

Management of  
Hepatitis C by the  
Primary Care Provider

# Monitoring Guidelines



Authored by  
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# TABLE OF CONTENTS

<b>1. Introduction</b> .....	<b>4</b>
<b>2. The HCV Virus</b> .....	<b>4</b>
<b>3. Natural History of HCV</b> .....	<b>5</b>
<b>4. Screening for HCV</b> .....	<b>6</b>
<b>5. Diagnosis of HCV</b> .....	<b>7</b>
<b>6. Evaluating Patients with HCV</b> .....	<b>8</b>
<b>7. Counseling Patients with HCV</b> .....	<b>9</b>
<b>8. Treatment of HCV</b> .....	<b>10</b>
<b>9. Side Effect Management</b> .....	<b>13</b>
<b>10. Conclusion</b> .....	<b>19</b>
<b>11. References</b> .....	<b>20</b>

## 1. INTRODUCTION

Hepatitis C is a global health problem. According to the World Health Organization, more than 170 million people are infected worldwide by the hepatitis C virus (HCV).<sup>1</sup> The Centers for Disease Control and Prevention (CDC) estimates that in the United States approximately 4 million people are infected with HCV, of whom 2.7 million have chronic HCV infection, and that 10,000-12,000 die per year from HCV.<sup>2</sup> Most patients with chronic HCV have yet to be diagnosed and only as few as 30% of persons may have actually been diagnosed so far.<sup>3,180</sup> Most HCV infected people are expected to first present for medical attention in the next decade which will result in a four-fold increase in diagnosed cases by 2015.<sup>3</sup> It has been projected that between 2010-2019, there will be \$11 billion in direct medical costs and \$75 billion in indirect costs (resulting from premature disability and mortality) from HCV.<sup>4</sup>

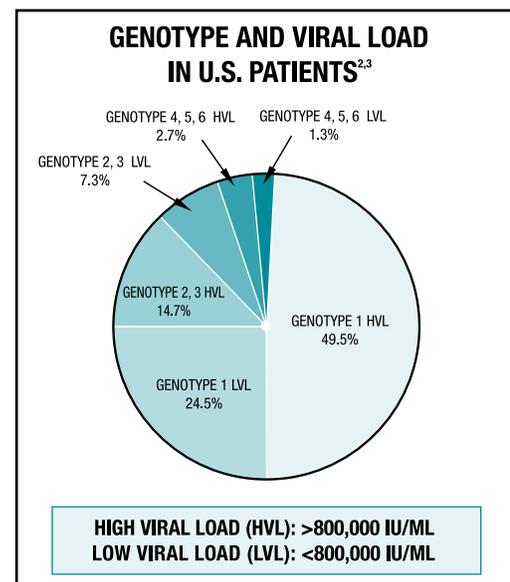
Most of the morbidity and mortality from HCV is caused by complications of decompensated cirrhosis. If identification and treatment of all persons with HCV with compensated cirrhosis occurred today, the number of cases of decompensated cirrhosis would be reduced by approximately one-third after 20 years.<sup>5</sup> To achieve this goal, the Primary Care Provider (PCP) must get more involved in the diagnosis and care of HCV. And because most HCV patients are asymptomatic and unaware of their disease, it is up to PCPs in their role as gate-keeper of healthcare to identify and screen patients who are at risk for HCV. The PCP can then initiate evaluation and referral of appropriate HCV patients to the gastroenterologist/hepatologist for treatment before the patient progresses to cirrhosis. However, three recent studies have shown that HCV in the PCP setting is under-diagnosed and under-referred and that testing is rarely initiated because of physician-identified risk factors.<sup>6-8</sup> It is also of the utmost importance that PCPs be knowledgeable about the side effects of treatment, so that when they see their patients who are being treated for HCV for routine and urgent care, they can help manage side effects. Our lecturing on HCV to PCPs around the country has convinced us that there is a need for a set of HCV guidelines directed towards the PCP. The purpose of this guide is to provide such guidelines for the management of HCV by the PCP. These guidelines are not meant to replace existing extensive reviews and guidelines intended for the specialist. Instead, they are designed to help the PCP understand the pathogenesis, natural history,

evaluation, and treatment of HCV in a simple, concise, and user-friendly manner, so that PCPs will be better able to take care of their HCV patients. The small size of these guidelines is intended so that they will be readily available when needed.

## 2. THE HCV VIRUS

Hepatitis C is a single-stranded RNA virus belonging to the Flaviviridae family. Unlike HIV, HCV does not integrate into the human genome making cure of HCV infection possible. HCV replicates preferentially in the hepatocyte, but is not itself directly cytopathic and therefore does not cause direct destruction of the hepatic cells.<sup>3</sup> Chronic HCV infection results from an immune response that induces hepatocyte destruction and fibrosis but does not eradicate the virus so that persistent infection results.<sup>9</sup>

There are 6 HCV genotypes and more than 50 subtypes. The genotypes differ from each other by 31-34% in their nucleotide sequences, while subtypes differ by 20-23%.<sup>3</sup> Genotypes 1,2,3, are found in the US, Europe, Japan, and Australia. Genotype 1 is the most common genotype in the US (75%). Genotypes 2 and 3 account for 22% while genotypes 4, 5, 6 account for 4%.<sup>2</sup> Genotype 4 is most commonly found in the Middle East, Egypt and Africa. Genotype 5 is found in southern Africa while Genotype 6 is most common in Southeast Asia and Hong Kong.



### 3. NATURAL HISTORY OF HCV

Identification of acute HCV is difficult because most patients are asymptomatic.<sup>3</sup> Reported rates of spontaneous viral clearance are between 15% and 30%.<sup>10-12</sup> Both host and viral factors have been implicated in the spontaneous clearing of HCV.<sup>13-19</sup>

Chronic infection is the hallmark of HCV. Some 70%-85% of people infected with HCV will develop chronic disease.<sup>10-12</sup> The most important consequence of chronic HCV infection is progressive liver fibrosis which can lead to cirrhosis in 20%, liver failure (decompensation) in 6%, and hepatocellular carcinoma (HCC) in 4%.<sup>3,11</sup> HCV is the most common indication for liver transplantation in the US and Europe. Cirrhosis represents the end-stage outcome of fibrosis progression. The median time from infection with HCV to cirrhosis is 30 years.<sup>20-22</sup>

#### PROGRESSION TO FIBROSIS, CIRRHOSIS, AND HCC

##### FACTORS ASSOCIATED WITH DISEASE PROGRESSION<sup>3,22</sup>

- Alcohol consumption >30 g/d in men and >20 g/d in women
- Acquisition at age 40 or greater
- Male gender
- HIV or Hepatitis B (HBV) coinfection
- Immunocompromised state
- Steatosis

Not all cases of HCV lead to cirrhosis or HCC.<sup>20,23</sup> There is a great deal of variability in the natural history of HCV regarding progression of fibrosis.<sup>20-23</sup> Fibrosis is the result of chronic inflammation and is characterized by the deposition of extracellular matrix, causing deformity of the liver architecture which

in turns leads to impairment of hepatic cell function. A variety of factors are associated with disease progression. Likewise there are factors that do not influence disease progression.

The best predictor of risk for progression to cirrhosis is the degree of hepatocellular necrosis, inflammation, and fibrosis on initial liver biopsy.<sup>23,24</sup> Liver

##### FACTORS NOT INFLUENCING DISEASE PROGRESSION<sup>3,22</sup>

- Genotype
- Alanine aminotransferase level (ALT)
- Viral Load
- Mode of transmission

enzymes have not been shown to be of value in predicting fibrosis.<sup>3</sup> Baseline liver biopsy is therefore considered the gold standard for determining the extent of disease in HCV.<sup>25</sup> A study

of progression to cirrhosis according to baseline fibrosis, utilizing multiple sequential liver biopsies in Japan, showed that all patients with severe fibrosis on baseline biopsy progressed to cirrhosis within 10 years. 43% of patients with moderate fibrosis on baseline biopsy progressed to cirrhosis by 17 years and only 30% of those with mild fibrosis on baseline biopsy progressed to cirrhosis by 13 years.<sup>24</sup> A study on nonalcoholic HCV patients from the Clinical Center of the National Institutes of Health showed that the initial inflammatory score was predictive of fibrosis progression.<sup>23</sup> Although a variety of serum fibrosis markers are under investigation, they should be considered investigational until validation studies are completed.<sup>26</sup>

Compensated cirrhosis is the presence of cirrhosis with the absence of complications.<sup>27</sup>

Not all patients with HCV cirrhosis develop decompensation. A 10-year longitudinal European study showed that the risk of developing decompensation was 3.9% per year.<sup>28</sup> The rate of decompensation at 5 years was 20% and at 10 years 30%. The survival rate was 91% at five years and 79% at 10 years.

