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Liver Disease: A Significant Cause of Morbidity and Mortality in American Indian and Alaska Native Peoples

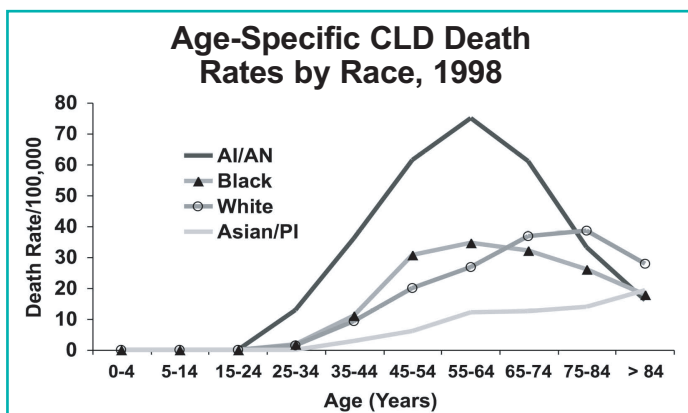
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Introduction

Although mortality due to chronic liver disease (CLD) is nearly as great as that due to diabetes mellitus among

American Indians and Alaska Native Peoples (AI/ANs), the large impact of CLD may not be fully appreciated by AI/ANs or their medical providers. A 2004 study of liver disease mortality in the United States highlighted a large disparity, reporting that liver disease was the sixth leading cause of death among AI/ANs, compared to twelfth in the overall US population. The age-specific death rate due to liver disease was over twice as high in AI/AN as in US Whites and Blacks, and over three times as high as in Asian/Pacific Islanders (Figure 1).¹

Figure 1: Age-specific CLD rates by race, 1998. Source: Vong S, Bell BP. Chronic liver disease mortality in the United States, 1990-1998. *Hepatology*; 2004;39(2):476-83.



In this Issue...

- 161 Liver Disease: A Significant Cause of Morbidity and Mortality in American Indian and Alaska Native Peoples
- 167 Sexually Transmitted Disease Surveillance: Summary Points from the Indian Health Service STD Surveillance Report, 2004
- 171 Implementing the Revised IHS Strategic Plan: A Clinician's View
- 174 Eight Years of Infant Mortality Reviews in the Aberdeen Area of the Indian Health Service
- 181 Open Door Forums on Health Initiatives: Forum4
- 182 Open Door Forums: A National Discussion Platform to Foster Integration Efforts of the Director's Health Initiatives
- 184 Heads Up! Tools for Physicians for Diagnosing and Managing Concussion
- 185 Postgraduate Course on Obstetric, Neonatal and Gynecologic Care
- 186 Meetings of Interest
- 188 Position Vacancies

In the United States, hepatitis C is the most common cause of CLD, followed by alcohol-related liver disease.^{2,3} Because none of the population-based studies of CLD in the US have included large numbers of AI/AN participants, little has been known until recently about the distribution of CLD or its etiologies in AI/ANs. To help address this knowledge gap, IHS and CDC researchers recently conducted a study of CLD among American Indians at two IHS-funded medical centers in the southwestern US (“Chronic Liver Disease Among Southwestern American Indians, 2000 - 2003”). In this study, approximately 6% of adult AI/AN patients who received care at these facilities had CLD. Alcohol-related liver disease, hepatitis C, or both conditions together were the most commonly identified etiologies of CLD, accounting for slightly more than half the cases.⁴

Persons with CLD usually have no symptoms during the early stages of their disease and may not come to medical attention until abnormal liver enzymes are discovered during laboratory evaluation for other medical problems. Persons with elevated liver enzymes that persist over three to six months should be evaluated for CLD. In the Chronic Liver Disease Among Southwestern American Indians, 2000 - 2003 study, nearly a quarter of the AI/AN patients with persistently elevated liver enzymes had never received a diagnosis of CLD.⁴ It was unclear why these patients did not appear to have undergone complete evaluation for CLD. Some may have received care exclusively in urgent care settings, received part of their medical care from outside providers, or had liver enzyme elevations attributable to hepatotoxic medications or pregnancy. It is concerning, however, if medical providers failed to recognize persistently elevated liver enzymes as a marker of CLD.

