

# **United Kingdom National Guideline on the Management of the Viral Hepatitis A, B & C 2008**

## **Clinical Effectiveness Group British Association of Sexual Health and HIV**

### Introduction and Methodology

The main objective is to reduce the number of sexually transmitted infections (STIs) and the complications that can arise in people either presenting with signs and symptoms of an STI, or undergoing investigation for possible infection.

This guideline offers recommendations on the diagnostic tests, treatment regimens and health promotion principles needed for the effective management of Hepatitis A, B and C. Covering, the management of the initial presentation, as well as how to prevent transmission and future infection.

It is aimed primarily at people aged 16 years or older (see specific guidelines for those under 16) presenting to health care professionals, working in genitourinary medicine departments within the United Kingdom. However, the principles of the recommendations could be adopted in other health care settings.

#### *Stake holder involvement*

This is the fourth revision of a guideline first written in 1998. Previous versions of the guideline have been reviewed by the Health Advisers professional association (SHASTD), the MSSVD, AGUM and Royal College of Physicians. All previous versions have also been on the MSSVD, AGUM and BASSH websites since 1998, where comments were invited from website visitors.

#### *Rigour of development*

##### Search strategy

For each type of hepatitis, a medline search was performed for the years 1966 - 2008 (Feb.) for hepatitis types A and B and 1990-2008 (Feb) for hepatitis C. From the MeSH terms "hepatitis A", "hepatitis B", and "hepatitis C", the following sub-headings 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 sub-headings other than these three the search was limited to "reviews". Textword searches for "hepatitis A", hepatitis B", and "hepatitis C" were combined, as appropriate, with textword searches for "complication", "diagnosis", "prevention", "transmission", "immunoglobulin", "vaccine", "non-response", "non-responders", "HIV", "randomized controlled trial".

##### Criteria for inclusion:

- Evidence from RCTs was used where possible, and failing that the studies using other rigorous scientific method.

- Recommendations were based on RCT or other scientific evidence and graded accordingly.
- No harms are anticipated

Prior to publication the final draft of the guideline was placed on the BASHH website, and copies circulated to the BASHH branch chairs, GUNA and SSHA chairs for comment and peer review. After a period of three months any comments received were reviewed by the guideline authors, and acted on appropriately, before final authorisation by the CEG was given and publication was undertaken.

Timescale for next revision: 2 years

## Hepatitis A virus infection

### Aetiology

Caused by a picorna (RNA) virus. It is particularly common in areas of the world where sanitation is poor (developing countries) and largely affects children there. In the developed world it is less common (784 cases reported in England and Wales, 2004) and causes disease in all age groups [1].

#### Transmission:

- Faeco-oral (via food, water, close personal contact) [2-7].
- Outbreaks have been reported in men who have sex with men, linked to oro-anal or digital-rectal contact, multiple sexual partners, anonymous partners, sex in public places and group sex [8-14]. However, several seroprevalence studies in the UK, Spain, USA and Italy show a similar rate of hepatitis A (IgG) antibodies in homosexual and heterosexual men [12,15,16].
- HIV-positive patients are not at increased risk but may be more infectious [17,18].
- Outbreaks have also been reported amongst injecting drug users [1,19], in institutions for people with learning difficulties, and in contaminated batches of factor VIII [20-22].
- Patients are infectious for approximately two weeks before and one week after the jaundice by the non-parenteral routes but virus can be found in the blood and stool until after the serum amino-transferase levels have peaked [23]. In HIV positive patients, Hepatitis A (HAV) viraemia may continue for over 90 days [17].

### Clinical Features

Incubation Period: 15-45 days [2,3,24]

#### Symptoms [24]

Most children and up to half of adults are asymptomatic or have mild non-specific symptoms with little or no jaundice.

In the more 'typical' case there are two phases of symptoms -

- *The prodromal illness:* flu-like symptoms (malaise, myalgia, fatigue), often with right upper abdominal pain. This phase lasts for 3-10 days. This is followed by -
- *The icteric illness:* jaundice (mixed hepatic and cholestatic) associated with anorexia, nausea and fatigue which usually lasts for 1-3 weeks. It can persist for 12 or more weeks in a minority of patients who have cholestatic symptoms (itching and deep jaundice) [25]. Fever is not found in this phase.

### Signs [16]

- None specific in the prodromal phase.
- Icteric phase - jaundice with pale stools and dark urine. Liver enlargement/tenderness and signs of dehydration are also common.

### Complications

- Acute liver failure (ALF) complicates approximately 0.4% of cases, although 15% of patients may require hospital care, of whom a quarter will have severe hepatitis (Prothrombin time P.T. > 3 seconds prolonged or bilirubin >170 $\mu$ moles/l) [26,27]. ALF due to hepatitis A is more common in patients already infected with chronic hepatitis B or C, although studies differ widely in measured rates [26,28].
- Chronic infection (>6 months) has only been reported in a tiny number of case-reports [29].
- The overall mortality is < 0.1% although rises to 40% on those with acute liver failure unless they receive a liver transplant [26,27].
- Pregnancy - The infection does not have any teratogenic effects but there is an increased rate of miscarriage and premature labour, proportional to the severity of the illness [30,31]. There have been case reports of possible vertical transmission [30,32,33].

Diagnosis (See also: Sexually Transmitted Infection Screening Guidelines) ([www.BASSH.org](http://www.BASSH.org))

#### Serology

- Confirmed by a positive serum Hepatitis A virus - specific IgM (HAV-IgM) which remains positive for six months or more [34,35]. HAV-IgG does not distinguish between current or past infection and may remain positive for life [34,36].

#### Other tests

- Serum/plasma amino-transferases (AST/ALT) 500-10,000 i.u./l. Bilirubin up to 500  $\mu$ moles/l. Alkaline phosphatase levels < 2x the upper limit of normal, but higher if there is cholestasis [24,26-28].
- Prothrombin time (PT) prolongation by more than 5 seconds suggests developing hepatic decompensation [24,26].