Cirrhosis of any cause is a major risk factor for the development of HCC. It has been estimated that HCC occurs in HCV cirrhosis at a rate up to 3% per year.<sup>3,28</sup>

#### EXTRAHEPATIC MANIFESTATIONS OF HCV

Extrahepatic clinical and biologic manifestations are often noticed in HCV patients. A large 1,614-patient French study found that 74% of patients have at least 1 clinical extrahepatic manifestation.<sup>31</sup> They involve most commonly the joints, muscles, and skin.

Risk factors found for the presence of extrahepatic manifestations were extensive liver fibrosis, advanced age, and female sex. There was no association with the level of histologic activity. Only vasculitis, purpura, arterial hypertension, arthralgia, lichen planus, and low thyroxin level were associated with the presence

##### COMPENSATED CIRRHOSIS

- No ascites
- No variceal hemorrhage
- No encephalopathy
- Preserved liver synthetic + excretory function
  - Albumin >3.5 g/dl
  - INR <1.5
  - Total bilirubin <1.5 mg/dl

##### DECOMPENSATED CIRRHOSIS

- Ascites
- Bleeding esophageal varices
- Hepatic encephalopathy
- Jaundice

##### RISK FACTORS FOR HCC IN HCV<sup>22,29,30</sup>

- Severe liver disease
- Alcohol abuse
- HBV or HIV coinfection
- Iron overload

of cryoglobulins.

Cryoglobulinemia is a lymphoproliferative disorder characterized by the occurrence of serum immune complexes which precipitate at cold temperatures. Laboratory testing for cryoglobulinemia is tricky. After the serum is drawn it must be kept at a constant

**CLINICAL EXTRAHEPATIC-MANIFESTATIONS OF HCV<sup>31</sup>**

- Arthralgias and arthritis (23%)
- Paresthesia (17%)
- Myalgia (15%)
- Pruritus (15%)
- Sicca syndrome (11%)
- Arterial hypertension (10%)
- Purpura (1.5%)
- Lichen planus (1%)
- Vasculitis (1%)
- Porphyria cutanea tarda (0.2%)

temperature and then put into an ice bath also at constant temperature for 1/2 hour to precipitate cryoglobulins. Rheumatoid factor, which is generally present in cryoglobulins, is a good method of screening for cryoglobulins because it does not require temperature parameters.<sup>32</sup>

Other studies have found both higher and lower frequencies of both porphyria cutanea tarda (PCT) and lichen planus.<sup>32,33</sup> A large meta-analysis of 50 studies with a total of 2167 patients with PCT found a prevalence rate for HCV of 50% with a distinct geographic variability.<sup>33</sup> The highest prevalence rates were in Italy, Japan and Spain (71% -85%) while the lowest prevalence rates were in France, the Czech Republic and Australia (20% -30%).<sup>33</sup> Clinically, there are no differences between familial PCT and HCV-acquired PCT. The skin lesions

**BIOLOGIC EXTRAHEPATIC-MANIFESTATIONS OF HCV<sup>31</sup>**

- Cryoglobulins (40%)
- Antinuclear antibodies (10%)
- Low thyroxin level (10%)
- Anti-smooth muscle antibodies (7%)

of PCT are fluid-filled vesicles and tense bullae developing on sun-exposed regions such as the face, forearms, legs, and dorsa of the hands and feet. The lesions of lichen planus are pruritic papules on skin particularly the wrists, lower back, shins, and genitalia. The scalp may be involved leading to hair loss. Mucus membranes, especially the buccal mucosa, can also be involved. The prevalence of HCV in patients with lichen planus in other studies was 0.1% -35%.<sup>34,35</sup>

HCV-related arthritis can be divided into 2 groups.<sup>36</sup> The most common type is a rheumatoid arthritis-like polyarthritis primarily involving small joints. Rheumatoid factor is often present, but the ESR is less frequently elevated than it is in classic rheumatoid arthritis. The other less common type of arthritis seen in HCV is a mono-oligoarthritis involving medium and large joints. This form is associated with the occurrence of serum cryoglobulins. There are 3 possible

mechanisms which have been proposed to explain HCV-related arthritis: immune complexes/cryoglobulin deposits in the joints; synovial autoimmune response caused by the virus; and direct viral invasion.<sup>37</sup>

## 4. SCREENING FOR HCV

*“All patients with chronic hepatitis C are potential candidates for antiviral therapy.”<sup>3</sup>*

The PCP therefore needs to screen every patient who has a risk factor for HCV. HCV is transmitted by parenteral exposure to infected blood or blood products. The incubation period of HCV is 14-160 days with a mean of 7 weeks.<sup>10</sup> The majority of people with HCV acquired their infection through: (1) transfusion of blood or blood products prior to 1992 (before routine testing of the blood supply was in place in the US) or (2) intravenous drug use. Injection drug use now accounts for 2/3 of all newly acquired infection.<sup>38</sup> The CDC recommends HCV testing based on increased risk for infection.<sup>39</sup> The HCV risk factor can be recognized with thorough questioning in greater than 90% of cases.<sup>40</sup>

### INDIVIDUAL RISK FACTORS

Vertical transmission occurs in 5% of infants born to HCV-infected women.<sup>39</sup> There appears to be no difference in transmission rates between cesarean delivery and vaginal delivery from non-HIV coinfecting mothers.<sup>41</sup> Cesarean section is correlated with a decreased risk of transmission only in mothers who were HIV coinfecting.<sup>42</sup> There appears to be no difference in transmission rates between cesarean delivery and vaginal delivery from non-HIV coinfecting mothers.<sup>41</sup> Most infants infected with HCV at birth have no symptoms. They should not be tested for anti-HCV until after 12-18 months of age when maternal antibodies have faded.

Sexual transmission occurs mainly in those who engage in high-risk sexual practices, including multiple sex partners and rough, traumatic sex.<sup>3,43</sup> The risk of HCV transmission between monogamous sexual couples is rare.<sup>44,45</sup> A recent prospective 10-year study of heterosexual monogamous partners of HCV positive individuals, who denied anal intercourse, vaginal intercourse during menstruation, condom use, and extramarital affairs, and who were told not to share personal items such as toothbrushes, razors, and nail

**RISK FACTORS FOR HCV**

- History of injection drug use
- Recipients of clotting factors made before 1992
- Hemodialysis patients
- Recipients of blood and/or solid organs before 1992
- People with undiagnosed liver problems
- Infants born to infected mothers after 12-18 mos. of age
- Healthcare/Public safety workers after known exposure

scissors, found an incidence rate of 0.37 per 1,000 person-years.<sup>45</sup> Interestingly, of the 3 individuals who developed HCV infection during the study, one had a needle stick with a patient coinfecting with HIV/HCV, one had a dental implant, and the third, who had no other risk factor, had a different strain of HCV than their partner had. The authors concluded

that “the risk of sexual transmission of HCV is extremely low or even null.”<sup>45</sup>

Percutaneous sources of infection other than IV drug use that have been identified as transmitting HCV include intranasal cocaine, tattooing, and body piercing, although the frequency of transmission of these sources has not been well-studied.<sup>3,46-48</sup>

Occupational risk of HCV in healthcare, emergency, and public safety workers after percutaneous exposure to HCV positive blood is thought to be low. A study on the risk of transmission in healthcare workers found an average risk of 1.8%.<sup>49</sup> The CDC has found that about 1% of hospital staff are antibody positive for HCV.<sup>50</sup>

Approximately 200,000 patients in the US are infected with both HCV and HIV.<sup>181</sup> The percentage of coinfection is higher in persons who obtained HIV through blood products and IV drug use rather than through sexual exposure.<sup>181</sup> HCV is now the leading cause of death in HIV-infected patients.<sup>182</sup> All patients with HIV should be tested for HCV as well as HBV.

All patients with HBV should be tested for HCV as well as HIV. Both HBV and HCV are transmitted by parenteral routes so coinfection is not infrequent especially in IV drug users and in regions of the world such as Asia where there is a high prevalence of both HBV and HCV.<sup>183</sup> Coinfection with both HBV and HCV results in more severe and progressive liver disease than either infection alone, including an increased risk of hepatocellular carcinoma.<sup>183-185</sup>

Approximately 240,000 persons emigrate annually to the US from Asia.<sup>186</sup> According to the US census of the year 2000, there are approximately 12 million Asians and Pacific Islanders living in the US.<sup>187</sup> In most of Asia, the prevalence of HCV infection is 2-6% and the prevalence of HBV infection is 8-10%.<sup>188,189</sup> The prevalence rate of HCV in Asian Americans is not

known but is estimated to be significantly higher than in Caucasians and closely resembles the prevalence of HCV in their countries of origin which is up to 3 times the overall US prevalence rate of 1.8%.<sup>190</sup> Most Asians with HCV are infected early in life from unsanitary medical practices (such as reusing needles and other medical supplies due to economic constraints) or blood transfusions and are therefore at higher risk for long-term complications such as liver cancer.<sup>190</sup> Therefore, Asian Americans born in HCV-endemic areas should be offered HCV testing.

