

European guideline for the management of hepatitis B and C virus infections, 2010

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Summary: These are the guidelines on hepatitis B and C management for IUSTI/WHO in Europe, 2010. They describe the epidemiology, diagnosis, clinical features, treatment and prevention of hepatitis B and C with particular reference to sexual health clinical practice.

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HEPATITIS B VIRUS INFECTION

Introduction

Hepatitis B is caused by an hepadna (DNA) virus. Despite the availability of a vaccine, hepatitis B virus (HBV) infection is endemic, estimated to affect 400 million people worldwide, with very high hepatitis B surface antigen (HBsAg) carriage rates (up to 20%) particularly in south and east Asia. High carriage rates (up to 10%) are also found in some regions of Central and South America, Africa and parts of Asia. The reported incidence of acute hepatitis B in 2004 was 0–10/100,000 population in most of Europe but was 10–50/100,000 in Albania and most of eastern Europe.^{1,2} There has been a steady decline in incidence, particularly in western Europe, in the last two decades. Chronic carriage in the general population occurs in >8% in parts of eastern Europe, 2–8% in southern Europe and 0.1–2% in northern and western Europe.³ However, much higher carriage rates are found in certain subgroups including injecting drug users (IDUs), men who have sex with men (MSM), female sex workers and immigrants from high endemicity countries.^{4–7}

Transmission

- Sexual transmission occurs in unvaccinated MSM and correlates with multiple partners and unprotected anal sex.^{5,6,8–11}

Transmission also occurs after heterosexual contact (e.g. 18% infection rates for regular partners of patients with acute hepatitis B).^{12–14} Sex workers are also at higher risk.^{7,15}

- Other routes are parenteral (blood, blood products, drug-users sharing needles and syringes, needle-stick exposures), vertical (infected mother to infant)^{9,13,16–18} and oro-anal sex.^{5,6,8–11}
- Sporadic infection occurs in people without apparent risk factors, in institutions for the mentally disabled and also in children in countries of high endemicity.^{19,20} Overall, HBV is much more transmissible than HIV.

Diagnosis

Clinical

Acute icteric hepatitis has an incubation period of 40–160 days. Virtually all infants and children, and 10–50% of adults (especially HIV positive) have asymptomatic acute infection.^{21–24} In chronic infection there are often no symptoms or physical signs. After many years of infection, there may be signs of chronic liver disease.^{10,24–27} There are four phases of chronic carriage:

- (1) Immune tolerant (hepatitis B e antigen [HBeAg] positive, normal aminotransferase levels, high serum HBV DNA, little or no necro-inflammation on liver biopsy);
- (2) Immune active, eAg-positive phase (HBeAg positive, raised aminotransferases, high serum HBV DNA, progressive necro-inflammation and fibrosis);
- (3) Inactive hepatitis B carrier (HBsAg positive, HBeAg negative, low levels of HBV DNA and normal aminotransferases);
- (4) eAg negative chronic active hepatitis (Pre-core or core-promoter mutations, HBeAg negative, intermediate serum HBV DNA levels, progressive inflammation and fibrosis) – reactivation.

Types 2 and 4 may progress to cirrhosis and liver cancer, with type 4 generally progressing fastest.^{25,26} Between 15% and 40% of patients with chronic infection will develop serious complications.

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Table 1 Hepatitis B serological and ALT patterns in different stages of the disease

Stage of infection	Surface antigen (HBsAg)	'e' antigen (HBeAg)	IgM anticore antibody	Total anticore antibody	Hepatitis B virus DNA	Anti-HBe	Anti-HBs	ALT
Acute (early)	+	+	+	+	+ / ++	-	-	+++
Acute (resolving)	+	-	+	+	+ / -	+ / -	-	++
Chronic (immune tolerant)	+	+	-	+	++	-	-	N [†]
Chronic (immune active)	+	+	-	+	+	-	-	+
Chronic (HBeAg negative)	+	-	-	+	+	+ / -	-	+
Chronic (inactive carrier)	+	-	-	+	- / +	+	-	N
Resolved (immune)	-	-	-	+	-	+ / -	+ / -	N
Successful vaccination	-	-	-	-	-	-	+	N

HBsAg = hepatitis B surface antigen; HBeAg = hepatitis B e antigen; ALT = aminotransferase

*In very early infection the IgM anticore can be negative and therefore so can the total anti-HBc

[†]N = normal (≤ 19 IU/L for women and ≤ 30 IU/L for men)

- = negative/normal; -/+ = positive or negative; += positive; +++ = high titre positive

