MANAGEMENT OF HEPATITIS C BY THE PRIMARY CARE PROVIDER:

MONITORING GUIDELINES

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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).[1] 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.[2] 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.[3,180] 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.[3] 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.[4]

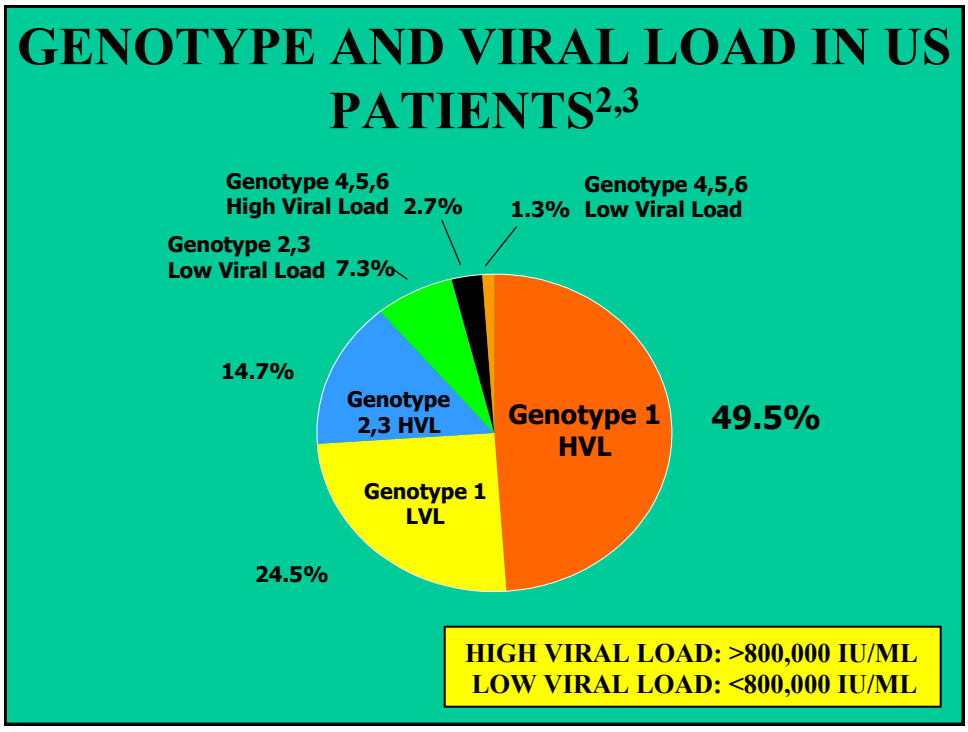
Most of the morbidity and mortality from HCV is caused by complications of decompensated cirrhosis. If identification and treatment of all persons with HCV with compensated cirrhosis occurred today, the number of cases of decompensated cirrhosis would be reduced by approximately one-third after 20 years.[5] 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 the PCP in their role as gatekeeper of healthcare to identify and screen their 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.[6-8] 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 it will be readily available when needed.

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.[3] 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.[9]

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%.[3] 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%.[2] 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.



NATURAL HISTORY OF HCV

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

Chronic infection is the hallmark of HCV. Some 70%-85% of people infected with HCV will develop chronic disease.[10-12] 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%.[3,11] 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.[20-22]

Progression to Fibrosis, Cirrhosis, and HCC

Not all cases of HCV lead to cirrhosis or HCC.[20,23] There is a great deal of variability in the natural history of HCV regarding progression of fibrosis.[20-23] 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.

FACTORS ASSOCIATED WITH DISEASE PROGRESSION[3,22]

- 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

Likewise there are factors that do not influence disease progression

FACTORS NOT INFLUENCING DISEASE PROGRESSION[3,22]

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

The best predictor of risk for progression to cirrhosis is the degree of hepatocellular necrosis, inflammation, and fibrosis on initial liver biopsy.[23,24] Liver enzymes have not been shown to be of value in predicting fibrosis.[3] Baseline liver biopsy is therefore considered the gold standard for determining the extent of disease in HCV.[25] 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.[24] 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.[23] Although a variety of serum fibrosis markers are under investigation, they should be considered investigational until validation studies are completed.[26]

Compensated cirrhosis is the presence of cirrhosis with the absence of complications.[27]

COMPENSATED CIRRHOSIS

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

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.[28] 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.

DECOMPENSATED CIRRHOSIS

- Ascities
- Bleeding esophageal varices
- Hepatic encephalopathy
- Jaundice

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.[3,28]

RISK FACTORS FOR HCC IN HCV[22,29,30]

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

Extrahepatic Manifestation 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.[31] They involve most commonly the joints, muscles, and skin.

CLINICAL EXTRAHEPATIC MANIFESTATIONS OF HCV[31]

- 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%)

BIOLOGIC EXTRAHEPATIC MANIFESTATIONS OF HCV[31]

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

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 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 keep at a constant 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.[32]

Other studies have found both higher and lower frequencies of both porphyria cutanea tarda (PCT) and lichen planus.[32,33] 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 variablity.[33] 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%).[33] Clinically, there are no differences between familial PCT and HCV-acquired PCT. The skin lesions 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%.[34,35]

HCV-related arthritis can be divided into 2 groups.[36] 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/cryoglobulins deposits in the joints; synovial autoimmune response caused by the virus; and direct viral invasion.[37]

SCREENING FOR HCV

"All patients with chronic hepatitis C are potential candidates for antiviral therapy."[3] 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.[10] 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.[38] The CDC recommends HCV testing based on increased risk for infection.[39] The HCV risk factor can be recognized with thorough questioning in greater than 90% of cases.[40]

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

Individual Risk Factors

Vertical transmission occurs in 5% of infants born to HCV-infected women.[39] There appears to be no difference in transmission rates between cesarean-delivery and vaginal delivery from non-HIV coinfected mothers.[41] Cesarean section is correlated with a decreased risk of transmission only in mothers who were HIV coinfected.[42] 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.[3,43] The risk of HCV transmission between monogamous sexual couples is rare.[44,45] 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 scissors, found an incidence rate of 0.37 per 1.000 person-years.[45] Interestingly, of the 3 individuals who developed HCV infection during the study, one had a needle stick with a patient coinfected with HCV/HIV, one had a dental implant, and the third, who had no other risk factor, had a different

strain of HCV than the partner had. The authors concluded that "the risk of sexual transmission of HCV is extremely low or even null."[45]

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.[3,46-48]

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%.[49] The CDC has found that about 1% of hospital staff are antibody positive for HCV.[50]

Approximately 200,000 patients in the US are infected with both HCV and HIV.[181] The percentage of coinfection is higher in persons who obtained HIV through blood products and IV drug use rather than through sexual exposure.[181] HCV is now the leading cause of death in HIV- infected patients.[182] 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[183] 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.[183-185]

Approximately 240,000 persons emigrate annually to the US from Asia.[186] According to the US census of the year 2000, there are approximately 12 million Asians and Pacific Islanders living in the US.[187] In most of Asia, the prevalence of HCV infection is 2-6% and the prevalence of HBV infection is 8-10%.[188,189] 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%.[190] 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.[190] Therefore, Asian Americans born in HCV-endemic areas should be offered HCV testing.

DIAGNOSIS OF HCV

Once the PCP has identified a risk factor, they 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%.[51] 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.[20] Anti-HCV cannot distinguish between new, chronic, or previous infection. Anti-HCV is not protective.

