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Review

Preventive Health in Liver Disease

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ABSTRACT

Preventive health strategies are the foundation of managing liver disease. Despite public health initiatives, incorporating preventive measures into clinical practice has not yet been fully achieved. Not only has this led to missed opportunities in preventing decompensation in patients, but it has further increased health care costs associated with end stage liver disease. While resource allocation also plays a role in this, lack of knowledge and awareness among providers significantly contributes to this ongoing issue. This review aims to serve as a comprehensive summary outlining preventive strategies in liver disease for use by providers to better serve their patients.

Keywords: *Cirrhosis, Hepatitis, Liver, Non-alcoholic fatty liver disease, Prevention.*

DIAGNOSING LIVER INJURY TO PREVENT PROGRESSION TO CHRONIC LIVER DISEASE

Screening for HBV and HCV

The presence of hepatitis B surface antigen (HBsAg) is indicative of a current infection with hepatitis B virus (HBV). Chronic infection is defined by persistent antigen positivity for more than 6 months. HBV is transmitted by perinatal, percutaneous, sexual exposure, and rarely close person-to-person contact if both people have exposed open wounds. Of note, breastfeeding is not prohibited in HbsAg positive women. The majorities of people infected with hepatitis B in the United States are immigrants, have immigrant parents, or were exposed by an infected household contact. Screening tests for HBV assess for both HBsAg and hepatitis B surface antibody (HBsAb). There are several high-risk groups who should be screened for HBV infection-notably people born in regions with high or intermediate HBV endemicity, persons who have ever injected drugs, men who have sex with men, all pregnant women, and people with known chronic liver disease.[1] The CDC also recommends that all persons receiving cytotoxic or immunosuppressive therapy be screened for HBsAg, anti-HBc, and anti-HBs. This includes candidates for chemotherapy, B-cell depletion, or TNF inhibition.[2]

Acute hepatitis C refers to the first 6 months after initial infection, with persistent infection diagnosed by persistent HCV RNA detectable levels. There is a 20% to 50% chance of spontaneous resolution during this period. Injection drug users, men who have sex with men, and people in jails and prisons have a high burden of chronic HCV infection. Screening is done by an HCV antibody test followed by confirmatory HCV RNA positivity. One-time hepatitis C testing is recommended for all persons born from 1945 to 1965, along with those with high risk behaviors or exposures. These behaviors and exposures include injection or intranasal illicit drug use, patients on long-term hemodialysis, history of incarceration, children born to HCV-infected women, and those with HIV. Screening with an HCV antibody assay is also newly recommended for pregnant women. Breastfeeding is not contraindicated in women with only HCV infection unless they have cracked, damaged, or bleeding nipples.[3]

Non-Alcoholic Fatty Liver Disease

Non-Alcoholic Fatty Liver Disease (NAFLD) is a steadily increasing cause of chronic liver injury that is estimated to affect 10% to 46% of the global general population. NAFLD includes a spectrum of conditions ranging from simple hepatic steatosis to Non-Alcoholic Steatohepatitis (NASH) with or without fibrosis and cirrhosis. Common risk factors include obesity, diabetes mellitus, hypertension, and hyperlipidemia. Early recognition and intervention can limit progression and may decrease liver injury. Physical symptoms are limited but include hepatomegaly, ascites, muscle wasting, and dermatological stigmata associated with chronic liver disease. Most patients are asymptomatic but have abnormalities revealed during routine, unrelated testing. It is also possible that hepatic steatosis be noted incidentally on an imaging study, such as ultrasound, CT, or MRI. Although liver biopsy allows definitive

detection of NASH, it is not a practical screening approach. There are multiple noninvasive methods of assessing underlying hepatic fibrosis, one of which is the FIB-4 index. The FIB-4 index, or FIB-4 = [age (yr) x AST (U/L)]/[Platelet count (109/L) x (ALT (U/L))1/2], uses accessible laboratory tests to assess the degree of fibrosis and is available to all physicians.[4] An index score of 1.30 or greater is suggestive of advanced liver fibrosis and at this point the patient should be referred for specialized liver evaluation.[5] Medical optimizations of medical co-morbidities (such as hypertension, hyperlipidemia, and diabetes) are key to reduce progression of NAFLD. Weight loss and exercise should be advocated to every patient with NAFLD, with treatment strategies discussed further below.

