

Medical Writers' Circle

a series of articles

written by medical
professionals about
the management
and treatment of

Hepatitis C

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Preventive Care in Chronic Liver Diseases

Chronic liver disease is the tenth leading cause of death in the United States (US) with over 25,000 deaths annually, according to federal statistics. There are an estimated 4 million known cases of hepatitis C in the US, some of which present with cirrhosis or will eventually become cirrhotic (1). Our current ability to treat hepatitis C and eliminate the infection has been improving with the advent of long acting interferons. After treatment, however, there will continue to be about 40-50% with continued evidence of chronic infection. The natural history of HCV is a progression from hepatitis to cirrhosis over many years, often twenty to fifty years. With an inability to cure the primary disease process in this non-responder group, it becomes important to prevent further insults thus optimizing the length of time between hepatitis to cirrhosis. Once cirrhosis occurs nothing currently can be done to reverse the process. Those with early cirrhosis (Child's A) may live on average 10 to 15 years before death or liver transplantation (2). Preventive strategies can be used to maximize this time. This review will discuss preventive

care methods that have been shown to be effective or have scientific rationale in the setting of chronic liver diseases both in the hepatitis and cirrhotic stages.

Avoidance of alcohol consumption:

Alcohol consumption is associated with an increased risk of cirrhosis, liver cancer and premature death when consumption is greater than four drinks daily (48 grams) (3). The types of injury that can occur to the liver directly related to alcohol include acute alcoholic hepatitis, fatty infiltration, and cirrhosis (4). There is little data available to determine what level of alcohol consumption might be safe in those with a chronic liver condition. In a recent report Corrao et al. examined the combined effect of hepatitis C and alcohol on the development of symptomatic cirrhosis. They found that alcohol had a synergistic (multiplies), not merely an additive role, in the development of cirrhosis in the patients infected with hepatitis C. The moderate alcohol consumption group carried an increased risk for the development of cirrhosis (5). Because the safe level of alcohol consumption is not known, it seems prudent to advise abstinence in

the face of chronic liver diseases with the information we now have available. When moderate to heavy alcohol use is present in the face of chronic liver disease, abstinence is likely to be the most important intervention made in prolonging the course and delaying the progression towards cirrhosis. Alcohol has a strong addiction potential and abstinence can be difficult. Support in the process of abstinence should be suggested in many of the cases where heavy use is present. Examples of effective support include Alcoholics Anonymous, in- and out-patient rehabilitation programs and individual counselors (6).

Immunizations

Case reports have raised the concern about the risks of superinfection with the hepatitis viruses in those with chronic liver diseases. Both hepatitis A and B are reported to cause more virulent (aggressive) acute infections when a chronic liver condition exists (7-10). A recent series by Vento et al. highlighted the risks of superinfection with hepatitis A. They followed prospectively (on an ongoing, current basis) 163 patients with chronic hepatitis B and 432 patients with hepatitis C. The study

showed a substantial risk of fulminant hepatic failure and death with hepatitis A superinfection, in particular in those with chronic hepatitis C. Less than 1:1000 cases of hepatitis A are fatal. In this series, when chronic hepatitis C was present, 35% of cases were fatal (a 350 fold risk of death above normal) (11). In another large series of 115,551 cases of acute hepatitis A, there were 381 deaths. Of the deaths, 107 (28%) were in those with chronic liver disease (9). Based on this data, it is important to first test for exposure to the hepatitis viruses. If no immunity (natural protection) is found, then the hepatitis A vaccine

(infection of fluid in belly) episodes and to prevent pneumococcal pneumonia (lung infection) in a group where infection would be poorly tolerated (15). Finally, all patients with cirrhosis should receive yearly influenza vaccine, given the higher risk of mortality (death) should they contract influenza (16).

