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Hepatitis C update: Implications of the blood transfusion "lookback"

ABSTRACT

Over the next several years, physicians will be called upon to notify past blood transfusion recipients of blood that may have been contaminated with hepatitis C virus (HCV). This article reviews the screening, care, and follow-up of persons at risk for hepatitis C virus infection from all sources.

KEY POINTS

Persons who may have received contaminated blood should be screened with an enzyme-linked immunosorbent assay (ELISA) and by measuring the alanine aminotransferase level. Other persons at risk can be screened in the same manner.

In low-risk populations, ELISAs have high false-positive rates, but persons with risk factors for HCV infection, a positive ELISA, and an elevated alanine aminotransferase level almost certainly are infected. Persons with normal alanine aminotransferase levels and a positive ELISA need further testing with a recombinant immunoblot assay (RIBA) or a polymerase chain reaction (PCR) test.

Treatments are still suboptimal. Standard treatment is with interferon alfa for 1 year. Ribavirin has recently been approved by the FDA for the treatment of chronic hepatitis C infection in conjunction with interferon.

EARLY THIS YEAR, US Health and Human Services Secretary Donna E. Shalala and US Surgeon General David Satcher, MD, PhD, announced that the federal government was initiating a "lookback" to identify units of transfused blood that may have been contaminated with hepatitis C virus (HCV).[1,2] The machinery to implement the lookback is almost in place, and physicians will soon be asked to play a key role in notifying patients who received this blood, ensuring that they are properly tested and, if infected, treated (see "How the lookback will be conducted," page 415).[3]

Federal officials estimate that approximately 300,000 Americans who received blood between January 1, 1988 and before June 1992 (when an accurate test for HCV was introduced) will be notified that the donor of their blood transfusion subsequently tested positive for HCV.[2] The Surgeon General estimates that the risk that these patients have acquired hepatitis C is between 40% and 70%.[2] Nonetheless, physicians need to remember that many patients who will be contacted during the lookback will not have been infected with HCV.

This article briefly reviews HCV testing and treatment, including the recent Food and Drug Administration approval of the use of ribavirin to treat patients who have relapsed after interferon therapy.

HEPATITIS C VIRUS IS COMMON

HCV was discovered in 1989, but is already considered the major cause of chronic liver disease in the United States. Approximately 4

million persons carry the virus—1.8% of the US population.

The prevalence of HCV infection is even higher in minorities: 3.2% in African-Americans and 2.1% in Mexican-Americans. By age, the highest prevalence rates are in persons 30 to 49 years old; among African-American men in this age group the prevalence is 9% to 10%.[4]

The US Centers for Disease Control and Prevention (CDC) estimates that in 1995 approximately 28,000 persons acquired HCV, but only 30% of new infections were clinically apparent.[5] Because HCV infection usually progresses silently and slowly, only 5% of infected persons may be aware of their infection.[4]

HCV is now the leading indication for liver transplantation in the US and the cause of 8,000 to 10,000 deaths per year. Further, HCV mortality is predicted to triple in the next 2 decades, making chronic hepatitis C one of the major chronic diseases in this country.[6]

HEPATITIS C INFECTION PROGRESSES SLOWLY

Approximately 15% of persons with HCV infection clear the virus from their bodies in the acute phase; in the remaining 85% the disease becomes chronic.

The usual course of HCV infection is slow progression from mild to moderate to severe hepatitis, with development of fibrosis and cirrhosis. Cirrhosis occurs in about 20% of chronic infections. Although progression to severe disease may take 15 to 25 years, in some cases cirrhosis develops rapidly, especially in persons who consume moderate to excessive amounts of alcohol.[4,5]

The best predictor of progression is the presence of histologic markers of aggressive disease on the initial liver biopsy. Persons with severe histologic features (severe inflammation, advanced fibrosis, or both) almost always develop cirrhosis within 10 years. On the other hand, only 20% to 25% of those without fibrosis and with minimal inflammation develop cirrhosis after 25 to 30 years.[7,8]

Once cirrhosis develops, 25% to 50% of patients develop liver failure. One study[9] estimated that the 5-year survival rate of patients with HCV-related compensated cirrhosis is 91%, but only 50% in those with decompensated cirrhosis. Hepatocellular carcinoma, another dreaded complication, occurs in 1% to 4% of patients with HCV-related cirrhosis each year.[10]

WHO IS AT RISK FOR HCV INFECTION?

