Counseling Patients with Chronic Hepatitis C

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Module 2: Evaluation, Staging, and Monitoring of Chronic Hepatitis C
Lesson 3: Counseling Patients with Chronic Hepatitis C

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Over-the-Counter Medications and Vitamins

Introduction: Because many medications are metabolized through the liver, it is important for the medical provider to know all of the medications a patient is taking, including over-the-counter medications. A current medication list should be solicited frequently.

Acetaminophen: Acetaminophen (*Tylenol*) is a known hepatotoxin that can cause clinically important hepatotoxicity, either through an acute overdose or when taken on a regular basis (even at lower doses): in one large study that examined causes of acute liver failure, patients taking a dose less than 4 grams per day accounted for 7% of the total cases and in some were taking doses as low as 1 gram per day. Among healthy volunteers taking 4 grams per day for 14 days, more than 30% developed alanine aminotransferase (ALT) values in excess of 3 times the upper limit of normal. Concurrent alcohol use greatly increases the chance of acute or chronic acetaminophen-induced hepatotoxicity. Studies have also shown an increased risk of acute liver injury in patients with chronic hepatitis C following acetaminophen overdose, but none have examined the safety of long-term, low dosages of acetaminophen in patients with chronic hepatitis C. Guidelines for the safe use of acetaminophen in HCV-infected persons do not exist. Considering many patients with chronic hepatitis C have limited pain treatment options, most experts believe low dosages of acetaminophen (up to two grams per day) can safely be used in most patients with chronic hepatitis C infection without cirrhosis; those with cirrhosis should limit their intake of acetaminophen to one gram per day. Patients drinking excess alcohol should avoid taking acetaminophen altogether. Clinicians should remind patients that many narcotic combination pills and over-the-counter cold and flu medications may contain acetaminophen. Patients taking acetaminophen should have laboratory monitoring for hepatotoxicity every 3 to 6 months.

Aspirin and Nonsteroidal Anti-inflammatory Medications: Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) are generally safe for patients with hepatitis C when taken at standard doses. The one exception is in patients who have cirrhosis: NSAIDS and aspirin are best avoided in patients with cirrhosis, especially those with decompensated cirrhosis. In patients with decompensated cirrhosis, the use of NSAIDS and aspirin may further increase the inherent risk these patients have for developing nephrotoxicity and gastrointestinal bleeding. Patients with chronic hepatitis C who do not have cirrhosis may take aspirin or NSAIDs at low or standard recommended dosages, with food and water. Those with cirrhosis who have short-term, minor pain should, in general, avoid taking aspirin or NSAIDs, but can take acetaminophen in this setting as long as the dose does not exceed one gram per day. In the unfortunate situation involving a patient with cirrhosis who has joint or musculoskeletal pain unresponsive to acetaminophen, NSAIDs can be used for a very brief period of time if given at the lowest daily dose possible.

Iron: Patients with chronic hepatitis C infection may store excess iron in their liver and excess hepatic iron has been associated with poor outcomes. Therefore, patients should limit foods high in

iron and avoid cooking in cast iron pans. Patients taking a daily multivitamin should make sure the multivitamin does not contain iron, unless a compelling reason exists to regularly take iron, such as iron deficiency anemia from gastrointestinal bleeding.

Vitamin D: Vitamin D deficiency is common in patients with chronic hepatitis C and levels of vitamin D may correlate inversely with liver disease severity. Several studies have shown patients with low vitamin D levels have poorer responses to interferon-based therapy, suggesting an important immunomodulatory role for vitamin D in patients with chronic hepatitis C infection. A more recent study, however, did not show any correlation with vitamin D levels and sustained virologic responses. Supplementation of vitamin D in patients who have 25(OH) Vitamin D levels less than 20 ng/mL is recommended, with initial therapy consisting of 50,000 IU of vitamin D once weekly for 8 weeks, to reach 25(OH) vitamin D levels of approximately 30 ng/mL. Thereafter, patients can take 1500 to 2000 IU per day for maintenance. For otherwise healthy adults, the Institute of Medicine recommends 600 IU per day of Vitamin D.

Vitamin A: Intake of vitamin A at levels contained in a multivitamin is considered safe. Vitamin A is a fat-soluble vitamin and should only be taken at standard doses of less than 10,000 units per day. Ingestion of mega-doses of vitamin A may potentially cause hepatotoxicity and is not recommended.

