

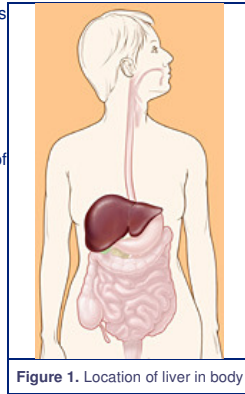
Viral Hepatitis C: Introduction

“Viral hepatitis,” refers to infections that affect the liver and are caused by viruses. It is a major public health issue in the United States and worldwide. Not only does viral hepatitis carry a high morbidity, but it also stresses medical resources and can have severe economic consequences. The majority of all viral hepatitis cases are preventable.

Viral hepatitis includes five distinct disease entities, which are caused by at least five different viruses. Hepatitis A and hepatitis B (infectious and serum hepatitis, respectively) are considered separate diseases and both can be diagnosed by a specific serological test. Hepatitis C and E comprise a third category, each a distinct type, with Hepatitis C parenterally transmitted, and hepatitis E enterically transmitted. Hepatitis D, or delta hepatitis, is another distinct virus that is dependent upon hepatitis B infection. This form of hepatitis may occur as a super-infection in a hepatitis B carrier or as a co-infection in an individual with acute hepatitis B. Hepatitis viruses most often found in the United States include A, B, C, and D.

Because fatality from hepatitis is relatively low, mortality figures are a poor indicator of the actual incidence of these diseases. The Centers for Disease Control and Prevention estimated that approximately 400,000–600,000 people were infected with viral hepatitis during the decade of the 1990s.

Hepatitis plagued mankind as early as the fifth century BC. It was referenced in early biblical literature and described as occurring in outbreaks, especially during times of war. Toward the end of the nineteenth century, hepatitis was thought to occur as a result of infection of the hepatic parenchyma. The infectious nature of hepatitis was established after World War II. In the mid-1960s, Blumberg and colleagues discovered the surface antigen and antibody of hepatitis B. This Nobel Prize-winning research opened the door to our appreciation of the morphological and immunochemical features of other forms of viral hepatitis.

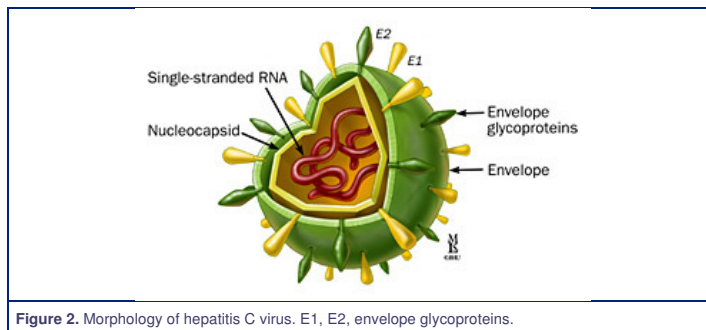


What is Hepatitis C?

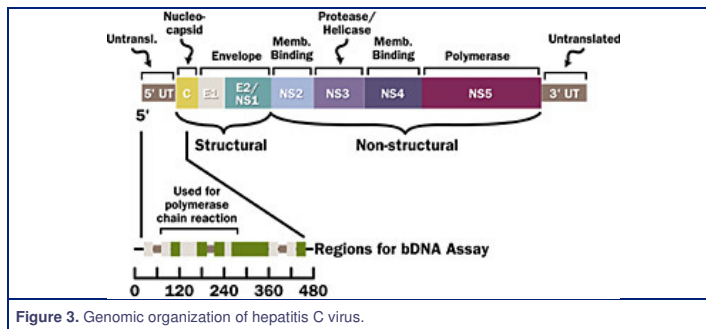
The hepatitis C virus (HCV) is a major cause of hepatitis (acute and chronic) and cirrhosis the world over. According to the Centers for Disease Control and Prevention, 21% of all acute viral hepatitis in the United States may be attributed to hepatitis C viral infection. Infection with hepatitis C almost always results in chronic infection. Sixty-seven percent of all cases develop chronic liver disease with accompanying elevation of liver enzymes. Hepatitis C viral infection is also thought to be a major contributing factor to hepatocellular carcinoma.

Discovered in 1990 as a causative agent for post-transfusion non-A, non-B hepatitis, ~3% of the U.S. population is now infected with hepatitis C (between 4–5 million seropositive individuals). There are approximately 30,000 new cases of acute hepatitis C diagnosed each year in the United States.

