Preventive Strategies in Chronic Liver Disease: Part I. Alcohol, Vaccines, Toxic Medications and Supplements, Diet and Exercise

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Chronic liver disease is the 10th leading cause of death in the United States. Hepatitis C virus infection is the most frequent cause of chronic liver disease and the most common indication for liver transplantation. Preventive care can significantly reduce the progression of liver disease. Alcohol and hepatitis C virus are synergistic in hastening the development of cirrhosis; therefore, patients with hepatitis C infection should abstain from alcohol use. Because superinfection with hepatitis A or B virus can lead to liver failure, vaccination is recommended. Potentially hepatotoxic medications should be used with caution in patients with chronic liver disease. In general, nonsteroidal anti-inflammatory drugs should be avoided; acetaminophen in a dosage below 2 g per day is the safest choice. Many herbal remedies are potentially hepatotoxic, and only milk thistle can be used safely in patients who have chronic liver disease. Weight reduction and exercise can improve liver function in patients with fatty liver. (Am Fam Physician 2001;64:1555-60.)

See editorial on page 1515.

This is part I of a two-part article on preventive strategies in chronic liver disease. Part II, "Cirrhosis," will appear in the next issue.

The term "chronic liver disease" encompasses a large number of conditions having different etiologies and existing on a continuum between hepatitis infection and cirrhosis. Chronic liver disease is the 10th leading cause of mortality in the United States and is responsible for the deaths of more then 25,000 Americans each year.[1]

Hepatitis C is a common parenterally acquired infection that affects an estimated 4 million persons in the United States.[2] From 75 to 80 percent of persons with hepatitis C virus infection develop chronic hepatitis (diagnosed by the presence of persistently elevated liver injury test results for more than six months), and more than 25 percent develop cirrhosis within 30 to 40 years.[2] Hepatitis C virus infection is the leading cause of chronic liver disease and the reason for 30 to 35 percent of liver transplantations.[3-5] Thus far, treatments for hepatitis C virus infection have been somewhat disappointing, with the best response rates to interferon and ribavirin therapy reported at 40 percent.[6]

Worldwide, hepatitis B is another major cause of cirrhosis and hepatocellular carcinoma. Many patients with hepatitis B virus infection fail standard therapy. The reported response rate to interferon is only 40 percent, and the response rate to second-line treatment using orally administered lamivudine is only about 30 percent.[7]

Other recognized categories of chronic liver disease include conditions induced by toxins or drugs (e.g., alcohol) and autoimmune chronic liver diseases such as primary sclerosing cholangitis, primary biliary cirrhosis and autoimmune hepatitis. Chronic liver disease also includes hereditary diseases (e.g., hemochromatosis, alpha$_1$-antitrypsin deficiency, Wilson's disease), nonalcoholic steatohepatitis and a group of liver diseases with no identifiable cause (i.e., cryptogenic liver disease).

In some liver diseases, such as primary biliary cirrhosis, treatment can slow but not stop the progression of liver injury.[8] Although each form of liver disease has a distinct natural history, most forms progress slowly from hepatitis to cirrhosis, often over 20 to 40 years.[9]

Chronic liver disease cannot be cured. Hence, it is imperative to prevent further

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exacerbation of the disease and to optimize the length of time between hepatitis and the development of cirrhosis. This article reviews preventive measures that have been shown to be effective or to have a scientific rationale in the management of chronic liver disease.

Preventive Strategies

ABSTINENCE FROM ALCOHOL

Alcohol consumption has been associated with alcoholic hepatitis, fatty infiltration of the liver, accelerated progression of liver disease, a higher frequency of cirrhosis, a higher incidence of hepatocellular carcinoma, and death. The daily consumption of more than four drinks of alcohol (48 g) increases the risk of cirrhosis, as well as death from other causes.[10,11]

Alcohol abuse and hepatitis C virus infection frequently coexist in patients with chronic liver disease. It is widely believed that alcohol and the hepatitis C virus act together to promote the development and progression of liver damage. Investigators in one study[12] found that the effect of alcohol in patients with hepatitis C virus infection is not merely additive but synergistic, and that even moderate use of alcohol can hasten the development of cirrhosis. The mechanism for the synergistic effect of alcohol and hepatitis C virus is not fully understood, but it has been attributed to the effects of alcohol on viral replication and the immune system, hepatic iron content and hepatic regeneration. Other investigators[13] have found that alcohol abuse in patients with hepatitis C virus infection is associated with a decreased response to interferon therapy.

