

Burden of liver disease in the United States: Summary of a workshop

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Abbreviations

HCC	hepatocellular carcinoma
FHF	fulminant hepatic failure
CDC	Centers for Disease Control and Prevention
NAFLD	nonalcoholic fatty liver disease
PSC	primary sclerosing cholangitis
PBC	primary biliary cirrhosis
HHC	hereditary hemochromatosis
AGA	American Gastroenterological Association
NASH	nonalcoholic steatohepatitis
NHANES	National Health and Nutrition Examination Survey
HCV	hepatitis C virus
HAV	hepatitis A virus
HBV	hepatitis B virus
A1AT	α_1 -antitrypsin deficiency
AIH	autoimmune hepatitis
WD	Wilson disease
GBD	gallbladder disease
LB	live births

Disease **burden** is a term that encompasses a number of aspects of the impact of a disease on the health of a population, ranging from (1) the frequency of the disease, as measured by incidence and prevalence, to its effect on (2) longevity, such as case-fatality rate and years of life lost due to premature death, (3) morbidity including decrease in health status and quality of life, and (4) finance, including direct health care expenditures and indirect costs related to lost income from premature death or disability.

Accurate knowledge of the **burden** of liver disease is essential in formulating health care policies to prioritize health interventions and research and to allocate resources accordingly. Liver disease is thought to be relatively rare. However, some liver diseases (e.g., nonalcoholic fatty liver disease or hepatitis C) are prevalent in the population and others (e.g., hepatocellular carcinoma [HCC] or fulminant hepatic failure [FHF]) are highly lethal. While effective treatment and prevention are available for many types of liver disease, long-term consequences of ongoing liver damage may necessitate liver transplantation, one of the most involved medical undertakings performed today.

This review represents a summary of a workshop conducted by the American Association for the Study of Liver Disease in May 2001 in conjunction with the Digestive Disease Week. The goal of the workshop was to assemble available data on epidemiology and **burden** of liver disease in the United States and identify areas in which further research is needed.

W. Ray Kim, M.D., M.B.A., Mayo Clinic, Rochester, MN***Frequency of liver disease in the United States***

Disease frequency may be measured either by the pool of existing cases or by the occurrence of new cases. Prevalence describes what proportion of the population has the disease in question at one specific point in time, whereas incidence describes the frequency of occurrence of new cases during a defined time period. As the onset of many types of liver disease is insidious, there is often a long time interval (latent period) between disease occurrence and detection. Further, many patients with liver disease remain asymptomatic until they develop hepatic decompensation. Thus, except for a small number of conditions (e.g., FHF), it is very difficult, if not impossible, to accurately ascertain incidence rates of liver disease. While estimating prevalence may in general be more feasible than incidence rates, many epidemiologic investigations are conducted based on referral patients, which may not represent the true disease prevalence in the whole US population.

Population-based studies of liver disease are necessary for accurate information on the **burden** of disease and the contribution of specific etiologies of liver disease to this **burden**. One such example is a population-based surveillance program being conducted by the Centers for Disease Control and Prevention (CDC) for chronic liver disease among adults since 1997.¹ As of 2002, three “sentinel” counties were performing surveillance: New Haven County, CT; Alameda County, CA; and Multnomah County, OR. Cases of newly diagnosed chronic liver disease are defined by persistently elevated liver enzymes, radiological evidence of cirrhosis, pathology consistent with chronic liver disease or primary liver cancer, or a clinical event diagnostic of chronic liver disease (e.g., variceal bleeding). Ascertainment methods vary by county, with some sites identifying cases by surveillance of Gastroenterology practices and others using computerized medical records of health plan members. The incidence of newly diagnosed chronic liver disease, based on cases identified in Alameda and New Haven counties between December 1998 and November 1999 and seen in gastroenterologists' offices was 72.3 per 100,000 population. The most common etiology of chronic liver disease in these two counties was hepatitis C (57%), followed by alcohol (24%), nonalcoholic fatty liver disease (NAFLD) (9.1%), and hepatitis B (4.4%). Other etiologies (primary sclerosing cholangitis [PSC], primary biliary cirrhosis [PBC], hereditary hemochromatosis [HHC], autoimmune hepatitis, α_1 -antitrypsin deficiency [A1AT], and liver cancer) accounted for less than 2% of all newly diagnosed cases of chronic liver disease seen by gastrointestinal specialists. The CDC plans to expand surveillance for chronic liver disease to other counties and gain additional information on patients who are not referred to gastrointestinal specialists.

In addition to geographic areas and referral pattern, demographic characteristics, such as age, gender, race, and ethnicity, are important determinants of epidemiology of liver disease. To make valid comparisons across disease categories, one needs to standardize data. For example, the measured frequency of PBC may vary depending on the proportion of middle-aged women in the study population. Where available, in this report, incidence and prevalence data are standardized to the general US population. Attempts were made to be consistent with the US Census Bureau, which, beginning with Census 2000, reports race and Hispanic origin as separate categories (*i.e.*, Hispanics may be of any race or races) and allows identification of more than one race.

Deaths from liver disease in the United States

The CDC compiles annual mortality data in the United States based on death certificates. Deaths are classified according to the diagnosis listed “underlying cause of death” on death certificates. The annual number of deaths attributed to chronic liver disease and cirrhosis, listed as the tenth leading cause of death as of 1998, has remained essentially the same (\approx 25,000 per year) for the past two decades (Table 1).²

Table 1. The ten leading causes of deaths in United States (1998)

Rank	Cause	No. of Deaths	%
1	Heart disease	724,859	31.0
2	Malignant neoplasms	541,532	23.2
3	Cerebrovascular disease	158,448	6.8
4	COPD	112,584	4.8
5	Accidents and adverse effects	97,835	4.2
6	Pneumonia and influenza	91,871	3.9
7	Diabetes	64,751	2.8
8	Suicide	30,575	1.3
9	Kidney diseases	26,182	1.1
10	Chronic liver disease and cirrhosis (ICD-9 = 571)	25,192	1.1

Data from Murphy.²

On a closer examination of the report, however, one notes that a single category, ICD-9 = 571, was used to define liver disease, when, in fact, deaths from liver disease may result from a number of other categories. Table 2 lists ICD-9 categories, which, when listed as the main cause of death, should be included in enumerating deaths from liver disease.³

Table 2. The number of annual deaths caused by liver disease (1998) as indicated by ICD-9 codes

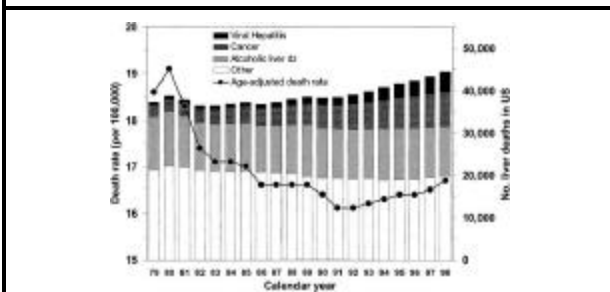
ICD-9	Description	Deaths
070	Viral hepatitis	4,796
155.0	Primary liver cancer	5,682
155.1	Intrahepatic bile duct ca	2,470
456	Esophageal varices	205
570	Fulminant liver disease	270
571	Chronic liver disease and cirrhosis	25,192
572.2	Hepatic coma	435
572.3	Portal hypertension	111
572.4	Hepatorenal syndrome	443
572.8	Other sequelae of chronic liver disease	2,819
573.3	Hepatitis, unspecified	693
573.8	Other specified disorder of the liver	158
573.9	Unspecified disorder of liver	1,403
	Total	44,677

Data from CDC.³

Incorporating these diagnoses increases the number of deaths attributable to liver disease from 25,192 to 44,677 (1.9% of all deaths) for 1998. This suggests that liver-related deaths may be the eighth leading cause of death ranking between diabetes and suicide.

