



Hepatitis and Hemophilia

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INTRODUCTION

Management of viral hepatitis is a major aspect of hemophilia nursing. A large majority of individuals with bleeding disorders have chronic hepatitis C infection, while a few are chronic carriers of hepatitis B virus, some of whom are co-infected with hepatitis D. Many also have hepatitis G virus or antibody.

An understanding of viral hepatitis is essential to providing appropriate patient education and support in order to prevent or moderate the effects of chronic infection. We must distinguish among these various viral infections and explain them to patients, interpret hepatitis tests and markers, explain how to prevent transmission to others, and encourage behaviors that protect the liver from further harm. Caring for those with chronic hepatitis and protecting those without hepatitis are integral to the practice of hemophilia nursing. This chapter will provide practical information on viral hepatitis for the hemophilia nurse and for other nurses who provide services to patients with bleeding disorders.

SIX TYPES OF VIRAL HEPATITIS

Of six hepatitis viruses described, hepatitis A and E are primarily found in community outbreaks and are associated with ingestion of contaminated water or food. They cause acute infection but do not persist as chronic infections. Hepatitis B, C, and D, which are transmitted through blood or contaminated needles, can become chronic infections.

Transfusions of blood components and clotting concentrates have exposed many persons with bleeding disorders to hepatitis B and C (1). The table below summarizes the 6 types of viral hepatitis currently recognized.

	Transmission	Chronicity	Vaccine
Hepatitis A (HAV)	Fecal-oral	No	Yes
Hepatitis B (HBV)	Blood	Yes	Yes
Hepatitis C (HCV)	Blood	Yes	No
Hepatitis D	Blood	Yes	No
Hepatitis E	Fecal-oral	No	No
Hepatitis G	Unknown	Unknown	No

TRANSMISSION OF VIRAL HEPATITIS

Prior to the 1990's, most adults and teens with hemophilia and other bleeding disorders who required transfusions with blood components or plasma-derived clotting factor concentrates developed hepatitis infections. The 1990's brought many advances in transfusion safety, most notably the development of a sensitive test for donor screening for hepatitis C. The development of mini-pool nucleic acid amplification produced a

significant improvement in the prevention of transmission of approximately 5 HIV-1 infections and 56 HCV infections annually (73). Moreover, this testing has helped reduce the residual risk of transfusion-transmitted HIV and HCV to approximately 1 in 2 million blood units (2). Consequently, these methods of viral reduction applied to plasma-derived clotting concentrates have almost eliminated the risk of new transmissions, even as plasma pools have become larger. Recombinant factor concentrates that are produced without human plasma additives further protect against new transmissions of viral hepatitis to bleeding disorders patients.

The Centers for Disease Control and Prevention (CDC)'s Universal Data Collection project screens patients with bleeding disorders nationwide who consent to participate for hepatitis infections and investigates any new transmissions in order to develop more effective prevention strategies. The CDC strongly recommends that anyone who has had a blood transfusion or clotting factor concentrates before 1992 should receive routine HCV testing (67). Additionally, all patients who have immigrated from other countries and who have received blood products while in those countries at any time should also be tested for hepatitis C.

Vaccines to protect patients from hepatitis A and hepatitis B are widely available and are strongly recommended for uninfected bleeding disorder patients.

HEPATITIS A

CLINICAL COURSE

Hepatitis A (HAV) is the most common form of acute viral hepatitis in the United States. After an average incubation period of one month, clinical symptoms range from asymptomatic infection to severe jaundice; symptoms are usually mild in children but increase in severity with age. In acute infection, alanine aminotransferase (ATL) levels become notably elevated and precede a rising anti-HAV antibody titer. This self-limited infection lasts only a few weeks for most patients, and there is no ongoing carrier state. The anti-HAV antibody persists after an infection has cleared and protects the individual from future exposure. In the United States, one third of the general population has evidence of prior HAV infection (3). Though rare, death from fulminant hepatitis A can occur, particularly in persons with chronic liver disease.

TRANSMISSION

The virus responsible for hepatitis A infection is highly contagious and is transmitted primarily by water or food contaminated with fecal matter (See Table). Unsanitary diapering practices can also foster transmission. Rarely, blood transfusions and clotting factor concentrates have transmitted hepatitis A.

A 1997 hepatitis surveillance study sponsored by National Hemophilia Foundation (NHF) collected data from hemophilia treatment centers on the hepatitis status of persons with hemophilia. Sixteen percent of the 2514 individuals tested for HAV were positive. (4) In 1995 three cases of acute HAV infections in children with hemophilia were acquired from one specific lot of clotting factor concentrate.

