HEPATITIS C

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HEPATITIS C

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Abstract

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Hepatitis C infection results in significant morbidity and mortality due to its high (80%) rate of chronicity (Alter, 1995). Annually, 10,000 deaths are estimated. The mutations of the hepatitis C virus during viral replication could be responsible for the high percentage of chronic cases, as well as impacting on therapeutic efficacy, vaccine development and accuracy of diagnostic testing (Bukh, Miller & Purcell, 1995).

Serologic assays, first developed in 1989, made it possible to diagnose hepatitis C. Identification of factors which contribute to the transmission of hepatitis C virus is incomplete. Also, prevalence rates of infection vary due to its vague symptoms and limitations of assays. Chronic viral hepatitis induces hepatocyte inflammation, injury and necrosis, which can lead to cirrhosis or cancer. Chronic hepatitis C is now the primary reason for hepatic transplantation in the United States.

There is no supportive treatment for acute hepatitis C. Standard treatment for chronic hepatitis C consists of alpha interferon for 52 weeks. Treatment response is determined by ALT levels and HCV RNA titers, and is assessed three months after initiation of therapy.
Only 25% of patients will have a sustained response one to seven years after completion of therapy (Fried & Hoofnagle, 1995). Improved response rates may be achieved with combination therapy with ribavirin. Other therapeutic options are being investigated.
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HEPATITIS C

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Epidemiology

Hepatitis C is an RNA virus whose annual incidence of new cases has decreased since 1989. Hepatitis C has been estimated at 30,000 per year in the United States (Centers for Disease Control, 1997). The major impact of this infection is due to its high rate of chronicity. Eighty percent of those with an acute hepatitis C infection develop chronic infection, resulting in significant morbidity and mortality (Alter, 1995). Currently, four million Americans are believed to have chronic hepatitis C. An estimated 10,000 deaths per year are due to hepatitis C infection. Without effective treatment, this is expected to triple in the next decade (Najm, 1997).

Viral Pathogenesis

Advances in molecular studies facilitated the cloning and sequencing of the hepatitis C virus. Consistent with studies of other RNA viruses, hepatitis C virus was found to mutate during viral replication, resulting in genetic heterogeneity (quasispecies). Different regions of the genome have varying rates of mutation. The mutations could be responsible for the inability of the immune system to eliminate the hepatitis C virus, and the high percentage of chronic cases which develop. Mutations may also be a factor in the efficacy (or lack) of treatment with interferon, and may impact vaccine development, and the sensitivity/specificity of assays used for diagnosis (Bukh, Miller & Purcell, 1995). There is no vaccine available to protect against hepatitis C.
Analyses of genetic sequences of hepatitis C virus have identified 9 major groups and 30 subgroups (Bukh, Miller & Purcell, 1995). There are several nomenclatures used for these groups. The most commonly accepted lists major hepatitis C virus types by Arabic numerals, and subgroups by numerals and lower case letters, all in order of discovery.

Prior to 1989, hepatitis C virus, known as the blood-borne virus, was diagnosed by eliminating hepatitis A and B from the differential diagnosis (Sjogren, 1996). There are now several tests available for the serologic diagnosis of hepatitis C virus. The first of these was developed in 1989 in California, and was used to determine the presence of antibody to hepatitis C (anti-HVC, Sjogren, 1996). Anti-HCV appears 2 to 6 months after initial infection and can persist for years, indicating that infection has been present at some time (Najm, 1997). The antibody is unable to eradicate the virus or provide immunity for a subsequent infection.

Diagnostic Tests

The first assays developed included enzyme-linked immunosorbent assay (ELISA) and the recombinant immunoblot assay (RIBA). Both were poor tests due to their low sensitivity and specificity. The ELISA made possible mass screening of blood donors, who were a significant contributor to hepatitis C virus transmission prior to 1989 (DeMedina & Schiff, 1995). This resulted in a dramatic decrease of new cases of hepatitis C virus by this route. The ELISA II (second generation) is the most commonly used test for initial diagnosis of hepatitis C virus (Sjogren, 1996).
The RIBA I test consists of two hepatitis C virus recombinant antigens on nitrocellulose strips. If antibody is present in the serum, it will react with the antigens. The test is considered positive (reactive), if antibody reacts with two or more bands on the strip. If only one band is visible the result is considered indeterminate, and lack of any visible bands constitutes a negative reaction. The antibody is not detectable for 22 weeks after initial infection and up to 15 weeks after the onset of clinical hepatitis with the first generation assays.

