



A PHARMACY CONTINUING EDUCATION PROGRAM

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April 2005 "Update on Hepatitis" 707-000-05-004-H01



THIS MONTH
"Update: Hepatitis"

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HAVE YOU RECENTLY MOVED? PLEASE NOTIFY US.

Hepatitis is a topic that appears often in pharmacy journals as well as in consumer publications. Our goal is to review the classification and treatment of hepatitis. This lesson provides 1.25 hours (0.125 CEUs) of credit, and is intended for pharmacists in all practice settings.

The program ID # for this lesson is 707-000-05-004-H01.

Pharmacists completing this lesson by April 30, 2008 may receive full credit.

To obtain continuing education credit for this lesson, you must answer the questions on the quiz (70% correct required), and return the quiz. Should you score less than 70%, you will be asked to repeat the quiz. Computerized records are maintained for each participant.

If you have any comments, suggestions or questions, contact us at the above address, or call toll free 1-800-323-4305. (In Alaska and Hawaii phone 1-847-945-8050). **Please write your ID Number (the number that is on the top of the mailing label) in the indicated space on the quiz page** (for continuous participants only).

The objectives of this lesson are such that upon completion the participant will be able to:

1. Discuss viral hepatitis in terms of epidemiology, transmission, pathophysiology, & treatment options.
2. Describe methods to prevent viral hepatitis.
3. List options for treating hepatitis.

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AN UPDATE ON HEPATITIS

Viral Hepatitis is a global health problem. Hepatitis A, B, or C affects millions of people worldwide. The magnitude and clinical consequences of chronic infection with either Hepatitis B or C create the need for effective prevention and treatment measures. The goal of this lesson is to review viral hepatitis (A, B, and C) in regards to the epidemiology, transmission, pathophysiology and treatment guidelines.

HEPATITIS A Epidemiology

Hepatitis A is one of the most frequently reported vaccine-preventable diseases in the U.S. There are about 100 fatalities each year as a result of acute liver failure due to hepatitis A, even though the case-fatality rate for fulminant hepatitis A is low (approximately 0.3% among all age groups.) Persons older than 50, as well as those with chronic liver disease, are at increased risk for fulminant hepatitis A. (1)

The incidence of hepatitis A in the U. S. varies by region, with the west and south having the greatest number of cases. It is estimated that between 1980 and 2001 an average of 25,000 hepatitis A cases occurred annually. Based on surveillance data, the highest incidence was found in children aged 5 to 14 years old. (2) The incidence of hepatitis A varies by race/ethnicity with the highest rates among American Indians/Alaska Natives and the lowest among Asians. The rates among Hispanics are higher than non-Hispanics. The racial/ethnic differences may reflect the risk factors for infection such as differences in socioeconomic levels/living conditions and contact with persons from countries where hepatitis A is endemic. (1)

Most cases of hepatitis A result from person-to-person transmission during community outbreaks. The risk factors for infections include household or sexual contact (14%) with a person with hepatitis A, men who have sex with men (10%), day care (8%), injection drug users (5%), and international travel (5%). The majority of the cases (48%) have an unknown risk factor. (1,2)

Clinical Illness

Hepatitis A virus (HAV) is a picornavirus that can cause asymptomatic or symptomatic infection. The average incubation period is 28 days, but ranges from 15 to 50 days. The illness caused by the HAV results in an abrupt onset of symptoms that include fever, malaise, anorexia, nausea, abdominal discomfort, dark urine and jaundice. The likelihood of having symptoms is related to a person's age. Over 70% of cases in children less than 6 years old are asymptomatic. In adults and adolescents, the infection is usually symptomatic with jaundice occurring in > 70% of patients. The signs and symptoms last less than two months in the majority of patients. (1,2)

In an infected individual, HAV replicates in the liver, is excreted in the bile and is shed in the stool. The concentration of the virus is the highest during the two-week period before the onset of jaundice or elevation of liver enzymes. HAV can be shed in children and infants for up to several months after the onset of clinical illness, which is shorter for adults. (1,2)

Diagnosis

Hepatitis A cannot be differentiated from other types of viral hepatitis by clinical symptoms alone. Serologic testing to detect immunoglobulin M antibody to the capsid proteins of HAV (IgM anti-HAV) is required for diagnosis of acute infection. The IgM anti-HAV appears 5-10 days before the onset of symptoms and can last

