UP DATE ON

HEPATITIS

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Dr. Ghulam Ali M.D.
Dr. Aftab Turabi M. Phil.
Prof. Dr. Mansoor Ahmed Ph.D.

Glossary

Liver One of the most important organs in the body, the liver is specially designed to perform many essential functions. However, its distinctive characteristics and activities render it susceptible to damage from a variety of sources, and such damage can have enormous impact on a person's health. Careful assessment of the nature and extent of liver disease is a necessary prerequisite to determine the most appropriate and effective treatment.

Glossary

Albumin a protein in the serum

Alkaline phosphatase protein found in bile duct cell membranes; blood levels may be increased in any liver disease, but more markedly with cholestasis.

Alhph 1 - antitrypsin: plasma protein produced by the liver that inhibits the activity of trypsin and other proteolytic enzymes

Aminotransferase: hepatocyte enzyme that modifies proteins; blood levels increase in the setting of hepatocellular necrosis (hepatocyte death).

Antibodies: proteins produced in response to a specific antigen, which can then combine with that antigen and neutralize it.

Antigens: a molecule with a specific configuration that is recognized by the immune system; usually part of a protein or sugar. It stimulates the formation of a specific antibody and can elicit an allergic reaction, or otherwise trigger an immune response.

Ascites: accumulation of fluid in the abdominal cavity

Autoimmunity: a state or disease in which the body's immune system attacks the bodies own tissues.

Bile: greenish fluid formed by the liver and emptied into the small intestine via the bile ducts; contains bilirubin, bile salts, phospholipids, and cholesterol.

Bilirubin a bile pigment cleared from the bolld by the liver; formed as a breakdown product of old red blood cells; marked increase in blood levels can lead to jaundice from deposition of bilirubin in skin, mucous membranes, and whites of the eyes.

Caput medusa; literally "Medusa's head"; dilated, varicose veins around the umbilicus, which may be seen in patients with cirrhosis of the liver.

Ceruloplasmin: copper transporter protein; blood levels are usually decreased in Wilson's disease.

Cholestasis: blockage or suppression of bile flow, from either intrahepatic or extrahepatic causes.

Cirrhosis: pathologically-defined disease characterized by diffuse, irreversible fibrosis of the liver surrounding regenerative nodules.

Coagulopathy: increased bleeding tendency due to decreased hepatic synthesis of clotting factors.

Decompensation: failure of the liver to compensate for damage or injury, resulting in a decrease in liver functions.

Dysplasia: alteration in size, shape, and organization of cells; may be precursor of cancer.

Encephalopathy: alteration in sleep patterns and mental status, ranging from forgetfulness and mild confusion to coma; may be caused by circulating gut-derived brain-toxic proteins not cleared by a dysfunctional liver.

Fibrosis: the formation of fibrous tissue, or scarring.

Fulminant: running a speedy course, with rapid worsening.

Hemochromatosis: toxic accumulation of iron in organs leading to dysfunction, including cirrhosis; may be genetic (inherited increase in gut iron absorption) or a result of massive blood transfusions.
Hepatitis: inflammation and damage to the liver; generally considered acute if duration is less than 6 months, chronic if greater than 6 months.
Hepatocellular necrosis: localized tissue death of hepatic cells.
Hepatocellular carcinoma (HCC): a primary liver tumor more common in patients with cirrhosis.
Hepatocytes: liver cells.
Hepatorenal syndrome: poorly understood terminal kidney failure in the setting of hepatic disease.(hepato renal shut down)
Homeostasis: tendency of the body to maintain a stable internal environment, using a variety of counterbalancing control systems.
Hyperbilirubinemia: abnormally high levels of bilirubin in the blood.
Icterus: see Jaundice.
Idiopathic: autoimmune chronic active hepatitis (IACAH): chronic hepatitis of unknown origin; associated with a variety of anti-self antibodies; progresses to cirrhosis and decompensation unless treated with corticosteroids.
Jaundice: hyperbilirubinemia, with deposition of bile pigment in the skin, mucous membranes, and sclera (whites of eyes), resulting in a yellow appearance of the patient; also called citrus.
Kayser-Fleischer rings: golden-brown rings in the corneas due to copper deposition in Wilson's disease.
Kupffer cells: "scavenger" cells that remove foreign matter, worn-out blood cells, and bacteria from the liver.
Limiting plate: layer of hepatocytes surrounding each portal triad and separating it from the surrounding sheets of hepatocytes.
Lobule: "structural" unit of the liver; shaped like a hexagon on cross section, with six portal triads at the periphery and a central vein.
Portal hypertension ;abnormal increase in portal blood pressure, usually due to obstruction of, or increased resistance to, portal blood flow.
Portal system: includes all the veins that drain the small and large intestines, stomach, and spleen and that converge into the portal vein to drain into the liver.
Portal triad (or tract): consists of three components: branch of the hepatic artery, branch of the portal vein, and a biliary duct, all held tightly together by a limiting plate of hepatocytes at the periphery of the lobule.
Porto systemic shunting: development of blood vessels that connect the portal and systemic circulation while bypassing the liver.
Prognosis: prediction as to the probable outcome of a disease.
Prothrombin time (PT): laboratory test that measures the clotting of blood in seconds; abnormally increased PT signifies bleeding risk due to deficient synthesis of clotting proteins.
Pruritus: itching.
Seroconversion: appearance of specific antibodies in the blood, indicating recovery from infection or successful vaccination.
Sinusoids: tunnels through hepatic tissue allowing exchange of nutrients and other substances between blood and hepatocytes.
Spider angiomas: red capillary tufts in the skin that blanches on pressure; often found in patients with cirrhosis.

Spontaneous bacterial peritonitis (SBP): bacterial infection of ascetic fluid.
Steatorrhea: decreased absorption of dietary fats, resulting in their passage to the distal bowel which causes foul-smelling diarrhea; can be caused by deficiency of bile salts.
Transaminase: see Aminotransferase.
Varices: dilated veins; lower esophageal varices form as collaterals from portal hypertension and can rupture, leading to massive bleeding.
Wilson's disease: inherited metabolic disorder in which copper accumulates in the liver and in the central nervous system, causing hepatitis, cirrhosis, and neuropsychiatry symptoms.

Inflammatory Disorders (Hepatitis). Hepatitis involves inflammation and damage to the hepatocytes. This type of insult may result from infectious agents, toxins, or immunologic In addition, other disorders such as Wilson's disease can cause hepatitis, and some diseases such as alpha 1 -antitrypsin deficiency can imitate hepatitis. However, the most common cause of hepatitis is viral infection.
a. Infection. Infection is a very important cause of hepatitis, since primary viral infection of the liver is common and viruses cause the majority of liver infections. Three major viruses cause hepatitis in the United States: hepatitis viruses A, B, and C. Together, they infect nearly 500,000 people in the United States every year.
In addition, bacteria, fungi, and protozoa can infect the liver, and the liver is almost inevitably involved to some extent in all blood-borne infections.
b. Toxins. Toxins such as alcohol, drugs, or poisons can cause hepatitis directly (by damaging liver tissue) or indirectly (by reducing defenses or stimulating an autoimmune response), but the exact mechanism is not always clear.
Alcohol. Alcohol is primarily metabolized by the liver, and these metabolites can cause liver damage. The risk of hepatic toxicity increases if more than 40 grams, or about four drinks, are consumed per day.
Drugs. Numerous medications can damage the liver, ranging from mild, asymptomatic alteration in liver chemistries to hepatic failure and death. Liver toxicity may or may not be dose-related. Dilating (an anti-convulsing) and ionized (an anti-tuberculosis agent) are examples of drugs that can cause "viral-like" hepatitis.
Chemicals/Poisons. Both environmental and industrial toxins can cause a wide variety of changes in the liver. Hepatic damage is not necessarily dose-dependent and can range from mild, asymptomatic inflammation to Fulminant failure or progressive fibrosis and cirrhosis.
c. Immunologic mechanisms. The immune system functions primarily to recognize "foreign" or 'non-self" antigens, for example, invading viruses, bacteria, and their proteins. These antigens may be recognized by antibodies, proteins that can specifically bind to them and help remove them from the body. Occasionally, autoimmunity develops, whereby the immune system incorrectly reacts against "self" antigens, (one's own cells). This occurs in autoimmune hepatitis and primary biliary cirrhosis, two diseases in which the immune system attacks and destroys portions of the liver. If unchecked, persistent inflammation can eventually lead to cirrhosis.

Hepatitis B: The Complexities

Hepatitis B: A Brief History:

Dr Blumberg was awarded noble prize to discovered Australian antigen, later the antigen was found in hepatitis patients. Three particles were present in hepatitis B infection Further research identified them as viron and surface protein.

Hepatitis B Virus: A Complex Structure

The hepatitis B viron consists core and surface. The DNA polymerase present in core part and the e antigen. The DNA is double staranded. There are four polypeptide called as S (surface) the C (core) the P (polymerase) and the X (transcriptional). There are three regionbs for the S gene called as pere S1-2 and encodes the surface proteins (HbsAg). Very rarely a mutation may occur in the S gene and may abort the HBsAg with the result that a person may be HBsAg negative but still have virus present as determined by HBV DNA. The C gene is divided into two regions, the pre-core and the core, and codes for two different proteins, the Core antigen (HBcAg) and the e antigen (HBeAg). A not uncommon mutant is the pre-core mutant, who may stop production of HBeAg, and these persons will be HBsAg positive, HBV DNA positive, but HBeAg negative. A third mutant which appears to have a mutant in the core has been described and is referred to as HBV2. These patients are HBsAg positive, but lack HBeAg and HBV DNA, thus also anti-HBc.

Multiple Tests are Available

Because of the complexity and the antigenic differences of the virus, there are a number of tests available for hepatitis B:

Antigens

HBsAg = presence of the virus

HBcAg = not detected in blood

HBeAg = correlates with the viral replication and infectivity

Antibodies

anti-HBs = antibodies to the surface

anti-HBc = antibodies to the core can be either IgM (acute) or IgG (chronic)

anti-HBe = antibodies to e and indicates low infectivity and probable recovery

Other Markers

HBV DNA = indicates virus presence and activity

DNA polymerase = determines the presence of HBV DNA

HBsAg in liver cells (Orcein stain = Shakata cells) = HBsAg inside hepatocytes

Hep B:The Complexities

Carrier Rates Vary Greatly

Carrier rates for hepatitis B vary enormously:

Country and Carrier rate%:

Scandinavia 0.1 USA/Canada 0.1 Spain 2.0 Southern Italy 3.0

Greece 5.0 Hong Kong 15.0 Taiwan 15.0 Alaskan Eskimos 45.0

High Infectivity

Hepatitis B DNA is found in many body fluids including saliva, urine, semen and menstrual blood. It has also been shown that the virus can be transmitted by ingesting contaminated blood. Hence, hepatitis B may be transmitted by:

» mother to infant at the time of birth

» sexually

» horizontally through shared utensils such as razors, toothbrushes, etc.

» through unitarily instruments such as tattoo needles, dental equipment, etc.

» parenteral drug use through shared needles, syringes, etc.
» hospital staff through needle prick
» blood sucking arthropods (usually in the tropics)
Extra-Hepatic Associations
A number of conditions associated with hepatitis B antigen/antibody complexes have been recognized although uncommon,.
These include:
Polyarteritis - usually involves medium and small arteries, appears early
Glomerulonephritis - largely in children, liver disease is usually mild
Polymyalgia rheumatica - usually in older persons
Essential mixed cryoglobulinemia - sometimes only a test tube finding
Guillain-Barre syndrome
Myocarditis

Chronic Viral Hepatitis in the United States

Key Concepts:
- Chronic liver disease, including cirrhosis, represents the 10th most common cause of death in the U.S. Viral hepatitis is the commonest cause of chronic liver disease with an estimated 1.25 million, 2.7 million and 70,000 individuals with chronic hepatitis B virus (HBV), hepatitis C virus (HCV) and hepatitis D virus (HDV) infection,respectively.

- In the U.S., the prevalence of markers of past or chronic HBV infection is low until age 12, increasing thereafter, and is similar among males and females. The factors associated with chronic HBV infection are ethnicity (highest in non-Hispanic blacks), number of sexual partners, marital status, foreign birth, level of education, and illicit druguse.

- In the U.S., chronic HCV infection is more common in males than females and the peak prevalence is in those aged 30-39 years. HCV alone or in combination with alcohol accounts for about (60% of newly diagnosed cases of chronic liver disease.

- The prevalence of HDV in the U.S. is low. The groups with the highest prevalence of infection are injection drug users and multiply-transfused individuals (e.g. hemophiliacs).

- The risk factors for acquisition of HBV, HCV and HDV are well-established. Understanding the modes of transmission is critical in designing prevention strategies to reduce the burden of chronic liver disease.

- The geographical distribution of viral genotypes of HBV, HCV and HDV are known. Correlations between specific viral genotypes and clinical outcomes, such as disease severity and response to anti-viral treatments, are under study.

Epidemiological studies conducted over the past several decades have provided estimates of disease burden due to hepatitis C virus (HCV), hepatitis B virus (HBV), and hepatitis D virus (HDV), not only in the U.S., but in order areas of the world. Studies have detailed the changing incidence and prevalence of chronic viral hepatitis and the shifting importance of specific risk factors for viral acquisition. Such studies are necessary for ongoing preventive strategies. Molecular methodologies have come to play an important role in studying chronic viral disease. Genotype and quasispecies analyses have proven to be invaluable in understanding the evolution of each virus over time within the population, investigating viral transmission events between persons, and understanding the role of viral heterogeneity in disease expression and clinical outcomes.

Contribution of Chronic Viral Hepatitis to the Burden of Disease in the U.S.

The burden of chronic liver disease in the U.S. is unknown, although estimates of prevalence and incidence indicate the chronic viral hepatitis is the commonest cause of chronic liver disease. The asymptomatic nature of chronic liver disease means that many persons affected with disease are unrecognized. Three different sources of information are available to estimate the relative contribution of HCV, HBV, and HDV to the total burden of chronic liver disease in the U.S. These include: (i) death registries; ii) population-based prevalence and incidence studies; and (iii) convenience samples or referred patients. Population-based studies provide the most accurate estimates of disease prevalence and incidence, whereas death registries and convenience samples generally provide information on the symptomatic subset of persons with chronic liver disease.

In 1997, chronic liver disease including cirrhosis ranked as the 10th most frequent cause of death (Table 1). Mortality varied by age with a rate of 16.7 per 100,000 among those 45-54 years, 24.1 per 100,000 among those 55-64 years, and 31.4 per 100,000 among those 65-74 years. Death rates among men were twice as high as women and rates among blacks and Hispanics were higher than whites. For example, the death rate per 100,000 among persons aged 45-64 years was 19.0 for whites, 27.5 for blacks, and 32.6 for Hispanics. Mortality from cirrhosis and chronic liver disease over the past four decades has changed. Death rates increased steadily in the 1950s and 1960s, peaked in the mid-1970s, and declined thereafter. In 1997, the age-adjusted death rate from chronic liver disease and cirrhosis was 7.4 per 100,000 populations, a decline of 38.3% since 1979.

The underlying etiology of liver disease among those dying of liver disease also has changed over time. Among the listed causes of death due to chronic liver disease in 1989, alcohol was the most common, present in 46.1%. However, nearly half of the liver-related deaths were of unspecified cause and HCV-associated liver disease was underrepresented because testing for HCV was not available at the time. A revised estimate of the causes of death due to chronic liver disease in the United States between 1970-1988, based upon prevalence data from other sources, showed that alcohol alone accounted for only 24% of deaths and viral hepatitis accounted for 54% (Figure1).

While useful in documenting changes in mortality due to chronic liver disease over time, death registries capture only the most severe end of the disease spectrum and interpretation of changes in death rate can be difficult in the absence of additional information. For example, a decline in death rate may be the result of a change in the rate of detection, a true reduction in incidence, or improved survival among prevalent cases.

Prevalence of Viral Hepatitis in the U.S.

This article is based on population studies esteems chronic HBVdiseases in the US.
Main part is derived from NHANES surveys in the US (Table 2) between 1976 and 1980 and 1988 and 1994.(Author)
Prevalence of Chronic Hepatitis B
In the NHANES III survey, serum samples from participants were tested for anti-HBc first, and if positive, HBsAg and anti-HBs were obtained. Chronic HBV infection was defined by the presence of HBsAg and anti-HBc. The age-adjusted seroprevalence of HBV infection was 4.9 with 0.5% of patients having anti-HBc as their only marker of past HBV infection. The prevalence was similar in males and females . The prevalence of past and chronic HBV infection was low until the age of 12 years thereafter increasing in all racial groups. The highest prevalence was in non-Hispanic blacks Independent predictors of chronic HBV infection after adjustment for age were non-Hispanic black ethnicity, high number of sexual partners, cocaine use, divorced or separated marital status, foreign birth, and having less than a high school education. However, there were interactions between race, sociodemographic variables and behavioral risk factors. The increased prevalence of HBV infection after age 12 (puberty) and the association of HBV infection with number of sexual partners and early age of first intercourse, are consistent with sexual contact being the primary mode of HBV transmission. The relative contribution of injection drug use to the burden of HBV disease cannot be discerned from the NHANES data since information on this risk behavior was not collected. Additionally, NHANES sampled only civilian, no institutionalized persons living in households, which may underestimate the seroprevalence of HBV by omitting persons (homeless and incarcerated) who would be predicted to be at higher risk of infection.

The seroprevalence of HBV in the U.S. is low compared to other areas of the world.

However, surveys among specific ethnic subgroups within the U.S. highlight focal areas of high prevalence. The prevalence of HBsAg-positivity among Alaskan natives was 6.4%, on average, with prevalence rates varying from 0-20% in different villages. In first-generation Asian-Americans from Taiwan, mainland China, the Philippines, Vietnam, Korea and Japan, HBsAg positivity ranged from 5% to 15%; other serological markers of HBV infection ranged from 43% to 65%. These high prevalence groups are often the target of specific intervention programs.
The age-adjusted seroprevalence of HBV infection was 5.5% survey and 4.9% in a difference that was not statistically different. These data suggest the prevalence of HBV did not change significantly between the years 1976 and 1994. Since routine immunization of infants only began in 1992 and adolescents in 1995, the study time period may be too short to detect the benefits of HBV vaccination on disease prevalence. Other studies in populations with higher endemic rates of HBV infection have demonstrated the positive impact of a comprehensive program of infant and childhood vaccination. In Taiwan, the prevalence of HBV infection (HBsAg-positivity) in children less than 9 years of age declined from 10% in 1984, prior to the vaccination program, to

<1% in 1994, 10 years after the implementation of the program. More importantly, the annual incidence of hepatocellular carcinoma in children decreased from 0.52 per 100,000 in 1974-1984 to 0.13 per 100,000 in 1984-1986. Thus, vaccination programs are changing the seroprevalence of HBV in the world. Prior to 1980, most countries in Southeast Asia were areas of high HBV endemicity with seroprevalence rates as high as 15-20%. Now, China is the only country in Asia considered to be hyper endemic for HBV infection. Korea, the Philippines, Taiwan and Thailand have intermediate endemicity (prevalence rates 2-7%), and Japan, Singapore, Sri Lanka and Malaysia have low endemicity (prevalence rates <2%).

Prevalence of Hepatitis C Virus

In the NHANES III survey, the prevalence of anti-HCV was 1.8% corresponding to an estimated 3.9 million persons who have been infected with HCV. Again, since this study excluded incarcerated and homeless individuals, the true seroprevalence may be slightly higher. The prevalence of HCV RNA detection among anti-HCV positive persons was 73.9% which corresponds to an estimated 2.7 million individuals with chronic HCV infection. HCV was more prevalent among males (2.5%) than females (1.2%) and more prevalent among non-Hispanic blacks (3. (1.5%). Those aged 2%) than non-Hispanic whites 30-39 years had the highest prevalence and accounted for 65% of all persons with detectable anti-HCV. The lowest rates of anti-HCV detection were among persons aged = 19 or (70 years.

Using NHANES III seroprevalence data and age-specific incidence rates from the CDC sentinel surveillance study, the annual incidence of acute HCV infection in the U.S. over the past 30-40 years has been estimated by modeling. This model predicts a low incidence period prior to 1965 (0-45 new infections per 100,000 persons), a transition period in the 1970s, and a high incidence period in the late 1980s with 100-200 new HCV infections per 100,000 persons per year. The model predicts that persons born between 1940-1965 would be at greatest lifetime risk of acquiring HCV infection. The model also was used to predict changes in prevalence over time. The number of persons with infection of (20 years' duration, who will be potentially at risk for cirrhosis and other complications, was estimated to increase substantially before peaking in 2015 (assuming no change in the incidence of HCV infection and ignoring the potential benefits of anti-viral therapy).

The prevalence of HCV in the U.S. varies with the population studied. For example, in blood donors, the seroprevalence of anti-HCV is only 0.3%, a lower prevalence than in the general population because blood donors are a highly select group of individuals that have been screened for risk factors and serologic markers of other infectious agents. Among referred or hospitalized patients with chronic liver disease, HCV infection is common and likely represents the "tip of iceberg" in terms of the total population of HCV-infected individuals. A referred or hospitalized population represents the subgroup of HCV-infected persons with more serious complications of disease and the demographics of hospitalized patients differs from that of HCV-infected persons in the general population. For example, in the Central Harlem study, the chronic liver disease cases were 65% male and 75% African-American and the case-fatality rate was 14%. The presumed etiology of chronic liver disease was HCV in 12%, alcohol 29%, and HCV plus alcohol in 46%; the remainder were of other etiologies.

A brief comparison of the results of NHANES with population-based surveys from other countries services to highlight geographical similarities and differences in HCV prevalence In a study of 6283 volunteers from 4 of 22 geographical regions in France, aged 20 to 59 years, the

age- and gender-adjusted anti-HCV positive rate was 1.15% (95% CI: 0.8%, 1.3%) and prevalence was inversely related to semiprofessional status. In the Dionysus study in Northern Italy, the prevalence of anti-HCV was 2.6%; prevalence increased with age and, in contrast to the U.S., was more common in women than men (ratio of men to women = 0.7)

Prevalence of Chronic Hepatitis D Virus

Since Hepatitis D is not a reportable disease and not included in the International Classification of Diseases, population-based data on the seroprevalence of chronic HDV are not available. An estimated 70,000 persons have chronic HDV infection in the U.S. Seroprevalence rates in the U.S. vary dramatically depending upon the subgroup evaluated but the pattern, in general, is typical of an area of low endemicity. Seroprevalence is low in blood donors (1.4% to 8%), intermediate in residents of mental institutions and other settings of less intense percutaneous or mucosal exposure, and highest in those with repeated percutaneous exposures such as injection drug users (20-53%) and hemophiliacs (48-80%). Among patients with chronic HBV infection referred to gastroenterologists, the HDV seroprevalence rates vary from 13% to 41%, average 27%.
Highly endemic areas are surprisingly disparate geographically and include the Amazon basin, parts of northern South America, parts of Africa, and Romania. In these areas, the HDV seroprevalence is 20% in HBsAg-positive persons and up to 90% in persons with HBV-associated chronic liver disease. Intermediate areas of HDV seroprevalence include southern Italy, parts of Eastern Europe, the Middle East, Africa and some Pacific Island groups. These areas have prevalence rates up to 15% among HBsAg-positive individuals and 30-50% in persons with HBV-associated liver disease. As the seroprevalence of HBV infection declines in response to vaccination programs, the prevalence of HDV infection can be expected to fall as well. A study from Italy found the prevalence of HDV infection decreased from 23.4% in 1987 to 14.4% in 1992 among the HBV patients referred to liver clinics. While ascertainment bias or changes in referral practices may explain the change in anti-HDV prevalence between 1987-1992, a lower prevalence of HDV infection in the 0-29 year's age group but not in the older subjects suggested there was a true decline in prevalence. In addition to a decreased pool of chronic HBsAg carriers, reductions in family size, improved socioeconomic conditions, and changes in intravenous drug use behaviors may be additional factors that contributed to the decline in prevalence.

