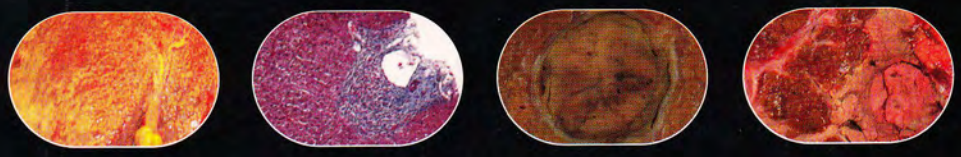

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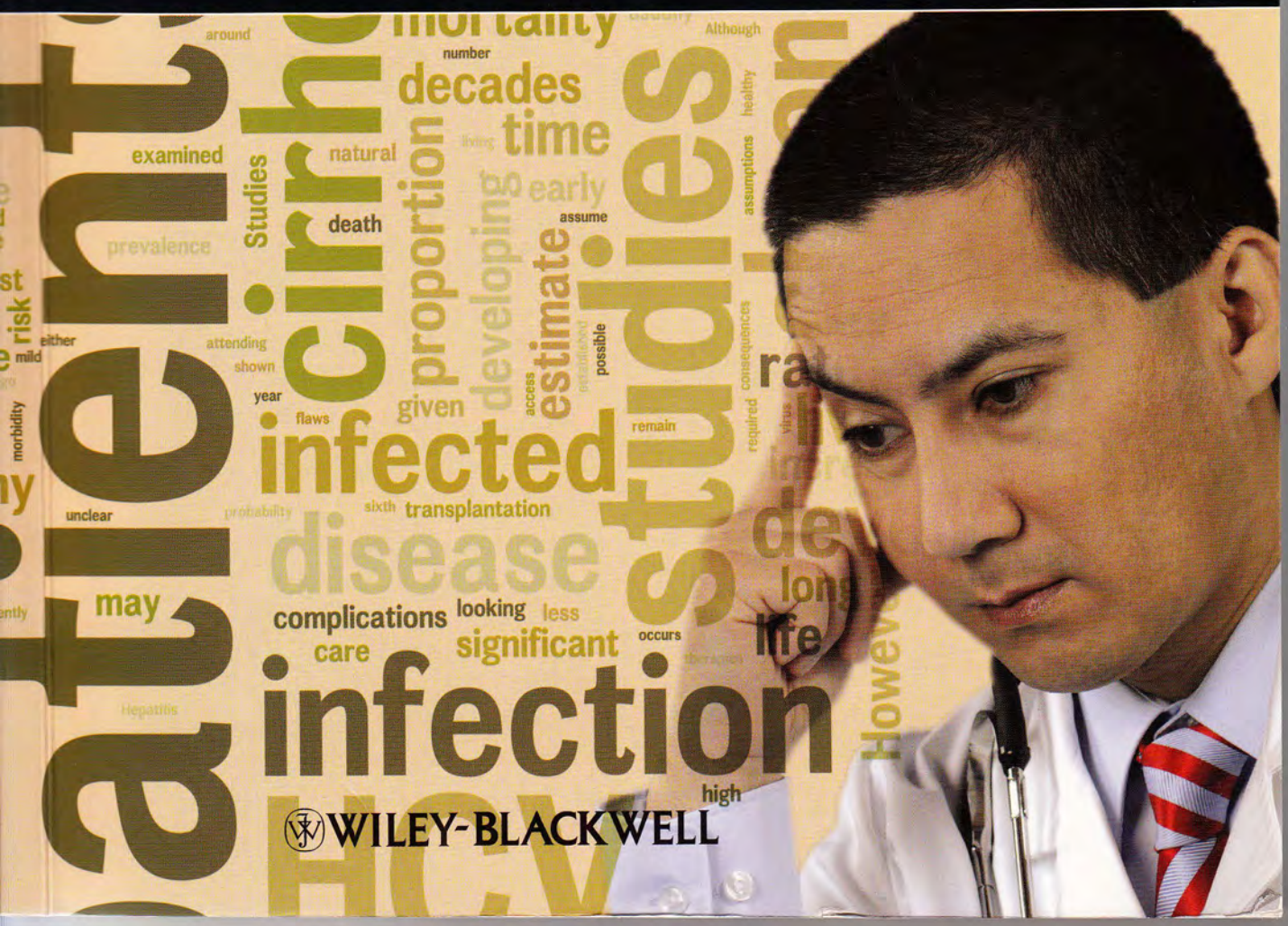

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26 Management of acute HBV

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LEARNING POINTS

- The management of acute HBV infection is controversial.
- There are some data suggesting that nucleoside analogues may be beneficial and may help to prevent progression to liver failure and evolution to chronic hepatitis B. However, the evidence is fragmentary at present.
- The value of therapy with direct-acting antiviral agents in fulminant hepatitis B in order to resolve liver failure and/or in anticipation of liver transplantation is controversial.

