Treatment of patients with chronic hepatitis B virus (HBV) infection who have advanced disease or comorbidities can be challenging, and recommendations may differ from standard guidelines. Among the special populations that merit specific consideration are patients with compensated or decompensated cirrhosis, organ transplantation, acute hepatitis B, pregnancy, coinfection with hepatitis C and/or D virus, chronic renal failure, and children. Major advances have been made in management of many of these special populations because of recent increasing availability of oral nucleosides, which are generally well tolerated and highly effective despite presence of other morbidities or viral infections. Also important have been changes in the management of hepatitis B during the peri-liver transplantation period that allows for prevention of reinfection in the majority of cases. However, much remains to be done to determine which patients should be treated and which should be monitored on no specific therapy. Outcomes of chronic HBV infection in persons with coinfection and in children have varied from different areas of the world, but it is not clear whether these differences are due to host and racial differences or to viral genotypic differences. Further studies are particularly needed in assessing the safety and efficacy of therapy in pregnant women, in children, and in patients with hepatitis D and C virus coinfection.

Introduction

Many patients with hepatitis B virus (HBV) infection have comorbidities that may seriously complicate the standard approach to management and treatment of hepatitis B or actually represent specific contraindications to treatment. Management of these patients with special comorbidities is challenging, and the medical evidence in support of specific therapies in these populations is usually inadequate. Furthermore, the role and safety of therapy with alpha interferon (standard interferon and peginterferon alfa) as opposed to nucleoside analogs has to be considered separately in these populations. Table 1 outlines the special populations with hepatitis B infection that merit specific consideration and the quality of evidence that supports current recommendations.

Compensated Cirrhosis

Alpha interferon has multiple side effects that are particularly difficult for patients with advanced hepatitis B. Small but convincing studies have shown that alpha interferon is rarely effective and has frequent, severe, and even life-threatening side effects in patients with decompensated cirrhosis. In contrast, patients with well-compensated cirrhosis can tolerate interferon therapy, and beneficial responses may be more frequent than in patients with lesser degrees of fibrosis.

In the large, European study of a 52-week course of peginterferon-α2b alone or in combination with lamivudine in hepatitis B e antigen (HBeAg)-positive chronic hepatitis B, patients with advanced fibrosis (Ishak stage 4-6)1 were eligible for enrollment as long as they did not have evidence of decompensated liver disease (ascites, encephalopathy, low albumin, or prolonged prothrombin time) or severe cytopenias.2 Among 70 patients with advanced fibrosis or compensated cirrhosis, sustained virological responses (loss of HBeAg and HBV DNA levels below 10,000 copies/mL) were more frequent than in patients with lesser degrees of fibrosis (25% versus 12%: P < 0.02). Serious adverse events were not more frequent in the advanced fibrosis group.
In contrast to interferon, the oral nucleoside analogs are well tolerated and effective in suppressing viral replication in the majority of patients with or without cirrhosis and with or without hepatic decompensation. The efficacy of nucleoside analogs in preventing progression of disease in patients with cirrhosis due to hepatitis B was convincingly shown in a landmark clinical trial from multiple Asian-Pacific centers including China, Thailand, Singapore, the Philippines, New Zealand, and Australia. A total of 651 patients with advanced chronic hepatitis B (bridging fibrosis or cirrhosis) were enrolled.\(^3\) Enrollment criteria required HBV DNA to be detectable in serum using an assay with a lower limit of detection of 0.7 mEq/mL (~200,000 IU/mL). Patients who were HBeAg-positive and HBeAg-negative were enrolled but all patients were required to have no evidence of hepatic decompensation or hepatocellular carcinoma (HCC). The primary endpoint of the study was time to disease progression which was defined by one of the following: an increase of at least two points in the Child-Pugh score, spontaneous bacterial peritonitis, bleeding gastric or esophageal varices, renal insufficiency, HCC, or death related to liver disease. The Child-Pugh score was chosen as an endpoint, because of its reliability in predicting liver disease outcome and because this endpoint (a Child-Pugh score of 7) was the major criterion for eligibility for liver transplantation when the study was begun. A total of 436 patients were randomized to receive lamivudine (100 mg daily) and 215 patients received placebo. Importantly, the study was halted early (~3.5 years) by its independent data safety and monitoring board because of significant differences in rates of endpoints between the treatment groups. Overall disease progression occurred in 17.7% of placebo-treated compared to 7.8% of lamivudine-treated patients (\(P = 0.001\)). Furthermore HCC was diagnosed in 7.4% of placebo-treated patients compared to 3.9% of lamivudine recipients (\(P = 0.047\)). Kaplan-Meier plots demonstrated a steady separation in occurrence of endpoints starting 6 months after initiation of treatment and separation of rates of HCC after 18 months. Lamivudine resistance developed in 49% of patients, and this group had a higher rate of progression than patients without resistance (13% versus 5%) but lower progression than those on placebo (21%).