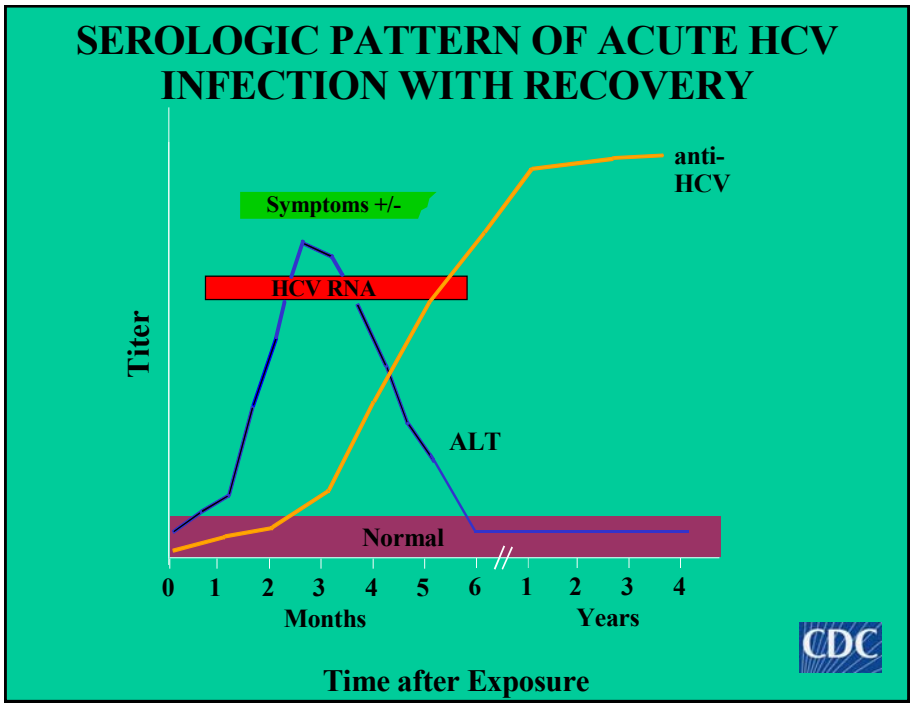
The confirmatory test of choice is an HCV RNA assay.[51] The HCV RNA tests detect the presence or absence of virus. HCV RNA becomes detectable 1-3 weeks after infection.[3] There are two types of HCV RNA assays: qualitative and quantitative. Qualitative tests results are reported as being either positive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

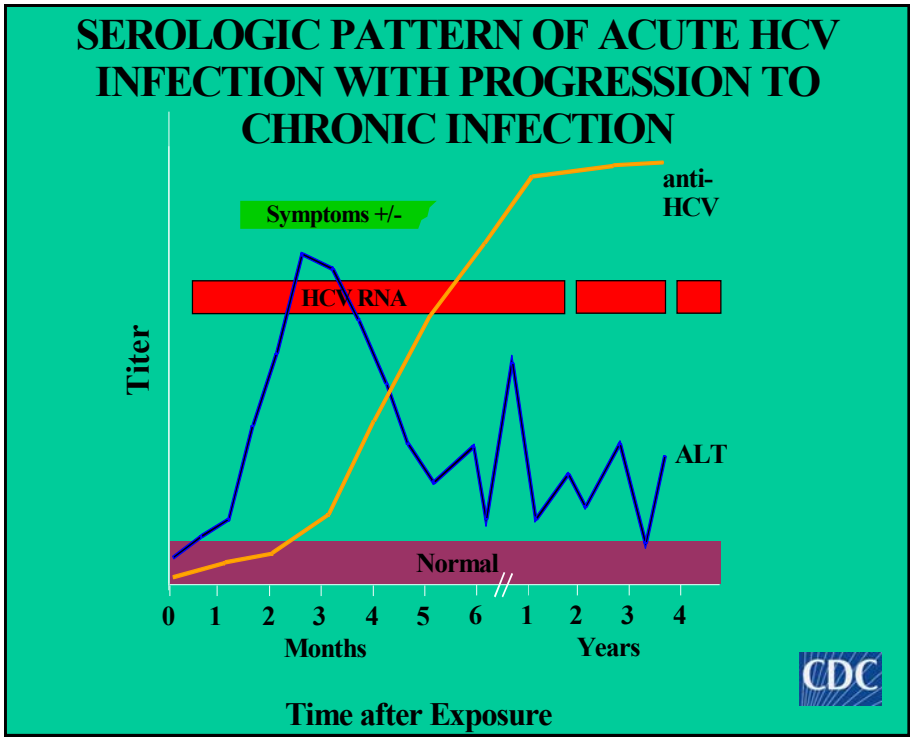
In the past, it was recommended that all positive anti-HCV be confirmed with a qualitative RNA because it was the more sensitive assay. Today, with availability of sensitive quantitative RNA assays with low ranges of detection that equal qualitative tests (such as the Quest Heptimax™ with a range down to 5 IU/ml), the PCP 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.

INTERPRETATION OF ANTI-HCV AND HCV RNA[53]

- 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


SEROLOGIC PATTERN OF ACUTE HCV INFECTION WITH RECOVERY
anti-HCV
Symptoms +/-
HCV RNA
Titer
ALT
Normal
0 1 2 3 4 5 6 1 2 3 4
Months
Years
CDC
Time after Exposure


SEROLOGIC PATTERN OF ACUTE HCV INFECTION WITH PROGRESSION TO CHRONIC INFECTION
anti-HCV
Symptoms +/-
HCV RNA
Titer
ALT
Normal
0 1 2 3 4 5 6 1 2 3 4
Months
Years
CDC
Time after Exposure

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 (peginterferon) 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.

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;[64] they may be treated with peginterferon monotherapy

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 immune-mediated 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[3,65]
- **Hemoglobinopathies, preexisting neutropenia (<1,500 cells/mm^3), preexisting anemia (hemoglobin <12g/dl in women and <13g/dl in men), and preexisting thrombocytopenia (<100,000 cells/mm^3):** 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

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

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 coinfected
- 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[54]
- An ophthamoloscopic exam by the PCP. All diabetics and hypertensives should see an ophthamologist 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

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.[3,20,25,84] 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.[3]

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.[3,54,55]

WHAT TO TELL THE HCV PATIENT[3,54,55]

- 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)

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.[56]

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.[57-59] 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.[60] 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.[60] The authors conclude that there is not enough evidence to recommend milk thistle for the treatment of chronic liver disease.[60]

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.[61] 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.[62] 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.[63]

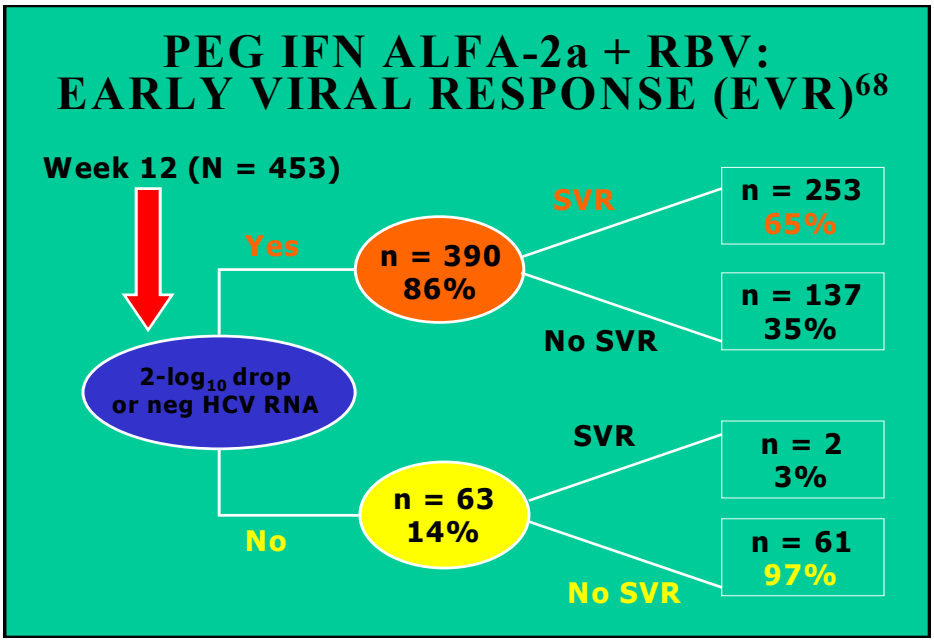
TREATMENT OF HCV

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**).[3,44] **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.[66-69] 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.[70] Histologic improvement occurs not only in those who clear the virus, but also in in those who do not.[71,72] The greatest improvement occurs in those who attain an SVR.[72] 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.[71-77,177] 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.[177]

