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# Public Health Service Inter-Agency Guidelines for Screening Donors of Blood, Plasma, Organs, Tissues, and Semen for Evidence

The Public Health Service staff members listed below

served as authors of Public Health Service Inter-Agency Guidelines for Screening Donors of Blood, Plasma, Organs, Tissues and Semen for Evidence of Hepatitis B and Hepatitis C.

## CENTERS FOR DISEASE CONTROL

Coordinator Miriam J. Alter, Ph.D.

Bruce L. Evatt, M.D. Harold S. Margolis, M.D.

## FOOD AND DRUG ADMINISTRATION

Robin Biswas, M.D. Jay S. Epstein, M.D. Stephen M. Feinstone, M.D.

John S. Finlayson, Ph.D.

Donald Tankersley, M.S.

## NATIONAL INSTITUTES OF HEALTH

Harvey J. Alter, M.D. Jay H. Hoofnagle, M.D.

The Hepatitis Branch, Centers for Disease Control, maintains an automated telephone system that provides information on the different types of viral hepatitis. Messages have been designed for both health-care

professionals and the lay public. The number is 404-332-4555.

These guidelines address the use of tests for the hepatitis B and C viruses to screen donations of blood and plasma collected for transfusion or further manufacture into injectable products, as well as to screen donors of organs, tissues, and semen. These guidelines are intended to serve as a resource to individuals and organizations involved in testing, counselling, and evaluating donors tested for these viruses, and are based on currently available knowledge.

## INTRODUCTION

Several infectious agents transmit through infected blood and blood products. To decrease the potential for disease transmission, donors are screened for risk factors by medical history and for evidence of infection by specific testing. The Food and Drug Administration (FDA) currently requires that all donations of whole blood and transfusable components as well as plasma for fractionation into injectable derivatives be subjected to a serologic test for syphilis, hepatitis B surface antigen (HBsAg), and antibody to the human immunodeficiency virus (anti-HIV). The FDA also currently recommends testing donations of whole blood and components for transfusion for antibody to human T lymphotropic virus type I (anti-HTLV-I) and antibody to hepatitis C virus (anti-HCV), and is considering recommending testing for antibody to hepatitis B core antigen (anti-HBc). Blood banks in the United States voluntarily began testing donations for anti-HBc and alanine aminotransferase (ALT) in 1986 and 1987 and for anti-HCV in 1990.

## HEPATITIS B

### Background

#### Post-Transfusion Hepatitis B

The discovery in 1965 of Australia antigen, now referred to as HBsAg, and its subsequent association with hepatitis B virus (HBV) led to the development of sensitive, specific markers of HBV infection (1-4). During acute and chronic HBV infection, HBsAg is produced in excess amounts, circulating in blood as both 22-nm spherical and tubular particles. HBsAg can be identified in serum 30-60 days after exposure to HBV and persists for variable periods depending on the resolution of the infection. Antibody to HBsAg (anti-HBs) develops after a resolved infection and is responsible for long-term immunity (5). Anti-HBc develops in both resolved acute infections and chronic HBV infections and persists indefinitely (6). Immunoglobulin M (IgM) anti-HBc appears early in infection and persists for greater than or equal to 6 months (7). It is a reliable marker of acute HBV infection.

Transmission of HBV by transfusion of blood or blood products is rare because of routine screening of blood donors for HBsAg and because of current donor selection and deferral procedures. Screening blood donors for HBsAg began in 1969 and became mandatory in 1972. Retrospective testing of blood donors using first generation tests such as immunodiffusion to detect HBsAg, found that 52%-69% of recipients of HBsAg-positive blood developed hepatitis B (8,9). In addition, recipients of blood from paid donors were at higher risk of developing post-transfusion hepatitis than were recipients of blood from non-paid donors (10,11). A combination of more sensitive third-generation tests (reversed passive hemagglutination and radioimmunoassay (RIA)) for HBsAg screening and exclusive use of non-paid donors reduced the rate of post-transfusion hepatitis B to 0.3%-0.9%/transfusion recipient by the mid-1970s (12,13).

A small number of HBV carriers appears to circulate HBsAg at undetectable levels, and anti-HBc may be the only serologic marker detectable in blood from these individuals. Thus, even with the greater than 99% sensitivity of the current tests for HBsAg, including both RIA and enzyme immunoassay (EIA), not all HBV carriers are detected by screening for HBsAg, and a small number of transfusion recipients still develop hepatitis B (14-16). Anti-HBc screening of blood donors was instituted in 1986 and 1987 as a surrogate marker for non-A, non-B hepatitis (17,18) and may have contributed to the prevention of hepatitis B. However, surveillance data from reported cases of acute hepatitis suggest that the incidence of post-transfusion hepatitis B declined before anti-HBc testing began (19,20). In the period 1982-1985, an average of 3% of acute cases of hepatitis B had a

history of blood transfusion in the 6 months preceding onset of illness. In the period 1986-1988, the percentage of cases reporting a history of blood transfusion declined to an average of 1%. Most of this decline occurred before anti-HBc testing was initiated and was temporally associated with changes in the donor population related to the prevention of human immunodeficiency virus (HIV) infection. The current incidence of post-transfusion hepatitis B is estimated to be around 0.002%/transfusion recipient (21 and CDC, unpublished data).

