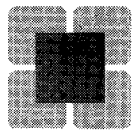

Viral hepatitis in the 1990s, part I: current principles of management

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■ Recent years have brought major advances in the diagnosis and treatment of viral hepatitis. Treatment of acute uncomplicated hepatitis is supportive rather than curative. Treatment of fulminant hepatic necrosis is directed towards preventing and treating complications while preparing suitable patients for liver transplantation. Corticosteroids do not improve survival rates in patients with fulminant hepatic necrosis and should be avoided in nearly all patients with hepatitis A. Although liver histology in acute viral hepatitis is highly characteristic, biopsy is usually superfluous, except in transplant patients with acute hepatic dysfunction. Hepatitis A virus infection is frequently asymptomatic, and data on its incidence are poor. The virus is frequently transmitted before the patient becomes ill; therefore, curtailing hepatitis A spread depends in large measure on hygienic practices. Passive immunization is possible with immune globulin. Inactivated and attenuated vaccines may be licensed within the next 2 years.

□ INDEX TERMS: HEPATITIS, VIRAL, HUMAN; HEPATITIS A □ CLEVE CLIN J MED 1992; 59:317–325

MAJOR ADVANCES in the diagnosis and treatment of viral hepatitis have occurred in recent years. The identification of hepatitis C and E viruses, the development of the hepatitis C antibody test for screening donor blood, and recent trials with interferon for management of B and C hepatitis are but a few examples. Internists and gastroenterologists frequently encounter this illness; therefore, a review of the changing concepts of its diagnosis and management is appropriate. This article, the first of three, describes the agents that cause hepatitis and explores its common clinical features and management. Clinical aspects of hepatitis A are discussed in detail. Two forthcoming articles will review hepatitis B, delta hepatitis, hepatitis C, hepatitis E virus, and some of the less common hepatotropic viruses.

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BACKGROUND

Awareness of hepatitis is centuries old, but it was not until 1963 that its first viral particle (then called the Australian antigen) was discovered by Blumberg.[1,2] In 1966 he recognized that this antigen is associated with one form of hepatitis, now referred to as hepatitis B. It proved to be one of a multitude of viruses which can cause acute hepatocellular dysfunction (*Table 1*).

The term "viral hepatitis" is generally reserved for infection of the liver caused by the small group of common hepatotropic viruses listed in *Table 1*. How-

TABLE 1
CAUSES OF ACUTE VIRAL HEPATITIS

Virus	Viral genome	Comments
Common hepatotropic viruses		
Hepatitis A	RNA	"Infectious" hepatitis; short incubation period; picorna virus; feco-oral transmission; severity is age related (eg, asymptomatic in children); acute infection diagnosed by IgM Ab; IgG provides lifelong immunity.
Hepatitis B	DNA	"Serum" hepatitis; long incubation period; parenteral transmission; hepadna virus; endemic in human population; hyperendemic in southeast Asia
Hepatitis C	RNA	Non-A, non-B hepatitis: parenteral transmission; major cause of posttransfusion hepatitis; related to flavivirus group; shares epidemiologic features with HBV; anti-C100-3 Ab assay identifies infectious donors; associated with chronic liver disease and primary liver cancer in some countries.
Hepatitis D	RNA	Always found with HBV; causes fulminant hepatitis and accelerated progression of preexisting HBV hepatitis.
Hepatitis E	RNA	Enterically transmitted non-A, non-B or epidemic waterborne non-A, non-B; self-limiting disease resembling hepatitis A; chronic liver disease or persistent viremia not seen; large epidemics in Indian subcontinent; extremely high mortality rate (up to 20%) in pregnant women.
Other hepatotropic viruses		
Causing mild hepatitis in immunocompetent host		
Herpes viruses		
Epstein-Barr virus		
Cytomegalovirus		
Varicella zoster		
Adenoviruses		
Exotic viruses (geographically limited but with frequent liver involvement and high mortality)		
Yellow fever virus		
Lassa fever virus		
Other arena viruses - Mopeia, Marburg, Ebola, Rift Valley fever		

ever, other viruses can cause hepatitis in fairly distinctive clinical settings. For example, yellow fever is a major and serious cause of hepatitis in tropical countries. Children may develop significant liver disease in the course of rubella, adenovirus, or enterovirus infections. The herpes viruses, particularly cytomegalovirus and Epstein-Barr virus, also commonly cause hepatitis.

CLINICAL COURSE OF ACUTE HEPATITIS

The typical clinical manifestations and course of uncomplicated acute viral hepatitis are similar for most of the hepatotropic viruses. Usually, the prodromal phase and the clinical illness with transaminase elevation each last less than 4 weeks. The prodromal phase usually lasts several days. Anorexia, malaise characterized by weakness, and easy fatigability are the most common symptoms. Disturbance of taste and (less often) of smell, with aversion to fried foods, meat, and other dietary proteins, is common. Aversion to cigarettes is also seen. Nausea can be associated with transient but sometimes severe vomiting. Epigastric or right upper quadrant abdominal pain or discomfort can persist for 1 or 2 weeks. Diarrhea or constipation may be present. Arthralgia, usually considered a feature of hepatitis B, has also been noted in 10% to 30% of patients with hepatitis A.[3] Mild cases may be completely inapparent or dismissed as "the flu."

