disease should be considered for treatment with interferon. However, for patients with ascites, variceal haemorrhages and/or cirrhosis, interferon is of little therapeutic value and may be hazardous.

Because treatment protocols recommended by hepatologists are very likely to be influenced by HCV genotype and HCV viral titre, these should be determined before treatment decisions are taken. Where individuals are infected with HCV genotype 1 and/or with high levels of circulating HCV viral titres (see above), it is strongly recommended that the results be discussed with a consultant hepatologist as it may be advisable for these patients to be treated for longer periods of time and with higher doses of interferon. Alternatively, better responses may be obtained by combination therapy with interferon and ribavarin. It should be appreciated, however, that the latter drug is not currently licensed for this indication.

Standard interferon treatment schedules are recommended for those patients who fulfil the criteria for treatment with interferon and who are infected with HCV genotypes other than type 1 and with high levels of circulating virus. Currently, Roferon-A (Roche) and Viraferon (Schering-Plough) are both licensed for the treatment of chronic HCV-related hepatitis. Recommended dose schedules are provided by the manufacturers.

Dr Peter Simmonds, Department of Medical Microbiology, The University of Edinburgh Medical School, Teviot Place, Edinburgh EH8 9AG, has kindly agreed to undertake, for UK Haemophilia Centre Directors, HCV genotyping by a highly standardized restriction fragment length polymorphism (RFLP) method designed to detect HCV genotypes1–6 and to differentiate between the common subypes of types 1, 2 and 3.

Co-infection with HIV

Irrespective of tests of liver enzymes, a polymerase chain reaction for HCV RNA should be undertaken in patients who are HIV-antibody positive and HCV-antibody negative. HCV genotype and viral quantification should be further undertaken in those who prove to be HCV RNA positive. Treatment decisions should be made following discussion of the results with a consultant hepatologist.

Role of liver biopsies

The Working Party felt that most patients can be managed without the necessity for a liver biopsy. A liver biopsy is indicated where a focal lesion has been identified by ultrasound examination, or where there is doubt regarding the aetiology of the chronic liver disease. It is strongly recommended that liver biopsies in haemophiliacs be performed by experienced operators.

Where liver biopsies are considered necessary we suggest the treatment regime provided below.

Day 0: Pre-biopsy dose: give calculated dose of factor VIII/IX to increase FVIII/IX to 1.0 U/ml (100%).
Dose 2 (p.m.): (FVIII). Further infusion to increase FVIII to 1.0 U/ml (100%).

Day 1: Assay FVIII/IX: give calculated dose of FVIII/IX to increase FVIII/IX to 1.0 U/ml (100%).

Day 2: Assay FVIII/IX: give calculated dose to increase FVIII/IX to 0.5 U/ml (50%).

Other investigations

Endoscopy is recommended every 5 years for patients over the age of 45 years, and/or those who have been infected with HCV for 30 years. Because there are suggestions that the progression of HCV-related chronic liver disease may be accelerated by co-infection with HIV this interval could be reduced in this group of patients.

Abdominal ultrasound is of little value in the staging of chronic HCV-related liver disease. In patients over the age of 45 years it is useful for screening for hepatocellular carcinoma. In patients known to have cirrhosis, an abdominal ultrasound examination and alpha fetoprotein determination are recommended at approximately 4-monthly intervals.

Role of alcohol

Excessive alcohol intake in patients known to be HCV-antibody positive is associated with an increased likelihood of the development of cirrhosis and hepatocellular carcinoma. Patients should be advised not to exceed a weekly consumption of 21 units of alcohol in men, and 14 units of alcohol in women. This is not an all or nothing

phenomenon, and the lower the alcohol intake the better the outcome. (One unit of alcohol is equivalent to 1/2 pint of beer, or 1 glass of wine, or 1 measure of spirits.)

Liver transplantation

Liver transplantation is of proven value in some patients with end-stage liver disease due to hepatitis C. However, recurrence of hepatitis C occurs in 90% of patients. Recommendations for this treatment option will be made by the consultant hepatologist in collaboration with the Haemophilia Centre Director.