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up to six months after the initial infection. In contrast, IgM anti-HAV becomes detectable early in infection and remains detectable for a lifetime. This confers lifelong protection against the disease. (2)

Transmission

HAV is transmitted via the fecal-oral route by person-to-person contact or ingestion of contaminated food or water. It is rarely transmitted by blood transfusions. HAV can be stable in the environment for months, but can be eliminated by heating food at temperatures greater than 185°F, or disinfecting surfaces with household bleach and tap water. (1)

In developing countries, HAV transmission goes unrecognized because HAV immunity is often developed early in childhood. Food borne outbreaks are uncommon in residents due to the high level immunity, but transmission to non-immune travelers might be an important source of hepatitis A. (1,2)

Prevention

Hepatitis A is one the most frequently reported vaccine preventable diseases. Using the hepatitis A vaccine for prevention of infection provides the opportunity to lower the incidence of disease and potentially eliminates the disease, by decreasing transmission and preventing fecal shedding of HAV. (1)

There are two methods of prophylaxis against hepatitis A virus infection. The first is the administration of Immunoglobulin. This is a concentrated antibody from pooled plasma that provides passive immunity. It can be used in patients that the vaccine is contraindicated in or in those individuals planning to travel within 2-4 weeks. When administered, it is given intramuscularly at a dose of 0.02 mL/kg; it provides short-term (for one to two months) protection. A higher dose of 0.06 mL/kg confers protection for three to five months. It can also be administered to those exposed to HAV within two weeks. In patients that are exposed to hepatitis A, Immunoglobulin is greater than 85% effective in preventing infection with HAV (at the dose of 0.02mL/kg) when given within 2 weeks of an exposure. (1)

Immunoglobulin for intramuscular administration (IGIM) is available in a single use 2mL vial or a 10mL multi-dose vial. Some formulations are made without a preservative, while others contain thiomerosal. Formulations that contain thiomerosal should not be used for infants or pregnant women. IGIM should be administered in either the deltoid or gluteal muscle. Adverse effects associated with IGIM are rare, but anaphylaxis has been reported after repeated administration. Immunoglobulin may interfere with the immune response with some live, attenuated vaccines such as measles, mumps, rubella (MMR) vaccine and varicella vaccine. (1)

The hepatitis A vaccines are inactivated vaccines, and include HAVRIX® (Glaxo Smith Kline) and VAQTA® (Merck & Co). Hepatitis A vaccine should be stored and shipped at temperatures that range from 35.6F° (2C°) to 46.4°F (8C°). The vaccine should not be frozen.

The dosing and schedule of the available vaccines are provided in Table 1.

TABLE 1. Hepatitis A vaccine (3,4, 5, 6)

| Product | Recipient's Age (years) | Dose (ELISA units) | Volume (mL) | Number of doses | Schedule (months) |
|---------|----------------------------|-----------------------|----------------|-----------------|----------------------|
| HAVRIX® | 2-18 | 720 * | 0.5 | 2 | 0, 6-12 |
| HAVRIX® | >18 | 1,440 | 1.0 | 2 | 0, 6-12 |
| VAQTA® | 2-17 | 25 U | 0.5 | 2 | 0, 6-18 |
| VAQTA® | >17 | 50 U | 1.0 | 2 | 0, 6 |

* Alternate dosing schedule provided in package insert

Both vaccines are immunogenic in adults older than 18 years old when administered according to the guidelines. Protective antibodies develop one month after the first dose in 94-100% of adults. Similar results are seen in children and adolescents. Protective concentrations are measurable in 2 weeks in 54-62% of patients, and greater than 90% by 4 weeks of receiving a single dose of the vaccine. A second booster given more than six months later provides long-term protection. Protection can last for more than 20 years. A third booster dose is currently not recommended. Misinterpretation of diagnostic tests can occur if IgM anti-HAV concentrations are checked shortly after administration of the Hepatitis A vaccine. After one month, less than

1% of vaccinated individuals had detectable IgM anti-HAV. (1)

The Recommended Adult Immunization Schedule is summarized in Table 2. These recommendations can change so, up to date recommendations can be found at www.cdc.gov.