Etiologies of Chronic Liver Disease

Although the prevalence of some etiologies of CLD may differ in AI/AN populations compared to the overall US population, the management of CLD is the same for AI/ANs as for other people. This article will highlight some of the most common causes of CLD among AI/ANs and discuss related diagnostic and treatment issues (Table 1). Clinicians interested in more comprehensive resources on diagnosis and management of CLD and its underlying etiologies can refer to the American Association for the Study of Liver Disease (AASLD) website (<http://www.aasld.org>) for evidence-based

Table 1. Common causes of chronic liver disease among American Indians and Alaska Native peoples

- Chronic hepatitis C
- Chronic hepatitis B
- Alcoholic liver disease
- Non-alcoholic fatty liver disease (NAFLD)
- Autoimmune liver diseases
- Autoimmune hepatitis
- Primary biliary cirrhosis

practice guidelines. The Alaska Native Tribal Health Consortium (ANTHC) Liver Disease and Hepatitis Program also has guidelines on its website (<http://www.anthc.org/cs/chs/hep>), including guidance on evaluating abnormal liver enzyme tests.

Chronic Hepatitis C. Hepatitis C virus (HCV) infection is the most common blood borne infection in the US and a leading cause of CLD.¹⁻⁵ The virus is primarily spread by parenteral exposure to the blood of an HCV-infected person, which can occur through injection drug use, receipt of a blood transfusion, or birth to an HCV-infected mother.⁶ Transmission of HCV can also occur in the health care setting and is generally associated with inadequate infection control practices, such as unsafe injection practices, contamination of multidose medication vials, or inadequate cleaning of equipment. Approximately 70 - 80% of persons who acquire HCV infection develop chronic infection, approximately 25% of whom will go on to develop cirrhosis and/or hepatocellular carcinoma (HCC) during their lifetime. Most of the 1.3% of Americans who have chronic HCV infection⁵ are asymptomatic, and many are unaware they are infected. Although the number of new HCV infections has declined since the 1980s, increased detection means that the number of patients diagnosed with chronic HCV infection is increasing. These patients are coming to medical attention, and many will need evaluation for treatment for HCV infection and care for CLD.

Hepatitis C is one of the leading causes of CLD among AI/AN patients.⁴ The IHS Divisions of Epidemiology and Disease Prevention and Program Statistics report that the number of IHS RPMS-documented visits that included a diagnosis code for hepatitis C increased from 114 in 1999 to 13,078 in 2004. The increase in IHS facility visits due to HCV infection is believed to be the result of increased screening of AI/AN patients and identification of persons with long-standing, previously undetected HCV infection, rather than an increase in newly acquired infections. In Alaska, over 1600 AI/ANs have been identified by the ANMC lab as anti-HCV positive. Of 1000 persons enrolled in an HCV follow-up study, over 700 have been found to have chronic HCV infection.⁷ Among those with chronic HCV infection, over 100 have developed cirrhosis over an 11 year follow-up period, and 20 have developed HCC. While antiviral treatment is available for anyone with chronic HCV in Alaska, few patients either qualify or want treatment.

Persons at risk for HCV infection should be tested for antibody to HCV (anti-HCV), including anyone who has ever injected illegal drugs, received a transfusion of blood products prior to 1992, or undergone long-term hemodialysis. Screening for HCV infection is also recommended for persons with persistently abnormal liver enzymes.⁶ Those found to be anti-HCV positive by enzyme immunoassay (EIA) should have this result confirmed by either radioimmunoblot assay (RIBA) or a nucleic acid test (NAT) such as HCV ribonucleic acid (RNA); EIA results with a high signal-to-cutoff ratio (generally

considered to be ≥ 3.8) are also considered a confirmed positive.⁷ Repeat testing of a negative HCV RNA test is recommended to help determine if a patient has active infection or has recovered. Between 15% to 30% of persons positive for anti-HCV will be negative for HCV RNA, indicating that they have recovered, and 70% to 85% will be HCV RNA positive and have chronic HCV infection.