Laboratory

See Table 1 for serology.^{10,23,25,28}

Other tests

- Acute HBV infection – serum aminotransferases (ALTs) raised: rarely $>10,000$ IU/L; serum bilirubin: rarely >300 mmol/L; alkaline phosphatase generally $<2\times$ the upper limit of normal, except in cases complicated by cholestasis. Prothrombin time is generally normal, although may be prolonged by up to five seconds; greater prolongation indicates developing hepatic failure.
- Chronic HBV infection – in most cases the only abnormality to be found will be mildly abnormal aminotransferase levels (usually <100 IU/L) and in many patients the liver function tests (LFT) will be normal, particularly in the immune tolerant and inactive carrier stages.^{10,23–27}

Indications for HBV testing

- (1) Patient with acute icteric hepatitis: Test for HBsAg (and LFT, prothrombin time, urea and electrolytes) [IIa, B]. If HBsAg positive, proceed to e antigen (HBeAg), anti-core IgM and hepatitis B virus DNA (HBV-DNA) [IIa, B]. Interpretation: see Table 1. Also test for hepatitis A and C.
- (2) Part of screening: If local prevalence of hepatitis B carriage is $<1\%$ consider screening high-risk groups only (patients from highly endemic areas, MSM, sex workers, heterosexual people with multiple partners, IDUs, HIV-positive patients, sexual assault victims and sexual partners of HBsAg-positive patients or those in these risk groups).^{5–20} [IIa, B]. If local prevalence of hepatitis B carriage is $>1\%$ consider testing all those attending for a STI screen.
- (3) All HIV patients, especially prior to initiation of highly active antiretroviral treatment (HAART).
- (4) All patients commencing immunomodulatory therapies and chemotherapy.

Screening tests in asymptomatic patients

Initial screening for hepatitis B can be achieved by using either the antihepatitis B core antibody (anti-HBc) or HBsAg tests or both, followed by further tests accordingly (see flow charts and table for interpretation). Anti-HBc as the first test has the advantage that it will detect evidence of current or past infection allowing decisions to be made about the need for

vaccination or treatment.^{28–33} However false-positive test results may occur and people who are anti-HBc positive, anti-HBs negative may be considered as possibly non-immune (see below). An alternative screening strategy is to test for HBsAg initially which detects active infection but does not allow vaccination decisions to be made unless the anti-HBc test is also used [IIa, B] (see Figures 1 and 2).

If, after screening, the patient is found to be non-immune, consider vaccination (see below)^{16,17,34,35} [Ia, A]. If found to be a chronic HBV carrier, consider referral for further assessment and possible antiviral therapy^{26,36,37} [Ia, A].

Primary prevention/vaccination

- Hepatitis B transmission can be reduced by avoiding unprotected penetrative anal and vaginal sex and oro-anal contact, or by using condoms if the partner is HBsAg positive or their status is unknown³⁸ [IIa, B].
- The World Health Organization (WHO) recommends universal HBV vaccination.³⁸
- Vaccination should be offered to non-immune patients in most of the high-risk groups (see above)^{16,17,34,35} [Ia, A]. The main exception is people born in countries of high endemicity but not at continuing risk who are being screened primarily to detect chronic HBV carriage^{29,30} [IIa, B].
- HIV-positive patients show a reduced response rate to the vaccine (approximately 40%) and initial responders can become anti-HBs-negative within a year^{39–41} [IIa, B].
- There are three possible vaccination schedules for both the monovalent and the combined hepatitis A + B vaccines: zero, one, six months; zero, one, two and 12 months ('rapid course') or zero, one, three weeks and 12 months ('ultra-rapid course')^{17,30,31,34,35} [IIa, B]. Non- or poor responders usually respond to further doses (up to three injections standard or double dose), ideally given as a repeat course^{42,43} [IIa, B]. Some newer vaccines are more immunogenic including FendrixTM, which has a novel adjuvant and the pre-S-antigen-containing vaccines. Currently FendrixTM is only licensed for use in patients with renal insufficiency and pre-S vaccines have not been launched commercially.^{44–48}
- If the primary course of vaccination is incomplete, the missing doses of vaccine needed to complete the course