Avoidance of potentially liver toxic medications / vitamins / herbs / and minerals

Most medications and ingested substances are altered chemically as they pass through the liver, which functions as a

one needs to take an extremely cautious approach. Medications should be started only when absolutely indicated and no other option exists. Each medication that is required should be evaluated for possible liver toxicity. If liver toxicity has been reported, an alternative with less or no hepatic adverse effects should be sought. If no options or safer alternatives exist, then the medication can be started under close observation. The chronic liver disease patient should be aware of liver related symptoms, for example, jaundice (yellowing of the skin), pruritis (itching), anorexia (loss of appetite), fatigue (tiredness)

available. The class of non-steroidal anti-inflammatory drugs (NSAIDs) encompasses the largest class of medications used for common maladies such as arthralgias or headache. NSAIDs can cause idiosyncratic (unpredictable) liver toxicity (19). A recent report by Riley et al. (20) described three cases of over-the-counter ibuprofen use in patients with hepatitis C which resulted in a greater than 10 fold rise in the transaminases (liver enzymes). In one of the cases a rechallenge occurred leading to a repeated equal rise in the transaminases. By nature of these unpredictable reactions (idiosyncratic), a risk is taken with each use of NSAIDs in the setting of chronic liver disease. NSAIDs are known to increase the tendency for bleeding by inhibiting platelet function in the setting of cirrhosis where there already is impaired coagulation (ability to clot). NSAIDs also decrease renal prostaglandins (hormones) in cirrhotic patients decreasing kidney blood flow, and thus filtration rates which can lead to renal failure (21).

Acetaminophen use leads to an intrinsic, dose dependent, and predictable toxicity to the liver. There are no cases of toxicity reported even in advanced liver disease when less than 2 grams of acetaminophen are ingested (22). For these reasons NSAIDs should be avoided in chronic liver diseases. When pain medications are required preference should be given to acetaminophen at a dose of up to 2 grams per day.

Vitamins and "alternative" natural remedies are commonly consumed in the US with annual sales over 1.6 billion dollars. In informal polls taken in hepatology clinics up to 31% of patients were taking "alternative"

Patients with chronic liver diseases should avoid excessive iron intake. If a patient with chronic liver disease takes a multivitamin, it should not have iron as a component unless iron deficiency anemia is demonstrated. No evidence exists to suggest that normal dietary iron is harmful.

(2 part series) and the hepatitis B vaccine (3 part series) should be administered. Both vaccines can be safely given in opposite deltoids (shoulders) at the same time, then the hepatitis B vaccine at one month for the second in the series, and finally both again for completion 6 months later (12-13). A study by Keeffe et al. recently described the safety and efficacy of vaccination in chronic liver disease (14). No vaccination currently is available for clinical use to protect against the acquisition of the hepatitis C virus.

Pneumovax is also recommended as a one time vaccination in all patients with cirrhosis. The rationale includes the prevention of pneumococcal spontaneous bacterial peritonitis

mechanism for clearance, detoxification, and excretion. Because of this central role of the liver in metabolic processing, the liver is vulnerable to toxicity from drugs and vitamins (17). In the setting of chronic liver diseases, the liver functions may variably become affected. The altered functions may enhance or predispose to toxicity from medications. In addition to a predisposition to medication toxicity, someone with a chronic liver condition may not tolerate a reaction. When these unpredictable reactions occur, patients with only a small amount of reserve function remaining may have a decompensation in their condition.

To avoid medication toxicity in those with chronic liver disease,

and right upper quadrant (under right rib cage) abdominal (belly) pain. Liver injury tests can be followed, at baseline, every two weeks for a month, monthly for three months, then every three months indefinitely while requiring the potentially toxic medication. If an increase in liver injury test occurs that is more than two to three times the baseline or liver-related symptoms develop the medication should be discontinued (18). When a question arises about the safety of a medication in an individual with chronic liver disease, a liver specialist's input may be helpful.