Introduction

Most cases of acute hepatitis B virus (HBV) infection in the developed world and other non-endemic countries develop in patients from high-risk groups, such as those who use intravenous drugs or who are sexually promiscuous, as well as in those who are not vaccinated and who live in communities with a large proportion of immigrants from regions where HBV is endemic such as the Indian subcontinent or the Far East. The majority of children with newly diagnosed HBV are immigrants, have immigrant parents, or become exposed through other household contacts [1]. Vaccination programmes have the potential to substantially reduce the frequency of acute and fulminant hepatitis B, and the consequent progression to chronic disease [2]. However, despite vaccination programmes, patients with acute HBV infection continue to present and their management remains challenging.

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Clinical manifestations and natural history

Acute HBV infection has a variable course, ranging from asymptomatic infection to fulminant hepatitis. Fulminant hepatitis is defined as encephalopathy developing within 8 weeks of the onset of jaundice [3]. Approximately 70% of patients with acute hepatitis B have subclinical or anicteric hepatitis, while 30% develop jaundice. Fulminant hepatitis develops in only 0.1–0.5% of patients and is believed to be due to massive immune-mediated lysis of infected hepatocytes. This explains why some patients with fulminant hepatitis B were thought to have no evidence of HBV replication at presentation [4]. Survival without liver transplantation in fulminant hepatitis B has been found to be 17–47% [5–7]. Survival rates following liver transplantation have not been studied in patients with fulminant HBV infection alone, but appear to be much in keeping with those transplanted for other conditions, with 5-year survival being approximately 75% [8]. The rate of progression from acute to chronic hepatitis B is primarily determined by the age at infection, being approximately 90% for perinatally acquired infection, 20–50% for infections acquired between the ages of 1 and 5 years, and less than 5% for adult-acquired infection. Treatment of the acute infection has traditionally been supportive and symptomatic.

Rationale for use of antivirals

The rationale for treatment of fulminant hepatitis B with antiviral therapy is to improve liver function and to prevent death or the need for liver transplantation. In acute hepatitis B, the rationale is to prevent progression to acute liver failure or transition to chronic infection and disease. Early studies of HBV replication in fulminant liver disease suggested that replication stopped after the development of

encephalopathy in the majority of cases [9–11], but these studies used HBeAg and insensitive HBV DNA assays. Later studies have used sequential measurements of HBV DNA and more sensitive assays and have showed that progression to chronic HBV infection is characterized by high levels of viral replication appearing early during the acute phase of infection [12] and that faster HBV DNA doubling time during the early infection predicts more severe disease [13].

Fulminant hepatitis B

Early reports of the use of lamivudine to treat acute severe hepatitis B took the form of case reports and small series. The case reports suggested that lamivudine reduced viral load in acute HBV [14,15] and small series of lamivudine therapy in acute severe hepatitis B were similarly hopeful. Schmilovitz-Weiss *et al.* [16] found that encephalopathy disappeared within 3 days of treatment and coagulopathy improved within 1 week. Serum HBV DNA was undetectable within 4 weeks, and serum liver enzyme levels normalized within 8 weeks. HBsAg became undetectable in all tested patients and the authors concluded that lamivudine may prevent the progression of severe acute disease to fulminant or chronic hepatitis and should be considered in selected patients. Tillmann *et al.* [17] reported that use of lamivudine resulted in greater survival without liver transplantation compared with historical controls (82.4 vs. 20%; $P < 0.001$).

More recently, Miyake *et al.* [18] published a retrospective cohort study of 33 patients with fulminant hepatitis B; 10 patients received lamivudine, 23 did not. Baseline characteristics were similar in the two groups. Using a multivariate Cox proportional hazard model the following factors were associated with a fatal outcome: age over 45 years ($P = 0.009$), systemic inflammatory response syndrome ($P = 0.025$) and non-administration of lamivudine ($P = 0.036$). Patients receiving lamivudine had an overall survival of 70% compared with 26% in those who did not receive it [18].

To date there has been only one randomized controlled trial of lamivudine to treat acute hepatitis B, performed by Kumar *et al.* [19]. The group studied 31 patients randomized to receive lamivudine 100 mg daily for 3 months compared with 40 randomized to receive placebo. Baseline characteristics including HBV viral load were similar in both groups, and similar numbers were classified as having 'severe' hepatitis, although the definition of severe was not given. At week 4, HBV DNA levels were significantly lower in the lamivudine group ($P = 0.037$), but thereafter there was no difference between the two groups. There was also no difference in loss of HBsAg at 1 year. There was a slightly lower rate of development of protective anti-HBs in the lamivudine group (67.7%) compared with the placebo group (85%) but this was not significant ($P = 0.096$). No mortality was observed in either group, and there was no significant difference in the clinical outcome between the groups.