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REVIEW ARTICLE

Guidelines on the diagnosis, management and prevention of hepatitis in haemophilia

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Introduction

Virtually all haemophiliacs treated with clotting factor concentrates before 1985 have been exposed to the hepatitis C virus (HCV) and almost 100% of these are HCV antibody-positive [1]. A major problem in respect of HCV infection is its propensity to cause chronic liver disease and it is generally acknowledged that this will occur in at least 50–75% of infected subjects [2]. Cirrhosis may occur in 20–30% of those with chronic infection [3]. Hepatocellular carcinoma is also a recognized complication of chronic HCV infection and usually occurs in association with hepatic cirrhosis [4,5].

Fluctuating abnormalities of liver enzymes are a characteristic feature of HCV-related chronic liver disease, but it should be stressed that there is no clear relationship between the degree of abnormality of enzyme levels and liver histology. Until recently alpha-interferon was the only drug of proven value for the treatment of chronic hepatitis C, but there is now evidence that improved biochemical and virological responses can be obtained by combined therapy with interferon and ribavirin. Factors associated with poor response to interferon include HCV genotype 1, high HCV viral titre, cirrhosis and increasing age at the time of infection [6] (level of evidence 1b).

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The Working Party wish to stress that, wherever possible, close collaboration should be established between the haemophilia centre director and a consultant hepatologist, and that the latter should play an important role in the management of haemophilia patients with chronic liver disease.

The patient should be kept fully informed of the results of all relevant laboratory tests. The clinical implications of the findings should also be discussed.

Clinical guidelines on the management of chronic hepatitis C have been produced by a number of bodies, but none has specifically addressed the issue of liver disease in haemophiliacs [7,8]. Because of specific differences pertaining to haemophiliacs these guidelines have been produced and are as far as possible compatible with the recently published European guidelines [8].

Diagnosis of HCV infection

All patients who have been treated with clotting factor concentrates should be tested by a second/third-generation HCV antibody test. It is also recommended that all patients should be assessed for current infection by polymerase chain reaction (PCR) for HCV RNA.

Although most patients will have been tested already, the working party recommends so far as possible tracing and testing every individual who has received clotting factor concentrate, especially those treated prior to 1987. Patients with von Willebrand's disease, mild haemophilia and haemophilia carriers are likely to constitute the main group of untested patients.

Sexual transmission of HCV

Sexual transmission of hepatitis C is rare but does occur. Currently the risk is estimated at < 3% to regular sexual partners [9], although the possibility of higher transmission risks under some circumstances cannot be excluded.

The current data on the rate of sexual transmission and the advantages of barrier contraception should be discussed. Patients should be encouraged to take joint decisions with their sexual partners.

HCV testing of sexual partners

Anti-HCV testing should be offered to all sexual partners of HCV antibody-positive patients. Although vertical transmission of HCV occurs only rarely, HCV testing of children of HCV-positive mothers should be offered, but the interpretation of this in children under 1 year of age may be difficult.

Follow-up of HCV infected patients

(1) HCV infected patients known to have abnormal serum ALT or AST levels should attend for regular review at approximately 4–6 monthly intervals. The review should include a clinical examination and laboratory determination of, at least, serum albumin level and prothrombin time.
(2) For those HCV antibody-positive patients without documented abnormal liver biochemistry results, ALT/AST levels should be determined and PCR for HCV RNA should be performed. This is to establish whether the patient has detectable viraemia despite normal serum ALT as occurs in some patients with chronic infection. If HCV RNA is detected, the results, implications and therapeutic options should be discussed with a hepatologist.
(3) HCV genotyping and quantification should be considered before treatment is initiated in all patients since this alters the recommended duration of combination therapy.