Pain medications are one of the most widely used medications, with both prescription and over-the counter medications

therapies (23). These non-traditional medications should be inquired about and reviewed for safety. Vitamin A (betacarotene, retinol) is a known hepatotoxin but is widely available over-the-counter. There are multiple reports of massive doses leading to liver injury, usually in doses greater than 100,000 IU / day (24). There are rare reports of vitamin A doses of as low as 25,000 IU / day leading to liver injury including steatosis (fatty liver), chronic hepatitis (inflammation to liver through time), and fibrosis/cirrhosis (scar tissue). Alcohol use is reported to potentiate the toxicity of vitamin A. Vitamin A has a dose dependent toxicity and is safe to ingest in the usual diet. Patients with chronic liver diseases should be warned about the risks of mega-dose vitamin A consumption. Other possible liver toxins available without

secondary hemosiderosis (iron loading) with up to 30% showing evidence of serum accumulation by iron studies and 10% with liver tissue excesses (25,26). The data has been accumulating along several lines of evidence that iron overload is detrimental to those with chronic liver diseases. Hepatic iron concentration, when high, has been shown by several investigators to be a predictor of non-response to interferon alfa therapy in chronic hepatitis C (27,28). In further support, when phlebotomy was used as the sole treatment in chronic hepatitis C in those with confirmed iron overload histologically, there was a significant improvement in serum transaminases (29). A study from India showed that when combining a low iron diet with traditional treatment of hepatitis C there was an increased response

injuries. The list of conditions that will produce fatty infiltration is extensive and includes alcoholic liver disease, non-alcoholic steatohepatitis (NASH), hepatitis C, drug reactions, Wilson's disease and other genetic diseases (32). Predisposing medical risk factors include diabetes mellitus, obesity, and elevated serum triglycerides (33). Fatty infiltration is often well tolerated with minimal to no inflammatory reaction. In some cases, however, an inflammatory reaction to the presence of fat can be intense leading to elevation of liver injury tests and histologic changes of necro-inflammation (death of liver cells from inflammation), fibrosis and cirrhosis (34). A study by Ueno et al. demonstrated in a controlled trial that a weight reduction diet and exercise program can improve liver injury blood tests, and liver

Table 1

Summary of Preventive Measures in Chronic Liver Diseases:

- 1. Avoidance of alcohol of all types (includes beer, wine, mixed drinks).**
- 2. Receive vaccinations against hepatitis A and B, if not already immune (your doctor can check blood work to determine this). Also receive a one time pneumovax and yearly fall flu shots.**
- 3. Avoid liver toxic medications, most common to be used is over-the-counter pain killers (aspirin-like medications), Tylenol (acetaminophen) in less than 2 grams per day is safest (one extra-strength every 6 hours). Review other medications with your doctor.**
- 4. Avoid iron supplementation unless your doctor has shown that you are iron deficient (If you take a multi-vitamin, there are brands that do not have iron as a component).**
- 5. A low fat, "heart smart" diet is good for your liver as well as your heart.**
- 6. Once cirrhosis develops, yearly screening should be done to follow your risk of bleeding with upper endoscopy and for the early detection of liver cancer with ultrasound.**

Several randomized controlled studies have shown that non-selective beta-blockers reduce the risk of the initial variceal bleed in high risk patients by about 50% (45% to 22% risk of bleeding over 2 years) (40). ■
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prescription include niacin, Chinese herbal tea, Jin Bu Huan, germander, Kalms tablets, gentian, asafetida, valerian, mistletoe, senna fruit extracts, chaparral leaf, comfrey, bush herbal teas, and pennyroyal oil (24).

Iron supplementation, usually in the form of a multivitamin preparation is not uncommon. In the usual state of health, excess dietary iron is not absorbed and is excreted in the stool. In the setting of many chronic liver diseases there is a propensity for excessive iron to accumulate in the liver. Hepatitis C and alcoholic liver diseases seem to have a particular tendency for

to treatment (30). Animal studies have demonstrated enhanced hepatotoxicity to alcohol in rat models when iron was co-administered (31). Given these findings, patients with chronic liver diseases should avoid excessive iron intake. If a patient with chronic liver disease takes a multivitamin, it should not have iron as a component unless iron deficiency anemia is demonstrated. No evidence exists to suggest that normal dietary iron is harmful.