### Modes of Transmission

Transmission of HBV occurs via percutaneous or permucosal routes, and infective blood or body fluids can be introduced at birth, through sexual contact or by contaminated needles. Infection can also occur in settings of continuous close personal contact (such as in households or among persons in institutions for the developmentally disabled), presumably via inapparent or unnoticed contact of infective secretions with skin lesions or mucosal surfaces. Persons at increased risk of acquiring HBV infection include members of the following groups: a) parenteral drug users, b) heterosexual men and women and homosexual men with multiple partners, c) household contacts and sexual partners of HBV carriers, d) infants born to HBV-infected mothers, e) patients and staff in custodial institutions for the developmentally disabled, f) recipients of certain plasma-derived products (including patients with congenital coagulation defects), g) hemodialysis patients, h) health and public-safety workers who have contact with blood, and i) persons born in areas of high HBV endemicity and their children.

Persons at risk of exposure to HBV, including those mentioned above, who are shown or judged likely to be susceptible should receive hepatitis B vaccine (22). Ideally, hepatitis B vaccine should be provided to such persons before they engage in behaviors, occupations, or treatments that place them at risk of infection. Prophylactic treatment (hepatitis B immune globulin and hepatitis B vaccine) to prevent HBV infection after exposure to HBV should be provided for infants born to HBsAg-positive mothers, persons with accidental percutaneous or permucosal exposure to HBsAg-positive blood, sexual partners of an HBsAg-positive person, and infants less than 12 months of age whose primary care giver has acute hepatitis B (22). Hepatitis B vaccine should also be given to all susceptible household contacts of HBV carriers.

### Natural History of Infection

HBV is a major cause of acute and chronic hepatitis, cirrhosis, and primary hepatocellular carcinoma worldwide (23). The most serious consequences of HBV infection are primarily the result of chronic HBV infection, which occurs in 6%-10% of infected adults, approximately 25% of infected children aged 1 to 5 years, and 70%-90% of infected infants (23-25). Each year in the United States, an estimated 300,000 persons, primarily young adults, are infected with HBV. Approximately half become ill with jaundice or other symptoms of hepatitis, more than 10,000 patients require hospitalization, and an average of 350 die of fulminant disease. The United States currently contains an estimated pool of 750,000-1,000,000 infectious HBV carriers. Approximately 25% of carriers develop chronic active hepatitis, which often progresses to cirrhosis. HBV carriers also have a risk of developing primary liver cancer that is 12-300 times higher than that of other persons. An estimated 4,000 persons die each year from hepatitis B-related cirrhosis, and more than 800 die from hepatitis B-related liver cancer.

A recent study reported that among patients with compensated chronic liver disease due to hepatitis B, alpha interferon was effective in inducing a sustained loss of HBV replication and achieving remission, assessed biochemically and histologically, among over a third of patients (26). In about 10% of patients treated with interferon, HBsAg disappeared from serum.

### Sensitivity of the Available Tests

Sensitive tests are available commercially for the detection of HBsAg by either RIA or EIA. Information from the package inserts of these tests indicates that the sensitivity of both the RIA and EIA for the detection of HBsAg is less than 0.5 ng/ml. As noted previously, despite these sensitivities, a small number of HBV carriers may have undetectable levels of HBsAg and test as a false negative. Most of these low level HBsAg carriers, however, will most likely be detected by the anti-HBc test currently performed on units of blood or blood

components for transfusion.