The hepatitis C virus (HCV) is a single-stranded RNA virus of the Hepacivirus genus in the Flaviviridae family (Figure 2).



The genomic organization of the hepatitis C virus shows highly conserved 5' and 3' nonstructural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) (Figure 3).



Hepatitis C virus protease, helicase, and polymerase activities are also encoded in this region and are currently the focus of intense research to develop specific hepatitis C viral inhibitors. The half-life of HCV RNA is approximately 2 ½ hours with 1012 virions produced per day.

The viral replication of hepatitis C is error prone, which enables the production of genotypes (60–70% homology), quasi species (97–98% homology), and individual clonotypes (Figure 5). The genetic diversity increases over time and may ultimately lead to the emergence of more virulent or treatment-resistant strains of the virus.

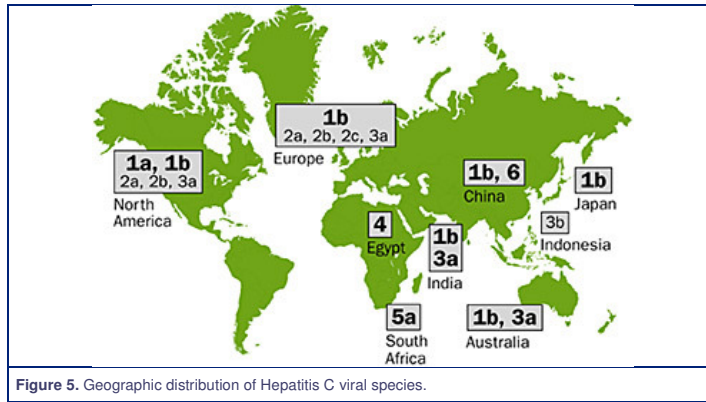


Figure 5. Geographic distribution of Hepatitis C viral species.

The predominant mode of transmission for hepatitis C has shifted from post-transfusion infection to injection drug use. Other modes of transmission include nosocomial (e.g., in hemodialysis units), intranasal cocaine use, tattoos, body piercing, sexual transmission, and perinatal exposure (Figure 6).

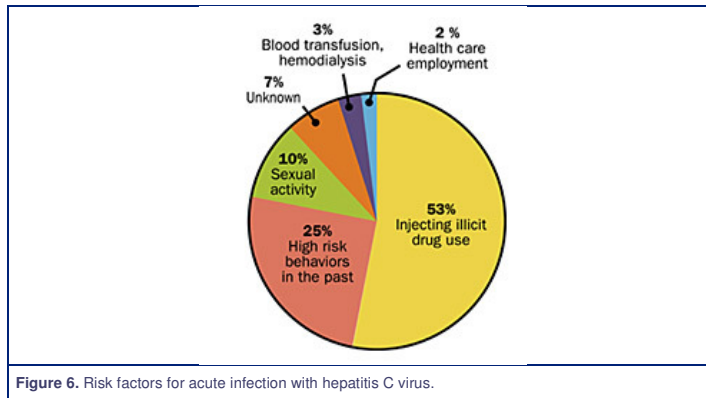


Figure 6. Risk factors for acute infection with hepatitis C virus.

Symptoms

Viral hepatitis may develop without clinical signs or symptoms, or nonspecific symptoms may appear for a short time with or without jaundice. These symptoms may vary from nonspecific flu-like symptoms to fatal liver failure. Diagnosis of viral hepatitis often depends on an accumulation of findings considered together.

Early in the disease process, generally called the prodromal phase, some patients experience a serum-type sickness that may include fever, arthralgia, arthritis, rash, and angioneurotic edema. These symptoms usually occur 2–3 weeks before jaundice and generally subside before jaundice develops, although in some cases they may be concomitant with its appearance.

In the pre-icteric phase of viral hepatitis, patients may experience respiratory and gastrointestinal tract symptoms, which may include malaise, fatigue, myalgia, anterior, nausea, and/or vomiting. They may also experience moderate weight loss, headache, coryza, fever, or pharyngitis and cough. Many patients complain of midepigastic pain, right upper quadrant discomfort, or diarrhea. Also characteristic of this phase is the development of dark urine and the lightening of stool color. The preicteric phase may range from 2–3 days to 2–3 weeks.