Most patients with viral hepatitis never develop jaundice. In those who do, the appearance of dark urine due to conjugated bilirubin indicates the onset of the icteric phase. Stools may turn pale as jaundice appears, and most of the prodromal symptoms disappear except for lethargy and tiredness. Mild pruritus is common but usually not severe. Although vascular "spiders" are usually associated with chronic liver disease, they may occur in acute hepatitis. Cardiac arrhythmias (bradycardia) and T-wave changes on electrocardiography may occur occasionally.[4]

TREATMENT OF UNCOMPLICATED HEPATITIS

Treatment of acute uncomplicated hepatitis is supportive, with reduction of physical activity being the main approach. Although there is some evidence that *vigorous* activity is occasionally deleterious, this view is challenged.[5] Enforced bed rest neither conserves calories nor improves the outlook in patients with viral A hepatitis.[6] In general, the patient's activity should be reduced to match available energy. We recommend that patients avoid work or school unless their work loads can be adjusted to match energy levels. Gradual resumption of activities is allowed as the patient's energy permits. The patient should be warned of the possibility of relapse, which would require that the treatment cycle be repeated.

Diet is unimportant in treating viral hepatitis.[6] The traditionally prescribed "high-protein diet" is unpalatable to most patients because of anorexia. There is no evidence that such a diet is beneficial; however, it is important to ensure adequate intake of fluid and electrolytes. In unusual cases characterized by severe anorexia and vomiting the patient may need to be admitted to the hospital for a few days. In general, however, hospitalization of patients with hepatitis should be discouraged from the standpoint of both public health and cost.

VARIANTS OF VIRAL HEPATITIS

Cholestatic viral hepatitis

Cholestatic viral hepatitis, an uncommon variant (5%), is characterized by intense pruritus. Jaundice is deeper and more prolonged, the alkaline phosphatase level is higher, and prothrombin time may be prolonged (though this is easily corrected with vitamin K).[7] Cholestatic viral hepatitis may be mistaken for obstructive jaundice; however, ultrasonography of the biliary tree will usually resolve this diagnostic issue.

Fulminant hepatic failure

Fulminant hepatic necrosis from viral hepatitis results in death within a few days or weeks. Hepatic encephalopathy secondary to hepatic necrosis occurs within 8 weeks after the first symptoms appear.[8] Fulminant hepatic failure may occur in any age group. In the United States and United Kingdom it is due mainly to hepatitis B or hepatitis C. Hepatitis B with coinfection by delta virus is particularly likely to cause fulminant hepatitis.[9,10] Viral hepatitis E, which is prevalent in the Indian subcontinent, also results in fulminant hepatitis, especially in pregnant women.[11] Hepatic necrosis due to acetaminophen overdosage or halothane use produces similar syndromes.[12–15]

Typically, patients with fulminant hepatic necrosis develop signs and symptoms characteristic of viral hepatitis and then rapidly (within hours or days) develop manifestations of hepatic failure—including metabolic encephalopathy (usually progressing to coma), coagulation defects, ascites, and edema. Hyperexcitability, irritability, insomnia, somnolence, or impaired mentation are evidence of impending hepatic failure in patients with acute hepatitis.

Patients with acute hepatitis may have hepatomegaly; a rapid *decrease* in the size of the liver (indicating loss of parenchymal mass through necrosis) is a particularly ominous sign, as is a rapidly falling transaminase level with progressive prolongation of the prothrombin time. The discordance between transaminase level and prothrombin time occurs when the remaining liver cell mass is small and relatively few liver cells remain to be destroyed. At the same time, coagulation factors normally synthesized in the liver are no longer being produced, so that the prothrombin time becomes progressively more abnormal. Hypoglycemia is an ominous occurrence, indicating that hepatic necrosis is far advanced. Common complications of fulminant hepatic necrosis include gastrointestinal hemorrhage, sepsis (bacterial and fungal), cerebral edema, lactic acidosis, renal failure, and disseminated coagulopathy.[16]

Mortality rates for fulminant hepatic failure have been reported as high as 84% in stage IV coma.[8,17] Mortality tends to be greater when encephalopathy and electroencephalographic abnormalities are more severe and prolonged.[18–22] In one series, survival was 18% for patients with stage IV encephalopathy, 48% for patients with stage III encephalopathy, and 66% for patients with stage II encephalopathy.[23] Patients below age 40, particularly children, tend to have better prognosis than older patients.[18,19,23–28] Attempts to predict which patients with fulminant hepatitis will succumb, based on serum measurements of various substances (including alpha-fetoprotein), have been unsuccessful.[29]

Treatment of fulminant hepatic necrosis is directed towards preventing and treating complications while preparing suitable patients for liver transplantation. An H-2 receptor antagonist may decrease the incidence of upper gastrointestinal bleeding.[30] Fresh frozen plasma should be administered if bleeding occurs, but it need not be used routinely to correct abnormal coagulation parameters. Antibiotics should not be used routinely to prevent sepsis, but infections should be treated aggressively. Mannitol seems to be the most effective agent to combat cerebral edema in patients with liver failure.[31] Intracranial pressure is measured directly via an intracranial "bolt" (subdural transducer).[32–34]

Corticosteroids do not improve survival rates in patients with fulminant hepatic necrosis[35,36]; in fact, those who get steroids do somewhat worse then those who do not. Other experimental treatments of no proven value include peritoneal dialysis, plasmapheresis, plasma perfusion over sorbents, cross-circulation with nonhuman primate livers, extracorporeal liver perfusion, and total body washout. While these are sometimes advocated, they are probably use-

less.[16,37] On the other hand, insulin and glucagon aid hepatic regeneration in experimental animals after partial hepatectomy,[38,39] and some studies in humans also suggest beneficial effects.[40,41]