Abstinence may reverse some of the deleterious effects of alcohol in patients with chronic liver disease. It may also improve the ultimate response to treatment. What constitutes a safe level of alcohol consumption in patients with chronic liver disease remains unclear. It is recommended that patients with hepatitis C virus infection or other chronic liver disease consume no alcohol. Abstinence is the most important measure in keeping chronic liver disease from progressing to cirrhosis.

Abstinence can be difficult because of alcohol's strong addictive potential. Support should be provided for patients who have been using alcohol heavily. Forms of support include Alcoholics Anonymous, inpatient and outpatient rehabilitation programs, community and church support, and individual counseling.[14,15]

VACCINATIONS

Superinfection with hepatitis viruses in patients with chronic hepatitis C virus infection can result in significant morbidity and mortality. Both hepatitis A and hepatitis B are associated with more virulent acute infections than hepatitis C. In some patients with chronic liver disease, superinfection with hepatitis A or B virus can lead to acute liver failure.[16,17] However, in the absence of coexistent liver disease, the mortality rate for hepatitis A virus infection is less than one death per 1,000 infected persons.[17]

Investigators in one prospective study[18] followed 163 patients with hepatitis B and 432 patients with hepatitis C virus infections. In this study, hepatitis A superinfection was associated with a substantially higher risk of fulminant hepatic failure. The mortality rate was 35 percent in patients with chronic hepatitis C and hepatitis A virus superinfection (a 350-fold higher fatality rate than would be expected in patients without chronic hepatitis C virus infection). In another large series,[19] death occurred in 381 of 115,551 patients with acute hepatitis A virus infection. Of the patients who died, 107 (28 percent) had underlying chronic liver disease.

Strong evidence supports vaccination against hepatitis A and B viruses in patients with chronic liver disease. All patients with chronic liver disease should be checked for hepatitis A total antibody and hepatitis B surface and core antibodies. If no immunity is found, these patients should be given hepatitis A vaccine (two doses, administered six months apart) and hepatitis B vaccine (three doses, with the second dose given one month after the first dose and the third dose given six months after the first dose). Both vaccines

can be given safely at the same time, in opposite deltoid muscles.[20-22] It should be noted that in a low-incidence population with past exposure (e.g., patients who lack classic risk factors for contracting hepatitis infection), it may be more cost-effective to forego antibody testing and proceed directly to vaccination.

In both the presence and the absence of chronic liver disease, seroconversion occurs in 94 percent of patients following hepatitis A vaccination and 100 percent of patients following hepatitis B vaccination.[22] It is important to understand that patients with decompensated cirrhosis and immunocompromised patients may show a decreased seroconversion success rate. Currently, no hepatitis C vaccine is available for clinical use.

EVALUATION OF DRUG TOXICITY

Most ingested substances are metabolized and chemically altered as they pass through the liver. In particular, the liver is the central site for the clearance, detoxification, excretion and activation of most medications. The liver is vulnerable to injury from some medications, vitamins and herbal remedies.[23]

Medications. Patients with chronic liver disease can have variably affected liver function. In recommended dosages, most medications are safe in these patients despite their altered metabolism and hepatic function. However, patients with chronic liver disease may be at increased risk for idiosyncratic drug reactions and less able to tolerate hepatotoxicity when it occurs.

Common drug classes with known hepatotoxicity include antidepressants, nonsteroidal anti-inflammatory drugs (NSAIDs, including cyclooxygenase-2 inhibitors), muscle relaxants, psychotropics, anticonvulsants, lipid-lowering drugs, oral antidiabetic agents, estrogens, anabolic steroids and antituberculous agents. Drugs with a known potential for idiosyncratic reactions include antibiotics, antifungals, antivirals, antiprotozoals and NSAIDs *(Table 1)*.