### Management

#### General Advice

- Patients should be advised to avoid food handling and unprotected sexual intercourse until they have become non-infectious (III,B) [2-4,7,37]
- 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.
- Hepatitis A is a notifiable disease.

#### Further Investigations

Screen for other sexually transmitted infections in cases of sexually-acquired hepatitis or if otherwise appropriate.

#### Acute icteric hepatitis

- Mild/moderate (80%) - manage as an outpatient emphasising rest and oral hydration (III, B) [24].

- Severe attack with vomiting, dehydration or signs of hepatic decompensation (change in conscious level or personality) - admit to hospital (III, B) [26,27].

#### Pregnancy and Breast Feeding

- Pregnant women should be advised of the increased risk of miscarriage/premature labour and the need to seek medical advice if this happens [30, 31].
- Breast feeding can be continued and most children will have mild or asymptomatic infection (IV,C) [38].

#### Sexual and Other Contacts

- Partner notification should be performed for at-risk homosexual contacts (oro/anal, digital/rectal and penetrative anal sex) within the period two weeks before to one week after the onset of jaundice. This to be documented and the outcome documented at subsequent follow-up. Other people thought to be at risk (household contacts, those at risk from food/water contamination ) to be contacted via the public health authorities (consultant in communicable control (CCDC) or equivalent). The CCDC has a duty of confidentiality to the index patient.
- Hepatitis A vaccine may be given up to 14 days after exposure providing exposure was within the infectious period of the source case (during the prodromal illness or first week of jaundice) (Ib, A) [38-41].
- Human normal immunoglobulin (HNIG) 250-500 mg. intramuscularly should also be considered for patients at higher risk of complications (concurrent chronic hepatitis B or C, chronic liver disease or age >50 yo) (Ib, A) [38-40]. HNIG that is effective against HAV is in short supply in the UK and can only be obtained from the Health Protection Agency (England and Wales), Health Protection Scotland or the Northern Ireland Public Health Laboratory Belfast [38].
- HNIG works best if given in the first few days after first contact with an efficacy of 90% and is unlikely to give any protection more than two weeks after first exposure, but may reduce disease severity if given up to 28days after exposure [39].
- Patients are most infectious for two weeks before the jaundice (i.e. before the illness is recognised).
- Hepatitis A vaccine schedule: doses at 0 and 6-12 months, 95% protection for at least ten years (Ib, A)[42-45]. Current advice is to revaccinate after ten years (IIb, B) [42-6], however there is increasing evidence that vaccine-induced immunity may be  $\geq 20$  years and possibly lifelong, so no further booster doses may be needed after the primary course in immunocompetent patients [42-44].
- HIV-positive patients respond (antibody production) in 46-88% but titres are lower than in HIV-negative individuals, and correlates with CD4 count (IIa, B)[45,46].
- If patients with a low CD4 count ( $< 300$  cells/mm<sup>3</sup>) are vaccinated, they should be revaccinated if the CD4 count rises above 500/mm<sup>3</sup> as a result of HAART if the HAV IgG remains negative on retesting [45-47].
- There is a combined Hepatitis A+B vaccine given on the same schedule as the hepatitis B vaccine and has similar efficacy to the individual vaccines although early immunity to hepatitis B may be impaired (IIa, B) [48,49].
- If an outbreak is suspected or if the index case is a food handler, notify the local CCDC/public health department by telephone (IV, C)[38,39].

#### Follow-Up

- See at one or two weekly intervals until amino-transferase levels are normal (usually 4 -12 weeks) (IV, C).

- Immunity is usually lifelong. [34,36]

### Primary Prevention

- Current evidence still suggests that most men who have sex with men are not at increased risk for hepatitis A infection [12,15,16] and therefore universal vaccination in this group cannot be firmly recommended (III, B). However, many outbreaks have been reported amongst homosexual men in large cities and therefore clinics in these areas (e.g. central London) should offer vaccination, particularly when increased rates of infection have been recognised locally (III, B) [8-14, 38,39].
- Screening for pre-existing hepatitis A exposure before vaccination has been found to be cost-effective( III,B) [51]
- Injecting drug users and patients with chronic hepatitis C infection should also be vaccinated (III, B) [17-19, 28, 38,39].
- Vaccination is also recommended for travellers to developing countries, people with haemophilia or chronic liver disease, those with occupational exposure and for people at risk in an outbreak (Ib, A) [1,38,39].
- Health/sex education should stress the routes of transmission and the higher incidence in developing countries (IV, C) [38].

## Hepatitis B virus infection

### Aetiology

Caused by an hepadna (DNA) virus. It is endemic world-wide, apart from isolated communities, with very high carriage rates (up to 20%) particularly in South and East Asia, but also in Southern Europe, Central and South America, Africa and Eastern Europe. In the UK carriage varies from 0.01-0.04% in blood donors to >1% in intravenous drug users and homosexual men [52]. In 2003 1151 cases were notified in England and Wales [52]. There are eight distinct genotypes (A-H) which vary in geographical distribution, pathogenicity and treatment susceptibility [53].

### Transmission

- Sexual transmission occurs in unvaccinated/non-immune men who have sex with men and correlates with multiple partners, unprotected anal sex and also with oro-anal sex ("rimming") [53-56]. Transmission also occurs after heterosexual contact e.g. 18% infection rates for regular partners of patients with acute hepatitis B [57-59]. Sex workers are also at higher risk [60,61].
- Other routes are: parenteral (blood, blood products, injecting drug-users sharing needles, syringes and other 'works', needle-stick, acupuncture) and vertical (infected mother to infant) [53, 58, 62-65].
- Sporadic infection occurs in people without apparent risk factors, in institutions for learning difficulties and also in children in countries of high endemicity, but in these cases the means of transmission is poorly understood [66,67].

