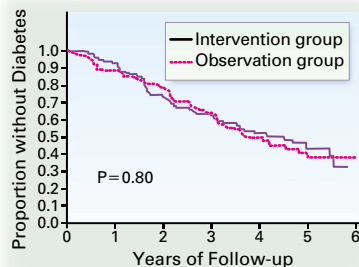




This Week in the Journal

May 30, 2002



Parenteral Insulin in Relatives of Patients with Type 1 Diabetes Mellitus

Persons who are at high risk for type 1 diabetes may be identified on the basis of islet-cell antibody levels, insulin antibody levels, and genetic studies. These investigators randomly assigned 339 high-risk first- and second-degree relatives of patients with diabetes (mean age, 11.2 years) either to observation or to low-dose subcutaneous ultralente insulin twice daily, plus an annual four-day continuous intravenous infusion of insulin. By the end of the study, diabetes had been diagnosed in 69 subjects in the intervention group and 70 in the observation group, an annualized rate of progression of 15.1 percent in the intervention group and 14.6 percent in the observation group.

Insulin in the dose and regimen used in this study neither delayed nor prevented type 1 diabetes in high-risk persons.

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“Monoclonal-antibody treatment resulted in improved metabolic control with reduced insulin usage during the first year after the diagnosis of type 1 diabetes mellitus.”

Monoclonal Antibody in New-Onset Type 1 Diabetes Mellitus

Mechanisms that destroy beta cells in type 1 diabetes mellitus involve both cytotoxic T cells and soluble T-cell products. In the present study, 24 patients with newly diagnosed diabetes received either a single course of a nonactivating monoclonal antibody against the T-cell antigen CD3 or no antibody; all the patients were then followed for one year. Treatment with the monoclonal antibody led to sustained or improved insulin responses in 9 of 12 patients, whereas only 2 of 12 control patients had sustained insulin responses. A significant decrease in the required dose of insulin occurred in the patients treated with the monoclonal antibody.

Treatment with anti-CD3 antibody may slow the deterioration in insulin production that occurs in early type 1 diabetes mellitus.

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PERSPECTIVE

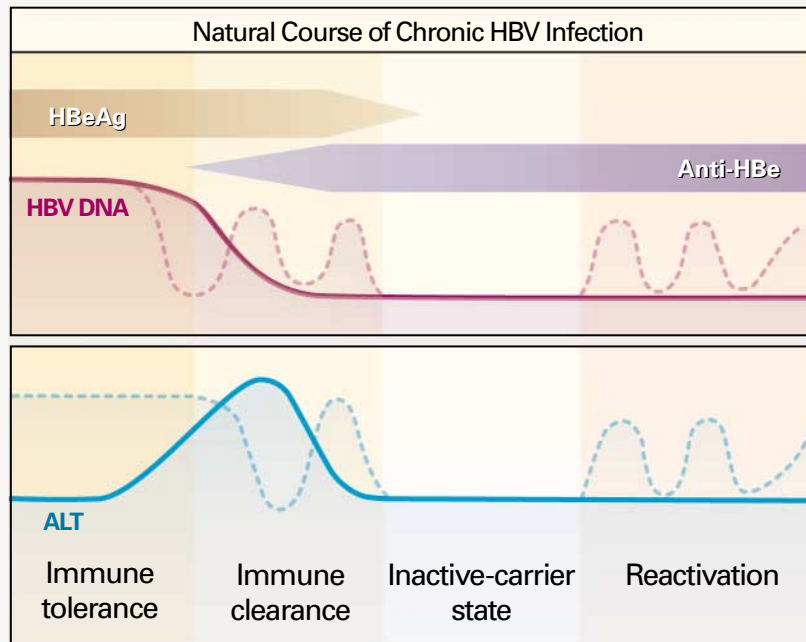
Chronic Hepatitis B

Chronic hepatitis B remains a major public health problem, affecting more than 350 million people worldwide. Cirrhosis, liver failure, or hepatocellular carcinoma will develop in approximately 15 to 40 percent of infected patients.