Heart / Liver Smart Diet

Fatty infiltration of the liver is a basic response to a variety of

biopsy appearance in patients with NASH (35). Liver tests often return towards normal with relatively minor weight reduction of 10 to 15 pounds. Deems et al. reported on a relationship between liver injury tests and dietary intake. A study of dietary intake on 42 chronic liver disease patients showed a correlation between high fat and oil food consumption and elevated liver injury tests (36). Recent studies have highlighted the detrimental effects of obesity and HCV infection, with a higher risk of advanced fibrosis as degree of obesity increases (37). These observations

suggest that a low fat diet and exercise program (supervised by a physician for appropriateness) would minimize hepatic steatosis. In those with chronic liver disease and obesity gradual weight reduction should be recommended.

Preventive Measures in Cirrhosis

Once cirrhosis is established, the disease is considered irreversible. Survival in early cirrhosis may be up to 15-20 years. Potential risks during this time interval include bleeding from esophageal varices (dilated veins in feeding tube) and the development of hepatocellular carcinoma. Preventive or early detection strategies have been evaluated for both of these conditions.

Beta-Blockade in prevention of first variceal bleed

Portal hypertension (increased blood pressure before the liver) is a frequent complication of cirrhosis. When the portal pressures are consistently high, portal-systemic collaterals (new channels form). The once small veins become enlarged and under pressure and form esophagogastric varices (dilated veins). Varices can be visualized in approximately 60% of patients with cirrhosis undergoing upper endoscopy (scopes). Patients with large varices will have bleeding episodes at a rate of ~40% per year. The first bleeding episode from varices may be associated with mortality rates as high as 50% (38). Endoscopic criteria have been defined which predict those patients who are at risk of variceal bleeding. These criteria include larger varices, red markings on variceal surface, and the patient's Child's score (an ABC system used to rank severity of cirrhosis) (39). The

ability to predict high risk patients aids in targeting preventive strategies, and allows those at low risk to avoid unnecessary medications. Several randomized controlled studies have shown that non-selective beta-blockers reduce the risk of the initial variceal bleed in high risk patients by about 50% (45% to 22% risk of bleeding over 2 years) (40). The pulse is indicative of adequate dosing, and beta-blockers are titrated (dose adjusted) to achieve a 25% reduction from baseline pulse. Usual starting doses are propranolol 10 mg three times per day. If either no varices or small varices are found on the initial endoscopy, medication prophylaxis may be withheld. These patients should subsequently undergo surveillance endoscopy every one to two years to determine subsequent risk of bleeding.

Screening for Hepatocellular Cancer

Cirrhosis, irrespective of the cause with few exceptions, carries a high risk for the development of hepatocellular carcinoma (HCC) (tumor of liver origin). HCC is the leading cause of death in a population of cirrhotic patients (41). Advanced HCC carries a poor prognosis, having a three year survival of 17% (42). If HCC lesions are discovered early, and are less than 2 cm at the time of resection, survival of up to 85% at 5 years has been reported (43). In those with decompensated liver disease where a small HCC is found, successful liver transplantation with minimal recurrence has been reported (44). Two tests have been suggested for screening, the serum measurement of alpha-fetoprotein (AFP) and liver ultrasonography. Although imperfect when either is used alone, multiple studies have confirmed the efficacy of

combined use of AFP and ultrasound in early detection. Some controversy still exists in the frequency of testing required and achievement of cost effectiveness (45). There is a lack of data to assure that early detection translates into better outcome, because randomized trials in this patient group are difficult to perform (46). Overall, the existing data suggests the need for at least yearly ultrasounds and every 6 month measurements of AFP in all patients with cirrhosis of the liver.

Conclusions

Many liver diseases have long natural histories with few treatments that directly alter the course. To maximize the time to cirrhosis, need for liver transplantation, or death it becomes important to avoid other injury to the liver. A handout for patients to remind them of good liver health is provided (Table 1).



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