* Alternate dosing schedule provided in package insert

Table 2. Recommendations for Hepatitis A vaccine for Adults (3)

| |
|--|
| <ul style="list-style-type: none"> • Persons with clotting disorders • Chronic liver disease • Men who have sex with men • Users of illegal drugs • Persons working with HAV-infected primates or with HAV in research setting • Persons traveling to or working in countries with high or intermediate endemicity of hepatitis A. |
|--|

The recommendations for children and adolescents for the Hepatitis A vaccine are determined by the rates of hepatitis A in the community and/or region. Local public health authorities should be contacted for recommendations.

Side effects associated with the hepatitis A vaccine include: soreness at injection site (56%), headache (14%), and malaise (7%) in adults. In children, similar side effects are reported including soreness at the injection site (15%), feeding problems (8%), headache (4%) and injection-site induration (4%). (1)

HEPATITIS B Epidemiology

Hepatitis B is endemic in many areas throughout the world such as Africa, Eastern Europe, the Middle East, Central Asia, China, Southeast Asia, the Pacific Islands and the Amazon basin of South America. It is estimated that 350 million people worldwide are chronically infected with Hepatitis B Virus (HBV), and over 2 billion have evidence of previous infection with HBV. In the U. S., there are 1.25 million hepatitis B chronic carriers (defined as persons positive for hepatitis B surface antigen (HBsAg) for more than six months.) Carriers have an increased risk of developing complications such as cirrhosis, decompensation and hepatocellular carcinoma (HCC). (7)

Hepatitis B Virus belongs to the family of hepadnaviruses. (7) From the time of exposure to the onset of symptoms, the incubation period varies between 6 weeks to 6 months. Infection with HBV can be self-limited or can cause chronic infection. Fifty percent of adults acutely infected are symptomatic, and 1% result in acute liver failure and death. The risk of developing chronic infection is inversely related to age. Ninety percent of infected neonates develop chronic infection; whereas, 60% of children under 5 years old and 2-6% of adults develop chronic infection. (7)

Diagnosis

The diagnosis of Hepatitis B cannot be based on clinical symptoms alone, but require serologic testing. (7) The symptoms include: jaundice, fatigue, abdominal pain, anorexia, nausea, vomiting and joint pain, but thirty percent of patients do not have any signs or symptoms. (7) The presence of the IgM antibody against hepatitis B core antigen (IgM anti-HBc) is diagnostic for acute HBV infection. Hepatitis B surface antigen (HBsAg) indicates either acute or chronic infection. Antibodies to HBsAg (anti-HBsAg) are produced after a resolved infection or following immunization. (7)

Table 3. Serologic Markers for Hepatitis B virus infection (7)

| Stages of HBV infection | HBsAg | Anti-HBs | Anti-HBc |
|-------------------------|-------|----------|----------|
| Acute | + | - | + |
| Chronic | + | - | + |
| Immunized | - | + | - |
| Resolved | - | + | + |

HBsAg – Hepatitis B surface antigen

Anti-HBs – Antibodies to hepatitis B surface antigen

Anti-HBc – Antibodies to hepatitis B core antigen

The carrier state is defined as the presence of HBsAg in the serum for at least 6 months. Some individuals may take a few more months to clear HBsAg, but HBsAg should be undetectable one year after the acute infection. In chronic HBV infection, serum HBV DNA levels are high and Hepatitis Be antigen (HBeAg) is present. Most patients will lose HBeAg and develop antibodies anti-HBe. In patients that undergo this seroconversion, HBV DNA levels will decrease, aminotransferases (ALT) will normalize, and inflammation in the liver decreases. Prognostic factors for the development of cirrhosis include HBeAg positivity, older age and elevated ALT levels. Clearance of HBeAg whether spontaneous or after antiviral therapy reduces the risk of hepatic decompensation and improves survival.(8)

Transmission

HBV transmission occurs from percutaneous or mucosal exposure to infected blood or bodily fluids by someone non-immune to hepatitis B. HBV is found in high concentrations in the blood and in lower concentrations in other body fluids such as semen, vaginal secretions and wound exudates. (7) Sources of exposure include: sexual contact, contaminated needles, contaminated blood or blood products and perinatal exposure. In up to one-third of cases, the source of exposure is unknown. Unlike HAV, HBV is not transmitted via the oral-fecal route. Adults aged 18 to 39 years old are at higher risk for infection due to the possibility of multiple sex partners, illicit injection drug use and other high-risk behaviors. (7,8)