### Clinical Features

Incubation period. 40-160 days

### Symptoms

- Virtually all infants and children have asymptomatic acute infection. Asymptomatic infection is also found in 10-50% of adults in the acute phase and is especially likely in those with HIV co-infection [24, 68-70].

- Chronic carriers are usually asymptomatic but may have fatigue or loss of appetite [69].
- The prodromal and icteric phases are very similar to hepatitis A, but may be more severe and prolonged [24].

### Signs

- As for hepatitis A in the acute phase.
- If chronic infection occurs there are often no physical signs. After many years of infection, depending on the severity and duration, there may be signs of chronic liver disease including spider naevi, finger clubbing, jaundice and hepato-splenomegaly, and in severe cases thin skin, bruising, ascites, liver flap and encephalopathy [54, 70-73].

### Complications

- Fulminant hepatitis occurs in less than 1% of symptomatic cases but carries a worse prognosis than that caused by hepatitis A [26,27].
- Chronic infection (>6 months) occurs in 5-10% of symptomatic cases but the rate is higher in immuno-compromised patients with HIV infection, chronic renal failure or those receiving immuno-suppressive drugs [53, 68, 70-72]. Immunosuppressive treatment can also reactivate hepatitis B [74]. A higher rate of chronic infection is also found in patients at institutions for learning disabilities [66]. Almost all (>90%) of infants born to infectious (HBeAg +ve) mothers will become chronic carriers unless immunised [62,64].
- There are 4 phases of chronic carriage: 1. Immune Tolerant (hepatitis B e antigen positive, normal aminotransferase levels, little or no necro-inflammation on liver biopsy), 2. Immune Active, eAg-positive phase (hepatitis B e antigen positive, raised aminotransferases, progressive necro-inflammation and fibrosis), 3. Inactive hepatitis B carrier (sAg+, eAg -, low levels of HBV DNA and normal aminotransferases) and 4. eAg negative chronic active hepatitis (Pre-core, core-promotor mutations, eAg -ve, detectable HBV DNA, progressive inflammation and fibrosis). Types 2 and 4 may progress to cirrhosis and liver cancer, with type 4 generally progressing fastest [53,70,71].
- Concurrent hepatitis C infection can lead to fulminant hepatitis, more aggressive chronic hepatitis and increased risk of liver cancer [75-77]. Concurrent HIV infection increases the risk of progression to cirrhosis and death [72, 78]. Hepatitis A co-infection can be severe acutely, but may lead to the reduction of long-term HBV replication [79]
- Concurrent Delta virus infection, or delta virus superinfection may lead to progressive fibrosis, cirrhosis and end-stage liver disease.
- Mortality is less than 1% for acute cases [26]. Between ten and fifty percent of chronic carriers will develop cirrhosis leading to premature death in approximately 50% [54, 68, 75]. Ten percent or more of cirrhotic patients will progress to liver cancer.[54, 68, 75, 77].
- Pregnancy- there is an increased rate of miscarriage/premature labour in acute infection [31]. There is a risk of vertical transmission (see above) [62,64]

Diagnosis (see also Sexually Transmitted Infection Screening and Testing Guidelines - Hepatitis A, B and C)

**Table 1 Hepatitis B serology [34, 53, 54, 69, 70, 71]**

Stage of infection	Surface antigen (HBsAg)	'e' antigen (HBeAg)	IgM anti-core antibody	IgG anti-core antibody	Hepatitis B virus DNA	Anti-HBe	Anti-HBs	ALT
Acute (early)	+	+	+	+	+	-	-	↑↑↑
Acute (resolving)	+	-	+	+	-	+/-	-	↑↑

<b>Chronic (immune tolerant)</b>	+	+	-	+	++	-	-	<b>N**</b>
<b>Chronic (immune active)</b>	+	+	-	+	+	-	-	↑
<b>Chronic (eAg Neg.)</b>	+	-	-	+	+	+/-	-	↑
<b>Chronic (inactive carrier)</b>	+	-	-	+	-	+	-	<b>N</b>
<b>Resolved (immune)</b>	-	-	-	+	-	+/-	+/-	<b>N</b>
<b>Successful vaccination</b>	-	-	-	-	-	-	+	<b>N</b>

\*in very early infection the IgM anti-core can be negative and by definition so can the IgG

\*\* N=normal

#### Other tests

- Acute infection - see hepatitis A

Chronic infection - in most cases the only abnormality to be found will be mildly abnormal amino-transferase levels (usually <100 i.u./l) and in many the liver enzymes will be normal. Only in severe late stage liver disease does the liver enzymes and liver function tests (LFTs) become grossly abnormal [53, 54, 69-72]. Disease activity correlates with HBV-DNA levels and a level >10<sup>5</sup>copies/ml is regarded as significant (in terms of risk of progression to cirrhosis and hepatocellular carcinoma) and meriting consideration of therapy [70,71].

#### Management

##### General Advice

- Patients should be advised to avoid unprotected sexual intercourse, including oro-anal and oro-genital contact until they have become non-infectious or their partners have been successfully vaccinated (see below) (III,B) [53,54,57 62].
- 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 blood (IV, C) [62].
- Hepatitis B is a notifiable disease

##### Further Investigations

- Screen for other sexually transmitted diseases in cases thought to have been sexually acquired or if otherwise appropriate (IIb,B)[52, 60].
- Other tests such as liver biopsy (for staging and grading of liver disease) should be performed by specialists in this field (IV,C) [54, 69-72].
- Non-invasive methods of assessing liver fibrosis such as hepatic elastography (e.g. fibroscan) may provide useful information to complement the liver biopsy [80].

##### Acute icteric hepatitis

- As for hepatitis A.