VACCINE

Vaccination against hepatitis A is now part of scheduled routine pediatric immunizations and is recommended for all persons with hemophilia and other inherited bleeding disorders unless immunity is documented. This vaccine is also recommended for those with chronic hepatitis C because of the increased risk for fulminant hepatitis if acute hepatitis A infection occurs in patients with chronic liver disease. Two types of inactivated vaccine for HAV are available for persons over the age of one. Havrix® (hepatitis A vaccine, inactivated; GlaxoSmithKline Biologicals, Rixensart, Belgium) is licensed in three formulations, 360 ELISA units, 720 ELU, and 1440 ELU. The pediatric/adolescent formulation of Havrix® is licensed for children aged 1-18 years. (70) Vaqta® (hepatitis A vaccine, inactivated; Merck & Co., Whitehouse Station, New Jersey) has two formulations, 25 units and 50 units. The pediatric/adolescent formulation of VAQTA® is approved for use in children aged 12 months-18 years (70). Depending on the vaccine and the patient's age, either two or three immunizations are required. Immunity is estimated to last at least 20 years in healthy adults.

Several investigations of the route of administration reported excellent development and persistence of immunity when the vaccine was administered subcutaneously rather than intramuscularly (6-8). People with chronic liver disease including hepatitis C infections also developed and maintained protective antibody to HAV after completing the immunization series. (9-10)

HEPATITIS B

CLINICAL COURSE

Hepatitis B (HBV) is a DNA virus that replicates in the liver. The clinical symptoms of acute hepatitis B may include loss of appetite, vague abdominal discomfort, nausea, vomiting and jaundice, or the patient may be asymptomatic. The infected individual sheds several markers including HBV surface antigen (HBsAg) into the blood, along with HBV DNA. Hepatitis B is diagnosed by finding HBsAg in serum. Some infected individuals also carry HBeAg.

A person's immune response determines whether the person clears the virus successfully or becomes a chronic carrier. About 30% of children infected under the age of six will develop chronic infection, while only 3% to 5% of adults with an acute HBV infection fail to clear the viral infection.

Chronic hepatitis B is determined by the finding of HBV DNA and usually HBeAg in the serum. In a 1993 multi-center hemophilia study in the United States, 8% of transfused patients had chronic hepatitis B, determined by HBsAg persisting over six months (1). Individuals with persistent HBeAg have a high level of infectivity and warrant referral to gastroenterology specialists and consideration for treatment. Many individuals with chronic hepatitis B will develop chronic liver disease, with histological changes and elevated liver enzymes. Chronic liver disease can progress to cirrhosis and increases the risk for primary hepatocellular carcinoma.

The natural history of chronic HBV includes periods of quiescence and exacerbation. An increase in clinical symptoms may be caused by superimposed infection with hepatitis C or hepatitis D or may be associated with an increased immune response leading to clearance of the e antigen. Over time, a few individuals may spontaneously clear the infection, initially losing HBeAg and many years later clearing HBsAg (12). In patients serving as controls for clinical trials, 12% spontaneously develop remission (13).

MARKERS

Serological test for hepatitis B antigens and antibodies are used to determine whether an individual has previously been infected, has a chronic infection, or is immune to hepatitis B.

The hepatitis B virus has three antigens. The core antigen (HBcAg) is surrounded by an outer surface antigen (HBsAg). This surface antigen circulates in the blood when either an acute or a chronic infection with hepatitis B is present. The e antigen (HBeAg) may also be present in serum and indicates viral replication and a high degree of infectivity (11).

Antibody to HBsAg (anti-HBs), produced in response to the surface antigen, confers protection from future infections. This antibody marker is detectable in individuals who have been immunized to HBV and in those who have recovered fully from infection. Antibody to HBcAg (anti-HBc) develops in all patients who have been infected by HBV, but it is not protective, and its presence cannot alone distinguish whether there is an acute, chronic, or resolved infection. IgM subtype of anti-HBc occurs during acute infection and usually disappears four to eight months after acute infection. Some patients with chronic infection will develop measurable IgM antibody during flares of their infection, however. Antibody to HBeAg (anti-HBe) disappears once the virus is no longer replicating (11).

TRANSMISSION

Most new HBV infections in the United States result from sexual transmission, injection drug use, or occupational exposure (See Table above). Transmission of HBV from blood and blood products is now rare. Healthcare workers, laboratory staff, and parents who infuse their children can be at risk if there is blood exposure through a small skin break or through needlestick injuries. Universal precautions to prevent viral transmission need to be applied in all situations, including the home setting.

Spouses, sexual partners, children, and household members of patients with chronic hepatitis B infection should be immunized with hepatitis B vaccine if serologic testing indicates they have not been infected. Needlestick or splash exposures and unprotected sexual contact with a hepatitis B carrier should be treated within hours with Hepatitis B immune globulin (HBIG) and begin hepatitis B vaccination. Perinatal transmission can successfully be interrupted by prophylaxis with HBIG and vaccination beginning immediately following birth (14).