Prevention

Strategies to prevent HBV infection include avoiding high-risk behavior, preventing exposure to blood or bodily fluids, screening of women in late pregnancy, actively immunizing populations at risk and passively immunizing with hepatitis B immune globulin before and after exposure. The most effective protection against HBV infection is achieved when the series of hepatitis B vaccine injections is completed before exposure occurs. There are several Hepatitis B vaccine formulations available in the U.S. They are produced with the use of yeast and recombinant techniques to generate the hepatitis B surface antigen (HBsAg) protein. From 1991 to 1999, the Advisory Committee on Immunization Practices (ACIP) developed comprehensive strategies to reduce the annual number of acute HBV infections, including universal vaccination of infants, and routine vaccination of adolescents. Due to the success of this program, the World Health Organization recommended that all countries provide universal HBV vaccination programs. (9)

The dosing and schedule of vaccines are provided in Table 4. Twinrix® contains both Hepatitis A and Hepatitis B vaccines. The vaccines should be stored between 2° and 8°C (36° and 46°F) and should not be frozen. The Hepatitis B vaccines should be administered in the deltoid muscles for children, adolescents, and adults and in the thigh for neonates and infants. (9)

Table 4. Hepatitis B vaccine (10,11,12)

| Product | Recipient's Age | Dose | Volume | Number of doses | Schedule (months) |
|------------------------------|------------------|------------------------------|--------|-----------------|-------------------|
| Recombivax® HB Adult | > 20 years | 10 mcg | 1 ml | 3 | 0,1,6 |
| Recombivax® Adult | 11-15 years | 10 mcg | 1 mL | 3 | 0,4-6 |
| Recombivax® dialysis | | 40 mcg | 1 mL | 3 | 0,1,6 |
| Recombivax® pediatric | 0-19 years | 5 mcg | 0.5 mL | 3 | 0,1,6 |
| Energix B® | >19 years | 20 mcg | 1.0 mL | 3 | 0,1,6 |
| Energix B® | Hemodialysis | 40 mcg | 2.0 mL | 4 | 0,1,2,6 |
| Energix B® | 11-19 years | 10 mcg | 0.5 mL | 3 | 0,1,6 |
| Energix B® pediatric | Birth – 10 years | 10 mcg | 0.5 mL | 4 | 0,1,2,12 |
| Energix B® pediatric | 5-10 years | 10 mcg | 0.5 mL | 3 | 0,12,24 |
| Twinrix® (Hepatitis A and B) | > 18 years | 720 ELISA units/20 mcg HBsAg | 1 mL | 3 | 0,1,6 |

Recombivax®, Merck & Co
 Energix B®, Glaxo Smith Kline
 Twinrix®, Glaxo Smith Kline

Approximately 50% of adults and adolescents (<40 years old) develop protective antibodies after the first dose, and subsequently 70% after the second dose, and >90% after the third dose. Due to the high rates of protection with the Hepatitis B vaccine, initiation should be considered, even if the completion of the series of vaccines is not ensured. No booster dose is recommended beyond the initial series of vaccines. (7)

The hepatitis B vaccine has been shown to be safe. Over 20 million adults and adolescents have been vaccinated. The most common side effects include pain at injection site or low grade fever. Anaphylaxis is estimated to occur in one of 600,000 doses given, but no deaths have been reported. Hepatitis B vaccine has not been associated with multiple sclerosis, diabetes, or other autoimmune or neurological diseases. (7)

Table 5. Recommended Immunization Schedule for Hepatitis B (3,8)

| |
|---|
| <ul style="list-style-type: none"> • All infants • All persons 18 years of age or younger • Hemodialysis patients or patients receiving clotting factor concentrates • Healthcare workers and public-safety workers • Persons in training for medicine, dentistry, nursing, laboratory technology, and other allied health professions • Injection drug users • Persons with more than one sex partner during the previous 6 months • Persons with recently acquired Sexual Transmitted Diseases • All clients at STD clinics • Men who have sex with men • Household contacts and sex partners of persons with chronic HBV • Clients and staff members working in institutions for the developmentally disabled • Inmates of correctional facilities • International travelers who will be in countries with high or intermediate prevalence of chronic HBV infection for more than six months |
|---|

To prevent transmission from mother to infant, women are routinely screened for HBsAg during initial prenatal visits. Women, who are pregnant, nonimmune, or uninfected with risk factors, may be given Hepatitis B vaccine because it is safe during any stage of pregnancy (NEJM). Infants born to women who are HBsAg positive should receive the vaccine along with Hepatitis B immune globulin (HBIG). Specific dosing and schedule can be found on the CDC website. (8)