#### Treatment of Chronic Infection

- Refer all HBsAg+ve patients to a hepatologist or physician experienced in the management of liver disease (IV.C)
- Treatment should normally be given in collaboration with a hepatologist or physician experienced in the management of liver disease (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 cut offs of  $10^5$ ,  $10^4$  and  $10^3$  copies/ml, are often used for HBeAg+ve chronic hepatitis, HBeAg – ve chronic hepatitis and cirrhosis respectively [70, 71]

- Patients should be considered for therapy with lamivudine, adefovir, tenofovir, telbivudine, entecavir (or combinations of nucleos(t)ide analogues) or pegylated interferon (Ib, A)[70-73, 81-87]. Additional treatments that may soon be licensed in HBV monoinfection include emtricitabine (FTC) (Ib,A), clevudine (II,B) and valtorcitabine (III,C) [81-88]. Treatment responders have long-term benefits in terms of reduced liver damage and decreased risk of liver cancer [80-88].
- All patients should have an HIV test prior to starting HBV therapy because of the different treatment strategies required and the significant risk of anti-retroviral-resistant HIV developing if lamivudine, tenofovir or entecavir are used as monotherapy (Ib,A) [89-93].
- Lamivudine, emtricitabine and tenofovir will suppress hepatitis B viral replication during therapy of HIV (see also the British HIV association guidelines on the treatment of HIV/HBV co-infection) [89-93], and may delay liver damage if given as part of triple antiretroviral therapy. (Ib, A)[91-93].
- Lamivudine and emtricitabine should only be given to HIV+ patients in combination with tenofovir as part of HAART because of the rapid high rate of resistance that occurs to these drugs if given as the only HBV-active agent (Ib,A) [91-93]. Entecavir should not be used in HIV+ patients without adequately suppressed HIV as it causes the M184V (lamivudine/emtricitabine) resistant mutation (84).
- Adefovir or telbivudine can be used alone in HIV+ patients (II,B) [91]
- Active surveillance of cirrhotic patients for Hepato-cellular carcinoma(HCC) leads to earlier detection and better treatment outcomes [94].
- In the context of HBV, there is a high risk of HCC development in some groups of non-cirrhotic patients. This includes African patients over the age of 20, Asian males over 40, Asian females over 50, and patients with a family history of HCC. HBV-infected patients meeting these criteria should be offered HCC screening [94].
- Specific therapy otherwise may not be indicated unless de-compensated liver disease ensues (IV, C) [54].

#### Pregnancy and Breastfeeding

- Vertical transmission (mother to infant) of infection occurs in ninety percent of pregnancies where the mother is hepatitis B e antigen positive and in about ten percent of surface antigen positive, e antigen negative mothers. Most (>90%) of infected infants become chronic carriers [95].
- Infants born to infectious mothers are vaccinated from birth, usually in combination with Hepatitis B specific Immunoglobulin 200 i.u. i.m. (Ia, A) [95,99]. This reduces vertical transmission by ninety percent.
- There is some evidence that treating the mother in the last month of pregnancy with lamivudine may further reduce the transmission rate if she is highly infectious (HBV-DNA  $\geq 1.2 \times 10^9$  geq/ml) (III,C), but this needs to be further substantiated [95-97].
- Infected mothers should continue to breast feed as there is no additional risk of transmission (II, B)[97].
- Hepatitis B may exacerbate after the end of pregnancy [98]

#### Sexual 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 (IV,C) [37]. The infectious period is from two weeks before the

onset of jaundice until the patient becomes surface antigen 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. Arrange screening for hepatitis B of children who have been born to infectious women if the child was not vaccinated at birth (IV,C)[62]. For screening of other non-sexual partners who may be at risk, discuss with the CCDC or equivalent.

- Specific hepatitis B immunoglobulin 500 i.u. intramuscularly (HBIG) may be administered to a non-immune contact after a single unprotected sexual exposure or parenteral exposure/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 (Ib, A) [62, 99].
- An accelerated course of recombinant vaccine should be offered to those given HBIG plus all sexual and household contacts (at 0, 7 and 21 days or 0, 1, 2 months with a booster at 12 months in either course) (Ib, A) [62, 63, 97, 98, 100, 101-105]. Vaccination theoretically will provide some protection from disease when started up to six weeks after exposure.
- Avoid sexual contact, especially unprotected penetrative sex, until vaccination has been successful (anti-HBs titres >10i.u./l.) (Ib, A) [62, 97, 98, 101-105].
- The ultra-rapid vaccination schedule (0,7,21 days) leads to an anti-HBs antibody response in only 80% of recipients 4-12 weeks after the third dose [101-105]. This rises to 95% just prior to the 12 month booster dose. It would be prudent to offer booster vaccinations of up to three further doses to the 20% of sexual or household contacts without detectable antibodies 4-12 weeks after the primary course (IV, C), even though most would have eventually developed an antibody response.