Incidence of Chronic Viral Hepatitis

Sentinel surveillance for chronic liver disease is a relatively new undertaking of the CDC and provides an additional measure of the disease burden associated with chronic viral hepatitis. Beginning in 1998, the CDC began surveillance for newly diagnosed cases of chronic liver disease among adults in three geographically district areas of the U.S. (Connecticut, California and Oregon). The goals of surveillance were to provide annual estimates of the number of patients with newly diagnosed chronic liver disease within the general population, determine the proportion of chronic liver disease cases due to viral hepatitis, and to examine risk factors and co morbid conditions that influenced disease expression. Data from the first 21 months of surveillance in New Haven County, Connecticut showed an "incidence" of chronic liver disease of 31/100,000 persons. Hepatitis C virus infection alone or in combination with alcohol was the

commonest cause of chronic liver disease, accounting for 58% of cases. Chronic HBV infection alone or in combination with HCV accounted for only 4% of cases. In 14% of cases insufficient information was available to make a diagnosis. A comparison of this incidence rate to that of Jefferson County, Alabama in 1989 shows a substantial increase in the incidence of chronic liver disease in the past decade and a greater proportion of chronic liver disease attributable to HCV infection.

Risk Factors for Chronic Viral Hepatitis

Risk Factors for Hepatitis B Virus

Hepatitis B virus is a parent rally transmitted virus which is acquired from exposure to infected blood or body secretions. Adolescents and adults account for the majority of reported cases of hepatitis B in the U.S. and sexual contact is the most common route of transmission. Perinatal and early childhood infections are much less frequent.

Perinatal Infection

The CDC estimates that at least 20,000 infants are at risk annually for HBV infection through perinatal sources. Rates of HBsAg-positivity in mothers vary among ethnic groups with higher rates among Asians (foreign-born), Hispanics and Blacks. The risk of transmission is higher in HBeAg-positive mothers. Rates of HBeAg-positivity average 30% among women of Asian descent and 20% among all other racial groups. Identification of HBsAg-positive mothers is critical for the prevention of HBV transmission from mother to infant. Currently, the CDC estimates that at least 90% of women are being screened for HBsAg prior to or at the time or delivery. However, the women who are not being screened are at greater risk of being HBsAg-positive.

Early Childhood Infection

Specific ethnic groups residing in the U.S., including Alaskan Eskimos, Pacific Islanders, and infants of first-generation immigrant mothers from countries of moderate to high HBV endemicity, are at risk of early childhood infection. The estimated risk of HBV acquisition within the first 5 years of life ranges from 5% to 40% for these children, with the highest risk for infants of HBsAg-positive mothers who are not infected at birth. Immunization of infants as part of the childhood immunization schedule and catch-up vaccination of susceptible children is the primary method of preventing infection. Focused vaccination programs, which started in the late 1980s, have successfully reduced the prevalence of HBV infection in children.

Infection Among Adults

Sexual activity is the most common mode of HBV transmission in North America and other countries where the prevalence of HBV infection is low. There was an initial decline in the incidence of HBV infection among men having sex with men in the 1980s, followed a subsequent decline among heterosexual men and women, and injection drug users in the 1990s. That being said, injection drug use and sexual activities remain the most frequently identified risk factors among adults with HBV infection. As with perinatal transmission, sexual transmission is facilitated by active viral replication in the infected individual. Factors positively correlated with HBV infection in adults are number of sexual partners, number of years of sexual activity, and a history of sexually transmitted diseases (STDs). In general, vaccination coverage of adults in high-risk groups, such as men who have sex with men and patients with STDs, has been low

In the U.S. and Western Europe, injection drug use remains an important mode of HBV transmission. Risk of infection increases with duration of drug use, so that serological markers of ongoing or prior HBV infection are almost universal after five years of use. Other recognized modes of HBV transmission include working in a health-care setting ((3% of cases in the U.S,); and transfusions, dialysis and other overt blood contacts (1% total). Nosocomial spread of HBV infection in hospitals, particularly in dialysis units, has been well described. HBV infection has been linked to multiple-use heparin vials and exposure to contaminated dental instruments and finger-stick devices. Transmission from health care worker to patient, while rare, has been reported. Acupuncture has been associated with outbreaks of HBV infection.

In about one-third of persons with HBV infection, no risk factor can be identified. These persons tend to be of lower socioeconomic level and belong to minority populations. Undisclosed sexual risks or illicit drug use may account for a proportion of these unknown cases.

Risk Factors for Hepatitis C Virus

Transfusion of infected blood or blood

Products, use of contaminated dialysis equipment, transplantation of infected organs, and sharing of contaminated needles among injection drug users are well-recognized modes of HCV transmission. Sexual contact and perinatal exposure are associated with HCV infection but HCV transmission by these routes is relatively inefficient.

The prevalence of specific risk factors in persons with HCV infection has changed over the past 10 years. Although transfusion of HCV-infected blood or blood products was a common mode of HCV transmission in the past, this currently represents a rare mode of transmission. Following the introduction of blood donor screening and surrogate hepatitis tests, the proportion of patients with acute community-acquired hepatitis who reported a history of blood transfusion declined from an average of 17% in 1982 - 85, to 6% in 1986-88, to 4% in 1990-93. As transfusion-related cases of HCV declined, the proportion attributed to non-transfusion-related causes increased. Therefore, in cross-sectional studies of risk factors among persons with HCV infection, blood transfusion and injection drug use account for an approximately equal proportion of cases (about 30% each) in those whose exposure occurred more than 10 years ago. In persons whose exposure occurred within the last 10 years, injection drug use is the most common mode of acquisition, accounting for 60% of cases. The prevalence of other risk factors (e.g. occupational) has remained relatively constant over time.

In addition to the changing prevalence of risk factors over time, the proportion of persons without identifiable risk factors, so called "sporadic" HCV infection, has decreased. Among acutely infected persons identified by the CDC Sentinel Surveillance study between 1989-1994, 33% had no identifiable risk factor. More recently, that proportion has dropped to 10%. Individuals with "sporadic" infection are characterized by lower socioeconomic status (in one third), reports of high-risk behavior such as imprisonment, a history of one or more STDs, and use of non-injection illicit drugs suggesting that some of the "Sporadic" cases may be secondary to occult percutaneous exposures . Underreporting of past high risk behaviors such as injection drug use, overlooked transfusions received in infancy, and unrecognized percutaneous exposure within the community may explain a proportion of the sporadic cases of HCV infection. The prevalence of HCV infection is different "risk" groups is summarized in Table 4.

Table 4. Estimated prevalence of hepatitis C in different "at risk" groups

Risk Factor	Prevalence of HCV
Persons with hemophilia treated before 1987	74 - 90%
Injection drug users	72 - 89%
Chronic hemodialysis	0 - 64% (average 10%)
Persons reporting history of STD	1 - 10% (average 6%)
Persons receiving blood transfusion prior to 1990	5 - 9%
Infants born to HCV RNA positive mothers	5% (average)
Men who have sex with men	4% (average)
Long-term sexual partners of HCV-infected persons in monogamous relationship	0.5 - 3%
General population	1.8%
Volunteer blood donors	0.16%

Adapted from MMWR: Recommendations for prevention and control of hepatitis C Virus (HCV) infection and HCV-related chronic disease. Centers for Disease Control and Prevention, 1998; 47-5.

Blood Transfusion

Prior to 1985, the incidence of transfusion-associated hepatitis (TAH) was 8-10 per 100 persons transfused. Transfusion practices changed in the mid-1980's in response to concerns regarding HIV, with a subsequent fall in the rate of TAH by about 50%. With the introduction of first generation anti-HCV tests in the early 1990's, the rate of HCV acquisition via blood products declined by a further 80%and current estimates of the incidence of TAH are <1%. Donation of blood by seronegative donors during the infectious window period prior to seroconversion, accounts for the vast majority of the current residual risk of TAH (-80%). Nucleic acid testing for HCV RNA can reduce the infectious window from 70 days (average) to 10-29 days. Thus, the use of nucleic acid testing to screen blood products is expected to reduce the risk of HCV from 1:100,000 (current risk per unit transfused) to 1:500,000 - 1:1,000,000.
Patients requiring blood products (clotting factors, immune globulin) from pooled donors have a high rate of HCV-positivity. The prevalence of anti-HCV in patients with hematological disorders who were transfused with clotting factors prior to the institution of viral inactivation and removal measures, is nearly 100%. Changes in product manufacturing as well as the use of screening assays have significantly reduced the incidence of HCV transmission in this population.

Injecting drug user

The prevalence of HCV infection among drug users in the U.S. varies from 72% to 89%. The factor most consistently associated with anti-HCV positivity is duration of drug use. In the largest study of injection drug users, HIV co infection, Black race, drug use within the preceding 6-month period, and use of injection cocaine were also found to be independently associated with HCV infection. Acquisition of HCV infection is rapid among drug users with anti-HCV seroprevalence rates of 54%, 78%, 83%, and 94%, among users of less than a year, 1 year, 5 years, and more than 10 years, respectively. Among newly diagnosed cases of chronic liver disease secondary to HCV in 1998, -60% reports an antecedent history of intravenous drug use (CDC, Chronic Liver Disease Surveillance, unpublished data).

Dialysis and Other Nosocomial Sources

Dialysis units are the commonest setting for nosocomial transmission of HCV. A 1995 national surveillance study of 2647 dialysis centers found an anti-HCV prevalence of 10.4% in patients and 2.0% in staff. However only 39% and 16% of dialysis units performed routine testing of patients and staff, respectively. Additionally, serological assays may underestimate the prevalence of HCV infection in dialysis patients, since they are relatively immunocompromised. Virological assays identify a greater proportion of infected individuals. The annual incidence of HCV infection in one study was 3% and none of the patients who seroconverted had received a transfusion or used injection drugs. Dialysis-specific risk factors associated with anti-HCV positivity include a history of prior blood transfusion volume of blood transfused, and duration of hemodialysis. Failure to ascertain community exposures to HCV, such as injection drug use, may lead to an overestimation of the contribution of dialysis to risk of HCV acquisition. The mechanism of HCV transmission in dialysis units is believed to be breaches in routine dialysis

unit procedures and precautions. Person-to-person transmission of HCV among patients not sharing dialysis equipment but treated in the same room has been documented. Although hemodialysis patients constitute a risk group for HCV acquisition, they account for only 1% of persons with chronic infection. Other than dialysis, nosocomial transmission of HCV is rare in the U.S.

The seroprevalence of anti-HCV among healthcare workers in the U.S. ranges from 0.7 to 2.0%. The variability in seroprevalence reflects the different exposures associated with specific healthcare jobs, the prevalence of HCV in the patient population served by the healthcare worker, and the frequency of other risk factors for HCV in the healthcare worker. The incidence of HCV seroconversion following needle stick injury or accidental cuts with sharp instruments is 1.8% on average (varies from 0% to 7%). The presence of viremia in the source is associated with a higher rate of seroconversion than if the source is anti-HCV positive alone. Other factors which may influence the risk of HCV seroconversion include whether the needle was hollow-bore, the size of the inoculums, and host susceptibility. Transmission from physician to patient has been documented with in the context of an invasive surgical procedure but such reports are extremely rare.

Perinatal Exposure

While passively acquired anti-HCV is frequent in newborns of HCV-infected mothers, transmission of infection only occurs in 5% (average). Factors that have been associated with the risk of transmission are presence of HCV viremia, maternal HIV status, and viral titer at the time of delivery. Breastfeeding does not appear to increase the risk of HCV transmission.

Sexual Contact

The available data suggests that HCV can be sexually transmitted but the efficiency of transmission is low. In long-term studies of heterosexual couples in relationships of 15-20 years duration, the rate of HCV-positivity among the sexual partners of HCV-infected persons was 0.5 to 3% and the vast majority of couples in these studies did not use condoms. One study suggested that transmission from an infected male to an uninfected female partner might be more efficient than from an infected female to an uninfected male partner. In contrast to the low frequency of anti-HCV positivity in couples in long-term relationships, 20% of persons with newly-identified HCV infection report sexual contact with a HCV-positive person or more than 2 sexual partners, in the preceding 6 month period, as their only risk factor for HCV acquisition. However, acquisition from an unacknowledged percutaneous exposure cannot be completely ruled out in these cases. Cross-sectional and case control studies have shown that persons with a high number of sexual partners, non-use of condoms, history of other STDs, and sex with trauma are more frequently HCV-positive than persons who do not report these high-risk sexual behaviors. Thus, recommendations regarding the prevention of HCV transmission differ for persons in long-term steady relationships and those with multiple partners.

Risk Factors for Hepatitis D Infection

Injection drug use is the commonest mode of HDV transmission in the U.S. . Sexual transmission of HDV is less efficient than transmission of HBV, but is a well-recognized risk factor. In men having sex with men who deny a history of injection drug use, the risk of HDV infection increases with the number of sexual partners and frequency of rectal intercourse . Among prostitutes, prevalence rates of HDV range from 6% to 21% with the highest rates among prostitutes who also use injection drugs.

Molecular Epidemiology of Viral Hepatitis in the U.S.

Chronic Hepatitis B Virus

Four subtypes of HBsAg named adw, ayw, adr and ayr were identified in the 1970's. An additional nine different subtypes were later identified, designated ayw 1-4, adw 1-4, and adrq +/ adrq-. Sequencing of viral genomes and comparison of complete genomes in the 1980's led to a reclassification of HBV heterogeneity into genotypes (Table 5). At the level of the S-gene, a difference of (4% nucleotides defines different HBV genotypes.

Table 6. Distribution of HCV genotypes in the U.S.

Author, Year	N	Population	Genotypes (%)	1a		1b		2a	
Alter, 2000	250	Randomly selected civilians from 89 locations (NHANES III)	57	17	3.5	11	7.4	0.9	3.2
Zein, 1996	179	Consecutive patients from 4 tertiary referral centers	58	21	2.0	13	5	1	--
Mahaney, 1994	98	Referred for treatment trials	36	38	6.1	9.2	6.1	1.0	--
Reddy, 1996	414	Participants in treatment trial	32	26	5	10	13	--	9
McHutchison,1998	456	Participants in treatment trial	72	18	9	--	--		
Davis, 1998	354	Participants in treatment trial	56	17	25	--	--		

While associations between HBV genotypes and specific clinical outcomes require further study, an interesting relationship between HBV genotype and the G-to-A mutation at nucleotide 1896 in the precore region has been elucidated. The precore mutation has been found to be most frequently associated with genotype D and rarely associated with genotype A. Mutations in the core region in genotype D HBV are predicted to increase the stability of the stem-loop structure, which is critical for the viral pregenomic encapsulation signal, whereas these same mutations in HBV genotype A have a destabilizing effect on the stem region. Additional studies have

suggested HBV genotypes may be important determinants of disease severity. Preliminary data have linked HBV genotype with responsiveness to interferon among HBeAg-negative patients and risk of HCC. Genotype D and total number of accumulated mutations throughout the HBV precore/core gene have been associated with more severe recurrent disease following liver transplantation.

Chronic Hepatitis C Virus

At least six different genotypes and more than 90 subtypes of HCV have been identified. HCV genotype 1 predominates in the U.S., accounting for approximately 65-75% of infections (Table 6). The genotype distribution among HCV RNA positive persons in NHANES III was 56.7% type 1a, 17.0% type 1b, 3.5% type 2a, 11.4% type 2b, 7.4% type 3a, 0.9% type 4 and 3.2% type 6. There was a lower prevalence of type 1b and higher prevalence of type 1a in the NHANES III study (population-based) compared to referred or treated patient populations (Table 6). In other parts of the world, genotypes 1b (Europe, East Asia), 2a (Southeast Asia), 3a (India), 4 (Egypt and the Middle East), and 5A (South Africa) predominate (Figure 4). The time of divergence of the HCV genotypes isolated from different geographical regions has been estimated to be more than 500-2000 years for viral types and more than 300 years for viral subtypes.

Whether specific HCV genotypes are associated with more severe histological disease or greater risk of cirrhosis or hepatocellular carcinoma is controversial. For example, several studies, predominantly from Europe and Southeast Asia, have found HCV type 1b to be more prevalent in patients with cirrhosis and hepatocellular carcinoma than in patients with chronic hepatitis or asymptomatic blood donors. This finding is compatible with HCV type 1b being more pathogenic, but additional studies have shown that the association is likely due to a cohort effect, i.e. there is an overrepresentation of HCV type 1b among older patients who had a longer duration of disease.

The relationship between HCV genotype and response to interferon and nterferon/ribavirin therapy is well established. Sustained response rates are significantly lower in patients with genotype 1 compared to genotypes 2 or 3.

Chronic Hepatitis D Virus

Genetic analyses of HDV isolates from different geographical areas indicate there are at least three genotypes. Genotype 1 is the most common and geographically diverse with distribution in Western Europe, North Africa, the Middle East, Turkey, Japan, Taiwan, and the U.S. Genotypes II and III have a much more restricted distribution. Type II has been isolated from patients in Japan and Taiwan, where it coexists with genotype I. Genotype III has been found in patients from Peru and Columbia. These different distribution patterns likely reflect interactions between the HDV genotypes and dominant HBV genotypes in specific geographical areas, such as has been described for HDV genotype III and HBV genotype F in northern South America. The genotype distribution also reflects the migration of populations over time, and geographical clustering of cases indicate that HDV was introduced relatively recently into the U.S. compared

to Southern Europe and Northern Africa. Studies on the relationship between HDV genotype and severity of disease are limited. Preliminary studies have linked genotype II with milder disease and genotype III with severe disease. Disease severity in patients with genotype I appear to vary from mild to severe.

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UPDATE ON VIRAL HEPATITIS

One additional dose of vaccination of hepatitis B gives an additional benefit to responder about 40 – 50 % benefit.

There was no added benefit in additional vaccination. In immunocompetent patients, immunity lasted 10-15 years even though anti-HBs was lost in 10-50% of patients, there was no disease noted. In immunocompromised patients, it is unclear how long immunity lasts and there is some discussion of whether a booster should be given when anti-HBs falls below 10 I.U. per ml. Pre-S vaccinations that include larger surface proteins have been shown to have a higher response: 60% response in those who have previously not responded to recombinant vaccinations.

Excellent data were presented on the natural history of Hepatitis C. This is a new and emerging area showing that Hepatitis C disease may be much less severe than previously thought. These are data from Ireland. Dr Kenny Walsh reported pregnant women who had received Rhogam for treatment of Rh-incompatibility. Subjects were studied 17 years after infection with genotype 1 and only 2% of patients had cirrhosis. Vogt studied 458 German children (New England journal) 20 years after infection. They found that 45% of them had recovered and lost RNA and only 0.3% had cirrhosis. Leonard Seeff studied patients 23 years after acquisition of hepatitis C. There was no difference in all cause mortality between the 500 patients who have had hepatitis and

1000 case controls. However, liver related deaths were higher in the hepatitis C group at 3.1% compared to 1.3% in case controls. However, 56% of individuals died (2% of liver disease). Patients died of causes related for their need for transfusion. This brings up the question: "Is the natural history of hepatitis C after transfusion with a large amount of virus worse than that after acquisition through other parenteral routes?"

Seeff and Alter discussed an algorithm that after acute infection at least 20% of individuals recovered. 80% developed persistent infection of whom 1/3 have stable chronic hepatitis, 1/3 have severe progression, and 1/3 have variable progression. This lead to a favorable outcome overall in 2/3 of patients and 1/3 of patients having on-going progressive disease. In prospective studies, after 10-20 years of exposure, the incidence of cirrhosis was 7-15%. In cohort studies, 17-45 years from exposure, the incidence of cirrhosis was 0.3-21%. This is much lower than previously thought.

David Thomas in JAMA this year studied 1667 patients who were HCV antibody positive and followed them for 8 years. 2.4% had end-stage liver disease. 374 people died of non liver related problems, and 22.4% had damage related to alcohol. He biopsied 210 patients, two of whom who had cirrhosis. Rogers who described 95 patients from Australia in Hepatology (2000). 95 patients acquired hepatitis C between 1971 and 1975. Twenty years later, 6% were PCR negative, only 51% were PCR positive and four of those 51% had cirrhosis. No individuals had hepatocellular carcinoma.

The rates of spontaneous recovery varied. In transfusion related HCV adults studied by Seeff the spontaneous recovery rate was 24%; in the NHANES 3 Study by Alter 26%; IN leukemic children BY Losasciulli, 29%; in the Irish Rhogam Study 45% and the transfusion related HCV study in children in Germany, the rate was 45%. Lessons from these studies are that 1) there is a higher spontaneous recovery than previously thought. 2) There is a favorable outcome in 64% of patients who develop hepatitis C with either recovery or stable benign disease. 3) There is a severe outcome in less than 1/3 of patients who develop progressive disease of whom somewhere between 7-15% develops cirrhosis.

Norah Terrault presented chronic liver disease and viral hepatitis in the US. Chronic liver disease is the 10th most common cause of death in the USA. In patients with chronic hepatitis C infection, 65% occurs in ages 30-39 years. Victor Navarro looked at a GI community practice in the northeast and found that 52% of patients with chronic liver disease had hepatitis C with or without alcohol . Looking in a large managed care group in California, abnormal LFTs for longer than 6 months was the definition of chronic liver disease and it occurred in 72 patients per 100,000 case subjects. 47 of these 72 were seen by gastroenterologists, but the rest were not referred. It was unclear whether they did not have liver disease or were not deemed suitable patients for therapy.

John McHutchison presented data on interferon and ribavirin therapy. His group evaluated whether the dose of ribavirin necessary to aid in the interferon's anti-viral effect. He showed data from Schering that Ribavirin at 400 mg dose led to a 1.6 log decrease in serum HCVRNA. A Ribavirin dose of 600mg led to 1.7 log decreases in HCV RNA and ribavirin at 800mg/ day led to 2.09 decreases in HCV RNA with 1000mg Ribavirin to 2.22 log decreases in HCV RNA. Thus, at Ribavirin doses less than 800mg there is fewer anemias but also the dose is less effective.

Dr J. Heathcote reviewed re-treatment of non-responders. She found that retreatment of those who had initially responded to therapy and then relapsed resulted in a 10-70% response to 6 or 12 months of interferon. However this was not seen in on responders to IFN. Regardless of the

dose, the length of interferon retreatment of non-responders up to 12 months lead to less than 10% sustained virologic response in the majority of patients. Genotype 2 or 3 patients had a 22% response in data reported by Dr. Solko Schalm.

Michael Manns presented the sustained virologic response of 1530 patients treated with 12 kd pegylated interferon and ribavirin. 65% of the patients were male, 68% had genotype 1, 69% had HCV RNA >2,000,000 copies per ml and 10% of the patients were cirrhotic. The overall response to 48 weeks of interferon was evaluated for standard therapy with interferon alpha-2B plus ribavirin or pegylated IFN low dose (that is, 0.5 µg/kg) or high dose (1.5µg/kg of pegylated interferon) plus ribavirin. In all patients, the results were around 50% for all groups: genotype-1 patients had a 33% response to standard ribavirin and a 42% response to high dose pegylated IFN. In genotype 2/3 80% of patients responded. He then showed data comparing ribavirin dose and interferon dose per body weight. They found that those weighing less than 65kg had a 57% response with a fixed dose of interferon, 47% with a fixed dose of ribavirin and a 62% response when both interferon and ribavirin were adjusted to body weight. Those weighing 65-85 kg showed 48% response to fixed interferon, 49% response to fixed ribavirin, a 55% response when both interferon and ribavirin were adjusted to body weight. In patients weighing greater than 65kg, the responses were overall lower with a 41% response to fixed interferon, 46% response to fixed ribavirin and a 49% response when both ribavirin and interferon were adjusted for body weight. The incidence of side effects were slightly higher in the high dose pegylated interferon with Neutrogena double that of standard interferon.