## 5. DIAGNOSIS OF HCV

Once the PCP has identified a risk factor, he or she should initially test for HCV by ordering an enzyme-linked immunoassay (EIA) to detect antibody against HCV (anti-HCV). The current EIA is a third generation assay with a specificity exceeding 99%.<sup>51</sup> False-negatives can occur in those undergoing hemodialysis and those with immunodeficiency, so RNA testing should be done on these patients as the initial test. The anti-HCV becomes detectable within 4-10 weeks after infection.<sup>20</sup> Anti-HCV cannot distinguish between new, chronic, or previous infection. Anti-HCV is not protective.

The confirmatory test of choice is an HCV RNA assay.<sup>51</sup> The HCV RNA tests detect the presence or absence of virus. HCV RNA becomes detectable 1-3 weeks after infection.<sup>3</sup> There are two types of HCV RNA assays: qualitative and quantitative. Qualitative tests results are reported as being either positive or negative. Qualitative tests do not measure a viral load. Quantitative RNA tests give a measurement of viral load reported in IU/ml.

In the past, it was recommended that all positive anti-HCV tests be confirmed with a qualitative RNA test because it was the more sensitive assay. Today, with availability of sensitive quantitative RNA assays

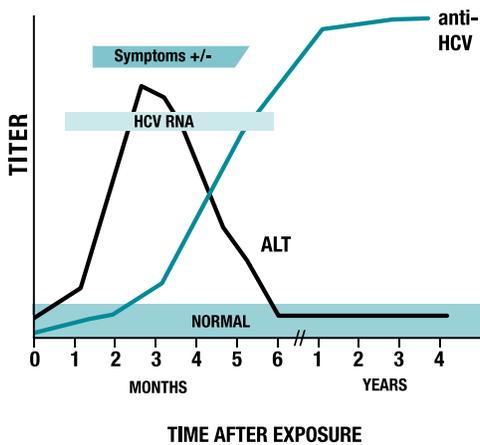
### INTERPRETATION OF ANTI-HCV AND HCV RNA53

- A negative anti-HCV and negative RNA = no infection
- A positive anti-HCV and positive HCV RNA = acute or chronic infection
- A negative anti-HCV and positive HCV RNA = early acute infection or chronic infection in an immunosuppressed state
- A positive anti-HCV and a negative HCV RNA = resolved infection, false-positive antibody, low-level or intermittent viremia, or passively-acquired antibody

with low ranges of detection that equal qualitative tests (such as the Quest Heptimax™ with a range down to 5 IU/ml), PCPs may choose one of them as the initial measurement of RNA if available at their local laboratory.

Using both anti-HCV and HCV RNA tests allows the PCP to establish the diagnosis of HCV.

**SEROLOGIC PATTERN OF ACUTE HCV INFECTION WITH RECOVERY**



**6. EVALUATING PATIENTS WITH HCV**

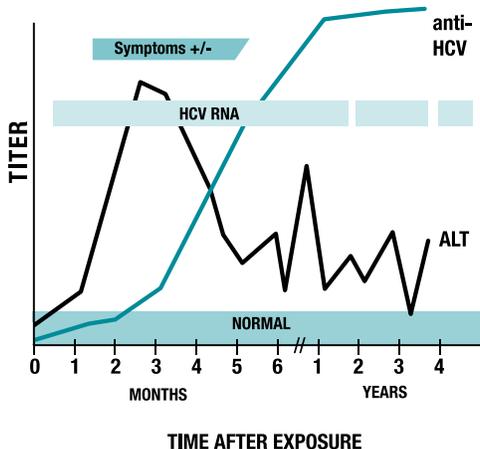
Once the PCP has diagnosed HCV, a further evaluation of the patient is necessary. By identifying risk factors, the PCP may be able to determine when the patient became infected with HCV. This is important because the longer the patient has been infected, the greater the chance of developing fibrosis and its complications.

The PCP should also determine if there are any contraindications to pegylated interferon (peginter-

**ABSOLUTE CONTRAINDICATIONS TO HCV TREATMENT**

- Pregnancy or patients who are unwilling or unable to practice 2 forms of contraception: ribavirin is teratogenic
- Poorly controlled psychiatric disease: peginterferon can cause and exacerbate depression, and lead to suicide and other psychiatric conditions
- Poorly controlled or symptomatic coronary heart disease: ribavirin induced anemia can bring on ischemia
- Kidney and heart transplants: increased risk of severe rejection with interferon
- Renal failure or renal insufficiency with a creatinine clearance less than 50 ml/min: these patients cannot be treated with ribavirin because it is eliminated through the kidneys;<sup>64</sup> they may be treated with peginterferon monotherapy

**SEROLOGIC PATTERN OF ACUTE HCV INFECTION WITH PROGRESSION TO CHRONIC INFECTION**



feron) and ribavirin treatment and assess for comorbid conditions. In the past, contraindications to treatment were divided into 2 kinds: absolute and relative. With increasing experience using peginterferon and ribavirin, many of the former absolute contraindications have become relative ones.

It is helpful to the treating gastroenterologist/hepatologist if the PCP performs comprehensive laboratory profiles on patients before referring them. This allows the specialist to offer a more comprehensive consultation with the first patient visit.

The PCP should leave it up to the gastroenterologist/hepatologist as to whether to do a liver biopsy before treatment. In the past, most specialists recommended a biopsy on almost all HCV patients. Regardless of the level of ALT, liver biopsy provides information on prognosis which can help the patients make informed choices about whether to be treated or not.<sup>3,20,25,84</sup> Today, most still are recommending liver biopsy, although some are not performing pretreatment biopsies on genotype 2 and 3 patients because of these genotypes' high response rate to treatment.<sup>3</sup>

**RELATIVE CONTRAINDICATIONS TO HCV TREATMENT**

- History of ongoing major depression: these patients need to be evaluated, treated, and cleared by a psychiatrist before HCV treatment begins, and the psychiatrist needs to follow the patient during treatment
- History of minor depression in the past or ongoing mild depression: antidepressants work well in both preventing and treating depression. The PCP can usually stabilize these patients with antidepressants before HCV treatment begins which will allow the patient to start and finish HCV therapy
- Decompensated cirrhosis: should only be treated at a transplant center because of the risk of inducing further liver failure
- Autoimmune disease: interferon exacerbates immunemediated diseases such as autoimmune thyroid disease or lupus. If these patients are closely followed by their endocrinologist or rheumatologist, the majority can start and complete therapy
- History of coronary heart disease: these patients need to undergo a stress test and evaluation by their cardiologist to make sure they can tolerate ribavirin-induced anemia if it occurs
- Active substance abuse: a very difficult group to treat. Preferably patients should be treated for substance abuse before beginning HCV treatment. Ongoing drug abuse is associated with poor compliance, coexisting psychiatric disease, and increased risk of reinfection (IV drugs and nasal cocaine). Successful treatment of these patients has been reported at academic centers with intensive psychological management<sup>3,65</sup>
- Hemoglobinopathies, preexisting neutropenia (<1,500 cells/mm<sup>3</sup>), preexisting anemia (hemoglobin <12g/dl in women and <13g/dl in men), and preexisting thrombocytopenia (<100,000 cells/mm<sup>3</sup>): in the past these were absolute contraindications because of the possibility of anemia from ribavirin and interferon, and interferon induced neutropenia and thrombocytopenia. With increasing experience with cytopenias and the advent of growth factors, many gastroenterologists and hepatologists will treat these patients

**LABORATORY EVALUATION OF THE HCV PATIENT**

- A complete blood count (CBC)
- A prothrombin time (PT), international normalized ratio (INR), and a partial thromboplastin time (PTT)
- A complete chemistry panel including AST, ALT, total and direct bilirubin
- Thyroid-stimulating hormone (TSH)
- HIV serology and hepatitis B surface antigen to see if the patient is coinfectd
- A chronic liver disease panel to ascertain for any co-existing liver disease:
  - Iron, iron binding capacity, and ferritin
  - Antinuclear, antismooth muscle, and antimitochondrial antibodies
  - Ceruloplasmin
  - Alpha-1 antitrypsin
  - Alfa-fetoprotein
- HCV genotype
- A quantitative HCV RNA if not already done
- Hepatitis A total antibody and hepatitis B core and surface antibodies to check for immunity. If either is negative, the CDC recommends vaccination to prevent coinfection which can make HCV liver disease worse<sup>54</sup>
- An ophthalmoscopic exam by the PCP. All diabetics and hypertensives should see an ophthalmologist if they haven't seen one in the past 6 months to get a baseline retinal exam
- A pregnancy test in all fertile females of childbearing age unless their partner has a vasectomy
- An ECG and stress test in all patients over 50

## 7. COUNSELING PATIENTS WITH HCV

Once HCV has been diagnosed, the PCP needs to counsel the patient about preventing transmission of HCV to others. The CDC and the NIH Consensus Panel have made recommendations on what to tell the patient.<sup>3,54,55</sup>

**HERBAL REMEDIES**

It seems that every patient diagnosed with HCV asks about herbal remedies. An analysis of 110 references on the use of alternative therapies in treating hepatitis C published in 2003 revealed that there were only 13 randomized studies fulfilling inclusion criteria and that none of the trials were adequately designed to show effectiveness in the treatment of HCV with alternative therapies.<sup>56</sup>