Alcohol, Tobacco, and Marijuana

Alcohol: In the United States, excessive alcohol consumption is one of the most common causes of cirrhosis and liver failure. The combination of excessive alcohol use with hepatitis C infection has a synergistic impact in causing hepatic damage, thereby significantly increasing the risk of developing cirrhosis and liver complications. It is clear that greater than 50 grams of alcohol per day is clearly hazardous to liver health, although an exact “safe” level has not been clearly established. Patients who have cleared hepatitis C, but continue to drink excessive amounts of alcohol, have no appreciable treatment-related benefit in terms of long-term hepatic complications and liver-induced mortality. Further, patients who drink excessive amounts of alcohol during therapy for hepatitis C have lower sustained virologic response rates. For these reasons, patients who have hepatitis C and a history of excessive alcohol use (including alcohol use associated with legal, working, or relationship problems) should abstain completely from alcohol. Women who never had an alcohol problem should have no more than one alcoholic drink per day and men with no history of alcohol problems should have no more than two alcoholic drinks per day. Patients with alcohol problems need to quit completely for at least 6 months prior to beginning therapy for hepatitis C. The Alcohol Use Disorders Identification Test Consumption questionnaire (AUDIT-C) is a useful screening test for problem drinking, especially in those who do not specifically admit to it.

Tobacco: The effects of tobacco smoking on the liver are controversial. In a study involving 244 patients with chronic hepatitis C infection, patients who were smokers had increased hepatic inflammation when compared with non-smokers, but no differences in rates of fibrosis were observed. In addition, other studies involving patients with chronic liver disease have shown increased rates of steatosis and advanced fibrosis, but these studies were retrospective and difficult to control for concurrent alcohol use and obesity. It is clear, however, that tobacco use increases the risk of hepatocellular carcinoma, working synergistically with alcohol and obesity. Because tobacco use is associated with numerous adverse health outcomes and may potentially adversely affect the liver, clinicians should counsel all smokers with chronic hepatitis C infection to quit tobacco completely.

Marijuana (Cannabis): In two separate, large studies, individuals who smoked marijuana on a daily basis had a threefold risk of developing cirrhosis, even after controlling for other factors, such as alcohol use and obesity. In addition, a biologically plausible mechanism exists for how marijuana use could accelerate hepatic fibrosis. Whether other routes of marijuana ingestion or sporadic use have a similar impact on liver fibrosis remains unknown. Some patients use marijuana for nausea or chronic pain, especially during peginterferon-based therapy. Therefore, clinicians should inform all patients of the potential hazards of smoking marijuana, but total abstinence should not be a requirement for hepatitis C therapy. For patients under consideration for a liver transplantation, many programs require complete abstinence from marijuana. In this setting smoking marijuana may carry the risk of pulmonary infection with fungal pathogens potentially contained in the marijuana.

Diet and Modifying Obesity

Introduction: In the United States and other Western nations, obesity is a growing problem. The average body mass index (BMI) for patients enrolled in hepatitis C therapy clinical trials frequently exceeds 25, a level generally considered overweight. Concurrent with the obesity epidemic, the prevalence of non-alcoholic fatty liver disease (NAFLD) has risen substantially as has the more severe form of NAFLD, known as non-alcoholic steatohepatitis (NASH). The worldwide prevalence of NAFLD and NASH are estimated at 6 to 33% and 3 to 5%, respectively. Even in the absence of hepatitis C infection, NASH can cause cirrhosis and end-stage liver disease.

Modifying Obesity: In clinical trials of peginterferon and ribavirin, obesity and hepatic steatosis consistently predicted a poorer response to therapy. Fortunately, patients with obesity and hepatic steatosis who receive treatment with directly acting antivirals have responses similar to non-obese patients who receive the same therapy. There are, however, concerns that patients successfully treated for hepatitis C, but who have continued NAFLD or NASH, could develop further liver disease and liver complications. For this reason, any patient with a BMI greater than 30 should be referred to a nutritionist for diet and weight loss counseling, with a goal of decreasing their BMI to less than 25. Obese patients should limit total caloric intake from fat to less than 30% (about 50 to 60 grams of fat per day); avoiding fried foods is a good way to reduce excessive caloric intake from fat. Although patients infrequently achieve their goal weight, they should receive counseling that any kind of weight loss can benefit them, even if they lose as little as 3 to 5% of their baseline weight. A combination of exercise and diet often produces the best long-term results.

Diet: In general, patients with hepatitis C should choose nutritious foods from each food group: fruits, vegetables, dairy, meat, and grains. A well-balanced diet can help patients receive appropriate amounts of all the vitamins, minerals, and other nutrients. Because drug-food interactions can occur, patients need to be aware of certain dietary restrictions if on therapy with one of these agents. Boceprevir, which is no longer recommended, can cause dysgeusia, but some patients obtain relief from this metallic taste by refrigerating the boceprevir or using plastic utensils when eating. All patients receiving therapy for hepatitis C should drink an abundant amount of water (at least 3 liters per day) to prevent dehydration.

