A **though we ended 2010 with the “Tale of Two Viruses,” focusing on the unique needs of those co-infected with HIV and HCV, we would be remiss if we did not also provide an update on the management issues related solely to HCV, which affects an estimated 48,000 Oregonians. Way back in 2000, computer models predicted that annual deaths related to hepatitis C virus (HCV) infection during the decade 2010–2019 would be double the 8,000 deaths reported in 1991; chronic liver disease deaths would exceed 180,000 during this 10-year span. Direct medical expenditures for HCV for the decade would exceed $10 billion.

So, a year into the decade of decompensating livers, this issue of the *CD Summary* will discuss recent practice guidelines from the American Association for the Study of Liver Diseases (AASLD) and promising new treatments for HCV infection.

**RECENT EPIDEMIOLOGY**

Data from the 1999–2002 National Health and Nutrition Examination Survey (NHANES) found a prevalence of HCV antibody of 1.6% in the U.S., corresponding to an estimated 4.1 million persons; 80% of these individuals had HCV RNA, indicating chronic infection. A history of injection drug use was still the strongest risk factor, and 66% of infections were in persons born between 1945 and 1964. Anti-HCV testing of persons 20–59 years of age who had ever injected drugs would identify nearly half of HCV chronic carriers; by adding those with elevated alanine aminotransferase (ALT) levels in this age group, 85% of HCV-infected persons could be identified by testing 18% of the population.

Hepatitis C became reportable in Oregon in 2006, and 6,000 persons with positive tests have been reported every year since. Of these, two-thirds have been in their 40s or 50s, and 63% have been male. Only 7.5% of cases have been <30 years of age, and just over half of these younger patients are female. Among the 152 acute cases of hepatitis C reported in Oregon since 2005, 42% occurred in persons <30, and 56% of them in females. This would suggest an evolving epidemiology of recent infections, with new cases occurring just as often in females as males. Sixty percent of acute cases reported in Oregon during 2009 admitted to injection of illicit drugs.

**TESTING**

The overall prevalence of HCV infection is too low to warrant universal screening. CDC’s recommendations for screening, which have not changed since first published in 1998, target the groups at highest risk (Table 1). Anti-HCV antibodies can be detected in the serum of plasma using a number of immunoassays. The specificity of current enzyme immunoassays (EIAs) is greater than 99%. False-negative results may occur in the setting of severe immunosuppression. Another change is in the choice of RNA assays. Previous pontifications recommended a qualitative assay to detect viremia in patients with positive EIAs. However, currently available quantitative assays have sensitivities of 10–50 IU/ml, making them optimal for confirmation of HCV infection as well as for monitoring viral load in patients undergoing therapy.

Genotyping is recommended for predicting the likelihood of response to, and determining the optimal duration of, therapy. HCV can be classified into at least 6 major genotypes based on a sequence divergence of 30% among isolates. Genotype 1 is the most common in the U.S., followed by genotypes 2 and 3.

The diagnosis of HCV infection — acute or chronic — generally requires testing of serum both for antibody to HCV and for HCV RNA. The differentiation of acute from chronic HCV depends on the clinical presentation, with a recent history of symptoms or jaundice and ALT elevation suggesting acute illness. HCV RNA can be detected as early as two weeks after exposure, but development of detectable anti-HCV antibodies may take 12 weeks.

**COUNSELING**

To prevent spread, advise patients to avoid sharing toothbrushes or shaving equipment, and to cover any bleeding wound. Obviously, those who inject drugs should cease doing so. Those who continue to inject should be counseled to avoid reusing or sharing syringes, needles, water, cotton or other paraphernalia; to clean the injection site with a new alcohol swab; and to dispose of syringes and needles after one use in a safe, puncture-proof container. They should be admonished not to donate blood, body organs, other tissue or semen. The risk of sexual transmission is low enough that barrier protection is not generally recommended for monogamous couples.

Patients also need to understand their own risks for cirrhosis and liver cancer and how to minimize them. Of those

† The World Health Organization established the first international standard in 1997 for HCV RNA nucleic acid technology, and the International Unit (IU) rather than number of viral copies is now preferred for reporting results.