The icteric phase is signaled by the development of jaundice. General constitutional symptoms may subside, however, there may be worsening of anorexia, nausea, and vomiting, along with scratching and irritated skin lesions related to pruritis.

Pathogenesis

The natural history of hepatitis C remains incompletely defined. Approximately 85% of acute hepatitis C viral infections become persistent (Figure 7).

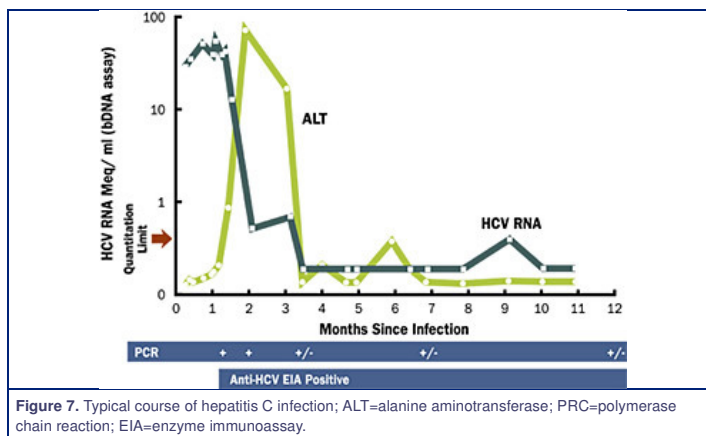


Figure 7. Typical course of hepatitis C infection; ALT=alanine aminotransferase; PRC=polymerase chain reaction; EIA=enzyme immunoassay.

In most of these individuals, there is biochemical and histological evidence of chronic hepatitis in addition to circulating HCV RNA. Fifteen percent of acutely infected patients who recover may retain the hepatitis C viral antibodies for several years, whereas others will have no serological markers of the infection on extended follow-up. In a smaller group (approximately 27%), viremia is persistent (or possibly intermittent), but serum alanine aminotransferase (ALT) levels are usually normal (Figure 8).

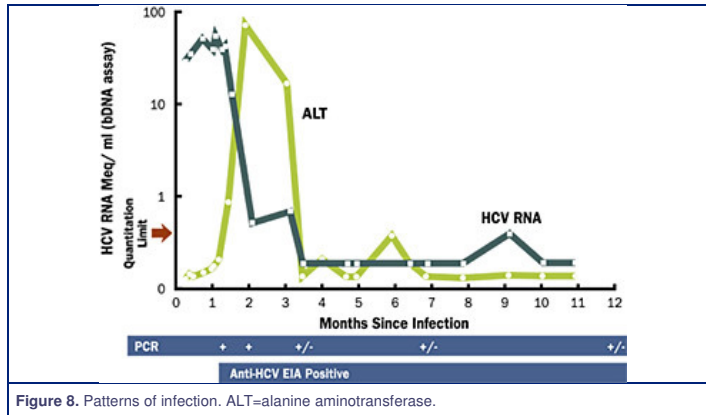


Figure 8. Patterns of infection. ALT=alanine aminotransferase.

In a recent study evaluating the fibrosis progression/year (= fibrosis stage/duration of infection), this group appeared to have a slower median rate of progression of fibrosis (0.05 vs. 0.13 units in patient with elevated ALT levels, $P < 0.001$). However, three patients with persistently normal ALT levels had cirrhosis (all heavy drinkers). In the group with persistently or intermittently elevated ALT, the median duration for disease progression was 13.7 10.9 years for chronic hepatitis, 20.6 10.9 years for cirrhosis, and 28.3 11.5 years for hepatocellular carcinoma. In a cross-sectional study of 2,235 patients in France, investigators found an increased rate of fibrosis progression with the following risk factors: age at infection > 40 years, daily alcohol use > 50 gm, and male gender. It was noted that the rate of fibrosis progression was not normally distributed, with 33% progressing to cirrhosis in less than 20 years, whereas 31% did not progress to cirrhosis for at least 50 years. No association was found between the progression of fibrosis and HCV genotype. Once patients develop cirrhosis, the rate of decompensation is 3.9% annually, the development of hepatocellular carcinoma occurs at an annual incidence of 1.4%, and mortality occurs at 1.9% per year (Figure 9).