Drug-induced Liver injury

Drug Induced Liver Injury (DILI) is the most common cause of acute liver failure in the United States. Women and patients with alcohol abuse are at higher risk, with acetaminophen toxicity being the most common etiology.[6] Antibiotics are the second most common cause of DILI with amoxicillin-clavulanate being the most common culprit. It is key that patients be educated about the potential hepatotoxicity of some medications and be advised to be cognizant of signs of liver injury (e.g. jaundice, new-onset ascites, or encephalopathy). Specifically, prevention of DILI involves counseling patients on the dosage limits and mixing of medications with other drugs including alcohol. If there are concerns for liver damage, management consists of early identification and subsequent discontinuation of the suspected drug causing toxicity. These patients should be referred for specialty evaluation or admitted to the hospital for workup. DILI has a variety of laboratory abnormalities and can be hepatocellular with aminotransferases over 1000 (with only mildly elevated bilirubin and alkaline phosphatase), follow a cholestatic pattern of liver injury, or a mixed pattern. If a medication causes hepatocellular injury with jaundice, as dictated in "*Hy's Law*", there is a high risk of fatal DILI. These patients should immediately be referred to hepatology. Serial monitoring of liver enzymes of patients on known hepatotoxic medications is controversial but recommended in patients taking medications with higher reported toxicity including isoniazid and methotrexate.

The US Drug-Induced Liver Injury Network ranks DILI from mild to fatal.[6] Mild DILI involves elevated ALT and/or ALP but Total Bilirubin (TBL) <2.5 mg/dl and INR <1.5. Moderate DILI is defined as an elevated ALT and/or ALP and Total Bilirubin (TBL) ≥ 2.5 mg/dl or INR ≥ 1.5. Severe DILI occurs with elevated ALT and/or ALP and TBL ≥ 2.5 mg/dl and at least 1 of the following criteria: Hepatic failure (INR >1.5, ascites or encephalopathy) or other organ failure due to DILI. Lastly, fatal DILI occurs with death or liver transplantation due to DILI. Patients with features of moderate DILI are at risk of future hospitalization and hepatic failure. It is recommended that they be referred to a hepatologist and possibly a liver transplant unit. Recovery from acute liver injury may span weeks to months. Thousands of medications have been identified as potentially damaging to liver health, a small number of which are listed below (Table 1).

Table 1. Common hepatotoxic medications

Isoniazid	Phenytoin
Trimethoprim/Sulfamethoxazole	Carbamazepine
Nitrofurantoin	Valproic acid
Amoxicillin	Statins (Simvastatin, Atorvastatin)
Disulfiram	Methyldopa
Propylthiouracil	Troglitazone
NSAIDs (Bromfenac, Diclofenac)	Stavudine with didanosine
Terbinafine	Sulfasalazine
Methotrexate	Amiodarone

Herbal and Nutritional Supplements

Supplements are a less commonly identified cause of acute liver injury due to the difficulty in identifying the substance and dose dependency. Many preparations may increase bleeding risk and could have adverse effects in patients with cirrhosis. Supplements including ginkgo biloba for memory enhancement, ginseng for mental performance, and saw palmetto for benign prostatic hypertrophy cause some degree of platelet dysfunction and should be monitored with caution (Table 2).

Table 2. Hepatotoxic supplements

Herbal Remedies	Herbs	Weight loss products
Jin Bu Huan	Horny goat weed	Herbalife products
Ma-Huang	Mistletoe	Hydroxycut
Syo-saiko-to	Germander	Garcinia cambogia
Chaso	Valerian	OxyELITE Pro
Green tea extract	Chaparral	
Pyrrolizidine alkaloids	Kava kava	
	Black cohosh	
	Flavocoxid	
	Saw palmetto	
	Deathcap(Amanita phalloides)	

HEALTH MAINTENANCE IN CHRONIC LIVER DISEASE

Immunizations

Immunizations remain a cornerstone of prevention of morbidity and mortality for patients with chronic liver disease. Despite availability since 1981 for HBV and 1995 for HAV, use of the HAV and HBV vaccines remains low. Administration amongst high-risk adults aged 18 to 49 is 12.1% for HAV,[7] and 34.2% for HBV vaccine (3 doses).[8] Inactivated vaccines are safe in patients with cirrhosis, while live, attenuated virus vaccinations should be avoided (including the live virus form of the influenza vaccination). A recommended vaccine schedule for patients with chronic liver disease can be found in Table 3.