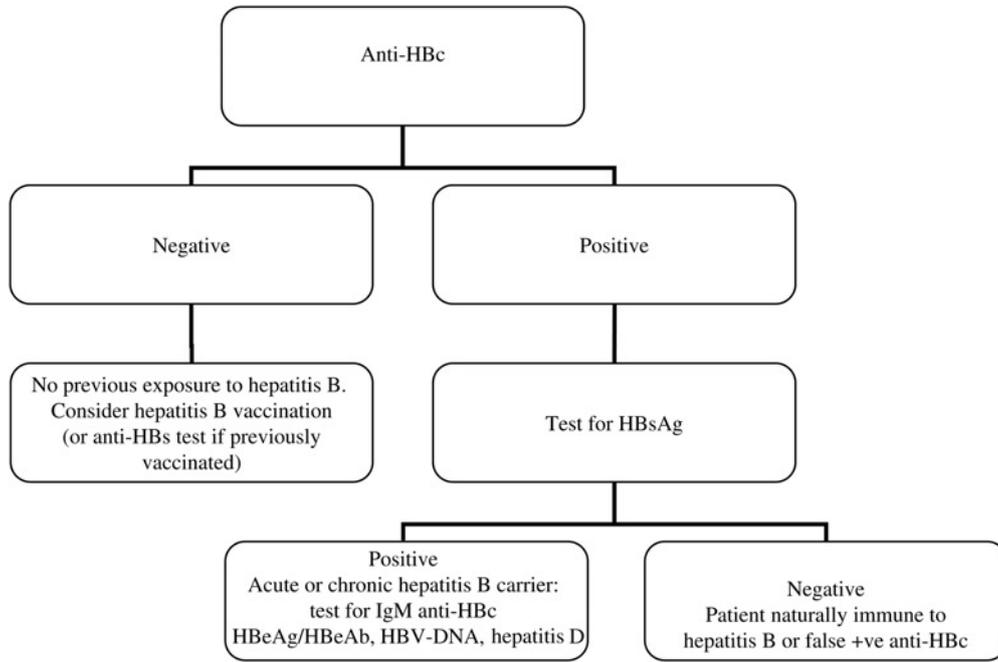


Figure 1 Flow chart for hepatitis B screening using serum anti-HBc

can be given up to four years later without the need to restart the full course^{49,50} [III, B].

- Some patients test anti-HBc positive but negative for anti-HBs and HBsAg. This could be due to either past infection or a false-positive test result. A single hepatitis B vaccine dose will induce anti-HBs if there has been past natural HBV exposure (amnestic response, measured 4 weeks after single dose of HBV vaccine). If anti-HBs is still negative after a single booster, regard as non-infected and give a full course of HBV vaccine [III, B].⁵¹

- Recent evidence suggests that immunocompetent adults and children who have responded to a primary course of HBV vaccine (>10 IU/L) do not require booster doses for at least 15 years⁵²⁻⁵⁵ [III, B], although a booster after five years is still recommended by some national bodies.¹⁶ However, immunocompromised patients, such as those with HIV or renal failure, should have an annual anti-HBs test following successful vaccination and should be given booster doses of vaccine when the anti-HBs level falls below 100 IU/L^{41,52,54} [IIa, B].