TREATMENT

The goal of treatment is the sustained loss of HBV DNA and HBeAg from serum. The only approved treatment is interferon alfa-2b either daily or three times week for four months, which induces a long-term remission in 25% to 40% of recipients. Candidates for treatment include those having elevated ALT levels, detectable HBV DNA and HBeAg, along with compensated liver disease (15). Identification of the specific genotype can also facilitate the prediction and likelihood of treatment response and, in many cases, determine the duration of treatment (68).

Several new treatments using nucleoside analogues, such as famciclovir and lamivudine, are being evaluated in clinical trials. Longer term therapy and drugs used in combination with interferon may provide more effective treatment in the future (15).

VACCINE

A safe and highly effective vaccine for hepatitis B is available. The initial vaccine was plasma derived, but a recombinant vaccine is now recommended for most persons. Hepatitis B vaccine is now included in the recommended infant immunizations. Adults at risk, including healthcare workers, should be immunized.

In the United States, three doses are given on a schedule of zero months, then one month and six months after the initial injection. The usual route of administration is intramuscular, but efficacy of greater than 90% was seen in children and adult who received the vaccine subcutaneously in the anterior-lateral thigh or upper arm (16,17). A month after completing the series, a positive titer for anti-HBs will give evidence of immunity. The duration of immunity is unknown, but most immunized adults will have a measurable titer four to seven years after their initial series.

If a person does not respond to the series of three injections, a second series of three injections should be given and the titer rechecked. Most individuals will respond to a second series, but those with immune compromise resulting from HIV infection may show loss of previous antibody titer and are less likely to respond to revaccination, although this should be attempted (14).

The side effects of the hepatitis B vaccine include minimal soreness at the injection site and brief myalgia. Since intramuscular injections can cause muscle bleeding in persons with moderate or severe hemophilia or von Willebrand disease, the immunization should be given at the same time a factor dose is given. The subcutaneous route is a safer alternative for those not receiving factor infusions on a regular basis. (6-7)

HEPATITIS C

CLINICAL COURSE

The hepatitis C virus (HCV) is an RNA virus that causes a silent acute infection in most patients, while some individuals may develop mild clinical symptoms similar to hepatitis B infection. During the acute phase, serum HCV RNA begins to appear within two weeks of exposure. One third of those infected will experience onset of symptoms at

about seven weeks (18). Antibody to hepatitis C (anti-HCV) will appear seven to 10 weeks after exposure (19).

Few individuals are able to clear the infection. Hepatitis C becomes a chronic infection for about 85% of those infected with the virus. Six genotypes of HCV have been described. An individual may have heterogeneous but closely related viral genomes, referred to as quasispecies, circulating simultaneously. This genetic diversity and the ability of the virus to mutate rapidly may allow the hepatitis C virus to evade the host's immune system. Because of the slow progression of liver disease, the majority of persons with chronic hepatitis C will remain asymptomatic for decades and some for their entire lives. However, host factors such as age, alcohol use, and coinfection with other viruses may enable a more rapid progression of liver disease in some individuals (20). Persons with hemophilia who are coinfecting with HIV are more likely to develop progressive, severe liver disease (21, 22).

A majority of people with chronic hepatitis C have elevated or fluctuating ALT levels. About one third, however, have normal levels but still have evidence of chronic liver disease on liver biopsy. Clinical symptoms at this stage are absent or nonspecific, with reports of fatigue, itching, and abdominal pain being the most common. More pronounced symptoms often appear with the development of advanced liver disease. Mild fibrosis leads to more severe fibrosis and cirrhosis in at least 20% of HCV-positive patients. There is a wide range of susceptibility to the development of cirrhosis. Risk factors include being male, becoming infected after the age of 50, and consuming substantial amounts of alcohol. A study to evaluate liver disease in persons with hemophilia and chronic HCV found direct or indirect evidence of cirrhosis in about 25% of this group of patients (20). Those with cirrhosis have an increased risk for hepatic decompensation and hepatocellular carcinoma.

LIVER CIRRHOSIS

Cirrhosis develops as liver tissue is replaced with nodules of fibrous tissue, but the individual may remain asymptomatic for years. The dense fibrous scar tissue and nodules can eventually impede portal blood flow and hepatic function, leading to portal hypertension and symptoms of varices, splenomegaly, ascites and peripheral edema. Visualization studies, such as endoscopy, and upper GI studies with barium may identify thin-walled varices in the lower esophagus and gastric fundus. Ultrasound studies and CT scans may also show the presence of fibrous tissue and impaired hepatic blood flow. Cirrhosis also leads to decreased hepatic synthesis of coagulation factors, particularly prothrombin, and decreased platelets due to splenomegaly.

Other symptoms of cirrhosis include weight loss, which may not be initially apparent because of fluid retention and ascites, and edema associated with decreased serum albumin levels. Jaundice and pruritis occur when the liver fails to metabolize and excrete bilirubin. Spider angiomas, which are arterial lesions formed by dilation of small blood vessels, and palmar erythema, the bright red appearance of palms and soles, may develop.