#### Follow-up.

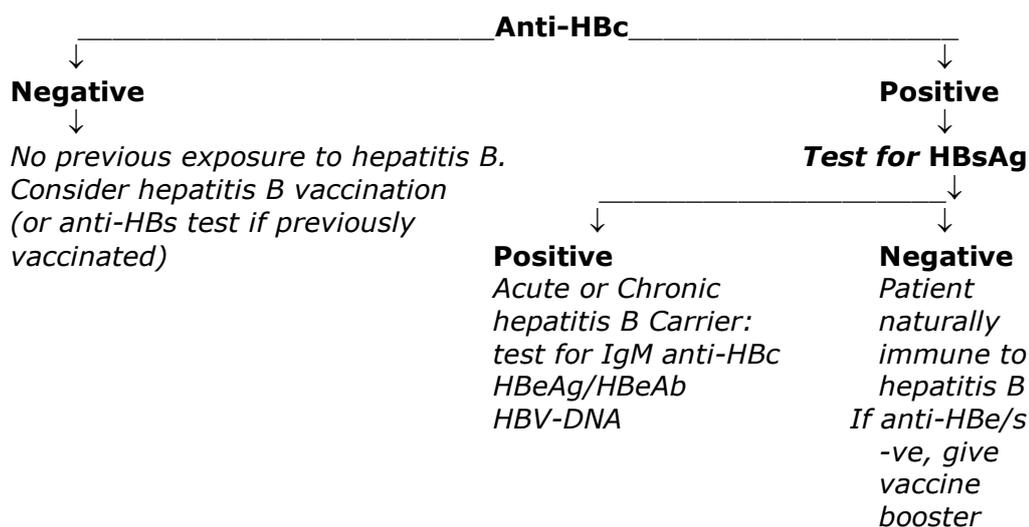
- Acute infection: as for hepatitis A. In view of the possibility of chronic infection, serology should be repeated after six months even if the LFT is normal [54, 68, 69].
- Chronic infection (HBeAg+ve or HBV-DNA >10<sup>5</sup>iu/ml): If untreated, patients should be regularly reviewed at intervals of one year or less, ideally by a physician with expertise in this disease (IV, C) [54, 68].
- Immunity after recovery from infection (surface antigen negative) is lifelong in over 90%.

#### Screening and Primary Prevention (see also UK Sexually Transmitted Infection Screening and Testing Guidelines - Hepatitis A, B and C: *Sexually Transmitted Infections 2006;82(Suppl IV):iv35-iv39*)

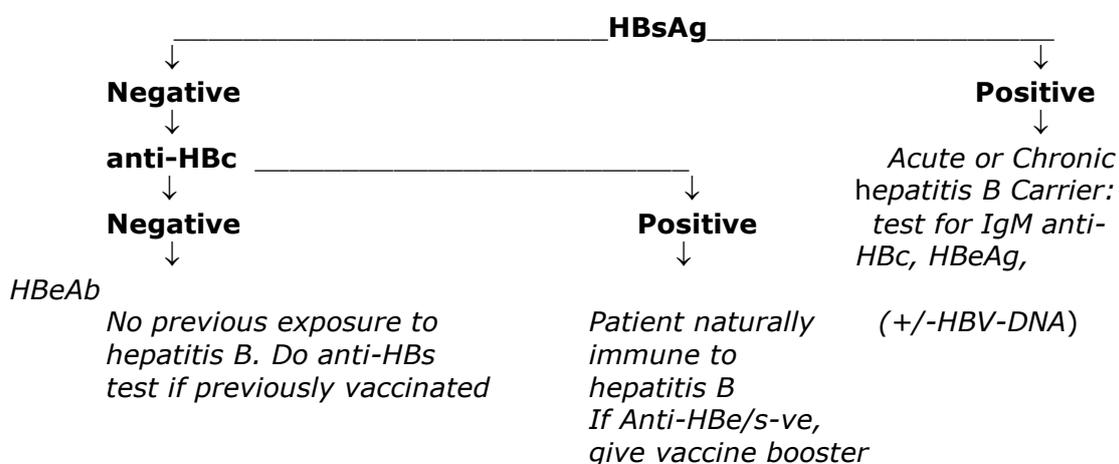
- Hepatitis B testing in asymptomatic patients should be considered in men who have sex with men, sex workers (of either sex), injecting drug users, HIV-positive patients, sexual assault victims, people from countries where hepatitis B is common (outside of Western Europe, North America and Australasia), needle-stick victims and sexual partners of positive or high-risk patients (IV, C) [61, 62, 79,97,98]. If non-immune, consider vaccination (see below) (Ib, A) [62, 63, 100-105]. If found to be chronic carriers consider referral for therapy (Ia, A) [70-73, 80-90].
- The simplest initial screening test in someone who is unvaccinated or is of unknown infection status is anti-HBc, with the addition of other tests as necessary (III,B)[106, 107]. Some also screen for HBsAg initially (IV, C)[79,107]. Measure anti-HBs in those who have been vaccinated (1b, A) [101-117].
- Lone anti-HBc positives. Measure anti-HBs and anti-HBe in those who are anti-HBc+ve, HBsAg -ve. If anti-HBs -ve and anti-HBe -ve, the anti-HBc may be a false positive. A single hepatitis B vaccine dose will induce anti-HBs if

there has been past natural HBV exposure (amenestic response, measured 4 weeks after single dose of HBV vaccine). If anti-HBs is still negative after a single booster, regard as non-infectious and give a full course of vaccine (III.B).[114]

**Flow chart for hepatitis B screening using serum anti-HBc**



**Flow chart for hepatitis B screening using serum HBsAg**



- Vaccination should be offered to non-immune patients in most of the above groups (Ib, A) [62, 63, 100, 101-105]. The main exception is people born in countries of high endemicity but not at continuing risk who are being screened primarily to detect chronic carriage (IV, C)[79].
- HIV positive patients show a reduced response rate to the vaccine and become anti-HBs negative more quickly, although double dose vaccine increases the response by 13% (IIb, B)[108-111]. Response correlates with CD4 count if not on ART but also with viral load and ART use. [108-111] Offer a repeat course of three doses of vaccine, which may be double dose, for HIV-positive vaccine non-responders (II, B). Vaccine response will also improve if the CD4 count rises and if patients have an undetectable viral load on ART. If patients do not respond to 6 doses initially, repeat vaccination once the CD4 is above 500 cells/mm<sup>3</sup> and the viral load is undetectable (II,B) [108-111]
- The vaccination schedule for both the monovalent and the combined hepatitis A+B vaccines is outlined in Table 2. The ultra-rapid 0, 7, 21 day regimen offers the advantage of a higher uptake of the full course and more rapid development of early immunity. Test for response (anti-HBs  $\geq 10$ i.u./l, ideally

>100i.u./l) 4 - 12 weeks after the last dose (Ib, A)[62, 63, 100, 101-105]. Only 80% of ultra-rapid vaccinees will have detectable anti-HBs antibodies at this stage (see 'Sexual and other contacts' above). If someone is at high risk of acquiring infection, and are in the 20% without an early antibody response, consider further booster doses (II, B). They usually respond to further doses (up to three injections), ideally as a repeat course (Ib, A) with response rates up to 100% (Ib, A)[112-114]. Alternatively, for those at lower risk, offer a booster at 12 months by which time 95% would be anti-HBs-positive [101-105].