Figure 1 summarizes the secular trend in liver-related mortality in the United States, encompassing all diagnoses listed in Table 2

Fig. 1. Secular trend in deaths from liver diseases in the United States. Data from Bell et al.¹



Click on image to view full size

There has been a steady increase in the number of liver-related deaths (bars) over time mainly attributable to viral hepatitis and hepatic malignancies. On the other hand, the age-adjusted death rate (deaths per 100,000 living persons, adjusted to the 2000 population census) from liver disease showed an overall decrease in the past two decades, suggesting that the increase in the number of deaths was partly due to the increase in population. One may note that there was a small increase in the age-adjusted death rate during the 1990s (from 16.1 per 100,000 in 1991 to 16.7 in 1998). In certain diseases, such as HCC, an increase in the age-adjusted death rate is well documented.⁴

Economic impact of liver disease in the United States

In 1999, the United States spent \$1.2 trillion on health care, including \$1,058 billion in personal health care and \$153 billion in administration and research.⁵ This represented 13% of the gross domestic product and a 5.6% increase from the previous year. Although there is a general interest in determining what proportions of these expenditures are attributable to specific conditions, such studies are difficult to conduct in an objective and accurate fashion.⁶

The most comprehensive data to date about the economic impact of liver disease in the United States were compiled by Everhart

et al., in which for 1985, the total direct costs (e.g., hospitalization, professional fees, and prescription) of liver disease were estimated at \$1.5 billion and indirect costs \$2.4 billion. Although these data are now outdated and the impact of advancing technology (e.g., liver transplantation) cannot be assessed, the data are still instructive in that indirect costs of liver disease, namely economic loss as a result of premature death, illness, and disability associated with liver disease, are substantial, as liver disease tends to affect people in their most productive phase of life.

The most up-to-date data are summarized in a recent report sponsored by the American Gastroenterological Association (AGA), which estimated the prevalence and economic burden of common gastrointestinal and liver disorders, including chronic liver disease and cirrhosis, chronic hepatitis C, liver cancer, and gallbladder disease.⁷ These estimates were derived from publicly available data sets, supplemented by proprietary third-party payer databases. As noted in Table 3, these four liver disease categories accounted for approximately one quarter (\$9.1 billion) of all direct costs associated with the 17 conditions in the report and also represented approximately 1% of all health care spending in the United States in 1998.

Table 3. The economic impact of liver disease as reported by the AGA study (1998)

	Prevalence*	Direct Cost	Indirect Cost	Total Cost
Chronic liver disease and cirrhosis	5,490	1,421	222	1,642
Chronic hepatitis C	2,530	693	51	744
Liver cancer	10	1,266	78	1,344
Gallbladder disease	20,500	5,755	294	6,049
Total	28,530	9,135	645	9,779
Total 17 common GI and liver disease	—	36,310	2,817	39,197

NOTE. Cost figures are in millions in 1998 US\$.

*1,000 persons in the United States.

Data from AGA.⁷

Thus, the cost of liver disease, although difficult to quantify exactly, is clearly substantial.

Alcohol-induced liver disease

TOP

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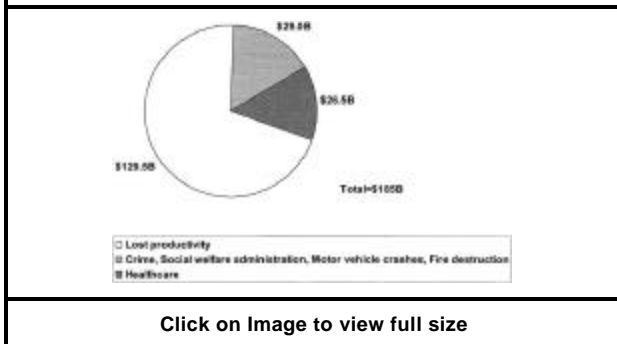
Alcohol consumption is common in the United States. Although the prevalence of excessive drinking has been declining since 1980, currently 67.3% of the population 18 years or older drink alcohol. However, only a minority are problem drinkers or consume sufficient quantities to suffer serious health consequences. For example, the top 20% of all current drinkers consume 80% of all alcohol, with the top 2.5% consuming 27%.⁸ Overall, it is estimated that 14 million Americans age 18 and older meet DSM-IV criteria for alcohol abuse and/or dependence.⁹ This corresponds to a prevalence of 7.4%, higher in men (11%) than in women (4%).

Not all heavy drinkers develop alcohol-induced liver disease, and the risk factors for alcohol-induced liver disease have not been fully elucidated. Genetic differences likely contribute to the susceptibility to alcoholism and alcohol-induced liver disease. In addition, alcohol may accelerate the progression of other coexisting liver diseases, such as hepatitis C.

Accurate estimates for the incidence and prevalence of alcohol-induced liver disease are not available, because many individuals with alcohol-induced liver disease are asymptomatic and national surveys (e.g., National Health Interview Survey) do not ask questions detailed enough to allow classification by specific causes of liver disease. In 1986, over 50% of deaths due to cirrhosis were attributed to alcohol, although this was prior to testing for hepatitis C. In 1997, the age-adjusted death rate from alcohol-induced liver disease was 3.8 per 100,000, which corresponds to 40% of deaths from cirrhosis or 28% of all deaths from liver disease. Among men, the death rate was the highest in Hispanic whites (12.6 of 100,000) followed by non-Hispanic African Americans (7.4), non-Hispanic whites (5.2), and Hispanic African Americans (1.8). Women had a significantly lower mortality rate of 1.8 per 100,000 with smaller racial and ethnic differences.

The economic impact of alcohol abuse is staggering (Fig. 2).

Fig. 2. Economic impact of alcohol abuse in the United States. Data from Harwood et al.¹⁰



The total costs of alcohol abuse are estimated to be \$185 billion, the majority of which are related to lost productivity, followed by motor vehicle accidents, social welfare, and results of crime.¹⁰ Health care costs account for 14% or \$26.5 billion, of which 70% are medical consequences and 30% drug and alcohol counseling and services. Of those costs related to medical consequences, only a small portion, between \$600 million and \$1.8 billion, represents hospitalization costs for alcohol-induced liver disease. According to the National Hospital Discharge Summary in 1997, 1.5% (n = 421,000) of all hospital discharges for people ages 15 and older from short-stay hospitals had a first-listed alcohol-related diagnosis, of which 22% were for cirrhosis. In the same survey, the average length of hospitalization for alcohol-induced cirrhosis was 7.8 days.