## Guidelines for Screening

### Testing

1. All donations of whole blood, plasma, and other components are required to be tested for HBsAg by a sensitive and specific FDA licensed test, such as RIA or EIA (27).
2. If the initial test result is non-reactive, the unit is considered to be non-reactive for HBsAg. The unit may be transfused or used for further manufacture into transfusable components, provided all other requirements are met.
3. If the initial test result is reactive, the unit is considered to be initially reactive.
  - The sample should be retested in duplicate in a single test run, using a test kit of the same type and from the same manufacturer as used for the initial test.
  - If the repeat test results are both non-reactive, the unit is considered to be non-reactive and may be used as mentioned earlier. The donor may return for subsequent donations.
  - If either one or both repeat tests are reactive, the result is designated repeatedly reactive and the unit should not be transfused or manufactured into other products that do not require HBsAg reactive source material. The donor with repeatedly reactive test results is deferred, but prior to notification it is recommended that the results be confirmed by neutralization according to the manufacturer's instructions.
  - If the neutralization test is positive, the donor is permanently deferred from future donations.
4. The donor of a repeatedly reactive unit that is not confirmed by neutralization may later, at the discretion of the blood center, be considered for reentry as a donor if the procedures are followed in accordance with the recommendations of the FDA (28).
5. It is recommended that a serum sample from donors of organs, tissues, or semen intended for human use be tested for HBsAg using the same procedures as outlined earlier. Every effort should be made to use material only from donors testing negative for HBsAg. It is recognized that emergency situations involving life-supporting organs may arise that do not permit the use of an HBsAg test before implantation or that involve the use of material from an HBsAg-positive donor. In such situations, the recipients should be informed by their medical-care providers that they will or have received untested tissue or tissue from an HBsAg-positive donor, and prophylaxis with hepatitis B immune globulin and hepatitis B vaccine (using the dosage recommended for immunocompromised patients) (22) should be considered.

### Notification of Donors

1. If the repeatedly reactive HBsAg test is confirmed as positive by neutralization or if neutralization tests are not performed, it is recommended that collection facilities ensure that donors are notified of their test results and their permanent deferral from donation. It is recommended that notification include written information, presented to the donor by sealed letter or at a face-to-face interview. Organ or tissue procurement organizations should report this information to the donor's physician when the donor is deceased.
2. It is recommended that the information contained in such notification inform donors that: a) a positive test result could indicate that they recently developed hepatitis B or that they may have chronic hepatitis; b) they are likely to be infectious to others; and c) there is a safe and effective vaccine that can prevent the spread of HBV to their household contacts and sexual partners. Donors should be referred to their medical-

care provider to determine the significance of a positive test and the need for screening and vaccination of contacts. These recommendations are similar to those for HBsAg-positive persons identified in other settings (22).

3. Collecting facilities also should be prepared to provide the results of all tests performed related to hepatitis screening (e.g., anti-HBc, ALT, and anti-HCV) to donors with a repeatedly reactive or confirmed positive HBsAg test result or to their physicians. The facility should transmit this information to the donors or inform donors that this information can be forwarded to their physicians by the facility.
4. Collecting facilities also should comply with state and local requirements for the reporting of HBsAg-positive results (29). If a transfusion recipient or a recipient of transplanted tissue develops hepatitis B, it is recommended that the diagnosing physician report the case to both the local health department and the collection facility.

### Recommendations for Medical Evaluation and Counselling

The following information may be of assistance to the medical-care provider in evaluating and counselling an HBsAg-positive individual:

1. The medical evaluation should first verify that HBsAg is present and whether its presence indicates acute or chronic HBV infection.
  - A follow-up serum specimen should be tested for HBsAg.
  - If negative, the donor most likely had a transient acute infection.
  - If HBsAg is still present, testing for IgM anti-HBc would be helpful in distinguishing between acute and chronic hepatitis B, as this antibody is usually detected only in acute hepatitis B. If IgM anti-HBc is not present and/or HBsAg persists for 6 months, chronic HBV infection is present.
2. If HBsAg is detected in follow-up specimens, the medical evaluation should also include an assessment of the extent of liver disease. This evaluation should include a history, physical examination, and laboratory studies such as ALT, aspartate aminotransferase (AST), bilirubin, albumin, and prothrombin time. If chronic HBV infection is present, serial determinations of aminotransferases would be appropriate. Patients should also be tested for hepatitis B e antigen (HBeAg), a serologic marker of high levels of virus (30). Healthy or inactive HBV carriers will have HBsAg but not HBeAg, and will have normal aminotransferase levels. The persistence of HBsAg with elevated aminotransferase values most likely indicates chronic hepatitis B. Most such patients will have HBeAg in serum. These patients should be evaluated for the potential need and benefit of therapy.
3. It is important that medical providers counsel chronic HBV carriers that they can transmit HBV to others or that they refer carriers to their local health department for counselling. Such counselling should also include screening sexual partners and household contacts of HBV carriers for susceptibility to HBV infection and, if susceptible, vaccinating them with hepatitis B vaccine. The best single test for screening in this setting is total (not IgM) anti-HBc. Vaccination of susceptible individuals should be carried out using age-appropriate doses and schedules as recommended for the available hepatitis B vaccines (22).
4. The individual should not donate blood, plasma, body organs, other tissue, or semen.
5. Household articles such as toothbrushes and razors that could become contaminated with blood should not be shared, and cuts or skin lesions should be covered to prevent the spread of infectious secretions or blood.
6. When seeking medical or dental care, HBsAg-positive persons should be advised to inform those responsible for their care of their HBsAg status so that they can be appropriately evaluated.