Hepatitis B Immune Globulin (HBIG) can be used to prevent hepatitis B infection in nonimmune persons who have been exposed to the virus by cutaneous or mucosal contact with HBsAg blood or bodily fluids or by sexual contact. In addition, HBIG may be given to infants born to HBsAg positive women, and infants 12 months or younger whose primary caregiver is currently diagnosed with acute Hepatitis B infection. (NEJM) The recommended dose for children and adults is 0.06mL/kg and 0.5mL for infants. (7) HBIG should be given as soon as possible after exposure along with the first dose of the Hepatitis B vaccine series. It is reported to be 85-95% effective in prevention of newborn infections, and approximately 75% effective for the prevention of infection after needle-stick or sexual exposure.

Treatment

Persons infected with hepatitis B should be referred for medical follow-up. Contacts should be vaccinated and receive post-exposure prophylaxis. There is no specific therapy for acute infection, rather it is supportive treatment.(7) Antiviral agents (i.e. interferon-alpha or lamivudine) are available for those with chronic hepatitis B. Chronic hepatitis B is defined by the American Association for the Study of Liver Diseases (AASLD) as Hepatitis B surface Antigen (HBsAg) positive for greater than 6 months, serum HBV DNA > 10⁵ copies/mL, persistent or intermittent elevation in aminotransferase (ALT), and a liver biopsy showing chronic hepatitis. Chronic Hepatitis B can be subdivided into HBeAg positive and HBeAg negative. (8)

The goals for treatment of chronic hepatitis B are suppression of viral replication of HBV, and remission of liver disease. The clinical endpoints used to assess response include: normalization of serum ALT, undetect-

able HBV DNA, loss of HBeAg with or without detection of anti-HB, and improvement in liver histology. It is difficult to compare results of clinical trials due to lack of standardization of HBV DNA assays, inconsistencies in the definition of response, and heterogeneity of patient populations. Currently, there are three approved agents for the treatment of chronic hepatitis B: interferon-alpha, lamivudine, and adefovir. (8)

Interferon

Interferon-alpha (IFN) is indicated for chronic hepatitis B. Interferon alpha-2b has antiviral, antiproliferative and immunomodulatory effects. Interferon has been used against both types of chronic hepatitis B with success. It is administered subcutaneously. The recommended doses for adults are either 5 million units (MU) weekly or 10 MU three times weekly for 16 to 24 weeks for patients with positive HBeAg. The clearance of HBeAg occurred in 80-90% of patients after a follow-up of 4 to 8 years. Patients with negative HBeAg may need treatment for at least 12 months for a sustained response because there may be relapse. The adverse effects are numerous with IFN and must be considered when initiating therapy. Prior to treatment, it is advised for patients to be screened for any psychological illnesses, as treatment may exacerbate some underlying conditions. Adverse effects include: flu-like symptoms, fatigue, leucopenia, and depression. The flu-like symptoms may subside after the first week of therapy, but fatigue, anorexia, hair loss and mood swings may continue throughout the course of therapy. Liver chemistries and complete blood counts should be tested every 2 to 4 weeks. IFN costs significantly more than the other options. (8,13)

Lamivudine

Lamivudine is an analog for the nucleoside cytosine. The phosphorylated form incorporates into growing DNA chains resulting in premature chain termination, thereby inhibiting HBV DNA synthesis. Lamivudine has shown to be effective in reducing HBV DNA levels, normalizing serum transaminases and improving histological measures. It can be used in both HBeAg-positive and negative chronic hepatitis B disease. Seroconversion rates in HBeAg-positive patients can be up to 50% in those treated with lamivudine. Using lamivudine has been associated with rebound viremia related to the development of resistance. In general, lamivudine is well tolerated. The recommended dose for patients with normal renal function without HIV infection is 100mg daily. Dose adjustment is necessary for those patients with renal insufficiency. The duration of lamivudine therapy is generally 1 year with the clinical endpoint being seroconversion of HBeAg. Liver chemistries and HBV DNA levels should be monitored every three months while on therapy to monitor progress. The benefits of continuing lamivudine therapy if seroconversion is not achieved must be weighed against the possible development of resistant mutants. Thirty percent of breakthrough infections are a result of noncompliance, and simply resuming lamivudine therapy can result in viral suppression. For patients with confirmed resistance, lamivudine can be discontinued with close monitoring, or lamivudine treatment can be continued while maintaining clinical benefits, or switching or adding another antiviral agent. (8,13)