The effect of response to therapy and normal ALT were studied by Estaban in Abstract 205. 249 patients were followed for over 8 years and had two liver biopsies 4 years apart. He compared those with normal ALT and those with abnormal ALT and found a higher percentage of females in the normal ALT (71%) compared to abnormal ALT (47%). Any alcohol intake was noted in 21% of those with normal ALT and 40% of those with abnormal ALT. Heavy alcohol use greater than 50g/day occurred in 6% of those with normal ALT and 17% of those with abnormal ALT. Liver biopsies differed between those with normal and abnormal ALT. In those with normal ALT, 64% were mild, 34% were moderate and 2% severe. In those with abnormal ALT, 34% had mild biopsies, 64% moderate and 20% severe. Four years later, a repeat biopsy in normal ALT patients showed no cirrhosis, decomposition, hepatocellular carcinoma or death. In 114 patients with abnormal ALT, 8% had progressed to cirrhosis, 2% decompensate, 2% had hepatocellular carcinoma and 2% had died.

De Martino from France in Abstract 203 studied 299 patients of whom 50 were co infected with HIV and HCV. Patients were followed over 28 months. The three year survival was 47% in HIV positive HCV patients and 72% in HIV negative HCV patients. 56% of HIV and HCV positive patients decompensate compared to 19% of HIV negative HCV patients. 29% of HIV positive patients had ascites whereas 10% of HIV negative did. Variceal bleeds and portal systemic encephalopathy occurred in 20% and 9% of HIV positive compared to 4% of HIV negative HCV positive patients. Analysis revealed that HIV positive and HCV positive patients were younger at the time of diagnosis. There were more males, more history of IV drug abuse, a higher alcohol intake, and prothrombin time. One-third of the patients had CD4 counts less than 200. There was no difference in virologic markers, metavir score, Childs Pugh score or biochemistry. In multivariate analysis, the relative risk of HIV was 3.4 and of alcohol>50g/day, 2.3.

Abstract 246 by Jenny Heathcote looked at histological response to 40KD pegylated interferon and compared it with standard interferon. The overall histological response in pegylated Ifn was 57% compared to 41% noted in those receiving standard IFN. In those with sustained virologic

response, the histological response was seen in 83% versus 79%. In virologic non-responders, histological improvements were noted in 44% of patients receiving pegylated IFN and 36% of those receiving interferon 2A. Histological improvement was assessed by greater than 2 HAI units on the Knodell score.
Thus these snapshots of AASLD showed that there are new therapies available, that fibrosis can be reversed to some extent with therapy and that the natural history of the disease is less severe than previously thought.

Key Concepts:
- Eliminate transmission of viral hepatitis in the United States
- Effective and widespread use of vaccines (for hepatitis A and hepatitis B)
- Reduce high-risk behaviors and activities that facilitate transmission
- Use appropriate and cost effective screening strategies to identify persons at highest risk
- Maintain adequate infection control procedures
- Develop safe and more effective therapies

Viral hepatitis refers to a primary infection of the liver caused by at least five unrelated viruses, and acute and chronic liver disease due to viral hepatitis accounts for substantial morbidity and mortality. Two of these viruses, hepatitis A virus (HAV) and hepatitis E virus (HEV), are primarily transmitted by the fecal-oral route and cause acute self-limited disease. The other three viruses, hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatitis D virus (HDV), are transmitted by percutaneous or per mucosal exposures to blood or body fluids that contain blood. All three can result in chronic infection that places the individual at risk for chronic liver disease or primary hepatocellular carcinoma.
Accomplishments during the past 50 years that have contributed to the prevention and control of viral hepatitis include identification of the viral agents, development of sensitive and specific serologic and nucleic acid tests for detection, implementation of donor screening, effective inactivation procedures for plasma-derived products; widespread use of universal precautions; development and use of safe and effective vaccines against hepatitis A and hepatitis B; and development and implementation of nationwide prevention programs based on well-described epidemiology of these diseases.
Challenges to be faced in the next 50 years include effective and widespread use of vaccines; reducing high-risk behaviors and activities; implementing appropriate and cost-effective screening strategies; maintaining adequate infection control procedures; and developing safe and more effective therapies for persons with chronic disease.
The three major types of viral hepatitis in the United States are hepatitis A, hepatitis B, and hepatitis C. The serologic exclusion of the known hepatitis viruses continues to leave cases of hepatitis that clinically appear to be viral in origin. The majority of these cases of "non-ABCDE" hepatitis appear to be parent rally transmitted. Several new viruses have been recently identified and proposed as the putative agents of non-ABCDE hepatitis, but to date, studies of these viruses have failed to show an association with either acute or chronic liver disease.

Table 1. Estimates of acute disease burden viral hepatitis, United States, 1997.

Type	Infections	Cases of Disease	Deaths
Hepatitis A virus	179,000	90,000	300
Hepatitis B virus	185,000	39,000	400
Hepatitis C virus	38,000	6,000	Rare
Hepatitis D virus	5,000	1,000	80
Hepatitis E virus	Unknown	Very rare	0

Hepatitis A

Hepatitis A virus is an RNA virus classified in the Picornavirus family. The severity of clinical disease associated with HAV infection increases with increasing age; icteric disease occurs among <10% of children younger than 6 years of age, 40%-50% of older children, and 70% - 80% of adults. In the United States, the overall reported case-fatality rate is low (<1 per 1000), but high case-fatality rates have been reported among children <5 years of age (1.5 per 1000) and among persons >50 years of age (27 per 1000). Chronic HAV infection does not occur. Most transmission is by the fecal-oral route leading to spread between close contacts. Hepatitis A is vaccine preventable.

In the United States, hepatitis A incidence varies by age, race/ethnicity, and geographic region. Almost 30% of cases occur among children <15 years of age, with the highest rates among children 5-14 years of age. Since many children have unrecognized asymptomatic infection, they likely represent a major reservoir for HAV transmission. Among racial/ethnic groups, rates among American Indians and Alaska Natives are highest, and more than 10 times that in order racial/ethnic groups. Rates among Hispanics are approximately three times higher than among non-Hispanics. Disease rates are substantially higher in the western and southwestern United States compared with other regions.

Data from disease surveillance systems indicate that the most commonly reported source for infection is household or sexual contact with a person who has hepatitis A (15% - 30% of reported cases). An additional 10% - 15% of reported cases occur among children and employees of child care centers and members of their households. International travel (5% to 7%) and

suspected food or waterborne outbreaks (2% - 5%) each account for a small proportion of cases, and vary little by year. In contrast, the proportions of cases associated with men who have sex with men or injection drug use vary widely (5% - 30% of cases) as a result of periodic outbreaks occurring in these subgroups in some communities.

Nearly 50% of patients with hepatitis A do not have a recognized source for infection. Many of these patients may have acquired their infection from household contact with persons, especially children, with asymptomatic or unrecognized infection. In one study of adults without an identified source of infections, 52% of their households included a child <6 years old, and the presence of a young child was associated with HAV transmission within the household. In studies where serologic testing of the household contacts of adults without an identified source of infection was performed, 25% - 40% of their contacts <6 years old had serologic evidence of acute HAV infection (IgM anti-HAV).

The Advisory Committee on Immunization Practices recommends pre-exposure hepatitis A vaccination for persons at increased risk, which includes travelers to countries with moderate or high HAV endemic rates; men who have sex with men; illegal drug users (injecting and non-injecting); recipients of clotting factor concentrates; and persons with chronic liver disease. Post exposure administration of immune globulin is recommended for household and sex contacts and for persons exposed to a common source (e.g., infected food handler or infected child in day care) if IG can be given within 14 days of the exposure.

Vaccination of persons at increased risk for hepatitis A will have little effect on national disease rates, because most cases do not occur among persons in these groups. To achieve a sustained reduction in national incidence of hepatitis A, widespread routine vaccination is needed. In the United States, routine vaccination of children beginning at or after 2 years of age is recommended in communities with persistently elevated rates of hepatitis A (approximately twice the national average) and should be considered in communities with rates greater than (but less than twice) the national average. Vaccination of successive cohorts of young children should significantly lower the incidence of hepatitis A over time and eventually provide the opportunity to eliminate HAV transmission. To achieve this goal, children throughout the United States will need to be vaccinated against hepatitis A. This effort would be facilitated by the availability of a vaccine for use in infants or children in the second year of life and combination vaccines that include hepatitis A vaccine.

Hepatitis B

Hepatitis B virus is a DNA virus classified in the Hepadnavirus family. It causes both acute disease and asymptomatic infection. The risk of developing acute icteric disease increases with age, but the risk of developing chronic HBV infection varies inversely with the age at infection. Only 10% of children and 30% - 50% of adults with acute HBV infection will have icteric disease. However, chronic infection occurs in 90% of infants infected at birth, 25% - 50% of children infected at 1-5 years of age, and about 2% - 6% of persons infected as older children or adults. HBV is both a blood borne and sexually transmitted infection and is vaccine preventable.

After a period of relative stability ending in 1987, incidence of hepatitis B declined by >70% in the United States. However, an estimated 185,000 new HBV infections occurred in 1997, with the highest incidence of disease among young adults (20-29 years old), and higher rates among blacks and Hispanics compared with whites.

The highest rate of decline was observed in persons aged 10 - 19 years and is most likely related to the cumulative effect of recent hepatitis B immunization recommendations. Routine hepatitis

B immunization of infants began in 1992 in the United States, and not enough time has elapsed for universal infant immunization to have directly influenced disease incidence. However, earlier recommendations issued in the 1980s to vaccinate infants and older children at increased risk for HBV infection probably contributed to some of the decrease in incidence in older children.

The decline in overall disease incidence reflects a decrease in the number of cases among adults in groups known to be at increased risk for HBV infection. The decrease in cases among health care workers and men who have sex with men began in the 1980's, and in the 1990's was followed by a decrease in the number of cases among injection drug users and heterosexual men and women engaging in high-risk sexual activity. Factors thought to have contributed to the overall and risk group-specific declines in disease incidence include hepatitis B immunization and changes in high-risk activities. Nevertheless, among adults, sexual exposure to an infected partner or to multiple partners and injecting drug use account for the majority of HBV infections.

Approximately one half of persons with acute hepatitis B report a lifetime history of having been treated for an STD or of imprisonment. Had hepatitis B vaccine been routinely administered in STD clinics or prisons, as is recommended, up to one half of all cases of acute hepatitis B could potentially have been prevented. With such a strategy, even persons who did not report a risk factor for their infection would have been vaccinated. This is compelling evidence for the need for routine hepatitis B vaccination programs in STD clinics and prisons, as well as family planning clinics, drug treatment centers, needle exchange programs, and juvenile detention centers. In addition, not vaccinating sexual and household contacts of persons with HBV infection represents another missed opportunity to administer hepatitis B vaccine. Surveillance data indicate that one-half to two-thirds of cases whose source for infection was a sexual or household contact knew their contact was infected, and appropriate prophylaxis could have prevented infection in the majority of these cases.

A substantial number of children become infected with HBV in well-defined settings and the epidemiology of these infections is quite different from that of infections acquired by adults. Since over 90% of childhood HBV infections are asymptomatic, the true incidence of childhood disease is not accurately represented by national surveillance data, which reflect reported cases of clinically apparent disease. Thus, only 1% - 3% of all acute HBV infections occurring in the United States are reported among children <5 years of age, but infections in this age group account for 20% - 30% of all chronic HBV infections.

The strategy for elimination of HBV transmission in the United States includes routine infant and adolescent vaccination, screening of pregnant women for HBsAg and administration of post exposure prophylaxis (HBIG and vaccine) to infants born to infected women, and vaccination of children, adolescents, and adults at increased risk for hepatitis B. Routine infant immunization ensures the prevention of HBV infections in subpopulations that have high rates of early childhood infection (i.e., Eskimos, Asian/Pacific Islanders, infants of immigrant women from high endemicity areas), assures high immunization coverage rates because of the proven vaccine delivery system, and should prevent infections in adolescents and young adults because of the proven long-term efficacy of hepatitis B immunization. However, because most clinical disease occurs in adults, the addition of routine adolescent vaccination will achieve a more rapid reduction in HBV transmission. Until the cohorts of vaccinated children reach adolescence and adulthood, efforts must be strengthened to vaccinate older adolescents and adults with high-risk behaviors or occupations.

Hepatitis C

Hepatitis C virus is an RNA virus classified in the Flavivirus family. Like HBV infection, infection with HCV can cause a broad spectrum of disease. Persons with acute HCV infection typically are either asymptomatic or have a mild clinical illness; <20% may have jaundice. The course of acute hepatitis C is variable, although elevations in serum alanine aminotransferase (ALT) levels, often in a fluctuating pattern, are its most characteristic feature. Normalization of ALT levels might occur and suggests full recovery, but this is frequently followed by ALT elevations that indicate progression to chronic disease. Fulminant hepatic failure following acute hepatitis C is rare. Transmission of HCV is usually by direct percutaneous exposure to infectious blood and less commonly by prenatal or sexual exposures. There is no vaccine for hepatitis C.

In the United States, the estimated annual incidence of acute HCV infection was low (18 per 100,000) before 1965, increased steadily through 1980, and remained high (130 per 100,000) through 1989, corresponding to an average of 240,000 infections per year in the 1980s. Since 1989, the incidence of HCV infection has declined by more than 80%, primarily as a result of a decrease in cases among injecting drug users. HCV infection occurs among persons of all ages, but the highest incidence of acute hepatitis C is found among persons 20-29 years old, and males predominate slightly. Non-Hispanic blacks and whites have similar incidence of acute disease; persons of Hispanic ethnicity have higher rates.

In the United States, the relative importance of the two most common exposures associated with the transmission of HCV, blood transfusion and injecting drug use, has changed over time. Blood transfusion, which accounted for 20% - 40% of HCV infections acquired >15 years ago, accounts for <5% of infections acquired during the past 15 years. In contrast, injecting drug use consistently has accounted for a substantial proportion of HCV infections and currently accounts for 60% of HCV transmission in the United States. An average of 20% of persons with HCV infection report sexual exposures (i.e., exposure to an infected sexual partner or to multiple partners) in the absence of percutaneous risk factors. Other known exposures (occupational, hemodialysis, household, perinatal) together account for about 10% of infections. Thus, a potential risk factor can be identified for approximately 90% of persons with HCV infection. In the remaining 10%, no recognized source of infection can be identified, although more than two-thirds of persons in this category are associated with low socioeconomic level.

Case-control and population-based studies have found no association between HCV infection and exposures resulting from medical, surgical, or dental procedures, tattooing, acupuncture, ear piercing, military service, or foreign travel. If transmission from such exposures does occur, the frequency may be too low to detect. Although any percutaneous or mucosal exposure has the potential for transferring infectious blood and potentially transmitting blood borne pathogens, there are no data showing that persons with a history of exposures such as intranasal cocaine use, tattooing, or body piercing are at increased risk for HCV infection based on these exposures alone. Further studies are needed to determine if these types of exposures and the settings in which they occur (e.g., correctional institutions, unregulated commercial establishments), are risk factors for HCV infection.

To prevent new infections, public health programs should focus on ensuring a safe blood supply, implementing appropriate infection control practices, and preventing initiation of high-risk drug and sexual behaviors. Risks for chronic disease might be reduced by identifying HCV-infected persons through diagnostic testing and by providing appropriate medical management and antiviral therapy. Identification of persons at risk for HCV infection also provides infected persons the opportunity to obtain information about how they can prevent further harm to their liver and prevent transmitting the infection to others. In addition, more effective therapies for

treatment of persons with chronic hepatitis C need to be developed, and approaches designed for treating current or former injecting drug users.

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ARTICLE FOR PARAMEDICAL AND NURSES

Knowledge is POWER

Take Control of Hepatitis C

Knowledge is POWER
Take Control of Hepatitis C
The Facts
* Hepatitis C virus (HCV) is an infection that affects the liver
* HCV is contracted through blood-to-blood contact
* As many as 300,000 Canadians are infected with the hepatitis C virus
* Only 25% of these Canadians are aware they carry the hepatitis C virus
* HCV affects each person differently
* Sometimes there are no symptoms; sometimes there are
* HCV can progress slowly, or become a serious threat to your health in as little as five years
* Hepatitis C patients should not use alcohol or recreational drugs

There is hope. There is treatment. It's up to you to take the first step!

You've been diagnosed

"For years I knew there was something wrong. I was tired all the time. When the doctor came up with the diagnosis of hepatitis C, I finally had an answer and could concentrate on getting better."

Kevin, Montreal

"I was healthy, I was happy; I never suspected there was anything wrong until I gave blood. They sent me a letter telling me I had hepatitis C and to contact my doctor. To say I was shocked, was an understatement."

Moira, Toronto

If you've just been diagnosed with the hepatitis C virus (HCV), you probably have a lot of questions. You may be confused, perhaps scared, and certainly concerned about what having hepatitis C means to you, your family, and your future. It is important to know you are not alone - you have the support of your health care professionals - and effective treatment exists than may be right for you.

This pamphlet, "Knowledge is Power - Taking Control of Hepatitis C" will give you a better understanding of HCV so you can choose your treatment with confidence and base your decisions on the facts, not the fear. A glossary of the terms, which are underlined in the text, are provided for you at the end of this booklet to help you understand the key medical/technical terms that are commonly used.

Your knowledge is power and you can use it as a weapon against hepatitis C.

What is Hepatitis C?

"I found out I had hepatitis C when I donated blood. The first thing that went through my mind was 'what's hepatitis C?' The next thing - 'how do I get rid of it?"

Alex, Saskatoon

Quite simply, hepatitis C is a disease caused by the hepatitis C virus (HCV) which has infected your liver. A virus is a very small organism that attaches itself to your healthy cells and forces them to make more of the virus. Your body tries to fight viruses with antibodies, but the hepatitis

C virus is particularly strong; it will change to fight back against your body's defenses. Unfortunately, antibiotics, which kill bacteria are not at all effective against viruses.
Experts have identified two types of hepatitis C: acute hepatitis C (short-term infection) and chronic hepatitis C , (long-term, progressive infection). These are broken into sub categories:

Chronic hepatitis C can occur on its own and is generally the more serious of the two types. In about 80% of cases, however, acute hepatitis C develops into chronic hepatitis C over time. Both chronic hepatitis C and acute hepatitis C can cause very different degrees of symptoms and liver function damage. In many cases, HCV infection can be treated effectively with medication.
How you may have become infected
"Yesterday I found my oldest son, a teenager, standing in front of the bathroom mirror, trying to shave for the first time. I reminded him that his dad has hepatitis C. He then realized that it wasn't a good idea to borrow his dad's razor."
Jan, Calgary
Hepatitis C is contracted from blood-to-blood contact. This means that you probably became infected by blood tainted with the virus entering your bloodstream. You may never discover how you contracted hepatitis C, but now that you are aware of your infection, it is up to you to take precautions to protect your family, friends, co-workers, or anyone else who may come in contact with your blood. If you use common sense and educate your loved ones with the facts about hepatitis C, you and they can live risk free.
Important facts to know
* The risk of spreading hepatitis C through normal household contacts is very low
* Oral transmission of HCV has not been proven, so you can hug and kiss your family and friends
* Breast milk, semen, urine, saliva, and tears may contain the hepatitis C virus
* Do not share razors, toothbrushes or any other personal hygiene instrument that could contain blood particles and infect another. You can share bathroom facilities
* There is a 2% to 3% chance that HCV can be transmitted through sexual intercourse. The presence of sexually transmitted diseases (STD's) increase the risk of transmitting hepatitis C. Inform your partner of your infection and if you are sexually active with multiple partners, you should always use a condom
* Menstrual blood is known to carry HCV - women should avoid sex during this time
* You must not give blood or donate organs
* There is a chance that the virus can be passed to your newborn during childbirth
Your liver and HCV
"My doctor thinks I've had hepatitis C for about 15 years, but I only found out two months ago. All this time and I didn't know. I've got liver damage now. Shouldn't feel sick or something?"
Harold, Winnipeg
Your liver works 24 hours a day, performing over 500 vital functions for your body. Almost all the blood returning from your intestinal tract to your heart passes through your liver. It is absolutely necessary to your body's healthy function and you cannot live without it.
The hepatitis C virus lives in your liver. When it invades healthy liver cells, it causes those cells to become inflamed. Over time, this will affect the way your liver functions. How hepatitis C affects you, and if or when you will experience decreased liver function, is different for

everyone. There is no way to predict how you will react to HCV. However, there are some things we do know:
* You can live with HCV for many years without experiencing any major symptoms, or you might experience minor symptoms such as fatigue. Symptoms can come and go over time, and the presence or absence of symptoms do not relate to the degree of liver damage that may be occurring
* Chronic, long-term inflammation of the liver can cause liver cell damage and result in fibrosis (liver scarring), or even cirrhosis. These changes can happen in as little as 5 years, or can take as long as 30 years. About 20% of chronic hepatitis patients develop cirrhosis within 10 to 20 years
* Use of recreational drugs or alcohol affect how fast inflammation develops into fibrosis or cirrhosis
* There is an increased risk of liver cancer in people with cirrhosis
Proper nutrition, plenty of rest, avoiding recreational drugs or alcohol, and a responsible approach to treatment can make all the difference in managing hepatitis C. Taking control of your HCV won't be easy; it will take commitment. Your knowledge of hepatitis C can give you the power to take control of your health and your future.

How your liver works for you:

Your liver:
* Cleans alcohol, drugs, harmful by-products, and other toxins from your blood
* Converts most medicines, like allergy medications, into forms your body can use
* Removes old red blood cells
Your liver makes essential proteins:
* That transport nutrients and other substances through the blood to other organs and tissues
* To clot your blood
* That provide resistance to infection and bacteria
Your liver maintains a healthy balance in your body of:
* Hormones
* Cholesterol - your liver produces it, excretes it, converts it
* Essential vitamins and minerals
* Glucose (simple sugars), by producing, storing and supplying it to the rest of your body
* Fat, by producing and supplying it to the rest of your body
Phases of Hepatitis C
Phase I: Infection
* HCV virus enters the blood stream, attaches to liver cells, and begins to reproduce
* New virus, made in infected liver cells, invades more liver cells and infects them

Phase II: Inflammation
* Infected liver cells become inflamed
* The inflammation causes liver cells to die

Phase III: Fibrosis
* Over time, hepatitis C commonly progresses to fibrosis
* Among the healthy and inflamed liver cells strands of scar tissue develop

* If your liver biopsy shows significant fibrosis, it usually means you've been infected with HCV for 10 years or more

Phase IV: Cirrhosis
* When fibrosis increases, cirrhosis begins to appear
* Cirrhosis affects how blood flows in and out of the liver. This impairs normal liver functions

Tests often used for Hepatitis C patients
The following chart will help you understand the tests and procedures commonly used to diagnose HCV and to monitor its progress in your liver.
Test
Definition and Comments
Hepatitis C antibody (Anti-HCV)
(Blood Test)
HCV antibodies are produced by your body to fight HCV, and then remain in your system for life. This test measures the presence of HCV antibodies in your blood.
Alanine aminotransferase (ALT)
(Blood Test)
When liver cells are injured or destroyed enzymes from those cells escape into your blood. This test measures the level of the enzyme ALT in your blood and is a general indicator of inflammation.
Hepatitis C RNA (HCV RNA) or
Polymerase Chain Reaction (PCR)
(Blood Test)
This blood test can be done for two different reasons:
a) the qualitative test tells whether or not there is HCV in your blood; and
b) the quantitative test measures the number of HCV particles in your blood.
Genotyping
(Blood Test)
There are different genetic strains of hepatitis C. It is extremely helpful to know the genotype of your virus because different types require different lengths of treatment.
Liver biopsy
(Tissue Analysis)
A liver biopsy involves removal of a small piece of liver tissue through a needle. The specimen is analyzed under a microscope to determine the amount of liver damage. A liver biopsy: 1) confirms the diagnosis and rules out other potential disorders; and 2) gives your doctor a true picture of the stage and degree of activity of hepatitis C in your liver.
Ultrasound
(Imaging Test)
An ultrasound uses sound waves to create a picture of the liver. It reveals the size and texture of your liver, and the size of bile ducts and blood vessels. It is a safe and painless way to investigate your liver and the supply of blood to it.
What's next
"You bet I'm going to do everything I can to increase my chances of beating this thing!"
Jack, Vancouver

You now have a good idea of what hepatitis C is, how it affects your liver, and what you can do to safeguard yourself and others. Now it's time to make some important decisions - to use the knowledge you've gained about HCV to take charge of your future health.