7. If the sexual partner of the HBV carrier is not immune to hepatitis B, the partner should be advised to take precautions. The most effective precaution is vaccination with hepatitis B vaccine. The efficacy of latex condoms in preventing infection with HBV is unknown, but their proper use may reduce the risk of transmission. For the prevention of many sexually transmitted diseases, including hepatitis and HIV infection, the number of sexual partners should be reduced, infected persons should inform prospective sexual partners so that they can take appropriate precautions, and infected persons should protect a partner during sexual activity by taking appropriate precautions to prevent that individual from coming into contact with the infected person's blood, semen, urine, feces, saliva, cervical secretions, vaginal secretions, or mucous membranes (31).
8. The high risk of perinatal transmission of HBV is well documented. Infants born to HBsAg-positive women should be given hepatitis B immune globulin and the hepatitis B vaccine series (22).

## HEPATITIS C

### Background

#### Transfusion-Associated Non-A, Non-B Hepatitis

In May 1990, serologic tests that detect anti-HCV by EIA were licensed and became commercially available in the United States. Studies have shown that HCV is the etiologic agent of the majority of parenterally transmitted or bloodborne non-A, non-B hepatitis worldwide (32-34). This type of non-A, non-B hepatitis was first identified and characterized in studies of post-transfusion hepatitis conducted in the early 1970s. Using sensitive tests for hepatitis virus infection, investigators showed that 90% of the post-transfusion hepatitis in the United States was not due to either hepatitis A or B. This form of hepatitis became known as non-A, non-B (35,36). In these early studies, the incidence rates of non-A, non-B hepatitis were as high as 21% after blood transfusion (9,12). The shift from a paid to a non-paid blood donor base substantially reduced the incidence of post-transfusion non-A, non-B hepatitis (12,37), and by the late 1970s, prospective studies of transfusion recipients showed an average incidence of 10% (38,39). Retrospective studies of donors implicated in the transmission of non-A, non-B hepatitis found that such donors were more likely to have anti-HBc and/or elevated ALT levels than were donors whose blood did not transmit non-A, non-B hepatitis (17,18,40,41). These studies suggested that screening donors for both of these surrogate markers would reduce the incidence of post-transfusion non-A, non-B hepatitis by as much as 50%. As noted, blood banks voluntarily began such testing in the United States during 1986 and 1987.

Surveillance data from reported cases of acute non-A, non-B hepatitis suggest that the incidence of post-transfusion non-A, non-B hepatitis declined in the 1980s even before surrogate testing of blood donors began (34). In the period 1982-1985, an average of 17% of acute cases of non-A, non-B hepatitis had a history of blood transfusion in the six months preceding onset of illness. In the period 1986-1988 the percentage of cases reporting a history of blood transfusion declined to an average of 6%, although the overall incidence of the disease remained stable. Most of this decline was temporally associated with changes in the donor population related to the prevention of HIV infection. Currently, the incidence of post-transfusion non-A, non-B hepatitis is estimated to be 1%-4%/transfusion recipient (42,43).

#### Hepatitis C Virus and Antibody Detection Studies

Recently, a portion of the genome of a virus believed to be the major etiologic agent of non-A, non-B hepatitis was cloned from the plasma of a chimpanzee with chronic non-A, non-B hepatitis (44). This original clone (clone 5-1-1) was shown to be derived from a single-stranded RNA molecule present only in parenterally transmitted non-A, non-B hepatitis infections and not related to any other hepatitis viruses. The expression product of clone 5-1-1 was used to develop a prototype RIA to detect circulating antibodies in parenterally transmitted non-A, non-B hepatitis-infected chimpanzees and humans. A more refined serologic assay (EIA) for these circulating antibodies was developed by expressing a variant of this clone (designated C100-3) in yeast to produce large quantities of recombinant viral antigen (32). The antibodies detected by use of this viral antigen appear to be

directed against non-structural proteins of hepatitis C virus (HCV). Using both the prototype RIA (developed for research) and the EIA (developed for commercial use), several research groups have shown that HCV is responsible for most cases of both post-transfusion and community-acquired non-A, non-B hepatitis (33,34). More recent studies have demonstrated that other recombinant antigens, some representing structural components of HCV, can be used to detect additional circulating antibodies. These additional antigens may provide the basis for future test kits with enhanced sensitivity and specificity.