Treatment

Although interferon is of proven value in chronic HCV-related liver disease, sustained remissions are achieved in only approximately 20% of nonhaemophilic patients treated with this drug for 12 months [6,7] (level of evidence 1b). In individuals with haemophilia, the sustained response rate appears to be even lower [10] (level of evidence 1b). Recently a number of factors that influence this response rate have been identified. Poor prognostic indicators are HCV genotypes 1a or 1b, high HCV viral titre, and the presence of cirrhosis [11]. In respect of viral load, patients with a virus level of 2×10^6 copies mL^{-1} or higher are less likely to respond to combination therapy, but this should not considered to be a definite reason to deny treatment.

In nonhaemophiliacs with chronic HCV-related hepatitis, significantly improved sustained virological and biochemical responses can be obtained using combination therapy with alpha-interferon and ribavirin [12,13]. Early results suggest that the responses in haemophiliacs are very similar. In a selected group of haemophiliacs, Shields and colleagues found that 16 months after discontinuation of combination therapy, 71% of haemophiliacs remained in complete remission [14]. Both interferon and ribavirin are now licensed for treatment of chronic HCV in the UK. With this background, the Working Party wishes to make the following recommendations:

(1) Haemophiliacs with biochemical and serological evidence of chronic HCV-related liver disease should be considered for treatment with the combination of alpha interferon and ribavirin irrespective of their HCV genotype. The optimal length of therapy is 6 months for patients with HCV genotypes 2 or 3 and 12 months for patients with genotype 1. Where the HCV genotype is unknown or multiple, treatment should be for 12 months (grade A, level 1b).
(2) In nonhaemophiliacs with chronic hepatitis C, who relapse after treatment with interferon, therapy with alpha-interferon and oral ribavirin results in higher rates of sustained virological, biochemical and histological response than re-treatment with interferon alone [15]. The working party recommends that haemophiliacs who relapse or fail to respond to treatment with interferon alone, should be considered for therapy with the combination of interferon and ribavirin, irrespective of their genotype (grade A, level 1b).
(3) It is recommended that all patients undergoing therapy have a PCR for HCV RNA after 12 weeks' treatment. If this remains positive, consideration could be given to increasing the dose of interferon or continuing therapy for a further 12 weeks as 10–20% of patients may still respond after this time [8] (grade C, level IV). If at 24 weeks, the patient remains HCV RNA-positive, therapy should be discontinued.

(4) Patients with persistently normal hepatic transaminases and positive HCV RNA should not be offered treatment at this stage unless a liver biopsy has shown evidence of significant liver disease. Combination therapy is also not indicated in patients with persistently abnormal transaminases and who are negative for HCV RNA. A liver biopsy should be considered in this group to investigate alternative hepatic pathology.
(5) Patients with decompensated liver failure should not receive interferon/ribavirin therapy. Where there is early histological evidence of cirrhosis but without decompensation, carefully monitored treatment with the interferon–ribavirin combination should be considered as this may limit the rate of progression.
(6) For patients with thrombocytopenia, leucopenia, ascites, variceal haemorrhages or hepatic encephalopathy, alpha-interferon is of less therapeutic value and is potentially hazardous.

Co-infection with HIV

This is a clinically important and complex issue. Irrespective of tests of liver enzymes, PCR for HCV RNA should be undertaken in patients who are HIV antibody-positive and HCV antibody-negative. This group of coinfected patients shows more rapid progression to liver failure [16] and should be considered for antihepatitis C therapy. This is, however, often difficult in patients who are already on several antiretroviral drugs. Furthermore, the datasheet for ribavirin specifically mentions zidovudine as a contraindication. Treatment decisions should be made on an individual basis following consultation with the patient and discussion of the results with a consultant hepatologist. There is at present little experience in the treatment of hepatitis C with the combination of interferon–ribavirin in patients already taking highly active antiretroviral therapy (HAART).

Because of the higher risk of liver disease progression, HIV positive patients not on HAART should be encouraged to consider treatment with interferon and ribavirin.