Your options

Let's be clear - there is no treatment that will work for every single patient with HCV infection. This is not to say that there isn't hope, but treatment of hepatitis C is a big decision - a commitment on your part. Talk to your doctor or nurse, discuss realistic treatment goals based on your diagnosis. Do you want:

* more energy. To feel less tired or fatigued?
* to reduce your chances of developing cirrhosis or liver cancer?
* to help your liver recover normal functioning?

Outlined below are treatment alternatives you should be aware of. Do some research and talk to your doctor or nurse about which choice is best for you.

Herbal remedies

Generally, there is little scientific proof to support claims made on behalf of herbal medicines. Alternative medicines are not rigorously controlled, so, proof of safety, possible side effects, exact ingredients, potency, purity, directions for use, and the effectiveness of the herb, may be difficult to determine. Some herbs may cause serious problems to your liver, and your general health, if not taken properly. It is very important that you inform your nurse or doctor about any herbal remedy you are taking or are thinking of taking.

Interferon therapy

Alpha interferon is approved for the treatment of HCV infection. Interferon treatment is injected three times per week and is effective for approximately 50% off patients - meaning that these patients had an undetectable amount of the HCV in their bloodstream immediately following the end of the treatment. However, when thee same patients were tested for the hepatitis C virus six months later, more than half had relapsed

Interferon seems to work best for chronic hepatitis C patients the sooner it is used after infection. The treatment course is twelve months. The side effects include flu-like symptoms, muscle cramping, headaches, fever, fatigue, or depression. As well, some patients may show a reduction in disease-fighting white blood cells, or a decrease in the number of platelets in their blood.

Combination therapy

According to recent Canadian guidelines, the recommended treatment for HCV infection is with a combination of interferon alfa-2b and ribavirin. Rebetron* is the combination of these two therapies which together have produced better results than either treatment used alone. Rebetron* combines ribavirin capsules (taken orally twice daily) and interferon alfa-2b (injected 3 times weekly).

Interferon is a biological response modifier. This drug helps your body's immune system to fight infection. Ribavirin, on the other hand, is an antiviral agent which fights HCV.

The success of any treatment is not measured by how effective it is while you are taking it, but whether the results can be maintained for at least six months after treatment. Studies, where combination therapy was the only treatment ever used by a patient, showed that 41% had undetectable levels of HCV-RNA in their blood six months following treatment, and 62% showed improvement in their liver tissue. As well, the use of combination therapy in patients who were previously treated with interferon and then relapsed, showed that 49% had undetectable levels of HCV-RNA in their blood.

The side effects of combination therapy will vary from patient to patient. In addition to the side effects of interferon therapy, ribavirin can also cause shortness of breath, coughing, and anemia. If you suffer from any form of heart disease, please notify your healthcare professional.
It is very important that both you and your partner use effective birth control methods while taking combination therapy, and for six months following the end of your treatment. Failure to do so may result in serious birth defects. Consult your doctor or nurse about the best form of birth control for you and your partner.
Combination therapy has been researched, tested, and approved for treatment of hepatitis C. No, it's not for everyone - but it may be for you. How well Rebetron* works for you will depend on a number of factors, but you should discuss Rebetron* with your doctor or nurse, and ask if this option is right for you.
"I researched my options, talked to my doctor and decided that Rebetron* was the right treatment for me. It wasn't easy, but I'm glad I stuck with it. It's been a year now, and I'm virus free."
Julie, Moncton

Hep C: Presentation, Diagnosis, Prevention
Presentation
Since many patients with hepatitis C are asymptomatic, presentation may be incidental or fortuitous. Some patients may progress to the point of cirrhosis or even decompensate liver disease without any antecedent symptoms. Some patients may present with a wide variety of symptoms, not all necessarily due to hepatitis C. Some of the ways in which patients present are:
abnormal Ast or Alt on routine screening:
- insurance exams
- prenatal clinic
- assessment for various symptoms, e.g. abdominal pain
positive anti hepatitis C on screening:
- Blood donor clinics
- Red Cross Lookback Program
contacts of positive case:
- partner: but sexual transmission has a lifetime risk of about 3% and most partners have contracted hep C by sharing needles
- children of positive mothers (Hepatitis Knowledge Network Vol.1 No. 2)

screening of high risk persons:
- previous blood transfusion or blood products (prior to 1990)
- previous or present IVDU
- multiple sexual partners (particularly if other STD's present)
- previous body piercing, tattoos
- snorting of cocaine with common straw
fatigue:
- a small number of persons present with fatigue (subsequent newsletter)
evidence of liver disease:
- spider angioma
- palmer erythema
decompensate liver disease:
- cirrhosis
- portal hypertension with varices and ascites
autoimmune diseases accentuated by hep C:
(see Hepatitis Knowledge Network Vol. 1 No. 1)
Although this means of presentation is not common, some presenting conditions are: - arthritis
- lichen planus
- diabetes
- thrombocytopenia
Diagnosis
Although the diagnosis of chronic hepatitis C can be made by checking for the antibodies and determining the presence of the HCV RNA, patients must be thoroughly assessed relative to their liver disease and other complications. A good progressive approach is as follows:
a medical history of risk factors and symptoms
a history of liver disease:
- jaundice, pale stools, dark urine
- bleeding (nose bleeds, bleeding gums), bruising
- pruritus
- abdominal swelling, peripheral oedema
examination for signs of liver disease:
- spider angioma
- jaundice
- gynecomastia, loss of body hair
- hepatomegaly
- testicular atrophy
- nail changes
examination for signs of portal hypertension:
- splenomegaly
- varices
- abdominal and chest wall veins
- ascites with or without peripheral oedema
hematological tests indicating liver disease:
- thrombocytopenia (and possibly neutropoenia)
- prolonged INR or prothrombin time

- macrocytic anemia, often with target cells biochemical tests of liver disease: - Ast, Alt over one and a half times normal for three months (alkaline phosphatase and gamma GT are cholestatic enzymes not hepatocellular enzymes)
- decreased albumin
- elevated bilirubin
- polyclonal increase in gamma globulins serological tests for hepatitis C:
- antibody positive (anti hepatitis C by ELISA then by RIBA)
- HCV RNA (usually by PCR, qualitative adequate)

rule out other causes of liver disease: (subsequent newsletter)

pathological confirmation by liver biopsy: (subsequent newsletter)

Prevention:

Treatment is important, prevention is vital. Hepatitis C is spread predominantly by blood to blood and other ways are infrequent. Logical means of prevention are:

® personal health measures:
- avoid sharing toothbrushes, razors, etc.
- avoid unprotected sex during menstrual period (Hepatitis Knowledge Network Vol.1 No. 2)
- clean all blood contamination with bleach
- cover open sores and burns with a bandage

® general health measures:
- do not share needles or rigs
- do not share straws to snort cocaine
- avoid unprotected, promiscuous sex
- only use tattoo parlours which use disposable needles
- do not share body piercing needles

Alcohol:

Consumption of alcohol makes hepatitis C more active and progress more rapidly. Thus, all patients with chronic hepatitis C should be advised to minimize, if not eliminate, alcohol use.

Hep C: Transmission

General Comments

The spectrum of the source of infection with hepatitis C has changed with the advent of testing all blood donors for hepatitis C beginning in 1990. Intravenous drug use is the most common route of infection. Many patients, however, have more than one risk factor. Up to 20% of patients who have had a previous blood transfusion have also used intravenous drugs and there is a high rate of intravenous drug use among highly sexually promiscuous persons.

Routes of transmission may be different in different geographical areas. For instance, some years ago common needles and syringes were used for mass vaccination in some European countries such as Italy.

The finding of hepatitis C by PCR in certain body fluids does not mean that this is a route of infection. Tears, for example, have been shown to test HCV RNA positive by PCR, but it has never been shown that tears have transmitted hep C.
Hep C has an increased incidence in alcoholics regardless of other factors, the reason for this is unknown.

Serological Testing

As will be further discussed, the anti-HCV test is a test for an antibody, and does not differentiate the 20% of persons who have recovered after the acute attack from the 80% who have developed chronic hepatitis C. The HCV RNA as measured by PCR determines the presence of persistent viremia.

Transmission Rates: Canada
Recent studies suggest that the route of transmission can be determined in 90% of patients.
Route: % of patients
- blood or blood products (prior to 1990) 27%
- intravenous drug use 43 - 58%
- intra-nasal cocaine 4 - 10%
- sexual promiscuity 17%
- ear/body piercing, tattoos 1 - 5%
- unknown 10%
(Routes of infection are not exclusive)
Studies have shown that:
- In persons contracting hep C through blood transfusions, the more units of blood transfused the more likely to have contracted hep C.
- In IVDU's the positivity rate increases with years of use and by 10 years 70% of IVDU's are positive for hep C.
- people using intra-nasal cocaine or "snorting" often share the same straw, are very likely to break small intra-nasal blood vessels and transmit hep C this way.
Special Risk Groups
Certain risk groups have increased incidence of hep C :
- maternal to fetal - maximum of 8%
- needle prick injury - 8 - 10%
- health care workers - 1.5% = same as general population
- hemophiliacs - about 60% but many are co-infected with HIV
1. IV drug users often claim they use only clean needles. Often memory is not good under the influence of drugs, particularly cocaine. Hep C may also be transmitted by sharing the "rigs" even though the actual needle may not be shared.
2. Studies have shown maternal to neonate (at time of birth) to be a maximum of 8%, most studies actually showing about 6%. Intra-uterine transmission is not thought to occur. Transmission is higher if the mother has a high viral load. Transmission is much more likely if the mother is also HIV positive. A cesarean section may reduce the risk even further. Note: the antibodies from the mother are transferred to the fetus and may remain present for up to 8 months after birth and thus, an infant will test antibody positive. If an infant is to be tested before

1 year he/she should be tested for HCV RNA by PCR. The infant may be tested for antibody after one year.

3. Sexual transmission is uncommon, and most studies suggest a lifetime risk for a sexual partner to be less than 6%. Sexual transmission is increased if another STD such as herpes genitals is present. Couples should make their own decision about protection but in many circumstances it is not mandatory. Certainly at menstruation or if there are any bleeding sites, protection is advisable. Usually a partner of the contact patient tests negative and remains negative.

4. Breastfeeding has not been shown to transmit hep C. HCV RNA has been shown in low titers in colostrums, but the oral route has not been shown to be a means of hep C transmission. Mothers are advised they can breastfeed as long as there is no obvious bleeding from the nipples.

5. While HCV RNA has been shown in other body secretions such as tears, no documented transmission of hep C by other routes has been shown.

6. Interfamilial transmission has not been shown. Common sense should apply however, and household family members of a person with hep C should not share razors, tooth brushes, etc.

7. The best disinfectant for hep C is bleach. If contaminated blood is exposed it should be washed with bleach.

8. The present risk of contracting hepatitis C from a blood transfusion is 1 per 200,000 units of blood.

Who Should Be Tested?

Note: Only 24% of persons testing positive for hep C had any idea that they might be positive. Wider testing is indicated.

The following should be tested:

- people who received blood or blood products, (gamma globulin, plasma, etc.) before 1990.
- all IV drug users.
- all sexually promiscuous persons
- all persons with tattoos done in other than very reputable parlors
- all partners of positive patient (low yield, however)
- needle stick injured persons from known contact case should be tested in 2 to 3 weeks post exposure using HCV RNA test (PCR).
- all persons with elevated Ast or Alt as part of overall investigation

The occurrence of hepatitis G virus, clinical and histo-pathological finds, therapy, in patients with the suspicion of diagnosed hepatitis

We followed the occurrence of HGV infection in patients with the suspicion of diagnosed hepatitis in our department of infectious diseases. This acted about accidentally choice of patients that were from whole Czech Republic. The occurrence of HGV infection in patients with this diagnoses was not followed so far totally and systematically in Czech Republic. We studied biochemical values, serological finds, histological finds after liver biopsies and ultrasonic wave's finds. We found, as introduced in world articles, that in our tested patients was the high occurrence of HGV RNA positive patients, it was more than 1/3 of our patients. We certified the high occurrence of HGV RNA positive patients (active HGV infection) in i.v. drug users. I.v. drug users created about 2/3 of HGV RNA positive patients. Between the group of i.v. drug users and group of patients with another supposed ways of transmission, that had active HGV infection, was no difference in count of the occurrence. In both of these observed groups was always 1/3 of HGV RNA positive patients. From the total count of examined males were in contact with the HGV infection 75% males and only 50% examined females (in all cases of females-i.v. drug users). Active HGV infection occurred always in the youngest age groups. Active HGV infection was found in our collection of patients once as standalone in acute viral hepatitis G form that confirmed again literature sources about the rare occurrence of this disease. In one case we expected persistent HGV infection and in other cases were proved in co-infection with HCV, HBV or along with both types, but mostly with HCV co-infection (in sum 58%). Mostly supposed way of transmission was definitely in cases of active HGV infection the i.v. drug using (in sum 64%) and this supposed way of transmission was as the only one in group of triple-infection HGV along with HBV and HCV. In one patient we also supposed the possibility of sexual transmission of HGV and HCV. The contact with the HGV infection (HGV RNA positive and anti-HGV positive) in our number of examined patients had approximately 3/4 of them. The presence of antibody anti-HGV occurred in 1/3 of our patients. More important are the histo-pathological finds, where the results of histo-pathological valuation showed that the dual infection HGV with HCV in early chronic phases of the disease could affect the development and relevance of inflammatory and fibrosis changes. We had histo-pathologically evaluated 7 patients with dual HGV and HCV infections (average term of disease 9, 7 months, average age of patients 28, 8 years). These results we compared with finds of group of 8 patients with chronic hepatitis C (average term of disease was 11,1 months, average age of patients was 26,6 years). For valuation of liver biopsies we used scoring system by Ishak et al.. In patients with dual infections HGV and HCV we obtained (from valuation of necroinflammatory activity-grading and valuation of fibrosis changes-staging) results with higher numerical score in all observed items, in comparing with group only with chronic hepatitis C.

Clinical symptoms of disease, dual infection and triple infection were not visible in 1/3 of patients. In the rest 2/3 of patients was present hepatomegalia in all cases with active HGV infection. The course of disease was not different between i.v. drug users and patients with another ways of transmission in sense of laboratory and clinical finds. From actual results of

therapies is certified, same as in world sources that doses of interferon alpha 10 MU daily for rightly long term (inductive phase of therapy of chronic active VHC or acute VHC) has bold and quick effect on the negativity of HGV RNA and also on HCV RNA in patient's serum along with ALT value normalization. Meanwhile also with the distance of time by all done therapies in essential part of patients after this therapy this status is still lasting. That discovery is not negligible in connection with histological finds, which were found in dual infection HGV with HCV. It dealt about the progression of liver disease in approximately same time term course of disease in comparison with histological finds of alone HCV viremy. In our patients with combined infection HGV with HCV, treated by higher doses of interferon alpha (10 MU) did not occur serious adverse events of therapy except common flu-like syndrome and find of leucopenia and thrombocytopenia in blood picture. These patients did not have before the treatment complicated diseases. Detailed description of therapies, therapeutic schemes, their just and results will be the subject of next contents. We can submit that pursuant of our results and relatively often occurrence of HGV infection in patients with the diagnose of viral hepatitis is necessary to load laboratory diagnostic of HGV RNA by method RT-PCR to common screening of viral hepatitis. That will be suitable for aspect of histological finds in dual infection HGV and HCV and the possibility of their therapeutic interference. The problem is still difficult availability of this examination. As far as the examination of antibody anti-HGV, we are only informed about the situation after passed HGV infection of unknown date and clinically has this examination only the anamnesis meaning.

Background

Hepatitis G virus is classified as Flavivirus (Hepacivirus). Genome structure is 9, 0-kb RNA, linear, ss, minus stranded. Virus particle has probably 30-60 nm. Morphology is enveloped. Transmission is parenteral, sexual, via salivas. Also exist the possibility of transmission from infected mother to a child during the birth giving and the possibility of vertical transmission. Incubation period is probably 30-120 days.

Prevalence of HGV infection among different groups of patients is: a) in acute hepatitis-cryptogenic 3-20%, HBsAg positive 5-25%, anti HCV positive 10-30%, Fulminant and sub acute hepatic failure 0 - more than 50%, b) in chronic hepatitis/cirrhosis-cryptogenic 3-40%, HBsAg positive 2-20%, anti HCV positive 10-40%, c) in general population - 3-10%, d) in parenteral risk groups more than 25%

This virus can cause asymptomatic a) light acute hepatitis when laboratory values and histological changes are quickly in normal status b) persistent infection or c) chronic infection with histological finds of steatosis, persistent or chronic active hepatitis with fibrosis or cirrhosis. Most patients infected by HGV show only a minor elevation in aminotransferase levels that lasts until the clearance of HGV RNA. A clinical and histological pattern of acute or chronic hepatitis, when present, is usually associated with co-infection with other hepatotropic viruses. The share HGV infection on Fulminant hepatitis is unknown exactly but studies about it are exist . Chronic hepatitis of HGV etiology has usually mild necroinflammation (9). Histological study of Fiordalisi shows that isolated HGV infection can cause persistent or chronic active hepatitis. Colombatto discovered that this infection could excite many histological changes from steatosis to fibrosis and cirrhosis. These authors proved non-specific inflammatory damages of portal ducts in 50% cases. They find that HGV infection is significantly frequently connected with elevation of homeostatic enzymes (GMT and ALP) in implication of ductal inflammatory changes.

The share of chronic HGV infection in frequency cryptogenic cirrhosis is unknown. The noticing of Ross was very important. HGV infection can influence clinical course of orthotopic liver transplantation and cause significant cholestasis. The cholestasis is probably caused by infliction of ducts with ductopenia. Many patients with liver transplantation and with positive find of HGV RNA did not have cholestasis and ductopenia of this type.
Other studies showed that in individuals with co-infection HGV and HCV the infection of HGV have not influence on replication HCV and concentration of HCV RNA level. Also its have not influence on course of liver damage. Other authors discovered that co-infection with
HGV have significant influence on histological find of HCV hepatitis. Also this co-infection can be significant for enhancement of liver damage.
This problem we tried verify on collection of our patients co-infected HGV and HCV. We compared clinical and histological results of this group with patients the same time handicapped by only chronic active hepatitis C.
Therapy is mainly connected with dual infection HGV with HBV, HGV with HCV or both. From the point of view of HGV infection is known that its sensitivity to interferon alpha is good. In all cases after ending of therapy disease was relapsed. The positive HGV RNA level was on values before interferon therapy.

From the viewpoint of therapy of active HGV infection it is for the present known that the virus is sensitive for interferon alpha (INFa). After the therapy is quickly falling the concentration of HGV RNA in serum, but after the finish of treatment return quickly the value like before the treatment. This can bear with the amount of served INFa or by the length of treatment lasting. The fall or fade-out of HGV RNA was guided by normalization of ALT activity or its drop. Optimal established treatment scheme of therapy by INFa for active HGV infection does not exist. It is so, because nowadays the virus of hepatitis G doesn’t have a big meaning as the possible etiologic agent of viral hepatitis as it was earlier. Active HGV infection was occurred in our collection of patients suitable for the future treatment together with HCV infection, which was in form of acute viral hepatitis C (next acute VHC, so at the elevation of transaminases only the HCV RNA positive) totally in 5 cases. As well in form of chronic active viral hepatitis C (next CHC), totally in 9 cases. In individual types of HCV infections (acute or chronic active) we used treatment schemes, which were already applied in our country with the usage of inductive phase of interferon therapy (so the application of 10 MU of INFa daily).

In acute VHC in combination with HGV infection we applied in 4 cases from 5 patients INFa of 10MU dosage daily during 3 weeks – inductive phase and then dosage of 3 MU 3 times in a week during 3 months) – continuing phase. The ALT value near before the therapy beginning was in 4 patients in expansion 1.0-3.2; in 1 case when the patient was then treated by inductive phase was the ALT value 5.5. Already after 2 weeks vanished in HGV RNA and HCV RNA serum in all patients and after 5 weeks in all cases the ALT value was normalized. In 1 case by patient request we applied INFa by standard process 5 MU 3 times weekly, where the HGV RNA and HCV RNA positive find surviving at therapy by then 3 months. Regarding results after 6 month after finishing already mentioned INFa therapy in acute VHC in combination with HGV infection, in 3 cases from above mentioned 4 patients is the negativity in HGV RNA and HCV RNA serum, in 4th patient meanwhile is not sufficient time distance for the therapy finish. The ALT value is in all patients also henceforth in norm.

In CHC in combination with HGV infection we made in 6 cases from 9 patients therapy of INFa in dose of 10MU daily in duration 56 days, so the inductive phase therapy of CHC. Then were in patients applied INFa of 5MU dosage 3 times a week in duration 4 weeks and finally INFa of 3MU dosage 3 times weekly in time to whole therapy term of 12 months. The ALT value near before the beginning of therapy was in all patients in scale of 1.6-4.4, when the highest values were in patients before the treatment by inductive phase. Already after 2 weeks was in all patients the negativity in HGV RNA and HCV RNA serum.

This last in 2 patients, which already finished the therapy 5 months ago, in other 4 cases will be this therapy finished in short time. Transaminases value including ALT was in these 3 patients in normal till 4-5 months since the therapy beginning. In the 3 cases of these 6 patients value of ALT was in normal to 56 days during inductive phase of therapy. In the rest of 3 cases from 9 treated patients, we used by request standard treatment scheme by INFa by 5MU dosage 3 times a week, in last patient then the therapy by INFa in 3MU dosage 3 times a week in combination with ribavirin cps. (200 mg each), in all during 12 months. In these 3 last patients during the treatment carried through months the positivity in HGV RNA and HCV RNA serum. Also the elevation of ALT value, in average longer about 2-3 months in comparison with already mentioned type of therapy (inductive phase therapy of CHC). In patient that is treated by combination of INFa and ribavirin henceforth after 5 months the light elevation ALT and HGV RNA and HCV RNA serum positivity are present. Quantitatively it acts about lower values than at the beginning of the therapy. In 1 of these 3 patients (one patient with standard treatment by INFa 5 MU 3 times a week) after 7 months of therapy in the negativity in the HGV RNA serum still present, HCV RNA positivity (quantitatively) is on limit values.

From actual therapy results it is proved that dosages of INFa enough higher – 10MU in rightly long time (inductive phase therapy of CHC and acute VHC) had violent and quick effect on the negativity in HGV RNA and HCV RNA serum including ALT values normalization. Meanwhile also with the distance of still finished treatments of essential part of patients after this therapy, the condition is lasting. That finding is not inconsiderable in context with histological finds that were found in dual infection HGV with HCV (high progression of liver disease in the same time interval) in comparison with histological finds at alone HCV viremy. In non of our patients with combined infection HGV with HCV treated by higher doses of INFa (10 MU) did not occur serious adverse events of the therapy except flu-like syndrome and in blood picture finds of leucopenia and thrombocytopenia. The fact is that these therapies navigated the group of young people, which were not pressed by any of associated diseases. Detailed description of therapies, types of treating schemes, and their motivation will be the subject of next articles.

Methods

In the examinations of our collection of patients we used these methods:

a) Biochemical
b) Ultrasonic waves
c) Serological (5, 6):

I. I. Isolation and detection of HGV RNA by method RT-PCR
II. II. Detection of anti-HGV antibodies
III. III. Detection of marks of another viral hepatitis

D) Histological (10, 11, 21, 22) – liver biopsies

Ad a) actual standard techniques

Ad b) standard examination

Ad c) The serum samples collected from the patients were stored at –20°C until they were tested. Testing for HGV-RNA and anti-HGV (E2) antibodies was performed on the same serum for each individual.

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Conclusions

The occurrence of HGV infection in the patients hospitalised in department of infectious diseases for the suspicion of diagnoses hepatitis. We tied to create the first detailed and systematic monitoring of this infection.

We went into clinical symptoms of disease, biochemical data, serological finds, ultrasonic wave's finds and histological finds of liver biopsies in some of patients and possibilities of therapeutic influence to this disease.