Nonalcoholic fatty liver disease

TOP

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NAFLD includes a spectrum of histologic abnormalities ranging from steatosis to steatohepatitis (NASH) with fibrosis.¹¹ Since the histologic characteristics of NASH overlap with those of alcoholic steatohepatitis, a clinical history of only “minimal” alcohol intake is required for the diagnosis of NASH. The pathogenesis of NAFLD has not been completely defined, but clinical and biochemical correlates include obesity, hyperlipidemia, type 2 diabetes mellitus, hyperinsulinemia, and insulin resistance. While fat in the liver is central to the disease, additional factors are believed to be important in determining progression from steatosis to steatohepatitis (multihit hypothesis).¹²

The clinical importance of NAFLD relates to its high prevalence in the population and its potential to progress to cirrhosis. NAFLD may be the most common cause of chronic asymptomatic liver enzyme elevation in the United States. A recent analysis of biochemical data in participants of the third National Health and Nutrition Examination Survey (NHANES III) suggested that the prevalence of liver enzyme elevation without evidence of hepatitis B or C and normal iron indices among nondrinkers may be as high as 24% in the United States.¹³ Although the extent to which NAFLD accounts for these abnormalities remains unknown, this group of individuals had several of the risk factors for NAFLD including obesity and diabetes. Other prevalence studies based on histologic sources (liver biopsy, autopsy, and post-mortem series) indicate that 10% to 40% (median ~20%) of the general population may have NAFLD (including steatosis alone) and 2% to 5% have NASH.¹⁴ A female predominance is found in some but not all studies.

Several lines of evidence suggest that a substantial proportion of patients with cryptogenic cirrhosis may have “burnt out” NASH. Among patients referred for liver transplantation with a diagnosis of cryptogenic cirrhosis, up to 70% have risk factors for NASH (*i.e.*, obesity and diabetes), a rate greater than that of other disease-specific controls.^{15,16} Hepatic steatosis may disappear in patients with advanced cirrhosis. Among patients with a pretransplantation diagnosis of cryptogenic cirrhosis, NAFLD posttransplantation has been documented in 10% to 38% of cases.^{17,18}

The natural history of NAFLD is only partially known. Steatosis, alone, does not appear to be a progressive condition.^{11,19} It is unclear whether this more prevalent condition has any impact, independent of obesity and associated comorbidities, on survival. In contrast, up to 46% of persons with NASH may show progressive histologic disease during follow-up periods up to 10 years. Rates of cirrhosis and liver-related death are higher among those with more severe histologic disease (NASH vs. steatosis).²⁰ Limitations of the available epidemiologic data include the relatively small number of patients followed longitudinally and the variable definition of the disease, with some studies focused on NASH and others including the broader spectrum of NAFLD. Additional limitations in assessing the natural history of disease include different methods of measuring and defining excessive alcohol ingestion and the occasional failure to exclude all other causes of chronic liver disease, especially chronic hepatitis C. To date, there are no data available for mortality or hospitalization rates specific to NAFLD.

The economic impact of NASH and NAFLD is unknown but could be substantial based on the high prevalence estimates. Currently, there are no proven therapies for NAFLD or NASH. Weight loss and control of glucose and lipid levels are frequently used in clinical practice, but the impact of these interventions on the clinical course of the disease is unknown. Agents such as

ursodeoxycholic acid, vitamin E, gemfibrozil, and metformin have been studied in small, uncontrolled studies only, and their efficacy remains unknown.²¹

Viral hepatitis: Hepatitis C

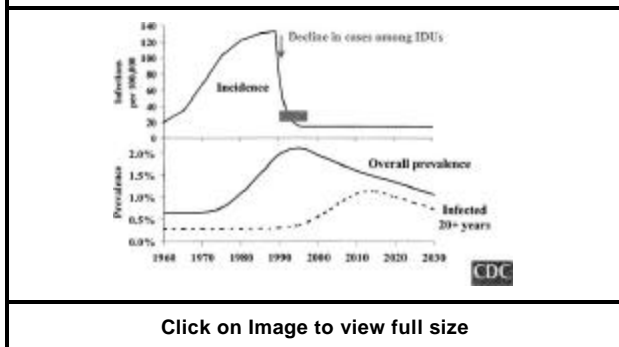
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The prevalence of hepatitis C virus (HCV) infection in the general population of the United States has been estimated based on NHANES III, a nationwide survey in a representative sample of noninstitutionalized, civilian Americans.²² The prevalence of antibodies against HCV (anti-HCV) was 1.8%, which corresponded to approximately 3.9 million Americans who have been infected with HCV. Of these, approximately 70%, or 2.7 million, had evidence of chronic infection as determined by the presence of the viral RNA in serum.²² This makes HCV the most common chronic blood-borne infection in the United States.²³

The incidence of reported new infections with HCV has been declining (Fig. 3).

Fig. 3. Estimates of past incidence and future prevalence of hepatitis C infection. Adapted and reprinted with permission.²⁴



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The peak incidence in the mid-1980s of over 100 cases per 100,000 persons per year has decreased to the current incidence of less than 20 per 100,000, or 40,000 new infections per year in the United States.

Because of the chronicity of HCV infection in most individuals, this decline in new infections does not translate to an immediate decrease in the prevalence. Using mathematical models, Armstrong et al. estimated that the prevalence of HCV in the United States peaked in the mid-1990s at slightly above 2.0% and would slowly decline to 1.0% by 2030.²⁴ Furthermore, the model predicted that the proportion of people with infection for 20 years or longer would increase with an anticipated peak in the mid-2010s. Indeed, there is a projected 4-fold increase in the number of persons with long-standing (more than two decades) infection between 1990 and 2015. The significance of this projection is that persons with a long duration of infection are at risk to develop serious complications of chronic liver disease such as cirrhosis and HCC.

According to NHANES, there are significant demographic variations in the prevalence of HCV. HCV is most prevalent among people between 30 and 49 years of age. Non-Hispanic whites have the lowest (1.5%) and non-Hispanic African Americans have the highest prevalence (3.2%). HCV infection is more common among men, with 70% of those infected individuals being male. The gender, racial, and ethnic differences in HCV prevalence likely represent differences in the prevalence of risk factors for hepatitis C as well as the degree of endemicity in their country of origin, in the case of recent immigrants.

Risk factors for hepatitis C are largely related to parenteral transmission. Intravenous drug use is the most common risk factor accounting for 60% of cases, transfusions prior to 1991 account for 10%, hemodialysis patients and health care workers comprise less than 5%, and sexual transmission is the only presumed risk factor in 15%. The risk of perinatal transmission is much lower with hepatitis C (6%) than hepatitis B (20%-60%). Intranasal cocaine and tattooing have been identified as independent risk factors in some populations, but the generalizability of the results is controversial.

FHF due to acute HCV infection occurs rarely. However, among individuals with long-standing infection, some will develop significant liver disease 20 to 30 years after initial infection. Depending on the patient population studied, the incidence of cirrhosis may range between 2% and 17% after 8 to 25 years of infection.²⁵⁻³¹ Mortality associated with HCV is increasing, as the prevalence of long-standing HCV infection and thus the incidence of decompensated cirrhosis and hepatocellular carcinoma increases. Cirrhosis caused by hepatitis C is the leading indication for liver transplantation and one of the most common causes of death due to liver disease. A common estimate, based on expert consensus, for the total number of deaths attributable to HCV is 8 to 10,000 per year.