Coffee: Coffee consumption may provide a benefit to patients with chronic hepatitis C infection by slowing fibrosis progression, decreasing the risk of developing hepatocellular carcinoma, and increasing the rates of sustained virologic responses with therapy. A large, NIH-sponsored study (referred to as the HALT-C Trial) found that patients who consumed 3 or more cups of coffee per day were half as likely to have progression of their liver disease and twice as likely to respond to peginterferon and ribavirin therapy. Thus, patients should be advised that consuming 3 cups of coffee per day may have a beneficial effect on their liver and chance of treatment response.

Sodium Intake: Patients with cirrhosis should limit sodium intake to less than 2 grams per day (88 mEq per day) because excessive sodium intake can lead to fluid retention in the form of lower extremity edema and ascites. As a rough guide, one teaspoon of table salt contains about 2 grams of sodium. Patients should not add salt to their food, but instead should replace salt with herbs or spices that can add flavor to the food, without the sodium load. Advise patients to choose fresh, unprocessed foods instead of salted, smoked, cured, canned, or dried meats, since these processed meats often contain large amounts of sodium.

Protein Intake: Patients with chronic hepatitis C, especially those with cirrhosis, should consume enough protein (at least 6 ounces per day for men and 4 to 5 ounces per day for women) to avoid muscle wasting and to promote tissue healing. Examples of high quality protein include chicken, fish, lean beef, pork, tofu, nuts, beans, milk, yogurt, and eggs.

Complementary and Alternative Medicines

Introduction: As many as 40% of patients with hepatitis C take complementary and alternative medications. Some of these complementary and alternative medications, however, may have harmful effects on the liver or cause serious interactions with medications used for hepatitis C therapy. Accordingly, clinicians should obtain a complete list of complementary and alternative medications taken by the patient (in addition to all prescription and over-the-counter medications) at the initial visit and at regular intervals thereafter. For patients taking complementary or alternative medications, clinicians should discuss whether it is wise for them to continue taking these alternative and complementary medications. The list of complementary and alternative medications should be reviewed again during therapy for hepatitis C, as some patients may seek out these options for relief of treatment-related side effects. The National Center for Complementary and Alternative Medicine (NCCAM) at the U.S. National Institutes of Health has an excellent website on the safety and efficacy of alternative medications.

Milk Thistle (*Silybum marianum*): Milk thistle is the most frequently taken alternative medication by patients with hepatitis C infection. It is produced from the seeds of a flowering herb and initial *in vitro* and animal studies suggested the active compound in milk thistle (silymarin and its derivatives) protected liver cells from injury and had antiviral activity. Investigation with an intravenous form of silymarin in patients with chronic hepatitis C following liver transplantation showed promising results, but a recent placebo-controlled, randomized study with high-dose oral silymarin found no significant improvement in alanine aminotransferase (ALT) or decreases in HCV RNA levels. Other studies have produced inconsistent results. Oral milk thistle can be purchased in health food stores without a prescription; the most frequently studied dose is 420 mg per day. The intravenous form of silymarin is available only in a research setting. The most common side effects are gastrointestinal (laxative effect, nausea, and epigastric discomfort). Milk thistle may also produce a hypoglycemic effect, so patients with diabetes or hypoglycemia should take milk thistle with caution or avoid it completely. Patients who have allergies to ragweed, chrysanthemum, marigold, or daisy may have a similar reaction to milk thistle. Oral preparations of milk thistle do not appear to cause hepatotoxicity, but it can decrease bilirubin conjugation and inhibit the cytochrome P450 enzyme system, potentially causing jaundice and drug-drug interactions. In summary, milk thistle taken orally does not appear to have any beneficial or toxic effects on the liver and it does not significantly alter HCV RNA levels. At this time, most experts recommend not initiating milk thistle for patients with chronic hepatitis C. Patients who continue to take milk thistle should be warned about the gastrointestinal and hypoglycemic side effects, and the potential for drug-drug interactions.

S-Adenosyl-L-Methionine (SAMe): S-adenosyl-L-methionine (also called S-adenosyl methionine, S-adenosylmethionine, SAMe, or SAM-e) is a molecule involved in multiple cellular reactions, acting as the principal methyl donor. Animal models have shown that SAMe depletion can enhance cellular proliferation and growth, such as fibrosis and cancer. *In vitro* models of hepatitis C demonstrated that SAMe enhances the antiviral effect of interferon, although SAMe does not have any direct antiviral activity. Patients with hepatitis C who took SAMe in conjunction with peginterferon and ribavirin had improved viral kinetics (improved early response), but this did not translate into better sustained virologic response rates. Most often, SAMe is taken at a dose of 1200 mg per day. There are no large, high-quality studies to date demonstrating a treatment outcome benefit of taking SAMe for patients with chronic hepatitis C. A meta-analysis of SAMe concluded that it is superior to placebo in controlling pruritus in patients with chronic liver disease.