In one recent study, 80% of patients with post-transfusion non-A, non-B hepatitis were found to develop anti-HCV detectable by EIA (42). The mean interval between date of transfusion and anti-HCV seroconversion was 18 weeks; 61% of patients seroconverted within 15 weeks of transfusion, about 90% by 26 weeks, but one patient did not seroconvert until 12 months. In a study of community-acquired non-A, non-B hepatitis, approximately 70% of patients developed anti-HCV (34); of these, 45% were anti-HCV-positive within 6 weeks after onset of illness, 99% by 6 months, but 1 patient did not seroconvert until 9 months.

Patients with non-A, non-B hepatitis who remain negative for anti-HCV even after prolonged follow-up may be infected with another non-A, non-B agent (45), may have another viral or nonviral etiology for their liver injury, or may have hepatitis C but lack (or have resolved) an antibody response that can be detected by the current assay (46).

### Modes of Transmission

Epidemiologic and experimental studies indicate that HCV is transmitted by the parenteral route. Persons at increased risk of acquiring hepatitis C include parenteral drug users; health-care workers with occupational exposure to blood; hemodialysis patients; and recipients of whole blood, blood cellular components, or plasma. Although in the past all recipients of coagulation factor concentrates were at increased risk of HCV infection, current manufacturing procedures for factor VIII (Antihemophilic Factor) include virus inactivation procedures effective against HIV and HBV that appear also to have reduced the risk of HCV transmission from these concentrates (47,48). Although viral inactivation procedures effective against HIV and HBV have also reduced the infectivity of factor IX concentrates, these preparations are still considered to carry a substantial risk of HCV transmission (47,48). To date, there has been no evidence of transmission of HCV from health-care workers to patients through medical care procedures (injections, surgery, and dental work) or transmission from other percutaneous exposures (acupuncture, tattooing) (49,50). However, 40% of patients with acute hepatitis C have no identifiable risk factor for infection.

Sexual activity and other types of person-to-person contact have not been generally recognized as important mechanisms of transmission for hepatitis C. However, two case-control studies found that non-A, non-B hepatitis patients with no history of parenteral exposures were more likely to have histories of exposures to sexual partners or household contacts who had had hepatitis in the past (49,50), and one of these studies also found an association between acquiring disease and a history of exposure to multiple heterosexual partners (50). Neither of these studies found an association between acquiring acute non-A, non-B hepatitis and homosexual activity. Because sexual transmission of blood-borne viruses generally is recognized to be more efficient between homosexual men compared with heterosexual men and women, it is unclear why heterosexual activity has been found to be associated with acquiring non-A, non-B hepatitis when homosexual activity has not. Some serologic surveys of heterosexual men and women and homosexual men who attended clinics for sexually transmitted diseases or who had a history of multiple partners have found the prevalence of anti-HCV to be 5- to 15-fold higher (5%-15%) than that of controls or blood donors (none-1%) (51-54). These increased rates, however, were substantially lower than the rates of serologic markers for HBV (30%-60%) or HIV (35%-96%) in the same sexually active populations. Several other studies have examined the prevalence of anti-HCV among the household and sexual contacts of patients with chronic hepatitis C. Among two of these studies, 6% of 34 family members (55) and 8% of 88 family members (56), respectively, were found to be anti-HCV positive. Anti-HCV-positive contacts included parents, spouses, children, and siblings. In the United States, one study found no anti-HCV-positive contacts among 34 sexual and 17 household contacts of 40 patients with chronic hepatitis C (57).

The risk of perinatal transmission of HCV is also unclear. Studies of infants born to women with non-A, non-B

hepatitis before testing for anti-HCV became available documented both transient and persistent ALT elevations in some infants (58,59). In two recent studies of infants born to anti-HCV-positive women, none of 17 and 1 of 11 (9%), respectively, seroconverted to anti-HCV (54,60). The one infant who seroconverted also had persistently elevated ALT levels. In a third study of 25 infants born to anti-HIV- and anti-HCV-positive women, 11 (44%) seroconverted to anti-HCV between 6 and 12 months of age (61). Four of these 11 infants had transient ALT elevations and two had persistent ALT elevations; all 11 were infected with HIV. Thus, in the absence of coexistent HIV infection, perinatal transmission of HCV rarely appears to occur.

Further definition of the role of sexual, perinatal, and other possible routes of transmission for hepatitis C are needed. There is no evidence that HCV is transmitted through such common exposures as sharing meals or eating utensils, sneezing or coughing, or other casual contact.