In summary, peginterferon can be used in patients with advanced chronic hepatitis B, but the better tolerance of oral nucleoside analogs and the strength of the evidence of benefit from the Asian-Pacific trial has led most experts and academic societies to recommend the use of nucleoside analog therapy for all patients with cirrhosis or advanced fibrosis due to hepatitis B, regardless of clinical features or serum aminotransferase levels, as long as HBV DNA is detectable.\(^4,6\) The level of HBV DNA used to recommend therapy is generally above 2000 IU/mL (~10\(^4\) copies/mL). It should be noted that this level is lower than that used to enroll patients in the Asian-Pacific trial (~200,000 IU/mL).

**Decompensated Liver Disease**

The 5-year survival of patients with chronic hepatitis B with compensated cirrhosis is approximately 84%, compared to only 14%-35% in patients with decompensated cirrhosis.\(^7,9\) Although alpha interferon can be used in patients with compensated cirrhosis,\(^2\) it is contraindicated in patients with decompensated disease, largely because of the high rate of serious adverse events and even mortality of interferon treatment in this group.\(^10,11\) In contrast, nucleoside analogs are well tolerated and safe in patients with advanced hepatitis B, and several studies have shown that their use is associated with improvement in or stabilization of liver decompensation, the avoidance of the need for liver transplantation, and may be associated with decreased frequency of HCC.\(^12-14\)

In cohorts of patients with decompensated cirrhosis due to hepatitis B who are on the transplant list, therapy with several nucleosides analogs (lamivudine, adefovir dipivoxil [adefovir], and tenofovir disoproxil fumarate [tenofovir]) has been associated with improved survival and a high rate of reversal of need for liver transplantation.\(^12,13,15\) In a study from the University of California San Francisco, Yao and coworkers compared a cohort of 23 patients with HBV-related end-stage liver disease referred for liver transplantation and who were treated with lamivudine, to a group of 55 historical controls.\(^16\) The lamivudine-treated patients had markedly improved survival, beginning 6 months after starting lamivudine (Fig.
1) with a decreased need for liver transplantation (35% versus 74%; \( P = 0.04 \)). Excluding patients who underwent liver transplant, none of the lamivudine-treated patients died (follow-up for 1-44 months) compared to six historical controls (within 3-12 months) (\( P = 0.009 \)).

Perrillo and colleagues from multiple liver transplant centers throughout North America treated 77 liver transplant candidates with end-stage chronic hepatitis B with lamivudine (100 mg daily). No control group was used, but results were compared to outcomes in two previously published studies of decompensated cirrhosis due to hepatitis B. HBV DNA levels decreased on lamivudine therapy, but levels were not reported. Alanine aminotransferase (ALT) values decreased and became normal in more than half of patients with elevations before treatment. Average serum bilirubin, albumin, and prothrombin times improved with treatment. The 4-year survival rate among lamivudine-treated patients was 70%, which was higher than historical cohorts (\( \sim 60\% \) and \( 30\% \)). Lamivudine was well tolerated. Antiviral resistance developed in a proportion of patients, and appearance of resistance was generally followed by reversal of the virological and clinical benefit.

In a third study, Schiff and colleagues from multiple clinical centers in North America, Europe, and Asia treated 128 patients with HBV-related cirrhosis awaiting liver transplantation with adefovir (10 mg daily). Therapy was associated with significant declines in HBV DNA levels (median decline of 4.1 log\(_{10}\) by week 48) and serum aminotransferase levels (normal ALT in 76% by week 48). The Child-Pugh score stabilized or improved in more than 90% of patients and the 1-year survival rate was 84%. A total of 43% of patients underwent liver transplantation, 36% were still on the waiting list, 21% had been removed from the waiting list, and 5% of patients died without undergoing liver transplantation.\(^{12,17}\) Antiviral resistance was not encountered; however, the analysis was limited to 48 weeks and subsequent studies have shown that adefovir resistance rarely arises during the first year of treatment.