All medications should be evaluated for toxic effects on the liver. If data indicate that a drug may be hepatotoxic, an alternative drug with less or no hepatotoxicity should be sought. When treatment with a potentially hepatotoxic medication is deemed necessary, the drug should be used with caution and under close supervision. Patients should be made aware of symptoms of liver injury, such as jaundice, anorexia, nausea, pruritus, fatigue and right upper quadrant abdominal pain.

Transaminase, total bilirubin and alkaline phosphatase levels are used to assess patients for possible drug-related hepatotoxicity. These levels should be obtained at baseline, every two weeks for the first month of drug therapy, every month for the next three months and then every three months. The medication should be stopped if measured values increase to more than two times the baseline levels or the patient develops liver-related symptoms.[24] If a question arises about the safety of a particular medication, consultation with a hepatologist may by helpful.

Prescription and over-the-counter arthritis and pain medications are widely used. NSAIDs, which are taken to alleviate headache and a variety of pain symptoms, can cause idiosyncratic liver toxicity. Fatalities associated with NSAID use have been reported.[25] In one study,[26] the use of ibuprofen was associated with a more than 20-fold increase in liver function values in three patients with hepatitis C virus infection. Because of the unpredictable hepatotoxicity of NSAIDs, patients who have chronic liver disease should not use these medications.

Acetaminophen has predictable hepatotoxicity and affects the liver in a dose-dependent

TABLE 1
Selected Potentially Hepatotoxic Medications

All nonsteroidal anti-inflammatory drugs
Lipid-lowering agents: statins, nicotinic acid (niacin; Nicolar)
Antidiabetic agents: acarbose (Precose), pioglitazone (Actos), sulfonylureas
Antibiotics: amoxicillin–clavulanate potassium (Augmentin), erythromycin, isoniazid (INH), nitrofurantoin (Furadantin), tetracycline
Antifungal agents: fluconazole (Diflucan), itraconazole (Sporanox), ketoconazole (Nizoral)
Retinoids: etretinate (Tegison)
Anticonvulsant agents: phenytoin (Dilantin), valproic acid (Depakene)
Psychotropic agents: bupropion (Wellbutrin), chlorpromazine (Thorazine), tricyclic antidepressants
Hormones: tamoxifen (Nolvadex), testosterone
Others: halothane (Fluothane), methotrexate (Rheumatrex)

When treatment with a potentially hepatotoxic medication is deemed necessary, the drug should be used with caution and under close supervision.

TABLE 2
Selected Potentially Hepatotoxic Supplements

Amanita species	Gentian	Nicotinic acid (niacin; Nicolar)
Asafetida	Germander	Pennyroyal oil
"Bush" herbal teas	Iron	Senna fruit extracts
Chaparral	Jin bu huan	Valerian
Comfrey	Kalms tablets	Vitamin A
Echinacea	Mistletoe	

manner. In patients with chronic liver disease who have pain symptoms, acetaminophen can be used safely in a dosage of no more than 2 g per day. However, acetaminophen hepatotoxicity has been reported with dosages of less than 4 g per day, usually in association with starvation or alcohol ingestion.[27]

Vitamins and Herbal Remedies. Annual sales of vitamins and herbal remedies approach $1.6 billion in the United States.[28] Investigators in one study[28] found that up to 31 percent of patients in a liver clinic used herbal remedies. Selected potentially hepatotoxic over-the-counter supplements are listed in *Table 2.*

Vitamin A is a known hepatotoxin that is available over the counter. Multiple cases of hepatotoxicity have been documented with the ingestion of vitamin A in high dosages, usually more than 100,000 IU per day, and rare cases have occurred with dosages of approximately 25,000 IU per day. The degree of liver injury associated with vitamin A depends on the dose. Alcohol potentiates the hepatotoxicity of this vitamin. Vitamin A can cause steatosis, perisinusoidal fibrosis, chronic hepatitis and cirrhosis.[29] Patients with chronic liver disease should consume less than 25,000 IU of vitamin A per day. Most multivitamin preparations contain 4,000 IU of the vitamin, which is well within the safe range for daily consumption.