**WHAT TO TELL THE HCV PATIENT<sup>3,54,55</sup>**

- Do not donate blood, body organs, other tissue, or semen
- Do not share personal items that might have your blood on them:
  - Toothbrushes
  - Dental appliances
  - Nail-grooming equipment
  - Razors
- Cover cuts and open skin lesions
- HCV is not spread by sneezing, hugging, coughing, food or water, sharing eating utensils, drinking glasses, or casual contact
- HCV patients should not be excluded from work, school, play, childcare, or other settings on the basis of their HCV infection
- If using illicit drugs, stop using them - If continue to use drugs, get into a treatment program and don't reuse or share syringes and needles
- For those who are not treatment candidates and are fertile with a fertile partner, use latex condoms for those who have multiple sexual partners or short-term sexual relationships. No condom use is recommended for long-term monogamous couples whose risk of transmission is extremely low
- For those who are treatment candidates and are fertile with a fertile partner, start practicing 2 forms of birth control so pregnancy doesn't result (ribavirin is teratogenic)

Most patients ask about milk thistle. The active ingredient of the milk thistle plant (*Silybum marianum*) is silymarin. Silymarin appears to have antioxidant and antifibrotic properties.<sup>57-59</sup> A review of published studies on the treatment of chronic liver disease with milk thistle found 1726 reports, but only 14 of these were randomized and controlled.<sup>60</sup> A meta-analysis of

the latter showed that, although milk thistle appeared to be safe and well-tolerated, there was no reduction in mortality, no improvement of liver histology, and no improvement of biochemical markers of liver function.<sup>60</sup> The authors conclude that there is not enough evidence to recommend milk thistle for the treatment of chronic liver disease.<sup>60</sup>

The other herbal that patients frequently ask about is Chinese herbs. A recently published randomized trial of US patients with HCV, using a combination of Chinese herbal medicines commonly given in Asia to treat chronic hepatitis, found no therapeutic benefit in using these compounds.<sup>61</sup> There was no improvement of viral load, quality of life, or liver chemistries.

All HCV patients should be questioned about their use of herbal remedies in a non-threatening, non-prejudicial way.<sup>62</sup> It is important to point out to patients that herbal remedies are not subject to FDA regulations for safety, efficacy, purity and potency, and that many herbs are hepatotoxic. Before herbal remedies can be recommended in the treatment of HCV, well-designed controlled trials looking at efficacy, drug interactions, and toxicity need to be performed.<sup>63</sup>

## 8. TREATMENT OF HCV

### ROLE OF THE PCP DURING TREATMENT

The PCP needs to understand current treatment strategies for HCV. The primary goal of treatment is permanent eradication of HCV. If HCV RNA is undetectable (using an assay with a sensitivity of 50 IU/ml or less) 6 months after completion of therapy, the patient has achieved a sustained virologic response (SVR).<sup>3,44</sup> **The gold standard of treatment for HCV is peginterferon plus ribavirin.** There are two types of peginterferon approved by the FDA for treatment of HCV: peginterferon alfa-2a (Pegasys®) and peginterferon alfa-2b (Peg-Intron®). Increasing experience with the 2 combinations of peginterferon and ribavirin, as well as experience with regular interferon plus ribavirin, indicates that subsequent relapse after achieving a SVR is highly unlikely.<sup>66-69</sup> Therefore, many clinicians consider achieving a SVR synonymous with a “cure.”

The secondary goal of treatment is histologic improvement of liver inflammation and fibrosis to delay progression of fibrosis to cirrhosis, prevent the development of decompensation, and avert the development of HCC.<sup>70</sup> Histologic improvement occurs not only in those who clear the virus, but also in those

who do not.<sup>71,72</sup> The greatest improvement occurs in those who attain a SVR.<sup>72</sup> Studies have shown that peginterferon plus ribavirin, as well as peginterferon and regular interferon given as monotherapy, decreases morbidity and mortality, probably by reducing fibrosis progression, reducing the incidence of cirrhosis, and reducing the development of HCC.<sup>71-77,177</sup> A recent prospective cohort study from Japan in cirrhotic patients with HCV showed that those treated with interferon had a lower incidence of HCC and improved survival, especially in those with a SVR, compared to untreated patients.<sup>177</sup>

Another important treatment strategy the PCP needs to understand is early virologic response (EVR).<sup>78,79</sup> EVR is the finding that the HCV RNA level, measured 12 weeks after starting treatment, is either nondetectable or has dropped by at least 2 logs (one hundred-fold drop) when compared to the baseline level. The initial study of peginterferon alfa-2a plus ribavirin showed that in those patients who did not achieve an EVR, the chance of achieving a SVR at the end of therapy was only 3%.<sup>68</sup> Patients who do not achieve an EVR are therefore highly unlikely to achieve a SVR and their treatment can be stopped at this point. In those patients who achieved an EVR, 65% went on to achieve a SVR,<sup>68</sup> so treatment should be continued. A retrospective analysis of the first study of peginterferon alfa-2b plus ribavirin showed similar findings.<sup>79</sup>

Multiple pre-treatment predictors of likelihood of treatment response have been identified.

### SPECIAL POPULATIONS

**Acute Hepatitis C:** Since most cases of acute HCV are asymptomatic, acute HCV is not frequently diagnosed. The majority of patients with chronic HCV have no history of acute hepatitis. Because the majority of cases today occur in IV drug users, treatment studies are difficult to design and perform.<sup>161,162</sup> A German prospective study on the natural course of acute HCV found that symptomatic patients with acute HCV presented with jaundice (68%), flu-like symptoms (55%), dark urine and light stool (39%), nausea (34%), and right upper quadrant pain (25%).<sup>163</sup> These symptomatic patients had a rate of spontaneous viral clearance of 52% usually within 3 months after the start of symptoms with no spontaneous clearance of the virus after 16 weeks. On the other hand, asymptomatic patients developed chronic HCV 100% of the time. The authors conclude that those with acute HCV who are symptomatic should be treated only if they

are RNA positive after 3 months of observation, while asymptomatic patients should be treated as soon as they are diagnosed.<sup>163</sup>

A recent U.S. prospective trial using peginterferon alfa-2a compared 24 weeks of peginterferon plus ribavirin versus peginterferon monotherapy versus a control

group of untreated patients in the treatment of acute HCV.<sup>164</sup> SVR was 85% in the peginterferon plus ribavirin group, 80% in the peginterferon group, and 36% in the control group. A German study using peginterferon alone for 24 weeks showed a SVR of >90%.<sup>165</sup> A recent Italian study showed that 39% of acute HCV patients were RNA negative after 12 weeks from onset of infection.<sup>166</sup> The remaining patients were treated with peginterferon alfa-2b for 24 weeks and then followed for an additional 12 months. 94% achieved a SVR which was unchanged at the 1-year follow-up. Ribavirin thus appears unnecessary for the treatment of acute HCV if treatment is started by 3 months after onset of infection.<sup>161</sup>

The PCP may see a patient with acute HCV after a needle-stick injury, after a known exposure, or in patients with acute, symptomatic hepatitis.<sup>162</sup> Although further research is needed, it appears from the above studies that treating acute HCV patients who are still RNA positive 3 months after infection with standard doses of peginterferon for 24 weeks is prudent to prevent the development of chronic HCV.

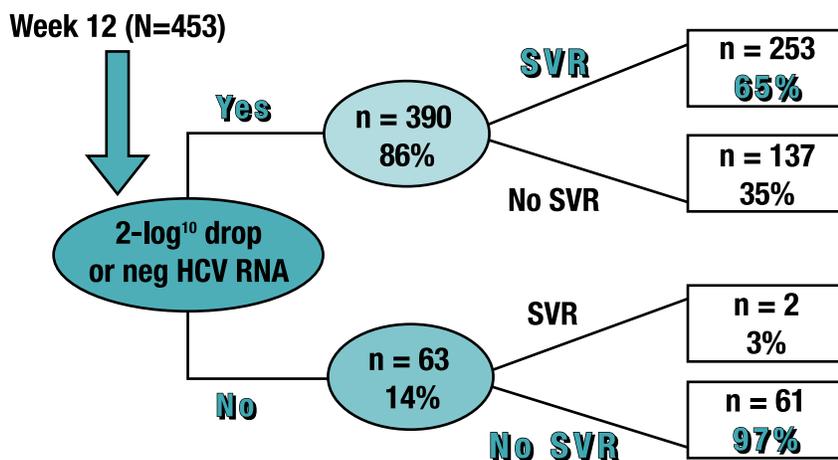
**Normal ALT:** Serum ALT levels are an insensitive

**PREDICTORS OF TREATMENT RESPONSE 20, 80**

- Genotype 2 or 3
- Low viral load (<800,000 IU/ML)
- Age <40
- Body weight <75 kg
- Female sex
- Absence of bridging fibrosis and cirrhosis on biopsy

way of determining hepatic inflammation and injury.<sup>3,167</sup> About 30% of patients with HCV have normal ALT levels.<sup>168</sup> Patients with normal ALT levels have been shown to achieve a SVR with interferon and ribavirin comparable to those with elevated ALT levels.<sup>169</sup> Two

**PEG IFN ALFA-2a + RBV: EARLY VIRAL RESPONSE (EVR)<sup>68</sup>**



recent studies have shown the efficacy of peginterferon alfa-2a and ribavirin in patients with normal ALT levels.<sup>170,171</sup> HCV patients with normal ALT levels should therefore be evaluated for treatment (including liver biopsy) the same as those with elevated ALT levels.