Another important treatment strategy the PCP needs to understand is early virologic response (**EVR**).[78,79] EVR is the finding that the HCV RNA level, measured 12 weeks after starting treatment, is either non-detectable 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%.[68] 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,[68] so treatment should be continued. A retrospective analysis of the first study of peginterferon alfa-2b plus ribavirin showed similar findings.[79]



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

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

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.[161,162] 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%).[163] 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.[163]

A recent U.S. prospective trial compared 24 weeks of peginterferon plus ribavirin versus peginterferon monotherapy versus a control group of untreated patients in the treatment of acute HCV.[164] SVR was achieved 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%.[165] A recent Italian study showed that 39% of acute HCV patients were RNA negative after 12 weeks from onset of infection.[166] 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.[161]

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.[162] 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 way of determining hepatic inflammation and injury.[3,167] About 30% of patients with HCV have normal ALT levels.[168] Patients with normal ALT levels have been shown to achieve a SVR with interferon and ribavirin comparable to those with elevated ALT levels.[169] Two recent studies have shown the efficacy of peginterferon alfa-2a and ribavirin in patients with normal ALT levels.[170,171] 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%).[2,172, 173] The higher prevalence of HCV in African Americans is thought to be due to the increased risk of exposure.[172]

African Americans also have a lower response rate to treatment compared to non-Hispanic whites.[172,174-176] 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.[174] 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%.[176] 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 decrease in renal clearance, proteolysis, cellular clearance, and immunogenicity. Therefore, pegylation increases the duration of biologic activity.[81] 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 alfa-2b compared to fixed dosing of peginterferon alfa-2a.[82] 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[67] and the 2 pivotal peginterferon alfa-2a trials[68,69] have shown similar response rates and similar adverse reactions.[20,84]

COMPARISON OF THE 2 PEGINTERFERONS[67-69]

- The 2 **peginterferon alfa-2a plus ribavirin** trials showed:
  - With 48 weeks of treatment an overall SVR of 56%[68] and 61%[69]
  - A SVR for genotype 1 of 46%[68] and 51%[69]
  - A SVR for genotypes 2 and 3 of 76%[68] and 78%[69]

- The **peginterferon alfa-2b plus ribavirin** trial showed:[67]
  - 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%

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.[3,69] 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.[69] 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. [67,84] 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.[67-69]

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.[84]

DOSING OF PEGINTERFERONS PLUS RIBAVIRIN[84]

- **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

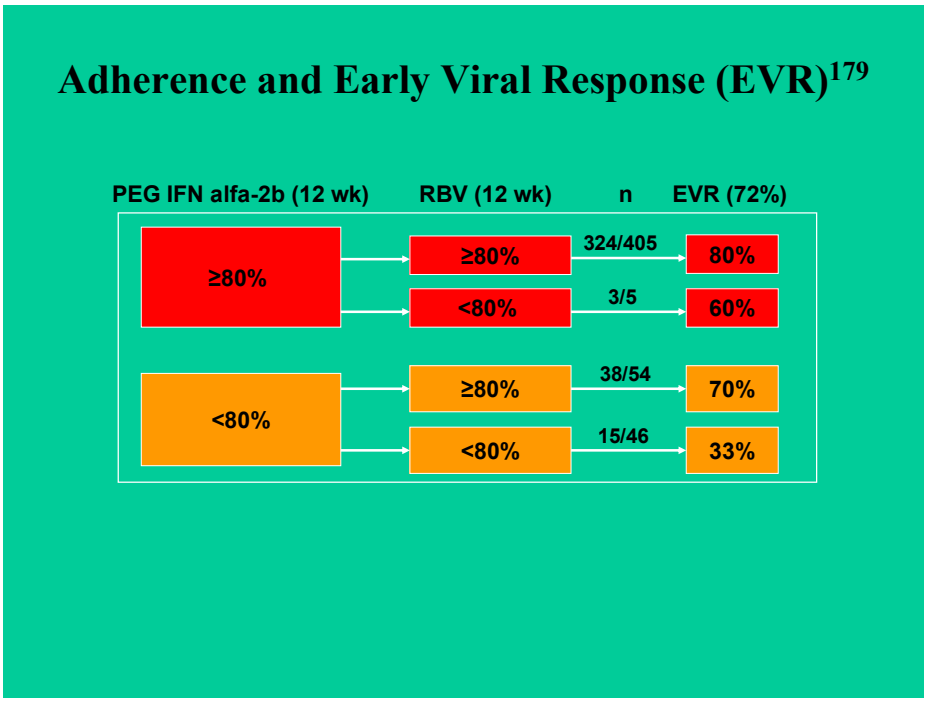
Helping the Patient Complete Treatment

The treatment of hepatitis C with peginterferon and ribavirin is complex and difficult. It requires self-injections, 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).[67-69,78,85,88]

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 in the first 12 weeks is critical. Dose reductions, especially to ribavirin, reduce the chance of achieving an EVR and therefore a SVR[179].



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.

100/100/100 RULE FOR HCV TREATMENT

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

Adherence is not easy with peginterferon and ribavirin 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 patient, all the physicians, and their nurses, is of utmost importance. **Talk** to your patient. Encourage open communication between yourself, your staff, and the patient. It's important to emphasize the positive not the negative each and every time the patient is seen. The patient needs 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. The patient should be encouraged to call about **any** problem or question. The patient should get their information from their physicians and nurses, **not** the Internet. The PCP needs to help the HCV

patient **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/hepatologists 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.

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. POST	X 6 T-TX
HCV RNA	X					X			X						X		X
TSH	X					X			X						X	X	

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.

THE MOST COMMON PEGINTERFERON SIDE EFFECTS:

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

THE MOST COMMON RIBAVIRIN SIDE EFFECTS:

- Hemolytic anemia
- Cough
- Dyspnea
- Rash and pruritis
- Anorexia
- Teratogenic 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 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.[89] 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 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-caffeinated 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 the patient 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, N-acetyl-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." [90]

Because acetaminophen's effects on the liver are dose dependent, it can be used safely even in cirrhosis.[90-94] There is no contraindication to acetaminophen, given in therapeutic doses, to patients with stable chronic liver disease.[95] 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.[91-94] 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.[93,94,96]

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.[137,138] Treatment with peginterferon has been reported in the pivotal studies to induce or exacerbate depression in 20%-30% of treated patients.[68-70] Patients with preexisting neuropsychiatric disease have been shown to have an increased susceptibility to interferon-caused depression.[141,142] 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 serotoninergic system.[138] Interferon has been shown to activate indoleamine 2,3-dioxygenase which reduces the production of 5-hydroxytryptamine (serotonin) by decreasing its precursor tryptophan.[142-145] These studies show that the plasma concentrations of both tryptophan and serotonin are reduced in patients treated with interferon.[142,145] Furthermore, decreased levels of tryptophan have been linked to the severity of depression during treatment with interferon.[143]

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.[145] 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 neuropsychiatic symptoms seen with interferon include changes in mood, cognition, and personality as well as anxiety, anger, hostility, fatigue, irritability, and insomnia.[89,138,139] Interferon treated patients can experience increased interpersonal problems.[137] 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.[146,147] 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 (CES-D)* in detecting depression in HCV patients.[146,147]

OFFICE-BASED 2-QUESTION HCV DEPRESSION INSTRUMENT (HEP-2Q)[146,147]

- 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

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.[148, 151] 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.[145,151-153]

Selective serotonin reuptake inhibitors (SSRIs) are now the drugs of choice for treating depression.[154] They are also used to treat generalized anxiety disorder, obsessive-compulsive disorder, panic disorder and social phobia.[154] SSRIs work by blocking the reuptake of serotonin into the presynaptic terminal. This enhances serotonin neurotransmission resulting in their antidepressant effect.[154] SSRIs have been the most studied antidepressants in treating interferon-induced depression and have been shown to be well- tolerated and effective.[145, 48-153] 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.[155] 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 norepinephine have also been found useful in treating peginterferon-induced depression.[149] Antidepressants with norepinephine 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.[154] Side effects are similar to SSRIs and include erectile dysfunction, nausea, and elevation of diastolic blood pressure with doses greater than 300 mg/day.[154] Venlafaxine has little effect on the P450 system.[156]

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.[156]

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.