- Pre-S-containing vaccines (currently unlicensed) are effective (Ib, A) and may also be used for conventional-vaccine non-responders when available (IIa, B) [115, 117]. Vaccines with novel adjuvants (e.g. Fendrix ®) are effective for haemodialysis patients and others who haven't responded to conventional vaccine (IIa, B)[116, 118].

**Table 2 Vaccination Schedules for Hepatitis B using monovalent vaccine or combined A+B vaccine [62, 63, 100, 101-105, 108-111].**

<b>Vaccination Schedule</b>	<b>Advantages</b>	<b>Disadvantages</b>
0,7,21 days, 12 months	<ul style="list-style-type: none"> <li>- Rapid immunity,</li> <li>- Short duration,</li> <li>- High antibody titres at 12 and 13 months</li> <li>- Better uptake</li> </ul>	<ul style="list-style-type: none"> <li>- Less information on HIV or other immune-compromised patients</li> <li>- Low antibody titres in the first year (but current evidence suggests that protection is still adequate in the immune-competent)</li> </ul>
0,1,2,12 months	<ul style="list-style-type: none"> <li>- Shorter time to early immunity than the 0,1,6 course</li> <li>- High antibody titres at 12 and 13 months</li> </ul>	<ul style="list-style-type: none"> <li>- Antibody titres lower than the 0,1,6 regimen in the first year</li> </ul>
0,1,6 months	<ul style="list-style-type: none"> <li>- Higher antibody titres at 7 months than the other two regimens although this may not be clinically important</li> <li>- Long established regimen</li> <li>- Most researched in HIV</li> </ul>	<ul style="list-style-type: none"> <li>- Poor uptake of the 6 month dose in the clinical setting</li> </ul>

- It is probable that booster doses of vaccine are not required for at least fifteen years in immunocompetent children and adults who have responded to an initial vaccine course (III,B) [119-121] although in those vaccinated in infancy 10% will be non-immune and show no immunological memory after 18 years [122]. HIV-positive and other immunocompromised patients will still need to be monitored and given boosters when anti-HBs levels fall below 100i.u./l (III,B) [108-111, 119].
- Evidence suggests that if vaccine courses are not completed in immunocompetent patients, the outstanding doses can be given four or more years later without the need to restart a three dose course (III,B) [123]. One or two doses of vaccine may provide immunity in 40% and over 90% of immunocompetent patients respectively [123, 124].

### 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 injecting drug users (IVDUs) and their sexual partners but also in female sex-workers, and sporadically in other groups [125]. 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 [24, 26, 54, 69]. There is a high rate of fulminant hepatitis and progression of chronic hepatitis to cirrhosis [24, 26, 54]. Diagnosis is confirmed by a positive anti-HDV antibody and HDV-RNA test [34, 69]. Response to anti-viral therapy is poor [126, 127]. Refer to physician with experience in managing HBV/HDV co-infections for assessment and treatment (IV,C).

## Hepatitis C virus (HCV) infection

### Aetiology

An RNA virus in the flaviviridae family. It is endemic world-wide with prevalence rates varying from 1% in Europe to 4-5% in Africa, Pacific Region and the Eastern Mediterranean [128]. UK prevalence rates vary from 0.53% in adults 15-59 to over 40% in IDUs [129]. 8346 cases were reported in England in 2006 [129].

### Transmission

- Parenteral spread accounts for the majority of cases through shared needles/syringes in IDUs, transfusion of blood or blood products (pre-1990s), renal dialysis, needle-stick injury or sharing a razor with an infected individual [130-135].
- Sexual transmission occurs at a low rate (generally <1% per year of relationship, or about 2% of spouses in long-term relationships) but these rates increase if the index patient is also HIV infected [136-143]. There has been a steadily rising incidence of acute HCV in Men who have sex with men (MSM) in the South of England since the year 2000 which is largely linked to HIV co-infection [137,138,140]. Associated factors include the presence of other STIs including syphilis and LGV, traumatic anal sex and use of recreational drugs [137,138,140]. There is also evidence of increased rates of infection in female sex workers [61, 139], former prisoners, tattoo recipients and alcoholics [145-147].
- Vertical (mother to infant) spread also occurs at a low rate (about 5% or less), but higher rates (up to 40%) are seen if the woman is both HIV and HCV positive [132, 136, 148-150]. Increased rates of transmission are seen in Japanese patients and in all groups transmission risk correlates with the presence of detectable HCV-RNA in the mother's blood [149, 151, 152].
- Amongst blood donors, 50% of those with HCV infection do not admit to having risk factors [153].

### Clinical Features

#### Incubation period

Four to 20 weeks for the uncommon cases of acute hepatitis. HCV serology is usually positive (90%) three months after exposure but can take as long as nine months. Occasional cases of infection proven by RT-PCR (see "diagnosis") do not result in positive antibody tests [131, 132, 153-156, 159].

#### Symptoms [131, 132, 153]

- The majority of patients (>60%) undergo asymptomatic acute infection.
- The uncommon cases of acute icteric hepatitis are similar to hepatitis A.