Transfusion-associated risk

Before 1990, when the first test for HCV antibodies was introduced, contaminated blood transfusions accounted for a large number of HCV infections. Beginning in 1992, a more accurate second-generation test was used to screen the blood supply. The CDC reports that between 1991 and 1995, transfusions accounted for only 4% of cases of acute HCV infection. Today, thanks largely to current blood donor screening programs, the risk of HCV infection is only 0.01% to 0.001% per unit transfused.

Sexual transmission, drug abuse, and other risk factors

Other persons at risk include:

- Injection drug users (who accounted for 43% of cases between 1991 and 1995, and who have an infection rate of more than 70%)
- Persons with high-risk sexual behavior.[11]
- Cocaine snorters (small amounts of blood from the nose of one person may spread HCV if cocaine users share a snorting tube).
- Recipients of other blood products (eg, patients with hemophilia)
- Hemodialysis patients (in whom the infection rate is about 20%).

HCV is now rarely transmitted by blood transfusion

TESTS FOR HCV INFECTION

All patients identified in the blood transfusion lookback as recipients of potentially contaminated blood should be tested for HCV infection. There are two types of tests for HCV, those that detect anti-HCV and those that detect HCV RNA itself (FIGURE 1).[12–14]

Antibody testing

Enzyme-linked immunosorbent assays (ELISAs) are the mainstay of screening for

the hepatitis C virus. The tests are automated and performed easily on a large number of specimens. Current screening programs use second-generation or third-generation ELISAs, which detect antibodies to different HCV antigens.

The accuracy of these tests depends on the prevalence of HCV in the tested population. In low-risk persons such as blood donors and those without any identifiable risk for viral hepatitis, the first-generation ELISAs had a 30% to 50% false-positive rate. The second-generation and third-generation ELISAs are somewhat more specific, but still have high false-positive rates in low-risk populations.

However, in persons at high risk for HCV, the current ELISAs have positive predictive values of over 95%, and in the presence of elevated liver enzymes, a positive test virtually establishes the diagnosis of chronic hepatitis C (FIGURE 1).

ELISAs from different commercial sources have only minimal differences in their sensitivity and specificity.

Recombinant immunoblot assays (RIBAs) have been used to confirm positive ELISA test results and reduce false-positive rates in persons at low risk. The antigens used are similar to those detected by ELISA. However, now that sophisticated, sensitive HCV RNA testing is widely available, the value of HCV RIBA test is being challenged.

A drawback of both ELISA and RIBA testing is that seroconversion can take 3 to 6 months to occur after the initial infection, so that results can be falsely negative early in the infection.

Cocaine snorting is a risk factor for HCV infection

HCV RNA assays

Tests that detect HCV RNA have several uses:

- They can confirm the presence of HCV infection in persons with a positive ELISA but with normal ALT levels.
- They can detect infection in the acute phase, before seroconversion occurs.
- They can predict the response to interferon therapy.

Qualitative assays for HCV RNA are based on the reverse transcriptase polymerase chain reaction (PCR) and can detect HCV RNA in quantities of less than 100 copies/mL. The result is given as positive or negative only.

Quantitative assays actually measure the quantity of HCV RNA present. There are two methods:

- Branched DNA (bDNA), using signal amplification (Quantiplex 2.2, Chiron Corporation, Emeryville, CA), which has a sensitivity of approximately 200,000 copies/mL
- PCR, which is more sensitive and capable of detecting viral load of less than 1,000 copies/mL.

A major drawback of currently available HCV RNA tests is that they are not standardized: different laboratories use different techniques. Of note: HCV RNA tests performed by different methods (bDNA vs PCR) or even by a similar method but at different laboratories are not equivalent and cannot be compared interchangeably.[12–14]

SHOULD ALL PRE-1992 TRANSFUSION RECIPIENTS BE TESTED FOR HCV?