Hepatic encephalopathy develops in advanced cirrhosis when toxic products of protein metabolism are not removed by liver and thus can get into the brain and interfere with

brain function. As blood is shunted around the liver by portal hypertension, blood ammonia levels increase. Symptoms of impaired neurological function include short attention span, slurred speech, asterixis, hyperactive muscle reflexes, and loss of consciousness. Bleeding from esophageal varices with the ensuing breakdown of blood in the gastrointestinal tract may also lead to elevated serum ammonia levels and symptoms of hepatic encephalopathy (24).

Dietary restrictions may reduce ascites and hepatic encephalopathy. Although protein is essential to regenerate hepatocytes, protein intake restriction may be necessary when encephalopathy is present. Sodium and fluid restrictions may stop the accumulation of ascitic fluid. Sudden weight gain, abdominal distention, and respiratory difficulty may signal fluid and electrolyte imbalance. Decreased potassium levels can precipitate hepatic coma. Lactulose may help to lower blood ammonia levels.

Patients should be aware of signs and symptoms of GI bleeding and report hematemesis and melena at once. During acute GI bleeding, endoscopy may be required to determine the source of bleeding. In addition to drug therapy with vasopressin, actively bleeding varices may require treatment with sclerotherapy to thrombose the vessels or with balloon tamponade to compress the gastric and esophageal varices. Surgical shunting by either a portacaval shunt or a distal splenorenal shunt may divert portal circulation and decrease variceal bleeding but may increase hepatic encephalopathy. In transjugular intrahepatic portosystemic shunting (TIPS), a cannula is placed in the portal vein with a stent to shunt circulation to the hepatic vein (24). These procedures do not lead to increased long-term survival.

HEPATOCELLULAR CARCINOMA

Over decades, hepatocellular carcinoma has occurred in 1% to 4% of those with chronic hepatitis C, primarily in the presence of cirrhosis. Non-Hodgkin's lymphoma has recently been associated with chronic HCV infection in those with long-standing cryoglobulinemia, glomerulonephritis, thyroid dysfunction and rheumatoid arthritis (25). Mortality from liver disease and hepatocellular cancer is higher for patients with hemophilia, particularly those infected with HCV at an older age who have moderate or high alcohol use, than for those without bleeding disorders (26).

A Transcatheter Arterial Chemoembolization / Transarterial Chemoembolization (TACE) is being used extensively in the palliative treatment of unresectable hepatocellular carcinoma, one of the most common malignancies not only in patients with hemophilia, but worldwide. The TACE procedure may be utilized to decrease tumor size and to help bring patients within the guidelines required for a liver transplant.

Liver transplantation: Liver transplant may be indicated for those with early hepatocellular carcinoma and end-stage cirrhosis. Outcomes are encouraging in individuals with hemophilia who do not have HIV co-infection. At this time more than 50 transplants have been performed in hemophiliacs worldwide. While the underlying hemophilia is cured, re-infection of the new liver with hepatitis C is common if the recipient was HCV RNA positive going into transplantation, as is the usual case (71). The primary post-transplant complications are acute rejection and risk of infection due to

steroids and immunosuppressive medications. The post-transplant patient will require life-long drug therapy to prevent organ rejection. Patients with established HCV infection post liver transplantation should be treated with interferon and riboviran (71).

Candidates for a new liver must meet rigid selection criteria. They must be in the final stage of hepatitis disease, free from alcohol use, have no bacterial or fungal infections outside the hepatobiliary system, and any malignancy must be limited to the liver. Liver transplantation is not contraindicated in HIV-positive patients provided that the HIV is fully suppressed with highly active antiretroviral therapy (HAART) (71). Psychological stability and an adequate support system are essential.

Risk of alcohol use: Because alcohol use clearly worsens the course of hepatitis C, more than one drink a day is strongly discouraged, and abstinence from alcohol is highly recommended (28). The extent and pattern of alcohol use should be ascertained for all patients, including young adolescents (29). Those addicted to alcohol or drugs should be counseled and referred for treatment. Chronic alcoholism in patients with chronic HCV increases their risk of cirrhosis and hepatocellular carcinoma (30).

Risk of Tylenol and herbal remedies: Over-the-counter medications should be used cautiously in the setting of chronic hepatitis. Medications such as acetaminophen may have deleterious effects in chronic hepatitis. Acetaminophen, if needed, should be limited to two grams per day (31). Some herbal medications are also toxic to the liver and interfere with platelet function. Since herbal remedies are not regulated by the FDA, safety and efficacy studies have not been done (32).