### Natural History of Infection

Adjusting both for disease underreporting (62) and for the proportion of HCV infections that are asymptomatic (12), an estimated 150,000 to 170,000 new HCV infections occur annually in the United States. Approximately 25% become ill with jaundice or other symptoms of hepatitis, greater than 4,000 patients require hospitalization, and about 600 die of fulminant disease. An average of 50% of patients with either post-transfusion or community-acquired hepatitis C followed for at least 12 months develop biochemical evidence of chronic liver disease (49,63,64). Of patients with transfusion-associated chronic non-A, non-B hepatitis who undergo biopsy within 5 years after onset, greater than or equal to 40% have histologic evidence of chronic active hepatitis and 10%-20% have evidence of cirrhosis (63); many of these patients have no clinical manifestations of their disease. In contrast, of biopsied patients with community-acquired chronic non-A, non-B hepatitis, less than 20% have evidence of chronic active hepatitis and 3% have evidence of cirrhosis within 4 years after onset of disease (64). Because serial biopsies have demonstrated progression from chronic active hepatitis to cirrhosis, studies that include prolonged follow-up of patients with chronic hepatitis C, regardless of the source for infection, ultimately might show a higher proportion of patients with cirrhosis.

Individual case studies have reported the development of hepatocellular carcinoma (HCC) after transfusion-associated non-A, non-B hepatitis (65-67). Several recent studies have reported high rates of anti-HCV among patients with HCC (68-70). The establishment of a direct link between HCV and HCC, however, must await the results of well-controlled studies.

Although it is apparent that chronic liver disease is a frequent outcome of hepatitis C, such disease may take years to develop, and the majority of infected individuals, even those with documented cirrhosis, may be asymptomatic. Some individuals, however, do suffer from severe disease. Recent studies have reported that alpha interferon therapy may have a beneficial effect among some patients (71,72). In these studies, such therapy resulted in marked improvement of serum aminotransferase activity among approximately half of the patients treated, with most of these patients also having improvement in liver histology. However, improvement of aminotransferase activity was sustained among only 10%-51% (71,72) of the patients, and the duration of the histologic response and the impact on the long-term course of the disease were not defined.

### Sensitivity and Specificity of Current Tests

The sensitivity and specificity of the currently available tests for anti-HCV are not well defined. Not all donors implicated in the transmission of hepatitis C are anti-HCV positive. In one study, approximately 25% of patients with post-transfusion hepatitis C received units from donors who tested negative for anti-HCV by EIA (42).

Limited data concerning the specificity of the licensed EIAs are available from studies using supplemental assays. Two supplemental tests for specificity have been used on an investigational basis: an immunoblot (IB) type assay and a neutralization or blocking (NT) type assay. In one study, of 28 EIA-reactive donors implicated in the transmission of hepatitis C, 89% were found to be anti-HCV positive by supplemental testing (IB); of 21 non-implicated donors reactive by EIA, only 33% were positive by supplemental testing (42). Most samples that were judged false positives had initial EIA absorbance readings of less than 1.0.

In two studies of randomly selected blood donors reactive for anti-HCV by EIA, only 19%-26% were anti-HCV positive on supplemental testing (IB) and 20%-24% were judged indeterminate (73,74). In both of these studies, EIA reactive donors who were positive by the supplemental test were more likely to have an elevated ALT level (or anti-HBc positivity) than were EIA reactive donors who were negative by the supplemental test.

As with any screening test, the proportion of repeatedly reactive EIA results that are falsely positive may vary depending on the prevalence of the infection in the population screened. Serologic surveys of groups other than blood donors have found that supplemental tests were positive among 84% (by IB) of EIA-reactive samples from previous transfusion recipients (74), among 80% (by NT) of EIA-reactive samples from parenteral drug users (CDC, unpublished data), and among 20% (by NT) of EIA-reactive samples from healthy adults randomly selected from the general population (CDC, unpublished data).

Thus, persons most likely to be infected with HCV, such as donors implicated in the transmission of HCV, donors with elevated ALT levels, and persons with identifiable risk factors for hepatitis C, are those in whom repeatedly reactive EIA results are most likely to be judged positive by supplemental tests. In contrast, persons less likely to be infected with HCV, such as donors not implicated in the transmission of HCV, donors with normal ALT values, and persons with no known risk factors for hepatitis C, are those in whom repeatedly reactive EIA results are most likely to be judged false positive by the supplemental tests.