Treatment for HCV infection includes pegylated interferon and ribavirin for 24 weeks for those infected with HCV genotype 2 or 3, and 48 weeks for those infected with genotype 1.⁹ There are potentially serious side effects from treatment with interferon and ribavirin, including flu-like symptoms, bone marrow suppression, and severe depression. As a result, up to one third of patients are unable to finish treatment. The probability of a sustained viral response for those who finish treatment is 40% to 50% for those infected with HCV genotype 1 and 70% to 80% for those with genotype 2 or 3. In addition, treatment is expensive. For these reasons, liver biopsy may be helpful for identifying patients who are most in need of treatment, such as those with moderate to severe fibrosis.⁹ Several new oral protease and polymerase inhibitors that target HCV are in clinical trials, and the future looks bright for better treatment regimens with a higher response rate, and hopefully shorter duration of therapy.

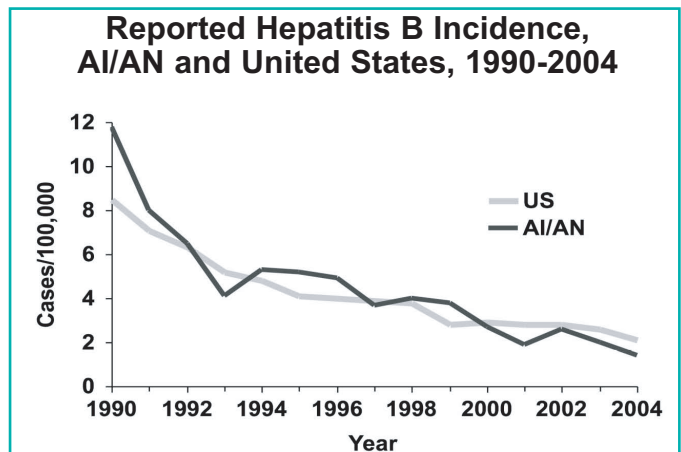
Alcohol-related liver disease. Alcohol-related liver disease (ALD) is one of the most common causes of CLD in the US. Although the prevalence of heavy alcohol consumption might be higher among AI/ANs compared to the overall US population,^{10,11} the prevalence of alcohol-related liver disease among AI/AN populations has not been well studied. In the Chronic Liver Disease Among Southwestern American Indians, 2000 - 2003, study, ALD (either alone or in combination with hepatitis C) was the cause of 48% of CLD in one site and of 26% of CLD at the other site.⁴ In persons infected with HCV, alcohol is an important co-factor in the development of cirrhosis. All patients with CLD, including those with liver disease from etiologies other than alcohol, should be counseled to minimize alcohol use or avoid it altogether.

Hepatitis B. Hepatitis B virus (HBV) infection is a blood borne infection that can be transmitted from mother to infant at birth, through sexual activity, and between persons who share drug injection equipment. HBV infection can be transmitted from contact with open cuts and scratches, most commonly seen among children in regions where HBV infection is endemic. Transmission can also occur in the health care setting and is generally associated with inadequate infection control practices, such as unsafe injection practices, contamination of multidose vials, or inadequate cleaning of equipment.¹² Chronic infection occurs in up to 90% of infants born of infected mothers, 30% of children infected before age 5 years, and 5% of those infected as adults. Approximately 15% to 25% of those who become chronically infected with HBV will die prematurely of hepatocellular carcinoma or cirrhosis.¹³ Potent antiviral medications are now available to control HBV in chronically infected persons, and can reduce the risk of

developing cirrhosis and hepatocellular carcinoma.¹⁴

Historically, the prevalence of chronic HBV infection among ANs was among the highest in the world before HBV vaccination programs were introduced into this population in the 1980s.¹⁵ As a consequence, ANs also had extremely high rates of HBV-related hepatocellular carcinoma.¹⁶ The AN population was the first in the world to receive routine hepatitis B vaccine for infants and susceptible children and adults. Routine infant and catch-up vaccination with hepatitis B vaccine led to a dramatic decline in the annual incidence of new HBV infections among ANs, and rates of new acute HBV infection are now lower in AI/ANs than those seen among the overall US population (figure 2).¹⁷ Over 1600 ANs who were chronically infected in infancy or early childhood prior to the availability of hepatitis B vaccine have been identified. Of these, 1350 are still alive, and are actively followed every 6 months with alpha-fetoprotein testing and ALT/AST to: 1) identify persons who have small HCC tumors that might undergo curable surgical resection or radiofrequency ablation; and 2) to identify persons with active liver disease who might benefit from antiviral therapy.¹⁷ These individuals remain at risk for hepatocellular carcinoma and cirrhosis.¹⁸