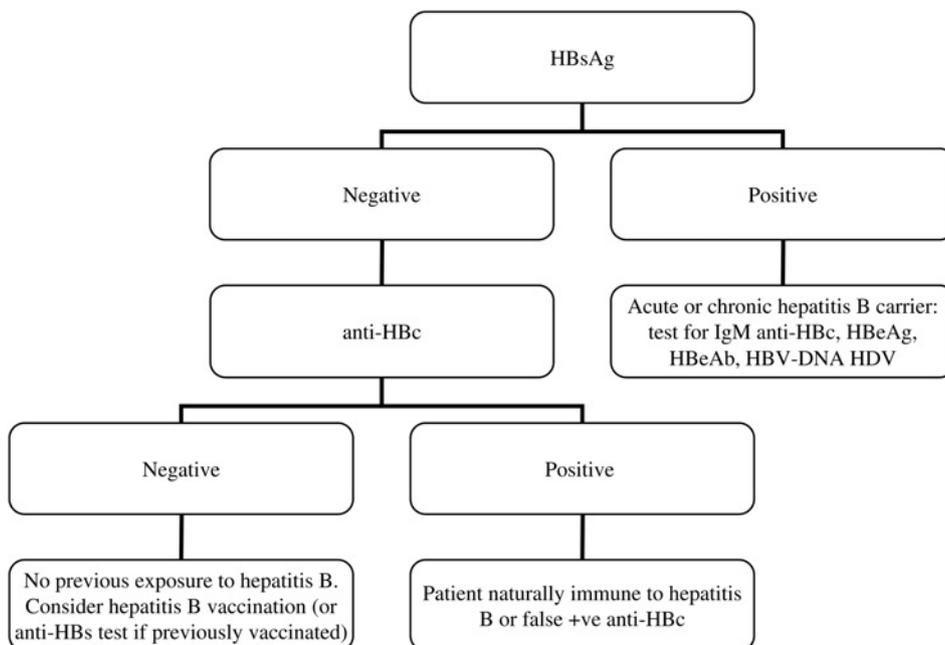


Figure 2 Flow chart for hepatitis B screening using serum HBsAg

Management of HBsAg-positive patients

General

- Patients should be advised to avoid unprotected sexual intercourse, including oro-anal contact until they have become non-infectious or their partners have been successfully vaccinated (see below)^{9,10,12,16,29} [IIa, B].
- Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s), routes of transmission of infection (see below) and advised not to donate blood¹⁶ [III, B].
- Hepatitis B is a notifiable disease in many European countries.^{1,2}
- If not performed already, screen for other sexually transmitted infections (STIs) in cases thought to have been sexually acquired or if otherwise appropriate^{8,12} [III, B].
- Other tests such as liver biopsy or assessment of liver fibrosis (for assessment of chronic disease) should be performed by specialists in this field^{10,23-26} [IV, C]. Among others, assessment of liver synthetic function (albumin, prothrombin time), disclosure of portal hypertension (platelets, ultrasonography) and liver fibrosis estimation using non-invasive markers (serum fibrosis indexes or imaging techniques such as elastometry) are warranted. Liver biopsy may be considered in patients in whom other hepatic diseases want to be excluded or when required by treatment protocols. Otherwise, liver biopsy is no longer mandatory as part of regular chronic hepatitis B assessment.
- All HBsAg-positive patients, but especially those with cirrhosis of high HBV-DNA levels, are at risk for hepatocellular carcinoma and should be followed by a specialist in liver disease.

Indications for therapy

Chronic infection

- Treatment should normally be given in collaboration with a hepatologist or physician experienced in the management of chronic viral hepatitis [IV, C]. The decision to treat depends on pattern of disease, HBV-DNA level, and presence or absence of significant necro-inflammation and hepatic fibrosis. HBV-DNA thresholds of 2×10^4 , 2×10^3 and 2×10^3 IU/mL are often used for HBeAg-positive chronic hepatitis, HBeAg -ve chronic hepatitis and cirrhosis, respectively, for initiating therapy.^{26,56}
- Patients should be considered for therapy with lamivudine, adefovir, tenofovir, telbivudine, entecavir (or combinations of nucleos(t)ide analogues) or pegylated interferon [Ib, A].^{26,56-62} For more detailed discussion on treatment read the relevant specialist guidelines.⁶² Additional treatments that may soon be licensed in HBV monoinfection include emtricitabine (FTC) [Ib, A], clevudine [IIa, B] and valorticitabine [III, C].⁶²⁻⁶⁴ Treatment responders have long-term benefits in terms of reduced liver damage and decreased risk of liver cancer.^{26,55-63}
- All patients should have an HIV test prior to starting HBV therapy because of the different treatment strategies required and the significant risk of antiretroviral-resistant HIV developing if lamivudine, emtricitabine, tenofovir or entecavir are used as monotherapy [Ib, A].^{26,56,63,65}
- Lamivudine, emtricitabine and tenofovir will suppress HBV replication when given as part of, or in addition to, an antiretroviral regimen⁶⁶⁻⁶⁸ and may delay liver damage if given as part of combination antiretroviral therapy [Ib, A].⁶⁶⁻⁶⁸

- Lamivudine and emtricitabine should only be given to HIV-positive patients in combination with tenofovir as part of HAART because of the high rate of resistance that occurs to these drugs if given as the only HBV-active agent (Ib,A).⁶⁶⁻⁶⁸ Entecavir should not be used in HIV-positive patients without adequately suppressed HIV as it causes the M184V (lamivudine/emtricitabine) resistant mutation⁶⁵ and there is an unconfirmed report that telbivudine may also have anti-HIV activity⁶⁹ [III, B].
- Adefovir can be used alone in HIV-positive patients⁷⁰ [IIa, B].
- Specific therapy may not be indicated, based on the HBV-DNA viral load, unless decompensated liver disease has ensued, but all HBsAg-positive patients should receive long-term follow-up due to the risk of liver cancer.¹⁰ All those with decompensated liver disease should be treated in close liaison with specialized liver units. Hepatitis A vaccination should be offered if non-immune, due to the worse prognosis of dual infection⁷¹ [III, B].

Acute infection

A small minority of patients with very severe acute infection may benefit from treatment with lamivudine, entecavir or telbivudine.⁶² Such patients should be referred to a liver specialist [III, C].