## Guidelines for Screening

### Testing

1. It is recommended that all donations of whole blood and components for transfusion be tested for anti-HCV by EIA.
2. If the initial test result is non-reactive, the unit should be considered non-reactive for anti-HCV. The unit may be transfused or used for further manufacture into injectable components, provided all other requirements are met.
3. If the initial test result is reactive, the unit is considered to be initially reactive.
  - The sample should be retested in duplicate in a single test run, using a test kit of the same type from the same manufacturer used for the initial test.
  - If the repeat tests are both non-reactive, the unit is considered to be non-reactive and may be used as mentioned earlier. The donor may return for subsequent donations.
  - If either one or both of the duplicate tests are reactive, the result is designated repeatedly reactive, and the unit must not be used for transfusion. The donor should be indefinitely deferred from donation of whole blood and components for transfusion.
4. The FDA does not currently recommend testing of plasma collected for fractionation for anti-HCV and currently permits the plasma from repeatedly reactive units to be used for further manufacture into injectable products. This position has been taken because it is unclear whether anti-HCV screening may adversely affect the safety of plasma derived products, particularly immune globulins. This provisional position of the FDA will be reevaluated in the light of additional information that may emerge, including the results of experimental studies that have been initiated.
5. Donors indefinitely deferred from donation of blood or components for transfusion because of repeatedly reactive anti-HCV test results should not be reentered into the donor pool at this time. When further information about HCV serology becomes available, and if highly sensitive confirmatory tests are developed and licensed, a procedure for reentering donors repeatedly reactive for anti-HCV in an isolated instance may be developed. Collecting facilities should be aware that such a procedure may require the retesting of a stored sample from the original repeatedly reactive donation.

6. Until the risk of sexual transmission of HCV is better defined, there is no recommendation to exclude sexual partners of anti-HCV repeatedly reactive donors from donating whole blood and components for transfusion provided all other requirements are met.
7. It is recommended that serum from donors of organs, tissues, or semen intended for human use be tested for anti-HCV by EIA using the same procedures as outlined earlier. This testing policy should apply both to newly acquired tissue and to material in inventory, whether such inventory is stored at the collection facility or at points of use. Every effort should be made to use material only from donors testing negative for anti-HCV. It is recognized that emergency situations involving life-supporting organs may arise that do not permit the use of an anti-HCV test before implantation or that involve the use of material from an anti-HCV repeatedly reactive donor. In such situations, the recipients should be informed by their medical-care provider that they will or have received untested tissue or tissue from an anti-HCV repeatedly reactive donor.

## Notification of Donors

1. It is recommended that collection facilities ensure that donors with repeatedly reactive test results are notified of these results and of their indefinite deferral from donation. Blood donors are indefinitely deferred from donation for transfusion products but currently remain eligible to give plasma for fractionation. It is recommended that notification include written information presented to the donor either by sealed letter or at a face-to-face interview. Organ or tissue procurement organizations should report this information to the donor's physician when the donor is deceased.
2. When the EIA is used to screen populations low in the prevalence of HCV infection, the proportion of positive results that are falsely positive will be high. The rate of anti-HCV repeat reactivity among U.S. blood donors has been reported at 0.5%-1.4% (73-75). Licensed confirmatory tests are currently not available. Supplemental tests for specificity, as discussed previously, are available as a testing service for research purposes performed by the manufacturers of licensed screening tests, or for distribution on an investigational basis. When such tests are utilized, research studies indicate that their results may be of value in the interpretation of a repeatedly reactive screening test.
3. It is recommended that donors testing repeatedly reactive for anti-HCV by EIA without supplemental testing be informed that this screening test result has not been confirmed and that the anti-HCV repeatedly reactive result may be a false positive. Donors should also be told that a repeatedly reactive test result could indicate infection with HCV. To determine the significance of a repeatedly reactive test, particularly if the donor also has an elevated ALT level, it is recommended that the donor be referred to a physician for further evaluation.
4. When a supplemental test \* is available and the result is positive, donors may be informed that the test indicates the presence of hepatitis C infection and should be referred to a physician for further evaluation.
5. When a supplemental test\* is available and the result is negative and the ALT level is within normal limits, the donor may be informed that the initial test is likely to be a false positive, although this is impossible to prove at present in the absence of a confirmatory test of proven sensitivity and specificity.
6. If the donor's ALT level is elevated, the donor should be referred to a physician for further evaluation, regardless of the results of supplemental anti-HCV testing.
7. Collecting facilities should be prepared to provide all the results of tests performed related to hepatitis screening (e.g., HBsAg, ALT, and anti-HBc) to donors with a repeatedly reactive anti-HCV test result or to their physicians. The facility should transmit this information to the donors or inform donors that this information can be forwarded to their physicians by the facility.
8. If a transfusion recipient or a recipient of transplanted tissue develops non-A, non-B hepatitis or hepatitis

C, it is recommended that the diagnosing physician report the case to both the local health department and the collection facility.