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 SX®) 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

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

Fatigue

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

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.[113] 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.[131-135] 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.[136] Modafinil has been recently been 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.[114] Peginterferon suppresses bone marrow function causing decreased red blood cell production.[115] Ribavirin causes a dose-dependent hemolytic anemia in all patients, though the degree of anemia can vary between patients.[91] 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.[116] Hemoglobin levels decrease in the first 4 weeks of treatment with a mean decrease of 2.5 g/dl.[117] The resulting anemia causes fatigue, reduces quality of life, and decreases adherence.[118] 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,[78] 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.[119,120]

Four recent randomized controlled trials have demonstrated the efficacy and value of treating ribavirin-induced anemia with once weekly epoetin alfa.[121-123,158] 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 their optimal ribavirin dose. Based on these trials, recommendations for the use of epoetin alfa have been developed.

RECOMMENDATIONS FOR USE OF EPOETIN ALFA[11-123]

- 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 ≥16 g/dl or ≥14 g/dl in women, the epoetin alfa should be stopped.
  - If the hemoglobin later falls to ≤15 g/dl in men or ≤ 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.

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.[91,117,124] The resulting neutropenia is not usually related to a risk of severe bacterial infections.[67,68,125] In one study of 119 patients who were treated with peginterferon and ribavirin, none of the 18% who developed bacterial infections were neutropenic.[125] 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.[115] HCV patients are **not** immunosuppressed oncology patients! [116] 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.[54,67,69] Since prolonged dose reduction will decrease the chance of achieving a SVR recombinant granulocyte colony-stimulating factor (GCSF), although not FDA approved, has been used to maintain neutrophil counts rather than reduce dose in the setting of peginterferon-induced neutropenia.[126-129] The dose of G-CSF is 300 ug subcutaneous 2-3 times per week given when the absolute neutrophil count (ANC) <750 cells/mm^3 and titrated to maintain the ANC>750 cells/mm^3.[119] 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.[91] There were no bleeding complications from thrombocytopenia reported in the 3 pivotal peginterferon plus ribavirin trials.[66,67,69] The thrombocytopenia seen is mainly from peginterferon-induced bone marrow suppression and is blunted by reactive thrombocytosis from ribavirin.[123] 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^3 and stopping it when the platelet count <50,000 cell/mm.^{3} The package insert for peginterferon alfa-2a recommends decreasing the dose in half when the platelet count is

<50,000 cell/mm^3 and stopping it when the platelet count is <25,000 cells/ mm.^{3} Because the platelets remaining are normal platelets and bleeding is unusual, 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.[129] 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.

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
- Laratadine 10 mg once a day
- Hydroxyzine 10-25 mg every 6 hours prn
- Diphendramine 25-50 mg every 6 hours prn
- Sunscreen

Three kinds of injection-site reactions can occur with interferon.[97] 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.[98] It may last as long as 3 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. The patient 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.[91,99-105] 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, sucrafate, 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.[91,99,106,107,159,160] 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.[107,160] Any new visual complaint such as blurry vision or loss of vision (blind spots) should be referred to an opthalmologist. 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 opthalmologist prior to treatment.

Thyroid

Patients treated with interferon can develop thyroid dysfunction, thyroid autoimmunity, or both in 6-20%.[91,108-113,178] 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.

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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REFERENCES

1. World Health Organization Weekly Epidemiological Report. 1999;74:421-428.
2. Alter MJ, Kruszon-Morgan D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *N Eng J Med* 1999;341:556-562.
3. National Institutes of Health Consensus Development Conference Statement: management of hepatitis C: 2002. Bethesda, MD: National Institutes of Health; June 10-12, 2002.
4. Wong JB, McQuillan GM, McHutchison JG, et al. Estimating future hepatitis C morbidity, mortality, and costs in the United States. *Am J Public Health* 2000;90:1562-1596.
5. Davis GL, Albright AJE, Cook S, et al. Projecting the future healthcare burden from hepatitis C in the United States. Presented at: 49th Annual Meeting of the American Association for the Study of Liver Diseases; November 4-10, 1998; Chicago Ill. Abstract 909.
6. Shehab TM, Sonnad SS, Lok ASF. Management of hepatitis C patients by primary care physicians in the USA: results of a national survey. *J Viral Hep* 2001;8:377-388.
7. Shehab TM, Orrego M, Chunduri R, Lock ASF. Identification and management of hepatitis C patients in primary care clinics. *Am J Gastroenterology* 2003;98:639-644.
8. Rocca, LG, Yawn BP, Wollan P, et al. Management of patients with hepatitis C in a community population: diagnosis, discussions, and decisions to treat. *Ann Fam Prac* 2004;2: 116-124.
9. Heydtman M, Shields P, McCaughnan G, Adams D. Cytokines and chemokines in the immune response to hepatitis C infection. *Curr Opin Infect Dis* 2001;14:279-287.
10. Hoofnagle JH. Hepatitis C: the clinical spectrum of disease. *Hepatology* 1997;26(suppl):S15-20.
11. Seeff LB. Natural history of chronic hepatitis C. *Hepatology* 2002;36(suppl):S35-S46.
12. Kennny-Walsh E. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin: Irish Hepatology Research Group. *N Engl J Med* 1999;340:1228-1233.
13. Farci P, Shimoda A, Coiana A, et al. The outcome of acute hepatitis C predicted by the evolution of the viral quasispecies. *Science* 2002;288:339-344
14. Kaplan M, Gawrieh S, Cotler SJ, Jensen DM. Neutralizing antibodies in hepatitis C virus infection: a review of immunological and clinical characteristics. *Gastroenterology* 2003;125:597-604.
15. Grakoui A, Shoukry NH, Woollard DJ, et al. HCV Persistence and immune evasion in the absence of memory T-cell help. *Science* 2003;302:659-675.
16. Thursz M, Yallop R, Goldin R, et al. Influence of MHC class II genotype on outcome of infection with hepatitis C virus. The HENCORE Group: Hepatitis C European Network for Cooperative Research. *Lancet* 1999;354:2119-2125.
17. Gerlach JT, Diepolder HM, Jung MC, et al. Recurrence of hepatitis C virus after loss of virus specific CD4 T-cell response in acute hepatitis C. *Gastroenterology* 1999;117:933-941.
18. Ishii K, Rosa D, Watanabe Y, et al. High titers of antibodies inhibiting the binding of envelope to human cells correlate with natural resolution of chronic hepatitis C. *Hepatology* 1998;28:1117-1120.
19. Alric L, Fort M, Izopet J, et al. Genes of the major histocompatibility complex class II influence the outcome of hepatitis C viral infection. *Gastroenterology* 1997;113:1675-1685.
20. Poynard T, Yuen M-F, Ratziu V, Lung Lai C. Viral hepatitis C. *Lancet* 2003;362:2065-2100.