Figure 2. Reported Hepatitis B Incidence in AI/AN and the United States, 1990 – 2003. Source: CDC. Hepatitis Surveillance Report No. 61. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2006.



Screening for HBV infection should be considered for people in groups with high prevalence of chronic HBV infection.¹³ CDC is in the process of updating its recommendations^{12,19}; full, updated recommendations will be available at <http://www.cdc.gov/hepatitis> and <http://www.aasld.org>. Evidenced-based guidelines for treatment of HBV and screening for liver cancer^{13,14} are located on the American Association for the Study of Liver Diseases web page at <http://www.aasld.org> and on the Alaska Native Health Consortium web page at <http://www.anthc.org/chs/cs/hep>.

An effective vaccine against HBV infection was licensed

in the US in 1981. It has been recommended for persons at high risk of HBV infection since 1982, including injection drug users, persons with multiple sex partners, household contacts of persons with chronic HBV infection, patients undergoing chronic hemodialysis, and health care providers who have contact with blood and body fluids.¹² Routine immunization of infants has been recommended in the US since 1991, and catch-up vaccination of all unvaccinated children and adolescents has been recommended in the US since 1999.¹⁹

Non-alcoholic Fatty Liver Disease (NAFLD). An increasingly prevalent cause of liver disease in Americans is non-alcoholic fatty liver disease (NAFLD). In the US, the rate of overweight and obesity in both adults and children has risen dramatically over the past three decades, more than tripling over this time. Coincident with increasing rates of obesity, there have also been increases in the prevalence of diabetes and other diseases associated with the metabolic syndrome, including hyperlipidemia and hypertension. A majority of persons with the metabolic syndrome also have NAFLD. It is estimated that 30% of American adults have NAFLD and that the majority of children who are overweight also have NAFLD.²⁰ About 70% to 80% of persons with NAFLD have benign fatty liver manifested by steatosis without inflammation, a condition that rarely progresses, but 20% to 30% of persons have non-alcoholic steatohepatitis (NASH). Persons with NASH are at risk of developing cirrhosis and HCC 20 - 30 years after the development of the metabolic syndrome.

The risk factors for metabolic syndrome (and, as a consequence, NAFLD) are commonly seen in AI/AN. In the Chronic Liver Disease Among Southwestern American Indians, 2000-2003 study, approximately 13% of patients with CLD had NAFLD alone as the cause of their CLD.⁴ The Alaska Native Tribal Health Consortium (ANTHC) has begun a registry of persons with NAFLD and is conducting studies among ANs with diabetes to determine the prevalence of NAFLD in this group.

NAFLD should be suspected in anyone who has one or more risk factors for the metabolic syndrome (abdominal obesity; triglycerides ≥ 150 mg/dL, HDL cholesterol < 40 mg/dl in men and < 50 mg/dl in women; hypertension; and elevated fasting glucose).²¹ Based on Guidelines from AASLD and the American Gastrointestinal Association (AGA), persons with these findings should have liver enzymes performed.²⁰ Those with abnormal liver enzymes should have hepatic ultrasound performed to determine if there is evidence of fat in the liver. Hepatic steatosis can often be found in persons with "normal" liver enzymes who have features of the metabolic syndrome. The main reason is believed to be due to the fact that laboratories' upper limit of normal for ALT and AST are too high. Recently studies have suggested that the upper limit of normal for ALT should be 19 U/L for women and 30 U/L for men. Thus, persons with features of the metabolic syndrome

with ALT above these levels should be considered for liver ultrasound. If abnormal liver enzymes are found in persons with the metabolic syndrome, tests for other liver diseases should be undertaken, as it is not uncommon to find other liver conditions present. These include testing for HCV and HBV infections (anti-HCV and HBsAg), iron studies, and, in females, tests for autoimmune liver diseases (see below). The decision to do a liver biopsy is controversial and the benefits of a liver biopsy, namely distinguishing benign fatty liver from NASH or ruling out other liver disease, are also controversial. Providers should discuss the benefits and risk of liver biopsy with patients suspected of having NAFLD and the patient should be involved in this decision.^{20,22}