Drugs which inhibit viral replication such as foscarnet (phosphonoformate trisodium) and antiviral therapy with interferon have been tried.[42,43] However, in most cases induced by hepatitis B virus or by delta virus, active viral replication appears to be lower than that seen in uncomplicated acute infection and may even have ceased by the time of admission. The use of these agents has given equivocal or negative results.[44,45] Some preliminary reports suggest that prostaglandins are efficacious in treating fulminant hepatic failure, but further investigations are needed.[46]

Improved survival of patients with fulminant hepatic failure can be achieved by earlier recognition and aggressive treatment of cerebral edema and by anticipation and improved management of complications such as gastrointestinal bleeding and bacterial and fungal sepsis.[47]

For established cases of fulminant hepatic failure, urgent liver transplantation is increasingly recognized as effective treatment, especially if performed before dense coma has occurred.[48–52] The success of orthotopic liver transplantation in fulminant hepatic failure has created a need for early prognostic indicators, so that patients most likely to benefit may be selected while liver transplantation is still feasible. The prognosis is poor in patients with any of the following features: age under 11 or over 40; jaundice for more than 7 days before the onset of encephalopathy; non-A, non-B hepatitis or drug-reaction etiology; prothrombin time >50 seconds (control 15 seconds); and serum bilirubin >17.6 mg/dL.[53,54]

In spite of the dangers associated with liver replacement for fulminant hepatic failure, current survival rates (55% to 75%) compare favorably with the most optimistic projections for medical management alone (20%). To improve results, early referral to transplantation centers, extremely aggressive evaluation, and an early decision for surgical exploration and biopsy with the option of immediate transplantation are necessary.[48,55]

Unusual complications of acute viral hepatitis

Unusual complications of acute viral hepatitis include aplastic anemia,[56] acute immune thrombocytopenia,[57,58] hemolytic uremic syndrome, and thrombotic thrombocytopenic purpura.[59,60] Hemolytic anemia is common in children with glucose-6-phosphate dehydrogenase deficiency who develop viral hepatitis. Raynaud's syndrome with fingertip infarcts during the prodrome,[61] a dermatomyositis-like syndrome,[62] and Schönlein-Henoch purpura have been reported with both hepatitis B and hepatitis A. One distinctive manifestation of acute hepatitis B is the Gianotti-Crosti syndrome, or infantile papular acrodermatitis. This is characterized by an erythematous papular rash on the face and limbs which clears completely in a few weeks. The accompanying hepatitis is usually anicteric and often asymptomatic; its diagnosis rests on correctly identifying the skin lesion.[63] This syndrome may also be seen with other viral infections.

Guillain-Barré syndrome has been described in association with acute hepatitis A and B.[64] Residual neurological signs such as facial palsy, ataxia, or areflexia have also been reported with both types of hepatitis. Aseptic meningitis, meningoencephalomyelitis, or myelitis can accompany acute viral hepatitis.[65] Mononeuritis of cranial as well as peripheral nerves has been described in both types of hepatitis.[66]

Renal manifestations such as proteinuria are common in acute viral hepatitis. Membranous/mesangiocapillary glomerulonephritis,[67,68] and renal lesions of essential mixed cryoglobulinemia,[69] and polyarteritis nodosa have been described in chronic hepatitis B.[70,71] One dramatic complication of acute and chronic hepatitis B is a vasculitis closely resembling polyarteritis nodosa.[72] Pancreatitis has been described in fulminant hepatitis[73] and in one case of serologically confirmed acute hepatitis A.

Cardiac complications of acute viral hepatitis include prolonged hypotension, progressive cardiomegaly, pulmonary edema, arrhythmias (atrial fibrillation, ventricular ectopy), other electrocardiographic abnormalities, and sudden death.[74] Pleural effusion has also been noted during the prodrome or in the early icteric phase of acute viral hepatitis, particularly in hepatitis B.[75–77]

ROLE OF LIVER BIOPSY IN ACUTE HEPATITIS

Although the histological characteristics of viral hepatitis are well defined, the clinician should consider whether a liver biopsy will contribute to diagnosis, management, or prognosis of patients with typical acute viral hepatitis. The clinical and biochemical parameters of viral hepatitis are usually quite distinctive; only occasionally does the clinician stumble on a diagnosis of acute viral hepatitis by doing a liver biopsy.

When the cause of abnormal liver tests is not clear, our practice is to defer biopsy until the liver dysfunction has been present for 3 months or more. During this time, if we cannot diagnose viral hepatitis without a biopsy, we prefer to let the lesion heal, if it will. This is appropriate particularly because there is no specific treatment for acute viral hepatitis.

It was formerly thought that certain histologic lesions seen in acute viral hepatitis are highly predictive for the subsequent development of chronic liver disease, cirrhosis, and death.[78] More recently, this view has been challenged, and we share the view that an early liver biopsy in acute viral hepatitis does not predict ultimate outcome.[79] Although the liver histology in acute viral hepatitis is highly characteristic, biopsy is usually superfluous, except in transplant patients with acute hepatic dysfunction. For these patients, biopsy provides specific information about such conditions as rejection and cytomegalovirus infection which can be used to guide therapy.