‡ We would advise telling one’s partner about one’s HCV infection, however.

* Basically, baby boomers.
with chronic HCV infection, 5%–25% develop cirrhosis over periods of 25–30 years; the risk of progression to cirrhosis may be accelerated in persons who are older, immunosuppressed, or obese, or who consume more than 3–4 drinks of alcohol daily. Persons with HCV-related cirrhosis are at risk for hepatic decompensation (30% over 10 years) and liver cancer (1%–3% per year). It’s hard to reduce one’s age, but the other risk factors are modifiable: counseling regarding drinking, diet and exercise could yield handsome hepatic dividends.

**TREATMENT**

Combination therapy with pegylated interferon and ribavirin has been the mainstay of therapy for hepatitis C, and it holds the promise of virologic cure. However, while 80% of persons with genotypes 2 or 3 achieve sustained viral response (SVR) following 24 weeks of therapy, only 40–45% of persons with genotype 1 achieve SVR following 48 weeks of treatment. Response rates are markedly lower in blacks (20%–25%) and in HIV-coinfected persons (20%). Moreover, interferon is poorly tolerated: 10%–15% of patients stop taking it because of adverse events. The AASLD guidelines urge clinicians to weigh for each patient the risks and benefits of HCV treatment; factors to consider are shown in Table 2.

Dozens of potential therapies are currently in development, notably nonstructural protein 3 (NS3) protease inhibitors; and nucleoside and non-nucleoside analogue nonstructural protein 5B (NS5B) polymerase inhibitors. NS3 protease inhibitors were the first clinically validated class of direct-acting anti-HCV drugs and are the furthest along in clinical trials. When used in combination with standard-dose peginterferon alfa plus ribavirin therapy, NS3 protease inhibitors may boost SVR rates in patients with HCV genotype 1 to as high as 75%. However, resistance to both telaprevir and boceprevir (investigational drugs now in phase III trials) develops in vivo within days, making the possibility of monotherapy with NS3 protease inhibitors unlikely. Among the NS5B polymerase inhibitors, the nucleoside analogues show potent activity against HCV with lower likelihood of developing resistance, but concern about tolerability and adverse effects may limit their use. It appears that, although new treatments may improve efficacy against genotype 1 HCV infection, combination drug therapy will remain the norm.

**REFERENCES**


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**Table 2. Characteristics of persons for whom HCV therapy is widely accepted (Thumbs Up) and persons for whom therapy is contraindicated (Thumbs Down).**

<table>
<thead>
<tr>
<th>Thumbs Up</th>
<th>Thumbs Down</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥18 years</td>
<td>Major uncontrolled depressive illness</td>
</tr>
<tr>
<td>HCV RNA positive</td>
<td>Solid organ transplant</td>
</tr>
<tr>
<td>Liver biopsy showing chronic hepatitis with significant fibrosis (bridging fibrosis or higher)</td>
<td>Autoimmune hepatitis or other autoimmune condition known to be exacerbated by peginterferon or ribavirin</td>
</tr>
<tr>
<td>Compensated liver disease</td>
<td>Untreated thyroid disease</td>
</tr>
<tr>
<td>Acceptable hematological and biochemical indices (hemoglobin ≥13 g/l for men and ≥12 g/dl for women; neutrophil count ≥1500/mm³; serum creatinine &lt; 1.5 mg/dl)</td>
<td>Pregnancy or unwillingness to comply with adequate contraception</td>
</tr>
<tr>
<td>Willingness to be treated and to adhere to treatment requirements</td>
<td>Severe concurrent medical disease such as severe HTN, significant coronary heart disease, poorly controlled diabetes, COPD</td>
</tr>
<tr>
<td>No contraindication (no thumbs-down criteria)</td>
<td>Age &lt;2 years</td>
</tr>
<tr>
<td></td>
<td>Known hypersensitivity to drugs used to treat HCV</td>
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*Defined as absence of detectable HCV RNA 24 weeks after ending treatment, SVR is the best predictor of long-term response.*