Acute infection with hepatitis A can present a significant mortality risk for persons with chronic hepatitis C. In a prospective study of 432 patients with chronic HCV who were negative for hepatitis A, 17 patients developed acute hepatitis A infection. Seven of those developed fulminant hepatic failure, and six patients died (8). None of the seven had cirrhosis, nor were they heavy drinkers. Immunization with inactivated hepatitis A vaccine is safe and effective for those with chronic liver disease and chronic hepatitis C (9-10) and is highly recommended for all patients with bleeding disorders. (6-7)

LABORATORY TESTS

The HCV antibody test (anti-HCV) can identify individuals with current or past infection with hepatitis C. Serum qualitative HCV RNA test using polymerase chain reaction (PCR) analysis can be used to determine the presence of active infection. A quantitative test reports the amount of virus in the serum, or viral load, but this level does not correlate with histologic features on biopsy. A high viral load appears to make a person more infectious and more resistant to interferon therapy (25). ALT is usually elevated, but the degree of elevation does not correlate with the amount of liver injury. Those with normal ALT levels can have significant fibrosis and even cirrhosis. Both genotyping and quasispecies are standard tests performed prior to starting therapy. Hepatitis C virus genotype is considered to be the most important baseline predictor of a sustained virological response in patients with chronic hepatitis C treated with pegylated interferon and ribavirin (72). Genotype testing provides information about potential response to

hepatitis C treatment with interferon monotherapy, interferon plus ribavirin and most recently with the two new oral HCV protease inhibitors, boceprevir and telaprevir (68).

LIVER BIOPSY

Nearly all patients with chronic hepatitis C develop histologic changes, including portal inflammation, interface hepatitis (formerly known as piecemeal necrosis), and lobular injury. The presence of steatosis and portal lymphoid aggregates and the appearance of bile duct injury are characteristic of hepatitis C (25). Disease severity cannot be predicted by ALT levels nor by the level of HCV RNA. Liver biopsy can determine the degree of inflammation and the severity of fibrosis or presence of cirrhosis but may not be necessary in deciding whether to begin drug treatment. A liver biopsy in a person with a bleeding disorder requires clotting factor replacement to prevent bleeding complications (20). A hematologist with experience in treating patients with bleeding disorders should be consulted to determine appropriate factor replacement for this procedure.

TRANSMISSION

HCV is transmitted primarily through blood and blood products. Transmission of hepatitis C to family and household members has been studied extensively and is probably rare (35). Among long-term sexual partners of asymptomatic blood donors, no transmission was found unless the partner also had a parenteral drug use risk factor. The few children who were identified with hepatitis C had acquired the infection perinatally (36). Numerous household studies found the HCV seroprevalence of sexual partners of persons with hemophilia to be very low, in the range of 0% to 3% (37). Barrier protection, such as latex condoms, is recommended for those with multiple sexual partners but for those in monogamous relationships, the decision is left to the couple (38).

Perinatal transmission may occur, particularly when the mother has a high level of HCV viremia or is coinfecting with HIV. Vertical transmission is estimated to occur in about 5% to 6% of infants born to HCV-infected mothers. There is no evidence that breastfeeding transmits hepatitis C (38).

Intravenous drug use is a major risk for transmission, but other illicit drug use, such as intranasal cocaine use, has also been associated with hepatitis C infections. Tattoos and ear and body piercing can lead to infection if contaminated equipment or supplies are used (36).

For persons with chronic hepatitis C, it is important to avoid behavior risks, such as injection or intranasal drug use and tattoos and body piercing, that may lead to re-infection with additional viral strains. Those with multiple sexual partners should use condoms. An honest and candid discussion with patients about these behaviors can help patients at risk to understand the danger these behaviors pose to themselves and others. Household members should not share personal hygiene items, such as toothbrushes, razors, and nail clippers.

By reinforcing safe home infusion practices, hemophilia nurses can also reduce household transmission from inadvertent needlestick injuries. One intra-family

transmission from an infected parent to a previously negative child with hemophilia has occurred during home treatment. The parent performing the infusion may have inadvertently sustained a needlestick and then used the contaminated needle to infuse the child (39).

If a needlestick from a patient with chronic hepatitis C occurs, the rate of infection for the injured caregiver is estimated to be under 10% (25). The current CDC guidelines do not recommend post-exposure prophylaxis with immune globulin or anti-viral agents (40). An occupational exposure study in Japan found four confirmed HCV transmissions to healthcare workers from 251 needlestick incidents, for a transmission rate of 1.6%. All four were treated with a four- to six-month course of interferon alfa-2b and developed sustained responses based on negative HCV RNA results after treatment (41).

TREATMENT

According to the most recent guidelines from the Centers for Disease Control (CDC) there are at least six known genotypes and more than 50 subtypes of HCV. The genotype information of a patient is helpful in defining the epidemiology of Hepatitis C and in making recommendations regarding treatment (68). Patients with genotypes 2 and 3 are almost three times more likely than patients with genotype 1 to respond to therapy with alpha interferon or the combination of alpha interferon and ribavirin. Additionally, the CDC indicates that, when using combination therapy, the recommended duration of treatment depends on the genotype. For patients with genotypes 2 and 3, a 24-week course of combination treatment is sufficient, while patients with genotype 1, a 48-week course is recommended. Once the genotype is identified, it does not require testing again; genotypes do not change during the course of infection (68).