VIRAL A HEPATITIS: AN OVERVIEW

Epidemiology and pathogenesis

Hepatitis A virus (HAV) occurs worldwide. Because the infection is frequently asymptomatic and because overt cases are underreported even in western countries, data on its incidence are poor.[80] HAV accounted for 39% of acute viral hepatitis reported in the United States in 1985.[81,82]

The disease is self-limited, although rarely it results in fulminant hepatic failure. Neither chronic hepatitis A nor a chronic carrier state seems to occur, despite recent reports to the contrary.[83,84] The virus, which has been identified in stool, is a 27-nm ribonucleic acid agent that is classified as a picornavirus. HAV can be grown in cell culture.[85]

The virus is no longer thought to be cytopathic; rather, the pathogenesis of the disease is believed to be immunologic and probably T-cell-dependent. Special techniques for staining blood and stool from patients experimentally infected with HAV have shown that fecal HAV concentration is maximum during the initial elevation of serum transaminase that occurs in the late incubation period and early acute disease; that is, greatest infectivity is during the 2-week period immediately before the onset of jaundice.[86] The mean incubation period of HAV is 28 days (range 15 to 40 days).[80] Once jaundice appears, viral shedding in stool—and risk of contagion—is very low.[87] Viremia is transient: it lasts for a short time before clinical illness begins. For these reasons, by the time the patient becomes ill with hepatitis A, contagion is no longer a concern.

Hepatitis A can be epidemic because fecal-oral spread of infected material occurs before the index case becomes ill. In light of these findings, the isolation imposed on patients, families, and hospitals where hepatitis A has occurred is questioned. HAV usually causes minor or unnoticed illness in children and young adults, and it is probable that, worldwide, fewer than 5% of cases are recognized clinically.[88] The typical epidemiologic pattern in western countries is sporadic disease in susceptible adults (men living in military camps, inmates of mental institutions, male homosexuals having anal-oral contact, travellers to endemic countries). In North America, drug abusers represent a substantial high-risk group. The American Viral Hepatitis Surveillance Program indicates that, although the annual incidence of acute HAV infection was roughly constant between 1982 and 1986, the proportion of patients admitting to drug abuse rose from 4% to 19%.[89] Although intravenous spread may explain part of this increase, it seems likely that other factors (crowding, poor hygiene) are more likely explanations.[90]

Diagnosis

Commercial laboratories are not equipped to find HAV particles in the blood or stool. Such assays would be of limited value in clinical practice because HAV disappears from the blood and stool by the time the patient becomes ill. Instead, diagnosis relies on serologic markers for detecting serum antibodies.[85,91] Soon after the virus disappears from the blood, specific antibodies against HAV are detectable in the blood; these are initially of the immunoglobulin M (IgM) type, but eventually a permanent immunoglobulin G (IgG) antibody to HAV is found. Low-cost kits are now routinely used in hospital laboratories to detect the presence of IgM antibody to HAV.

Most patients become seronegative by 120 days, while others (approximately 14%) remain positive for IgM anti-HAV for prolonged periods (more than 200 days). Awareness of this marked variability is important in the interpretation of IgM anti-HAV as a serologic marker of recent HAV infection.[92] IgG antibody persists for years, perhaps for life, providing extended immunity against reinfection with HAV. Saliva secretes both IgM and IgG anti-HAV, and testing for these antibodies in saliva was reported by one group to be a simpler way of investigating outbreaks.[93]

TABLE 2
RECOMMENDATIONS FOR PASSIVE IMMUNIZATION FOR HEPATITIS A WITH IMMUNE GLOBULIN

Entry	Comment
Preexposure prophylaxis	
International travellers	IG not recommended for travel to developed areas (western Europe, Japan, Australia, New Zealand); recommended for travel to developing countries. If expected length of stay is less than 3 months, dose is IG 0.02 mL/kg body weight; for prolonged travel dose is 0.06 mL/kg every 5 months. For persons requiring repeated IG prophylaxis, screening for total anti-HAV before travel will eliminate unnecessary doses for immune travellers.
Postexposure prophylaxis	
Recommended	
Close personal contact	Household and sexual contacts
Daycare centers	Staff and attendees and all members of household whose diapered children attend if a case of hepatitis is discovered in daycare center.
Institutions	Residents and staff of prisons and facilities for custodial care developmentally disabled, when outbreak occurs.
Common-source exposure	IG might be effective in preventing foodborne or waterborne hepatitis A if recognized in time. IG is recommended for other food handlers (kitchen employees) when a food handler has been diagnosed with hepatitis A. Patrons may be considered if all of the following conditions exist: a) source is directly involved in handling, without gloves, food that will not be cooked before eaten, and b) the hygienic practices of source area deficient or the food handler has had diarrhea, and c) patrons can be identified and treated within 2 weeks of exposure.
Not routinely recommended	
Schools	IG is not indicated for pupils and teachers in contact with a patient. (except when epidemiologic evidence shows the existence of a school or classroom-centered outbreak).
Hospitals	IG is not recommended for either roommates or staff caring for a patient with hepatitis A. (In rare outbreaks with a fecally incontinent patient, prophylaxis of persons exposed to feces of infected patient may be indicated.
Offices and factories	IG not indicated under the usual conditions for persons exposed to a fellow worker with hepatitis A.

IG = immunoglobulin, HAV = hepatitis A virus

Serologic confirmation of index patients is recommended before contacts are treated, as hepatitis A cannot be reliably diagnosed on clinical grounds. Serologic screening of contacts for anti-HAV before they are given IG is not recommended for cost effectiveness. IG should be given as soon as possible after last exposure; giving it more than 2 weeks after exposure is not indicated. Recommended dose is single intramuscular dose of 0.02 mL/kg.