Special situations

Pregnancy and breastfeeding

- Vertical transmission (mother to infant) of infection occurs in 65-90% of pregnancies where the mother is HBeAg positive and in about 10% of HBsAg-positive, HBeAg-negative mothers. Most (>90%) of infected infants become chronic carriers.^{18,20,72}
- Infants born to HBsAg-positive mothers are vaccinated from birth, sometimes in combination with hepatitis B-specific immunoglobulin (HBSIg) 200 IU intramuscularly if the mother is HBeAg positive or has a high viral load^{18,72} [IIa, B]. This reduces vertical transmission by approximately 90%. There is some evidence that lamivudine may further reduce vertical transmission if given to women with a high HBV-DNA viral load in the third trimester⁷³ [Ib, A]. However, if HBSIg is not available, vaccination alone prevents vertical transmission in 66-100%⁷² [IIa, B]. Infants should be tested for hepatitis B (HBsAg and anti-HBs) four to six weeks after the final dose of vaccine [IV, C].
- Infected mothers should continue to breastfeed, as there is no additional risk of transmission.

Management of partners and other contacts

- Partner notification should be performed and documented and the outcome documented at subsequent follow up. Contact tracing to include any sexual contact (penetrative vaginal or anal sex or oro-anal sex) or needle sharing partners during the period in which the index case is thought to have been infectious^{29,30,31,74} [IIa, A]. The infectious period is from two weeks before the onset of jaundice until the patient becomes HBsAg negative. In cases of chronic infection trace contacts as far back as any episode of jaundice or to the time when the infection is thought to have been acquired although this may be impractical for periods of longer than two or three years [IV, C]. Arrange screening for hepatitis B

in children who have been born to infectious women if the child was not vaccinated at birth¹⁶ [IV, C].

- If available, HBsIg 500 IU intramuscularly may be administered to a non-immune contact after a single unprotected sexual exposure or parenteral exposure or needle-stick injury if the donor is known to be infectious. This works best within 48 hours and is of no use after more than seven days^{16,75} [IIa, A].
- An accelerated course of recombinant vaccine should be offered to those given HBsIg plus all sexual and household contacts (at 0, 1, 2, 12 months or 0, 1, 3 weeks and 12 months)^{16,17,30,31,34} [IIa, B].
- Avoid sexual contact, especially unprotected penetrative sex, until vaccination has been successful (anti-HBs titres >10 IU/L)^{16,30,31,52} [IIa, B]. Condoms will reduce the rate of transmission of hepatitis B if the patient and partner continue to have sex³⁸ [III, B].

Follow up

- Acute infection: Regular LFTs (1–4 weekly) until normal. In view of the possibility of chronic infection, serum HBsAg should be repeated after six months even if the LFT is normal^{10,22,23} [III, B].
- Chronic infection: If untreated, patients should be regularly reviewed at intervals of one year or less, ideally by a physician with expertise in this disease^{10,25,26} [IV, C].
- Immunity after recovery from infection (HBsAg negative) is lifelong in all but a very tiny minority who may reactivate infection after immunosuppression²⁵ [III, B].

Hepatitis D (delta virus infection, HDV)

This is an incomplete RNA virus that requires the hepatitis B virus outer coat. It is only found in patients with hepatitis B. It is largely an infection of IDUs and their sexual partners, but also in female sex-workers, and sporadically in other groups.⁷⁶ Suspect HDV in hepatitis B, particularly if the acute hepatitis is severe, if chronic hepatitis B carriers get a further attack of acute hepatitis or if the liver disease in chronic HBV is rapidly progressive^{10,21,23,77} [III, B]. There is an increased rate of fulminant hepatitis and progression of chronic hepatitis to cirrhosis^{21,22,77} [III, B]. Diagnosis is confirmed by a positive anti-HDV antibody or HDV-RNA test^{23,28} [III, B].