21. Poynard T, Ratziu V, Benhamou Y, et al. Fibrosis in patients with chronic hepatitis C: detection and significance. *Semin Liver Dis* 2000;20:47-55.
22. Poynard T, Bedossa P, Opolon P, for the OBSRIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Natural history of liver fibrosis progression in patients with chronic hepatitis C. *Lancet* 1997;349:825-872.
23. Ghany MG, Kleiner DE, Alter H, et al. Progression of fibrosis in chronic hepatitis C. *Gastroenterology* 2003;124:97-102.
24. Yano M, Kumada H, Kage M, et al. The long-term pathological evolution of chronic hepatitis C. *Hepatology* 1996;23:1334-1340.
25. Dienstag JL. The role of liver biopsy in chronic hepatitis C. *Hepatology* 2002;36(suppl) S152 -160.
26. Fontana RJ, Everson GT, Tuteja S, et al. Controversies in the management of hepatitis C patients with advanced fibrosis and cirrhosis. *Clinical Gastro Hepatology* 2004;2:183-197.
27. Wright,TL. Treatment of patients with hepatitis C and cirrhosis. Hepatology 2002; 36 (suppl): S185-194.
28. Fattovich G, Giusting G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology 1997;112:463-472.
29. Tutlin B, Juguet F, Moirand R, et al.. Increased liver iron stores in patients with hepatocellular carcinoma developed in a noncirrhotic liver. Hepatology 1995;22:446-450.
30. Tagger A, Donato F, Ribero ML, et al. Case controlled study on hepatitis C virus (HCV) as a risk factor for hepatocellular carcinoma: the role of HCV genotypes and the synergism with hepatitis B virus and alcohol. Brescia HCC Study. *Int J Cancer* 1999;81:695-699.
31. Cacoub P, Poynard T, Ghillani F, et al. Extrahepatic manifestations of chronic hepatitis C. *Arthritis & Rheumatism* 1999;42:2204-2212.
32. Jackson JM. Hepatitis C and the skin. *Dermatologic Clinics* 2002;20:13-23.
33. Gisbert JP, Garcia-Buey L, Mara-Pajares J, Moreno-Otero R. Prevalence of hepatitis C virus infection in porphyria cutanea tarda: a systemic review and meta-analysis. *J Hepatol* 2003;39:620-627.
34. Sanchez-Perez J, Decastro M, Buezo GF, et al. Lichen planus and hepatitis C virus: prevalence and clinical presentation of patients with lichen planus and hepatitis C virus infection. *Br J Dermatol* 1996;134:715-719.
35. Beaird LM. Kahloon N, Fairly JA. Incidence of hepatitis C in lichen planus. *J Am Acad Dermatol* 2001;44:311-312 .
36. Olivieri I, Palazzi C, Padula A. Hepatitis C virus and arthritis *Rheumatic Diseases Clinics of North America* 2003;29:97-102.
37. Zuckerman E, Yeshuran D, Rosner I. Management of hepatitis C virus-related arthritis. *BioDrugs* 2001*;*15:573-584.
38. Alter MJ. Hepatitis C virus infection in the United States. *J Hepatol* 1999;31(suppl):S88-91.
39. Centers for Disease Control and Prevention. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. *MMWR* 1998,48(RR19): 1-38.
40. Alter MJ. Prevention of spread of hepatitis C. *Hepatology* 2002;36(suppl):S93-98.
41. Resti M, Azzari C, Mannelli F, et al. Mother to child transmission of hepatitis C virus: prospective study of risk factors and timing of infection in children born to women sero-negative for HIV-1. Tuscany Study Group on Hepatitis C Virus Infection. *BMJ* 1998;317:437-441.

42. Manzini P, Saracco G, Cerchier A, et al. Human immunodeficiency virus infection as risk factor for mother-to-child hepatitis C virus transmission; persistence of anti-hepatitis C virus in children is associated with the mother's anti-hepatitis C immunoblotting pattern. *Hepatology* 1995;21:328-332.
43. Lissen E, Alter HJ, Abad, MA, et al. Hepatitis C virus infection among sexually promiscuous groups and the heterosexual partners of hepatitis C virus infected index cases. *Eur J Clin Microbiol Infect Dis* 1993;12:827-831.
44. Terrault NA, Busch M, Murphy E, et al. Sexual transmission of hepatitis C virus in heterosexual monogamous couples-the HCV Partners Study *Hepatology* 2003;38:183A
45. Vandelli C. Sexual transmission of hepatitis C virus is rare in monogamous heterosexual couples. *Am J Gastro* 2004;99:855-859.
46. Alter MJ. Viral hepatitis C. *Hepatology* 2002;36(Suppl):S93-98.
47. Haley, RW, Fischer, RP. Commercial tattooing as a potentially important source of hepatitis C serologic status. *Medicine* 2001;80:134-151.
48. Sun DX, Zhang FG, Geng YQ, et al. Hepatitis C transmission by cosmetic tattooing in women. *Lancet* 1996;347:541.
49. Puro V, Petrosillo N, Ippolito G. Italian Study Group on Occupational Risk of HIV and Other Bloodborn Infections. Risk of hepatitis C seroconversion after occupational exposures in healthcare workers. *Am J Infect Control* 1995;23:273-277.
50. Centers for Disease Control and Prevention. Risk of acquiring hepatitis C for health care workers and recommendations for prophylaxis and follow-up after occupational exposure. *Hepatitis Surveillance Report* Number 56, 1995.
51. Pawlotsky J M. Use and interpretation of hepatitis C diagnostic assays. *Clin Liver Dis* 2003*;7:64-68.*
52. Pawlotsky J M. Use and interpretation of virologic tests for hepatitis C. *Hepatology* 2002; 36(suppl):S65-73.
53. Centers for Disease Control and Prevention. *Morbidity and Mortality Weekly Report* 2003;(RR-3):1-16.
54. Centers for Disease Control and Prevention. Chronic hepatitis C: current disease management; 2003.
55. Centers for Disease Control and Prevention. Viral Hepatitis C: frequently asked questions. *www.cdc.gov* April 4, 2004.
56. Liu J, et al. Medicinal herbs for hepatitis C virus infection: a Cochrane hepatobiliary systematic review of randomized trials. *Am J Gastroenterol* 2003;98:538-544.
57. Feher J, Lang I, Nekam KJ, et al. In vivo effect of free radical scavenger hepatoprotective agents on superoxide dismutase (SOD) activity in patients. *Tokai J Exp Clin Med* 1990;15:129-134.
58. Campos R, Garrido A, Guerra R, et al. Silybin dihemisuccinate protects against glutathione depletion and lipid peroxidation induced by acetaminophen on rat liver. *Planta Med* 1989;55:417-419.
59. Boigk G, Stroedter L, Herbst H, et al. Silymarin retards collagen accumulation in early and advanced biliary fibrosis secondary to complete bile duct obliteration in rats. *Hepatology* 1997;26:643-649.
60. Jacobs BP, Dennehy C, Ramirez, G, et al. Milk thistle for the treatment of liver disease: a systematic review and meta-analysis. *Am J Med* 2002;113:506-515.