From Centers for Disease Control, 1990.[106]

Management and prevention

As discussed above, management of hepatitis A requires no specific therapy. The virus is resistant to antiviral drugs. Although corticosteroids may expedite recovery from late cholestasis,[7] a well-designed small trial of methylprednisolone in severe acute infection showed a substantially higher mortality in corticosteroid-treated patients than in those receiving placebo.[94] Corticosteroids should be avoided in patients with hepatitis A.

Preventing HAV infection depends on stopping transmission of the virus and rendering susceptible individuals resistant to infection by high-risk passive immunization. The fecal-oral route is the principle mode of spread of HAV; hence, the most effective control measures would prevent fecal contamination of food, water, or other sources by infected individuals. However, maximum shedding of HAV occurs before clinical disease becomes apparent, and this increases communicability of the virus.[95] Thus, curtailing HAV spread depends in large measure on hygienic practices. Medical personnel in contact with infected patients and laboratory workers who handle infective specimens should carefully wash their hands; the importance of this cannot be overemphasized. Considering the low infectivity during the icteric stage of the disease, strict enteric precautions for hospitalized adult patients with hepatitis A are not necessary;[96] however, hepatitis A patients with diarrhea or fecal incontinence appear to represent a significantly greater risk to hospital personnel[97]; therefore, enteric precautions should be instituted for these patients.

Transmission of HAV via food can be decreased by good personal hygiene on the part of food handlers, and by minimizing the extent to which food is touched, particularly if it is to be eaten without further cooking. Recent evidence suggests that microwaving food that has been handled by an infected person reduces the risk of HAV transmission.[98] Standard water sanitation practices in the United States provide water that is free of infectious HAV, but water-borne hepatitis A may result from inadvertent or unrecognized contamination of drinking water with sewage.[99,100]

Passive immunization is possible with immune globulin prepared from pooled solutions of human plasma (formerly immune serum globulin, or ISG). Although standardized titers of anti-HAV activity have not been established, immune globulin has considerable anti-HAV activity and affords up to 90% protection rate.[101] The sooner it is used after exposure, the more likely it is to be protective. Immune globulin is safe, although anaphylactoid reactions have been noted after inadvertent intravenous or intra-arterial injections. Given properly (ie, subcutaneously or intramuscularly), only local soreness or swelling with occasional low-grade fever may occur. The theoretical risk that passive immunization might promote the spread of viruses, as the recipients become symptomless excreters, has not been shown. Guidelines issued by the Centers for Disease Control for the administration of immune globulin for exposures to hepatitis A are summarized in *Table 2*.[102,103]

Preexposure prophylaxis is recommended by the Centers for Disease Control for travelers to areas where hepatitis infection is endemic. For prolonged travel, a booster dose (0.06 mL/kg) should be given every 5 months. Groups planning a long stay in an endemic area may be screened for anti-HAV to eliminate unnecessary doses. For postexposure prophylaxis, serologic confirmation in the index patient is recommended before treating that patient's contacts.

Active immunization for HAV is not yet available. Both inactivated and attenuated vaccines have been developed which appear to be safe, antigenic, and protective in laboratory animals.[104,105] If studies in man support the data obtained in other primates, commercially available vaccines may be licensed within the next 2 years.[106] When such vaccines become available, specific guidelines for their use will be elaborated, as they have been for hepatitis B.