Role of liver biopsies

Currently, the necessity for liver biopsy is uncertain. Not all patients are managed with a liver biopsy and until comparative patient outcome data is available no definitive recommendations can be made by the Working Party. A liver biopsy is indicated where there is doubt regarding the aetiology of the chronic liver disease [17]. The decision to perform a liver biopsy must be balanced against the cost and side-effects of the procedure. It is strongly recommended that liver biopsies in haemophiliacs are only performed by experienced operators. Transjugular liver biopsy may be considered. Many patients can be managed without a liver biopsy.

Where liver biopsies are considered necessary, we suggest the treatment regimen detailed in Table 1.

Treatment by continuous infusion is also a possible option [18].

Other investigations

Upper gastrointestinal endoscopy is recommended every 5 years for patients over the age of 45 years, and/or those who have been infected with HCV for 30 years (grade C, level IIa). Because there are suggestions that the progression of HCV-related chronic liver disease may be accelerated by coinfection with HIV, this interval could be reduced in this group of patients [2,19].

Abdominal ultrasound is of little value in the staging of chronic HCV-related liver disease but is useful for screening for hepatocellular carcinoma. An abdominal ultrasound examination is recommended at approximately 6-monthly intervals for patients who have clinical or other evidence of cirrhosis (grade C, level IV). Alpha-fetoprotein determination is recommended at 6-monthly intervals for screening for hepatocellular carcinoma.

Table 1. Treatment regimen.

Day 0
Pre-biopsy dose
Give calculated dose of VIII/IX to increase factor VIII/IX to 1.0 U mL^{-1} (100%).
Dose 2 – pm
(Factor VIII). Further infusion to increase factor VIII to 1.0 U mL^{-1} (100%).
Day 1
Assay factor VIII/IX
Give calculated dose of VIII/IX to increase factor VIII/IX to 1.0 U mL^{-1} (100%).
Day 2
Assay factor VIII/IX
Give calculated dose to increase factor VIII/IX to 0.5 U mL^{-1} (50%).

Role of alcohol

Excessive alcohol intake in patients known to be HCV antibody-positive is associated with an increased likelihood of the development of cirrhosis [20] and hepatocellular carcinoma. HCV-infected individuals should be advised not to take alcohol (grade B, level IIa). For those who persist there should be a strong recommendation not to exceed a weekly consumption of 21 units of alcohol for men, and 14 units of alcohol for women (grade C, level IV). This is not an all-or-nothing phenomenon, and the lower the alcohol intake, the better the outcome. One unit of alcohol is equivalent to ½ pint of beer, or one glass [100 mL] of wine, or one measure of spirits.

Liver transplantation

Liver transplantation is of proven value in subjects with endstage liver disease due to hepatitis C, and the clinical indications for liver transplantation in HCV-infected haemophiliacs are no different from those in other clinical groups [21]. The major indication for liver transplantation in HCV-positive patients is decompensated cirrhosis evidenced by poorly controlled ascites and/or variceal bleeding. The serum albumin level and prothrombin time are probably the best indicators of hepatic decompensation. A serum albumin falling to 26 g L^{-1} is usually associated with ascites that is increasingly difficult to control by the standard measures of salt restriction, diuretics, etc. At that point, rather than subjecting the patient to repeated paracenteses, and assuming that there are no contraindications, the patient should referred for transplantation. Liver transplantation is also indicated in those without the features of hepatic decompensation but in whom a small (less than 3 cm) primary liver cancer is detected by alpha-fetoprotein screening and abdominal ultrasound or CT examination. Liver transplantation is preferred to resection in those subjects with a small (< 3 cm), solitary, primary liver cancer associated with hepatic cirrhosis.

Contraindications to liver transplantation in patients with haemophilia who are not coinfected with HIV are identical to those that pertain to other groups of HCV-infected individuals and decisions relating to this should be taken jointly between the haemophilia centre director and the liver transplant team. HIV seropositivity is no longer considered to be an absolute contraindication to liver transplantation. Currently it is unlikely that individuals with AIDS would be considered as suitable candidates for transplantation.