The direct economic impact of hepatitis C is, in large part, related to complications of cirrhosis and HCC. Thus, hospital care of HCV-related liver disease represents a large proportion of expenditures, although hospitalization is relatively rare among people with HCV infection. For example, in 1995, approximately 27,000 hospitalizations in the United States were attributed to liver disease from HCV, corresponding to a crude incidence of 1 hospitalization per 1,000 persons infected. Nonetheless, hospital

service utilization for HCV was characterized by high per-patient costs, most likely due to the high cost of care for decompensated cirrhosis including liver transplantation. The estimated annual total expenditure for hospital care of HCV-related liver disease was between \$129 and \$514 million. The other item that accounted for a large proportion of expenditure was outpatient service including antiviral therapy. An estimated 317,000 physician office visits for hepatitis C incurred \$23.9 million in physician services in 1998. In addition, there were 46,000 visits to hospital outpatient departments (including emergency department) with total costs of \$10.5 million. Prescription and over-the-counter medications were the single largest item in outpatient costs related to hepatitis C. For example, the reported sales of the combination of interferon alfa-2b and ribavirin (Rebetron; Schering Corporation, Kenilworth, NJ) for the year 1999 was \$530 million. The total cost of treating hepatitis C across health care settings and including pharmaceutical therapy was estimated to be \$693 million. Finally, the AGA study estimated the indirect costs of HCV to be \$51 million (Table 3). As was cautioned in the AGA report, this is likely to be a gross underestimate because the impact of premature deaths from liver disease was not fully accounted for in the study. Overall, the total economic impact of HCV-related liver disease in the late 1990s is estimated to have been \$1 to \$1.3 billion per year.

Viral hepatitis: Hepatitis A, B, and D

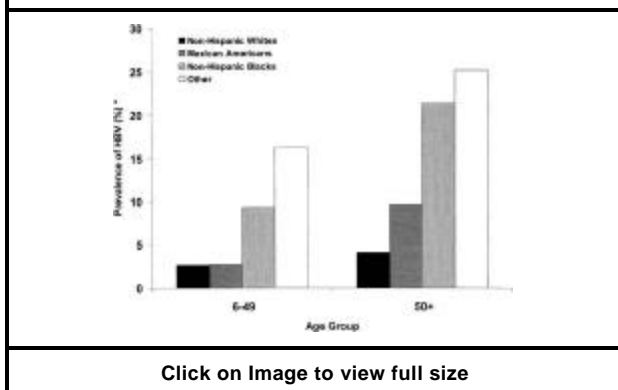
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Population-based estimates of the prevalence of viral hepatitis are derived primarily through NHANES. Comparison of the prevalence rates in NHANES II, conducted between 1976 and 1980, and NHANES III, conducted between 1988 and 1994, allows assessment of the impact of specific interventions such as vaccination on disease prevalence and incidence. NHANES samples only civilian, noninstitutionalized persons living in households, which may underestimate the seroprevalence of hepatitis A virus (HAV) and hepatitis B virus (HBV) by omitting persons who are homeless, incarcerated, or in the military.

Based on NHANES III data, the overall age-adjusted prevalence of prior HAV infection, defined by the presence of anti-HAV, is 30.6%. The age-adjusted seroprevalence of current and prior HBV infection, defined by the presence of hepatitis B surface antigen (HBsAg) or antibodies to hepatitis B core antigen, is 4.9% (95% confidence interval: 4.3-5.6%).³² Prevalence rates vary by age, race, ethnicity, and geographic region. The prevalence of HAV infection increases with age, reaching approximately 50% by age 45. HAV infection is more prevalent in Hispanics and African Americans than whites and more frequent in the western and southwestern states compared with other regions. HBV prevalence rates are low until age 12, then increase in all racial groups. HBV infection is more prevalent in nonwhites than whites in all age categories (Fig. 4).

Fig. 4. Age- and race-specific prevalence of hepatitis B. *The reported prevalence is based on HBsAg and HBcAb status. Data from NHANES III.³²



Unfortunately, the small size of ethnic groups commonly thought to be at high risk for HBV, such as Alaskan Natives, American Indians, or Asian Americans (both those born in the United States or who immigrated), in the NHANES III sample prevents accurate estimation of HBV seroprevalence in those individual subgroups. There are no incidence or prevalence data currently available for hepatitis D virus infection.

Estimating the incidence of new HAV and HBV infections occurring annually is more complex. No population-based incidence data are available. The CDC conducts acute viral hepatitis surveillance using the National Notifiable Disease Surveillance System (NNDSS), the Viral Hepatitis Surveillance Program (VHSP), and the Sentinel Counties Study of Acute Viral Hepatitis. NNDSS and VHSP are passive reporting systems, whereas the Sentinel Counties Study is a more intensive active-passive reporting system involving the county health departments in four representative areas in the United States. All surveillance programs suffer from underreporting and an unknown degree of case ascertainment bias since the minority of infections are symptomatic. The number of incident infections is determined by a complex modeling system that utilizes incidence data from the passive or active/passive reporting systems and known prevalence rates in adults and children with corrections for underreporting, unrecognized anicteric infections, and the changing incidence of acute infection over time.³³

The most recent model estimated that approximately 240,000 new HBV infections occurred annually between 1988 and 1994.³³ The incidence of HBV appears to be on the decline. In 1997, the estimated number of incident HBV cases was 185,000. This

decline likely reflects reductions in risk behaviors related to awareness and prevention programs for human immunodeficiency virus (HIV) infection and more widespread use of HBV vaccination. Using similar modeling strategies, the average number of new HAV infections annually between 1980 and 1999 was estimated to be 271,000. The incidence of HAV appears to be declining, although it may be too early to determine the role of HAV vaccine in this decline. To enhance the accuracy of the incidence estimates, the CDC has plans to use laboratory rather than physician-based reporting and to perform intensive surveillance in immunized populations to assess for the expected decline in infection rates.

Cholestatic and autoimmune liver disease

TOP

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Classic examples of autoimmune and cholestatic liver diseases include autoimmune hepatitis (AIH), PBC, and PSC. In addition, there are individuals with apparent autoimmune liver disease who do not fit into these well-established categories, including the so-called overlap syndrome in which features of more than one autoimmune disease are present. The natural history of disease in patients with autoimmune and cholestatic liver diseases typically includes a prolonged asymptomatic period. This makes the diagnosis of these syndromes difficult to ascertain on a population-wide basis, and accurate epidemiologic data on autoimmune and cholestatic liver diseases are not easy to obtain.

Primary biliary cirrhosis

Antimitochondrial antibodies, a reliable hallmark for the diagnosis of PBC, have been instrumental in the generation of population-based epidemiologic data, although they are largely limited to white populations. In both Europe and the United States, the incidence of PBC among adults (>20 years) has been measured between 2 and 3 per 100,000 persons per year with a strong female predominance. The peak incidence, namely among women over 40 years of age, is 4 to 6 persons per 100,000 persons per year. While the incidence has remained unchanged in the past two decades, the prevalence has risen, suggesting that the survival is longer, which may, in part, be due to early diagnosis. The reported prevalence in the mid-1990s ranges from 21 to 40 per 100,000 among adults of both genders and 59 to 65 per 100,000 among adult women.

The mortality rate for PBC in the United States has remained stable over the past 20 years at 0.5 per 100,000 per year, whereas liver transplantation and ursodeoxycholic acid therapy may have shifted the time of death to later in life. For example, between 1983 and 1997, the death rate among women with PBC 64 years or younger decreased from 0.6 to 0.3 per 100,000, while there was a reciprocal increase in mortality among women 65 or older from 1.1 to 1.5 per 100,000. Based on the Healthcare Utilization Project data, the total hospital charges for PBC were estimated between \$69 and \$115 million annually.³⁴ Reports from individual centers as well as UNOS suggest that the number of liver transplants for PBC have decreased recently. Comprehensive economic data related to PBC in the United States are not available.³⁵ For example, indirect costs associated with fatigue, a prominent symptom among PBC patients, are difficult to quantify.

Primary sclerosing cholangitis

The lack of easily obtainable diagnostic markers in PSC patients makes it difficult to conduct large-scale epidemiologic studies. In addition, characteristic cholangiographic features of PSC may be absent from patients during the early phase of disease. The only available population-based epidemiologic data to date, derived from Norway, described an incidence of PSC of 1.3 per 100,000 per year. In the same study, the prevalence of PSC in 1995 was 8.5 per 100,000, which is likely an underestimate because the long duration of the disease and incidence estimates would predict a higher prevalence rate.