REFERENCES

1. Blumberg, BS. Polymorphism of the serum proteins and the development of iso-precipitins of transfused patients. Bull N Y Acad Med 1964; **40**:377–386.
2. Hussey HH. The hepatitis B saga. JAMA 1981; **245**:1317–1318.
3. Rotenberg JA, Dienstag JL, Harrison WO, et al. Food borne outbreak of hepatitis A and laboratory features of acute and protracted illness. Am J Med Sci 1979; **278**:123–137.
4. Forbes A, Williams R. Changing epidemiology and clinical aspects of hepatitis A. Br Med Bull 1990; **46**:303–318.
5. Kekler DM. Hepatitis and activity. Postgrad Med J 1971; **47**:490–492.
6. Nefzger MD, Chalmers TC. The treatment of acute infectious hepatitis: ten year follow-up study of the effects of diet and rest. Am J Med 1963; **35**:299–309.
7. Gordan SC, Reddy KR, Schiff L, Schiff ER. Prolonged intrahepatic cholestasis secondary to hepatitis A. Ann Int Med 1984; **101**:635–637.
8. Trey C, Davidson CS. The management of fulminant hepatic failure. In: Popper H, Schaffer F, editors. Progress in liver disease. New York: Grune and Stratton, 1970:282–298.
9. Shattock AG, Irwin FM, Morgan BM, et al. Increased severity and morbidity of acute hepatitis in drug abusers with simultaneously acquired hepatitis B and hepatitis D infections. Br Med J 1985; **290**:1377–1380.
10. Smeldie A, Farci P, Verme G, et al. Influence of delta infection on severity of hepatitis B. Lancet 1982; **2**:945–947.
11. Bradley DW. Enterically transmitted non-A, non-B hepatitis. Br Med Bull 1990; **46**:442–461.
12. Zimmerman HJ. Drug induced liver disease. Hepatotoxicity. New York: Appleton Century-Croft, 1978:349–369.
13. Zimmerman HJ. Anesthetic agents. Hepatotoxicity. New York: Appleton Century-Croft, 1978:370–394.
14. Kaplowitz N, Aw TY, Stolz A. Drug induced hepatotoxicity. In: Gitnick G, Hollander D, Kaplowitz N, Samloff IM, Schoenfield LJ, editors. Principles and practice of gastroenterology and hepatology. New York: Elsevier Science Publishing, 1988:1089–1102.
15. Caravati CM, Hooker TH. Acute massive hepatic necrosis with fatal hepatic failure. Am J Dig Dis 1971; **16**:803.
16. Benhamou JP, Reuff RL, Sicot C. Severe hepatic failure: a critical study of current therapy. In: Orlandi F, Jezequel AM, editors. Liver and drugs. New York: Academic Press, 1969:213–228.
17. Trey C, Lipworth L, Chaomers TC, et al. Fulminant hepatic failure, presumable contribution of halothane. N Engl J Med 1968; **279**:798.
18. Tygstrup N, Ranek L. Assessment of prognosis in fulminant hepatic failure. In: Williams R, editor. Seminars in liver disease. Vol 6, No 2. New York: Thieme, 1986:129.
19. Auslander MO, Gitnick GL. Vigorous medical management of acute fulminant hepatitis. Arch Int Med 1977; **137**:599.
20. Psacharsopoulas HT, Mowat AP, Davies M, et al. Fulminant hepatic failure in childhood: an analysis of 31 cases. Arch Dis Child 1980; **55**:252.
21. Saunders SJ, Terblanche J. Prognosis in acute hepatic failure. In: Williams R, Murray-Lyon IM, editors. Artificial hepatic support. Tunbridge Wells, England: Pitman Medical, 1975:217.
22. Van der Rijt C, Schalm SW. Quantitative EEG analysis and survival in liver disease. Electroencephalogr Clin Neurophysiol 1985; **61**:502.
23. Trey C, Lipworth L, Davidson CS. Parameters influencing survival in the first 318 patients reported to the Fulminant Hepatic Failure Surveillance Study. Gastroenterology 1970; **58**:306.
24. Tandon BN, Joshi YK, Tandon M. Acute liver failure, experience with 145 patients. J Clin Gastroenterol 1986; **8**:664.
25. Peters RL, Edmondson HA. Fulminant hepatitis, relationship of patient age to liver morphology. Gastroenterology 1970; **58**:289.
26. Rueff B, Benhamou JP. Acute hepatic necrosis and fulminant hepatic failure. Gut 1973; **14**:805.
27. Rakela J, Lange SM, Ludwig J, et al. Fulminant hepatitis: Mayo Clinic experience with 34 cases. Mayo Clin Proc 1985; **60**:289.
28. Chalmers TC. Acute viral hepatitis. In: Bockus HL, editor. Gastroenterology, Vol. 3. WB Saunders, 1976:247–264.
29. Bloomer JR, Waldman TA, McIntire KR, Klaskin G. Serum alpha-feto protein in patients with massive hepatic necrosis. Gastroenterology 1977; **72**:478–482.
30. MacDougall BRD, Bailey RJ, Williams R. H2 receptor antagonists and antacids in the prevention of acute gastrointestinal hemorrhage in fulminant hepatic failure. Lancet 1977; **617**:619.
31. Canalese J, Gimsson AES, Williams R, et al. Controlled trial of dexamethasone and mannitol for the cerebral oedema of fulminant hepatic failure. Gut 1982; **23**:625–629.
32. Williams R, Ede RJ. Occurrence and management of cerebral edema in liver failure. Clinics in Critical Care Medicine 1986; 26–46.