Should persons who received blood transfusions before June 1992, but whose transfusion units are not identified in the HCV lookback, be tested for infection? It is not an easy question to answer. As this article went to press, federal health officials had issued no guidelines for these patients. Unfortunately, despite the considerable effort that the lookback will entail, it will leave many pre-1992 transfusion recipients uncertain of their HCV status. Among the sources of uncertainty:

- The lookback can only identify potentially contaminated units from donors who donate again and subsequently test positive for HCV.
- Donors may have moved; therefore, a donor who tested HCV-positive in one part of the country may have donated previously in another part of the country, and it may difficult to account for all units donated.
- Transfusion recipients may have moved more than once in the last decade, making it difficult to locate and notify them.
- The lookback will not look further back than January 1988. However, people who received blood transfusions before that date could have been exposed to HCV and still be asymptomatic.

How the lookback will be conducted

ALTHOUGH FEDERAL GUIDANCE governing the lookback was not finalized as this article went to press, some blood donation groups, such as the American Red Cross, are beginning their lookback on the basis of proposed guidelines[3] published by the Food and Drug Administration on March 20, 1998 (personal communication, Michael Fulwider, spokesman, American Red Cross). Although the procedure is subject to modification, here are the current plans for how the lookback will work:

IDENTIFYING POTENTIALLY CONTAMINATED UNITS

Current donors who test positive for HCV

For current blood donors whose blood tests are confirmed positive for HCV infection, blood banks must determine if that person has donated blood previously and if so, identify potentially infected units from that person that were distributed in the last 10 years. If a previous donation from that donor was negative for antibodies to HCV (anti-HCV), the blood bank must only identify units donated in the 12 months prior to the seronegative donation. (Seroconversion is presumed to occur within 12 months.)

Past donors who tested positive for HCV

Blood banks must also examine their records for donors who tested positive for HCV between the time the more accurate second-generation HCV screening tests became available in June 1992 and the present. For these donors, the blood banks must identify all units collected from the same donor back to January 1, 1988, or the date 12 months prior to the donor's most recent negative second-generation test for anti-HCV.

NOTIFYING THE PATIENTS

After blood banks identify potentially contaminated units, they are to notify the hospitals and transfusion services that received the blood. These hospitals must then search their records to determine which patients received the blood.

Then, the hospitals and transfusion services must notify the physicians who cared for the patients at the time of transfusion. The physicians are expected to notify the patients of their receipt of potentially contaminated blood. TABLE 1 contains information that transfusion recipients should receive. Notification of patients or notification attempts should be documented in the patient's medical records.

TABLE 1

What to tell recipients of blood potentially contaminated with hepatitis C virus

Explain the basic need for HCV testing and counseling
Provide basic oral or written information so the transfusion recipient can make an informed decision about HCV testing
Provide a list of places where a patient can obtain HCV testing and counseling, including any requirements or restrictions the program may impose

HOW LONG WILL THE NOTIFICATION TAKE?

The American Red Cross will conduct the lookback in two stages. It began a "prospective lookback" in July 1998, to analyze the donation history of all current donors who test positive for HCV.

A "retrospective lookback" examining the HCV status and donation history of previous donors is scheduled to begin this fall.

The federal guidelines are expected to require that the entire lookback process be completed within 2 1/2 years. (Personal communication, Michael Fulwider, American Red Cross)

TABLE 2

Relative contraindications to interferon therapy

Leukopenia (polymorphonuclear leukocytes < 0.75 x 10^9/L)
Thrombocytopenia (< 75 x 10^9/L)
Severe psychiatric disorders
Decompensated liver disease
Terminal comorbid conditions
Unreliable patients
History of autoimmune disease

SOURCE: YOUNOSSI ZM. CHRONIC HEPATITIS C: A CLINICAL OVERVIEW. CLEVE CLIN J MED 1997; 64:259–268.

Given the large number of people believed to be infected with HCV, but who are unaware of that infection, it is reasonable to test any person with an identifiable risk factor (intravenous drug abuse, blood transfusion prior to June 1992, sexual partners of infected persons) for HCV infection.

FURTHER WORKUP AND TREATMENT

The presence of cirrhosis and severe fibrosis on biopsy is associated with aggressive disease

Once the diagnosis of chronic HCV infection has been established on the basis of positive serologic tests and elevated ALT levels, the next possible steps are a liver biopsy and then treatment with interferon. At this point, the clinician may wish to refer the patient to a gastroenterologist experienced in these decisions. Input from a gastroenterologist or hepatologist will not only be helpful in performing and interpreting liver biopsy findings, but also in assuring that the most up-to-date treatment for HCV is provided.

Patients should be counseled that even moderate alcohol consumption may be harmful to HCV-infected persons.