**African Americans:** African Americans have a prevalence of HCV that is 2 to 3 times more

common than whites and have a higher prevalence of genotype 1 (90%) than whites (70%).<sup>2,172,173</sup> The higher prevalence of HCV in African Americans is thought to be due to the increased risk of exposure.<sup>172</sup>

African Americans also have a lower response rate to treatment compared to non-Hispanic whites.<sup>172,174-176</sup> A recent study of genotype 1 African Americans and Caucasians treated with peginterferon alpha-2a and ribavirin found a SVR rate of 26% in Blacks compared to a 39% rate in White patients.<sup>174</sup> A negative EVR among the African Americans had a 100% negative predictive value for SVR. In addition, histologic improvements in Black patients not achieving SVR was observed in 22%.

In another study of 100 African Americans and 100 non-Hispanic White patients treated with peginterferon alfa-2b and ribavirin, where 98% of both groups were genotype 1, African Americans had a SVR of 19% while non-Hispanic Whites had a SVR of 52%.<sup>176</sup> The authors found that race was the only predictor of response. Multivariate analyses showed that adherence was similar in both groups, and there were no other sociodemographic differences to explain the lower rate of response. The mechanisms responsible for the decreased response rate of African Americans to interferon-based therapy are unknown.

**DOSING OF PEGINTERFERON PLUS RIBAVIRIN**

As mentioned above, there are 2 kinds of peginterferon: peginterferon alfa-2a and peginterferon alfa-2b. Peginterferon is inert polyethylene glycol (PEG) linked covalently to interferon. This results in a larger molecule than native interferon. This larger molecule has

an increased half-life because of decreases in renal clearance, proteolysis, cellular clearance, and immunogenicity. Therefore, pegylation increases the duration of biologic activity.<sup>81</sup> This allows for peginterferon to be dosed less frequently than native interferon. Both peginterferon alfa-2a and peginterferon alfa-2b are FDA approved for once weekly administration.

Peginterferon alfa-2a has a branched chain PEG resulting in a peginterferon with a molecular weight of 40 kilodaltons. This very large molecule has a narrow volume of distribution (volume of fluid in which a drug is distributed). This results in distribution limited to the circulatory system and highly perfused organs such as the liver. Since the blood volume among all adults is approximately the same (about 5 liters), peginterferon alfa-2a is dosed the same for all weights.

Peginterferon alfa-2b has a linear PEG resulting in a peginterferon with a molecular weight of 12 kilodaltons. This molecule has a wide volume of distribution with extensive tissue distribution and lower plasma concentrations compared to tissue concentrations. Therefore, it must be weight-dosed.

At the present time there is no pharmacologic advantage to weight-based dosing of peginterferon

**COMPARISON OF THE 2 PEGINTERFERONS<sup>67-69</sup>**

- The 2 peginterferon alfa-2a plus ribavirin trials showed:
  - With 48 weeks of treatment an overall SVR of 56%<sup>68</sup> and 61%<sup>69</sup>
  - A SVR for genotype 1 of 46%<sup>68</sup> and 51%<sup>69</sup>
  - A SVR for genotypes 2 and 3 of 76%<sup>68</sup> and 78%<sup>69</sup>
- The peginterferon alfa-2b plus ribavirin trial showed:<sup>67</sup>
  - With 48 weeks of treatment an overall SVR of 54%
  - A SVR for genotype 1 of 42%
  - A SVR for genotypes 2 and 3 of 82%

alfa-2b compared to fixed dosing of peginterferon alfa-2a.<sup>82</sup> The different dosing of the 2 peginterferons just reflects the differences in the pharmacokinetic characteristics of the 2 drugs.

There have been no published head-to-head trials comparing both peginterferons plus ribavirin. Results from the pivotal peginterferon alfa-2b trial<sup>67</sup> and the 2 pivotal peginterferon alfa-2a trials<sup>68,69</sup> have shown similar response rates and similar adverse reactions.<sup>20,84</sup>

The 2002 NIH Consensus Panel recommended that genotype 2 and 3 patients be treated with 800 mg of ribavirin a day plus peginterferon for 24 weeks, based on the findings from the pivotal peginterferon alfa-2a trial that genotypes 2 and 3 do as well with 800 mg of ribavirin a day for 24 weeks as they do with 1000-1200 mg of ribavirin a day for 48 weeks.<sup>3,69</sup> This same trial also showed that for genotype 1, the optimal dose of

ribavirin was 1000 mg a day for those who weighed < 75 kg, and 1200 mg a day for those who weighed > 75 kg, with the optimal duration of therapy being 48 weeks.<sup>69</sup> A retrospective analysis of the pivotal peginterferon alfa-2b and ribavirin trial showed that it used a sub-optimal dose of ribavirin (800 mg) and that those patients treated with at least 10.6 mg/kg of ribavirin achieved the highest SVR rates.<sup>67,84</sup> Based on this analysis and the pivotal peginterferon alfa-2a and ribavirin trials, the European regulatory agency approved weight-based ribavirin dosing for both peginterferons.<sup>67-69</sup>

In the US, the currently most utilized dosing schedules for both of the peginterferons plus ribavirin differs from the FDA approved dosing, but is supported by the 3 pivotal studies.<sup>84</sup>

**HELPING THE PATIENT COMPLETE TREATMENT**

The treatment of hepatitis C with peginterferon and ribavirin is complex and difficult. It requires self-injec-

**DOSING OF PEGINTERFERONS PLUS RIBAVIRIN<sup>84</sup>**

- Peginterferon alfa-2a: 180 ug SQ once a week
- Peginterferon alfa-2b: 1.5 ug/kg SQ once a week
- Ribavirin for genotype 1:
  - For weight <75 kg: 1000 mg/day po in 2 divided doses
  - For weight >75 kg: 1200 mg/day po in 2 divided doses
- Ribavirin for genotypes 2 and 3: 800 mg/day po in 2 divided doses

tions, taking pills, having many blood tests, making numerous office visits, and enduring multiple side effects. Once the patient is started on treatment, the goal of both the PCP and the gastroenterologist/hepatologist is to help the patient complete the full course of treatment, not just start it. Analysis of the studies in HCV as well as those in HIV indicates that those patients who take > 80% of their prescribed doses have the best response (80/80/80 rule).<sup>67-69,78,85,88</sup>

Adherence in the first 12 weeks is critical. Dose reductions, especially to ribavirin, reduce the chance of achieving an EVR and therefore a SVR<sup>179</sup>.

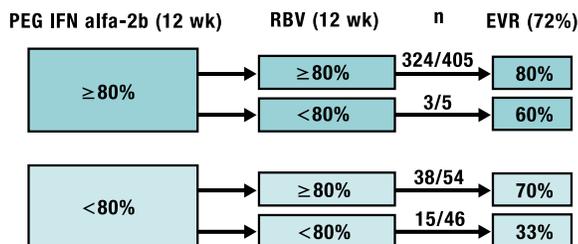
The treatment goal for all patients should be for them to take 100% of their prescribed doses (100/100/100 rule). The PCP needs to help the patient adhere to therapy to achieve this goal.

Adherence is not easy with peginterferon and riba-

**80/80/80 RULE FOR HCV TREATMENT**

- > 80% of the expected peginterferon dose
- > 80% of the expected ribavirin dose
- > 80% of the recommended duration

## Adherence and Early Viral Response (EVR)<sup>179</sup>



gists will see their patients and monitor labs once treatment has begun at 1, 2, and 4 weeks after initiation of treatment, and then once a month until the treatment is complete. It is very important that patients be seen sooner if they have any problems.

## 9. SIDE EFFECT MANAGEMENT

The side effects of combination peginterferon and ribavirin are consistent with the side effect profile of each drug. There are no synergistic or additive side effects.

Side effect management should begin before treatment even starts. As mentioned above, the patient should be educated about the side effects of treatment and how they are managed. The patient needs to know that the side effects are usually controllable. This will allow patients to recognize adverse effects

### THE MOST COMMON PEGINTERFERON SIDE EFFECTS

- Flu-like symptoms
- Psychiatric
- Hematologic
- GI
- Injection-site reactions
- Alopecia
- Thyroid toxicity

early so they can seek medical intervention quickly.

Encourage the patient to sign up for the Family Medical Leave Act (FMLA), so if they have to take time off from work once treatment has begun, they won't be penalized for missing work.

We have found that many patients do better if they take a week off from work when they begin treatment.