33. Fagan EA, Williams R. Fulminant viral hepatitis. Br Med Bull 1990; **46:**462–480.
34. O'Grady JG, Williams R. Acute liver failure. Baillieres Clin Gastroenterol 1989; **3:**75–89.
35. Mosley JW, Combes B, Volwiler W, Zimmerman HJ. Corticosteroids in fulminant hepatitis. N Engl J Med 1976; **296:**898–899.
36. Ware AJ, Cuthbert JA, Shorey J, Burian LE, Eigenbrodt EH, Combes B. A prospective trial of steroid therapy in severe viral hepatitis. Gastroenterology 1981; **80:**219–224.
37. Akamatsu K, Tada K. Plasma exchange therapy in patients with fulminant hepatic failure and limitations of effectiveness. Prog Clin Biol Res 1990; **337:**239–241.
38. Starzl TE, Terblanche J. Hepatotrophic substances. Prog Liver Dis 1979; **6:**135–151.
39. Starzl TE, Francavilla A, Halgrimson CG, et al. Origin, hormonal nature, and action of hepatotrophic substances in portal venous blood. Surg Gynecol Obstet 1973; **137:**179–199.
40. Okita K, Matsuda S, Hauta T, Yasunaga M, Sanuki K, Takemoto T. Clinical evaluation of glucagon and insulin in therapy of fulminant hepatitis. Gastroenterol Jpn 1987 Oct; **22(5):**607–613.
41. Watanabe A, Higashi T, Hayashi S, et al. Effects of insulin and glucagon on serum amino acid concentrations in liver disease. Acta Med Okayama 1982 Dec; **36(6):**441–446.
42. Hedin G, Weiland O, Ljunggren K, et al. Treatment of fulminant hepatitis B and fulminant B and D coinfection with Foscarnet. Prog Clin Biol Res 1987; **234:**309–320.
43. Price JS, France AJ, Moaven LD, Welsby PD. Foscarnet in fulminant hepatitis B [letter]. Lancet 1986; **2:**1273.
44. Milazzo F, Galli M, Fassio PG, et al. Attempted treatment of fulminant viral hepatitis with human fibroblast interferon. Infection 1985; **13:**130–133.
45. Sanchez-Tapias JM, Mas A, Costa J, et al. Recombinant alpha 2c-interferon therapy in fulminant viral hepatitis. J Hepatol 1987; **5:**205–210.
46. Sinclair SB, Greig PD, Blendis LM, et al. Biochemical and clinical response of fulminant viral hepatitis to administration of prostaglandin E. A preliminary report. J Clin Invest 1989 Oct; **84(4):**1063–1069.
47. Feinman SV, Berris B, Bojarski S. Post transfusion hepatitis in Toronto, Canada. Gastroenterology 1988; **95:**464–469.
48. Bismuth H, Samuel D, Gugenheim J, et al. Emergency liver transplant for fulminant hepatitis. Ann Int Med 1987; **107:**337–341.
49. Emond JC, Aran PP, Whitington PF, Broelsch CE, Baker AL. Liver transplantation in the management of fulminant hepatic failure. Gastroenterol 1989; **96:**1583–1588.
50. Ringe B, Pichlmayr R, Lauchart W, Müller R. Indications and results of liver transplantation in acute hepatic failure. Transplant Proc 1986; **18:**86–88.
51. Vicker C, Neuberger J, Buckels J, McMaster P, Elias E. Liver transplantation for fulminant hepatic failure [abstract]. Gut 1987; **28:**A1345.
52. Brems JJ, Hiatt JR, Ramming KP, et al. Fulminant hepatic failure: the role of liver transplantation as primary therapy. Am J Surg 1987; **154:**137–141.
53. O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989; **97:**439–445.
54. O'Grady JG, Gimson AES, O'Brien CJ, et al. Controlled trials of charcoal hemoperfusion and prognostic factors in fulminant hepatic failure. Gastroenterology 1988; **94:**1186–1192.
55. Starzl TE, Demetris AJ, Van Thiel. Liver transplantation. N Engl J Med 1989; **321:**1014–1021.
56. Zeldis JB, Dienstag JL, Gale RP. Aplastic anemia and non-A, non-B hepatitis. Am J Med 1983; **74:**64–68.
57. Ibarra H, Zapata C, Inostroza J, Mezzano S, Riedemann S. Immune thrombocytopenic purpura associated with hepatitis A. Blut 1986; **52:**371–375.
58. Klienman Y, Friedman G. Transient autoimmune thrombocytopenia associated with acute infectious hepatitis. Hepatogastroenterology 1982; **29:**144–145.
59. Cronin CM, Fennel JS, McKiernan J, Murnaghan DJ. Haemolytic uraemic syndrome associated with hepatitis A virus infection. Ir Med J 1983; **76:**357.
60. Furgiuele TL. Hemolytic uremic syndrome presenting as hepatitis. Tex Med 1981; **77:**55–56.
61. Cosgriff TM, Arnold WJ. Digital vasospasm and infarction associated with hepatitis B antigenaemia. JAMA 1976; **235:**1362–1363.
62. Pittsley RA, Shearn MA, Kauffman L. Acute hepatitis B simulating dermatomyositis. JAMA 1978; **239:**959.
63. Giannotti F. Papular acrodermatitis of childhood. An Australian antigen disease. Arch Dis Child 1973; **48:**794–799.
64. Tabor E. Guillain Barré syndrome and other neurological syndromes in hepatitis A, B, and non-A, non-B. J Med Virol 1987; **21:**207–216.
65. Bromberg K, Newhall DN, Peter G. Hepatitis A and meningo-encephalomyelitis. JAMA 1982; **247:**815.
66. Pelletier G, Elghozi D, Trepo C, Laverdant C, Benhamou J-P. Mononeuritis in acute viral hepatitis. Digestion 1985; **32:**53–56.
67. Combes B, Statsny B, Shorey J, et al. Glomerulonephritis with deposition of Australian antigen-antibody complexes in glomerular basement membrane. Lancet 1971; **2:**234–237.
68. Gocke DJ. Immune complex phenomenon associated with hepatitis. In: Vyas GN, Cohen SN, Schmid R, editors. Viral hepatitis. Philadelphia: Franklin Institute Press, 1978:277–284.
69. Levo Y, Gorevic PD, Kassab HJ, Zucker-Franklin D, Franklin EC. Association between hepatitis B virus and essential mixed cryoglobulinemia. N Engl J Med 1977; **296:**1501–1504.
70. Drueke T, Barbanel C, Jungers P, et al. Hepatitis B antigen associated periarteritis nodose in patients undergoing long-term hemodialysis. Am J Med 1980; **68:**86–90.
71. Gocke DJ, Hsu K, Morgan C, et al. Association between polyarteritis and Australian antigen. Lancet 1970; **2:**1149–1153.
72. Anuras S, McMahon BJ, Chow KC, Summers RW. Severe abdominal vasculitis with hepatitis B antigenaemia. Am J Surg 1980; **140:**692–695.
73. Lopez Morante A, Rodriquez de Lope C, San Miguel G, Pons Romero F. Acute pancreatitis in hepatitis A infection. Postgrad Med J 1986; **62:**407–408.
74. Bell H. Cardiac manifestations of viral hepatitis. JAMA 1971; **218:**387–391.
75. Gross PA, Gerding DN. Pleural effusion associated with viral hepatitis. Gastroenterology 1971; **60:**898–902.
76. Cocchi P, Silenzi M. Pleural effusion in HBsAg-positive hepatitis. J Pediatr 1976; **89:**329–330.
77. Tabor E, Russell RP, Gerety RJ, et al. Hepatitis B surface antigen and e antigen in pleural effusion. Gastroenterology 1977; **73:**1157–1159.
78. Boyer JL, Klatskin G. Pattern of necrosis in acute viral hepatitis: prognostic value of bridging (subacute hepatic necrosis). N Engl J Med 1970; **283:**1063–1071.
79. Ware AJ, Cuthbert JA, Shorey J, et al. A prospective trial of steroid therapy in severe viral hepatitis. Gastroenterology 1981; **80:**219–224.
80. Alter MJ, Mares A, Hadler SC, Maynard JE. The effect of under reporting on the apparent incidence and epidemiology of acute viral hepatitis. Am J Epidemiol 1987; **125:**133–139.
81. Centers for Disease Control. Hepatitis surveillance report No. 51. Atlanta (GA): Centers for Disease Control; 1987 Mar.
82. Francis DP, Hadler SC, Prendergast TJ, et al. Occurrence of hepatitis A, B, and non-A, non-B in the United States. CDC Sentinel County Hepatitis Study I. Am J Med 1984; **76:**69–75.
83. McDonald SA, Courtney M, Shatrock A, et al. Prolonged IgM antibodies and histopathological evidence of chronicity in hepatitis A. Liver 1989; **9:**223–228.
84. Liaw VF. Chronic hepatitis caused by the hepatitis A virus. Hepatology 1990; **6:**1089–1090.
85. Routenberg JA, Dienstag JL, Harrison WO, et al. Foodborne outbreak of hepatitis A: clinical and laboratory features of acute and protracted illness. Am J Med Sci 1979; **278:**123–137.
86. Dienstag JL, Szmuness W, Stevens CE, Purcell RH. Hepatitis a virus infection: new insights from seroepidemiological studies. J Infect Dis 1978; **137:**328–340.