The next generation of assays developed had much improved their degree of sensitivity and specificity. The second generation assays are able to detect antibody at 10 to 18 weeks (4 to 12 weeks sooner than first generation), and as soon as 12 weeks after the onset of clinical disease. RIBA II uses the same two antigens from RIBA I and two other hepatitis C virus antigens. It is considered a supplementary test to confirm diagnosis. Comparable to RIBA II is the Matrix test hepatitis C Virus Dot Blot Immunoassay, also used as a supplemental test to detect anti-HCV. RIBA III (third generation) is not yet approved for use. Consistent with RIBA I and II, it utilizes additional antigens to test for reactivity. Time periods for detection of antibody by RIBA III has not yet been established.

Hepatitis C virus RNA (HCV RNA) testing allows for earliest detection of hepatitis C virus, as soon as 1 to 3 weeks after initial infection, which is prior to antibody production or elevation of aminotransferase. This test is recommended for use to confirm viremia when ELISA is positive. If ELISA is positive but HCV RNA is negative, there probably has been recovery from the initial infection. In addition to early detection, benefits of HCV RNA include its ability to determine
dose and duration of therapy, as well as to detect infection in immunocompromised or immunosuppressed patients who may have antibody titers too low for detection by other methods. It can also be used to document perinatal transmission of hepatitis C virus, and can be used on serum or tissue from liver biopsy (DeMedina & Schiff, 1995).

Tests for HCV RNA include branched DNA (bDNA), which has a sensitivity of 95%, and is a second generation assay. Other tests are Amplicor, a polymerase chain reaction (PCR) which amplifies the HCV RNA, and Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR), a quantitative test which amplifies viral DNA to make detection possible. The latter is used to monitor viral load and is considered the "gold standard" against which other assays are measured (Table 1).

Diagnosis of hepatitis C virus is initially based on ELISA, and confirmed with supplemental assays (RIBA II or Matrix) or HCV RNA testing before determination of therapy is made (DeMedina & Schiff, 1995). A positive ELISA II with risk factors for hepatitis C virus is diagnostic. Confirmation is necessary, if ELISA II is positive with no identifiable risk factors (Najm, 1997), or if ELISA II is negative in the immunocompromised patient (Figure 1). A positive diagnosis necessitates liver biopsy, the only reliable indicator of the degree of pathology. This is essential to rule out other possible differentials of liver disease. Vaccination against Hepatitis A and B should be offered to these patients in order to avoid additional insult to the liver (National Institutes of Health, 1997).
Determination of eligibility for treatment can generally be based on Alanine aminotransferase (ALT) levels and biopsy results. A normal ALT with minimal histologic abnormalities by liver biopsy every 3 to 5 years is considered sufficient. Those with elevated ALT levels and fibrosis demonstrated by biopsy should be considered for pharmacologic treatment (Morbidity and Mortality Weekly Report, 1998). Patients with decompensated cirrhosis would not benefit from combination or monotherapy and organ transplant must be considered (NIH Consensus, 1997).

ALT rises within 50 days of initial infection to a greater degree than aspartate aminotransferase (AST), but may be normal in up to 30% of infected patients (Scotiniotis, Brass & Malet, 1995). Importantly, transaminase levels do not correlate with degree of pathology present.

**Prevalence and Transmission**

There has been difficulty ascertaining the true prevalence of hepatitis C due in part to its subclinical or asymptomatic presentation, as well as the limitations of the available laboratory assays. Surveys have found prevalence rates from 1.4% to, as high as 21%. Future refinement of assays are necessary to obtain a clearer picture of the true prevalence rate. While hepatitis B is responsible for a much greater percentage of acute hepatitis (43%) than hepatitis C (21%), 80% of those with acute hepatitis C develop chronic hepatitis, while only 5% of acute hepatitis B develop chronic hepatitis (Alter, 1995). Thus, chronic hepatitis C has become much more prevalent.
It has not yet been completely determined which factors contribute to transmission of hepatitis C virus (Table 2). There are high-risk factors which have been shown as the mode of transmission for this blood-borne disease (Figure 2), such as intravenous drug use (IVDU) and transfusion recipients, including hemophiliacs, but there is a large infected population for which route of transmission is unclear. Parenteral transmission has been ruled out in as many as 50% of these cases and until further research can identify the specific mode of transmission these cases are labeled "sporadic", and limits our ability to prevent transmission (Table 3). There is no increased risk for homosexual practices. Body fluids shown to contain HCV RNA by PCR include saliva, urine, seminal fluid, ascites, and breast milk, although breast feeding is not contraindicated.