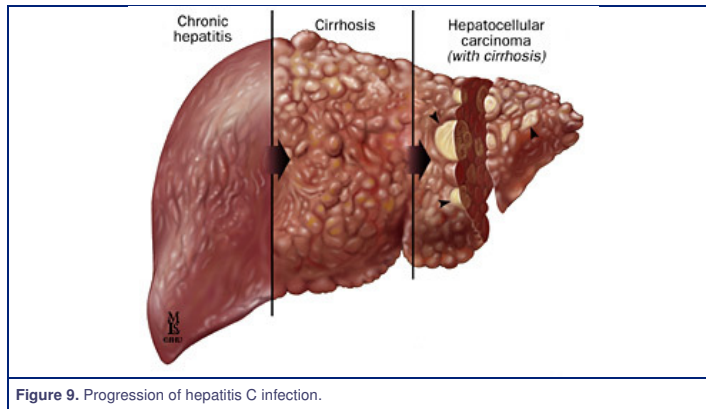


Figure 9. Progression of hepatitis C infection.

Viral Hepatitis C: Anatomy

The liver is located in the right upper quadrant, from the fifth intercostals space in the midclavicular line down to the right costal margin. The liver weighs approximately 1800 g in men and 1400 g in women. The surfaces of the superior, anterior, and right lateral regions of the liver are smooth and convex. Indentations from the colon, right kidney, duodenum, and stomach are apparent on the posterior surface.

The line between the vena cava and gallbladder divides the liver into right and left lobes. Each lobe has an independent vascular and duct supply. The liver is further divided into eight segments, each containing a pedicle of portal vessels, ducts, and hepatic veins (Figure 10).

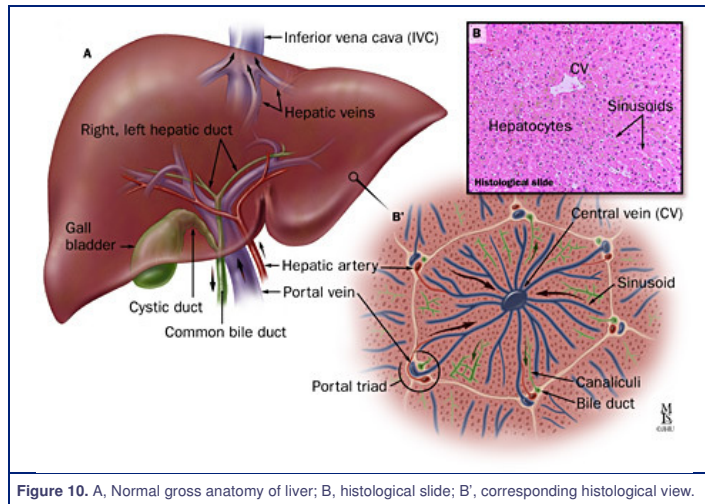


Figure 10. A, Normal gross anatomy of liver; B, histological slide; B', corresponding histological view.

Viral Hepatitis C: Causes

Overview

To date, most hepatitis C studies have focused on transfusion as the major source of viral transmission; however, most infections are acquired outside this setting. Studies conducted by the Centers for Disease Control and Prevention in 1992 revealed 4% of cases of acute hepatitis C were associated with blood transfusions; 29% of cases were associated with injection drug use; 2% with exposure to blood in the workplace; 12% with exposure to sexual contacts or household contacts who were infected; and 46% with low socioeconomic level or other high-risk characteristics. In many patients, no specific source is identified.

Viral Hepatitis C: Diagnosis

Overview

Since many patients do not have symptoms from hepatitis C, many are diagnosed only after they are found to have abnormal liver enzymes (e.g. ALT or AST). These liver enzymes are, at times, part of routine blood work, insurance physicals, pre-operative evaluations, etc. Patients may then be surprised by the diagnosis. Other patients may be tested because of specific risk factors, such as a remote history of blood transfusions or exposure to needles.

Hepatitis C antibody is detected in almost all persons with hepatitis C. Since, however, the antibody takes weeks to months to develop, it can be falsely negative, especially earlier after exposure. If the hepatitis C antibody is positive, the actual presence of virus should be confirmed with a PCR-based test. "Qualitative" PCR tests are super-sensitive, and detect minute amounts of hepatitis C within the blood. These tests are either positive or negative. "Quantitative" PCR tests are less sensitive, but offer precise viral count, also known as "viral load." Since some persons (perhaps 15%) clear hepatitis C without treatment, they may have a positive hepatitis C antibody but negative PCR tests. Such persons do not require treatment.