The worldwide prevalence of carriage of hepatitis B virus (HBV) ranges from 0.1 to 20 percent. The wide range is largely related to differences in age at the time of infection — a factor that is inversely related to the risk of chronic infection. Perinatal infection is the predominant mode of transmission in high-prevalence areas, and horizontal transmission during early childhood is the most common form in areas with an intermediate prevalence, whereas sexual contact and injection-drug use in adults are the main routes of spread in low-prevalence areas.

Chronic hepatitis B generally consists of an early replicative phase involving active liver disease and a late phase involving low or undetectable levels of viral replication and remission of liver disease (see Figure). In patients with perinatally acquired infection, the first phase is characterized by the presence of hepatitis B e antigen (HBeAg) and high levels of serum HBV DNA but normal levels of aminotransferases. These patients are believed to have immune tolerance to HBV, thus accounting for the very low rates of spontaneous and treatment-related clearance of HBeAg.

The first phase of chronic hepatitis B acquired during childhood or adulthood and the second phase of perinatally acquired HBV infection are characterized by the presence of



Phases of Chronic Hepatitis B Virus (HBV) Infection.

HBeAg denotes hepatitis B e antigen, anti-HBe antibody against HBeAg, and ALT alanine aminotransferase. Solid lines indicate a smooth transition from replicative to nonreplicative or minimally replicative infection and remission of liver disease. Dotted lines indicate flares of hepatitis associated with abortive immune clearance or reactivation of HBV.

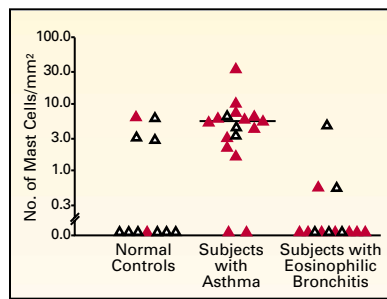
HBeAg and high serum levels of HBV DNA and aminotransferases (referred to as HBeAg-positive chronic hepatitis). Immune clearance of HBV and the destruction of infected hepatocytes may be manifested by increases in aminotransferase levels. Spontaneous as well as treatment-related development of HBeAg seroconversion is more common and is related to the extent of the elevation in aminotransferase levels.

The development of antibody against HBeAg is usually accompanied by low or undetectable serum levels of HBV DNA and normal aminotransferase levels and is referred to as the inactive-carrier state. However, some patients continue to have high levels of HBV DNA

and aminotransferase (referred to as HBeAg-negative chronic hepatitis). These patients may have residual wild-type HBV or HBV variants that prevent the production of HBeAg.

The goals of treatment of chronic hepatitis B are sustained suppression of HBV replication and remission of liver disease. In patients with HBeAg-positive chronic hepatitis, a response to treatment is usually defined by the reduction of serum HBV DNA to levels that cannot be detected with non-polymerase-chain-reaction assays and by the loss of HBeAg.

Approved treatments for chronic hepatitis B include interferon alfa and lamivudine. A three-to-six-month course of interferon alfa is



Mast-Cell Infiltration of Airway Smooth Muscle in Asthma

Although asthma is a chronic inflammatory disease of the airways, exactly which components of inflammation relate to the expression of the asthma phenotype is not known. In this study, the number of mast cells in the airway smooth muscle was determined by biopsy of the airways of normal subjects, subjects with asthma, and subjects with eosinophilic bronchitis. There were significantly more mast cells in the airway smooth muscle of the subjects with asthma than in that of either normal subjects or subjects with eosinophilic bronchitis, a condition that is similar to asthma and therefore provides an appropriate control.

These data may shift the focus of asthma research to abnormalities of airway smooth muscle and away from the general study of airway inflammation.

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associated with a response rate of 30 to 40 percent. The rate of response in children is similar to that in adults. Lamivudine is an orally administered nucleoside analogue that inhibits HBV replication. Results of double-blind, randomized, controlled trials in adults showed that a one-year course of lamivudine was associated with HBeAg seroconversion in 16 to 18 percent of patients, as compared with 4 to 6 percent of controls. Longer periods of treatment are associated with increased rates of response, but long-term treatment also leads to higher rates of drug resistance — from 20 percent at one year to 50 percent at three years. HBV mutations leading to lamivudine resistance reduce the replicative fitness of the virus. Most patients with lamivudine-resistant HBV infection have lower serum levels of HBV DNA and aminotransferases while still receiving treatment than before treatment, suggesting that the short-term outcome for these patients remains favorable. However, an exacerbation of hepatitis and liver fail-

ure have been reported in a small proportion of patients with lamivudine-resistant HBV infection, and additional mutations that may restore replicative fitness have been observed.