61. Jakkula M, Boucher TA, Beyendorff U, et al. A randomized trial of Chinese herbal medicines for the treatment of symptomatic hepatitis C. *Arch Intern Med* 2004;164:1341-1346.
62. Seeff LB, Lindsay KL, Bacon BR, et al. Complementary and alternative medicine in chronic liver disease. *Hepatology* 2001;34:595-603.
63. Coon JT, Ernst E. Complementary and alternative therapies in the treatment of chronic hepatitis C: a systematic review. *J Hepatol* 2004;40:491-500.
64. Meyers CM, Seeff LB, Sktehman-Breen CO, et al. Hepatitis C and renal disease: an update. *Am J Kidney Dis* 2003;42:631-657.
65. Loftis JM, Hauser P. Hepatitis C in patients with psychiatric disease and substance abuse: screening strategies and comanagement models of care. *Current Hepatitis* Reports 2003;2:93-100.
66. McHutchison J, David GL, Esteban-Mur R, et al. Durability of sustained viral response in patients with chronic hepatitis C after treatment with interferon alfa-2b alone or in combination with ribavirin. *Hepatology* 2001;34:244A.
67. Manns MP, McHutchison JG, Goden SC, et al. Peginerferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial. L*ancet* 2001;358:959-965.
68. Fried MN, Shiftman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002;347:975-982.
69. Hadziyannis SJ, Sette H, Morgan TR, et al. Peginterferon alfa-2a and ribavirin combination therapy in chronic hepatitis C. *Ann Intern Med* 2004;140:346-355.
70. Lindsay KL. Introduction to therapy of hepatitis C. *Hepatology* 2002;36 (suppl):S114-120.
71. Poynard T, McHutchison J, Manns M, et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. *Gastroenterology* 2002; 122:1303-1313.
72. Camma C, Di Bona D, Schepis F, et al. Effect of peginterferon alfa-2a on liver histology in chronic hepatitis C: a meta-analysis of individual patient data. *Hepatology* 2004;39:333-342.
73. Bruno, S, Battezzati PM, Bellati G, et al. Long term beneficial effects in sustained responders in interferon-alfa therapy for chronic hepatitis. *J Hepatol* 2001;34:748-775.
74. Camma C, Guiuta M, Anderone P, et al. Interferon and prevention of hepatocellular carcinoma in viral cirrhosis: an evidence-based approach. *J Hepatol* 2001;34:593-602.
75. Yoshida H, Shrier I, Sherker AH, et al. Interferon therapy reduces the risk for hepatocellular carcinoma: National Surveillance program of Cirrhotic and Non-cirrhotic Patients with Chronic Hepatitis C in Japan. *Ann Intern Med* 1999;131:174-181.
76. Baffis V, Sjrier I, Sjerker AH, et al. Use of interferon for prevention of hepatocellular carcinoma in cirrhotic patients with hepatitis B or hepatitis C virus infection. *Ann Intern Med* 1999;131:696-701.
77. Nishiguchi S, Kuroki T, Nakatani S, et al. Randomized trial of effects of interferon alfa on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. *Lancet* 1995;346:1051-1055.
78. Davis GL, Wong JB, McHutchison JG, et al. Early virologic response to treatment with peginterferon alfa 2-b plus ribavirin in patients with chronic hepatitis C. *Hepatology* 2003;38:645-652.
79. Davis GL. Monitoring of viral levels during therapy of hepatitis C. *Hepatology* 2002;36(suppl):S145-S151.

80. Poynard T, Mc Hutchison J, Goodman Z, et al. Is an "a la cart" combination interferon alfa-2b plus ribavirin regimen possible for the first line treatment in patients with chronic hepatitis C? The ALGOVIRC Project Group. *Hepatology* 2000;31:211-218.
81. Karnam US, Reddy KR. Pegylated interferons. *Clinics in Liver Dis* 2003;7:72-77.
82. Pockros PJ. The Role of interferon in the management of chronic hepatitis C. *Consults in the Management of Chronic Hepatitis C* 2004;2:1-12.
83. Rosenberg WM, Bennett LB, Parkes J, et al. Differences between antiviral therapy trials may be attributable to chance *Hepatology* 2002;36:378A.
84. Strader DB, Wright T, Thomas DL, et al. Diagnosis management and treatment of hepatitis C. *Hepatology* 2004;39:1147-1171.
85. Shiffman M. *Consults in the Management of Chronic Hepatitis C* 2001;1:5.
86. Chesny MA. *Clin Infect Dis* 2000;30S171.
87. McHutchison JG, Patel K, Manns MP, et al. Lower levels of adherence to therapy influence sustained response rates in chronic hepatitis C patients receiving peginterferon alfa-2b plus ribavirin. *Hepatology* 2002;36:287A.
88. McHutchison JG, Manns M, Patel K, et al. Adherence to combination therapy enhances sustained response in genotype 1 infected patients with chronic hepatitis C. *Gastroenterolgy* 2002;123:1061-1069.
89. Hultman E, Harris RC, Spriet L. Work and exercise. In *Modern Nutrition in Health and Disease*, Shils ME, Olson JA, Shole M. eds, Lea & Febiger, Philadelphia, 1994.
90. Acetaminophen safety. *The Medical Letter 20002;44:91-93.*
91. Russo MW, Fried MW. Side effects of therapy for chronic hepatitis C. *Gastroenterology* 2003; 124:1711-1719.
92. Schiodt FV, Rochling FA, Sasey DL, et al. Acetaminophen toxicity in an urban county hospital. *N Engl J Med* 1997;337:1112-1117.
93. Di Bisceglie AM. Preventive strategies for chronic liver disease *Am Fam Physician* 2001;64:1153-1154.
94. Riley TR, Bhatti AM. Preventive strategies in chronic liver disease: Part II. Cirrhosis. *Am Fam Physician* 2001;64:1735-1740.
95. Benson GD. Acetaminophen in chronic liver disease *Clin Pham &* Therap 1983;33:95-101.
96. Riley TR, Smith JP. Ibuprofen-induced hepatotoxicity in patients with chronic hepatitis C: a case series. *Am J Gastroenterol 1998:98:1563-1565.*
97. Elgart GW, Sheremata W, Ahn YS. Cutaneous reactions to recombinant human interferon beta-1b. *J Am Acad Dermatol* 1997;37:553-558.
98. Tosti, A, Misciali C, Bardazzi F, et al. Telogen effluvium due to recombinant interferon alfa-2b. *Dermatology* 1992;184:124-125.
99. Okanoue T, Sakamoto S, Itoh Y, et al. Side effects of high dose interferon therapy for chronic hepatitis C. *J Hepatol* 1996;25:283-291.
100. Oagata K, Koga T, Yagawa K. Interferon-related bronchiolitis obliterans organizing pneumonia. *Chest* 1994;106:612-613.
101. Kumar KS, Russo MW, Borczuk AC, et al. Significant pulmonary toxicity associated with interferon and ribavirin therapy for hepatitis C. *Am J Gastro* 2002;97:2432-2440.
102. Roothfuss KS, Bode JC. Interstitial pneumonitis during combination therapy with interferon-alfa and ribavirin in a patient with chronic hepatitis C. *Gastroenterology* 2002;40:807-810.