If a person is found to have a positive hepatitis C PCR test (also known as "active viremia"), a test for genotype is indicated. While there is no known correlation between either viral load or genotype and disease severity, these factors can impact treatment, and accordingly are indicated.

The role of liver biopsy in the diagnosis and management of hepatitis C is somewhat controversial. Biopsy is an outpatient procedure where a needle is used to obtain a small amount of liver tissue for examination by a pathologist under a microscope. Serious risks of a liver biopsy include bleeding, infection, perforation of a visceral organ (e.g. bowel), puncture of the lung, and others. These occur rarely, perhaps 1/1,000 biopsies or less. Liver biopsy remains the "gold standard" test in liver medicine; it allows a clinician and pathology to "grade" and "stage" liver disease (i.e. determine the amount of on-going disease activity and resultant fibrosis, respectively). It also allows the clinician and pathologist the opportunity to evaluate for other causes of liver disease that may be unsuspected by blood work. Unfortunately, despite intensive research and experience, no amount or combination of blood work or radiology tests can completely replace the information available from liver biopsy.

Some clinicians recommend liver biopsy routinely to all patients with hepatitis C while others do so only selectively. At times, a patient may find biopsy helpful in deciding about whether to pursue treatment. For example, some patients may choose to defer treatment if their biopsy is near normal, but pursue treatment if their biopsy shows extensive disease.

Many clinicians also screen for other causes of liver diseases, e.g. hepatitis B, autoimmune hepatitis, etc, during the initial evaluation, since a person can have more than one liver disease process. The finding of hepatitis C should not preclude a thoughtful evaluation for other causes of abnormal liver enzymes.

Viral Hepatitis C: Therapy

Overview

General recommendations for persons with hepatitis C include:

- Discontinue alcohol use. The combination of alcohol with hepatitis C seems particularly dangerous for many persons
- Maintain a healthy weight. Patients who are close to their ideal weight may have greater success with treatment and a more benign disease course than patients who are obese
- Consider vaccination against hepatitis A and B if not already immune. Antibody tests can determine if these vaccines are indicated.

Presently, the cornerstone of therapy involves a combination of pegylated interferon and ribavirin. The former is generally given subcutaneously once a week, while the latter is given orally on a daily basis. Both medicines should be taken together for duration of therapy to achieve optimal results. Patients with "genotype 1" (the most common genotype in America) can expect a sustained virologic response rate (SVR) of around 40-50%, depending on various patient factors. An "SVR" means that the virus is no longer detectable, even using super-sensitive assays, for an extended period of time after treatment is concluded. An SVR may be similar to a "cure", but since it is hard, if not impossible, to establish the absolute absence of the virus, many physicians are uncomfortable using the term "cure." A portion of patients will initially achieve undetectable viral levels, but "relapse" shortly after therapy is stopped. Persons with "genotypes 2 or 3" enjoy a much higher likelihood of achieving an SVR, presently around 80-90%. Additionally, patients with genotypes 2 or 3 are generally treated for a shorter period of time (generally 3-6 months vs 12 months for genotype 1).

Physicians have learned to gauge a person's likelihood of achieving an SVR by checking a patient's viral load relatively early in the treatment course. This "early virologic response" (or EVR) can be very helpful. Conventionally, for an EVR estimation, a viral load is checked after 12 weeks of therapy and compared with the pre-treatment level. A significant (e.g. two log or 100-fold) drop in viral load can indicate a high likelihood for SVR at the end of treatment. On the other hand, failure to achieve a significant drop indicates that a patient will not likely achieve SVR, and therefore may consider discontinuation of therapy. More recently, some physicians have been using an even earlier viral load check (e.g. at 4 weeks) in order to identify a subset of patients who are "super responders." Such patients may be candidates for shorter duration of therapy (e.g. 6 months for genotype 1) without compromising the likelihood of achieving an SVR. Because knowledge in these areas is rapidly evolving according to new research, patients should discuss the latest data with their physicians at the time of treatment.