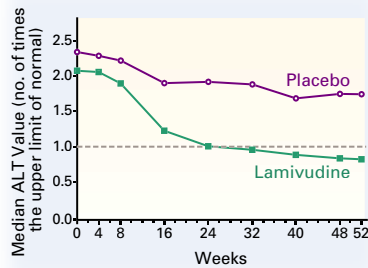
In this issue of the *Journal*, Jonas and colleagues report that a virologic response occurred in 23 percent of children who received a one-year course of lamivudine and 13 percent of those who received placebo ($P=0.04$) (see pages 1706–1713). Treatment was well tolerated, but lamivudine-resistant HBV mutants were detected in 19 percent of children in the lamivudine group. As is true in adults, the pretreatment aminotransferase level was the strongest predictor of response.

The availability of oral therapy with minimal side effects has increased the level of enthusiasm regarding the use of therapy for chronic hepatitis B. However, the patient's age, the severity of liver disease, the likelihood of a response, and potential adverse effects must be taken into account before treatment is initiated. The current rec-

ommendation is to monitor patients in the immune-tolerant phase of disease, because the response to currently available treatment is poor. Treatment is indicated for patients with HBeAg-positive or HBeAg-negative chronic hepatitis but is not necessary for those in the inactive-carrier state.

Clinical trials indicate that interferon alfa and lamivudine have similar efficacy. The advantages of interferon alfa include the finite duration of treatment and the absence of resistance; the disadvantages are its costs and side effects. Lamivudine is less expensive and is well tolerated, but the durability of the response and the long-term clinical significance of the resistant mutants, particularly in children, are uncertain. As is the case for other illnesses, prevention is better than cure in the global control of HBV infection.

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Lamivudine in Children with Chronic Hepatitis B

Chronic hepatitis B can be successfully treated in adults with the antiviral agent lamivudine. In this international, randomized, double-blind, placebo-controlled trial, children with hepatitis B, some of whom had had no response to treatment with interferon, received either lamivudine or placebo for 52 weeks. The rate of virologic response was 23 percent in the lamivudine group, as compared with 13 percent in the placebo group ($P=0.04$). A two-year open-label extension of the trial is in progress.

Neither interferon nor lamivudine is a wonder drug in this group of patients. Lamivudine is an alternative treatment with efficacy similar to that of interferon and may be easier for children with chronic hepatitis B to tolerate.

see page 1706 (Perspective, page 1682)

“A higher proportion of hours of nursing care provided by registered nurses and a greater number of hours of care by registered nurses per day are associated with better care for hospitalized patients.”

Special Article: Nurse-Staffing Levels and Quality of Care

A shortage of nurses and cuts in nursing hours as hospitals try to save money have intensified concern that patients will be more likely to have complications or die. This study used 1997 data for 799 hospitals in 11 states to examine the relation between the level of staffing by nurses and the quality of care. It found an association between a higher proportion of registered nurses or more registered-nurse-hours per day and lower rates of specific adverse outcomes, such as upper gastrointestinal bleeding, hospital-acquired pneumonia, and shock or cardiac arrest.

These findings, although subject to a variety of limitations related to the weaknesses of the available data, focus attention on the importance of adequate numbers of nurses to the protection of patients and to improvement in the quality of care.

see page 1715



Current Concepts: Cryptosporidiosis

Cryptosporidium is an intracellular parasite that can infect the gastrointestinal epithelium to produce a profuse diarrhea that can be life-threatening in immunocompromised hosts. This Review Article summarizes information on the clinical manifestations, pathophysiology, and diagnosis of cryptosporidiosis. The authors emphasize measures to protect against this common infection, for which there is no effective treatment.

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