Dehydration makes all side effects worse. Studies have shown that 75% of all Americans are chronically dehydrated.<sup>89</sup> Even mild dehydration slows down

metabolism as much as 3%. The biggest activator of daytime fatigue is dehydration. A 2% drop in body water can trigger fuzzy short-term memory, trouble with basic math, and difficulty focusing on a computer screen or printed page. Since water cushions joints, dehydration can cause back, joint, and muscle pain.

Correction of dehydration alleviates fatigue, reduces muscle and joint pain, increases metabolism, and increases mental clarity. Prevention of dehydration is

### THE MOST COMMON RIBAVIRIN SIDE EFFECTS

- Hemolytic anemia
- Cough
- Dyspnea
- Rash and pruritis
- Anorexia
- Teratogenic effects

virin which have significant side effects.

We have found that using 2 strategies improves adherence. The first strategy, which is to develop a strong bond and trust between the patients, all the physicians, and their nurses, is of utmost importance.

**Talk** to your patients. Encourage open communication between yourself, your staff, and the patients. It's

important to emphasize the positive not the negative each and every time the patient is seen. Patients need to be educated about their disease, the drug regime, and side effects **before** treatment begins. Likewise, the patient needs

to be educated about the importance of adherence as well the consequences of non-adherence. Encourage patients to call about any problem or question. Patients should get their information from their physicians and nurses, not the Internet. The PCP needs to help the HCV patients **believe** in their treatment.

The second and equally important strategy is aggressive management of side effects. Not only will this help patients complete therapy at full dose, but it will also help avoid serious complications. To observe for side effects, it is very important to monitor the patient on a regular basis. Most gastroenterologists/hepatolo-

### 100/100/100 RULE FOR HCV TREATMENT

- 100% of the expected peginterferon dose
- 100% of the expected ribavirin dose
- 100% of the expected duration

### LABORATORY MONITORING

WEEK	0	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52	72
CBC/DIFF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LFT'S	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PREG. TEST IF FERTILE	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	MO: X6	POST-TX
HCV RNA	X					X			X						X		X
TSH	X					X			X						X	X	

therefore very important. The optimal fluid intake in fluid ounces is 1/2 of the patient's weight in pounds. In practice, this is very hard to do. Not everyone can drink lots of water. On every visit, encourage patients to drink fluids. In addition to water, they can drink sports drinks, such as Gatorade®, and other non-cafeinated drinks.

## FLU-LIKE SYMPTOMS

Flu-like side effects are very common. They include headache, fatigue, fever, chills, arthralgias and myalgias. They occur within a few hours after injection of peginterferon. They are most severe after the first dose and usually improve spontaneously by the third or fourth injection. Patients do better if they can take their peginterferon injection at bedtime the night before their 2-day weekend; for most people this is Friday night. But those people who have days off in the middle of the week should take their injection the night before their first day off. Taking the peginterferon at night allows patients to sleep through their symptoms.

Acetaminophen can be taken for the flu symptoms. There is a widespread misconception that acetaminophen cannot be given to HCV patients. Acetaminophen is a much misunderstood medication. The *Medical Letter* states:

*“at usual doses in healthy people, acetaminophen has virtually no adverse effects. Hepatic injury from acetaminophen is due mainly to a single toxic metabolite, Nacetyl- p-benzoquinoneimine, which is formed by oxidation of the drug. With therapeutic doses in healthy subjects, oxidation is a minor metabolic pathway, and glutathione conjugates and inactivates the toxic metabolite... the weight of the evidence indicates that recommended doses of acetaminophen do not cause hepatotoxicity even in chronic alcoholics. [They conclude] acetaminophen is an effective analgesic with virtually no adverse effects except for those related to overdosage.”<sup>90</sup>*

Because acetaminophen's effects on the liver are dose dependent, it can be used safely even in cirrhosis.<sup>90-94</sup> There is no contraindication to acetaminophen, given in therapeutic doses, to patients with stable chronic liver disease.<sup>95</sup> One 500 mg tablet of acetaminophen taken 1/2 hour before and every 4-6 hours after the injection (not to exceed 2 g/day in cirrhosis and severe fibrosis and 3 g/day in non-cirrhosis) can be given safely and helps reduce symptoms.<sup>91-</sup>

<sup>94</sup> Patients need to be warned that exceeding this dose may lead to liver failure and even death.

Over the counter NSAIDs such as ibuprofen can be taken, except in severe fibrosis and cirrhosis, as long as the recommended dose is not exceeded. NSAIDs should never be given to patients with severe fibrosis or cirrhosis where sodium excretion in the urine is preserved by high prostaglandin synthesis in the kidneys. NSAIDs, by inhibiting renal prostaglandin synthesis, will worsen sodium retention and may lead to fluid retention and renal failure.<sup>93,94,96</sup>

Pushing fluids (**hydration, hydration, hydration**), having the patient get plenty of rest the “weekend” after their injection, and avoiding strenuous exercise helps ameliorate symptoms. Many patients also find taking warm baths helps.

## NEUROPSYCHIATRIC

Neuropsychiatric symptoms in HCV require careful and serious attention. Preexisting depression occurs in 35%-57% of HCV patients even before treatment.<sup>137,138</sup> Treatment with peginterferon has been reported in the pivotal studies to induce or exacerbate depression in 20%-30% of treated patients.<sup>68,70</sup> Patients with preexisting neuropsychiatric disease have been shown to have an increased susceptibility to interferon-caused depression.<sup>141,142</sup> Depression is the most common reason for stopping HCV treatment.

The exact mechanisms by which interferon causes depression are unclear, but the most likely cause may be related to stimulation of cytokines that modulate the serotonergic system.<sup>138</sup> Interferon has been shown to activate indoleamine 2, 3-dioxygenase which reduces the production of 5-hydroxytryptamine (serotonin) by decreasing its precursor tryptophan.<sup>142-145</sup> These studies show that the plasma concentrations of both tryptophan and serotonin are reduced in patients treated with interferon.<sup>142,145</sup> Furthermore, decreased levels of tryptophan have been linked to the severity of depression during treatment with interferon.<sup>143</sup>

A prospective study assessing the incidence of interferon-induced major depression showed that the mean time for the development of major depression was 12.1 weeks after the start of interferon.<sup>145</sup> The range was 1-32 weeks with most of the patients being diagnosed between 6-22 weeks. In the majority of patients, major depression was found to develop extremely rapidly, within 2 weeks or less, after the onset of depressive symptoms.

Other neuropsychiatric symptoms seen with inter-

feron include changes in mood, cognition, and personality as well as anxiety, anger, hostility, fatigue, irritability, and insomnia.<sup>89,138,139</sup> Interferon-treated patients can experience increased interpersonal problems.<sup>137</sup> Fatigue is often a symptom of depression. Insomnia can also result from depression because depression can result in inadequate sleep patterns.

Management of depression in HCV patients should begin before the start of treatment and continue throughout treatment. Therefore, PCPs need to screen for depression in all their HCV patients every time they see them, both before and during HCV treatment, even if they present with other unrelated problems.

**SIGNS & SYMPTOMS OF INTERFERON-INDUCED NEUROPSYCHIATRIC SIDE EFFECTS**

- Sadness
- Crying
- Loss of interest
- Social withdrawal
- Sense of guilt
- Suicidal ideation
- Psychomotor slow down
- Agitation
- Irritability
- Aggression
- Anxiety
- Emotional lability
- Insomnia
- Can't concentrate

A variety of effective but lengthy screening instruments, such as the *Beck Depression Inventory* and the *Center for Epidemiologic Studies' Depression Scale (CES-D)* have been used to diagnose depression in HCV research studies and in academic practices. In the cost-conscious office setting, the health care provider's

time with the patient is brief, and without a research assistant to administer these extensive tests, such written instruments are too cumbersome and time-consuming to administer.

We have modified a verbal office based 2-question depression instrument for use in hepatitis C.<sup>146,147</sup> This modified instrument (HEP-2Q) can be administered verbally by the PCP or gastroenterologist/hepatologist directly to the patient, and we have shown that it is as effective as the *Center For Epidemiologic Studies' Depression Scale (CESD)* in detecting

**OFFICE-BASED 2-QUESTION HCV DEPRESSION INSTRUMENT (HEP-2Q)<sup>146, 147</sup>**

- During the past year (administered at initial visit) or
- Since your last visit (administered at all follow-up visits during treatment)
  - Have you been bothered by crying, agitation, anger, irritability, sadness, feeling down, depressed, or hopeless?
  - Have you often been bothered by little interest or pleasure in doing things and have you not been as involved with friends and family?

A "yes" response to either of the 2 questions is considered positive for depression

depression in HCV patients.<sup>146,147</sup>

All HCV patients with active major depression including bipolar disorder, a history of major depression, or prior psychiatric hospitalization should be referred to a psychiatrist familiar with the neuropsychiatric side effects of interferon for evaluation and treatment. Peginterferon and ribavirin should not be started until the psychiatrist determines that the patient is stable enough on antidepressants to undergo HCV treatment. The patient must see the psychiatrist on a regular basis during HCV treatment.