These three studies support the safety of using nucleoside analog therapy in patients with decompensated cirrhosis due to hepatitis B and provide strong, although indirect, evidence of marked benefit of therapy which usually requires 6 months or more to become fully evident. As a result of these studies, antiviral therapy is routinely offered to patients with decompensated hepatitis B. Because of the problems of antiviral resistance, either combination therapy or use of agents with a high barrier to resistance (entecavir, tenofovir) is usually recommended. The time to clinical benefit with these more potent antivirals is not yet established, and whether more patients will avoid transplantation because of a more rapid clinical response is not yet known. The safety and efficacy of these newer agents for hepatitis B deserve careful study.

The recommendation for combination therapy in patients with decompensated cirrhosis due to HBV is based on the desire to prevent virological breakthrough, which may lead to multiple negative clinical consequences including death and need for transplantation.\(^{18}\) Uncontrolled studies in patients with lamivudine-resistant strains of HBV suggest that combination therapy with lamivudine and adefovir resulted in less resistance,\(^{19,20}\) although clinical benefit could not be demonstrated in small, short-term studies.\(^{21,22}\) In a study of 79 HBeAg-positive, treatment-naïve patients who completed 104 weeks of a randomized controlled study of lamivudine and placebo versus lamivudine and adefovir, the combination was associated with lower rate of virological breakthrough (19% versus 44%), less antiviral resistant mutations (15% versus 43%), and a higher rate of ALT normalization (45% versus 34%) than lamivudine alone. The combination did not result in a higher rate of HBeAg seroconversion than monotherapy (13% versus 20%).\(^{23}\) Combination therapy does not appear to increase the rate of decline of HBV DNA or result in a more rapid clinical improvement, even in decompensated patients. Thus, the major reason for using combination nucleoside analog therapy is to prevent antiviral resistance to one or both of the agents.

In summary, current recommendations include therapy directed at suppressing HBV DNA levels to undetectable levels\(^{24}\) and use of either a single potent nucleoside analog or combination of nucleoside analogs to prevent resistance. Prevention of resistance is particularly important, because the ensuing flares of disease may be life-threatening in this category of patients.
decompensated cirrhosis due to hepatitis B should also be referred for liver transplantation.

**Organ Transplantation**

The treatment of patients with end-stage HBV-related liver disease in the peritransplantation and posttransplantation period with nucleoside therapy in addition to hepatitis B immune globulin (HBIG) has improved the 5-year posttransplant survival of patients with hepatitis B from 40%-60% to 81% (Fig. 2). Between 1987 and 1991, the 5-year posttransplant survival of patients with hepatitis B averaged 50% (compared with 60%-65% among patients who underwent transplantation for other causes), and many centers considered hepatitis B to be a relative contraindication to liver transplantation. In the following decade, this attitude changed when outcomes improved as a result of use of high doses of HBIG and the introduction of lamivudine. Presently, outcomes and survival after liver transplantation are as good or better for hepatitis B as for other etiologies.

Thus, use of HBIG after transplantation, in combination with nucleoside analogs starting before or at the time of liver transplantation, is now considered the standard of care in managing patients with hepatitis B in order to prevent reinfection. A continuing controversy surrounds the optimal dose and duration of HBIG therapy, and which nucleoside analog or combination of these agents is preferable. There have been many studies of different regimens of HBIG with and without nucleoside analogs, but most have lacked concurrent controls and have been limited in size and duration of follow-up. These studies have been, nonetheless, informative and show that the presence and level of HBV DNA and antiviral resistance status immediately before transplantation are the major determinants of ultimate outcome and whether HBV will recur in the graft. In a prospective trial from Spain, patients with chronic hepatitis B and relatively low levels of HBV DNA were randomized to receive both HBIG and lamivudine indefinitely or for a limited period after undergoing transplantation, after which lamivudine alone was continued. The recurrence rate was similar for the nine patients who received both HBIG and lamivudine long-term as for the 20 patients who stopped HBIG after 1-18 months (the actual duration of HBIG prophylaxis varied). Four patients had HBV recurrence, three of whom were believed to have been noncompliant with taking lamivudine.