Studies have shown that losing 10 to 15 pounds (4 to 6 kg) can mobilize fat out of the liver and lower liver enzyme levels. Rapid weight loss can worsen fatty liver, so the goal should be weight loss of 10 to 15 lbs per year. In addition, exercise is beneficial for NAFLD by improving insulin resistance as well as aiding in weight loss. The recommendation is 30 to 60 minutes a day of exercise five days a week. Some studies report improvement in NASH and reduction in liver fibrosis in those who have followed these diet and exercise regimes.²²

Currently, other than diet and exercise, no evidenced-based treatment for NAFLD is available. Drugs to improve insulin resistance such as metformin and rosiglitazone may be effective in improving NASH, and large multicenter randomized controlled trials of these agents are well underway. In diabetics with NAFLD, it makes sense to attempt to include a drug that improves insulin sensitivity to their medication regime. Hyperlipidemia should be treated because, in addition to lowering cholesterol and triglycerides, these medications might benefit NAFLD. It is very important to note that drugs that improve insulin resistance or lower lipids are extremely safe and can be used in persons with elevated liver enzymes who need them. In persons with NAFLD who take these agents, there is no increased risk of severe hepatitis compared to those who do not have NAFLD, and the need for increased monitoring of liver enzymes in this situation is unclear.^{20,22} Other promising drugs include antioxidants, especially SAME (S adenylyl methionine), vitamins E and C, tissue necrosis factor or TNF inhibitors such as pentoxifylline, and lipid lowering agents, but these need to be verified in large randomized controlled trials.

Autoimmune hepatitis. Although less frequently seen, autoimmune liver diseases may be an important contributor to CLD morbidity and mortality in AI/AN. Autoimmune liver diseases are often associated with other autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus and Sjogren's syndrome. There are three distinct autoimmune liver diseases: autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC). AIH and PBC may occur more frequently in AI/AN than in other populations, and ANs have been found to have the highest prevalence rate of AIH in the world.²³ The prevalence

of PBC is also among the highest in the world in ANs, and PBC is the number one reason for liver transplant in First Nations persons from British Columbia, Canada. AIH and PBC are predominant in females. Any AI/AN woman with chronically elevated liver enzyme tests of unknown etiology should be evaluated for AIH and PBC. Tests for AIH include ANA, anti-smooth muscle (actin) antibody, and serum IgG. AIH, if not recognized, can be fatal within 2 - 3 years, but, if diagnosed, prolonged remission can occur in over 90% of patients with treatment with corticosteroids and azathioprine.²⁴ PBC is diagnosed by testing for anti-mitochondrial antibody (AMA). The presence of AMA is 90% sensitive and 100% specific for PBC. PBC is slowly progressive, but treatment with ursodeoxycholic acid can retard the disease progression in most persons who are diagnosed early, and may prevent the need for future liver transplantation.²⁵ PSC occurs primarily in males and is often associated with inflammatory bowel diseases such as ulcerative colitis and Crohn's disease. To diagnose PSC, an MRI cholangiogram, and, if negative, an ERCP cholangiogram, are needed.²⁶

What Can be Done to Address the Disparity in Death Due to Liver Disease in AI/AN?

CLD continues to cause significant morbidity and mortality in AI/AN patients, some of which could be prevented by prompt detection and treatment. Although alcoholic liver disease is an important cause of CLD in AI/ANs, it is far from the only cause, and the differential diagnosis of liver disease in AI/AN populations should include viral hepatitis, NAFLD, and autoimmune hepatitis. Every AI/AN with evidence of liver dysfunction should be offered a prompt, complete, and accurate workup to detect treatable causes of CLD. Currently, there are few hepatologists or infectious disease specialists within the IHS system who are available to manage patients with CLD. However, there are a number of steps that can be taken in the near future to improve care for AI/AN patients with CLD.