Poor prognostic criteria for severe acute hepatitis B have been identified by O'Grady *et al.* [20] and Bernuau *et al.* [5] and these allow stratification of patients into high- and low-risk groups.

- O'Grady: age > 40 years, jaundice to encephalopathy time > 7 days, bilirubin > 17.65 mg/dL (300 μmol/L), prothrombin time > 50 s.
- Bernuau: age > 40 years, cerebral oedema, bilirubin > 15 mg/dL (255 μmol/L), prothrombin time > 25 s more than control.

We cannot directly compare the patients in Kumar's study against these criteria as the details are not published for each individual patient in the trial. However, the summary data for the trial patients are reproduced in Table 26.1 and it can be seen that the median and mean data for these

TABLE 26.1 Baseline characteristics of patients in randomized trial of lamivudine.

Group	Mean age (years)	Median age (years)	Mean INR	Mean bilirubin (mg/dL)	Median bilirubin (mg/dL)
Lamivudine ($N = 31$)	37.2	35	2.0	10.9	1.68
Placebo ($N = 40$)	36.4	36	1.89	12.3	1.74

Source: based on data from Kumar *et al.* [19].

patients do not reach the poor prognostic criteria defined by O'Grady and Bernuau. Thus, the majority of patients reported by Kumar suffered disease with a good prognosis. Under these circumstance, the survival rate in the non-treated group was predictably excellent, and treatment with lamivudine could not be expected to enhance survival in such a cohort. Larger studies that include patients with more severe acute liver disease would be required to examine the putative survival benefit of antiviral therapy in this setting.

Miyake *et al.* [18] argue that the better results seen in their cohort study may be related to the early reduction of viral load in the lamivudine group, preventing the development of systemic inflammatory response syndrome, and it has been shown that systemic inflammatory response syndrome is a poor prognostic marker in fulminant hepatitis B [7]. There is thus evidence that lamivudine in fulminant hepatitis B may improve outcomes, but its use in all cases of acute hepatitis B cannot be recommended.

Prevention of chronic infection

In renal dialysis patients recently infected with HBV, there is a much higher rate of progression to chronic hepatitis, approximately 30–60% [21,22]. Progression to chronic HBV infection is predicted by high peak levels of viral replication and higher peak HBeAg levels [12] and persistence of HBeAg during the acute phase [23]; thus it is tempting to use lamivudine (or other antiviral agent) to try to reduce the viral load and thereby risk of progression to chronic disease in these patients. At present, although there have been some case reports [15], there are no rigorous trials of lamivudine in HBV-exposed dialysis patients and routine use therefore cannot be recommended.

Another group with higher progression to chronic carriage of hepatitis B following acute exposure are immunosuppressed individuals, such as transplant recipients. Data on the use of lamivudine in these groups are similarly very scarce. In a study of 12 patients with *de novo* HBV infection after liver transplantation given lamivudine, 43% became HBsAg negative and negative for HBV DNA by PCR, although viral resistance occurred in 27% [24]. There are, unsurprisingly, no randomized controlled trials in this area. As patients would require lifelong prophylaxis to prevent possible reactivation of HBV in any case, use of nucleoside or nucleotide analogues in acute infection would seem sensible.

Summary

There are data to encourage the use of lamivudine in fulminant HBV and in acute HBV infection of immunosuppressed patients such as transplant recipients, although the data remain patchy. There is no evidence to show that lamivudine is harmful in these settings, so clinicians may choose to use lamivudine for patients with severe acute hepatitis and in the immunosuppressed. Larger studies would be useful, but studies may be difficult to design and conduct. The value of agents other than lamivudine in these settings remains untested and whether the third-generation antivirals with enhanced efficacy and lower resistance profiles will prove to be more effective remains to be determined.

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27 Rethinking the inactive carrier state: management of patients with low-replicative HBeAg-negative chronic hepatitis B and normal liver enzymes

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LEARNING POINTS

- The inactive carrier state is characterized by persistence of HBsAg, absence of HBeAg, low level or absence of HBV DNA, and normal liver function tests.
- ALT can fluctuate widely during the course of chronic HBV infection and therefore serial ALT assessments are required for the correct diagnosis of the inactive carrier state.
- There is a small yet significant increased risk of progressive liver disease, cirrhosis or hepatocellular carcinoma with even the lowest levels of HBV viraemia.
- Individuals with low-level replication (< 2000 IU/mL) should be classified as having low-replicative HBeAg-negative chronic hepatitis B.