103. Perez-Alvarez R, Perez-Lopez R, Lombrofana JL, et al. Sarcoidosis in two patients with chronic hepatitis C treated with interferon, ribavirin, and amantadine. *J Viral Hepat* 2002;9:75-79.
104. Hoffmann RM, Jung MC, Motz R, et al. Sarcoidosis associated with interferon-alfa therapy for chronic hepatitis C. *J Hepatol* 1998;28:1058-1063.
105. Karim A, Ahmed S, Steinberg H, et al. Insterstitial pneumonitis in a patient treated with alpha-interferon and ribavirin for hepatitis C infection. *Am J Med Sci* 2001;322:233-235.
106. Kawano T, Shigehira M, Uto H, et al. Retinal complications during interferon therapy for chronic hepatitis C. *Am J Gastroenterol* 1996;91:309-313.
107. Jain K, Lam WC, Waheeb S, et al. Retinopathy in chronic hepatitis C patients during interferon treatment with ribavirin. *Br J Ophthalmol* 2001;85;1171-1173.
108. Carella C, Mazziotti G, Morisco F, et al. Long-term outcome of interferon-alpha-induced thyroid autoimmunity and prognostic influence of thyroid autoantibody autoimmunity and prognostic influence of thyroid autoantibody pattern at the end of treatment. *J Clin Endocrinol Metab*. 2001;86:1925-1929.
109. Fernandez-Soto L, Gonzalalez A, Escobar-Jimenez F, et al. Increased risk of autoimmune thyroid disease in hepatitis C vs hepatitis B before, during, and after discontinuing interferon therapy. *Arch Intern Med* 1998;158:1445-1448.
110. Huang MJ, Tsai DL, Huang BY, et al. Prevalence and significance of thyroid autoantibodies in patients with chronic hepatitis C virus infection: a prospective controlled study. *Clin Endocrinol (Oxf)* 1999;50:503-509.
111. Deutsch M, Dourakis S, Manesis EK, et al. Thyroid abnormalities in chronic viral hepatitis and their relationship to interferon-alfa therapy. *Hepatology* 1997;26:206-210.
112. Koh LK, Greenspan FS, Yeo PP. Interferon-alfa induced thyroid dysfunction: three clinical presentations and a review of the literature. *Thyroid* 1997;26:206-210.
113. Malik UR. Interferon-mediated fatigue. *Cancer* 2001;92(suppl):S1664-8.
114. Afdhal NH, Dieterich DT, Pockros PJ, et al. Epoetin alfa maintains ribavirin dose in HCV-infected patients: a prospective, double-blind, randomized controlled study. *Gastroenterology* 2004;126:1302-1311.
115. Peck-Radosavljevic M, Wichlas M, Hornoncil-Krami M, et al. Rapid suppression of hematopoiesis by standard of pegylated interferon-alfa. *Gastroenterology* 2002;123:141-151.
116. DeFranceschi L, Fattovich G, Turrini F, et al. Hemolytic anemia induced by ribavirin therapy in patients with chronic hepatitis C virus infection: role of membrane oxidative damage. *Hepatology* 2000;431:997-1004.
117. Maddrey WC. Saftey of combination interferon alfa-2b/ribavirin therapy in chronic hepatitis C-relapsed and treatment-naive patients. *Semin Liver Dis* 1999;19(suppl):S67-75.
118. Fried MW. Side effects of therapy of hepatitis C and their management. *Hepatology* 2002; 369(suppl):S237-244.
119. Dieterich DT, Spivak JL. Hematologic disorders associated with hepatitis C virus infection and their management. *Clin Inf Dis* 2003;37:533-541.
120. Sulkowski MS. The use of EPO for HCV treatment associated anemia. *Clin Inf Dis 2003; 37(suppl):S315-S322.*
121. Afdhal NH, Dieterich DT, Pockros PJ, et al. Epoetin alfa maintains ribavirin dose in HCV-infected patients: a prospective, double-blind, randomized controlled study. *Gastroenterology* 2004;126:1302-1311.

122. Dieterich DT, Wasserman R, Brau N, et al. Once-weekly epoetin alfa improves anemia and facilitates maintenance of ribavirin dosing in hepatitis C virus-infected patients receiving ribavirin plus interferon alfa. *Am J Gastro* 2003;98:2491-2499.
123. Brau N. Epoetin alfa treatment for acute anaemia during interferon plus ribavirin combination therapy for chronic hepatitis C. *J Viral Hepatol* 2004:3:191-197.
124. Ong JP, Younossi ZM. Managing the hematologic side effects of antiviral therapy for chronic hepatitis C: anemia, neutropenia, and thrombocytopenia. *Clev Clin J Med* 2004; 71(suppl): S17-21.
125. Soza A, Everhart JE, Ghany MG, et al. Neutropenia during combination therapy of interferon-alfa and ribavirin for chronic hepatitis C. *Hepatology* 2002;36:1273-1279.
126. Van Thiel DH, Faruki H, Friedlander L, et al. Combination treatment of advanced HCV associated liver disease with interferon and G-CSF. *Hepatogastroenterology* 1995,42:907-912.
127. Fukuda A, Kobayashi H, Teramura K, et al. Effects of interferon-alfa on peripheral neutrophil counts and serum granulocyte colony-stimulating factor for the treatment of chronic hepatitis C. *Cytokine* 2000;12:165-170.
128. Shiffman ML, Hofmann CM, Luketic VA, et al. Use of granulocyte macrophage colony stimulating factor alone or in combination with interferon-alfa-2b for the treatment of chronic hepatitis C. *J Hepatol* 1998;28:382-389.
129. Rustgi VK, Lee P, Finnegan S, et al. Safety and efficacy of recombinant human IL-11 (oprelvekin) in combination with interferon/ribavirin in hepatitis C patients with thrombocytopenia. *Hepatology* 2002;36:361A.
130. Poynard T, Cacoub P, Ratziu V, et al. Fatigue in patients with chronic hepatitis C. *J Viral Hepatitis* 2002;9:295-303.
131. Crone CC, Gabriel GM, Wise TN. Managing the neuropsychiatric side effects of interferon-based therapy for hepatitis C. *Cleveland Clinic J of Med* 2004;71(suppl):S27-S32.
132. Hauser P, Khosla J, Aurora H, et al. A prospective study of the incidence and open-label treatment of interferon-induced major depressive disorder in patients with hepatitis C. *Mol Psychiatry* 2002;7:942-947.
133. Bruera E, Driver L, Barnes EA, et al. Patient-controlled methylphenidate for the management of fatigue in patients with advanced cancer: a preliminary report. *J Clin Oncol*. 2003;21:439-443.
134. Breitbart W, Rosenfeld B, Kaim M, et al. A randomized, double-blind, placebo-controlled trial of psychostimulants for the treatment of fatigue in ambulatory patients with human immunodeficiency virus. *Ann Intern Med* 2001;161:411-420.
135. DeBattista C. Doghramji K, Menza MA, et al. Adjunct modafinil for the short-term treatment of fatigue and sleepiness in patients with major depressive disorder: a preliminary double-blind, placebo-controlled study. *J Clin Psychiatry* 2003;64:1057-1064.
136. Schwartz AL, Thompson JA, Masood N. Interferon-induced fatigue in patients with melanoma: a pilot study of exercise and methylphenidate. *Oncol Nurs Forum* 2002;29:85-90.
137. Zdilar D, Franco-BronsonK, Buchler N, et al. Hepatitis C, interferon alfa, and depression. *Hepatology* 2000;31:1207-1211.