The pretransplant level of HBV DNA and presence of antiviral resistance mutations have been shown to correlate with the amount of HBIG needed to reach protective levels of antibody to hepatitis B surface antigen (anti-HBs) in the perioperative period and with the risk of HBV recurrence. In a study from Australia of 147 patients undergoing liver transplantation for chronic hepatitis B and receiving lamivudine and HBIG prophylaxis, reinfection of the graft occurred only in five patients at 6-19 months after transplant, all of whom had developed lamivudine-resistant strains of HBV. An additional eight patients had lamivudine-resistant strains of HBV at the time of transplantation, and reinfection was prevented by combination therapy of lamivudine, adefovir, and HBIG. Posttransplant anti-HBs titers were lower in patients with higher levels of HBV DNA at the time of transplant, and lower titers were associated with HBV recurrence. In those patients with undetectable HBV DNA (<300 copies/mL) at 1 year after transplant, combination therapy of lamivudine and adefovir appeared to allow for discontinuation of HBIG without increasing the risk of recurrence.

Thus, these findings together led to recommendations that patients at low risk of recurrence (HBV DNA <10,000 IU/mL) who have wild-type HBV are candidates for lower doses of HBIG and monotherapy with nucleoside analogs, whereas those with higher levels of HBV DNA (≥20,000 IU/mL) and/or with drug-resis-
tant HBV mutations should receive long-term HBIG and potent antivirals that target resistant virus.33

**Acute Hepatitis B**

Acute hepatitis B is not usually an indication for therapy because the majority of adults who develop acute infection recover spontaneously.34 In small randomized controlled studies of lamivudine35 and interferon36 therapy, a more rapid decrease in HBV DNA levels resulted but this had no effect on clinical outcome, which was largely benign. In small case series of severe acute or fulminant hepatitis B, lamivudine was well tolerated and safe and appeared to be associated with improved outcomes, at least as compared to historical controls.37,38 Despite the absence of randomized controlled trials demonstrating the benefit of nucleoside analog therapy for acute hepatitis B, these agents are usually recommended for patients with protracted or severe acute disease.6

**Pregnancy**

Pregnancy offers several challenges in making recommendations for therapy of hepatitis B. Interferon has antiproliferative actions and is considered contraindicated during pregnancy. The nucleoside analogs with activity against HBV have not been adequately evaluated in pregnant women, nor has their safety been proven (or disproven). Tenofovir and telbivudine are considered “Category B”, indicating that they have been found to be safe in animal models and there is limited data in humans, whereas lamivudine, adefovir, and entecavir are considered “Category C”, indicating that their safety has not been shown adequately either in animal models or humans. In pregnancy registries, there is extensive experience with use of lamivudine during pregnancy and no evidence for its teratogenicity or adverse effects on pregnancy (www.apregistry.com). Because of these concerns, patients on antiviral therapy for hepatitis B are asked to practice birth control. Nevertheless, the question arises about what to do if a young woman on therapy becomes pregnant or wants to become pregnant. In this situation, interferon should be stopped and therapy with nucleoside analogs either stopped or changed to agents that have at least some record of safety during pregnancy (such as lamivudine or telbivudine).

A second issue regarding therapy is use of antiviral agents to help prevent maternal-infant transmission of hepatitis B. Current recommendations are for all pregnant women to be screened for the presence of hepatitis B surface antigen (HBsAg) and that the children of the HBsAg-positive mothers receive prophylaxis using HBIG and HBV vaccine. The HBIG and first dose of vaccine should be administered within 12 hours of birth, and subsequent doses of vaccine given at 1 and 6 months of age.6 This regimen is effective in preventing transmission of hepatitis B in more than 95% of children. The 5% of children who fail to be protected by this regimen and develop hepatitis B are usually those who fail to receive the full regimen of vaccination, who fail to develop antibody (anti-HBs), or who are born to mothers with very high levels of HBV DNA (>8 Log10 IU/mL). These findings have led to the suggestion that HBsAg-positive mothers with high levels of viremia be given antiviral therapy during the last trimester in order to reduce the level of virus at the time of delivery, the time at which actual transmission is thought to occur. Several uncontrolled studies of this approach have suggested that lamivudine therapy may reduce the likelihood of transmission and, importantly, is safe both to the mother and the newborn. In a study from the Netherlands, eight women with high levels of HBV DNA (>10⁹ genome equivalents/mL) were treated with lamivudine during the last 6 to 40 days of pregnancy.39 Only one of eight children born to these mothers developed chronic hepatitis B, compared to seven of 24 historical controls with similar levels of HBV DNA. In a study from China, 12 women with HBsAg and HBeAg were treated with lamivudine starting during the first trimester of pregnancy, and none of their infants were infected during the first year of life. In comparison, among historical controls of children receiving HBV vaccine alone, 26%–36% of newborns were infected.40 In a second study from China, 56 HBsAg-positive pregnant women were given HBIG every 4 weeks from 28 weeks of gestation while 43 were given lamivudine and 52 were given no specific therapy. Transmission was assessed by testing newborns at birth, at which time 16% of treated versus 33% of untreated newborns were either HBsAg-positive or HBeAg-positive.41 Interpretation of these results is difficult because of the problems of sample contamination at birth and the lack of correlation between HBsAg-positivity at birth and subsequent transmission of infection. Finally, in a recently published randomized controlled trial from China,42 150 mothers with HBsAg and high levels of HBV DNA (>10⁹ genome equivalents/mL) were randomized to receive lamivudine or placebo from week 32 of gestation to 4 weeks postpartum. A high drop-out rate made interpretation of the results difficult, but three of 49 (6%) infants of mothers given lamivudine compared to five of 41 given placebo (12%) had evidence of HBV transmission at 1 year of age (P = 0.368). There were no obvious safety concerns and adverse events were similar in the two groups.