### Signs

- Acute icteric hepatitis - see hepatitis A.
- Chronic hepatitis - see hepatitis B

### Complications

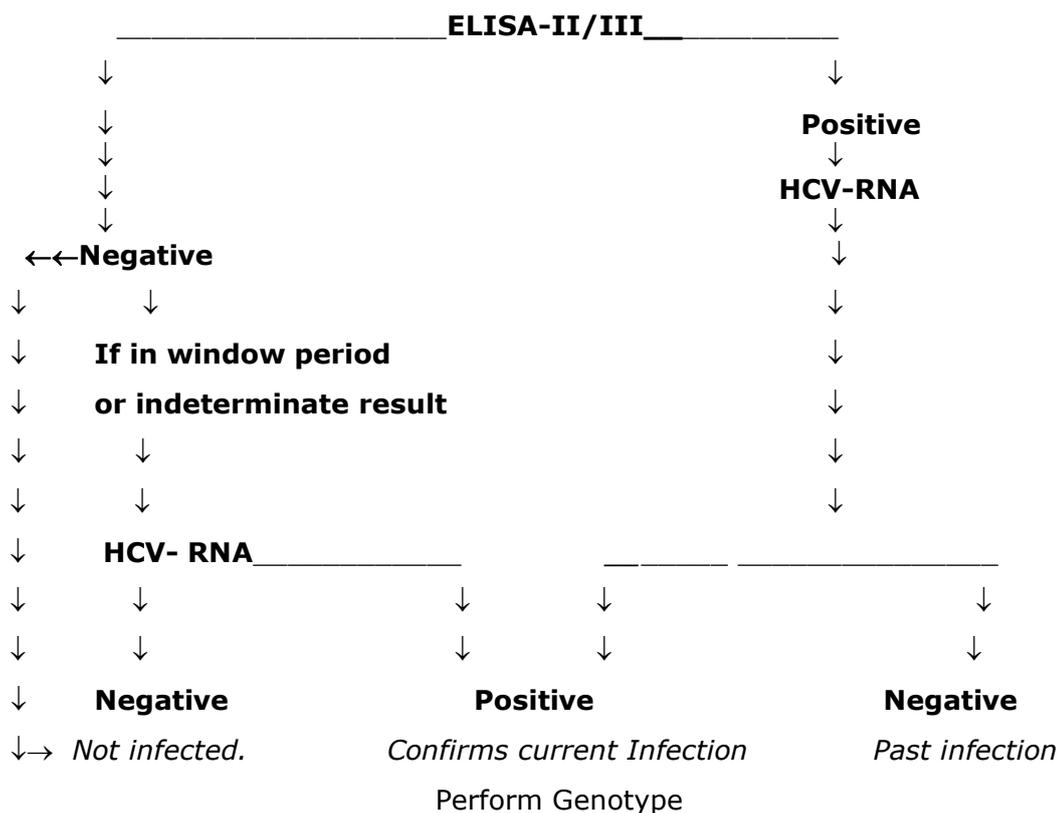
- Acute fulminant hepatitis is rare (<1% of all hepatitis C infections), but is more common after hepatitis A super-infection of chronic hepatitis C carriers [28, 131, 132, 157]. However, acute hepatitis A can reduce HCV replication and may improve long-term prognosis [79].
- Approximately 50-85% of infected patients become chronic carriers - a state which is normally asymptomatic but may cause non-specific ill health [153, 159-160]. Type 1 genotype is more likely to clear spontaneously but leads to more severe chronic infection (159). Once established, the chronic carrier state rarely resolves spontaneously (0.02%/year)[131-2]. Symptoms/signs are worse if there is a high alcohol intake or other liver disease [161-164]. Significant liver disease can be present in the 35% of carriers who have normal serum aminotransferase levels, [131, 132, 165, 166].
- Mortality in acute hepatitis is very low (<1%) but up to 30% of chronic carriers will progress to severe liver disease after 14-30 years infection, with an increased risk of liver cancer (approximately 1-4% of all patients and up to 33% of those with cirrhosis) [68, 69, 81, 131, 132, 177, 163, 168-170]. HIV co-infection worsens the prognosis although this may be ameliorated to some degree by ART [140,171-173].
- Pregnancy- Complications of acute icteric hepatitis: as for hepatitis A [21]. For risk of vertical transmission see "transmission".

### **Diagnosis** (see also Sexually Transmitted Infection Screening and Testing Guidelines - Hepatitis A, B and C)

#### Serology

- A screening antibody test such as an Enzyme immuno-assay (EIA) or other immunoassay is initially performed and RT-PCR for RNA is used to confirm active infection [23,78,79,154-156,174]. In HIV+ patients with a low CD4 count (<200 cells/mm<sup>3</sup>) the EIA may be negative and an RT-PCR may be needed for diagnosis (176). An antibody test may not become positive for three or more months after acute infection but a test for HCV-RNA will be positive after only two weeks. 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. All patients being considered for therapy should have a viral RNA test to confirm viraemia and genotype assay (see below).

### Flow chart for hepatitis C testing using an ELISA Assay



#### Other tests

- Acute infection - as for hepatitis A.
- Chronic infection - as for hepatitis B.

#### Management

##### General Advice

- Patients should be told not to donate blood, semen or organs and given advice on other routes of transmission (see below) (III, B) [128].
- 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.
- Acute hepatitis C infection is a notifiable disease.
- Refer all HCV +ve patients to a liver specialist for consideration of treatment (Ia,A) [175-185].

##### Further Investigations

- As for hepatitis B. Non-invasive methods of assessing liver fibrosis such as hepatic elastography (e.g. fibroscan) may provide useful information to complement the liver biopsy [80].