Adefovir

Adefovir is a nucleotide analog of adenosine monophosphate. It inhibits reverse transcriptase and DNA polymerase activity, by incorporating into HBV DNA causing chain termination. It has been shown to be effective against wild-type HBV and lamivudine resistant HBV mutants. Adefovir has been shown to be effective in both HBeAg-positive and HBeAg-negative patients. Treated patients had histologic response, HBeAg loss, normalization of ALT and reduction in HBV DNA. Adefovir may also be used in patients with lamivudine resistance. Clinical trials indicated that lamivudine resistant HBV would virologically respond with stabilization of ALT and Child-Pugh Scores. (14) Adefovir has not been studied in children. Nephrotoxicity has been reported in 2.5% of patients with compensated liver disease. Higher rates of nephrotoxicity were seen in patients with cirrhosis, and transplant recipients. The current dosing regimen is 10mg orally daily. Dosing adjustment is required for renal insufficiency. The optimal duration of adefovir therapy is unclear at this point. A major advantage to adefovir is the lack of resistance within the first year in comparison to lamivudine. (8,13)

Table 6. Hepatitis B treatment (8,13)

| Indications | Interferon alpha-2b | Lamivudine | Adefovir |
|----------------------------|--|---|---|
| HBeAg +, normal ALT | Not indicated | Not indicated | Not indicated |
| HBeAg +, chronic hepatitis | Indicated | Indicated | Indicated |
| HBeAg -, chronic hepatitis | Indicated | Indicated | Indicated |
| Dose – Adult | 5 MU QD or 10 MU TIW | 100mg daily, adjust for renal function | 10 mg daily, adjust for renal function |
| - Children | 6 MU/m ² TIW (max 10 MU) | 3 mg/kg/day (max of 100mg/day) | Not studied |
| Route | Subcutaneous | Oral | Oral |
| Side Effects | Many: flu-like, leucopenia, fatigue, depression | Negligible | Nephrotoxicity |
| Resistance | None | 20% in year 170% in year 5 | None, year 1 |
| Cost | \$\$\$\$ | \$ | \$\$\$ |

When evaluating treatment options, long-term efficacy, costs of medications, monitoring tests, clinic visits and patient preference should be considered.

HEPATITIS C

It is estimated that 2.7 million persons in the U.S. are chronically infected with Hepatitis C, making it the most common blood borne infection in this country. The majority of patients infected are less than 50 years of age. Acute illness is either asymptomatic or a mild clinical illness. From the time of exposure to seroconversion is approximately 8 to 9 weeks. Antibodies to HCV are detected in greater than 97% of persons exposed longer than 6 months prior. Chronic infection develops in 75-85% patients after acute infection, and 60-70% have evidence of active liver disease. (7)

HCV is a small RNA virus from the genus Hepacivirus, within the Flaviridae family. HCV is divided into six genotypes that do not correlate with outcome, but respond to therapy. (14)

Transmission

The most efficient method of transmission is by HCV-infected blood or blood products. In the U.S., injection drug use is the main mode of transmission and should be screened for HCV. Persons who received blood transfusions prior to 1992 should also be tested. Occupational, perinatal, and sexual exposures can result in transmission, but this is a less efficient route of transmission. Sexual partners of those with HCV should be counseled regarding notifying current partners even though the risk of sexual transmission is low. (7,14)

Diagnosis

Persons for whom HCV testing is recommended include: 1) Injection-drug users (past or present); 2) Persons with conditions associated with high prevalence of HCV (HIV patients, hemophiliacs, hemodialysis, abnormal ALT levels); 3) Recipients of transfusions or organ transplants prior to 1992; 4) Children born to HCV-infected mothers; 5) Health care workers after a needle stick injury; 6) Current sexual partners of HCV-infected persons. (14) The diagnosis of HCV infection can be made by detecting anti-HCV antibodies or HCV RNA. (7)

Prevention

Currently, there is no vaccine available for the prevention of HCV infection, nor is prophylaxis with immune globulin effective in preventing infection after exposure. (7)