Studies in the Eastern hemisphere identified two age groups with a higher prevalence of hepatitis C infection. Highest infection rates occurred in older populations in Japan, Taiwan and Yemen, while in Australia, where the major route of transmission is intravenous drug use, the peak occurred in the 30-to 40-year-old group. Use of intravenous drugs for more than 10 years revealed a 90% incidence of hepatitis C (Mansell & Locarnini, 1995). Prevalence of hepatitis C infection in Japan is estimated at 2.3 million (1993), and in Australia at 100,000 (Mansell & Locarnini, 1995). Due to the asymptomatic nature of the infection, and problems with sensitivity and specificity of assays, it is impossible to determine firm statistics at this time.
Clinical Manifestations

Acute hepatitis C is asymptomatic in 75% of cases (Najm, 1997). The incubation period of 6 to 8 weeks may be followed by nonspecific systemic symptomatology such as fatigue, malaise, hepatomegaly, and fever (34%), jaundice (20 to 30%), anorexia and abdominal pain (38%), and transaminase levels elevated 2 to 8 times the normal range of 10-35 IU/L (Najm, 1997).

Hepatitis C is considered chronic when infection is present more than 6 months. As yet there is no consensus on how best to categorize or label chronic hepatitis C; i.e. mild, moderate or severe, versus using descriptions based on etiology, grade and stage. The chronic phase is typically asymptomatic until there is progression to cirrhosis, liver failure or hepatocellular carcinoma.

Since the development of serologic tests for antibody to hepatitis C virus in 1989, it has been determined that up to 90% of cases of non-A, non-B hepatitis are due to the hepatitis C virus (Goodman & Ishak, 1995). Consequently, research completed since the 1970’s on the pathologic effects of non-A, non-B hepatitis can be applied to the growing study of hepatitis C virus (Goodman & Ishak, 1995).

Pathophysiologic changes seen in HCV

Chronic viral hepatitis induces hepatocyte inflammation, injury and necrosis. Progression of the disease leads to fibrosis, and if severe, eventually to cirrhosis. Cirrhosis consists of repeated cycles of fibrosis and regeneration. Cirrhosis occurs in 20% of patients within approximately 20 years. Rarely, cirrhosis can develop within 5 years (Najm, 1997). The development of cirrhosis increases the
risk of hepatocellular carcinoma (HCC) by 1 to 4% per year. The projected course of development of HCC is 30 or more years.

The typical pathology associated with hepatitis C is not absolutely definitive and may confound correct diagnosis. Histopathologic changes characteristic of chronic hepatitis C are not specific for this virus and are variable in presentation. Included are "steatosis, sinusoidal inflammatory infiltrates, prominent kupffer cells, lymphoid follicle formation and bile duct epithelial changes" (Goodman & Ishak, 1995, p. 76). Alcohol consumption negatively affects the course of illness. Chronic hepatitis C is now the primary reason for hepatic transplantation in the United States.

Syndromes associated with chronic hepatitis C include arthritis, lichen planus, glomerulonephritis, essential mixed cryoglobulinemia and porphyria cutanea tarda (Davis & Lau, 1997). Manifestations of more advanced liver disease may include spider angiomas, palmar erythema, hepatosplenomegaly, muscle wasting and edema. Portal hypertension contributes to the development of anorexia, varices and ascites.

Treatment

There is no treatment for acute hepatitis C. Antiviral therapy used at this stage is considered experimental. Recovery is determined by a negative qualitative HCV RNA in serum and normalized ALT.

The goal of treatment of chronic hepatitis C is to eliminate the virus and treat the hepatic inflammation and fibrosis to prevent progression. Interferon is produced by the body in response to viral and bacterial infections and is known
to have antiviral and immunomodulatory properties. Produced synthetically since the 1980s, recombinant alpha interferon was initially used for treatment of hepatitis C in 1986 (Scotiniotis, Brass & Malet, 1995). Standard treatment consists of 3 million units by subcutaneous injection 3 times per week. Duration of therapy was initially recommended to be 24 weeks, but studies have shown that a longer course of treatment may have a higher sustained response rate (Scotiniotis, Brass & Malet, 1995). Accordingly, treatment is now recommended for 52 weeks (National Institutes of Health, 1997).