We discovered that the contact with the HGV infection had 3/4 of our patients, from who had the active HGV infection 1/3 of them. Active HGV infection was mostly occurred in group of i.v. drug users, which was the most common way of transmission. Also the dual infection along with HCV was occurred very often (1, 25). However there was no difference in the occurrence of active HGV infection in the group of i.v. drug users and in the group of patients with another ways of transmission, so we didn't confirm the facts in world's literature sources. We didn't confirm the higher occurrence anti-HGV antibodies in comparison with the occurrence of HGV RNA as well, because in our examined patients were always in both cases only 1/3 of positive patients. In one case we discovered acute viral hepatitis type G that agrees with facts in world's literature sources about the rare occurrence of this disease. In one case we could also suggested persistent HGV infection. The higher occurrence of active HGV infection was found in population of males than in females and in very young patients also.

However important were histological finds from liver biopsies, when we found the progression of liver disease in the course of dual infection HGV and HCV in the same course interval of disease in comparison with liver deteriorating only in the course of HCV viremy. But histopatological study was made on two smaller collections of patients with chronic active hepatitis C and chronic active hepatitis C along with HGV viremy. The study showed that patients with dual infection deported in scoring of histological changes (by Ishak) higher average score in rate of necroinflammatory activity (HAI), so higher average values of histological grading. Similar results were obtained also by valuation of architectonic changes, scale of fibrosis etc. (staging). Patients with dual infection had higher staging score contrary to group of patients with chronic hepatitis C.

The observation but also have its own limitation. Even the length of disease in both collections is approximately comparable, as well like the average age of patients, these collections are quantitatively in number of patients very small and results of histological scoring valuation is not possible to statistically evaluate. In addition (Hübsher1998) every scoring system is rather forced created and not often definitely is known the prognostic meaning of individual valued changes in category of necroinflammatory changes (for example discussed meaning piecemeal necrosis versus intralobular inflammatory activity)(10).
Less is debatable the scale of fibro tic changes, but also there has their limitation, for example the representation of biopsies.

Descriptions of histopathological changes in isolated HGV infection are very small number. Mostly is the disease allowed to be light hepatitis that quickly grew over on its own. Some of clinic-histological observations show that the infection can be presented like persistent or chronic with histologic picture of steatosis, persistent or chronic active hepatitis with fibrosis and eventually till cirrhosis (Colombato (12), Fiordalisi (14)).
The number of messages about the histological changes and clinical course of disease in co-infections (f.e. also HGV and HCV) is very small. The largest study is by Manolakopoulos (15), who proved in large collection of patients that the dual infection HGV and HCV in comparison with the group of patients only with HCV infection can significantly influence the clinical course and histological picture of the disease. He used Sheuer's scoring system (21). In dual infection he proved significantly higher necroinflammatory activity in item PM necrosis (piecemeal), but not in intralobular inflammatory activity. The scale of fibrosis changes was in co-infected patients also higher, but it was not statistically important. Higher scale of fibrosis changes in liver biopsies in dual infection described also Diamantis (13).

In our study we proved similar changes, even if for the counting limitation of examined patients we can't make statistical valuation, so higher necroinflammatory activity in co-infected patients with early chronic hepatitis C and G and also greater scale of fibrosis changes. The difference was only that in our collection of patient was higher number of necroinflammatory changes located especially intralobulary. This is to certify that histopathological finds that were presented in another studies in the world (13,15), even that nowadays the HGV in some literature is not used as possible etiologic agent of viral hepatitis. It is indicated that is necessary to think about its clinical meaning. It is not still excluded the possibility of pathogenic activity in depend on dual infections. A lot of foreign studies have incongruousness. The role of HGV infection depending on acute or chronic hepatitis is not still fully defined. Henceforth are recommended studies about HGV infection staying alone, but in regard of our results should be suitable also in dual infection with HCV. According our results we can say that in some of patients with active HGV infection can have the influence to course of liver disease, especially if it is co-infection with HCV. Then should be suitable using the HGV RNA examination into the screening examination of viral hepatitis. Depending on the therapy of dual infections HGV with HCV we also proved quick influence of interferon alpha in short time term, applied daily in higher doses (10 MU) to markers negativity of both types of hepatitis including normalization of ALT values. Meanwhile in important part of patients half a year after treatment we certify that this state continuing. Results in other patients including results of longer time term after treatment with the motivation of interferon therapy of acute VHC in combination with HGV and motivation of therapeutic schemes will be subjects of future reports.

HEPATITIS B QUICK FACTS

1. Worldwide, 1 out of 3 people have been infected with the hepatitis B virus.
Hepatitis B is one of the most common and serious diseases in the world. According to the Hepatitis B Foundation, there are approximately 400 million chronic carriers of hepatitis B virus (HBV) worldwide. Over 75 percent of these carriers reside in the Asia-Pacific region. 1 million people die each year from hepatitis B virus infection, from acute and chronic liver disease, making it the ninth leading cause of death worldwide. Nearly 300,000 people become infected each year with the Hepatitis B virus. Of that number, one out of 10 becomes a chronic carrier.
2. HBV is 100 times more infectious than the AIDS virus. In the U.S., approximately 2 health care workers are infected each day with HBV. Yet, hepatitis B can be prevented with a safe and effective vaccine. For the 400 million people worldwide who are already chronic carriers of HBV, the vaccine is of no use.
3. Part of the natural history that has only recently been appreciated is spontaneous reactivation of chronic infection. This occurs in HBeAg-negative, anti-HBe-positive HBV carriers who had previously seroconverted into a nonreplicative phase, many years ago. The inactive virus spontaneously becomes active again, with the re-emergence of HBeAg and HBV-DNA, with or without loss of anti-HBe. There is usually a significant spike in serum ALT activity, sometimes associated with symptomatic' acute' hepatitis, manifested by jaundice, nausea, flu-like illness and fever. Spontaneous reactivation may occur in 15% to 20% of previously nonreplicative patients.
4. The greatest risk of chronic Hepatitis B lies in developing chronic liver disease such as cirrhosis or liver cancer. About one fourth of chronic Hepatitis B sufferers will develop one or the other of these diseases. Worldwide, 16% to 59% of carriers have hepatic inflammation and viral replication. This group is at the highest risk for developing progressive liver disease. Worldwide, Hepatitis B is the leading cause of liver cancer once cirrhosis is established; the diagnosis of hepatic decompensation is rather straightforward. Studies suggest the annual rate patients with cirrhosis will decompensate ranges from 3.8% to 9.5%.
5. People at HIGH RISK for becoming infected with HBV:
Sexually active adults and teenagers
Health, Dental, and Emergency Care personnel
Adoptive families
Injecting drug users
People who live with HBV Carriers
Children born to mothers who are HBV carriers
Men Having Sex with Men
People who get tattoos, ear piercing or body piercing

People who travel to high-risk countries - High risk countries include places in which over two percent of the population are HBV carriers, which include Asia, Africa, South America, and Eastern and Mediterranean Europe.
6. Hepatitis B virus can be transmitted through any infected person's mucus membranes if you come into contact with infected body fluids such as semen, vaginal secretions, saliva, and blood. However, the highest concentration of the virus is found in the blood.
7. Exposure - You need to receive Hepatitis B immune globulin (HBIG) within 2 weeks of exposure. HBIG differs from the vaccine, which you also need to receive. The Hepatitis B vaccine is given in a series of 3 injections; one at zero months, one at 3 months, and again at 6 months. YOU MUST COMPLETE THE VACCINE SERIES AND RECEIVE ALL THREE SHOTS!
8. the vaccine provides immunity to about 90% of the adult population who complete the series, and about 95% of vaccinated children.
9. Children are now routinely offered the Hepatitis B vaccine as part of their immunization series.
10. Hepatitis B is the most preventable STD (sexually transmitted disease) as there is a vaccine for prevention. Didn't think of it as an STD did you?
11. Check with your local health department for vaccine information. In many places, you can receive the vaccine free of charge! Even if you have to pay a little for it, take it from me that it is well worth it not to get this horrible disease.
12.HBV infection has been linked etiologically with several extra hepatic manifestations. These may be caused by deposition of complexes of viral antigen and antibody related to the surface, core and the e proteins of the virus. These conditions include:polyartertitis nodosa, glomerulonephritis, mucocutaneous vasculitis and essential mixed cryoglobulinemia (although this is more often related to hepatitis C).
13. Practice safe sex, know your partner's sexual history, practice good hygiene such as good hand washing after coming into contact with anyone's body fluids, GET THE VACCINE!
14. The following is a list of some of the possible symptoms of HBV infection.
HBV causes no symptoms at all in about 50 percent of cases.
Approximately 49 percent of the people who are infected will have some symptoms. The usual signs and symptoms of HBV may include fever, fatigue, muscle or joint pain, loss of appetite, nausea and vomiting. When infected with HBV, many people think they have the flu and do not attribute their symptoms to HBV infection.
A very small number, about one percent, develop life-threatening acute Fulminant hepatitis from the virus. These people may suddenly collapse with fatigue, have yellowing of the skin and eyes (jaundice) and develop swelling in their abdomen. Acute Fulminant hepatitis develops very suddenly and acutely, and can be fatal if not treated immediately.
About 90 percent of the total number of people infected with HBV will develop antibodies against the disease and will totally clear the virus from their bodies. Although they may experience some symptoms, these people will recover without complication.

CONSEQUENCES OF HEPATITIS B

Acute hepatitis B

The incubation period of acute hepatitis B ranges from about 4 weeks to 6 months. Many childhood infections are sub-clinical, but most adults infected with HBV have some non-specific symptoms such as malaise and anorexia, or may experience jaundice. Myalgia and arthralgia can occur and a skin rash may develop. Acute hepatitis is usually self-limiting and benign. However, about one per cent of adults will develop a very severe infection resulting in the destruction of much of the liver, termed Fulminant hepatitis, which can lead to fatal liver failure.

Chronic Hepatitis B

While it has been widely accepted that HBV is completely cleared in individuals who make a full recovery from acute hepatitis, it has recently been shown that low levels of HBV DNA can sometimes be detected in the blood many years later despite the presence of serum antibodies and HBV-specific cytotoxic T-lymphocytes. The results suggest that the immune system controls the virus lifelong in these individuals, although the infection is never eradicated. It may be that decision of acute hepatitis B and progression to chronic disease represents the extremes of a spectrum of outcomes rather than discrete clinical entities. The likelihood of developing chronic hepatitis B is greatly affected by the age when infection occurs. Exposure to virus at birth almost invariably results in persistent infection. Infection between birth and the age of 2 years results in persistent infection in about 40 per cent of cases. However, for individuals infected from 2 years of age onwards, the risk of developing chronic hepatitis B is typically about 5 per cent. For immunocompromised individuals such as transplant recipients and those infected with human immunodeficiency virus (HIV), the risk of developing chronic infection is greatly increased. The natural course of chronic hepatitis B can be considered in three phases: a period of immune tolerance towards HBV is followed by active immune-mediated disease. Clearance of the virus coupled with resolution of disease may occur during this period. Finally, a transition to a phase of reduced viral replication occurs. At some stage during the course of chronic hepatitis B, the HBV genome becomes integrated into the hepatocyte DNA, but it is not understood how this affects subsequent disease progression.

Life threatening results of HBV

Cirrhosis

A cirrhotic liver is degenerate and physically distorted as a result of fibrosis. The damage is permanent and serious because liver function is impaired, and may lead to liver failure. Patients in the early stages of liver failure experience malaise and fluid retention and have an enlarged liver and spleen. Pressure within the portal vein which serves the liver increases and can result in the rupture of the esophageal veins. Rapid and extensive blood loss can follow, requiring urgent medical treatment. Reduced levels of clotting factors in the blood increases the severity of this problem. During the final phase, the patient becomes jaundiced and may become mentally confused and eventually lapses into a coma and dies.

Hepatocellular carcinoma

Primary hepatocellular carcinoma is among the most common cancers in the world. The incidence of hepatocellular carcinoma shows geographical variation and is most common in Asia and Africa, where HBV infection is highly endemic and infection is usually acquired in early infancy. The association between HBV and hepatocellular carcinoma, which develops years after the initial infection, is now well-established. Chronic carriers are about 200 times more likely to develop hepatocellular carcinoma than uninfected individuals living in the same area. Approximately 20 per cent of patients with cirrhosis will develop hepatocellular carcinoma. When symptoms appear, the patient is already at the terminal stage and survival times are generally only a few months, depending on existing liver function at the time of diagnosis. Typically the development of hepatocellular carcinoma occurs 30-50 years after the time of infection; consequently hepatocellular carcinoma is far more likely to be seen in individuals exposed to HBV in early life rather than in adult life10. In areas where HBV infection is acquired in infancy, male carriers have a 40 per cent risk of dying from hepatocellular carcinoma compared with 15 per cent for females. This correlates with the observation that female patients with chronic hepatitis B are more likely to clear HBeAg than males11. For individuals infected with HBV as adults, the risk of developing hepatocellular carcinoma is less than one per cent.

Key points

Symptoms of acute HBV infection are non-specific, but may include malaise, anorexia or jaundice

Exposure to HBV parentally or in early infancy usually leads to chronic infection

The natural course of chronic hepatitis B progresses through three stages: immune tolerance, active disease, and a late phase with reduced viral replication

Approximately 25 per cent of patients with chronic hepatitis B will develop cirrhosis, causing permanent and serious liver damage.

Chronic carriers of HBV are far more likely to develop hepatocellular carcinoma than non-carriers

The course of hepatitis B is determined by many factors, including immune response, host genetic factors, and HBV mutations.

Interferon Treatment of Viral Hepatitis Dr Ghulam Ali MD

This page provides general information on treatment options for viral hepatitis B and C. It is not an endorsement of the any of the products by the author or by any institution with which the author is affiliated.

Various type I interferon's administered by intramuscular or subcutaneous injection are indicated for the treatment of chronic hepatitis B and chronic hepatitis C. Interferon Alfa is a naturally occurring glycoprotein that is secreted by cells in response to viral infections. It exerts its effects by binding to a membrane receptor. Receptor binding initiates a series of intracellular signaling events that ultimately leads to enhanced expression of certain genes. This leads to the enhancement and induction of certain cellular activities including augmentation of target cell killing by lymphocytes and inhibition of virus replication in infected cells. Various recombinant forms of interferon alpha (interferon alpha-2a and interferon alpha-2b) and a recombinant non-naturally occurring type I interferon (interferon alfacon-1) are approved to treat viral hepatitis.

ONLY AN INTRODUCTION TO TREATMENT OF CHRONIC HEPATITIS B OR HEPATITIS C WITH INTERFERON. YOU SHOULD CONSULT A PHYSICIAN EXPERIENCED IN THE CARE OF PATIENTS WITH LIVER DISEASES FOR ADDITIONAL INFORMATION.

Chronic Hepatitis B

Interferon alfa-2b is effective in the treatment of adults with chronic hepatitis B virus infection and evidence of viral replication. The patient should have evidence of infection with hepatitis B virus, documented by the presence of hepatitis B surface antigen in the blood, for six months. The patients should also have evidence of virus replication, documented by the presence of hepatitis B e antigen in the blood. Ongoing inflammation of the liver should also be present as documented by an elevation in serum aminotransferase activities. A liver biopsy should also be performed prior to treatment. Patients with severe, decompensate liver disease (eg. encephalopathy, ascites, very high serum bilirubin, prolonged prothrombin time, etc.) should not generally be treated with interferon alfa-2b except in the setting of an approved clinical study.

The recommended dose of interferon alfa-2b for the treatment of chronic hepatitis B is 5,000,000 units daily, administered by subcutaneous or intramuscular injection, for a total of 16 weeks. The patient must be monitored carefully during the treatment period for side effects including flu-like symptoms, depression, rashes, other reactions and abnormal blood counts.

A meta-analysis of several randomized trials of interferon alfa-2b in the treatment of patients with chronic hepatitis B showed such treatment to be cost-effective (Wong et al. Annals Intern. Med. 1995;122:664-675). This analysis showed that treatment with interferon alfa-2b decreased viral replication, documented by loss of serum hepatitis B e antigen, in about 45% of patients compared to less than 10 % of untreated patients. About 8% of patients also lost hepatitis B virus surface antigen (cured) within one year of treatment compared to a rate of about 1% a year for untreated patients.

Interferon alfa-2b treatment of chronic hepatitis B requires careful medical attention. Consult a physician who has experience with this type of treatment for more information.

Chronic Hepatitis C

Interferon alfa-2a interferon alpha-2b and interferon alfacon-1 are all approved in the United States for the treatment of adults with chronic hepatitis C. The patient should have evidence of chronic liver disease and infection with hepatitis C virus as documented by the presence of serum antibodies against this virus or serum viral RNA. Inflammation of the liver should also be present as documented by elevations in the serum aminotransferase activities and liver biopsy. Treatment of patients without evidence of inflammation (e.g. normal serum aminotransferase activities), or treatment of patients with decompensate liver disease (e.g. encephalopathy, ascites, very high serum bilirubin, abnormal prothrombin time, etc.), should only be considered in the setting of an approved clinical study.

The recommended dose of interferon's alfa-2b and alpha-2a for the treatment of chronic hepatitis C is 3,000,000 units three times a week, administered by subcutaneous or intramuscular injection. For interferon alfacon-1, the recommended dose is 9mcg three times a week for first time treatment. Six months of treatment was originally recommended for interferon's alpha 2a and 2b, however, several studies have shown that treatment for a year or longer may be more effective (Poynard et al. Hepatology. 1996;24:778-789). Treatment times of 1 to 2 years with these drugs are now approved by the FDA. For interferon alfacon-1, a six month treatment course of 9 mcg three times a week is approved and a dose of 15 mcg three times a week for another six months is approved for patients who do not respond or relapse. During the treatment periods with any of these recombinant interferon's, the patient must be monitored carefully for side effects including flu-like symptoms, depression, rashes, other unusual reactions and abnormal blood counts.

The results of several published clinical studies demonstrate that about 50% to 70% of patients with chronic hepatitis C respond to treatment with interferon alfa-2b as documented by reductions in the serum aminotransferase activities to near normal. Several studies have also shown that about 70% of patients have a decrease in liver inflammation on follow-up liver biopsy. Unfortunately, most patients relapse and have recurrent liver inflammation after treatment is discontinued.

Several studies have tested a combination of interferon alfa-2b and ribavirin. This drug combination was approved by the United States Food and Drug Administration in June, 1998 for patients with chronic hepatitis C who have been treated previously with interferon alone and "relapsed" after treatment was discontinued. It may also be useful in patients never treated previously or in those who did not respond at all to previous interferon treatment. Study results suggest that a combination of interferon alpha-2b and ribavirin induce a sustained response in more patients than treatment with interferon alpha-2b alone. Patients interested in such treatment should consult their physician.

Interferon treatment of chronic hepatitis C requires careful medical attention. Consult a physician who has experience with this type of treatment for more information.

Hepatitis C

HCV was discovered in 1989 by investigators at Chiron, Inc. Portions of the HCV genome were isolated by screening cDNA expression libraries made from RNA and DNA from chimpanzees infected with serum from a patient with post-transfusion non-A, non-B hepatitis. [Prior to the

discovery of HCV, hepatitis following blood transfusion that was not caused by hepatitis A or hepatitis B was referred to as non-A, non-B hepatitis]. To identify portions of the genome that encoded viral proteins, the libraries were screened with antibodies from patients who had non-A, non-B hepatitis. These investigators went on to show that the virus they identified was responsible for the vast majority of cases of non-A, non-B hepatitis. They called the new virus hepatitis C virus (HCV). Subsequently, the complete genomes of various HCV isolates were cloned and sequenced by several groups.

HCV is a positive, single-stranded RNA virus in the Flaviviridae family. The genome is approximately 10,000 nucleotides and encodes a single polyprotein of about 3,000 amino acids. The polyprotein is processed by host cell and viral proteases into three major structural proteins and several non-structural proteins necessary for viral replication. Several different genotypes of HCV with slightly different genomic sequences have since been identified that correlate with differences in response to treatment with interferon alpha.

Despite the discovery of HCV by molecular biological methods and the sequencing of the entire genome, a permissive cell culture system for propagating HCV has yet to be established. A non-primate animal model also does not exist. As a result, the production of specific drugs against HCV has been impeded although excellent diagnostic methods for have been developed.

Risk Factors for HCV Infection

Approximately 170,000,000 people worldwide and 4,000,000 in the United States are infected with HCV. The virus is transmitted primarily by blood and blood products. The majority of infected individuals has either received blood transfusions prior to 1990 (when screening of the blood supply for HCV was implemented) or has used intravenous drugs. Sexual transmission between monogamous couples is rare but HCV infection is more common in sexually promiscuous individuals. Perinatal transmission from mother to fetus or infant is also relatively low but possible (less than 10%). Many individuals infected with HCV have no obvious risk factors. Most of these persons have probably been inadvertently exposed to contaminated blood or blood products.

Consequences of HCV Infection

About 85% of individuals acutely infected with HCV become chronically infected. Hence, HCV is a major cause of chronic (lasting longer than six months) hepatitis. Once chronically infected, the virus is almost never cleared without treatment. In rare cases, HCV infection causes clinically acute disease and even liver failure, however, most instances of acute infection are clinically undetectable.

The natural history of chronic HCV infection can vary dramatically between individuals. Some will have clinically insignificant or minimal liver disease and never develop complications. Others will have clinically apparent chronic hepatitis. Of these, some go on to develop cirrhosis, however, the exact percentages are not known. About 20% of individuals with hepatitis C who does develop cirrhosis will develop end-stage liver disease. Cirrhosis caused by hepatitis C is presently the leading indication for orthotropic liver transplantation in the United States. Individuals with cirrhosis from hepatitis C are also at an increased risk of developing hepatocellular carcinoma (primary liver cancer).

A major problem in discussing prognosis in patients with chronic hepatitis C is that it is difficult to predict who will have a relatively benign course and who will go on to develop cirrhosis or cancer. One fairly clear factor for progression to cirrhosis is concurrent alcohol abuse. Certain findings on liver biopsy can also be helpful in predicting a relatively benign or progressive

course. Viral genotype may also play a role. Additional research is urgently needed to identify host factors that are important in determining prognosis in chronic hepatitis C.

Diagnosis

The diagnosis of chronic hepatitis C is made by history, serological testing and liver biopsy. Most patients with chronic hepatitis C will be asymptomatic or have non-specific symptoms such as fatigue. In some individuals, the diagnosis will be suspected from the results of blood tests obtained for other reason (usually elevations in the serum alanine and aspartame aminotransferase activities).

Individuals suspected of having chronic hepatitis C include:

- Those with symptoms of chronic liver disease
- Those with risk factors such as past or current intravenous drug use or blood transfusions prior to 1990
- Those with abnormal laboratory tests suggesting liver disease

Such individuals should be tested for the presence of serum antibodies against HCV. The presence of anti-HCV antibodies in a person with a risk factor or evidence of liver disease strongly suggests the diagnosis of chronic hepatitis C. The absence of anti-HCV antibodies generally rules out the diagnosis. Tests for HCV RNA in blood should be done in those individuals with anti-HCV antibodies to confirm the diagnosis and in the rare patient who does not have anti-HCV antibodies but in whom the diagnosis is still strongly suspected on clinical grounds. Such testing should also be performed in patients who will undergo treatment. After making the diagnosis, a liver biopsy is usually indicated to assess the degree of liver inflammation and fibrosis and the presence or absence of cirrhosis.

Treatment

All patients with chronic hepatitis C should be evaluated by a specialist for possible treatment with these agents. In general, adults less than 70 years old with evidence of active inflammation on liver biopsy and without advanced cirrhosis are good treatment candidates. Indications for treatment of patients with very mild disease on liver biopsy are less clear. Such individuals should be considered for possible participation in clinical studies. Patients with advanced cirrhosis secondary to hepatitis C should be referred for evaluation for possible liver transplantation.

Click here for information on current treatments for chronic hepatitis C. Considerable research is also devoted toward new treatments for chronic hepatitis C.