##### Treatment

- Acute icteric hepatitis: There is firm evidence that high dose alpha interferon or pegylated interferon given during the acute phase will reduce the rate of chronicity to only 10% or less (IIb, B) [175,177]. Spontaneous resolution of acute hepatitis C is signified by a loss of HCV-RNA within the first 2 months. Only those HCV-RNA positive for more than two months need to be treated

[177]. Genotype 1 infections require 24 weeks therapy whereas other genotypes need only 12 weeks treatment [177]. Otherwise manage as for hepatitis A.

- Chronic infection: Peginterferon alfa with ribavirin will abolish chronic infection in approximately 50% of patients and is the approved therapy of the National Institute for Clinical Excellence (NICE) (Ia, A) [178]. Treatment should be for 14-24 weeks for patients with genotypes 2 or 3. Other genotypes should be treated for 12 weeks and treatment only continued if there has been a reduction in HCV viral load to 1% of the level at the start of treatment. Patients achieving this 2 log<sub>10</sub> reduction should be treated for 24-72 weeks depending on how quickly the viral load becomes undetectable. Patients are more likely to respond if they have less severe liver disease (low fibrosis index on liver biopsy), low serum HCV-RNA levels (<2million RNA copies/ml), if they are infected with certain HCV sub-types (types 2 and 3) or if they become HCV-RNA negative in the serum within 12 weeks (Ib, A) [178-182].
- HIV-positive patients respond to treatment, although not as well as HIV-negative patients, and should be considered for therapy (Ib, A) [47, 183-185]. Sustained virological response in those completing therapy is 11-29% for genotypes 1/4 and 43-73% for genotypes 2/3 (1b, A) [183-185]
- Patient selection for therapy depends on HCV genotype and viral load although a liver biopsy is not always necessary for making treatment decisions [178-185]
- Given the potential for fulminant hepatitis in co-infection hepatitis A & C and the worse prognosis of hepatitis B & C co-infection, patients with hepatitis C should be vaccinated against hepatitis A and B (III,B) [28, 157,158].

#### Pregnancy and Breast feeding

- There is at present no known way of reducing the risk of vertical transmission. Women should be informed of the potential risk of transmission in pregnancy (see transmission) (II, B) [136, 148-152].
- Breast feeding: there is no firm evidence of additional risk of transmission except, perhaps in women who are symptomatic with a high viral load (III,B)[148-152 186]

#### Sexual 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 needle sharing partners during the period in which the index case is thought to have been infectious (IV,C)[37]. The infectious period is from two 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. Consider testing children born to infectious women (IV,C)[136]. For other non-sexual contacts thought to be at risk, discuss with the CCDC or equivalent.
- There is currently no available vaccine or immunoglobulin preparation that will prevent transmission.
- Sexual transmission should be discussed. It seems likely that if condoms are used consistently then sexual transmission will be avoided, but given the very low rate of transmission outside of HIV co-infection (see above), monogamous partners may choose not to use them (IV,C).

#### Follow-up

- As for hepatitis B (IV, C).
- Immunity is probably sub-type specific only - there are at least seven sub-types and re-infection/dual infection is well documented [154-156].

### Screening and Primary Prevention.

- Consider testing for hepatitis C in all IDUs, especially if equipment has been shared, in haemophiliacs or other patients who received blood or blood products pre-1990 and in people sustaining a needle-stick injury if the donor HCV status is positive or unknown (III, B) [128, 130, 133-135, 138, 187]. Other groups to be considered for testing are sexual partners of HCV positive individuals, MSM, all HIV-positive patients, female sex workers, tattoo recipients, alcoholics and ex-prisoners (III, B)[61, 128, 137, 138, 141-146]. It may take three months or more for the anti-HCV test to become positive after exposure (see "incubation period").
- Since 1990 all donated blood in the UK has been screened for HCV and all blood products rendered incapable of transmitting infection (III, B) [188].
- Needle and syringe exchange schemes have led to a fall in parenterally transmitted infections including HCV, HBV and HIV, although not consistently (III, B) [189-191].

### Qualifying statement

"The recommendations in this guideline may not be appropriate for use in all clinical situations. Decisions to follow these recommendations must be based on the professional judgement of the clinician and consideration of individual patient circumstances and available resources."

"All possible care has been undertaken to ensure the publication of the correct dosage of medication and route of administration. However, it remains the responsibility of the prescribing physician to ensure the accuracy and appropriateness of the medication they prescribe."

### Auditable Outcomes

#### Acute hepatitis (A, B or C)

- Patients with acute hepatitis infection should be assessed clinically for severity, and have blood samples taken for serology, liver function, prothrombin time and renal function, all taken on the initial visit (target >90%)
- A clear treatment and follow-up plan should be stated in the notes (target 100%).

#### Hepatitis A

- If the clinic policy is to test and vaccinate gay men,
  - test for immunity (target >90%)
  - offer vaccination (target >90%)
- Provide written information on transmission and outcome of hepatitis A to infected patients (target >95%)

#### Hepatitis B

- Test patients in known at-risk groups for infection/immunity (target >90%)
- Offer vaccination to all non-immune patients at continuing risk (target >90%)
- In those offered vaccination, give a full course and test for post-vaccination response (target >50%)
- Provide written information on transmission and outcome of hepatitis B to infected patients (target >95%)
- Perform liver function tests once the diagnosis is known (target >80%)
- Write a clear long-term management plan in the notes of HBV-infected patients (target >95%)

### Hepatitis C

- Ascertain the Hepatitis C and B status of injecting drug users (target >80%)
- Provide written information on transmission and outcome of hepatitis C to infected patients (target >95%)
- Test all HCV+ve patients for Hepatitis A and B immune status( target >90%) and offer vaccination if non-immune (target >90%)
- Perform liver function tests once the diagnosis is known (target >80%)
- Write a clear long-term management plan in the notes of HCV-infected patients (target >95%)
- For chronic HBV carriers, test for hepatitis A immunity (target >90%) and vaccinate if non-immune (target >90%).

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