The mortality from PSC is also harder to estimate than PBC because the currently used diagnostic coding system (ICD-9) does not distinguish between primary and secondary types of sclerosing cholangitis, the latter being associated with biliary calculi, neoplasm, or infection (e.g., HIV-associated cholangiopathy). With that caveat, the reported mortality from sclerosing cholangitis in the United States for 1979 to 1998 was stable at 0.5 to 0.6 per 100,000 and comparable with that of PBC. Unlike PBC, however, there has been no change in the age-specific mortality pattern.³⁴ Currently, there are no available data on the economic burden of PSC in the United States.

Autoimmune hepatitis

The epidemiology of AIH is also difficult to study because of a lack of specific diagnostic markers. A recently developed scoring system is a major step toward a reliable and valid tool for the diagnosis in clinical practice, but is likely to be of limited use as an epidemiologic tool because of the need for a large number of clinical details.³⁶ Similar to the other disorders in this section, AIH is considered uncommon, although a proportion of cryptogenic cirrhosis cases may represent AIH in a “burnt-out” stage, as some patients with AIH remain asymptomatic until they present with hepatic decompensation. In the Norwegian study, the incidence of AIH was slightly higher than PBC at 1.9 per 100,000 per year, and the prevalence was 17 per 100,000. Similar to PBC, there was a female preponderance (female/male ratio, 4:1).³⁷ Earlier data from the 1980s are in general agreement with the Norwegian data, although they are difficult to interpret because of likely inclusion of hepatitis C cases prior to HCV antibody testing. There are no mortality or economic data specific to AIH available at this time.

Metabolic liver disease

TOP

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The term “metabolic liver disease” can be applied to inborn or acquired errors of metabolism in which liver disease is a major manifestation. This summary focuses on metabolic liver diseases caused by inborn errors of metabolism presenting largely in adulthood, namely HHC, Wilson disease (WD), and A1AT.

Hereditary hemochromatosis

The term HHC is usually used to indicate HLA-linked hemochromatosis, the most common genetic disease among persons of Northern European descent. The disease is inherited in an autosomal recessive manner, and the prevalence of homozygosity has been estimated to be 1:200 to 1:500. A screening study from Utah among 11,000 blood donors found a prevalence of 1:450 based on transferrin saturation screening.³⁸ Two mutations in the hemochromatosis (HFE) gene have been associated with HHC, including the so-called C282Y and H63D mutations, although the latter is currently thought to be of little significance as a cause of clinically significant disease. A recent study among individuals attending a health maintenance clinic in San Diego found a prevalence of 1 in 237 based on screening for the homozygous C282Y mutation.³⁹ In another study that analyzed chromosomes of 2,978 people, the allele frequency was 1.9% for C282Y and 8.1% for H63D.⁴⁰ The highest allelic frequency for the C282Y mutation is in Northern Europe (6.4%-9.5%). This mutation has not been found in indigenous populations in the Americas, Indian subcontinent, Africa, or the Middle East.⁴¹

While the genetic prevalence of HHC has been described, the frequency with which significant end-organ damage occurs, including liver disease, is less well defined. Among 352 homozygous patients referred to specialty clinics, 18% (14% in women and 26% in men) had cirrhosis.⁴² The frequency may be lower (3%) among asymptomatic individuals whose hemochromatosis was identified through screening.⁴¹ The age-adjusted rate of hemochromatosis-associated death was 1.5 per million in 1992, although this is likely an underestimate because of underdiagnosis or underreporting.⁴³ The death rate was twice as high among men than in women. Liver disease was a contributing cause in 76% of deaths associated with hemochromatosis. Nonmalignant liver disease was 14 times more common and hepatic neoplasm was 26 times more common among deaths associated with hemochromatosis than among deaths from all causes. Long-term follow-up studies have established that patients with hemochromatosis diagnosed before the development of cirrhosis have normal life expectancy when treated with phlebotomy, whereas those diagnosed after the development of cirrhosis have significantly decreased survival rates when compared with an age- and sex-matched control population.⁴⁴

A population-based description of the economic impact of HHC in the United States is not available. Health economic considerations in HHC have focused on the cost effectiveness of screening for HHC. The rationale for screening includes the high prevalence, the availability of inexpensive and sensitive screening tests, and evidence to suggest that early diagnosis and implementation of effective and safe therapy improves survival. Several studies have concluded that screening for HHC using serum transferrin saturation is cost effective among siblings and children of patients with hemochromatosis, asymptomatic blood donors, and in the general population.⁴⁵

Wilson disease and α_1 -antitrypsin deficiency

WD is an autosomal recessive inherited disorder of copper metabolism and is much less common than HHC, with an estimated prevalence of 1:30,000 to 1:50,000. The gene frequency is estimated to be 1:90 to 1:150. Since 1993, when the gene associated with WD was identified as a copper transporter (ATP7B), over 60 mutations have been described in patients with WD; thus, genetic screening is not feasible.⁴⁶

Most patients with WD present with hepatic symptoms between the ages of 10 and 14. Patients with neurologic symptoms present at an older age, between 19 and 22 years. Untreated, WD is uniformly fatal, primarily due to complications of liver disease. Early detection and institution of D-penicillamine, trientine, or zinc therapy may improve the prognosis.⁴⁷ Liver transplantation has been effective for patients with FHF, decompensated cirrhosis, or progressive neurologic disease, although the latter indication remains controversial.^{48,49}

A1AT is the most common genetic liver disease in infants and children. A1AT deficiency is present in 1:1,600 to 1:2,800 babies born in the United States and Northern Europe.⁴⁶ An estimated 10% to 20% of affected neonates develop significant liver disease, whereas up to 70% may have abnormal liver tests.⁵⁰ In subjects reaching adulthood, cirrhosis is rare before the age of 20. The risk of cirrhosis may increase to approximately 40% during mid-late adulthood. There is an increased risk of HCC in patients who have A1AT deficiency. The deficiency is better identified by phenotype than enzyme activities in the serum.

Given the low prevalence of WD and A1AT, there are no national statistics available about mortality or economic burden associated with these conditions in the United States. WD and A1AT combined account for less than 5% of liver transplantations performed in the United States as reported by UNOS. Difficulty in studying these conditions includes genotypic versus phenotypic markers for diagnosis, variability in phenotypic expression, and lack of long-term longitudinal data.

Fulminant hepatic failure

TOP

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FHF is a clinical syndrome characterized by the rapid onset of hepatic encephalopathy in conjunction with a marked decline in liver synthetic function in persons without a prior history of liver disease. The natural history of disease is relatively short (days to months) and there are usually no chronic sequelae in survivors, except in those with AIH and WD. Therefore, **burden** of disease is best represented by incidence data. At present, no comprehensive registry or population-based surveillance program exists. However, estimates of incidence can be made from (1) liver transplantation programs, (2) population-based surveillance programs for acute liver disease (e.g., CDC Viral Hepatitis Surveillance Programs), and (3) single hospital or county reports. Each of these data sources suffers from referral and ascertainment bias, but, in composite, they estimate an incidence of FHF of 2,300 to 2,800 cases per year in the United States.