HEPATITIS C VIRUS INFECTION

Introduction

A RNA virus in the flaviviridae family. It is endemic worldwide with high prevalence rates (>10%) in Mongolia, Egypt, Cameroon, Guinea and Bolivia.^{4,78} The WHO estimates that 3% of the world's population is infected, with four million carriers in Europe. The prevalence in most European countries is 1–2.5% with the highest rates in Moldova and Romania (2.5–10%).⁷⁹ Within most countries the highest rates are in IDUs and men with haemophilia.^{4,79}

Transmission

- Parenteral spread accounts for the majority of cases through shared needles/syringes and other drug paraphernalia (e.g. filters, water) in IDUs, transfusion of contaminated

blood or blood products (pre 1990s), renal dialysis, sharing razors with infected individuals or needle-stick injury.^{79–85}

- Sexual transmission occurs at a low rate (approximately 0.2–2% per year of relationship), but this rate increases if the index patient and/or the recipient or both are HIV-infected.^{86–92} There has been a steady rise in acute HCV throughout Europe in MSM over the last 10 years, mostly associated with HIV-co-infection.^{11,87,88,90} Other factors linked to HCV in MSM include ulcerative STIs such as syphilis and lymphogranuloma venereum, traumatic anal sexual practices and recreational drugs such as cocaine snorting.^{11,87,88,90} There is also evidence of slightly increased risk of HCV infection in female sex workers, former prisoners, tattoo recipients and alcoholics.^{7,93–96}
- Vertical (mother to infant) spread also occurs at a low rate (5% or less) in HCV-RNA-positive women.^{86,97–101} Higher rates (usually around 20% but up to 40%) are seen if the woman is both HIV and HCV positive, most likely associated with high serum HCV-RNA levels in these carriers.^{97–101}
- Among blood donors, 50% of those with HCV infection do not admit to having recognizable risk factors (sporadic cases).¹⁰²

Diagnosis

Clinical

Incubation period: 4–20 weeks for symptomatic acute hepatitis C.

When considering a clinical diagnosis of hepatitis C, there are no features that distinguish it reliably from HBV or HAV. The clinical pointers to hepatitis C would be whether there was a history of travel, parenteral and sexual exposures and the incubation period.

The majority of patients (>80%) undergo asymptomatic acute infection.^{81,82,103}

- More than twenty percent have acute icteric hepatitis^{81,82,103} but fulminant hepatitis is particularly common after hepatitis A super-infection of chronic hepatitis C carriers.¹⁰⁴
- Approximately 70–85% of individuals with acute hepatitis C become chronic carriers – a state which is generally asymptomatic but may cause non-specific ill health.^{103,105,106} Some reports suggest that HCV genotype 1 could clear spontaneously more often, but leads to more severe liver disease.¹⁰⁵ Once established, the rate of progression of the liver disease varies from patient to patient (0.02%/year).^{81,82} Liver cirrhosis and decompensated liver disease appears earlier if there is a high alcohol intake or other liver disease, including steatohepatitis.^{107–110} Significant liver disease can be present in up to 35% of carriers who have normal serum aminotransferase levels.^{81,82,111,112}

Laboratory

- A screening antibody test such as an enzyme immunoassay (EIA) or other immunoassay is initially performed and RT-PCR for RNA is used to confirm active infection [IIa, B].^{114–117} In HIV-positive patients with a low CD4 count (<200 cells/mm³) the EIA may occasionally be negative and an RT-PCR may be needed for definitive diagnosis [IIb, B].¹¹³ An antibody test may not become positive for three or more months after acute HCV infection but a test for HCV-RNA will be positive after only two weeks [IIb, B].^{114–117} Chronic infection is confirmed if an HCV-RNA assay is positive six months after the first positive test. Patients with low-level viraemia may require HCV-RNA

levels testing on two or more occasions to confirm infection [IIb, B].¹¹⁴⁻¹¹⁷ All patients being considered for therapy should have a viral RNA test to confirm viraemia and be genotyped. A positive antibody test with persistently negative RNA tests indicates resolved infection [IIb, B].¹¹⁴⁻¹¹⁷

- Acute HCV infection – ALT levels are raised but rarely >1000 IU/L; serum bilirubin: rarely >300 mmol/L; alkaline phosphatase is generally <2× the upper limit of normal, except in cases complicated by cholestasis. Prothrombin time is rarely prolonged by up to five seconds; greater prolongation indicates developing hepatic failure.
- Chronic HCV infection – in most cases the only abnormality to be found will be mildly abnormal aminotransferase levels (usually <100 IU/L) and in a third of patients the LFTs will be normal (defined as ≤19 IU/L for women and <30 IU/L in men).