Treatment

The approved treatments for chronic liver disease with HCV include interferon-alpha alone or in combination with oral ribavirin for 6-12 months. (14)

Fifteen to forty-five percent of persons with acute HCV clear the infection (i.e. HCV RNA is undetectable) and do not require treatment. When chronic infection persists, there is risk for the development of cirrhosis

and end-stage liver disease, as well as hepatocellular carcinoma (HCC.) (14)

The goals of treatment include: prevention of complications of HCV infection, and eradication of HCV. The currently available treatments are summarized in Table 7. The highest responses to treatment have been achieved with the combination of ribavirin and the subcutaneous injection of long-acting peginterferon-alpha. (14)

Ribavirin

Ribavirin is a synthetic nucleoside used in combination with interferon products against HCV. The exact mechanism has not been fully elucidated. The dose ranges between 800mg to 1200mg divided twice daily. Ribavirin should be taken with food approximately 12 hours apart. The higher doses may be required for those patients with genotype 1, whereas patients with genotype 2 or 3, 800mg daily is sufficient. It should not be combined with didanosine due to increased risk of toxicities (i.e. peripheral neuropathy, pancreatitis, etc). Ribavirin should not be combined with either zidovudine or stavudine due to potential antagonism of these antiretroviral medications.

Adverse effects associated with ribavirin are numerous, including hemolytic anemia, fatigue, itching, rash, sinusitis, birth defects and gout. The primary clinical toxicity of ribavirin is hemolytic anemia. In clinical trials, approximately 13% of treated patients had hemolytic anemia. The anemia occurs usually within the first 2 weeks of therapy; therefore, it is important to monitor hemoglobin prior to starting, and 2-4 weeks thereafter. Fatal and nonfatal cardiac events (i.e. myocardial infarctions) have occurred in patients treated with ribavirin.

Because of the risk of birth defects with ribavirin, it is imperative for patients (both male and female) to be using 2 methods of birth control. Male patients with female partners of childbearing potential must also use two methods of birth control. Ribavirin accumulates in many compartments. It is not known if it accumulates in sperm, but precaution must be taken to prevent possible teratogenicity of fertilization of an ovum. Due to the long half-life of ribavirin (approximately 12 days), effective contraception must be used six months after therapy is completed. (16)

Interferon

Peginterferons are interferons with a polyethylene glycol moiety attached which prolongs the half-life allowing for once weekly administration. There are two licensed products in the U.S. (See Table 7.) In clinical trials, the combination of peginterferon-alpha with oral ribavirin had superior virologic response to using peginterferon alone. The two interferon products (PegIntron® and Pegasys®) have not been studied head to head with similar ribavirin doses, so their relative efficacies cannot be compared. Responses to the combination of peginterferon and ribavirin are dependent on genotype and pretreatment HCV RNA levels. Higher response rates have been seen with patients with genotype 2 or 3, younger ages, lower body weights and the absence of fibrosis, and treated with peginterferon alpha-2b and ribavirin. Similar results were seen with peginterferon alpha-2a. The response rates are lower for African American patients with genotype 1 than for Caucasians. Duration of the therapy is also dependent on the genotype of the HCV. (14)

There are multiple adverse effects similar to those mentioned earlier in the hepatitis B section. Adverse effects related to interferon-alpha include: neutropenia, thrombocytopenia, depression, hypo- and hyperthyroidism, irritability, concentration and memory disturbances, visual disturbances, fatigue, muscle aches, headaches, nausea, vomiting, skin irritation, low-grade fever, weight loss, insomnia, hearing loss, tinnitus, interstitial fibrosis and hair thinning. Deaths related to the use of interferons due to suicide, myocardial infarctions, sepsis and stroke have occurred. Growth factors such as erythropoietin and granulocyte colony-stimulating factors (G-CSF) have been used to treat the hematological adverse effects of ribavirin and interferon. The adverse effects seem to be the worst in the beginning of treatment. Often the mild side effects of fever and flu-like symptoms can be treated with low-dose acetaminophen (<2.0 grams/day) or nonsteroidal anti-inflammatory drugs. (14)

The peginterferons are available in pre-filled syringes and powder for injection. Both should be refrigerated. They are administered subcutaneously in the upper arm, abdomen (avoiding the navel or waistline), or thigh area. The injection site should be rotated to avoid injection site reactions. Refer to specific package information regarding the preparation of the products.