Liver transplantation is the only established treatment for FHF. Of up to 2,800 patients with FHF each year, only 250 to 350 of patients with FHF undergo liver transplantation. Not all patients with FHF are referred for consideration of liver transplantation, and not all patients referred for liver transplantation undergo the procedure. Groups that might be underrepresented among the FHF cases referred for liver transplantation include the elderly and those with serious medical comorbidities or psychosocial problems. The NIH Acute Liver Failure Study Group (ALFSG) prospectively collects information on both referred and transplanted patients from 17 adult and 10 pediatric centers in the United States.⁵¹ This registry has found that only about 30% of referred patients undergo transplantation, with the remainder either recovering or dying. Medical and psychosocial contraindications to liver transplantation are present in 66% and 34%, respectively. Based on those proportions and the number of liver transplantations performed in 1999, the estimated number of patients with FHF referred for liver transplantation is approximately 1,150.^{51,52}

Temporal changes in the etiology of FHF are evident. In historical series from the 1980s, viral hepatitis (HAV, HBV, non-A non-B hepatitis) was the most common etiology of FHF, whereas series from the 1990s list drug-induced (especially acetaminophen) as the most common cause of FHF in the United States.⁵³⁻⁵⁵ Between 1998 and 2001, the cause of FHF among patients referred to liver transplant centers was acetaminophen in 38%, drug-induced in 14%, hepatitis A in 4%, hepatitis B in 8%, miscellaneous other known causes in 19%, and indeterminate in 18%.⁵¹ Since contraindications for liver transplantation may be frequent in patients with acetaminophen-induced FHF, the true proportion of cases of FHF due to acetaminophen in the population is likely underestimated by studies conducted in transplant centers. A retrospective analysis of all acetaminophen-associated liver injury cases admitted to a single urban hospital, which did not perform liver transplantation, estimated the annual incidence of acetaminophen-associated FHF to be 0.75 per 100,000 population.⁵⁶ This suggests that a substantial proportion of acetaminophen-associated FHF cases are not referred to liver transplant centers.

The CDC conducts population-based surveillance for acute viral hepatitis. Case-fatality rates capture the severe end of the spectrum of viral-associated FHF. In 1999, the estimated case-fatality rate was 0.14% for HAV and 0.24% for HBV, which translates into 196 and 300 persons, respectively.⁵⁷ Fatal cases of HCV were not measured specifically but were listed as "rare." Among patients referred to liver transplant centers for FHF, HAV and HBV account for 4% and 8% of cases, respectively.⁵¹ Cases of HAV superimposed on HCV have not been identified among FHF cases reported to the ALFSG registry (W. Lee, personal communication).

A proportion of the FHF cases are of indeterminate etiology. This cryptogenic group likely includes patients with non-A-E viral hepatitis, unrecognized drug toxicity (including over-the-counter medications and herbal preparations), and possibly unrecognized metabolic or genetic diseases (more likely in the pediatric population).

Hepatocellular carcinoma

TOP

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The incidence of HCC is rising in the United States. Population-based incidence data from the SEER database of the National Cancer Institute indicate that the age-adjusted incidence rate of HCC increased from 1.4 per 100,000 during 1976 to 1980 to 4.7 per 100,000 during 1996 to 1997.⁴ These figures probably underestimate the true incidence by approximately 30% because they represent only histologically confirmed HCC and many patients with HCC succumb to liver failure before the presence of HCC is detected.

Although the incidence of HCC increases with age, there has been a recent shift in the incidence from typically elderly patients to relatively younger patients between the ages 40 to 60.⁴ Asian Americans have the highest incidence rates (up to 23 per 100,000 in Asian men above 60 years of age) of HCC, followed by African Americans, whose incidence is 2 to 3 times that of whites. However, all ethnic groups have been affected by the recent increase in incidence. The reasons for these ethnic differences relate to the prevalence and time of acquisition of the major HCC risk factors (HCV, HBV, and alcohol), all of which are 2- to 3-fold more frequent in African Americans and Hispanics than whites.

An increase in the prevalence of viral-induced cirrhosis is the likely explanation of the rising incidence of HCC. Data from the national VA computerized hospitalization database show a 3-fold increase in the age-adjusted rates for primary liver cancer associated with HCV (from 2.3 per 100,000 between 1993 and 1995 to 7.0 per 100,000 between 1996 and 1998).⁵⁸ HCV infection accounted for at least half of the increase in HCC cases among US veterans. In the same data, age-adjusted rates for primary

liver cancer with either HBV (2.2 vs. 3.1 per 100,000) or alcohol-induced cirrhosis (8.4 vs. 9.1 per 100,000) remained relatively stable.⁵⁸ Due to the large pool of HCV-infected persons, it is likely that the rising incidence of HCC will continue. In addition, recent immigrants from Northeast and Southeast Asia have a high prevalence of HBV infection and likely contribute to the rising incidence of HCC.

Mortality from HCC has followed a similar pattern of increase in incidence. The overall age-adjusted mortality rate for primary liver cancer (ICD-9 155.0) has risen significantly from 1.7 per 100,000 during 1981 to 1995 to 2.4 per 100,000 during 1991 to 1995. It is estimated that the total number of deaths in the United States due to liver cancer (which includes cholangiocarcinoma and possibly metastatic liver cancer) increased from 13,833 per year in the early 1980s to 22,307 between 1991 and 1995.⁵⁹ The AGA report estimated the total costs associated with liver cancers in the United States to be \$1.3 billion. However, this analysis was not able to distinguish secondary (metastatic) liver cancers from primary liver cancers, and the former may account for 3% to 10% of all hospitalizations for liver cancers. According to the National Hospital Discharge Survey, HCC was listed as a first diagnosis in 14,000 hospitalizations with an estimated 98,000 days of care in 1997.

Portal hypertension and liver transplantation

TOP

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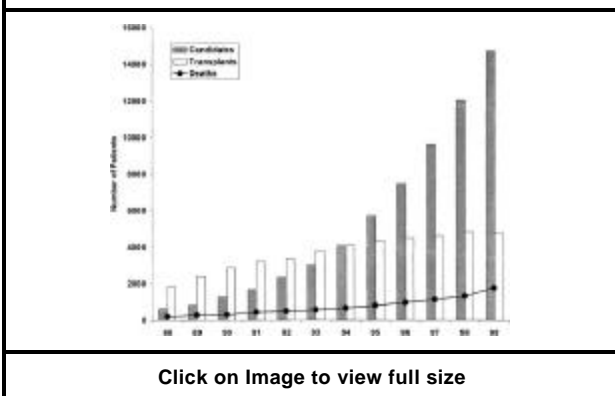
Portal hypertension is most frequently a manifestation of cirrhosis and is responsible for the majority of morbidity and mortality from liver disease. Complications related to portal hypertension among patients with end-stage liver disease constitute the major indication for liver transplantation in the United States.

Population-based prevalence data for portal hypertension are not available. It has been estimated that about 5.5 million Americans or 2,000 per 100,000 population have cirrhosis.⁶⁰ Although the prevalence appears similar across races, there are differences by gender in that over 60% of patients with chronic liver disease and cirrhosis are men. Among patients with cirrhosis, portal hypertension is common and is usually assessed based on its manifestations such as varices, ascites, or portosystemic encephalopathy.

Incidence data for portal hypertension are difficult to determine and have only been studied in patients with known cirrhosis. Moreover, since portal hypertension may be the presenting symptom of cirrhosis, determining the appropriate population at risk is challenging. The prevalence of portal hypertension increases with severity of liver disease and is present in the minority of patients with Child's class A cirrhosis and virtually all patients with Child's class B or C cirrhosis. Varices are present in 17% to 67% of patients with cirrhosis. Likewise, among cirrhotic patients, 10% develop ascites and up to 20% develop encephalopathy per year.⁶¹

The number of liver transplantations performed each year in the United States gradually increased during the 1990s.⁵² The number of transplantation candidates rose far more dramatically during the same time. Consequently, the length of waiting time and deaths on the list increased (Fig. 5).