Management of Hepatitis C

NIH Consensus Statements are prepared by a no advocate, non-Federal panel of experts, based on (1) presentations by investigators working in areas relevant to the consensus questions during

a 2-day public session; (2) questions and statements from conference attendees during open discussion periods that are part of the public session; and (3) closed deliberations by the panel during the remainder of the second day and morning of the third. This statement is an independent report of the panel and is not a policy statement of the NIH or the Federal Government.

The statement reflects the panelist assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research.

Abstract

Objective.

To provide health care providers, patients, and the general public with a responsible assessment of current available methods to diagnose, treat, and manage hepatitis C.

Participants.

A non-Federal, no advocate, 12-member panel representing the fields of general internal medicine, hematology, gastroenterology, infectious diseases, medical ethics, transfusion medicine, epidemiology, biostatistics, and the public. In addition, 25 experts from these same fields presented data to the panel and a conference audience of 1,600.

Evidence.

The literature was searched through Medline and an extensive bibliography of references was provided to the panel and the conference audience. Experts prepared abstracts with relevant citations from the literature. Scientific evidence was given precedence over clinical anecdotal experience.

Consensus Process.

The panel, answering predefined questions, developed their conclusions based on the scientific evidence presented in open forum and the scientific literature. The panel composed a draft statement that was read in its entirety and circulated to the experts and the audience for comment. Thereafter, the panel resolved conflicting recommendations and released a revised statement at the end of the conference. The panel finalized the revisions within a few weeks after conference

Conclusions.

Hepatitis C is a common infection with variable course that can lead to chronic hepatitis, cirrhosis, and hepatocellular carcinoma. The course of illness may be adversely affected by various factors, especially alcohol consumption. Therefore, more than one drink per day is strongly discouraged in patients with hepatitis C, and abstinence from alcohol is recommended. Initial therapy with interferon Alfa (or equivalent) should be 3 million units three times per week for 12 months. Patients not responding to therapy after 3 months should not receive further treatment with interferon alone, but should be considered for combination therapy of interferon and ribavirin or for enrollment in investigational studies. Individuals infected with the hepatitis C virus should not donate blood, organs, tissues, or semen. Safe sexual practices, including the use of latex condoms, are strongly encouraged for individuals with multiple sexual partners.

Expansion of needle exchange programs should be considered in an effort to reduce the rate of transmission of hepatitis C among injection drug users.

Introduction

The hepatitis C virus (HCV) is one of six viruses (A, B, C, D, E, and G) that together account for the majority of cases of viral hepatitis. According to the National Health and Nutrition Examination Survey of 1988-94 and other population-based surveys, estimates of the incidence and prevalence of HCV infection have been made. Nearly 4 million Americans are infected with hepatitis C. The infection is more common in minority populations (3.2 percent of African-Americans and 2.1 percent of Mexican-Americans) than in non-Hispanic whites (1.5 percent). The incidence of hepatitis C infection appears to be declining since its peak in 1989. Currently, approximately 30,000 acute new infections are estimated to occur each year, about 25-30 percent of which are diagnosed. Hepatitis C accounts for 20 percent of all cases of acute hepatitis. Currently, hepatitis C is responsible for estimated 8,000-10,000 deaths annually, and without effective intervention that number is postulated to triple in the next 10-20 years. Hepatitis C is now the leading reason for liver transplantation in the United States.

The switch from commercial to volunteer blood donors and the development of a diagnostic blood test for hepatitis B in the early 1970s led to screening of blood donors and reduced from 30 to 10 percent the incidence of hepatitis following multiple transfusions. The remainder of these transfusion-associated cases were termed "non-A, non-B" hepatitis. In 1989, Michael Houghton and his colleagues ushered in a new era for the discovery of infectious agents when they used molecular biologic techniques to clone hepatitis C, the agent responsible for 80-90 percent of non-non-B hepatitis. This was a scientific tour de force because the technique was successful in identifying an agent that had not been visualized, grown in culture, or immunologic ally defined. Following the introduction of sensitive and effective blood tests for the detection of hepatitis C, the risk of transfusion-related hepatitis is now in the range of 1 in 100,000 units transfused.

Hepatitis C is transmitted primarily by the parenteral route, and sources of infection include injection drug use, needle-stick accidents, and transfusions of blood or blood products. Since 1990 and the introduction of tests for anti-HCV, new cases of post transfusion hepatitis C have virtually disappeared. Hepatitis C virus is not easily cleared by the host's immunologic defenses. Thus, a persistent infection develops in perhaps as many as 85 percent of patients with acute hepatitis C. This inability to clear the virus by the infected host sets the stage for the development of chronic liver disease. The range of disease states following hepatitis C infection is broad. Lastly, in contrast to hepatitis A and B, there is no effective vaccine to prevent acquisition of hepatitis C infection.

For the reasons listed above, the National Institute of Diabetes and Digestive and Kidney Diseases and the Office of Medical Applications of Research of the National Institutes of Health, along with cosponsors the National Institute of Allergy and Infectious Diseases, National Heart, Lung, and Blood Institute, National Institute on Drug Abuse, and Centers for Disease Control and Prevention, sponsored a Consensus Development Conference on March 24-26, 1997. Following 1-1/2 days of testimony by experts in the relevant fields and discussion from the audience, a consensus panel representing general internal medicine, hepatology, gastroenterology, infectious diseases, medical ethics, transfusion medicine, epidemiology, biostatistics, and the public considered the evidence and formulated a consensus statement to address the following six predefined questions:

What is the natural history of hepatitis C?

- What is the most appropriate approach to diagnose and monitor patients?
- What is the most effective therapy for hepatitis C?
- Which patients with hepatitis C should be treated?
- What recommendations to patients can be made to prevent transmission of hepatitis C?
- What are the most important areas for future research?

1. What Is the Natural History of Hepatitis C?

The Virus

The hepatitis C virus is an RNA virus of the Flaviviridae family. Individual isolates consist of closely related yet heterogeneous populations of viral genomes (quasispecies). Probably as a consequence of this genetic diversity, HCV has the ability to escape the host's immune surveillance, leading to a high rate of chronic infection. Comparing the genomic nucleotide sequences from different HCV isolates enables classification of viruses into several genotypes and many more subtypes. The extensive genetic heterogeneity of HCV has important diagnostic and clinical implications, perhaps explaining variations in clinical course, difficulties in vaccine development, and lack of response to therapy.

Clinical Course

Data on the natural history of hepatitis C are limited, because the onset of infection is often unrecognized and the early course of the disease is indolent and protracted in many individuals. Prospective cohort studies are few, are typically small, include relatively few subjects whose date of infection can be well documented (e.g., blood transfusion recipients and victims of accidental needle sticks), and have relatively short follow-up. The natural history of this disease appears to differ according to geography, alcohol use, virus characteristics (e.g., genotype, viral load), co infection with other viruses, and other unexplained factors.

Acute Infection

After initial exposure, HCV RNA can be detected in blood in 1-3 weeks. Within an average of 50 days (range: 15-150 days), virtually all patients develop liver cell injury, as shown by elevation of serum alanine aminotransferase (ALT). The majority of patients are asymptomatic and anicteric. Only 25-35 percent develops malaise, weakness, or anorexia, and some become icteric. Fulminant liver failure following HCV infection has been reported but is a rare occurrence. Antibodies to HCV (anti-HCV) almost invariably become detectable during the course of illness. Anti-HCV can be detected in 50-70 percent of patients at the onset of symptoms and in approximately 90 percent of patients 3 months after onset of infection. HCV infection is self-limited in only 15 percent of cases. Recovery is characterized by disappearance of HCV RNA from blood and return of liver enzymes to normal.

Chronic Infection

About 85 percent of HCV-infected individuals fail to clear the virus by 6 months and develop chronic hepatitis with persistent, although sometimes intermittent, viremia. This capacity to produce chronic hepatitis is one of the most striking features of HCV infection. The majority of patients with chronic infection have abnormalities in ALT levels that can fluctuate widely. About

one-third of patients have persistently normal serum ALT levels. Antibodies to HCV or circulating viral RNA can be demonstrated in virtually all patients.

Chronic hepatitis C is typically an insidious process, progressing, if at all, at a slow rate without symptoms or physical signs in the majority of patients during the first two decades after infection. A small proportion of patients with chronic hepatitis C -- perhaps less than 20 percent -- develop nonspecific symptoms, including mild intermittent fatigue and malaise. Symptoms first appear in many patients with chronic hepatitis C at the time of development of advanced liver disease.

In chronic hepatitis, inflammatory cells infiltrate the portal tracts and may also collect in small clusters in the parenchyma. The latter instance is usually accompanied by focal liver cell necrosis. The margin of the parenchyma and portal tracts may become inflamed, with liver cell necrosis at this site (interface hepatitis). If and when the disease progresses, the inflammation and liver cell death may lead to fibrosis. Mild fibrosis is confined to the portal tracts and immediately adjacent parenchyma. More severe fibrosis leads to bridging between portal tracts and between portal tracts and hepatic veins. Such fibrosis can progress to cirrhosis, defined as a state of diffuse fibrosis in which fibrous septae separate clusters of liver cells into nodules. The extent of fibrosis determines the stage of disease and can be reliably assessed. Severe fibrosis and necroinflammatory changes predict progression to cirrhosis. Once cirrhosis is established, complications can ensue that are secondary to liver failure and/or to portal hypertension, such as jaundice, ascites, variceal hemorrhage, and encephalopathy. The development of any of these complications marks the transition from a compensated to a decompensate cirrhosis.

The rate of progression is highly variable. Long-term studies suggest that most patients with progressive liver disease who develop cirrhosis have detectable ALT elevations; these can, however, be intermittent. The relationship is inconsistent between ALT levels and disease severity as judged histological. Although patients with HCV infection and normal ALT levels have been referred to as "healthy" HCV carriers, liver biopsies can show histological evidence of chronic hepatitis in many of these patients.

Cirrhosis of the Liver

Chronic hepatitis C infection leads to cirrhosis in at least 20 percent of patients within 2 decades of the onset of infection. Cirrhosis and end-stage liver disease may occasionally develop rapidly, especially among patients with concomitant alcohol use.

Hepatocellular Carcinoma (HCC)

Chronic infection by HCV is associated with an increased risk of liver cancer. The prevailing concept is that hepatocellular carcinoma (HCC) occurs against a background of inflammation and regeneration associated with chronic hepatitis over the course of approximately 3 or more decades. Most cases of HCV-related HCC occur in the presence of cirrhosis.

The risk that a person with chronic hepatitis C will develop HCC appears to be 1-5 percent after 20 years, with striking variations in rates in different geographic areas of the world. Once cirrhosis is established, the rate of development of HCC increases to 1-4 percent per year. Among patients with cirrhosis due to hepatitis C, HCC develops more commonly in men than in women and in older than in younger patients.

Extra hepatic Manifestations of HCV

Patients with chronic hepatitis C occasionally present with extra hepatic manifestations or syndromes considered to be of immunologic origin, including arthritis, keratoconjunctivitis sicca, lichen planus, glomerulonephritis, and essential mixed cryoglobulinemia. Cryoglobulins may be detected in the serum of about one-third of patients with HCV, but the clinical features of essential mixed cryoglobulinemia develop in only about 1-2 percent of patients. Chronic hepatitis C may be a major underlying cause of porphyria cutanea tarda.

Mortality

After an average followup of 18 years, a prospective study of patients who received blood transfusions showed no difference in overall mortality between HCV-infected cases and noninfected controls. Liver-related mortality, although rare, was twice as high in the cases (3.2 percent vs. 1.5 percent). A recent European study showed that survival among hepatitis C patients with compensated cirrhosis was 91 percent after 5 years and 79 percent after 10 years. Among patients developing decompensated cirrhosis, however, 5-year survival was only 50 percent.

2. What Is the Most Appropriate Approach to Diagnose and Monitor Patients?

A variety of tests are available for hepatitis C diagnosis. Tests that detect antibody against the virus include the enzyme immunoassays (EIAs), which contain HCV antigens from the core and nonstructural genes, and the recombinant immunoblot assays (RIBAs), which contain the same HCV antigens as EIA in an immunoblot format. In addition, several polymerase chain reaction (PCR)-based assays for HCV RNA have been developed to detect the RNA virus directly. Liver biopsy can determine the extent of liver injury due to HCV. Although some histological findings are characteristic of HCV infection, such as portal lymphoid aggregates, steatosis, and bile duct injury, these alone are not sufficiently specific to establish a diagnosis of hepatitis C. There are currently no reliable, readily available tests for detection of HCV antigens in the liver.

The EIA tests are reproducible and inexpensive and have been automated. They are suitable for screening low- and high-prevalence populations and as an initial test for patients with clinical liver disease. The RIBA test is most frequently used as a supplemental assay. Qualitative HCV RNA detection by reverse transcription (RT)-PCR is generally accepted as the most sensitive test, and a standardized assay has been developed. However, significant variability of results among laboratories has been reported in proficiency surveys. Clinicians should be aware of the proficiency record of laboratories performing HCV RNA testing to ensure test accuracy for their patients.

Using carefully standardized research PCR tests for HCV RNA as a reference standard, the sensitivity of the second-generation enzyme immunoassay, EIA-2, is 92-95 percent. Its specificity has not been precisely established. Studies performed to date indicate that 25-60 percent of blood donors with no risk factors for hepatitis C who are positive by the EIA-2 test are also positive by the PCR test for HCV RNA. Of low-risk donors who are both EIA-2 and RIBA-positive, 70-75 percent is positive for HCV RNA. Positive predictive values are much higher in patients with hepatitis C risk factors, elevated ALT levels, or clinical liver disease.

Practitioners frequently encounter patients suspected of having HCV infection. In low-risk populations, such as blood donors who report no risk factors for HCV (e.g., parenteral drug use, history of transfusion, multiple sexual partners), a negative EIA test is sufficient to rule out infection. However, low-risk individuals with positive EIA tests should undergo supplementary RIBA testing. If the RIBA is negative, the anti-HCV EIA result is likely to have been a false positive, and the patient is unlikely to have hepatitis C. If the RIBA is positive, the patient can be assumed to have or to have had hepatitis C. These patients can benefit by testing for HCV RNA by PCR, the result of which will indicate whether the patient has ongoing viremia or not. A single positive assay for HCV RNA by PCR confirms HCV infection; unfortunately, a single negative assay does not prove that the patient is not viremic or has recovered from hepatitis C. Followup testing for ALT levels and perhaps repeating the HCV RNA in the future may be needed. If the results of the RIBA are "indeterminate," followup testing is indicated to demonstrate whether HCV RNA is present. It is hoped that further advances in anti-HCV testing will eventually decrease the percentage of false-positive EIA and indeterminate RIBA results.

Individuals with even mildly elevated ALT levels, with or without risk factors for hepatitis C, should be tested for anti-HCV by EIA and, if positive, the results confirmed by either supplemental RIBA or qualitative HCV RNA by PCR. Obviously anti-HCV testing is very helpful in all patients with clinical liver disease.

In patients presenting with biochemical or clinical evidence of liver disease (e.g., repeatedly elevated ALT levels), a positive EIA test is sufficient to diagnose hepatitis C infection, especially if risk factors are present. A qualitative HCV RNA test can be used for confirmation. If the patient is being considered for antiviral therapy, liver biopsy is of value to assess disease severity.

Testing for serum ALT levels is the most inexpensive and noninvasive means of assessing disease activity. However, a single determination of ALT levels is not always accurate in reflecting the severity of the underlying liver disease. In most studies, there is only a weak association between ALT levels and severity of the histopathological findings on liver biopsy. Serial determinations of ALT levels over time may provide a better means of assessing liver injury, but the accuracy of this approach has not really been shown. Nevertheless, the resolution of elevated ALT levels with antiviral therapy does appear to be an important indicator of disease response, and serial determinations of ALT levels can be recommended as the general means of monitoring patients with this disease.

Testing for HCV RNA by PCR can be very helpful in initial diagnosis, but repeat testing over time is generally not helpful in management of untreated patients; almost all remain viremic, and a negative result may merely reflect a transient fall of viral titer below the level of detection rather than permanent clearance. On the other hand, repeat testing for HCV RNA during antiviral therapy can be helpful, because loss of HCV RNA with treatment is a strong predictor of a sustained beneficial response.

Testing for HCV RNA level (or viral load) by a quantitative assay, either quantitative PCR (qPCR) or the branched DNA signal amplification assay (bDNA), can provide accurate information on viral titer. In many studies, the likelihood of a response to interferon alfa has correlated with a low level of HCV RNA present before treatment. However, there is no level of HCV RNA that absolutely precludes the possibility of a response and there is little or no correlation between disease severity or disease progression and level or titer of HCV RNA. Furthermore, current assays are not as sensitive as the standard, qualitative PCR test and suffer

from lack of standardization. Thus, sequential testing for HCV RNA levels is not clinically helpful in management of patients.

At least 6 genotypes and more than 30 subtypes of HCV RNA have been identified. HCV genotype may be an independent predictor of response to interferon alfa therapy. In many studies, patients with genotypes 2 and 3 are more likely to have a sustained treatment response than those with genotypes 1a or 1b. Methods of genotyping include PCR-based techniques and, more recently, less expensive serotyping (antibody) assays. However, both genotyping and serotyping should be considered research tools and not part of a diagnostic or therapeutic algorithm in clinical practice.

Liver biopsy is considered the gold standard for assessment of patients with chronic hepatitis. When combined with serial determinations of ALT levels, liver biopsy is very helpful in judging the severity or activity of the liver disease and the stage or degree of fibrosis. Liver biopsy is recommended before treatment to assess the grade and stage of disease and to exclude other forms of liver disease or complications (such as concurrent alcoholic liver disease, medication-induced liver injury, and iron overload). However, liver biopsy is expensive and is associated with some morbidity. Therefore, serial ALT and qualitative HCV RNA testing are recommended for monitoring patients under treatment.

3. What Is the Most Effective Therapy for Hepatitis C?

Although several different forms of interferon have been evaluated in the treatment of patients with chronic hepatitis C, the bulk of available evidence pertains to the alpha interferons (interferon alfa). The efficacy of interferon alfa therapy currently is defined biochemically as normalization of serum ALT and virologically as loss of serum HCV RNA. Serum ALT and HCV RNA are measured at two time points: at the end of treatment (End-of-Treatment Response [ETR]) and 6 months post treatment (Sustained Response [SR]). Based on these markers, randomized clinical trials have demonstrated that treatment with interferon alfa benefits some patients with chronic hepatitis C. In terms of biochemical response, treatment with interferon alfa at a dosage of 3 million units administered subcutaneously three times weekly for 6 months has produced a biochemical ETR of 40-50 percent and a biochemical SR of 15-20 percent. In terms of virological response, the 6-month course of treatment has produced an ETR of 30-40 percent and an SR of 10-20 percent. The biochemical and virological improvement has been accompanied by histological improvement.

Increasing the duration of treatment to 12 months is not associated with higher biochemical or virological ETR, but the biochemical SR is increased to 20-30 percent. For patients who do not achieve a biochemical or virological ETR (nonresponders), retreatment with a standard dose of interferon alfa is rarely effective. Further therapy with newer interferons and/or higher dosages may achieve a virological SR of only 10 percent. For patients who achieve a biochemical ETR with 6 months of treatment, but who relapse during followup, retreatment for 12 months has been associated with a biochemical ETR rate of 75-85 percent and an SR rate of 30-40 percent. The benefit of treatment of longer duration is still being evaluated. It should be recognized that although interferon treatment may be associated with favorable effects on biochemical and virological markers, its effects on important clinical outcomes such as quality of life and disease progression remain undetermined.

Three months after beginning an initial course of therapy, patients who are unlikely to respond to that dosage and frequency can be identified by persistent elevation of serum ALT levels and presence of HCV RNA in the serum. In this situation, therapy should be discontinued because

the likelihood of future response is extremely low. If either HCV RNA is negative or ALT levels are normal (or both), therapy should be continued for 12 months. Nonresponders should be encouraged to participate in clinical trials directed toward this difficult-to-treat group.

Most of the clinical trials in chronic hepatitis C have evaluated interferon alfa-2b. Other trials have used interferon alfa-2a, interferon alfa-n1, consensus interferon, interferon beta, and interferon alfa-n3. All forms of interferon appear to have similar efficacy in chronic hepatitis C.

Because most patients do not experience sustained response, attempts have been made to identify individuals who are more likely to respond to therapy. The important factors associated with a favorable response to treatment include HCV genotype 2 or 3, low serum HCV RNA level (less than 1,000,000 copies/ml), and absence of cirrhosis.

Flu like symptoms (fever, chills, malaise, headache, arthralgia, Myalgia, tachycardia) occur early in the majority of patients who receive interferon, but generally diminish with continued therapy. Later side effects include fatigue, alopecia, bone marrow suppression, and neuropsychiatry effects such as apathy, cognitive changes, irritability, and depression. Relapse of drug and/or alcohol abuse may occur. Nocturnal administration of interferon reduces the frequency of side effects, and the flu-like syndrome is ameliorated by pretreatment with acetaminophen. A reduction in interferon dosage is required in 10-40 percent of patients because of side effects, and treatment must be discontinued in 5-10 percent. Higher dosages tend to be associated with higher rates of side effects.

Severe side effects are observed in less than 2 percent of patients. These include autoimmune disease (thyroid disease being most common), depression with suicidal risk, seizure disorder, acute cardiac and renal failure, retinopathy, interstitial pulmonary fibrosis, hearing impairment, and sepsis. Rare deaths have occurred due to liver failure or sepsis, principally in patients with cirrhosis.

An important side effect of interferon in hepatitis C is a paradoxical worsening of liver disease with therapy. This exacerbation of hepatitis is probably an autoimmune reaction, and it can be severe. Indeed, fatal occurrences have been reported. Thus, patients with hepatitis C whose serum ALT levels increase on therapy should be followed more carefully, and if levels rise to greater than twice the baseline, interferon should be promptly discontinued.

It is appropriate that a percutaneous liver biopsy be obtained before initiating therapy with interferon in order to assess the degree of necroinflammatory activity, the extent of fibrosis, and the presence of any other cause of liver injury. Laboratory tests that should be obtained before starting therapy include liver chemistries (serum ALT, bilirubin, albumin, and prothrombin time), complete blood count (CBC) with differential and platelet count, antinuclear antibodies, thyroid stimulating hormone, serum HCV RNA, and glucose. Monitoring during therapy should be done at 2- to 4-week intervals with serum ALT and CBC. Both serum ALT and serum HCV RNA testing should be done after 3 months to assess whether the patient is responding to therapy. This should be repeated at the end of therapy to document end-of-treatment response. Followup testing, with serum ALT and serum HCV RNA, should be done 6 months after therapy is stopped to determine whether there has been a sustained response. Followup liver biopsy is not necessary.

Disappointing results with interferon have prompted interest in new treatment approaches to chronic hepatitis C. Early work with corticosteroids, ursodiol, and thymosin has produced scant or no evidence of sustained benefit. High concentrations of iron in liver tissue may blunt the response to interferon. This has sparked interest in iron reduction therapy, through phlebotomy

or chelation, in an attempt to enhance the response to interferon. Thus far, studies of iron reduction have been inconclusive.

The adjunctive drug of most promise, at present, is ribavirin, an oral antiviral agent that, when used alone, reduces serum ALT levels in approximately 50 percent of patients. However, ribavirin by itself does not lower serum HCV RNA levels, and relapses occur in virtually all patients when therapy is stopped. Of greater promise are recent reports that the combination of interferon alfa and ribavirin leads to higher sustained virological response rates (40-50 percent) than interferon alfa alone in 6-month clinical trials. Ribavirin has not been licensed or approved for use in hepatitis C by the Food and Drug Administration. Large-scale trials of the combination in hepatitis C are now under way. Combination therapy with ribavirin and interferon has also shown promise in the retreatment of those who relapse. Hemolytic anemia has been the major side effect of ribavirin, necessitating a dosage reduction in more than 10 percent of patients.

4. Which Patients With Hepatitis C Should Be Treated?

All patients with chronic hepatitis C are potential candidates for specific therapy. However, given the current status of therapies for hepatitis C, treatment is clearly recommended only in a selected group of patients. In others, treatment decisions are less clear and should be made on an individual basis or in the context of clinical trials.