Table 3. Recommended vaccine schedule

IMMUNIZATION	RECOMMENDATION	SCHEDULE	NOTES
INACTIVATED NFLUENZA	Yes	Yearly	Less effective than in healthy individuals; may prevent hepatic decompensation
23-VALENT PNEUMOCOCCAL POLYSACCHARIDE VACCINE (PPSV-23)	Yes	Dose 1 given at the time of diagnosis if ≥ 19 years	Likely less effective than in healthy individuals
		Dose 2 given 5 years later	
		Dose 3 given at age 65 years (if ≥ 5 years or more since previous vaccination)	
13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV-13)	No	—	Generally, not indicated as it confers less immunity then the PPSV-23, but may be considered on a case by case basis[9]
HEPATITIS A	Yes	Dose 1 given at time zero	Lower rates of seroprotection in decompensated cirrhosis
		Dose 2 given at 6-12 months	
HEPATITIS B	Yes	Dose 1 given at time zero	Patients with cirrhosis should receive a double dose (40 µg) with the standard schedule. If there is no response to the standard series, can repeat with repeated high-dose (80 µg) vaccinations[10]
		Dose 2 given at 1 month	
		Dose 3 given at 6 months	
HERPES ZOSTER (ZOSTAVAX®)	No	—	Limited data for safety and efficacy in cirrhosis
HERPES ZOSTER (SHINGRIX®)	Yes	Dose 1 given at time zero	Recommended if ≥ 50 years old, irrespective of prior chickenpox or shingles
		Dose 2 given at 2-6 months	

Malabsorption of Vitamin D

Vitamin D deficiency is caused by malabsorption in patients with chronic liver disease. Vitamin D is lipophilic and unabsorbed in chronic liver disease due to disruption in bile synthesis. Patients are at greater risk of accelerated bone loss, weakness, fractures and even osteomalacia. Routine bi-annual vitamin D screening in patients with chronic liver disease is recommended as they remain relatively asymptomatic until their stores are depleted.[11] If deficiency is found, cirrhotic patients require larger oral doses of Vitamin D than normal for treatment (initial dose of at least 6000 to 10,000 IU/d followed by maintenance therapy of at least 3000 to 6000 IU/d).[12]

Abstinence from Alcohol

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) in the US estimates that alcohol consumption greater than 14 standard drinks per week on average in men less than 65 (or more than 4 drinks on any day) and women or adults age 65 or older with more than 7 standard drinks per week (or more than 3 drinks on any day) are at increased risk of alcohol-related hepatic complications. According to the AASLD guidelines from 2010,[13] fatty liver develops in 90% of individuals who consume >60 grams or 5 standard US drinks per day, and potentially in those who drink less. Screening surveys including CAGE, AUDIT, and the Michigan Alcohol Screening Test (MAST) have been used in clinical practice. Regardless of which survey is utilized, it is important for physicians to routinely incorporate these surveys into clinical practice with every patient and advocate for complete abstinence in patients with cirrhosis and reduced consumption in those with unhealthy drinking habits.

PREVENTING CIRRHOSIS BY TREATING CHRONIC LIVER DISEASE

Treating Non-Alcoholic Fatty Liver Disease

Primary and secondary prevention of NAFLD requires aggressive management of obesity, diabetes, and metabolic syndrome.[14] Therapy for most patients with NAFLD focuses on lifestyle modifications such as diet modification and exercise. Weight loss, a major factor in treatment, can lead to improvement in liver histology, serum insulin levels, and quality of life. Small reductions (3% to 5% body weight loss) can reduce hepatic steatosis and act as an intermediary goal of treatment. Greater weight loss (7%) is required to significantly improve or resolve steatohepatitis.[15] This is challenging, and bariatric intervention may need to be considered in those who fail a therapeutic trial of weight loss. Patients assessed using non-invasive methods, as described earlier, with advanced fibrosis should be referred to specialty care. In diabetic patients, there is no single agent to date that prevents the progression of NASH to NAFLD. The Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis (PIVENS) trial by the NIDDK showed that pioglitazone was effective in reducing hepatic steatosis and lobular inflammation; however, it was not effective in reducing overall NASH and led to overall weight gain. Vitamin E, an antioxidant that prevents liver injury by protecting against oxidative stressors, can improve histological NASH and contribute to resolution at a dose of 800 IU/day. Its use is controversial as there are concerns regarding long-term use and increased risk of hemorrhagic stroke or prostate cancer. AASLD guidelines suggest that vitamin E be used in nondiabetic adults with biopsy-proven NASH but it does not recommend using it as treatment for NASH in diabetic patients or NAFLD without liver biopsy.[16] Additionally, metformin and statins, while they did not improve the histopathology of NAFLD, should be continued in patients with diabetes or hyperlipidemia. The REGENERATE trial, an ongoing phase 3 study, has tested the use of obeticholic acid, a famesoid X receptor agonist, in the treatment of NASH. Interim results have shown that use of obeticholic acid 25 mg leads to significant improvement in fibrosis and key components of NASH disease activity. It is predicted that this clinically significant change in histopathology will predict clinical benefit, though the trial is yet to assess clinical outcomes.[17]