In terms of medication regimens, four forms of alpha interferon, a cytokine with immune modulatory effects, have been used extensively in clinical trials, including recombinant alpha interferon (interferon alfa-2a and interferon alfa-2b), lymphoblastoid interferon (interferon alfa-n1), and consensus interferon. Additionally, there have been major efforts to develop improved and effective therapies to help patients improve outcomes. This will be outlined further later in this chapter.

A review and meta-analysis conducted in 1997 of 32 trials with recombinant alpha interferon found a sustained response, specifically a negative test for HCV RNA for six months following treatment, in 8% to 11% of treated patients. A larger portion, 22%, demonstrated a sustained biochemical response, consisting of normal ALT levels for six months following treatment. Patients on the other forms of interferon had similar responses in clinical trials and similar side effects (43-45). In a clinical trial with consensus interferon, those who relapsed during the six months following the end of treatment were retreated for 12 months longer and had a 58% sustained response rate, suggesting that longer treatment may be more effective for some. The adverse side effects of consensus interferon were similar to the other interferons (45). Since 1995, these regimens have led to significantly improved response rates in treatment of chronic hepatitis C. However, there is an imperative need to continue to investigate new anti-viral

therapies in order to improve outcomes in patients who have been non-responders to pegylated interferon and ribavirin (68).

The new therapies which have been recently approved by the FDA include two new oral HCV protease inhibitors, boceprevir and telaprevir (68). When used in combination with current standard therapy (peg-interferon and ribavirin [PR]), these new drugs substantially improve cure rates and often reduce the overall duration of therapy (68). Telaprevir with peg-interferon-ribavirin, as compared with peg-interferon-ribavirin alone, was associated with significantly improved rates of sustained virologic response in patients with HCV genotype 1 infection who had not received previous treatment (68). Furthermore, the majority of patients who were treated with telaprevir had undetectable HCV RNA at weeks 4 and 12 and only required a total of 24 weeks of therapy. Even higher response rates with a small increment in reversible adverse events were observed with a regimen of 12 weeks, as with 8 weeks, of telaprevir combined with peg-interferon-ribavirin, followed by additional weeks of peg-interferon-ribavirin alone (68). The significantly improved virologic response rates with telaprevir-based therapy and the capacity for response-guided therapy to decrease the duration of exposure to peg-interferon-ribavirin among those patients who have a significantly rapid response demonstrates significant advances in the treatment of patients with HCV genotype 1 infection. Although data are still emerging, these new drugs are likely to benefit HIV-coinfected patients as well (68).

Common side effects of alpha interferon include fever, sweating, chills, headache, fatigue, and joint and muscle aching, especially with the initial injections. These symptoms often improve over the first two weeks of therapy. Some clinicians recommend administering the interferon dose in the evening and using acetaminophen to ameliorate side effects. Acetaminophen should be used in moderation (46).

Later side effects of continued treatment include fatigue, irritability, malaise, apathy, loss of appetite and difficulty with concentration. School or work performance of complex or involved task may be impaired. Some will develop serious neuropsychiatric symptoms, most often depression and attempted suicide, and these need to be recognized and reported promptly. The myelosuppressive effects on platelets, white blood cells, and red blood cells are usually mild and do not require altering the course of drug therapy for most patients. Interferon also has stimulated autoimmune antibody formation, especially in susceptible patients. Altered thyroid function is the most common manifestation of autoimmune disease. A few patients have developed insulin-dependent diabetes in association with interferon use (51). The use of the oral agent telaprevir in combination with peg-interferon-ribavirin, as compared to peg-interferon-ribavirin alone, has a higher incidence of adverse events such as rash, gastrointestinal disorders, and anemia. In one study, rashes resolved with the discontinuation of telaprevir, while anemia led to the discontinuation of ribavirin in a few patients (68).

It is likely that developments in combination treatment will lead to more effective treatment. The standard of care has been ribavirin combined with alpha interferon, particularly for those who have relapsed after an initial response to interferon therapy.

Patients likely to show a low response rate to interferon, such as those with genotype 1 cirrhosis, seem to have a twofold or threefold increase in sustained response from this combination therapy. Several studies of interferon-naïve patients have reported a sustained response in about 45% of patients receiving ribavirin plus a form of alpha interferon. The primary side effect of ribavirin is a decreased hemoglobin level resulting from hemolysis (47). Interferon is administered as a subcutaneous injection, while ribavirin is taken orally. With the aforementioned treatment the length of treatment is usually six to 12 months.

The new therapies recently approved by the FDA, including two new oral HCV protease inhibitors, boceprevir and telaprevir, will likely help reduce the overall duration of therapy (68). When used in combination with current standard therapy (peg-interferon and ribavirin [PR]), these new drugs should significantly improve cure rates and help to reduce the overall duration of therapy. Clearly there will be a new range of side effects which will occur with the new therapies as well. These patients will require close and appropriate management by hepatologists and infectious disease specialists (71).