138. Schaefer M, Engelbrecht MA, Gut O, et al Interferon alpha and psychiatric syndromes: a review. *Prog Neuropsychopharmacol Bio Psychiatry* 2002;26:731-746. Emotional state, coping styles, and somatic variables in patients with chronic hepatitis C. *Psychosomatics* 2000;41:377-384.
139. Kraus MR, Schafer M, Faller H, et al. Psychiatric symptoms in patients with chronic hepatitis C receiving interferon alfa-2b therapy. *J Clin Psychiatry 2003;64:708-71*.
140. Fattovich G. A survey of adverse events in 11,241 patients with chronic viral hepatitis treated with alfa interferon. *J Hepatol* 1996;24:38-47.
141. Wichers M, Maes M. The psycho-immuno-pathophysiology of cytokine-induced depression in humans. *Int J Neuropsychopharmacol* 2002;3:375-388.
142. Capuron L, Ravaud A, Neveu PJ, et al. Association between decreased serum tryptophan concentrations and depressive symptoms in cancer patients undergoing cytokine therapy. *Mol Psychiatry* 2002;7:468-473.
143. Bonaccorso S, Marino V, Puzella A, et al. Increased depressive ratings in patients with hepatitis C receiving interferon-alfa based immunotherapy are related to interferon-alfa induced changes in the serotonergic system. *J Clin Psychopharmacol* 2002;22:86-90.
144. Capuron L, Neurauter G, Musselman DL, et al. Interferon-alfa induced changes in tryptophan metabolism: relationship to depression and paroxetine treatment. *Bio Psychiatry* 2003;54:906-914.
145. Hauser P, Khosla J, Aurora H, et al. A prospective study of the incidence and open-label treatment of interferon-induced major depressive disorder in patients with hepatitis C. *Mol Psychiatry* 2002;7:942-947.
146. Winston DH, Winston DC. A 2-question questionnaire for detecting depression in hepatitis C is as effective as a more detailed questionnaire. *Irish J Med Sci* 2003;172(suppl): S40-41.
147. Winston DH, Winston DC. Use of an office-based 2-question instrument for detecting depression in hepatitis C patients. *Gastroenterology* 2004;126(suppl):A-432.
148. Loftis JM, Hauser P. Comanagement of depression and HCV treatment. *Psychiatr Ann* 2003; 33:385-391.
149. Hauser P, Soler R, Reed S, et al. Prophylactic treatment of depression induced by interferon-alfa. *Psychosomatics* 2000;41:439-441.
150. Musselman DL, Lawson DH, Gumnick JF, et al. Paroxetine for the prevention of depression induced by high-dose interferon-alfa. *N Engl J Med* 2001;344:961-966.
151. Schramm TM, Lawford BR, Macdonald GA, et al. Sertraline treatment of interferon-alfa induced depressive disorder. *Med J Aust* 2000;173:359-361.
152. Gleason OC, Yates WR, Isbell MD, et al. An open-label trial of citalopram for major depression in patients with hepatitis C. *J Clin Psychiatry* 2002;63:194-198.
153. Kraus MR, Scjafer A, Faller H, et al. Paroxetine for the treatment of interferon-alfa-induced depression in chronic hepatitis C. *Aliment Pharmacol Ther* 2002;16:1091-1099.
154. Ables AZ, Baughman OL. Antidepressants: update on new agents and indications. *Am Fam Phy* 2003;67:547-554.
155. Preskorn SH. Clinically relevant pharmacology of selective serotonin reuptake inhibitors. An overview with emphasis on pharmacokinetics and effects on oxidative drug metabolism. *Clin Pharmacokinet* 1997;32(suppl): S1-21.
156. Owen JR, Nemeroff CB. New antidepressants and the cytochrome P450 system: focus on venlafaxine, nefazodone, and mirtazapine. *Depress Anxiety* 1998;7(suppl):S24-32

157. Kupher DJ, Frank E, Perel JM, et al. Five-year outcome for maintenance therapies in recurrent depression. *Arch Gen Psych* 1992;49:773-796.
158. Pockros PJ, Schiffman ML, Schiff, ER, et al. Epoetin alfa improves quality of life in anemic HCV-infected Patients Receiving Combination Therapy. *Hepatology* 2004;40:1450-1458.
159. Willson RA. Visual side effects of pegylated interferon during therapy for chronic hepatitis C infection. *J Clin Gastroenterol* 2004;38:717-722
160. Cuthbertson FM, David M, McKibbin. Is screening for interferon retinopathy in hepatitis C justified? *Br J Ophthalmol* 2004;88:1518-1520.
161. Wedemeyer H, Jackel E, Woegand J, et al. Whom? When? How? Another piece of evidence for early treatment of acute hepatitis C. *Hepatology* 2004;39:1201-1203.
162. Hoofnagle JH. Therapy for acute hepatitis C. *N Engl J Med* 2001;345:1495-1497.
163. Gerlach JT, Diepolder HM, Zachoval R, et al. Acute hepatitis C: high rate of both spontaneous and treatment-induced viral clearance. *Gastroenterology* 2003;125:80-88.
164. Kamal SM, Ismail A, Graham CS, et al. Pegylated interferon alpha therapy in acute hepatitis C: relation to hepatitis C virus-specific T-cell response kinetics. *Hepatology* 2004;39:1721-1731.
165. Wiegand J, Boecher W, Buggisch P, et al. 24 weeks of monotherapy with pegylated interferon alfa-2b in patients with acute hepatitis C. *Hepatology* 2003,38:277A
166. Santantonio T, Fasano M, Sinisi E, et al. Efficacy of a 24-week course of PEG-interferon alpha-2b monotherapy in patients with acute hepatitis C after failure of spontaneous clearance. *J Hepatol* 2005;42:329-333.
167. Bacon BR. Chronic hepatitis C and normal ALT: considerations for treatment. *Am J Gastroenterol* 2004;99:1706-1707.
168. Bacon BR. Treatment of patients with hepatitis C and normal serum aminotransferase levels. *Hepatology* 2002;36:S179-184.
169. Jacobson, IM, Ahmed F, Russo MW, et al. Interferon alpha-2b and ribavirin for patients with chronic hepatitis C and normal ALT. *Am J Gastroenterol* 2004;99:1700-1705.
170. Zeuzem S, Diago M, Gane E, et al. Peginterferon alfa-2a (40 kilodaltons) and ribavirin in patients with chronic hepatitis C and normal aminotransferase levels. *Gastroenterology* 2004;127:1724-1732.
171. Keating GM, Plosker GL. Peginterferon alpha-2a (40KD) plus ribavirin: a review of its use in the management of patients with chronic hepatitis C and persistently 'normal' ALT levels. *Drugs* 2005;65:521-526.
172. Howell C, Jeffers L, Hoofnagle JH. Hepatitis C in African Americans: summary of a workshop. *Gastroenterology* 2000;119:1385-1396.
173. Whiley TE, Brown J, Chan J. Hepatitis C infection in African Americans: its natural history and histological progression. *Am J Gastroenterol* 2002;97:700-706.
174. Jeffers LJ, Cassidy W, Howell CD, et al. peginterferon alfa-2a (40kd) and ribavirin for black American patients with chronic HCV genotype 1. *Hepatology* 2004;39:1702-1708.
175. Hepburn MJ, Hepburn LM, Cantu S, et al. Differences in treatment outcome for hepatitis C among ethnic groups. *Am J Med* 2004;117:163-168.
176. Muir AJ, Bornstein JD, Killenberg PG. Peginterferon alfa-2b and ribavirin for the treatment of chronic hepatitis C in Blacks and Non-Hispanic Whites. *N Engl J Med* 2004;350:2265-2271.

177. Shiratori Y, Ito Y, Yokosuka O, et al. Antiviral therapy for cirrhotic hepatitis C: association with reduced hepatocellular carcinoma development and improved survival. *Ann Intern Med* 2005;142:105-114.
178. Doi F, Kakizaki S, Takagi H, et al. Long-term outcome of interferon-alfa-induced auto-immune thyroid disorders in chronic hepatitis C. *Liver International* 2005;25:242-246.
179. Davis GL, Wong JB, McHutchison JG, et al *Hepatology* 2003;38:645-652.
180. Shaw-Stiffel T. Critical issues in HCV. *www.hivandhepatitis.com*:11/24/03.
181. Thomas DL. Hepatitis C and human immunodeficiency virus infection. *Hepatology* 2002; 36(Suppl 1):S201-209.
182. Sulkowski MS, Thomas DL. Hepatitis C in the HIV-infected person *Ann Intern Med* 2003; 138:197-207.
183. Zarski JP, Bohn B, Bastie A, et al. Characteristics of patients with dual infection by hepatitis B and C viruses. *J Hepatol* 1998;28:27-33.
184. Sato S, Fujiyama S, Tanaka M, et al. Coinfection of hepatitis C virus in patients with chronic hepatitis B infection. *J Hepatol* 1994;21:159-166.
185. Maruasawa H. High prevalence of anti-hepatitis B virus serological markers in patients with hepatitis C virus related chronic liver disease in Japan. *Gut* 1999;45:284-288.
186. www.uscis.gov.
187. www.cenus.gov/population/www/socdemo/race/api.html.
188. World Health Organization Fact Sheet WHO/164. Hepatitis C. October 2000.
189. World Health Organization Fact Sheet WHO/204. Hepatitis B. October 2000.
190. Nguyen MH, Keeffe EB. Chronic hepatitis B and hepatitis C in Asian Americans. *Rev Gastroenterol Disord* 2003;3:125-134.