Thus, there are no convincing prospective controlled trials demonstrating the benefit of therapy of HBsAg-
positive mothers in reducing the likelihood of maternal-infant transmission, particularly when prophylaxis using HBIG and vaccination is applied to the newborn. The studies do indicate that lamivudine can be given safely during pregnancy. An important and still unresolved issue is whether this approach is safe for the mother, the major issues being posttreatment flares of disease and development of antiviral resistance because of use of a nucleoside analog with a low barrier to resistance in a patient with high levels of HBV DNA.

**HBV-HCV Coinfection**

Hepatitis C virus (HCV) shares many but not all risk factors with HBV, and thus coinfection with both viruses is not rare. In nonendemic areas, HBV-HCV coinfection is seen predominantly in injection drug users. In endemic areas, the frequency of HBV infection provides the basis for an appreciable rate of HBV-HCV infection in the general population. Overall, HCV coinfection is found in 7%-15% of persons with chronic HBV infection and is usually associated with more severe liver disease. In a cross-sectional study of 837 HBsAg-positive patients seen in 14 medical centers in Italy, antibody to HCV was present in 7%, but was most frequent in persons over the age of 50 (15%). Independent predictors of HBV-HCV coinfection were age greater than 42 years, history of injection drug use or blood transfusion, and residence in Southern Italy. A separate study from Italy on therapy suggested that higher doses of interferon were required for clearance of both viruses. Importantly, rates of response to therapy of hepatitis C were similar in individuals with HBV-HCV coinfection as in monoinfected individuals.

Viral interference occurs between hepatotropic viruses, and levels of viremia vary over time. Most commonly, HBV replication is inhibited by HCV as opposed to vice-versa. A study of 103 untreated HBV-HCV coinfect ed patients in Italy followed for 1 year with bimonthly evaluation showed that both HBV DNA and HCV RNA were detectable in 24 subjects, HBV DNA alone in 15, HCV RNA only in nine, and neither in 15 subjects. Importantly, 32 subjects had fluctuating levels of virus. An additional 30 patients had evidence of infection with three hepatitis viruses—HBV, HCV, and hepatitis D virus (HDV)—of whom 15 (50%) had detectable HBV DNA and/or HCV RNA and eight (27%) had fluctuating levels over the year of evaluation. Treatment of both infections with peginterferon alfa-2a (180 μg/week) and ribavirin was attempted in a study of 161 patients with coinfection from Taiwan. Among 97 coinfected patients with HCV genotype 1 treated for 48 weeks, 72% had a sustained virological response, remaining HCV RNA negative at least 6 months after stopping therapy. Among 64 coinfect ed patients with HCV genotype 2 or 3, 83% had a sustained virological response, rates that were similar to those in monoinfected patients with chronic hepatitis C. In addition 11% of patients became HBsAg-negative and thus, in a small proportion, therapy was effective for both infections. Therefore, HBV coinfection does not appear to affect response rates to therapy of hepatitis C. Whether HCV coinfection affects rates of response to hepatitis B is unclear, but there is no evidence that HBV suppression with nucleoside analog therapy is affected by concurrent HCV infection. It may be advisable to attempt to treat hepatitis C (with peginterferon and ribavirin) before embarking on long-term nucleoside analog therapy of hepatitis B.