Primary care providers can develop expertise to diagnose and treat many patients with CLD. Providers should obtain accurate risk factor histories, particularly of intravenous drug use, and test patients for viral hepatitis as indicated. Providers should also evaluate patients with persistently abnormal liver enzyme tests (i.e., two elevations of ALT or AST at least 3 to 6 months apart) for CLD. Even patients with mildly elevated liver enzymes may have significant liver fibrosis and could benefit from treatment and counseling. Persons with cirrhosis should be screened for hepatocellular carcinoma with hepatic ultrasound and alpha-fetoprotein testing as per published guidelines, as early detection may improve survival.²⁷

Increasingly efficacious treatments for chronic hepatitis B and C are available.^{9,14} Although some treatments for chronic viral hepatitis can have serious side effects, these treatments can be effectively and safely administered by primary care providers, especially working in conjunction with pharmacists, nurses, and mental health providers, and, utilizing as consultants, physicians who are skilled in treating CLD caused

by HBV and HCV. Although many of the medications used to treat hepatitis B and C are expensive and not available on IHS formularies, pharmaceutical companies have programs to provide the medications at no cost to patients with limited financial resources.

The ANTHC in Alaska has developed a hepatology program to care for AN patients with chronic viral hepatitis and CLD. The program follows over 1350 AN with chronic HBV infection, 1,000 with chronic HCV infection and over 100 with autoimmune liver disease statewide. The ANTHC hepatology program consists of two MDs, two nurse practitioners and three nurses, along with administrative and computer support persons. Computerized registries have been developed that generate letters every six months to patients on these registries, most of whom live in isolated communities, to remind them to undergo monitoring for their specific condition. A list of patients from each community who are due for testing is sent to each hospital and rural clinic. Once a patient's blood is drawn at his/her community clinic, it is sent to a centralized laboratory at ANMC for testing. Results are automatically downloaded into the specific registry's database and reviewed weekly by a trained RN. A computer-generated letter is sent to each patient and provider informing them of the results. Abnormal results are reviewed by one of the programs MDs or nurse practitioners, and appropriate steps for further evaluation or treatment are taken. The software for this program is in Microsoft Excel, is available to other providers for AI/AN, and can be adapted to any health care program. The ANTHC hepatology program identifies patients with HBV and HCV infections who need antiviral treatment and screens for HCC to try to detect these cancers at a stage in which they can be surgically removed or ablated by radiofrequency ablation. The program provides consultation to primary care providers by conducting referral liver clinics at ANMC and all other Alaska Native tribally-owned rural clinics and hospitals throughout the state and providing statewide telephone consults. The program also conducts studies on the outcome of long-term HBV and HCV infection, autoimmune liver diseases, NAFLD, and conducts some of the longest ongoing studies of hepatitis A and B vaccine effectiveness in the world.

Several IHS clinical sites have developed innovative hepatitis C treatment programs, often in collaboration with academic institutions, to overcome barriers to treatment. At the Santa Fe Indian Hospital (Albuquerque Area), clinical providers from pharmacy, nursing, and the medical staff have been working successfully with the University of New Mexico's (UNM) Extension for Community Healthcare Outcomes (Project ECHO) to deliver comprehensive hepatitis C treatment services. The program relies upon telemedicine to deliver specialty hepatology consultation from Dr. Sanjeev Arora, a hepatologist from UNM. In Tahlequah, Oklahoma, at the W. W. Hastings Indian Hospital, a specialty clinic to treat hepatitis C has been established by the Department of Internal Medicine.

The ANTHC website (<http://www.anthc.org/chs/cs/hep>) has guidelines that primary care providers working for IHS, tribally-

owned hospitals and clinics, and other health care providers can use to help determine the diagnosis and proper treatment of AI/AN with CLD. This website has links to the website at the CDC Division of Viral Hepatitis and other websites that providers can use to learn more about how to manage patients with liver disease. In addition, the AASLD website (<http://www.aasld.org>) has evidence-based guidelines for liver diseases such as chronic hepatitis B, chronic hepatitis C, AIH, and PBC.

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