Fig. 5. Number of liver transplantation candidates, cadaveric liver transplantations, and deaths on waiting list by calendar year. Data from UNOS.⁶²



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In patients who do undergo liver transplantation, 1-year mortality rates fell from about 40% in the early 1980s to less than 20% in the late 1990s. The current 5-year survival rate after liver transplantation is 75%, which is significantly better than the survival rate for patients suffering from complications of portal hypertension (currently less than 50%) without a transplantation at 5 years.

Reflecting the gender distribution of cirrhosis in the population, there is a male preponderance in patients undergoing liver transplantation with over 50% of patients being men. The racial and ethnic distribution among liver transplant recipients mirrors the general population of the United States. However, the prevalence of African Americans in the transplant recipient population is lower than the percentage of African Americans with liver disease. There are marked regional variations in patient listings per 100,000 population, leading to large regional variation in waiting time for transplantation. The average cost of a liver transplantation

is approximately \$100,000 per year, which gives an overall expenditure of approximately \$500 million per year with ongoing medication costs of \$10,000 to \$30,000 per patient per year. However, these costs are balanced by improvement in length and quality of life and also potentially by cost savings due to decreases in medical care for cirrhosis.

The AGA report estimated the direct cost of chronic liver disease and cirrhosis to be \$1.4 billion, most of which was hospital inpatient care (\$1.2 billion).⁷ The remainder included physician fees (\$134 million), physician office visits (\$65 million, 758,000 visits), hospital outpatient and emergency departments (\$64 million, 241,000 visits), and drug costs (\$17 million). In addition, indirect costs were estimated to be \$222 million in 1998, with the total costs attributable to chronic liver disease and cirrhosis at \$1.6 billion. This is likely an underestimation because of the way hospital costs were calculated in the report for hospitalizations for which cirrhosis was listed as secondary diagnosis.⁷

Gallstone disease

TOP

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The use of ultrasonography has permitted population-based determinations of prevalence, incidence, and risk factors for gallbladder disease (GBD). In a national population-based study, NHANES III, diagnostic gallbladder ultrasound examinations were performed on 14,238 participants between 1988 and 1994.⁶² It was estimated from this study that a total of 20.5 million persons in the United States, 6.3 million men and 14.2 million women, have GBD. The determination of GBD incidence is more difficult as it requires at least 2 ultrasonographic examinations over a defined period. Such a study has not been conducted in the United States. Studies from Europe have indicated an incidence of gallstones among adults of approximately 0.5% to 0.6% per year. In the United States, cholecystectomy rates derived from hospital databases were stable for many years but have recently fallen, which may be due to a reporting artifact.

The prevalence of gallstones and cholecystectomy is higher among women than men for all age groups, except that men have a slightly higher prevalence of gallstones at age 60 to 74 years. More than half the men with GBD are age 60 years or older. Among persons with GBD, 30.4% of men and 48.2% of women have had a cholecystectomy. There is a substantial ethnic difference in the risk of gallstones. Among women, risk is highest among American Indians followed by Mexican Americans, non-Hispanic whites, and non-Hispanic African Americans. A similar pattern is apparent among men, except that Mexican Americans and non-Hispanic whites have a similar prevalence. Currently there is no satisfactory explanation for these differences. Several risk factors for GBD other than ethnicity and sex have been well defined.⁶³ The strongest risk factor appears to be substantial weight loss among overweight persons. Excess weight alone, particularly among women, is also a major risk factor, but it is uncertain to what extent obesity and subsequent weight loss interact. Central adiposity, as measured by waist circumference, may also increase the risk of GBD, independent of the degree of obesity. Other risk factors include lack of physical activity, high parity, hormone replacement therapy, cigarette smoking, high serum triglyceride, and low HDL cholesterol levels. Moderate alcohol consumption and possibly low fiber consumption may be protective, but little effect of other dietary constituents has been found.

Despite its high prevalence, mortality related to GBD is rare. In the United States, mortality related to GBD has progressively declined to an all-time low of 0.7 per 100,000 in 1998. On the other hand, because gallstones are common and hospitalization is expensive, GBD is one of the most expensive digestive diseases. The AGA report estimated that the total direct cost for GBD for 1998 was \$5.8 billion. This included \$3.5 billion in hospital facility costs and \$820 million in physician services, followed by hospital outpatient costs (\$940 million), emergency room costs (\$240 million), office visits (\$230 million), and pharmaceuticals (\$2.2 million). Indirect costs associated with GBD are proportionately less than parenchymal liver diseases because of shorter duration of hospitalization and less frequent long-term disability; yet, because of the high prevalence, the estimated indirect costs were substantial at \$294 million, bringing the total costs to over \$6 billion.⁷

Pediatric liver disease

TOP

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The overall prevalence of liver disease at birth is approximately 1 in 2,500 live births (LB); the major disorders are biliary atresia (1 in 10,000 LB), metabolic disease (e.g., A1AT, 1 in 2,800 LB), and forms of intrahepatic cholestasis ("neonatal hepatitis," 1 in 7,000 LB).¹⁻³ The predominant forms of liver disease in older children and adolescents are metabolic disorders (e.g., WD), chronic intrahepatic cholestasis, and viral hepatitis. The overall prevalence of liver disease in children is not known; however, it is estimated that each year ~15,000 children are hospitalized in the United States for liver disease.⁶⁴ On the other hand, the prevalence has been defined for a few specific conditions; for example, chronic infection with HCV is present in 1 in 500 children aged 6 to 11 years and 1 in 250 children aged 12 to 19 years in the United States.⁶⁵

Biliary atresia, a neonatal obstructive cholangiopathy that affects the bile ducts, is the most frequent cause of chronic end-stage liver disease and the leading indication (36%) for liver transplantation in children.^{66,67} In the United States, biliary atresia is more common in African American babies (0.96 of 10,000 LB) than in white infants (0.44 of 10,000 LB) and in girls than in boys.^{67,68}

Seasonal variation in the occurrence of biliary atresia has been suggested in some studies. There is no known curative treatment for biliary atresia. Even with early surgical hepatopertoenterostomy (Kasai procedure), the majority of patients (60% to 80%) will eventually develop end-stage biliary cirrhosis and require liver transplantation.⁶⁹ If the Kasai procedure is used for initial management, the cost of the hospitalization and surgical care of these infants through the first year of life has been estimated to be \$17,000 to \$20,000.⁶⁷ In the United States, the annual cost for biliary atresia has been estimated to be \$65 million, mostly related to the cost of transplantation.^{64,66,67}

Children under 18 years of age represent 12.5% of all liver transplantations in the United States.⁶⁶ An average of 536 liver transplantations were performed each year in this age group from January 1, 1995 to December 31, 1999 (UNOS data). The major indications compiled from the UNOS data are shown in Table 4.