**HBV-HDV Coinfection**

Hepatitis D (delta) virus (HDV) only infects persons who have coincidental HBV infection. HBV-HDV infection is relatively common in Mediterranean areas and in South America where it is estimated to affect 5% of patients infected with HBV. Chronic HDV infection is less common in the United States and Northern Europe where only 1% of HBV-infected individuals also carry HDV infection. HDV coinfection is associated with more severe disease with a higher incidence of cirrhosis. A Taiwanese study of acute HCV or HDV in patients infected with HBV followed for as long as 20 years showed that one-third of coinfect ed patients developed hepatic decompensation with a mortality of 10% in HCV-coinfected and 7% in HDV-coinfected patients. Cirrhosis developed in 48% of the patients who were HBV-HCV coinfect ed compared to 21% of those who were HBV-HDV coinfect ed. But 23% of patients in both groups lost HBsAg by 20 years. These results were in contrast to an Italian study in which cirrhosis was found in 15% of patients with HBV monoinfection, compared to 43% of patients coinfect ed with HBV-HDV, and 29% of patients coinfect ed with HBV-HCV. In one study, therapy with high doses of interferon for 48 weeks improved survival in adults, but in another study it was not beneficial in children. More recently, 12 patients with chronic hepatitis D received peginterferon alfa-2b for 48 weeks. Six months later, undetectable HDV RNA and normal ALT were noted in 17%. However, in those who did not achieve a 3 log₁₀ decrease in HDV RNA levels by month 6, no patient had a lasting response (negative predictive value was 100%). Liver histology improved in responders compared with nonresponders at the end of follow-up (13.5 versus 8.0; P < 0.02). A study of 38 patients evaluated the utility of addition of 24 weeks of ribavirin with peginterferon alfa-2b for 72 weeks. Addition of ribavirin was not beneficial and almost 30% of
patients stopped therapy early because of toxicity. Overall, 20% of patients had undetectable levels of HDV RNA at follow-up. Several studies have shown that lamivudine has little effect on HDV infection, suppressing levels of HBV DNA but not of HDV RNA and having limited effect on serum aminotransferase levels or histology.54 Thus, patients with HDV-HBV coinfection are more likely to develop cirrhosis than those with HBV monoinfection, and require therapy directed primarily at HDV infection.

**Children**

Children with chronic hepatitis B often have mild and asymptomatic disease with minimal ALT elevations despite high levels of circulating HBV DNA. This virological pattern of minimal disease with high levels of HBV DNA and HBeAg in serum is usually referred to as the immune-tolerant phase of infection. Therapy of patients with immune-tolerant patterns of HBV infection is usually ineffective in inducing sustained clearance of HBV DNA or HBeAg.55 In contrast, in children with active disease (high levels of ALT and active histology), both alpha interferon and several nucleoside analogs have been shown to be effective in inducing loss of HBeAg, normalization of serum ALT levels, and improvements in liver histology.56–58 In a study of interferon alfa-2b given for 24 weeks, 26% of children became HBeAg-negative and 10% HBsAg-negative compared to 11% and 1% in untreated controls.58 In a study of lamivudine given for 48 weeks to HBeAg-positive children with ALT >1.3 upper limit of normal with inflammation on liver biopsy, 23% became HBeAg-negative and 2% became HBsAg-negative compared to 13% and 0%, respectively, without therapy.59 Mutations in the YMDD region of the HBV polymerase gene indicative of lamivudine resistance developed in 19%-24% of children after 12 months, in 49%-59% after 24 months, and in 64% after 36 months of lamivudine therapy.

Whether therapy of hepatitis B in childhood results in lasting improvement in outcomes or prevents cirrhosis has not been proven. The natural history of hepatitis B in children appears to be complex. In a study from Italy, long-term follow-up (median 12.1, range 5-23 years) of 67 untreated children with chronic HBV infection found that the majority continued to have mild or inactive disease for many years and that the children with active disease often lost HBeAg spontaneously with subsequent maintained improvement in disease activity55 (Fig. 3). Only rare children developed cirrhosis and none exhibited end-stage liver disease, required liver transplantation, or developed HCC during the period of follow-up. Of course, chronic HBV infection can be a lifelong disease, and the clinically important outcomes (cirrhosis, HCC) of infection in childhood are expected to arise largely in adulthood.