Patients with chronic liver disease should be asked specifically about the use of alternative therapies. Such patients commonly use milk thistle (Silybum marianum). There is no evidence of toxicity related to the pure form of milk thistle, and there is weak evidence of a hepatocyte plasma cell membrane protective effect. For these reasons, it is reasonable not to discourage the use of milk thistle.[28]

INFLUENCE OF IRON

Patients with chronic liver disease have a tendency to accumulate an excessive amount of iron in their liver parenchyma. Those with alcoholic liver disease, nonalcoholic steatohepatitis or hepatitis C virus infection have a particular tendency toward secondary hemosiderosis.

Patients who have secondary iron overload must be distinguished from those with hereditary hemochromatosis, in which a primary genetic defect leads to an excessive hepatic and total-body iron load. The level of iron loading is much greater in patients with primary hemochromatosis than in those with secondary hemosiderosis.

As many as 30 percent of patients with liver disease have high serum iron levels, and 10 percent have excessive amounts of iron in their liver tissue.[30,31] The reason for the iron excess is not known, but postulated mechanisms include the release of iron from injured hepatocytes and their uptake by Kupffer cells, acute-phase reactions associated with chronic inflammatory states, increased uptake of iron through the gastrointestinal tract, and ineffec-

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TABLE 3
Preventive Measures in Chronic Liver Disease

Complete abstinence from alcohol
Vaccination against hepatitis A and B viruses (if patient not already immune)
Avoidance of hepatotoxic medications, especially nonsteroidal anti-inflammatory drugs*
Assessment of vitamins and herbal remedies for safety
Avoidance of iron supplements unless iron deficiency anemia is present; multivitamins without iron should be used
Low-fat, "heart-smart" diet

**—The safest choice is acetaminophen, in a dosage of less than 2 g per day.*

tive erythropoiesis with redistribution of iron from sites of utilization to sites of storage. The most likely mechanisms of liver injury from excess iron are increased generation of free radicals and increased peroxidation of lipids, which, in turn, lead to mitochondrial dysfunction, lysosomal fragility and cell death.

Iron has recently been shown to influence the natural history of hepatitis C virus infection and the response of chronic hepatitis C to treatment. Several studies[32,33] in patients with chronic hepatitis C virus infection have found a high iron concentration in the liver to be predictive of failure to respond to interferon therapy. Some evidence indicates that phlebotomy improves liver function tests in patients with chronic hepatitis C virus infection.[34] Recent studies have also shown an increased response of the hepatitis C virus to interferon combined with phlebotomy, although not all studies are in agreement.[35] However, the practical implications of these findings have not been determined.

To date, no evidence suggests that dietary iron is harmful. Further studies are needed to study the effect of iron depletion in chronic liver disease.

DIET AND EXERCISE

A liver is termed "fatty liver" if lipids account for more than 5 percent of its weight. The mechanisms for the development of fatty liver are varied. A reduction in the hepatic oxidation of fatty acids as a result of mitochondrial dysfunction can lead to microvesicular steatosis. Another mechanism is related to an imbalance between fat uptake and secretion, with high insulin-to-glucagon ratio states leading to macrovesicular steatosis.

Fatty liver can be the consequence of many diseases, including alcohol excess, nonalcoholic steatohepatitis, hepatitis C virus infection, metabolic disorders (e.g., Wilson's disease), medication effects and nutritional disorders.[36] Predisposing factors include diabetes mellitus, elevated serum triglyceride levels and obesity.[37]

Most patients with fatty liver are asymptomatic, and the condition is usually discovered because of hepatomegaly or mild abnormalities of serum aminotransferase or alkaline phosphatase levels found on a routine physical examination. In some patients, however, necroinflammation can be intense, leading to fibrosis and cirrhosis.

One controlled study[38] demonstrated that a weight reduction program (combined diet and exercise) can improve liver function test results and liver histology in patients with nonalcoholic steatohepatitis. With a weight loss of 4.5 to 6.8 kg (10 to 15 lb), liver transaminase levels often return to normal. Investigators in another study[39] found a correlation between high fat and oil consumption and elevated liver transaminase levels. The findings of these studies suggest that a low-fat diet and exercise (supervised by a physician for appropriateness) could minimize hepatic steatosis. Gradual weight reduction should be recommended in patients with chronic liver disease and obesity.

Measures that can be effective in preventing the progression of chronic liver disease to cirrhosis are summarized in *Table 3*.

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