Interferon and ribavirin cause numerous adverse effects. The impact of these adverse effects on a given individual can be unpredictable. However, there are certain medical conditions which generally preclude treatment with interferon and ribavirin. These include, but are not limited to, severe heart disease, kidney disease, poorly controlled psychiatric disease, ongoing infection, autoimmune disease, pregnancy or planned pregnancy, blood disorders including low hematocrit (red blood cells), neutrophils (a kind white blood cell), or platelets. Treatment, even in otherwise very healthy patients, requires close monitoring to ensure safety. This includes frequent blood work and office visits.

In general, the management of adverse effects has improved greatly over the last 10 years, due largely through the experience of trial and error. Well developed algorithms now exist to support patients on therapy. However, since each individual's experience is different, open and frequent discussion is encouraged between the patient and the patient's care providers.

Factors associated with higher likelihood of SVR include non-1 genotype, low baseline viral load, baseline weight < 75 kg (165 pounds), non-African American race, minimal fibrosis on biopsy, and ability to tolerate full-dose medicine for the length of treatment. SVR is synonymous with treatment success, and means that no virus is detectable in the blood 24 weeks after the end of treatment. SVR may be the same as a "cure;" however, a small number of patients may experience recurrent viremia months to years after achieving SVR. It is uncertain if this represents re-infection or re-activation of disease.

The decision to initiate treatment should only occur after a thorough medical evaluation and extensive discussion between the clinician and patient to review risks and benefits.

Controversies with Present Treatment Options

There are a variety of controversies in the treatment of hepatitis C. Clinicians, even those who are expert in liver disease and hepatitis C, may disagree. Thus, clinicians must decide with their patients on a case-by-case basis what options are best.

"Relative" contraindications

As noted above, interferon and ribavirin cause numerous adverse effects, and many persons have medical conditions which cause added risk. Some patients may have medical conditions which are considered "absolute" contraindications to treatment; that is, present treatment options are too risky regardless of the situation. However, other patients may have medical conditions which increase the risk of treatment somewhat, but do not entirely eliminate the possibility of treatment. These "relative" contraindications may change over time as new research becomes available and clinicians gain even more experience with interferon and ribavirin. Cirrhosis is an example. Until recently, clinicians avoided treating patients with cirrhosis due to concern that the side effects would be intolerable and that the liver disease would worsen. Now, however, many clinicians believe that patients with early cirrhosis can tolerate treatment.

Re-treatment

Some patients previously treated with interferon based therapy may be considered for re-treatment, especially if their first treatment course was inadequate in some fashion (e.g. use of older, three-times weekly preparations, etc). Also, at times clinicians and patients may want to try a different pegylated interferon product. However, there is no general agreement as to whether and how-often re-treatment is effective or cost-effective.

Treatment of patients with persistently normal liver enzymes

Some believe that patients with persistently normal liver enzymes carry have a relatively benign prognosis for their hepatitis C, and accordingly may not need treatment. Others, however, note that patients can develop scarring and even cirrhosis in the presence of normal liver enzymes, and believe that everyone should be treated.

"Maintenance" interferon for relapsers to therapy

Some rationale exists for the extended use of therapy, often at reduced doses, in patients whose viral counts "relapse" or rebound when therapy is discontinued altogether. Interferon itself may have some anti-fibrotic (or anti-scarring) properties which may be beneficial even if an SVR is not achieved. Several studies are ongoing to evaluate the risks and benefits, if any, of such a treatment strategy. However, by their very nature, these are long-term studies, and the results are pending.

Future Directions

There is an ongoing global effort to find treatments which are more effective, safer, better tolerated, and less expensive than present options. This effort includes many universities, government agencies, and pharmaceutical companies. The "pipeline" of putative new therapies is deep, and includes multiple candidate drugs in various classes, including novel interferons, ribavirin alternatives, specific alternatives of viral enzymes, immune modulatory drugs, and anti-fibrotic agents. The process from drug discovery to final drug approval can take years. Patients interested in clinical trials for hepatitis C (or any other condition) are encouraged to visit

Prevention

Routine screening of blood donors has significantly reduced the incidence of post-transfusion hepatitis C. Anti-HCV screening is recommended for donors of organs, tissues, and semen. Modification of high-risk behavior in injection drug users, such as safer needle practices, has also reduced disease incidence. No vaccine is currently available for hepatitis C. Ultimately, control of hepatitis C, as well as other viral hepatitis infections, can only be achieved with a vaccine that provides long-term immunity. Additionally, universal vaccination of infants and adolescents at high risk may be a means of controlling disease transmission.

Hepatocellular Carcinoma