Is liver biopsy necessary?

The role of liver biopsy in hepatitis C is still being debated. The current antibody-based and RNA-based tests are sufficient to establish the diagnosis of HCV without the need for a liver biopsy.

Moreover, despite typical bile duct damage, portal inflammation, and steatosis, the histologic findings on liver biopsy in patients with chronic hepatitis C are not specific.[15]

However, liver biopsy does provide important information on the disease stage and prognosis. Liver biopsy is the only way to assess directly the degree of inflammatory activity and the stage of the disease (fibrosis or cirrhosis). Histologic cirrhosis or histologic features associated with more aggressive disease (severe hepatitis and fibrosis) are important prognostic indicators. Therefore, although a pretreatment liver biopsy is not mandatory, most experts recommend one.

Interferons

Currently, interferons are the first-line drugs for treating chronic hepatitis C. Three products are FDA-approved: Intron A (interferon alfa 2b), Roferon (Interferon alfa 2a) and Alfergen (consensus interferon). Despite some minor differences, these products have similar efficacy and side-effect profiles. The sustained virologic response (eradication of HCV that is sustained 6 to 12 months after completion of therapy, as confirmed by a PCR test) occurs in approximately 20% to 25% of patients with chronic hepatitis C treated with a standard, 12-month course of therapy.

Starting interferon therapy. If the patient has no contraindications to interferon treatment (TABLE 2), the physician should obtain a baseline quantitative HCV RNA assay by PCR before starting.

The viral load has important prognostic implications.[17] A high viral load (> 2 million copies/mL) is associated with a lower response rate to interferon therapy, although it should not be used to deny therapy to anyone who is an otherwise appropriate candidate for treatment.

Patients who respond to interferon do so in the first few months, as reflected by absence of viral RNA by 12 weeks. Such patients should continue with a full 12 months of therapy.

Conversely, patients who still have viral RNA detectable in their blood at 12 weeks of therapy are unlikely to achieve a sustained virologic response with interferon only. A recent NIH consensus conference suggested that such patients be considered for alternative regimens and research protocols.[18] On the