9. It is recommended that professional societies make a concerted effort to educate physicians and other health-care providers about a) the known and potential risks for HCV infection, including blood transfusion; b) the need to ascertain complete risk behavior histories from their patients; c) the appropriate evaluation of high-risk patients for evidence of infection; and d) the current status of investigations on the use of alpha interferon to treat chronic non-A, non-B hepatitis.
10. Targeted "lookback" (tracing prior recipients of blood products from donors who now test positive for anti-HCV) or general screening programs for populations at increased risk of HCV infection are not recommended because: a) currently available screening tests cannot distinguish between ongoing infection and recovery, and thus, the meaning of a reactive test result in any one individual is not clear; b) available knowledge about routes of transmission for HCV other than parenteral is limited; and c) only selected persons are eligible for therapy for their chronic liver disease, and the potential long-term benefits of such therapy are unknown.
11. Screening programs aimed at prior transfusion recipients also are not recommended because they are likely to be ineffective for several reasons: a) most HCV- infected former donors self-deferred or were excluded as a consequence of earlier screening policies; b) few hospitals have transfusion records prior to the early 1980s, thus most recipients at risk will not be traceable; and c) based on the results of "lookback" programs for HIV, response by prior recipients to notification is poor (76).

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- No supplemental test for anti-HCV has yet been licensed by the FDA. When licensure occurs, specific guidance for notification can be obtained from the package insert or directions that accompany the product, and will be provided by the FDA otherwise as appropriate.

#### Recommendations for Medical Evaluation and Counselling

The following information may be of assistance to medical-care providers in evaluating and counselling an anti-HCV-positive individual:

1. The medical evaluation should first verify that anti-HCV is present; then, attempt to assess whether the repeatedly reactive test result is a true positive; and finally, determine whether the patient has acute or chronic HCV infection.
  - A follow-up serum specimen should be tested for anti-HCV.
  - If the specimen is positive, supplemental testing should be performed when available.
  - The patient should be asked about risk factors for hepatitis C as a part of a medical history and examined for evidence of liver disease. Laboratory tests might include ALT, AST, bilirubin, albumin, and prothrombin time. The history of a risk factor, clinical evidence of liver disease, and abnormal aminotransferase levels all support the specificity of an anti-HCV positive result.
2. Currently available tests do not distinguish between acute or chronic HCV infection or between ongoing infection and recovery. Sequential tests for ALT levels may be helpful in distinguishing acute and chronic hepatitis.
  - If ALT levels remain elevated for greater than or equal to 6 months, chronic hepatitis C is likely.
  - If initially elevated ALT levels fall to within the normal range and remain there greater than or equal to 6 months, acute hepatitis C was likely.

- If ALT levels are initially and repeatedly normal: a) the anti-HCV result may have been a false positive; b) the patient may have resolved acute hepatitis C; or c) the patient may have chronic HCV infection with no or minimal associated liver disease.
3. All individuals found to be anti-HCV positive need to be considered potentially infectious and should be counselled concerning infectivity.
  4. Individuals should not donate blood, body organs, other tissue, or semen.
  5. Household articles such as toothbrushes and razors that could become contaminated with blood should not be shared, and cuts or skin lesions should be covered to prevent the spread of infectious secretions or blood.
  6. When seeking medical or dental care, anti-HCV-positive individuals should be advised to inform those responsible for their care of their anti-HCV status so that they can be appropriately evaluated.
  7. The magnitude of the risk of infecting others by sexual intercourse is unknown, but appears to be much less than that for other bloodborne sexually transmitted diseases (e.g., HBV, HIV).

Transmission of HCV has rarely been documented from persons with chronic disease to their steady sexual partners despite long-term, ongoing sexual activity. Although anti-HCV-positive individuals should be informed of the potential for sexual transmission, at this time there is insufficient data to recommend changes in current sexual practices for persons with a steady sexual partner.

Having multiple sexual partners has been associated with an increased risk of acquiring hepatitis C. For the prevention of many sexually transmitted diseases, including hepatitis and HIV infection, the number of sexual partners should be reduced, infected persons should inform prospective sexual partners so that they can take appropriate precautions, and infected persons should protect a partner during sexual activity by taking appropriate precautions to prevent that individual from coming into contact with the infected person's blood, semen, urine, feces, saliva, cervical secretions, vaginal secretions, or mucous membranes (25). The efficacy of latex condoms in preventing infection with HCV is unknown, but their proper use may reduce transmission. Consideration may be given to testing exposed sexual partners for anti-HCV and, if positive, evaluating them for the presence or development of chronic liver disease.

8. The risk of perinatal transmission appears to be very low. At the present time, there is no evidence to support advising against pregnancy based on anti-HCV status alone, or to advise any special treatments or precautions for pregnant women or their offspring.
9. The prognosis for an asymptomatic anti-HCV-positive individual over the long term is not known. Many may not suffer any consequences. Some may develop permanent scarring of the liver and develop severe consequences such as chronic active hepatitis and cirrhosis. It is hoped that in the future more information will become available on the natural history of this infection and the benefits of potential therapies.

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