Treating Hepatitis

In the management of chronic hepatitis B, assays may be used to quantify HBsAg (qHBsAg) using viral DNA with limited specificity. Levels of HBsAg are generally higher in those patients whom are HBeAg-positive. Higher qHBsAg levels are associated with progression to cirrhosis. A high viral load is defined as qHBsAg greater than 20,000 IU/mL. The

quantification of HBsAg also permits tracking of viral load during treatment. All patients with chronic HBV should be referred to a hepatologist.

In chronic hepatitis C, progression is dependent on a patient's age at the time of diagnosis along with other risk factors (such as co-infection with other viruses, heavy alcohol usage, or fatty liver disease). Patients with hepatitis C should undergo treatment with antiviral agents and may require referral to a specialist (which can include Infectious Disease or Hepatology). Additionally, patients with chronic hepatitis B or C should be screened for HIV.

Immune Suppression in Autoimmune Hepatitis

Autoimmune hepatitis predominantly occurs in women with an approximate annual US incidence of 1 per 100,000 cases.[18] Genetic susceptibility to autoimmune hepatitis is related to HLA alleles encoding the DRB1 polypeptide and CTLA-4 gene polymorphism.[19] Primary care physicians should be diligent to the fact that CTLA-4 polymorphisms are associated with a host of other autoimmune diseases including type 1 diabetes, Graves' disease, celiac disease, SLE, and rheumatoid arthritis.[20] Patients with these diseases are at increased risk for concurrent autoimmune hepatitis and should be closely monitored. Standard antibodies including antinuclear antibodies (ANA), smooth muscle antibodies (SMA), and antibodies to liver kidney microsome type 1 (anti-KLM1) characterize most patients with autoimmune hepatitis and should be assessed in disease workup. Disease activity can be assessed with serum AST, serum IgG, and γ-globulin levels.[21] All patients thought to have autoimmune hepatitis should be referred to Hepatology, as these patients typically require a liver biopsy for diagnostic confirmation, assessment of underlying fibrosis, and specialty care. Therapy typically involves glucocorticoids, with or without azathioprine or 6-mercaptopurine.

Treatment of iron overload in Hemochromatosis

Hereditary Hemochromatosis (HH) is an autosomal recessive genetic disorder most commonly diagnosed in Caucasian males.[22] Typically patients are not symptomatic at presentation but rather come to attention after abnormal liver studies on routine screening or abnormal iron studies. However, they can present with nonspecific symptoms including weakness, lethargy, arthralgias, and impotence.[23] Screening is conducted with a fasting transferrin saturation, and if greater than 45% (often in the setting of an elevated ferritin), HFE gene mutation analysis should be performed. The most common genetic mutation associated with primary hemochromatosis is C282Y homozygosity. H63D gene mutation (even if homozygous) rarely causes clinical iron overload. First degree relatives of patients with HH should have initial screening of fasting transferrin saturation and ferritin between the ages of 18 and 30 in order to diagnose the disease prior to end-organ damage.[24] The primary method of treatment for iron overload is phlebotomy. Phlebotomy should be performed weekly or biweekly with hemoglobin/hematocrit evaluation prior to each session. The goal is to reach a ferritin level of 30 to 100 ng/mL and transferrin saturation <50%.[25] Patients with hemochromatosis, especially those with advanced fibrosis, should be referred to Hepatology for specialty care.

CONCLUSION

Improved management of liver disease begins with prevention. This summary aims to provide an overview of opportunities to improve outcomes in individuals who are at risk for disease progression. There are many avenues for patients to improve the health of their liver and it is frequently the primary care physician who must guide them. Adherence to evidence-based guidelines and proper screening can allow early intervention and in turn prevention of advanced disease. Even when the cause of liver disease is genetic or a case is complicated, it is the objective of the primary care physician to identify such scenarios and seek referral to a specialist. Improved diagnostic modalities and systems have made this more manageable but this cannot preclude integration of preventive measures in widespread clinical practice.

CONFLICTS OF INTEREST

None.

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