About one-fourth of patients with chronic hepatitis C and viremia have persistently normal ALT levels. This group seems no more likely to develop a sustained response to interferon alpha but may actually be harmed by treatment, during which abnormal ALTs often develop and persist afterwards, possibly by altering the host immune response. A majority of patients in this group have mild inflammation on liver biopsy, with fibrosis and cirrhosis being extremely rare (48). The NIH Consensus Development Conference panel has recommended against treating this group with interferon (28).

Patients with compensated cirrhosis are less likely to have a sustained response to interferon; only 5% to 10% of those with histologically confirmed cirrhosis respond to treatment. These responders, however, have a very low risk for hepatocellular carcinoma or decompensation and have excellent survival rates following treatment. Patients who fail to clear virus by the first month of interferon therapy are unlikely to respond later. When treated with interferon in combination with ribavirin, this group had twice the rate of response than with interferon alone. On the other hand, patients with chronic hepatitis C and decompensated cirrhosis are unlikely to benefit from drug therapy and may develop severe side effects. For these patients, liver transplantation should be considered the treatment of choice (49).

OTHER THERAPY OPTIONS

Additional therapeutic approaches have undergone clinical trials, either alone or in combination with alpha interferon. Iron reduction through therapeutic phlebotomy failed to promote a better response to interferon, and it is unclear whether the elevated iron levels seen in serum and liver occur as a result of a more severe chronic infection or whether the increased iron predisposes the patient to a more severe chronic hepatitis. Antioxidants, immunomodulators, and other antiviral agents have also been evaluated in combination with interferon. Larger studies are needed to determine whether these drugs offer benefit as an adjunct to other therapy. It is likely that management of hepatitis C in

the future will involve combinations of drugs that affect viral replication in a variety of ways.

PREDICTORS OF RESPONSE TO TREATMENT

Many researchers have looked for host characteristics and viral parameters to predict who will respond to interferon treatment. Patients who are younger, female, with short duration of infection, and without fibrosis or cirrhosis are more likely to respond. Prior to treatment, a low HCV RNA level, less viral diversity as determined by the number of dominant quasispecies, and virus genotypes 2 and 3 portend successful treatment (51). Among heavy drinkers, those who abstain from alcohol for at least three years before beginning interferon are more likely to respond. Interferon is less effective in the alcoholic, even after a period of abstinence (30). Once treatment has begun, normalization of ALT levels and early loss of HCV RNA can help identify those who are likely to develop a sustained response. Although these factors may help to explain outcomes for groups of patients, it is not possible to accurately predict how well an individual will respond, and these factors should not be used to exclude a patient from therapy (68).

HEPATITIS D

Hepatitis D is the least common type of chronic viral hepatitis. The hepatitis D virus is a defective RNA virus that replicates only in the presence of hepatitis B surface antigen (HbsAg). The presence of antibodies to HDV (anti-HDV) and HDV RNA in serum confirm a chronic infection (52).

Hepatitis D infection can occur simultaneously with an acute HBV infection and is mostly self-limited because of the brief infection of HBV, or it can be superimposed on hepatitis B carrier state and persist as a chronic infection. (11) If a person has anti-HBs as a result of previously cleared hepatitis B infection or in response to hepatitis B immunization, he/she will not become infected if exposed to hepatitis D. In addition to transfusion-associated transmission, HDV is transmitted sexually and by intravenous drug use.

Chronic hepatitis D infection can readily lead to cirrhosis and is difficult to treat. Treatment with high doses of alpha interferon, such as 9 million units three times a week for 12 months, led to remission in 36% of patients in one clinical trial. Sustained remission, including loss of HBsAg, was seen in 15% to 25% of patients (68).

HEPATITIS E

Outbreaks of hepatitis E have been identified in several regions of the world, but acute hepatitis E infection is extremely rare in the United States. The clinical illness and transmission routes are similar to hepatitis A, and there are no chronic sequelae. Hepatitis E antibody (anti-HEV) develops during convalescence (53). There is no evidence of transmission by clotting factors concentrates manufactured from US plasma donors (54).

Although a hepatitis F organism was described, it was later found not to exist.

HEPATITIS G

Hepatitis G is caused by a small RNA virus with similarities to HCV. The virus, although it causes persistent viremia for at least six months and often many years, does not cause appreciable clinical symptoms. Jaundice, fatigue, nausea, and loss of appetite can occur in the acute phase (55).

In one study, hepatitis G infection was commonly seen in patients with hepatitis A, B, and C. HGV was detected in 25% of those with hepatitis A, 32% of those with hepatitis B, and 20% of those with hepatitis C. The viral infection with HGV persisted with intermittent viremia (55).