Indications for HCV testing

- (1) Patient with acute icteric hepatitis: also measure LFT, prothrombin time, urea and electrolytes. If HCV antibody test is negative, consider re-testing three and nine months after the onset of jaundice or test immediately using RT-PCR if available [IIb, B].¹¹⁴⁻¹¹⁷ Also test for hepatitis A and B (and hepatitis E in travellers to, or immigrants from, endemic areas) (see below);
- (2) Part of screening
 - (i) Consider testing for hepatitis C in all current/past IDUs, especially if equipment has been shared, in men with haemophilia or other patients who received blood or blood products pre-1991 and in people sustaining a needle-stick injury if the donor HCV status was positive or unknown [IIb, B].⁸⁰⁻⁸⁴
 - (ii) Other groups to be considered for testing are sexual partners of HCV-positive individuals, MSM, especially if HIV-infected, female sex workers, tattoo recipients, alcoholics and ex-prisoners [III, B].^{7,11,87,88,90,93-96} It may take three months or more for the anti-HCV test to become positive after exposure (see 'diagnosis').
- (3) All HIV-infected persons, especially from the countries where the HIV epidemic has been driven by IDUs and especially prior to HAART.

Primary prevention vaccination

- Needle and syringe exchange schemes for drug users have led to a fall in parenterally transmitted infections including HCV, HBV and HIV in most studies [IIb, B].¹¹⁸⁻¹²¹ Harm reduction strategies around injecting drug use should also be discussed.
- It seems likely that if condoms are used consistently, then sexual transmission of HCV will be avoided [III, B].³⁸
- Since 1991 donated blood has been screened for HCV and blood products rendered almost incapable of transmitting infection in most European countries [III, B].^{103,122}
- There is no effective HCV vaccine currently available.

Management of HCV-positive patients

General

- Patients should be clearly advised not to donate blood, semen or organs and should be given advice on other routes of transmission, including unprotected anal and vaginal sex [IIb, B].^{7,11,87,88,90,93-96}

- Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s). This should be reinforced by giving them clear and accurate written information [IV, C].
- Acute hepatitis C infection is a notifiable disease in many countries.^{78,79}
- If not performed already, screen for other STIs in cases thought to have been sexually acquired or if otherwise appropriate [III, B].^{8,16}
- Other tests for assessing chronic liver disease should be performed by specialists in this field [III, B].^{81,123,124} Among others, assessment of liver synthetic function (albumin, prothrombin time), disclosure of portal hypertension (platelets, ultrasonography) and liver fibrosis estimation using non-invasive markers (serum fibrosis indexes or imaging techniques such as elastometry) are warranted. Liver biopsy may be considered in patients in whom other hepatic diseases want to be excluded or when required by treatment protocols. Otherwise, liver biopsy is no longer mandatory as part of regular chronic hepatitis C assessment.
- All patients with cirrhosis should be screened for hepatocellular carcinoma, ideally every six months, by a specialist in liver disease.

Indications for therapy

- Acute icteric hepatitis: There is firm evidence that pegylated interferon (with or without ribavirin) given during the acute phase will reduce the rate of chronicity to only 10% or less [Ia, A].¹²⁵⁻¹²⁷ Spontaneous resolution of acute hepatitis C is presumed when there is a loss of HCV-RNA within the first 12 weeks, although fluctuations are not rare during the first year following acute HCV exposure. Only those HCV-RNA positive for more than 12 weeks need to be treated.¹²⁶ HCV genotype 1 and 4 infections require 24 weeks' therapy whereas HCV genotypes 2 or 3 need only 12 weeks' treatment¹²⁶ [Ia, A]. If HIV positive, the patient may need to be treated earlier than 12 weeks and should see a specialist in this area of management.
- Chronic HCV infection: Pegylated interferon alfa with ribavirin will cure chronic infection in approximately 50% of patients [Ia, A].¹²⁸⁻¹³³ However, the treatment required will vary according to the genotype, initial treatment response and other factors. Treatment should be for 12–24 weeks for patients with genotypes 2 or 3,^{131,133} although HCV genotype 3 patients with advanced liver fibrosis and detectable HCV-RNA at week 4 of therapy may benefit from longer treatment duration (12 months). All other HCV genotypes (including 1 and 4) should be treated for 12–18 months. Treatment should be discontinued if there has not been a reduction in HCV viral load >2 log at week 12 of therapy or undetectable levels at week 24. Patients achieving undetectable viral load at week 4 (rapid virological responders) have the greatest chances of cure and may benefit from shorter courses of therapy.¹³² Patients are more likely to respond if they do not have cirrhosis, have low serum HCV-RNA levels (<500,000 IU/mL), if they are infected with certain HCV genotypes (types 2 and 3) [Ib, A].¹²⁸⁻¹³³
- HIV-positive patients respond to treatment, although not as well as HIV-negative patients [Ib, A].¹³⁴⁻¹³⁷ Sustained virological response in those completing therapy is 11–29% for genotypes 1 or 4 and 43–73% for genotypes 2 or 3 [Ib, A].¹³⁴⁻¹³⁷