87. Mosley JW. Epidemiology of HAV infection. In: Vyas GN, Cohen SN, Schmid R, editors. Viral hepatitis. Philadelphia: Franklin Institute Press, 1978:84–104.
88. Gust ID, Feinstone SM. Epidemiology. Hepatitis A. Florida: CRC Press, 1988:163–191.
89. Centers for Disease Control. Hepatitis A among drug users. MMWR 1988; **37:**297–300.
90. Jenkerson SA, Middaugh JP, Pittman SL, et al. Hepatitis A among drug users. JAMA 1988; **259:**3255–3256.
91. Badley BW, Fields HA, McCaustland KA, et al. Serodiagnosis of viral hepatitis A by a modified competitive binding radioimmunoassay for immunoglobulin M anti-hepatitis A virus. J Clin Microbiol 1979; **9:**129–127.
92. Kao HW, Ashcavai M, Redeker AG. The persistence of hepatitis A IgM antibody after acute clinical hepatitis A. Hepatology 1984; **4:**933–936.
93. Bull AR, Kimmance KJ, Parry JV, et al. Investigations of an outbreak of hepatitis A simplified by salivary antibody testing. Epidemiol Infect 1989; **103:**371–376.
94. Gregory PB, Knauer CM, Kempson RL, Miller R. Steroid therapy in severe viral hepatitis A: a double blind, randomized trial of methylprednisolone versus placebo. N Engl J Med 1976; **294:**681–687.
95. Mosley JW. Epidemiology of HAV infection. In: Vyas GN, Cohen SN, Schmid R, editors. Viral hepatitis. Philadelphia: Franklin Institute Press, 1978:104.
96. Favero MS, Maynard JE, Leger RT, Graham DR, Dixon RE. Guidelines for the care of patients hospitalized with viral hepatitis. Ann Int Med 1979; **91:**872–876.
97. Goodman RA, Carder CC, Allen JR, Orenstein WA, Finton RJ. Nosocomial hepatitis A transmission by an adult patient with diarrhea. Am J Med 1982; **73:**220–226.
98. Mishu B, Hadler SC, Boaz VA, Hutcheson RH, Horan JM, Schaffner W. Foodborne hepatitis A: evidence that microwaving reduces risk. J Inf Dis 1990; **162:**655–658.
99. Bowen GS, McCarthy MA. Hepatitis A associated with a hardware store water fountain and a contaminated well in Lancaster County, Pennsylvania, 1980. Am J Epidemiol 1983; **117:**695–705.
100. Bloch AB, Stramer SL, Smith JD, et al. Recovery of hepatitis A virus from a water supply responsible for a common source outbreak of hepatitis A. Am J Public Health 1990 Apr; **80(4):**428–430.
101. Seeff LB, Hoofnagle JH. Immunoprophylaxis of viral hepatitis. Gastroenterology 1979; **77:**161–182.
102. Center for Disease Control. Immune globulins for protection against viral hepatitis. Ann Intern Med 1982; **96:**193–197.
103. Centers for Disease Control. Protection against viral hepatitis: recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR 1990; 39(No. RR-2):3–5.
104. Ticehurst JR. Hepatitis A virus: clones, cultures and vaccines. Semin Liver Dis 1986; **6:**48–55.
105. Hadler SC. Vaccines to prevent hepatitis A and hepatitis B virus infections. Infect Dis Clin North Am 1990; **4:**29–46.
106. Gust ID. Design of hepatitis A vaccines. Br Med Bull 1990; **46:**319–328.