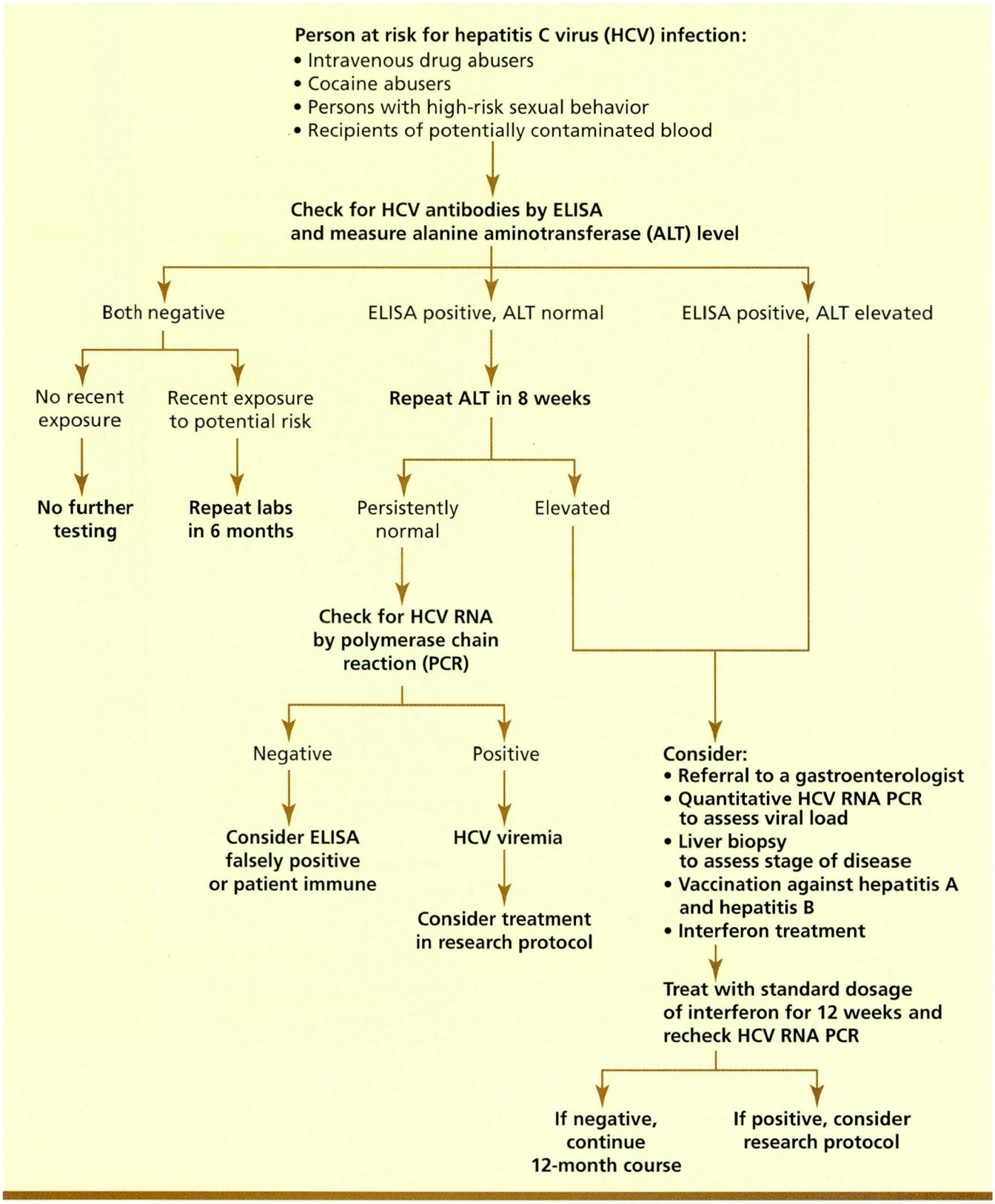

FIGURE 1. Suggested algorithm for diagnosing and treating hepatitis C virus infection

other hand, a recent study[19] suggested that some patients who continue a full course of interferon treatment despite a lack of viral clearance will have histologic improvement and reduced risk of hepatocellular carcinoma.

Ribavirin

Given the suboptimal efficacy of interferon in eradicating HCV, new antiviral agents are being developed and tested alone or in combination with interferon. One of the promising agents used for combination therapy is ribavirin, a guanosine analogue with a broad spectrum of activity against RNA and DNA viruses. Trials using ribavirin alone in treating chronic hepatitis C were associated with biochemical improvement (ie, a decrease in liver enzyme levels) but no effect on viral titers. However, in persons who have never been treated or who were treated but relapsed, combinations of interferon and ribavirin resulted in sustained viral eradication in 40% to 45% of patients.[20–22]

How to treat patients who did not respond to previous interferon therapy is even more problematic. It is now clear that retreating these patients with another course of interferon may not result in any substantial gain in efficacy. However, combination therapy with other agents may result in response rates of approximately 15% to 20%.

In the next two decades, HCV mortality will triple

Side effects of ribavirin are few; these include hemolytic anemia, mild abdominal discomfort, and mild hyperuricemia. Ribavirin is also considered teratogenic and should not be used during pregnancy.

Protease and helicase inhibitors

The most promising agents for future treatment of chronic HCV infection are protease inhibitors and helicase inhibitors. These agents, which target viral enzymes that are essential in the replication of HCV, are currently in the development phase and are expected to become available in the next few years.

If a patient has persistent viremia with normal ALT levels

From 30% to 35% of patients with chronic HCV viremia have persistently normal ALT levels. Liver biopsy findings in these patients range from minimal disease to severe hepatitis and cirrhosis, although most have findings consistent with mild disease.

Although currently approved interferon regimens may reduce the level of viremia, they have not been proven to produce sustained responses. The recent NIH consensus conference suggested that these patients should be treated only under a research protocol.

Vaccination against hepatitis A and B

In patients with chronic HCV infection (with or without cirrhosis), superinfection with hepatitis A virus or hepatitis B virus may result in a more aggressive and fulminant course. To prevent this, it was recently recommended that patients with chronic HCV infection receive vaccinations against these other hepatotropic viruses.

A reasonable strategy is to look for natural immunity by testing for IgG antibodies to hepatitis A and for antibodies to hepatitis B surface antigen, and if negative to vaccinate against both viruses. Although the efficacy of these vaccines (especially in early disease) is established, the feasibility and cost-effectiveness of vaccinating all patients with HCV remains unproven.

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