In summary, these studies taken together indicate that children who have active and potentially severe disease on examination of liver biopsy warrant therapy. Children with mild or inactive disease can be monitored without treatment, reserving therapy for children in whom the disease becomes active or when evidence of more severe hepatitis arises. Because of the possible requirement for

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**Fig. 3.** Long-term outcomes after a 24-year follow-up of 67 untreated children with chronic HBV infection.55 Initially, 62 children were HBeAg-positive and five were HBeAg-negative. Outcomes are shaded in blue and described as inactive (HBeAg-negative with low or undetectable HBV DNA); resolved (HBsAg-negative, positive antibodies to hepatitis B surface and core antigens); or continuing chronic hepatitis B, with or without HBeAg. Seven HBeAg-negative children had unusual findings: four had normal ALT values but were persistently HBV DNA positive, while three had mild ALT elevations but no detectable HBV DNA. No child developed end-stage liver disease or hepatocellular carcinoma. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
long-term therapy with nucleoside analogs, these agents should not be started in children without careful assessment of the need for therapy.

Chronic Renal Failure

Patients with chronic renal failure are at increased risk of acquiring hepatitis B as a result of nosocomial infection or exposure to blood and blood products. Furthermore, patients with renal insufficiency may be more likely to develop chronic infection once exposed to HBV. Chronic HBV infection is not uncommon among patients with end-stage renal disease and those on dialysis.\textsuperscript{60} Introduction of risk management has led to a decrease in the prevalence of HBV infection in dialysis patients (currently reported at 0%-10%). However, the presence of HBV infection is associated with decreased survival after renal transplantation and more frequent need for retransplantation.\textsuperscript{60} Vaccination to HBV is recommended in all dialysis patients, but renal failure is associated with a poor response to HBV vaccination.\textsuperscript{61} Lamivudine,\textsuperscript{62} adefovir,\textsuperscript{63} and entecavir\textsuperscript{14} have been used successfully in patients with chronic hepatitis B on dialysis or after renal transplantation, although antiviral resistance in this situation may be common. Dose modification of all nucleosides is required in patients with renal insufficiency. HBV-associated glomerulonephropathy has been treated in one randomized controlled study with interferon therapy\textsuperscript{64} and in cases with lamivudine\textsuperscript{65,66} or adefovir.\textsuperscript{67} A combined analysis of six clinical trials (84 unique patients) of antiviral therapy of glomerulonephritis due to HBV found that 65% of patients had remission of proteinuria.\textsuperscript{68} There are only case studies of HBV-related polyarteritis nodosa using nucleoside therapy, and therapy had limited success.\textsuperscript{69}

Thus, antiviral therapy is warranted in patients with renal insufficiency, but its overall long-term effect in changing the outcome of HBV infection has not been shown. In treating patients with renal disease, careful attention to dose modification is necessary; agents with a high barrier to resistance should be used.

Needs for Future Research

Recommendations for management and therapy of hepatitis B among special populations are largely based on small, often uncontrolled, short-term studies. Careful cohort studies in these populations and comparisons of different approaches to therapy are warranted. Areas of particular challenge and questions for the future include:

1. In patients with advanced hepatitis B (bridging fibrosis or cirrhosis), is de novo combination therapy with nucleoside analogs superior to monotherapy, particularly in view of the availability of newer, more potent agents with higher barrier to resistance?

2. In patients who have undergone liver transplantation for hepatitis B, when can HBIG be stopped? Which patients can be managed with nucleoside analogs alone? Are the newer, more potent antivirals sufficient as monotherapy and in which patients?

3. In a pregnant woman with high levels of HBV DNA in serum, should antiviral therapy be used in the third trimester to decrease the likelihood of maternal-infant transmission? Which agent should be used, starting at what time and at what level of HBV DNA?

4. In children with mild hepatitis B or the immune-tolerant phase of infection, is therapy with the newer, more potent nucleoside analogs effective in altering the outcome of infection? Is such therapy safe?

5. In children with active forms of hepatitis B, what criteria should be used to recommend therapy and which regimen is optimal for which child or with which HBV genotype? Is long-term therapy with nucleoside analogs safe and can monotherapy be used without concern about ultimate development of antiviral resistance?

6. Better therapies are needed for HDV infection that specifically target steps in HDV replication.

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