Table 4. The indications for OLT in children

	N	%
Biliary atresia	955	35.6
Hepatitis (presumed viral)	349	13.0
Acute HAV	12	3.4
HBV (acute & chronic)	23	6.6
HCV	28	8.0
Unknown	286	81.0
Metabolic liver disease	306	11.4
A1AT	120	39.2
Oxalosis	32	10.5
Wilson disease	29	9.4
Tyrosinemia	21	6.9
Hemochromatosis	19	6.2
Other	85	27.8
Intrahepatic cholestasis	212	7.9
Alagille syndrome	123	58.0
Byler disease	17	8.0
"Neonatal hepatitis"	46	21.7
Other	26	12.3
TPN-associated cholestasis	145	5.4
Idiopathic cirrhosis	129	4.8
Autoimmune liver disease	117	4.4
Autoimmune hepatitis	69	59.0
PSC	48	41.0
Tumors	93	3.5
Hepatocellular carcinoma	16	17.2
Hepatoblastoma	44	47.3
Hemangioendothelioma	23	24.7
Other	10	10.8
Congenital hepatic fibrosis/Caroli	57	2.1
Cystic fibrosis	52	1.9
Drug-induced liver disease	30	1.1
Miscellaneous (trauma, Budd-Chiari)	15	0.6
Other	221	8.2
Total	2681	100

Data from UNOS registry (January 1, 1995 to December 31, 1999).

Liver transplantation costs up to \$250,000, and the expenditure for posttransplantation care is estimated to be \$20,000 per year. Pretransplantation care and life-long immune suppression adds to the **burden** of health care costs, particularly considering the prolonged survival of pediatric transplantation patients. Of great importance is the fact that some hepatobiliary disorders that arise in childhood, such as HCV, NASH, and alcohol-induced liver disease, are precursors of adult liver disease. In addition to chronic

liver disease, acute liver failure is the indication for 11% to 13% of the liver transplantations in children compared with 5% to 7% in adult patients.⁷⁰ Patients with acute liver failure younger than 10 years of age have a survival rate of less than 10% without transplantation compared with 30% to 35% in patients between the ages of 10 and 40 years.⁷⁰

Finally, the incidence and prevalence of pediatric NASH are unknown. However, it is likely on the rise due to the epidemic of obesity in children.⁷¹ The NHANES III conducted in the United States from 1988 to 1994 documented that 16% to 20% of children ages 12 to 17 years were overweight (body mass index >85th percentile) and 8% to 17% were obese (body mass index >95th percentile). Elevated alanine transaminase values were present in 10.8% of obese boys and 7.8% of obese girls and in ~15% of both boys and girls aged 16 to 18 years in NHANES III.⁷²

Conclusions

TOP

Liver disease is an important cause of morbidity and mortality in the United States (Table 5).

Table 5. Epidemiology and impact of liver disease in the United States

Disease Categories	Incidence*	Prevalence	Mortality	Expenditure
Alcoholic liver disease	—	7.4% (alcohol abuse/dependence)	3.8/100,000	\$26.4 billion†
Nonalcoholic fatty liver disease	—	20% (fatty liver) 2% (NASH)	—	—
Viral hepatitis				
Hepatitis A	270,000	30.6%‡	200	—
Hepatitis B/D	185,000	4.9%§	5,000-6,000	—
Hepatitis C	40,000	1.8%	8,000-10,000	\$1-1.3 billion
Primary biliary cirrhosis	3,500	21-40/100,000	450	\$69-115 million¶
Primary sclerosing cholangitis	2,000	—	450	—
Metabolic liver disease				
Hemochromatosis	—	200-500/100,000	—	—
WD	—	2-3/100,000	—	—
A1AT	—	40-60/100,000	—	—
Fulminant hepatic failure	2,300-2,800	—	—	—
Hepatocellular carcinoma	16,200	4.5/100,000	3.3/100,000	\$1.3 billion#
Gallstone disease	0.5%-0.6%	8%	0.7/100,000	\$6 billion

*Cases per year.

†Medical consequences of alcohol abuse/dependence.

‡Individuals with anti-HAV positive.

§Individuals with HBsAg or anti-HBc.

||Individuals with anti-HCV.

¶Hospital charges alone.

#Includes secondary hepatic malignancies.

Currently, up to 2% of all deaths are attributable to liver disease. The economic **burden** associated with liver disease is also substantial with approximately 1% of the total national health care expenditure devoted to the care of patients with liver disease. Moreover, the **burden** of liver disease appears to be on the rise, due in part to the increasing prevalence of NAFLD, HCV, and HCC. Many liver diseases with relatively low frequency have substantial impact on the longevity (e.g., FHF and pediatric liver diseases) or on the quality of life (e.g., PSC) of those affected.

It is important to point out that there are significant gaps in our current understanding of the epidemiology and **burden** of liver disease at the population level. This is partly because of the fact that many investigations in hepatology are conducted at referral centers based on selected patients. As most liver diseases have a substantial latency period during which patients have mild asymptomatic liver disease, studies based on referral patients only recognize patients with the most severe or advanced disease and fail to obtain information on the entire spectrum of disease. Population-based data are especially important for those diseases whose prevalence is on the rise.

Although the need and benefits of population-based epidemiologic data are easy to recognize, it is much harder to execute such studies. Because of the individualistic health care system in the United States, it is extremely difficult to completely track the occurrence and impact of disease conditions at the population level. Only a limited number of opportunities currently exist, examples of which include national data sets such as survey of general populations (NHANES), compilation of mandatory reports

(death certificates, reportable transmissible diseases), or billing data (Medicare); active surveillance programs (Sentinel Counties); and proprietary data derived from large third-party payers (Kaiser-Permanente). Because of the scope and size of these endeavors *vis-à-vis* the relatively low prevalence of liver disease, it is probably impractical for the hepatology community to initiate extensive population-based programs. Instead, strategic partnerships between research or government entities could be used to enhance our ability to obtain necessary data on the **burden** of specific chronic liver diseases. Clearly, increasing awareness of the impact and need for intervention by the public and funding agencies appears to be a prerequisite for a continued expansion of research in the area as it has in other fields such as heart disease, diabetes, and HIV infection. In that regard, recent programs initiated by the NIDDK and CDC, such as the NASH and biliary atresia database consortium and the Chronic Liver Disease Surveillance study, are encouraging.

Hepatology specialists can further contribute to a better understanding of the epidemiology of liver disease by continuing to endeavor to understand pathophysiologic mechanisms and thereby be able to classify diseases by clear-cut diagnostic criteria. For example, as was pointed out in the text, epidemiologic investigation of NAFLD is difficult because of lack of diagnostic markers that are applicable to the population. Further, investigation in many liver diseases that are infrequent will continue to depend on patients seen at referral centers. However, for a meaningful progress to be made, concerted efforts across specialty centers are needed. One such example is the Acute Liver Failure Study Group, which began as a grass-root effort and since has received support from the NIH. For better understanding of the epidemiology of liver diseases, collaborative, as opposed to single center, studies are in general necessary. Such systematic efforts supported by private and public funding are essential to advance our knowledge in the most efficient manner. Finally, a growing recognition within the hepatology community that well-designed and executed epidemiology and health service research in liver disease is as important as, and complementary to, traditional “wet-bench” research needs to continue to gain acceptance within our academic societies. In that regard, the increasing number of qualified individuals with extended didactic and clinical research training in our discipline is encouraging.

All in all, to improve our understanding of the epidemiology and impact of liver disease and to enhance our ability to institute effective means of diagnosis, therapy, and prevention of liver disease at the population level, objective and generalizable data, appropriate personnel with necessary qualification and expertise, and research infrastructure and funding are key ingredients. Although some of these pieces are already in place, as discussed in this article, continued commitment and support for all parties involved are necessary to move the field forward. Results of such programs will best inform policy-making decisions for formulating guidelines for the diagnosis, treatment, and prevention of liver disease, as well as resource allocation.

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