Treatment is recommended for the group of patients with chronic hepatitis C who are at the greatest risk for progression to cirrhosis. These patients are characterized by persistently elevated ALT, positive HCV RNA, and a liver biopsy with either portal or bridging fibrosis or at least moderate degrees of inflammation and necrosis.

Indication for therapy is less obvious in other groups of patients. One such group consists of patients with persistent ALT elevations, but with less severe histological changes -- that is, no fibrosis and minimal necroinflammatory changes. In these patients, progression to cirrhosis is likely to be slow, if at all; therefore, observation and serial measurements of ALT and liver biopsy every 3-5 years is an acceptable alternative to treatment with interferon. Another such group consists of patients with compensated cirrhosis (without jaundice, ascites, variceal hemorrhage, or encephalopathy), in whom current data do not definitively show that interferon therapy will prolong survival or delay development of hepatocellular carcinoma. Similarly, firm recommendations on treatment with interferon cannot be made for patients below age 18 or over age 60 because of incomplete data. In all these groups of patients, treatment decisions should be made jointly between patient and physician, after full discussion of risks and benefits. However, where possible, treatment in these instances should be undertaken in the context of clinical trials, so that data become available for future decision making.

Patients with decompensated cirrhosis should not be treated with currently available therapy for hepatitis C and should be considered for liver transplantation. Therapeutic trials for hepatitis C in these patients should be performed only in the setting of clinical trials carried out in collaboration with liver transplant centers.

Data suggest a benefit from interferon treatment with higher clearance of HCV RNA in patients with acute hepatitis C. In light of these findings, interferon treatment of patients with acute hepatitis C could be recommended.

Current studies suggest that treatment of patients with persistently normal ALT is not beneficial and may actually induce liver enzyme abnormalities. Therefore, these patients should not receive therapy outside of placebo-controlled clinical trials.

Nonspecific symptoms such as fatigue are difficult to interpret and should not influence treatment decisions. However, patients with clinical evidence of essential mixed cryoglobulinemia could benefit from long-term therapy with interferon.

Because severity of disease or progression to cirrhosis has not been conclusively related to the mode of acquisition of hepatitis C or to particular risk groups, therapy should not be denied on the basis of these factors. However, treatment of patients who are drinking significant amounts of alcohol or who are actively using illicit drugs should be delayed until these habits are discontinued for at least 6 months. Such patients are at risk for the potential toxic effects of alcohol and other drugs and also present problems with compliance. Treatment for addiction should be provided prior to treatment for hepatitis C.

Patients with chronic hepatitis C and concurrent HIV infection may have an accelerated course of disease. Therefore, patients who have stable HIV infection with good clinical and functional status should be considered for treatment, according to guidelines outlined in this statement.

Even though high HCV RNA levels or genotype 1 predict a less favorable response to therapy, treatment should not be withheld on the basis of these parameters.

Contraindications to treatment with interferon that must be carefully considered are history of major depressive illness, cytopenias, hyperthyroidism, renal transplant, and convincing evidence of autoimmune disease.

5. What Recommendations Can Be Made to Patients to Prevent Transmission of Hepatitis C?

The large reservoir of individuals infected with HCV globally provides a source of transmission to others at risk. Prior to the identification of HCV, the majority of non-A, non-B hepatitis cases were associated with blood transfusion, injection drug use, health care, employment, or sexual or household exposure to a contact with hepatitis. HCV is now rarely transmitted by transfusion because of screening tests that exclude infectious donors.

Direct percutaneous exposure is the most efficient method for transmitting HCV.In drug users, HCV infection is acquired rapidly after beginning injection drug use, with 50-80 percent of new users becoming positive for antibody to HCV within 6-12 months. Injection drug use accounts for half of all new infections annually and perhaps greater than 50 percent of chronic infections. In addition, it is thought that the majority of the rest of the cases can be explained by transfusion prior to 1990, occupational exposures to blood, hemodialysis, high-risk sexual activity (multiple partners, history of sexually transmitted diseases), and no injection illegal drug use (intranasal cocaine). Percutaneous exposures such as body piercing and tattooing are potential sources of transmission if contaminated equipment or supplies are used, although their role in transmission of HCV in the United States has not been confirmed. It is now considered that the route of transmission is unknown in less than 10 percent of newly acquired cases of hepatitis C.

Data regarding transmissibility by sexual contact have been conflicting. Based on studies in sexually transmitted disease clinics, sexual transmission appears to occur; however, even with multiple sexual partners the risk is low. The risk appears to be increased by co infection with HIV or other sexually transmitted diseases. Although transmission in long-term monogamous relationships may occur, the risk is thought to be minimal.

There is some evidence for occupational and nosocomial transmission of HCV infection. Health care workers have a higher prevalence than the general population, although many may have acquired it from other sources. However, inadvertent needle stick injuries and lack of application of universal precautions may be contributing factors. The risk of infection from needle sticks in hepatitis C is intermediate between that of HIV and hepatitis B. HCV transmission between patients in dialysis centers may be related to poor infection control practices. Although transmission from health care workers to patients has been documented, such transmission is thought to be rare.

Perinatal transmission between mother and baby has been documented, although the risk is estimated at no more than 6 percent. The risk is increased if the mother is coinfected with HIV. Although data are limited, there is no evidence that breast-feeding transmits HCV from mother to baby.

6. What Are the Most Important Areas for Future Research?

- Continued monitoring of the epidemiology of acute and chronic hepatitis C is necessary. Additional studies of the specific mode of transmission in minority groups, low socioeconomic groups, institutionalized individuals, and injection and intranasal drug users are needed, as well as more information on sexual, household, occupational, nosocomial, and perinatal transmission.
- Large-scale, long-term studies are needed to better define the natural history of hepatitis C and especially to identify factors associated with disease progression to cirrhosis. Studies of the natural history are needed in special groups, such as minorities, children, those over 60, HCV-infected patients with normal ALT, HCV-infected patients coinfected with HIV, and injection drug users. Information is also needed about the role of ultrasound and alpha fetoprotein monitoring for early detection of hepatocellular carcinoma in patients with chronic hepatitis C.
- Studies are needed on the recovery from and persistence of viral infection as well as the pathogenesis and mechanism of liver cell injury by HCV. Is damage due to cytopathic effects of the virus on the liver cell, or is it immunologically mediated? What is the mechanism of hepatic fibrosis? Can fibrosis be separated from inflammation/necrosis of the liver? Such studies would be greatly facilitated by development of suitable animal and cell culture models. The mechanism of development of hepatocellular carcinoma in patients with hepatitis C needs elucidation.
- Given the large number of persons who are already infected with HCV, there is an urgent need for effective antiviral therapeutics capable of inhibiting virus replication and stopping or delaying the progression of liver disease. A major bottleneck to the drug discovery process is the absence of a readily available cell culture system that is fully permissive for viral replication. Thus, development of such systems should be a high priority. An improved understanding of the molecular virology of HCV is also critically important to antiviral drug development. These studies should include the development of infectious molecular clones, which would allow analyses of structure-function relations among HCV nonstructural proteins that participate in the viral replication cycle.
- Alcohol ingestion clearly worsens the course of hepatitis C, but the reasons for this interaction are unknown. Studies of the interaction between HCV and obesity, diabetes mellitus, iron, and medications are also needed.
- Unresolved questions remain regarding the diagnostic tests for hepatitis C. What is the prevalence of significant liver disease among RIBA-positive, HCV RNA-negative individuals? What should be the gold standard for HCV RNA assays? What is the frequency of intermittent

viremia in untreated patients? What are the criteria for selecting patients for, or withdrawing patients from, treatment? How can the reliability of HCV RNA tests be improved? How can the dynamic range and intra-assay variability of the HCV RNA test be improved?

- Future clinical trials should expand the range of outcomes studied to include quality of life from the patient's point of view, as well as costs and survival. In addition, those trials should include minorities, patients over age 60, patients under age 18, HIV-coinfected patients, and liver transplant patients. We need to identify effective, nontoxic therapeutic agents. Clinical trials are also needed to identify optimal treatment regimens for those who do not respond to interferon therapy, or who relapse following interferon therapy. Prospective studies are needed to identify and test prospectively the factors that predict response to therapy. In addition, studies are needed of possible drug interactions, especially between the antiretroviral drugs used to treat HIV infection and those drugs used to treat hepatitis C.
- Although continued education of risk groups and screening of blood, organs, tissue, and semen remain vitally important, the key to prevention is development of an effective and safe vaccine for hepatitis C. This will require a better understanding of the molecular determinants of both cellular and humoral immunity to HCV, the nature of antigenic variation as related to viral quasispecies diversity, and the mechanism(s) by which HCV regularly eludes the host immune system and establishes persistent infection.
- Strategies should be developed to educate at-risk groups concerning transmission of disease, as well as provide access to diagnosis and treatment. It would be helpful also to evaluate the role of intranasal cocaine use as a possible route of infection.

Conclusions and Recommendations

- Individuals who have a history of transfusions of blood or blood products prior to 1990, who are on chronic hemodialysis, who have a history of injection drug use, who have had multiple sexual partners, who are the spouses or close household contacts of hepatitis C patients, and who share instruments for intranasal cocaine use should be tested for hepatitis C.
- Hepatitis C is a common infection with variable course that can lead to chronic hepatitis, cirrhosis, liver failure, and hepatocellular carcinoma. The course of illness may be adversely affected by various factors, especially alcohol consumption. Therefore, more than one drink per day is strongly discouraged in patients with hepatitis C, and abstinence from alcohol is recommended. Those addicted to alcohol or drugs should be helped to obtain treatment for their addiction so that they might qualify for anti-HCV therapy.
- An EIA test for anti-HCV should be the initial test for diagnosis of hepatitis C.In low-risk populations, a supplemental RIBA test and/or a qualitative PCR test for HCV RNA should be performed in those whose EIA test is positive. In patients with clinical findings of liver disease, HCV RNA by PCR can be used for confirmation.
- Because of assay variability, qualitative and quantitative PCR testing for HCV RNA must be interpreted cautiously. Rigorous proficiency testing is recommended for clinical laboratories performing this assay. The branched DNA signal amplification assay for viral level has been standardized, but may fail to detect low titers of HCV RNA. Sequential measurement of HCV RNA levels (viral load) has not, to date, proven useful in managing patients with hepatitis C.
- Liver biopsy is indicated when histological findings will assist decision making regarding patient management. In patients who are not treated with antiviral therapy initially, liver biopsy can be considered to assess disease progression.

- HCV genotyping and tests for HCV RNA levels (viral load) may provide useful prognostic information, especially regarding response to therapy, but at present must be considered research tools.
- Currently available therapy for chronic hepatitis C is indicated for patients who have persistently abnormal ALT (greater than 6 months),a positive HCV RNA, and liver biopsy demonstrating either portal or bridging fibrosis or at least moderate degrees of inflammation and necrosis. Patients with milder histological disease, compensated cirrhosis, or who are under age 18 or over 60 should be managed on an individual basis or in the context of clinical trials. Patients with decompensated cirrhosis should not be treated with interferon but should be considered for liver transplantation. Patients with persistently normal ALT and minimal histological abnormalities should not be treated outside clinical trials. Contraindications to treatment of patients with interferon that must be considered are a history of major depressive illness, cytopenia, active alcohol use or illicit drug use, hyperthyroidism, renal transplantation, or autoimmune disease. Therapy should not be limited by mode of acquisition, risk group, HIV status, HCV RNA level, or genotype.
- Because 12-month regimens with interferon are more successful in achieving sustained responses, initial therapy with interferon alfa (or its equivalent) should be 3 million units three times weekly subcutaneously for 12 months.
- Nonresponders to interferon therapy can be identified early by assessing the serum ALT level and presence of serum HCV RNA after 3 months of therapy. If the ALT level remains abnormal and the serum HCV RNA remains detectable, interferon therapy should be stopped, because further treatment is unlikely to produce a response. Nonresponders should not be retreated with the same regimen, but should be considered for combination therapy or enrollment in investigational protocols using different dosages or agents.
- Patients who have an end-of-treatment response to a 6-month course of interferon alfa, but then relapse, should receive retreatment with a 12-month course of interferon alfa or be considered for combination therapy with interferon plus ribavirin or other regimens, preferably in a clinical trial.
- Hepatitis A and B vaccination is recommended for all HCV-positive patients.
- Patient support groups should be encouraged, especially for those undergoing therapy, those who fail therapy, and also those recovering from addiction.

The following recommendations are made to avoid transmission of hepatitis C:

1. In health care settings, adherence to universal (standard) precautions for the protection of medical personnel and patients is essential.
2. HCV-positive individuals should refrain from donating blood, organs, tissues, or semen. In some situations, the use of organs and tissues from HCV-positive individuals may be considered. For example, in emergency situations the use of a donor organ in which the HCV status is either positive or unknown may be considered in a HCV-negative recipient after full disclosure and informed consent. Strategies should be developed to identify prospective blood donors with any prior history of injection drug use. Such individuals must be deferred from donating blood.
3. Safer sexual practices should be strongly encouraged in persons with multiple sexual partners, including the use of latex condoms. In monogamous long-term relationships, transmission is rare. Although HCV-positive individuals and their partners should be informed of the potential for transmission, there are insufficient data to recommend changes in current sexual

practice in persons with a steady partner. It is recommended that sexual partners of infected patients should be tested for antibody to HCV.

4. In households with an HCV-positive member, sharing razors and toothbrushes should be avoided. Covering open wounds is recommended. Injection needles should be carefully disposed of using universal precaution techniques. It is not necessary to avoid close contact with family members or to avoid sharing meals or utensils. There is no evidence to justify exclusion of HCV-positive children or adults from participation in social, educational, and employment activities.

5. Pregnancy is not contraindicated in HCV-infected individuals. Perinatal transmission from mother to baby occurs in less than 6 percent of instances. There is no evidence that breast-feeding transmits HCV from mother to baby; therefore, it is considered safe. Babies born to HCV-positive mothers should be tested for anti-HCV at 1 year.

6. Needle exchange and other safer injection drug use programs may be of benefit in reducing parent rally transmitted diseases. Expansion of such programs should be considered in an effort to reduce the rate of transmission of hepatitis C.

7. It is important that clear and evidenced-based information be provided to both patients and physicians regarding the natural history, means of prevention, management, and therapy of hepatitis C.

Hepatitis C: Current Treatment

By Howard J. Worman, M. D.

This page provides general information on the currently available treatment options for chronic hepatitis C. It is not an endorsement of the products by the author or by any institution with which the author is affiliated. A patient must see a doctor regarding individual treatment options

Patients with chronic hepatitis C should consult their doctors regarding possible treatment. Eligible patients should have evidence of chronic liver inflammation, diagnosed by liver biopsy, and infection with hepatitis C virus, documented by the presence of viral RNA in the blood. Not all patients with chronic hepatitis C, however, are good candidates for treatment with currently available drugs and the judgment of an experienced specialist is critical in determining which individual patients should be treatment.

The main goal of treatment of chronic hepatitis C is to eliminate detectable viral RNA from the blood. Lack of detectable hepatitis C virus RNA from blood six months after completing therapy is known as a sustained response. Studies suggest that a sustained response is equated with a very favorable prognosis and that it may be equivalent to a cure. There may be other more subtle benefits of treatment, such as slowing the progression of liver scarring (fibrosis) in patients who do not achieve a sustained response.

All current treatment protocols for hepatitis C are based on the use of various preparations of interferon alpha, which are administered by intramuscular or subcutaneous injection. Interferon alpha is a naturally occurring glycoprotein that is secreted by cells in response to viral infections. It exerts its effects by binding to a membrane receptor. Receptor binding initiates a series of intracellular signaling events that ultimately leads to enhanced expression of certain genes. This leads to the enhancement and induction of certain cellular activities including augmentation of target cell killing by lymphocytes and inhibition of virus replication in infected cells.

Interferon alfa-2a (Roferon-A; Hoffmann-La Roche), interferon alpha-2b (Intron-A; Schering-Plough) and interferon alfacon-1 (Infergen; Amgen) are all approved in the United States for the treatment of adults with chronic hepatitis C as single agents. The recommended dose of interferons alfa-2b and alpha-2a for the treatment of chronic hepatitis C is 3,000,000 units three times a week, administered by subcutaneous or intramuscular injection. Treatment is administered for six months to two years. For interferon alfacon-1, the recommended dose is 9 mcg three times a week for first time treatment and 15 mcg three times a week for another six months for patients who do not respond or relapse. During the treatment periods with any of these recombinant interferons, the patient must be monitored carefully for side effects including flu-like symptoms, depression, rashes, other unusual reactions and abnormal blood counts. Treatment with interferon alone leads to a sustained response in less than 15% of subjects. Because of this low response rate, these interferons alone are rarely used for the treatment of patients with chronic hepatitis C.

More recently peg interferon alpha, sometimes called pegylated interferon, has been available for the treatment of chronic hepatitis C. There are two preparations of peg interferon alpha that have been studied in patients with hepatitis C: peg interferon alpha-2b (Peg-Intron; Schering-Plough) and peg interferon alpha-2a (Pegasys; Hoffmann-La Roche). The differences between these two preparations are subtle and most data suggest that they are equivalent with regards to efficacy and side effect profile. Peg interferon alphas differ from the older, unmodified interferon alphas in that a polyethylene glycol (antifreeze) molecule is attached to the interferon molecule. As a result its elimination from the body is slowed and higher, more constant blood levels of interferon alpha are achieved with less frequent dosing. In contrast to unmodified interferon alpha, which must be injected three times a week to treat chronic hepatitis C, peg interferon alpha needs to be injected only once a week. With peg interferon alpha-2a alone, approximately 30% to 40% of patients achieve a sustained response to treatment for 24 to 48 weeks (Zeuzem et al. New England Journal of Medicine. 2000; 343:1666-1172; Heathcote et al. New England Journal of Medicine. 2000; 343: 673-1680).

The addition of ribavirin to interferon alpha is superior to interferon alpha alone in the treatment of chronic hepatitis C. Ribavirin is a synthetic nucleoside that has activity against a broad spectrum of viruses. In the United States, it was first approved in aerosol form for the treatment of a certain type of respiratory virus infection in children. In several studies, oral ribavirin was examined as a single agent for the treatment of adults with chronic hepatitis C. Although decreases in serum ALT activities were seen with treatment, the overall results of these studies were discouraging as sustained-responses were rarely achieved. The FDA did not approve ribavirin alone for hepatitis C. Because of its partial effectiveness, ribavirin was studied in subsequent trials in combination with interferon alpha. FDA approval of interferon alpha-2b plus ribavirin for the treatment of individuals with chronic hepatitis C who "relapsed" after previous interferon alpha therapy was based on the results of two controlled, double-blind clinical trials involving 345 subjects. "Relapsers" were defined as patients who had normal serum ALT activities at the end of up to 18 months of alpha interferon therapy with abnormal ALT activities within one year following the end of the most recent course of therapy. Subjects in these trials received either injections of interferon alpha-2b at a dose of 3 million units three times a week and either oral ribavirin at a dose of 1.0 g to 1.2 g daily or a matched placebo for 24 weeks of treatment. Six months after treatment was discontinued, 45.7% of subjects who received interferon alpha-2b plus ribavirin had undetectable serum viral RNA as compared to 4.7% who received only interferon alpha-2b.

Subsequent studies showed that the combination of interferon alpha-2b plus ribavirin is more effective in achieving a sustained response than interferon alpha-2b alone in the treatment of patients with chronic hepatitis C not previously treated with interferon. This led to FDA approval for this indication in December 1998. Results from three double-blind, placebo-controlled trials supporting this were published in 1998 (Reichard et al. Lancet. 1998; 351:83-87; Poynard et al. Lancet. 1998; 352:1426-1432; McHutchison et al. New England Journal of Medicine. 1998; 339:1485-1492). The controlled trial by Reichard et al. studied 100 previously untreated patients with chronic hepatitis C and compared 24 weeks of interferon alpha-2b (3,000,000 units three times a week) alone to the same regimen in combination with ribavirin (1.0 g or 1.2 g daily). In the interferon alpha-2b plus ribavirin group, 36% of 50 subjects had undetectable serum virus RNA 24 weeks after stopping treatment as compared to 18% of 50 in the interferon alpha-2b alone group ($P = 0.047$). Sustained responses were also significantly greater in the combination group one year after stopping treatment. Seven subjects were withdrawn from the combination group because of non-compliance or side effects compared to 3 subjects receiving interferon alpha-2b alone. The difference in response rates was greater in the subjects with higher (>3,000,000 equivalents per ml) pre-treatment concentrations of viral RNA in serum than in those with lower concentrations. In the trial by Poynard et al., 832 patients were enrolled and randomly assigned to receive either interferon alpha-2b plus placebo for 48 weeks, interferon alpha-2b plus ribavirin for 48 weeks or interferon alpha-2b plus ribavirin for 24 weeks. Sustained responses were achieved in 43% of patients who received combination therapy for 48 weeks, 35% of patients who received combination therapy for 24 weeks and 19% of the patients who received interferon alpha-2b alone. Both combination groups had statistically significant better responses than the group who received interferon alpha-2b alone. McHutchison et al. randomized 912 patients with chronic hepatitis C to receive either interferon alpha-2b alone or in combination with ribavirin for 24 or 48 weeks. The sustained response rates were 31% and 38% for those receiving combination therapy for 24 or 48 weeks, respectively, compared to 6% and 13% for those receiving interferon alpha-2b alone for 24 or 48 weeks respectively. The differences were significant between the combination and mono therapy groups. More patients in the combination group also had improvements in liver biopsy after treatment.

Currently, the FDA is considering the combination of peg interferon alpha plus ribavirin for approval for the treatment of chronic hepatitis C. As ribavirin capsules (Rebetol; Schering-Plough) are available for doctors to prescribe in the United States, many are already prescribing this combination. For eligible patients with chronic hepatitis C, a peg interferon alpha plus ribavirin is likely to be the best treatment option in the near future. Preliminary studies show that the sustained response rate is around 50% of patients given this combination for 24 to 48 weeks.

Interferon alpha, with or without ribavirin, is associated with may side effects. During treatment, patients must be monitored carefully for side effects including flu-like symptoms, depression, rashes, other unusual reactions and abnormal blood counts. Ribavirin is associated with a significant risk of abnormal fetal development and women of childbearing potential should not begin therapy until a report of a negative pregnancy test has been obtained and not become pregnant during treatment. In general, the patient probably needs to have blood tests approximately once a month, and somewhat more frequently at the beginning of treatment. Patients considered for treatment with interferon alpha-2b plus ribavirin should not have the complications of serious liver dysfunction and such subjects should only be considered for treatment of hepatitis C in specialized studies. Certain groups of patients who cannot take

ribavirin, for example those with anemia, heart disease or kidney disease, may be treated with peg interferon alpha alone.

The question of viral genotype often comes up in discussing treatment of chronic hepatitis C. Most studies indicate that genotypes 1a and 1b are more resistant to treatment with any interferon alpha-based therapy than non-type 1 genotypes. For this reason, some doctors may prescribe longer durations of treatment for patients infected with viral genotypes 1a or 1b.

In summary, the best available current treatment for chronic hepatitis C of peg interferon alpha plus ribavirin leads to an overall sustained response rate in over 50% of all patients. The sustained response rates are even better for individuals infected with non-type 1 genotypes of the hepatitis C virus. As the currently available interferon alpha-based treatments for chronic hepatitis C are associated with many side effects and effective in only about half of patients, more research is definitely needed to develop safer, more effective and cheaper drugs (see).

New and Future Treatments for Chronic Hepatitis C

Treatment of chronic hepatitis C is presently based on the use of interferon-alpha. Interferon-alpha is a protein that is given by injection, usually three times a week. The addition of ribovirin, a non-specific, orally administered anti-viral agent, improves the efficacy of interferon-alpha. Although interferon-alpha with or without ribovirin works for some patients with hepatitis C, most do not achieve a "sustained response" of undetectable virus in blood 6 months after stopping therapy. Interferon-alpha is also associated with myriad adverse events and is relatively expensive. Ribavirin may also cause side effects. Better drugs are unequivocally needed for the treatment of chronic hepatitis C. What will they likely be?