Treatment response is categorized in one of three ways and is determined by ALT levels and HCV RNA titers. Nonresponders (25%) have no improvement within 3 months of initiation of therapy. Partial responders (25%) have transient improvements which worsen at a later point of therapy. Complete responders return to normalized ALT levels and diminished or eradication of HCV RNA by the end of therapy. Of the 50% of patients who are complete responders, one-half of these will relapse within 1 year of cessation of therapy with an elevated ALT and recurrence or increase of HCV RNA titer (Brady, 1997).

Overall, 25% of patients who receive alpha interferon will have a sustained response with normalized ALT and decreased or absent HCV RNA 1 to 7 years after cessation of therapy (Fried & Hoofnagle, 1995). Ongoing studies will hopefully better define the most efficacious dose and duration of therapy. There is no clear consensus on parameters to determine who should receive retreatment with alpha interferon, if initial therapy does not result in a sustained
response. Some studies have shown a response to retreatment in 25 to 30% of patients (Scotiniotis, Clifford & Malet, 1995).

It is unclear at this time which factors can help predict a sustained response rate. Initial analysis has implicated viral genotype, histology of biopsy, shorter disease duration, lower HCV RNA titers (level of viremia), and low serum iron (King, 1996). Those factors which have not been predictive of a sustained response rate include ALT level, anti-HCV titres, gender and route of transmission (Dusheiko, Khakoo, Soni & Grellier, 1996).

Flu-like symptoms such as fever, chills, myalgia, and fatigue may occur within hours of interferon administration and last 4 to 12 hours. Pretreatment with acetaminophen may lessen these effects. Continued therapy may result in a flu-like syndrome, neutropenia with a resultant increased susceptibility to bacterial infections, thrombocytopenia, mild anemia, reversible alopecia, hepatotoxicity, autoimmune thyroiditis and dose-related psychiatric side effects, such as irritability, anxiety and depression (Fried & Hoofnagle, 1995).

Contraindications to interferon therapy include major depressive disorder, cytopenia, alcohol or illegal drug use, thyroid dysfunction, organ transplant or autoimmune disease (Reichard, Schwarcz & Weiland, 1997). Autoimmune hepatitis must be ruled out prior to treatment with interferon, as it can exacerbate pathologic changes ("NIH Consensus, 1997).

Therapy is recommended, if ALT level is persistently elevated longer than 6 months, HCV RNA is positive, and liver biopsy shows fibrotic pathology. Serial determinations at weekly to monthly intervals are made of serum
aminotransferase levels, blood counts and thyroid function. Prior to initiation of therapy, baseline liver and thyroid function tests, and blood counts should be established. Autoimmune hepatitis should be ruled out by testing for serum anti-smooth muscle and ANA titer.

ALT and HCV RNA should be redrawn 3 months after initiation of therapy. If there has been no response, therapy should be discontinued or combination therapy with alpha interferon and ribavirin should be considered (National Institutes of Health, 1997). Relapse after a complete course of therapy may benefit from retreatment with interferon alone, or combined with ribavirin for an additional 12 months (National Institutes of Health, 1997).

Though Ribavirin has little antiviral activity, it can suppress alanine aminotransferase activity, and when combined with interferon alfa-2b, has been shown to obtain a higher sustained response (Brady, 1997). A dose of 1000 to 1200 mg. per day for 24 to 48 weeks suppressed ALT level with no effect on HCV RNA levels. The ALT level increased to pretreatment level upon cessation of therapy. When combined with interferon there was a significant sustained improvement in ALT and HCV RNA levels. The major dose related adverse effect is hemolysis. Other effects include anorexia, nausea, vertigo, fatigue and depression (Levine, 1998).

Other therapies being investigated for treatment of chronic hepatitis C include nonsteroidal anti-inflammatory drugs, amantadine hydrochloride or N-acetylcysteine combined with interferon, iron reduction therapy, ursodiol, pentoxifylline and herbal remedies (Bonkovsky, 1997). The lack of specific
treatment for acute hepatitis C and the low percent of those chronically infected
who achieve a sustained response rate with treatment necessitate a search for
other therapeutic options.