Patients with current or past history of minor depression and those at risk for developing depression (i.e., stressful life event) should be treated with an antidepressant for at least 4-6 weeks before HCV treatment is begun. Several studies in HCV and malignant melanoma have shown that prophylactic antidepressant treatment can prevent the development of interferon-induced depression.<sup>148,151</sup> In those patients who develop depression during treatment, early identification and treatment with antidepressants have been shown to alleviate depression and allow for completion of treatment without dose reduction.<sup>145,151-153</sup>

Selective serotonin reuptake inhibitors (SSRIs) are now the drugs of choice for treating depression.<sup>154</sup> They are also used to treat generalized anxiety disorder, obsessive-compulsive disorder, panic disorder and social phobia.<sup>154</sup> SSRIs work by blocking the reuptake of serotonin into the presynaptic terminal. This enhances serotonin neurotransmission resulting in their antidepressant effect.<sup>154</sup> SSRIs have been the most studied antidepressants in treating interferon-induced depression and have been shown to be well-tolerated and effective.<sup>145,148-153</sup> SSRIs work well for depressed mood and anxiety, but do not work well for fatigue. Side effects include erectile dysfunction, transient nausea and diarrhea, headaches, and weight gain with long-term use. The effects on the P450 pathway vary according to the individual agent.<sup>155</sup> Citalopram has little effect, sertraline has moderate inhibition, and fluoxetine and paroxetine have strong inhibition of the P450 system.

Antidepressants that target both serotonin and norepinephrine have also been found useful in treating peginterferon-induced depression.<sup>149</sup> Antidepressants with norepinephrine effects work well for treating fatigue and anorexia. Venlafaxine produces strong inhibition of serotonin and norepinephrine and has a faster onset of action than SSRIs.<sup>154</sup> Side effects are similar to SSRIs and include erectile dysfunction, nausea, and elevation of diastolic blood pressure with doses greater than 300 mg/day.<sup>154</sup> Venlafaxine has

little effect on the P450 system.<sup>156</sup>

Bupropion is a norepinephrine and dopamine reuptake inhibitor that, unlike SSRIs and venlafaxine, has no sexual side effects. Because it is energizing, it can be used alone or added to an SSRI when there is depression with significant fatigue; side effects include nausea and anxiety. In combination with protease inhibitors, there is an increased seizure risk. Bupropion has little effect on the P450 system.<sup>156</sup>

The choice of which antidepressant to use should be based on efficacy, speed of action, side effects and drug-drug interactions. All antidepressants should be started at a low dose for the first week to prevent anxiety and panic attacks and then increased to a therapeutic dose.

Antidepressants should be continued for at least 6

#### EXAMPLES OF ANTIDEPRESSANTS USED IN HCV

- SSRIs i.e., Paroxetine (Paxil®) 20-60 mg/day
  - Works well for depressed mood and crying
  - Start at 10 mg q am
- Venlafaxine XR (Effexor XR®) 75-225 mg/day
  - Faster onset than SSRIs
  - Works well for fatigue and anorexia
  - Start at 37.5 mg q am
- Bupropion SR (Wellbutrin SR®) 150-400 mg/day
  - No sexual side effects
  - Can be added to a SSRI if fatigue develops
  - Start at 150 mg q am

months after stopping peginterferon to prevent relapse of depression.<sup>89, 157</sup> In order to prevent a discontinuation syndrome (withdrawal), anti-depressants should be slowly tapered over the next 6-12 months.<sup>91,154</sup> Withdrawal symptoms include headache, nausea, dizziness, lethargy, agitation, and panic attacks.<sup>154</sup>

## FATIGUE

Fatigue is a very common side effect of HCV treatment and is multifactorial in etiology. HCV by itself can cause fatigue.<sup>130</sup> Fatigue is the most common side effect of all interferons, including pegylated interferon, occurring in 70%-100% of treated patients.<sup>131,132</sup>

The etiology of interferon-induced fatigue is also multifactorial. Besides interferon-mediated hypothyroidism, interferon suppresses the hypothalamic-pituitary-adrenal axis which may contribute to fatigue.<sup>113</sup> Interferon-induced depression is an important etiologic cause of fatigue.

Anemia, changes in blood sugar, work-related and social activities, and insomnia can also contribute to fatigue. Therefore, when the patient complains of

fatigue, a TSH, CBC, and chemistry panel including glucose and electrolytes should be obtained. An assessment of activities and sleep patterns needs to be ascertained. Depression should be evaluated and treated if present. Advise the patient to get plenty of rest and to avoid strenuous exercise. Light exercise, good nutrition, and hydration should be advocated.

If the patient has insomnia, good sleep habits should be encouraged. The patient should avoid caffeine after 4PM. If pharmacologic intervention is necessary, first try diphenhydramine 25-50 mg or diphenhydramine plus acetaminophen, 1-2 tablets 1/2 hour before bed. Or if these don't help, trazodone 25-50 mg or lorazepam 0.5 mg given 1/2 hour before bed often induces sleep.

If the patient develops profound fatigue that does not respond to anything else, the psychostimulants methylphenidate 5-20 mg twice a day or modafinil 100-400 mg per day may be helpful.<sup>131-135</sup> Both have been used to treat fatigue in patients with cancer, HIV, multiple sclerosis, and depression with improvement not only of fatigue, but also of daytime wakefulness, quality of life, and psychological distress. A pilot study in melanoma patients receiving interferon showed that the combination of methylphenidate and aerobic exercise resulted in improvement of fatigue and cognitive function, compared to the group with only exercise.<sup>136</sup> Modafinil has been recently approved by the FDA for treatment of excessive daytime sleepiness due to chronic obstructive sleep apnea and night shift work disorder. Further studies for both of these agents in the treatment of interferon-induced fatigue are needed.

## HEMATOLOGIC

Anemia, neutropenia, and thrombocytopenia can occur with peginterferon and ribavirin treatment. Traditionally, these side effects have required dose reduction which can have a negative impact on the ability to obtain a SVR (80/80/80 rule). The increasing experience with growth factors over the past several years has demonstrated that the majority of hematologic side effects can be handled without the need for dose reductions, thereby enhancing quality of life and the ability to obtain a SVR.

**ANEMIA:** Combination peginterferon and ribavirin causes a multifactorial anemia.<sup>114</sup> Peginterferon suppresses bone marrow function causing decreased red blood cell production.<sup>115</sup> Ribavirin causes a dose dependent hemolytic anemia in all patients, though the degree of anemia can vary between patients.<sup>91</sup> The mechanism of ribavirin-induced anemia is impairment

of red blood cell antioxidant defenses which causes oxidative damage to the red blood cell membrane resulting in extravascular hemolysis by the reticuloendothelial system.<sup>116</sup> Hemoglobin levels decrease in the first 4 weeks of treatment with a mean decrease of 2.5 g/dl.<sup>117</sup> The resulting anemia causes fatigue, reduces quality of life, and decreases adherence.<sup>118</sup> The package inserts for both peginterferons and ribavirin recommend dose reduction of ribavirin when the hemoglobin is less than 10g/dL.

Because dose reduction of ribavirin particularly during the first 12 weeks of treatment decreases the chance of a successful SVR,<sup>78</sup> use of erythropoietin to maintain the ribavirin dose, although not FDA approved, has become an important option in treating ribavirin induced anemia. Erythropoietin is a hormone created predominantly in the kidneys that stimulates erythropoiesis in the bone marrow. Recombinant human erythropoietin (epoetin alfa) has been demonstrated to be safe, effective, and to increase the quality of life in the treatment of anemia resulting from chronic renal failure, cancer chemotherapy, antiretroviral therapy in HIV patients, and in elective noncardiac surgery patients.<sup>119,120</sup>

Four recent randomized controlled trials have

#### RECOMMENDATIONS FOR USE OF EPOETIN ALFA<sup>111-123</sup>

- Epoetin alfa can be initiated when the hemoglobin level is <11 g/dl
- Give epoetin alfa at a dose of 40,000 IU SQ once a week
- If the hemoglobin does not increase at least 1 g/dl after 4 weeks, the dose can be increased to 60,000 IU SQ once a week.
- If there is no response to 60,000 IU after 4 weeks, the epoetin alfa should be stopped.
- If the hemoglobin in men reaches  $\geq 16$  g/dl or  $\geq 14$  g/dl in women, the epoetin alfa should be stopped.
  - If the hemoglobin later falls to  $\leq 15$  g/dl in men or  $\leq 13$  g/dl in women, the epoetin alfa should be restarted at a dose of 30,000 IU and increased to 40,000 if needed.

demonstrated the efficacy and value of treating ribavirin-induced anemia with once weekly epoetin alfa.<sup>121-123,158</sup> All 4 studies showed that epoetin alfa increased hemoglobin levels, maintained ribavirin dosing, and improved quality of life during treatment. Thus, the use of epoetin alfa has emerged as an important strategy to treat ribavirin-induced anemia and, unlike dose reduction, allows the patient to stay on the optimal ribavirin dose. Based on these trials, recommendations for the use of epoetin alfa have been developed.