Longer Acting Interferon-alpha

The next drug available for the treatment of chronic hepatitis C will be peg interferon-alpha (sometimes called "pegylated interferon"). The active agent in peg interferon-alpha is the same old interferon-alpha. However, the protein is attached to polyethylene glycol (antifreeze), an inert compound that slows the elimination from the body. More constant blood levels of interferon-alpha are achieved with less frequent injections, usually once a week. This results in enhanced compliance and clinically superior anti-viral activity.

Published studies have shown that peg interferon-alpha alone results in "sustained response" rates of 30% to almost 40%. The side effect profile is similar to unmodified interferon-alpha. Preliminary data show that addition of oral ribavirin to pegylated interferon-alpha results in "sustained response" rates of approximately 50%. Hence, pegylation enhances the efficacy of interferon-alpha for the treatment of chronic hepatitis C.

The United States Food and Drug Administration (FDA) has recently approved peginterferon-alpha-2b (Peg-Intron, Schering-Plough) for the treatment of chronic hepatitis C. Peginterferon-alpha-2a (Pegasys, Hoffmann La Roche) will likely be approved in the near future. Within a year, the FDA will likely approve the combination of peg interferon-alphas with ribavirin. Clinical trials of peg interferon-alpha with a compound called VX-497 (Vertex Pharmaceuticals)

are also in progress. VX-497 has some features similar to ribavirin and inhibits a cellular enzyme know as inosine monophosphate dehydrogenase that may responsible for some of its effects.
An even longer acting form on interferon-alpha is currently in early stage clinical testing. This is a fusion protein between albumin and interferon alpha (Albuferon, Human Genome Sciences). Data on its clinical efficacy are not yet available. It is also probable that other long acting preparations of interferon-alpha will be developed in the next few years.

Drugs that Affect the Immune Response Against the Virus

Several drugs known as "immune modifiers" or "immunomodulators" that alter the immune response are being tested in clinical trials for chronic hepatitis C. Some are being studied along with interferon-alpha. There drugs alter the inflammatory response against liver cells infected with the virus; however, their mechanisms of action are poorly understood. Compounds of this type currently being tested in humans include thymosin-alpha-1 (Zadaxin, SciClone Pharmaceuticals) and histamine dihydrocholoride (Ceplene, Maxim Pharmaceuticals).
Therapeutic vaccines are also being developed to enhance the immune response against the hepatitis C virus. In contrast to a preventive vaccine, which is likely to be a very long way off for hepatitis C, a therapeutic vaccine is administered to already-infected individuals to stimulate the immune system to fight the infection. Several therapeutic vaccines are in preclinical development for hepatitis C. The most promising of these are DNA vaccines involving injection of DNA copies of the hepatitis C virus's RNA genome, which are taken up by certain immune system cells. These cells then express viral proteins, stimulating an immune response against the virus. These theoretically appealing therapeutic vaccine for hepatitis C remain to be shown effective in human subjects

Specific Agents against Hepatitis C Virus Proteins

A new generation of drugs to treat hepatitis C will be those designed specifically to inhibit functions of the hepatitis C virus. One target for such drugs is the hepatitis C virus RNA genome. Ribozymes are catalytic RNA molecules, some of which can cut other RNA molecules. A ribozyme (Hepatazyme, Ribozyme Pharmaceuticals) has been designed to cleave the hepatitis C virus RNA genome in a region that the virus needs to survive. Its efficacy in cutting hepatitis C virus RNA has been established in the test tube and the drug is now in early clinical trials. ISIS-14803 (Isis Pharmaceuticals) is a antisense inhibitor complementary to a conserved sequence of the hepatitis C virus RNA. This molecule binds to the viral RNA and inhibits the expression of proteins required for replication. ISIS-14803 is currently in early stage clinical trials. A small molecule known as VP-50406 (ViroPharma) has also been demonstrated to inhibit hepatitis C virus RNA in the laboratory and is in early stage clinical development. Inhibitors of a unique structure of the hepatitis C virus RNA necessary for protein synthesis, known as the internal ribosome entry site or IRES, are also under study in the laboratory.
Three favorite targets of the hepatitis C virus for pharmaceutical chemists are its N3S RNA polymerase, NS3 RNA helicase and NS5B RNA polymerase. Compounds directed against these targets are in various stages of preclinical development. The targets are all enzymes (proteins that catalyze chemical reactions) essential for hepatitis C virus replication. They are expressed in cells infected with the virus but not in mature viral particles themselves. Armed with knowledge of the three-dimensional structures of these enzymes deduced using X-ray crystallography, scientists can identify molecules that inhibit their activities.

NS3 has two parts with distinct enzymatic activities. One part is a protease that cuts a larger precursor protein encoded by the hepatitis C virus RNA into smaller functional proteins. Inhibition of NS3 would result in a failure of the virus to make the smaller proteins necessary for its replication. The other part of NS3 is a RNA helicase that unwinds the hepatitis C viral RNA. RNA unwinding is necessary for its efficient replication and translation into protein. Specific inhibitors of NS3's enzymatic activities would theoretically not influence critical host cell functions, limiting the side effect profiles. NS5B of the hepatitis C virus is an essential RNA-dependent RNA polymerase that copies the virus's RNA genome. Animal cells do not copy RNA; they make RNA copies from DNA. Therefore, specific inhibitors of the NS5B should not affect host cell processes.

Of course, one cannot accurately predict the adverse event profile of a given drug until it is tested in human. Drugs designed as best as possible against specific viral targets may still prove to have side effects. However, well-designed drugs directed against the hepatitis C virus RNA, NS3 protease, NS3 RNA helicase and NS5AB RNA polymerase are very likely to be more effective and better tolerated than currently available treatments for hepatitis C. The timeline from the laboratory to the clinic is likely to be several years.

Drugs that Affect the Liver's Response to Injury

Chronic hepatitis (inflammation of the liver) can lead to fibrosis (scarring) and cirrhosis (fibrosis plus abnormal regeneration of liver cells). Virtually all of the serious complications of chronic hepatitis C result from cirrhosis. For this reason, several groups are developing drugs to prevent fibrosis and cirrhosis. Recent data suggest that fibrosis, and perhaps even early cirrhosis, may be reversible to some extent.

Very little is known about why the liver becomes fibrotic in response to chronic inflammation. Furthermore, it is not known why some individuals infected with the hepatitis C virus develop significant fibrosis or cirrhosis while others never do. Some drugs that may prevent liver fibrosis and cirrhosis are in early clinical trials. IP-501 (Interneuron Pharmaceuticals) is an orally administered anti-fibrotic compound being tested for the treatment of including alcoholic and hepatitis C-induced cirrhosis. Animal models suggest that IP-501 is effective in preventing the development of alcohol-induced cirrhosis, however the exact mechanism by which this compound works is not fully understood. Clinical trials of IP-501 in alcohol-induced liver disease and chronic hepatitis C are underway. Preliminary studies in humans have also shown that interleukin-10 (Schering-Plough) may prevent liver fibrosis in chronic hepatitis C. Clinical trials of interleukin-10 need to be carried out on a larger scale to demonstrate safety and efficacy. Increasing scientific effort is being devoted to the study of liver fibrosis in response to injury and exciting new drugs to prevent it will hopefully be available someday.

Re-grow a Damaged Liver?

When a liver is damaged beyond repair, the only hope today is orthotopic liver transplantation. However, considerable research effort is being devoted to the study of stem cells. Stem cells are undifferentiated cells, such as those in the early embryo that can be directed to form many different tissues of the body. In the past few of years, investigators have shown that liver stem cells reside in the bone marrow. Theoretically, these bone marrow stem cells can be isolated and grown into hepatocytes and bile duct cells in the laboratory. Some animal studies have also shown that expression of the enzyme telomerase in liver cells enhance their ability to regenerate. Although considerable challenges remain to be overcome, this early stage research provides promise that liver transplantation may someday be a thing of the past.

Pharacogenomics

Some drugs work in some patients but not in others. Similarly, some drugs have side effects in some patients while others tolerate them well. For example, less than half of patients with chronic hepatitis C have a "sustained response" to treatment with interferon-alpha and many experience intolerable side effects. Most of this is a result of different individuals' different genetic make-ups.

Pharmacogenomics is the science of understanding the correlation between an individual patient's genetic make-up and response to a drug. The discipline is evolving rapidly as a result of the extensive work recently completed on sequencing the entire human genome. Phamacogenomics aims to identify genetic markers that predict response to a drug. The genetic markers commonly assessed are known a single nucleotide polymorphisms (SNPs) and haplotypes. SNPs are changes at a single base of DNA between individuals. Haplotypes are linear arrays of slightly different forms of particular genes on a chromosome. By studying populations of patients and their responses to a drug, inheritance of a collection of SNPs or different haplotypes can be correlated with successful treatment, unsuccessful treatment or development of side effects. This knowledge can them be used to "customize" drug therapy for a particular patient based on first examining their DNA.

HEPATITIS B VIRUS INFECTION IN GENERAL

Prof. Dr. Mansoor Ahmad, I.F.

Research Institute of Pharmaceutical Sciences,
Faculty of Pharmacy,
University of Karachi, Karachi-75270

Introduction

Hepatitis B virus (HBV) is responsible for the cause of hepatitis among many types of hepatitis and this virus alone has infected approximately 400 million people through out the world, making HBV one of the most popular human pathogen. Liver cancer or hepatocelluar carcinoma (HCC), one of the most common cancers affecting human body, is primarily related to chronic HBV infection. Recent reports on HBV & HCC show the well-established relationship and rate of incidence but the mechanism by which HBV transforms hepatocytes remains unclear. Before HBV can transform a cell, the virus must first infect it. However, the mechanism through which HBV enter hepatocytes has not been resolved despite further understanding of the viral protein involved.

Vaccines are available against HBV, but they may not be 100% effective against all variants of HBV. Furthermore, there is no cure for individuals already infected. Much more research is needed before we fully understand and control the spread of this infectious agent.

HAV is considered predominantly transmitted via the fecal-oral route while HBV is believed to primarily transmit parentally. In 1963, when a research was carried out for the search of polymorphic serum proteins, Blumberg discovered a previously known protein in the blood of an Australian aborigine [1]. This protein was denoted as the Australia (Au) antigen. It becomes apparent that this serum protein is related to HBV. It becomes clearer in 1968 when other researcher like Prince, Okochi and Murakami recognized Au antigen (now known as HBs Antigen), found only in the serum of HBV infected person [2,3]. In 1973 Dane reported the presence of virus-like particles in the serum of patients suffering from hepatitis B [4]. Later these particles were recognized as hepatitis B virus. The non-related hepatitis viruses were discovered later, but scientists retained the name HBV.

Kaplan (1973) and Robinson (1974) discovered the viral nature and HBV genome [5,6]. HBV has been estimated by World Health Organization (WHO) to infect over 2 billion people Worldwide. Approximately 500 million are chronic careers.

Pathogenesis of HBV

The pathogenesis of both acute and chronic viral hepatitis is slowly being unraveled. Thus, far most data show that members of the hepadnaviridae family are not highly cytotoxic per se. It

appears that the intense levels of cellular death are primarily due to host defense mechanism against HBV infection [7].

The reports of Kaplan (1973) explain the nature of this viral particle when he detected the endogenous DNA-dependent DNA polymerase with in virus core [5]. On the basis of the discovery of DNA polymerase Robinson detected and characterized the HBV genome [6]. The HBV genome is unique in the world of viruses due to its compact nature, use of overlapping reading frames and dependence on a reverse-transcriptional step, though the virion contains primarily DNA. Therefore, HBV becomes the archetype of hepadnavirus family, Hepadnaviridae.

HBs Ag (hepatitis B surface antigen) from HBV has already been detected in other primate but human remain its primary host. Recent researches show many related viruses in other species, but each particular virus is specific to its species. The human HBV archetype includes in hepadnaviridae family, which consists of Duck hepatitis B virus (DHBV), Ground squirrel hepatitis virus (GSHV), Snow goose hepatitis B virus (Sg HBV), Woodchuck hepatitis virus (WHV), and Wooley monkey hepatitis virus (Wm HV).

Transmission of HBV is primarily through blood and/or sexual contact, through other methods of transmission. The larger reservoir of infected individuals sustains a satellite virus known as the hepatitis D virus (HDV). HDV can only replicate in cells already infected with HBV since HDV uses hepatitis B surface proteins to package its own RNA. However, the nature of HDV is quite different from HBV.

Signs and Symptoms of HBV

Acute HBV infection can be divided into four different stages i.e. a) incubation period, which is the time between initial viral entry into the cell to first day of symptoms, b) pre-icteric or prodromal period, c) icteric period, and d) recovery period. The symptoms of acute HBV infection usually vary and depending on individual to individual. Many children and some adults infected with virus but never show any remarkable symptom. In general often-infected individual experience a certain level of jaundice, which leads to develop soon after the virus can be detected in the blood. Usually jaundice is preceded by mild fevers, fatigue, malaise, loss of appetite and some time nausea and vomiting.

During icteric period or blood borne phase the urine of infected person become dark golden brown and this is often followed by the lightening of stool as well as the yellowing of the skin, typically seen in jaundice.

There are some common signs and symptoms that suggest the patient (sufferer) may have liver problem. But, however, not all liver problems are related to HBV. Hepatitis A, C, D, E, G viruses as well as alcohol, chemical bacterial and other conditions can damage the liver. The following are the common symptoms of liver damage:

a) yellow discoloration of skin and/or eyes

b) abdominal swelling or sever abdominal pain
c) prolong itching of the skin
d) very dark urine
e) pale stool
f) passage of bloody or tar-like stool and
g) chronic fatigue, nausea or loss of appetite

If somebody suspects that he/she has above-mentioned conditions, it is strongly recommended to take advise from doctor and go for blood & other tests.

Transmission of HBV

HB Virus is usually present in the blood of infected individuals; therefore, it can also be detected in the body fluids including urine, saliva, nasopharangeal fluids, semen and menstrual fluids [8, 9]. HBV does not occur in feces, may be due to inactivation and degradation with in the intestinal mucosa and/or by the bacterial flora [10].

Transmission of HBV is usually occur most effectively through precutaneous introduction that is possible through the use of infected (HBV) needle, sexual contact, children through mothers, living with active HBV carrier [11].

High Risk Groups in HBV infection are:

a) individual living in close proximity to a known infected individual
b) user of intravenous drugs, particularly those who share their needles
c) individuals who have multiple sexual partners
d) health care workers i.e. doctors, dentists, paramedics, nurses etc.
e) cleaning staff in health care facilities
f) staff of institutions for people with developmental disabilities
g) fire fighters
h) police officers
i) mortuary attendants
j) day care worker
k) any one who may/has come into contact with human body fluid from an unknown or known HBV carrier source

Diagnosis of HBV by Blood Tests

Several methods of serological assays are in use for the detection of viral infection as well as the differentiation of chronic and acute HBV infection. But the most sensitive and specific methods used commercially for diagnosis purpose are radio-immuno-assay (RIA), and enzyme-linked immuno-sorbent-assay (ELISA). In these bioassays specific antibodies are used against various HBV proteins and and can be detected as HbsAg protein (as low as 0.25 ng/mL and anti-HBs

antibodies at a level of 1 ml U/mL). PCR has also been used in detecting low levels of HBV DNA present in both blood and liver tissues.

Hepatitis B Virus Blood Test Results and their Interpretation

HBsAg	Anti-HBs	Anti-HBc	Interpretation
+ve	-ve	-ve	early acute HBV infection
+ve	+ve or –ve	+ve	acute or chronic HBV infection
-ve	+ve	+ve	previous HBV infection & current immunity to virus
-ve	-ve	+ve	Not Clear, may be due to previous HBV infection, low level HBV infection or false-positive/non-specific reactions, if present anti-HBs helps validate anti-HBc reactivity
-ve	-ve	-ve	liver toxicity due to some other agent than HBV
-ve	+ve	-ve	vaccination

Other Biochemical tests in support of above-mentioned tests are:

1. Serum Glutamic-Oxalocetic Transaminase (SGOT) or Aspartate Aminotransferase (AST): This is an enzyme usually present in heart, kidney, liver, muscles and pancreatic tissues. Upon damage the tissue releases it and increases the level in blood. It can be detected with specific test. During pregnancy and deficiency in vitamin B decreases it actual level in blood. Its normal range in blood is 5–54 U/L.

2. Serum Glutamic-Pyruvic Transaminase (SGPT) or Alanine Aminotransferase (ALT): This enzyme occurs mainly in liver but it has also been detected in heart, muscles and other tissues in negligible amount. Its increased level in blood indicates liver damage, kidney infection, chemical toxins or even cardiac infarction. Its range in blood is 0-36 U/L.

3. Alkaline Phosphatase: This is also an enzyme usually occur in bone and liver tissues. Its increased level in blood indicates liver and bone marrow damage. Its rang in blood level for adults is 40-120 U/L and for children is 40-400 U/L.

4. Gamma Glutamyltransferase (γGT): This enzyme chiefly found in liver cells and is quite sensitive to alcohol consumption. This enzyme level increases in blood when there is a liver disease, bile-duct obstruction and/or drug abuse. Its range in blood level is 3-59 U/L.

5. Lactose Dehydrogenase (LDH): This enzyme is primarily found in brain, heart, kidney, liver, lungs and skeletal muscles tissues. Its increased level in blood shows cells death and decreased level malnutrition or low tissue organ activity. Its range in blood level is 135-225 U/L.

6. Albumin: This is a protein and is synthesized in liver. It is involved in maintaining the blood protein base level. Liver damage or disease may result in decrease of level of albumin in blood. Its range in blood is 35-50 g/L.

When albumin level drops to extremely low levels, fluid from the blood may leak into surrounding tissues, resulting in swelling/edema.

7. Bilirubin-Total (non-neonatal; conjugated and unconjugated): Bilirubin is a byproduct of RBCs breakdown. It is actually produced when the hemoglobin ring is opened through other enzyme activities. Bilirubin is typically excreted into the bile, giving bile its pigmentation. Increased levels are associated with liver disease, mononucleosis toxicity due to some types of drugs and hemolytic anemia. Its range in blood is 1-17 □ mol/L.
8. Bilirubin-Direct (non-neonatal-conjugated): Same as above but its range is 0-5 □ mol/L.

9. Prothrombin Coagulation Time (PT): Its usual time is 10-12 seconds, but the changes take place in serological pattern during acute HBV infection are given above in graphic form.

Treatment and Prevention

Treatment of Acute HBV infection: Recent treatment of HBV has no specific medicine for the cure of acute viral hepatitis. In most of hepatitis and liver damage cases minimum consumption of alcohol is recommended, if not stopped completely. This helps in the recovery of liver. In some cases adrenocorticosteroids are recommended, but no effect has been recorded for hidden HBV infections. It has also been observed that use of steroid in early treatment of HBV infection may result in the development of persistent infection. Therapeutic affectionness of interferon use on the prognosis and course of acute HBV infection remain unknown.

Treatment of Chronic HBV infection: In this case a number of methods are in use, but the objective of all these treatments are:

a) to eliminate infectivity and transmission of HBV to others,

b) to arrest the progression of liver disease and improve the clinical prognosis, and

c) to prevent the development of hepatocellular carcinoma (HCC).

Nowadays there are many other treatments in use, but the most commonly used treatment is Interferon alpha, but most recent is lamivudine (3TC) being looked at as potential therapeutic agent. The other agents are as follows and they are still in experimental stages.

ANTIVIRAL:

1. Acyclovir (Zovirax) Glaxo-Wellcome

2.	Adefovir	(GS 840)	Gilead Science Inc.
3.	Adenine	Arabinoside	ARA-AMP
4.	Famciclovir	(Famvir)	Smithkline Beecham
5.	Ganciclovir	(GanciclovirIV)	Roche-Syntex
6.	Lamivudine	(3TC, Epivir, Zeffix)	Glaxo-Wellcome
7.	Lobucavir		Bristal-Myers-Squibb
8.	N-acetyl-cysteine		

IMMUNE SYSTEM MODULATOR:

1.	Hepagene		Medeva
2.	Interferon Alpha		
3.	Thymosin Alpha	(Zadaxin)	SciClone Pharmaceuticals

MIXED TREATMENT:

1. Interferon Alpha + Famciclovir
2. Thymosin Alpha (Zadaxin) + Famciclovir
3. Thymosin Alpha (Zadaxin) + Lamivudine

ALTERNATIVE TREATMENT:

1. Dandelion Roots
2. Liquorice Roots
3. Milk Thistle (Silymarin)
4. Selenium
5. Vitamin E (Cod liver oil)

LIVER TRANSPLANTATION: Liver transplants are recommended when there is an extensive liver damage due to viral or non-viral causes. However, there are many risk factors in liver transplantation for example transplanting a liver into a chronic HBV patient present the like-hood that newly transplanted liver may become re-infected. Transplant operations are relatively expensive and every hospital can not perform such operation.

To overcome the transplant problem, the scientists are trying to use animal organ or grow new liver cells of the same individual for transplant. However, this technology is still in its initial development stage.

DIET CONTROL TREATMENT: To minimize any excessive damage a balance diet is necessary. This helps in fast liver recovery.

1. Nutrition and balance diet means food from each of the food groups.
2. No in take of deep-fried and fatty food.
3. Minimize or stop alcohol consumption.

4. Minimize consumption of smoked, cured and salted food, use lemon juice, onion vinegar, garlic, pepper, cloves etc.
5. Consumption of meat and seafood should be reduced since digesting/processing these form of food can further make load (tax) on the liver.
6. Use bread and cereals, these provide carbohydrates, niacin, thiamin, riboflavin and fibers.
7. Use fruits and vegetables that provide vitamin A, vitamin C, fiber and folacin.

8. Milk and milk products provide calcium, riboflavin, niacin, folacin, vitamin A and B12.
9. Increased intake of high-fiber food (i.e. fresh fruits and vegetables, whole grain, breads, rice and cereals etc.).
10. Avoid to-take uncooked or half-cooked food that contains harmful bacteria, and other toxic substances.

PREVENTION FROM HBV ATTACK

a) Universal Blood and Body Fluid Prevention: As a precaution all body fluids and blood should be treated (cleaned) prior to use as if they are infected with HIV, HBV, malaria and other blood borne-pathogens. Gloves and other protective materials should be used during the handling of such kind of material. Hands and other open areas of body should be washed regularly. Needles and other sharp/pointed objectives should be handled with care and discard with proper method.

In laboratories, hospitals and home the suspected contaminated surfaces should be disinfected and cleaned with suitable disinfectants, later used material should be discarded according to prescribe methods. Usually0.5 % sodium hypochlorite, 2% aqueous alkalinized derivatives are used as germicide and disinfectant.

a) Vaccination: Most recent method to prevent HBV infection is through vaccination. The most common vaccines available in market are obtained from recombinant technology (recombinant yeast source). Yeast cells generate small hepatitis B surface protein (SHBs) and the expression of this protein by yeast results in SHBs particle formation. However, yeast does not release particles until disruption of yeast is not performed. On disruption the yeast cells liberate the produced spheres into the solution. The particles are then purified through clarification, ultra-filtration, chromatography and ultra-centrifugation. The purified particles are then absorbed onto aluminum hydroxide to which thimersal is added to preserve the solution.

Recombinant yeast derived vaccine producing pharmaceutical companies, like SmithKline-Beecham (Engerix-B), and Merck & Co. (Recombivax HB), are usually giving two years expiry date to their products with special instruction (the vaccine should not allow to keep in frozen condition, because it decreases/minimizes the immunity). Engerix-B and Recombivax HB are chemically similar in structure with 2% yeast remaining in solution. As both are yeast derived, therefore, S-protein is not glycosylated, because yeast does not

possess the post translation mechanism, but both drugs are quite effective in immunization against various form of HBV.

There are many other forms of vaccine/immunization but the most common and effective ones are Engerix-B & Recombivax HB. There are two vaccination schedules 0, 1 and 6 months and 0, 1, 2, and 10 months. It is also recommended that a booster dose be taken after every 5 to 7 years of initial dose.

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