Summary

Hepatitis C virus infection is responsible for significant morbidity and mortality
worldwide. Advances in detection and monitoring of hepatitis C virus infection,
as well as treatment protocols, have contributed to the medical focus on this high
profile disease. Presence of risk factors should increase the clinicians index of
suspicion for this symptomatically nonspecific disease.
Table I: Laboratory and Diagnostic Studies for Hepatitis C Infection

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Cost</th>
<th>Time for Result</th>
<th>Pt Education</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELISA I (negative)</td>
<td>70% Low</td>
<td>Low for 22</td>
<td>N/A</td>
<td>48 hours</td>
<td>N/A</td>
<td>Not used</td>
</tr>
<tr>
<td></td>
<td>50% if screen</td>
<td>wks after initial infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELISA II (negative)</td>
<td>95% Low</td>
<td>Low for 1st</td>
<td>$43.00</td>
<td>48 hours</td>
<td>Explain blood draw. No special prep.</td>
<td>Most commonly used test</td>
</tr>
<tr>
<td></td>
<td>50% if screen</td>
<td>10-18 wks. After initial infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RIBA II (negative)</td>
<td>95%</td>
<td>Low for 1st</td>
<td>$149.80</td>
<td>48 hours</td>
<td>Blood draw</td>
<td>Supplementary test to confirm diagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10-18 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV RNA by RT-PCR (negative)</td>
<td>&gt;95%</td>
<td>&gt;95%</td>
<td>$276.00</td>
<td>4 to 8 days</td>
<td>Blood draw. No special prep.</td>
<td>Confirms viremia. Used on serum or tissue. Detects 700 ve/ml</td>
</tr>
<tr>
<td>HCV RNA bDNA (negative)</td>
<td>95%</td>
<td>100%</td>
<td>$269.50</td>
<td>4 to 8 days</td>
<td>Blood draw. No special prep.</td>
<td>Confirms viremia. Detects 200,000 ve/ml. For research only.</td>
</tr>
<tr>
<td>ALT (10-35 IU/L)</td>
<td>High</td>
<td>High</td>
<td>$12.35</td>
<td>10 minutes</td>
<td>Blood draw</td>
<td>Rises within 50 days. Transient elevations NL in up to 30% of pts.</td>
</tr>
<tr>
<td>AST (20-48u/L)</td>
<td>99%</td>
<td>99%</td>
<td>$12.35</td>
<td>10 minutes</td>
<td>Blood draw</td>
<td>Milder elevation than ALT. Transient elevations.</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>High</td>
<td>High</td>
<td>$238.65</td>
<td>3 days or longer</td>
<td>Invasive. NPO 8 hrs. may require overnight stay</td>
<td>Only reliable indicator of degree of pathology. * histopathologic finding may be characteristic but not specific for HCV.</td>
</tr>
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</table>

Table 2

Risk Factors for Hepatitis C infection

High Prevalence:
- Intravenous drug use
- Transfusion before 1990
- Hemophilia (clotting factor concentrate before 1987)

Moderate Prevalence:
- Hemodialysis

Low Prevalence:
- Needlestick
- Sexual contact
- Household contact
- Perinatal
- Intranasal cocaine
- Organ transplant before 1990
Table 3

Decrease of Transmission

Needle exchange programs
Universal Precautions
Non-donor status, if HCV plus safer sex
If multiple partners
No razor/toothbrush sharing
Cover open wounds
Diagnosis of Hepatitis C virus

S/S:
- Asymptomatic 60-70%
- Nonspecific symptoms of anorexia, malaise, abd pain
- Jaundice 20-30%

ALT elevated 2-8 x nl
- no → Consider repeat ALT at future date
- yes → ELISA II

ELISA II
- neg → Immunosuppressed
- yes → Risk Factors

Risk Factors
- no → Probable recovery
- yes → Diagnostic

Diagnostic
- Liver Biopsy
- Offer vaccines for Hepatitis A and B

Offer vaccines for Hepatitis A and B
- Elevated ALT > 6 mo, HCV RNA (+) & Bx shows fibrosis: consider RX
- Decompensated cirrhosis: consider transplant

Decompensated cirrhosis: consider transplant
- Normal ALT & minimal abnormality by Bx: observe & follow-up q3-5 yrs
Prevalence of HCV infection determined by route of transmission

- 10% Unknown
- 10% Occupational HD Household Perinatal
- 20% Sexual exposure
- 60% IVDU
REFERENCE LIST