Table 7. Treatment Options for Hepatitis C (14)

| Generic (Trade Names) | Adult Recommended Dose | Comments |
|---|--|--|
| Peginterferon alpha-2a (Pegasys®) | 180 mcg SC once weekly | Store in refrigerator |
| Peginterferon alpha-2b (Peg-Intron®) | 1.5 mcg/kg SC once weekly | Store in refrigerator |
| Ribavirin (Rebetol®, Copegus®, generic) | 800-1200mg po daily (given twice daily) | Dose depends on infection, genotype and patient weight |

Table 8. Populations that HCV therapy is Contraindicated (14)

| |
|---|
| <ul style="list-style-type: none"> • Major, uncontrolled depressive illness • Renal, heart, or lung transplant recipient • Autoimmune hepatitis • Untreated Hyperthyroidism • Pregnant or willing to use contraception • Poorly controlled diabetes, hypertension, coronary artery disease, obstructive pulmonary disease, or heart failure. • Younger than three years old • Known hypersensitivity to drugs used to treat HCV |
|---|

Reduction in the incidence of new HCV infections and improved management of current treatment strategies are critical to reduce the numbers of patients with cirrhosis and HCC.

CONCLUSION

Viral Hepatitis effects millions of people in the U.S. and worldwide. The morbidity and mortality can be high, and requires proper prevention and treatment strategies. Understanding these strategies is important for improved community health.

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LESSON EVALUATION

Please fill-out this section as a means of evaluating this lesson. The information will aid us in improving future efforts. Either circle the appropriate evaluation answer, or rate the item from 1 to 7 (1 is the lowest rating; 7 is the highest).

1. Does the program meet the learning objectives?

| | | |
|--|-----|----|
| Discuss hepatitis in terms of epidemiology, transmission, pathophysiology, & treatment options | Yes | No |
| Describe methods to prevent viral hepatitis | Yes | No |
| List options for treating hepatitis | Yes | No |
 2. Was the program independent & non-commercial?

| | | |
|--|-----|----|
| | Yes | No |
|--|-----|----|
-
- | | | | | | | | |
|--|------|--|--|---------|--|--|-----------|
| | Poor | | | Average | | | Excellent |
|--|------|--|--|---------|--|--|-----------|
4. Relevance of topic to your practice

| | | | | | | |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
 5. Author's ability to communicate

| | | | | | | |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
 6. What did you like most about this lesson? _____
 7. What did you like least about this lesson? _____
 8. How would you improve this lesson? _____
 9. Further comments or suggestions for future programs _____

Please Select the Most Correct Answer

- | | |
|---|--|
| <ol style="list-style-type: none"> 1. Hepatitis A treatment includes: <ol style="list-style-type: none"> A. Interferon-alpha B. Immunoglobulin C. Adefovir D. Lamivudine 2. Hepatitis A is most commonly transmitted via: <ol style="list-style-type: none"> A. Oral-fecal route B. Sexual contact C. Injection drug use D. None of these 3. Routine vaccination is required for all children in which of the following: <ol style="list-style-type: none"> A. Hepatitis A B. Hepatitis B C. Hepatitis C D. None of these 4. Hepatitis B chronic infection can be treated with: <ol style="list-style-type: none"> A. Ribavirin B. Lamivudine C. Interferon D. Both B & C 5. Ribavirin should not be used in which patients? <ol style="list-style-type: none"> A. Pregnant females B. Unstable coronary artery disease C. Advanced liver disease D. All of these | <ol style="list-style-type: none"> 6. Hepatitis C treatment includes: <ol style="list-style-type: none"> A. Ribavirin B. Peginterferon C. Both A & C D. None of these 7. Peginterferons should not be used in which of the following patients? <ol style="list-style-type: none"> A. Major depression B. Thyroid disease C. Organ transplant D. All of these 8. Long-term use of lamivudine in Hepatitis B treatment results in: <ol style="list-style-type: none"> A. Resistance B. Adverse effects C. Poor compliance D. None of these 9. Which blood test should be routinely drawn while on Hepatitis C treatment? <ol style="list-style-type: none"> A. Thyroid function test B. Complete blood count C. Liver enzymes D. Both B & C 10. All of these are true regarding adefovir, EXCEPT: <ol style="list-style-type: none"> A. Not studied in children B. Administered via IM route C. May cause nephrotoxicity D. No resistance for 1 year |
|---|--|

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