- Patient selection for therapy depends mainly on HCV genotype and viral load. A liver biopsy is not necessary for making treatment decisions [1b, A] although may be indicated in specific circumstances.^{123,124,128,129,130–137}
- Hepatitis A and B vaccination should be offered to hepatitis C carriers due to the worse prognosis of dual infection [III, B].^{104,138} They should be informed of the increased risk of liver damage related to alcohol abuse [III, B].^{107–110}

Special situations

Pregnancy and breast feeding

- There is at present no clear knowledge about how to reduce the risk of vertical transmission. However, minimizing blood exposure from the mother to the child is expected to be beneficial, as in HIV infection. Women should be informed of the potential risk of transmission in pregnancy (see transmission) [IIb, B].^{86,97–101}
- Breast feeding: there is no evidence of additional risk of transmission, but caution warrants the avoidance of breast-feeding when possible in women who harbour a high HCV viral load [III, B].^{97–101,139}

Management of partners and other contacts

- Partner notification should be performed and the outcome documented at subsequent follow-up [IV, C]. Contact tracing to include needle sharing partners and any sexual contact (penetrative vaginal or anal sex) or during the period in which the index case is thought to have been infectious.^{11,79,80,86–92} The infectious period is from four weeks before the onset of jaundice in acute infection. If there was no acute infection, trace back to the likely time of infection (e.g. blood transfusion, first needle sharing) although this may be impractical for periods longer than two or three years [IV, C]. Consider testing children born to infectious women [III, B].^{87,98–102} For other non-sexual contacts thought to be at risk, discuss with the public health physician.
- There is currently no available vaccine or immunoglobulin preparation that will prevent HCV acquisition.
- Sexual transmission should be discussed. It seems likely that if condoms are used consistently then sexual transmission will be avoided [III, B],³⁸ but given the very low rate of transmission outside of HIV co-infection [III, B],^{86–92} monogamous partners may choose not to use them.

Follow up

- Acute infection: Regular LFT (1–4 weekly) until normal. In view of the possibility of chronic infection, serum HCV-RNA should be repeated after six months even if the LFT is normal [III, B].^{114–117}
- Chronic infection: If untreated, patients should be regularly reviewed at intervals of 6–12 months, ideally by a physician with expertise in this disease [IV, C].
- There is no protective HCV immunity. Infection with another HCV variant, belonging to the same genotype or another, is well documented, among patients engaged in risk practices [III, B].^{114–117,140}

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APPENDIX A

EVIDENCE BASE

Medline

For each type of hepatitis, a medline search was performed for the years 1966-2009 (May) for hepatitis type B and 1990-2009 (May) for hepatitis C. From the MeSH terms 'hepatitis B', and 'hepatitis C', the following subheadings were used: complications, drug therapy, diagnosis, epidemiology, etiology, mortality, prevention and control, therapy, transmission, virology. The searches were limited to 'human' for all searches. For drug therapy, prevention & control, and therapy searches were limited initially to 'randomized controlled trials' but in the absence of enough publications this was changed to 'controlled clinical trials', 'clinical trials' or 'reviews' in that order. For the subheadings other than these three the search was limited to 'reviews'. Textword searches for 'hepatitis B' and 'hepatitis C' were combined, as appropriate, with textword searches for 'complications', 'diagnosis', 'prevention', 'transmission', 'immunoglobulin', 'vaccine', 'non-response', 'non-responders', 'HIV', 'PubMed; randomized controlled trial', 'lamivudine', 'telbivudine', 'entecavir', 'tenofovir', 'pegylated', 'adefovir', 'ribavirin'.

Cochrane Library

The Cochrane Library Database of Systematic Reviews was searched for all relevant articles using the textword 'hepatitis'.

APPENDIX B

LEVELS OF EVIDENCE

- Ia Evidence obtained from meta-analysis of randomized controlled trials.
- Ib Evidence obtained from at least one randomized controlled trial.
- IIa Evidence obtained from at least one well designed study without randomization.
- IIb Evidence obtained from at least one other type of well designed quasi-experimental study.
- III Evidence obtained from well designed non-experimental descriptive studies such as comparative studies, correlation studies and case-control studies.
- IV Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

GRADING OF RECOMMENDATIONS

A (evidence levels Ia, Ib) requires at least one randomized control trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.

B (evidence levels IIa, IIb, III) requires availability of well conducted clinical studies but no randomized clinical trials on the topic of recommendation.

C (evidence IV) requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.

APPENDIX C

DECLARATIONS OF INTEREST

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