Hepatitis A virus

Hepatis A virus (HAV) is a nonenveloped RNA virus normally transmitted by the faecal–oral route. Most persons in developing countries, and a significant number in the developed world, show evidence of past infection. A carrier state does not exist and lifelong immunity develops after acute infection or vaccination. Acute HAV infection can be asymptomatic or present with diarrhoea and jaundice. Fulminant hepatitis has been described, but is extremely rare [22]. More recently, liver failure has been reported in HCV-infected individuals superinfected with HAV [23]. Outbreaks of acute HAV infection have been reported from several countries in nonimmune haemophiliacs receiving solvent/detergent-treated clotting factor concentrates [24,25]. This process of viral inactivation does not destroy HAV because the virus does not possess a lipid envelope [25].

Hepatitis B virus

Hepatis B virus (HBV) is an enveloped DNA-containing hepadnavirus, approximately 42 nm in size with a 27-nm core. Acute infection may result in persistent infection leading to chronic hepatitis, cirrhosis and hepatocellular carcinoma [26]. Despite screening of blood donors for HBsAg and virucidal treatment of coagulation factor concentrates with heat and/or solvent/detergent mixtures, the risk of transmission of hepatitis B has not been entirely eliminated and there have been reports of transmission of hepatitis B by 'virally inactivated' clotting factor concentrates [27]. Approximately 3–5% of haemophiliacs in the UK are HbsAg- positive, indicating continuing viral replication; 50% have evidence of past exposure [3]. In some individuals previously exposed to HBV, the infection becomes latent; reactivation may occur, particularly in those who are immunosuppressed, e.g. with HIV [28].

The potential for transmission of hepatotropic viruses by coagulation factor concentrates

At present, most licensed coagulation factor concentrates (including recombinant ones) contain plasma proteins derived from blood donors. Despite improved donor selection and donor screening combined with increasingly effective viral inactivation processes used in their manufacture, there remains a potential risk of transmitting hepatotropic viruses by these products [25].

Available vaccines

Currently vaccines are only available against hepatitis A and B viruses, and by their appropriate use, the transmission of these infectious agents can be prevented. The response to vaccines in those with familial coagulopathies is probably similar to that observed in other individuals; a better response is seen in younger recipients.

Hepatitis A vaccine (Avaxim and Havrix) is prepared from formaldehyde-treated hepatitis A virus cultured in human diploid cell lines. It is only licensed for those over the age of 1 year. The adult dose of each vaccine is 1 mL, but for those aged 15 years or less a smaller dose should be given (Avaxim: 0.5 mL; HavrixL 'Junior' preparation). By 1 month after the first injection, almost all immunocompetent individuals have protective immunity with antibody levels over 20 mU mL^{-1} [29] (grade B, level IIb). For long-term protection, a booster dose is recommended at approximately 6 months. For adults this should provide protection for more than 10 years [30]. Children aged from 1.0 to 6.8 years who received three-dose inactivated HAV vaccination at 0, 1 and 6 months remained seroprotected for at least 5 years. Theoretically, this vaccination programme can provide seroprotection for over 20 years [31] (grade B, level IIb).

Hepatitis B vaccine (Engenix B and HB-VAX II) is prepared from HBsAg using recombinant technology in yeast. It is licensed for use from birth. The adult dose of either vaccine is 20 mg, but for those less than 15 years a dose of 10 mg should be given. After the initial injection, further boosters are given at 2 and 6 months (a schedule for a more rapid response is to give the follow-up injections at 1 and 2 months) [32] (grade B, level IIB). It is necessary to give a booster injection at 1 year. Following a primary course of vaccination, the anti-HBs level should be assessed. Individuals are considered to be protected if their anti-HBs level is > 10 mU mL^{-1} [33,34]. If the initial antibody response at 1 month after the last injection is less than 10 mU mL^{-1}, further doses of vaccine should be given. The anti-HBs level should be checked periodically and a booster given if it falls below 10 mU mL^{-1}.