HGV RNA has been found in 1% to 2% of healthy blood donors, and 9% had antibody for HGV, called anti-E2 (56). This antibody is usually not seen in the presence of HGV RNA and appears to develop as infection resolves. Among intravenous drug users, 38% had HGV RNA, while 41% were positive for anti-E2 (57). In a British cohort of persons with hemophilia, 11% had evidence of HGV RNA, and a larger percent had anti-E2, which suggests clearance of the virus (58). Another European study of 168 persons with hemophilia reported 39% of patients who had used clotting concentrates without viral inactivation were found to have either HGV RNA or antibody for HGV. No evidence of HGV was seen in seven patients who had only used recombinant factor. Of the three patients who had HGV without HCV, none had ALT elevations that would suggest chronic liver disease. (59) A study of hemophilia patients in France found that over half had evidence of HGV infection (60).

Although HGV is a coinfection for many individuals with chronic HCV, it does not alter the clinical course of HCV nor interfere with the response of HCV to interferon. It is clearly associated with transmission by transfusions. Mild elevations of ALT and rarely jaundice have been seen in transfusion recipients, but none were found to have chronic liver disease associated with HGV alone. About one third cleared the virus within three years of becoming infected with HGV (61). This pattern was similar in several hemophilia cohorts (62-64), and infection with HGV did not alter the course of chronic hepatitis C.

NURSING IMPLICATIONS

Bleeding disorders treatment in the past carried a high risk for exposure to blood-borne viruses, in particular hepatitis B, hepatitis C, hepatitis D, and hepatitis G. Measures can now be taken to protect patients from viral hepatitis and reduce complications for those with chronic hepatitis.

All persons with bleeding disorders should be vaccinated for hepatitis A and hepatitis B if no evidence of antibodies is present. Immunization with hepatitis B vaccine offers

protection from exposure to HBV and HDV. The response and duration of vaccine-induced immunity for hepatitis B should be monitored so that booster doses can be considered if immunity wanes. For those with chronic hepatitis B and especially chronic hepatitis C, the vaccine for hepatitis A provides protection from the inordinately high risk for mortality from a fulminant course of acute hepatitis A infection.

Knowing the specific hepatitis status of a patient will enable the nurse to provide pertinent education and counseling. Patients with chronic hepatitis B should be assessed for HBeAg and anti-HBeAb and for hepatitis D. Individuals with chronic hepatitis C must be vaccinated promptly for hepatitis A if not already immune. Patients with chronic hepatitis should be referred for specialty care to define their underlying liver disease and to consider participation in drug therapy or clinical trials for newer treatment. Helping patients cope with side effects and with the possibility of less than optimal outcomes after treatment can be addressed. Support groups and individual counseling may be helpful to maintain optimism while living with a chronic illness without knowing how slow or progressive the disease will be.

Information and counseling should be offered regarding behaviors that protect the liver from further harm. Alcohol use should be minimized, and abstinence is highly encouraged. The provider needs to carefully assess for alcohol use and provide counseling and referral for those with moderate or high reported use (66). With the adolescent patient, counseling should include attitudes toward alcohol and drugs, family history of addiction, and an assessment of potential risk. Behaviors that are high risk for transmission should be discussed with all patients, including risk of transmission from intranasal and intravenous use of illicit drugs. Safer sex behaviors, including condom use, are recommended for those with multiple sexual partners. Patients should be advised about the potential risks of tattoos and body and ear piercing from contaminated equipment or unsterile technique.

Non-essential medications should be avoided. Any use of acetaminophen should be minimized, keeping in mind that many combination pain medications include acetaminophen. Alternate measures for pain management should be explored. Some herbal remedies may pose a risk for further liver impairment. Environmental toxins such as pesticides and cleaning solvents should be avoided as well as occupational exposure to hepatotoxic chemicals.

Hemophilia treatment products that are least likely to lead to viral transmissions should be selected. For patients with rare bleeding disorders that require fresh-frozen plasma or cryoprecipitate, components prepared from a single volunteer donors will reduce the exposure to multiple donors. By participating in the CDC's universal Data Collection project, patients will have free annual testing for hepatitis A, B, and C, and a large cohort of patients nationwide will be monitored for unexpected transmissions.

Ensuring home infusion safety is vital. In teaching and reinforcing safe behaviors, nurses must consider the ability of young children to cooperate before moving treatment from the clinical setting to the home. Families must be aware of the risk to household

members from IV equipment and must use and dispose of sharps canisters appropriately. If a needlestick or other exposure of a household member occurs, there should be a means for prompt notification of medical providers who can assess the risk and provide counseling or post-exposure drug treatment if indicated.

It is a challenge for the nurse to keep informed about new treatment options and resources in the community in order to assist with referrals and address barriers. The bleeding disorders nurse is in a key position to protect patients with hemophilia from viral hepatitis and to reduce risks and complications for those living with chronic hepatitis and their family members.

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