Licorice Root (*Glycyrrhiza glabra*): Licorice root contains a compound called glycyrrhizin (or glycyrrhizic acid). Although preliminary studies suggested intravenous glycyrrhizin had some beneficial effects for patients with hepatitis C, the intravenous formulation is not available outside of the research setting. There are minimal reliable data on oral licorice root for hepatitis C, so no specific recommendations can be made regarding its use. When taken in large amounts, however, licorice root containing glycyrrhizin can cause high blood pressure, salt and water retention, low potassium levels, and alterations in serum cortisol levels. For these reasons, it is not recommended

for patients on diuretics or those with cirrhosis or cardiovascular problems.

St John's Wort (*Hypericum perforatum*): The St. John's wort plant (*Hypericum perforatum*), and its derivative hypericin and hyperforin, are commonly used herbal medicines for the treatment of depression. The evidence for its effectiveness in depression is mixed, with several large studies showing no benefit over placebo for major depression. St. John's wort does not have anti-HCV activity, but it is a strong CYP3A inducer and thus can significantly lower the levels of HCV medications that are substrates of CYP3A. Specifically, St. John's wort is contraindicated for use with boceprevir, daclatasvir, ledipasvir-sofosbuvir, ombitasvir-paritaprevir-ritonavir, ombitasvir-paritaprevir-ritonavir and dasabuvir, simeprevir, and sofosbuvir. Essentially, any patient taking a direct-acting antiviral agent (DAA) should not concomitantly take St. John's wort. Other significant drug-drug interactions with St. John's wort include digoxin, warfarin, oral contraceptives, and anti-epileptics.

Thymus Extract: Produced from the thymus gland of cows, thymus extract is touted as an immune system booster. One small study found no benefit in patients who had previously failed conventional therapy. Overall, insufficient evidence exists to support its use in patients with chronic hepatitis C. In addition, some have raised concerns of contamination of thymus extract products as well as the potential for zoonotic disease transmission given its bovine source.

Ginseng: Ginseng is purported to benefit patients with hepatitis C by boosting the immune system. There are insufficient data with ginseng in patients with hepatitis C to make any recommendations on its use. Importantly, it can lower blood glucose, so it should be used cautiously in patients with a history of hypoglycemia or diabetes mellitus.

Schisandra (Magnolia Vine): Schisandra is a vine native to eastern Asia and is used an herbal medicine. One small study suggested an antiviral effect, but larger confirmatory studies are needed before routine use can be recommended.

Lactoferrin: Lactoferrin, also known as apolactoferrin or lactotransferrin, is a protein found in milk and other body fluids that binds and transports iron. The highest concentration of lactoferrin is in colostrum. Bovine lactoferrin is the formulation of lactoferrin most often used when taken as a dietary supplement, with a typical dose of 1.8 to 3.6 grams per day; lactoferrin can also be produced via recombinant technology. In several small studies, lactoferrin lowered HCV RNA levels. At this time, follow-up studies are required before any lactoferrin preparation can be recommended for patients with hepatitis C, but lactoferrin appears to be safe.

Red Yeast Rice Extract: Red yeast rice extract is a dietary supplement commonly used in Asia to lower blood cholesterol. It contains a compound (monacolin A) that is biochemically similar to HMG-CoA-reductase inhibitors. Since these compounds can potentially interact with some of the HCV DAAs, patients should be advised to not consume red yeast rice while on these hepatitis C treatment medications.

Summary Points

- Patients with chronic hepatitis C and no cirrhosis may take up to 2 grams per day of acetaminophen. Patients with cirrhosis should limit daily intake of acetaminophen to 1 gram per day. Those with excessive alcohol intake should not take acetaminophen.
- In general, NSAIDS are safe for patients with hepatitis C, except for those with cirrhosis, in which case they should be avoided or used sparingly.
- Patients with a history of excessive alcohol use should quit alcohol completely and maintain a period of sobriety for at least 6 months prior to consideration of antiviral therapy. Patients without a history of excessive alcohol may consume up to 1 alcoholic beverage a day (for women) or 2 drinks per day (for men).
- Obese patients are encouraged to lose at least 3 to 5% of their body weight, with a goal body mass index of less than 25.
- Patients can take a multivitamin without iron. Vitamin D levels should be checked and repleted if less than 20 ng/mL.
- A balanced, low-fat (less than 30% of total calories) diet is recommended. Patients with cirrhosis should limit sodium intake to less than 2 grams per day and consume at least 6 ounces per day of protein.
- Drinking 3 or more cups of coffee per day may have beneficial effects for the liver and increase the likelihood of antiviral response.
- No complementary or alternative medications have shown a definite benefit for patients with hepatitis C. St. John’s wort should not be given to patients taking DAAs. Ginseng can cause hypoglycemia and licorice root can cause fluid retention and hypokalemia.

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