A poor response to vaccination may be observed in those with impaired immunity [35]. This is observed particularly in individuals infected with HIV. In these subjects, previous exposure to HBV infection may theoretically go unrecognized because the specific immune response may fail [28].

Combined hepatitis A and hepatitis B vaccine (Twinrix) is prepared from inactivated hepatitis A virus and recombinant (DNA) hepatitis B surface antigen adsorbed onto aluminium hydroxide and aluminium phosphate. Adult and paediatric prefilled syringes are available. For adults, a primary course consists of three doses of 1 mL, the second 1 month and the third 6 months after the first dose. A 1-mL booster dose 5 years after the start of the primary course is recommended for those at continued risk. For children aged from 1 to 15 years, the recommended dose is 0.5 mL.

The subcutaneous route is recommended for those with haemophilia. It should be noted that the immune response may be less than that associated with vaccination by the intramuscular route.

Who should be vaccinated?

For reasons presented above, all individuals with a congenital haemostatic disorder should be considered for vaccination against hepatitis A and B viruses. It is prudent to vaccinate everybody at diagnosis, even if treatment is not required immediately. This policy will help ensure that individuals are immune if they are given concentrate at a later date. It will also alleviate the necessity to give vaccines during pregnancy. A further reason for vaccinating those with coagulopathies is to protect their close contacts, e.g. family members and sexual partners, from becoming secondarily infected. In particular, individuals with known chronic liver disease, from whatever cause (e.g. hepatitis C virus), will also potentially benefit from vaccination against hepatitis A and B because in such individuals a superimposed infection with these viruses, however acquired, may result in acute liver failure [23]. In those who administer treatment with clotting factor concentrates there is a real risk of a needlestick injury, and therefore of hepatitis B infection, from either concentrate or from infected individuals. This group of subjects should therefore be considered also for vaccination, particularly against hepatitis B.

Which vaccines should they receive?

New patients less than 1 year of age should be offered vaccination against hepatitis B. After the child's first birthday hepatitis A vaccine should be offered.

Those presenting in their second year of life or later should be offered vaccination against both hepatitis A and B viruses.

Hepatitis G virus

Hepatitis G is a flavi-virus related to hepatitis C virus. Although this agent frequently causes persistent viraemia, current evidence suggests that it does not cause chronic liver disease. Active infection is determined by the detection of HGV RNA by the PCR technique, while past infection is indicated by the presence of anti-E2 antibodies. In western countries, 1–2% of the population are HGV RNA-positive. In haemophilia, the figure is approximately 12–15% [36]. A further 30–40% have anti-E2 antibodies, indicating resolution of previous HGV infection. Chronic liver disease is no more severe in HCV-infected individuals who are coinfected with HGV compared with those infected with HCV alone [37,38].

In the absence of evidence that HGV causes disease, it is difficult to justify screening haemophiliacs at present. It is the view of the Working Party that it is not necessary to test subjects with haemophilia for HGV infection either by PCR or by ELISA for anti-E2 antibodies. Currently, these investigations should be considered research tools.

TT virus

This is a recently discovered virus, originally isolated from a Japanese patient with chronic hepatitis. Although it can clearly be transmitted by blood products and many haemophiliacs show evidence of exposure to this virus, there is no convincing evidence that it is a hepatotropic virus [39]. The working party recommends that haemophiliacs should not routinely be tested for this virus.

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Appendix 1: Graded recommendations

Grade of recommendation

A Requires at least one randomized controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib).
B Requires availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation. (Evidence levels IIa, IIb, III).
C Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities; indicates absence of directly applicable studies of good quality. (Evidence level IV).

Levels of evidence

Ia Meta-analysis of randomized controlled trials.
Ib At least one randomized controlled trial.
IIa At least one well-designed controlled study without randomization.
IIb At least one other type of well-designed quasi-experimental study.
III Well-designed nonexperimental descriptive studies, such as comparative studies, correlation studies and case-control studies.
IV Expert committee reports or opinions and/or clinical experience of respected authorities.