**NEUTROPENIA:** Neutropenia from peginterferon is due mainly to bone marrow suppression, tends to

occur within the first 2 weeks of treatment, remains stable during treatment, and then returns to pretreatment levels after treatment is finished.<sup>91,117,124</sup> The resulting neutropenia is not usually related to a risk of severe bacterial infections.<sup>67,68,125</sup> In one study of 119 patients who were treated with peginterferon and ribavirin, none of the 18% who developed bacterial infections were neutropenic.<sup>125</sup> The package inserts of both peginterferon alfa-2a and alfa-2b, listing dose reductions of peginterferon for neutropenia of less than 750 cells/mm, are based on studies of cancer patients undergoing chemotherapy.<sup>115</sup> HCV patients are not immunosuppressed oncology patients!<sup>116</sup> Except in those with cirrhosis, coinfection with HIV, or liver transplant recipients, most gastroenterologists/hepatologists do not get concerned until the absolute neutrophil count reaches 500 cells/mm.

In the 3 pivotal peginterferon plus ribavirin trials, neutropenia was a frequent cause for peginterferon dose reduction.<sup>54,67,69</sup> Since prolonged dose reduction will decrease the chance of achieving a SVR, recombinant granulocyte colony stimulating factor (G-CSF), although not FDA approved, has been used to maintain neutrophil counts rather than reduce dose in the setting of peginterferon-induced neutropenia.<sup>126-129</sup> The dose of G-CSF is 300 ug subcutaneous 2-3 times per week given when the absolute neutrophil count (ANC) < 750 cells/mm<sup>3</sup> and titrated to maintain the ANC > 750 cells/mm<sup>3</sup>.<sup>119</sup> G-CSF should be given 24 hours before peginterferon and the trough WBC measured 3 days later.

**THROMBOCYTOPENIA:** Thrombocytopenia is rarely a problem with peginterferon plus ribavirin except in cirrhosis with preexisting thrombocytopenia.<sup>91</sup> There were no bleeding complications from thrombocytopenia reported in the 3 pivotal peginterferon plus ribavirin trials.<sup>66,67,69</sup> The thrombocytopenia seen is mainly from peginterferon-induced bone marrow suppression and is blunted by reactive thrombocytosis from ribavirin.<sup>123</sup> Therefore, interventions for thrombocytopenia are seldom needed. The package insert for peginterferon alfa-2b recommends decreasing the dose in half when the platelet count is < 80,000 cell/mm<sup>3</sup> and stopping it when the platelet count is < 50,000 cell/mm<sup>3</sup>.<sup>3</sup> The package insert for peginterferon alfa-2a recommends decreasing the dose by half when the platelet count is < 50,000 cell/mm<sup>3</sup> and stopping it when the platelet count is < 25,000 cells/mm<sup>3</sup>.<sup>3</sup> Because the platelets remaining are normal platelets and bleeding is un-usual, most clinicians use the peginterferon alfa-2a guideline for both peginterferons.

Recombinant human interleukin-11 is a growth factor that has been used to treat thrombocytopenia in cancer patients undergoing chemotherapy. A pilot study using interleukin-11 to treat thrombocytopenia in 13 HCV patients receiving interferon and ribavirin showed that, although platelet counts increased, fluid retention occurred in all patients and 10 of these required diuretics.<sup>129</sup> Therefore, interleukin-11 can not be recommended for use in HCV.

## DERMATOLOGICAL

Dermatological side effects include rashes, pruritus, injection-site reactions, and alopecia. Rash and pruritus are common and usually due to ribavirin. A variety of therapies help.

Three kinds of injection-site reactions can occur with interferon.<sup>97</sup> Subtle uninflamed sclerotic dermal lesions are the most common with development of erythema at the injection site 1-2 days after the injection and lasting up to 2-3 weeks. Large erythematous plaques occur in up to 10% and usually require a medium or high strength topical cream. Cutaneous ulcers develop in only 0.5% and need wound care with antibiotic ointment. Large lesions should be referred to a dermatologist.

To attempt to minimize injection-site reaction, the GI nurse will instruct the patient in the proper way to give the SQ injection. Prior to the injection, the site

should be cleaned with an antibacterial hand sanitizer such as Purell® which is allowed to dry before giving the injection. The peginterferon should be at room temperature when injected. The injection site should be changed every week. In patients with multiple injection-site reactions, premedicating 30-60 minutes before the injection with diphenhydramine or loratadine may help.

Reversible alopecia from peginterferon occurs in about 20% of patients; the texture of hair may be altered, making it more prone to breakage.<sup>98</sup> It may last as long as 3

### TREATMENT FOR RIBAVIRIN-INDUCED RASHES

- Topical antihistamine cream (Zonalon®)
- Calamine lotion
- Aveeno® oatmeal baths
- Topical corticosteroid creams:
  - Low strength (hydrocortisone 1%)
  - Only one to use on the face
  - Medium strength (triamcinolone 0.1%)
  - High strength (fluocinonide .05%)
  - No longer than 2 weeks to avoid suppression of the pituitary-adrenal axis
- Loratadine 10 mg once a day
- Hydroxyzine 10-25 mg every 6 hours prn
- Diphenhydramine 25-50 mg every 6 hours prn
- Sunscreen

months after the end of treatment. Women need constant reassurance that this is a temporary condition. Patients who are affected should avoid coloring, permanents, ponytails, braiding and blow-drying. Patients can be told that it is not necessary to shampoo their hair daily and that they should use a gentle shampoo like baby shampoo. Very gentle combing and brushing should be encouraged. Minoxidil is of no value.

## RESPIRATORY

Dyspnea and cough can occur from ribavirin. Pulmonary disorders such as pulmonary infiltrates, interstitial lung disease, bronchiolitis obliterans (organizing pneumonia and interstitial pneumonitis), and sarcoidosis are rare complications of interferon.<sup>91,99-105</sup> When patients develop dyspnea or cough, a chest x-ray should be considered to rule out pulmonary causes as well as a CBC to rule out anemia. The patient should avoid irritants such as cold air, smoke, and allergens. A humidifier may help. Cough medication with dextromethorphan can be of value, such as Robitussin CoughGels®.

## GASTROINTESTINAL

Nausea and vomiting are caused mainly by ribavirin. Taking it with food decreases symptoms. If symptoms persist, antiemetics, such as promethazine and ondansetron, Pepto-Bismol®, or a scopolamine patch can help.

Patients on treatment who develop diarrhea need to be evaluated for other causes of diarrhea. If indicated, stool samples for C + S, O + P, and *C. difficile* toxin should be obtained. Diarrhea resulting from peginterferon and ribavirin can usually be managed with loperamide, Citrucel®, Metamucil®, or Pepto-Bismol®. Again, hydration is very important.

Dyspepsia and anorexia can also occur. Dyspepsia can be treated with antacids, sucralfate, Pepto-Bismol®, or omeprazole. The anorexia that occurs, usually from ribavirin, can result in significant weight loss. Other causes of weight loss, especially depression and hyperthyroidism, need to be ruled out. Hydration is critical in these patients. Having the patient eat smaller, more frequent meals is often helpful. Some patients can tolerate nutritional supplements such as Carnation Instant Breakfast®, Ensure®, or Boost®. All patients with weight loss should take a daily multivitamin and mineral supplement.

## OPHTHALMOLOGIC

All interferons can infrequently (< 1%) cause a retinopathy resembling diabetic retinopathy with retinal hemorrhage and cotton wool spots.<sup>91,99,106,107,159,160</sup> The retinopathy is more common among diabetics and hypertensive patients, usually occurs during the first 2 months of treatment, and is usually mild and goes away while the patient is still being treated.<sup>107,160</sup> Any new visual complaint such as blurry vision or loss of vision (blind spots) should be referred to an ophthalmologist. As mentioned above before treatment begins, all patients should undergo an ophthalmologic exam by the PCP. All patients with diabetes, hypertension, or visual complaints should have a baseline retinal exam by an ophthalmologist prior to treatment.

## THYROID

Patients treated with interferon can develop thyroid dysfunction, thyroid autoimmunity, or both in 6-20%.<sup>91,108-113,178</sup> Interferon-mediated hypothyroidism is associated with the development of the same features seen in autoimmune thyroiditis: antithyroid antibodies, antithyroid globulin, and antithyroid peroxidase. Painless thyroiditis is most common. Interferon-induced thyroid disorders may be irreversible. A TSH level should be checked before therapy, every 12 weeks during therapy, and after therapy is finished. Any abnormalities of TSH should be evaluated and treated. HCV treatment can usually be continued.

## 10. CONCLUSION

HCV presents unique challenges for the PCP. It is up to the PCP to screen, diagnose, and refer these mostly asymptomatic patients. The PCP also plays an important role in helping monitor the patient on treatment and helping them adhere to and finish treatment. Successful management of the HCV patient during treatment therefore requires a close partnership between the PCP and the gastroenterologist/hepatologist.

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