Introduction

With nearly 400 million people infected, hepatitis B virus (HBV) is the leading cause of chronic liver disease worldwide. The clinical spectrum of chronic hepatitis B (CHB) ranges widely from subclinical disease to active hepatitis, hepatocellular carcinoma (HCC) and decompensated cirrhosis [1]. Many infected individuals are said to exist in the *inactive carrier state*, characterized by persistence of the hepatitis B surface antigen (HBsAg), low-level or undetectable HBV DNA, normal serum alanine aminotransferase (ALT) and minimal histological disease activity [2].

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Historically, these individuals were referred to as 'healthy' or 'asymptomatic' carriers, which erroneously implied a durable absence of HBV replication or the potential for clinically significant liver disease. Consequently, clinical attention and research on this large CHB population was limited. With improved molecular diagnostic testing, it is clear that the inactive carrier state encompasses a heterogeneous population of patients, including those who are truly inactive and those with low-level viral replication. Moreover, the term 'inactive carrier state' belies the fact that longitudinal natural history studies demonstrate a small but significant risk of progressive liver disease in patients with low-level viraemia, suggesting that these individuals are better classified as having low-replicative HBeAg-negative CHB. In this chapter, we review the natural course of the inactive carrier state and use it as a framework to appraise current management guidelines.

Natural history of chronic HBV infection

From natural history studies, four distinct phases of HBV infection have been defined [3]. During the *immune-tolerant phase*, individuals are asymptomatic, HBeAg is detectable, HBV viral titres are markedly elevated, serum ALT levels are normal or marginally elevated, and histological activity is minimal. Transition to the *immune clearance phase*, or perhaps more descriptively the *immune clearance phase* (HBeAg-positive CHB), is characterized by fluctuations in the ALT and HBV DNA titre with necroinflammatory injury observed on liver biopsy. This phase is highly variable in duration, with persistent injury resulting in progressive necroinflammation and fibrosis.

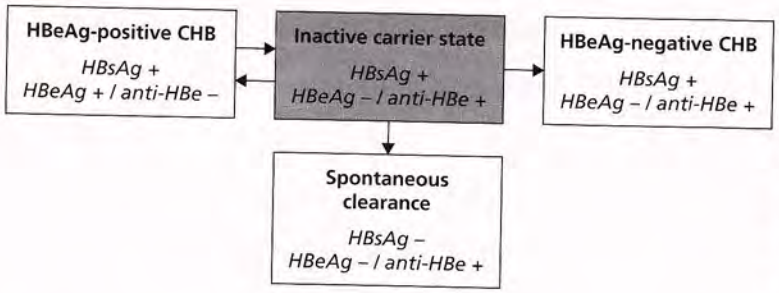

FIG. 27.1 Dynamic nature of the inactive carrier state with potential for reversion to HBeAg-positive hepatitis, spontaneous loss of HbsAg or, more frequently, reactivation to HBeAg-negative chronic hepatitis.

The end of this phase is characterized by HBeAg seroconversion (loss of HBeAg and formation of anti-HBe) and passage into the *inactive carrier state*, a low-replicative phase of chronic HBV infection characterized by the presence of HBsAg and anti-HBe in serum, absence of HBeAg, persistently normal ALT, and markedly reduced (< 2000 IU/mL) or undetectable HBV viral DNA. The inactive carrier state is a potentially dynamic phase in the natural history of chronic HBV infection (Figure 27.1) with the capacity for reversion to HBeAg-positive hepatitis, spontaneous loss of HBsAg or reactivation to *HBeAg-negative chronic hepatitis*, featuring populations with a preponderance of precore and/or core promoter mutations.

Serological and biochemical testing

Serologically, the inactive carrier state is indistinguishable from HBeAg-negative chronic HBV infection; both conditions are characterized by the presence of HBsAg in the serum for at least 6 months, HBeAg negativity and detectable anti-HBe antibodies. These two phases of HBV infection are distinguished by the level of viral replication and the degree of biochemical activity. Recently, the American Association for the Study of Liver Diseases (AASLD) guidelines and a US expert panel algorithm for the treatment of CHB have published updated criteria to better define the inactive carrier state (Table 27.1) [3,4]. Both groups require a single baseline HBV DNA of less than 2000 IU/mL, accompanied by a persistently normal ALT using the recently adopted values for healthy men (< 30 IU/mL) and women (< 19 IU/mL) [5]. Since ALT can fluctuate widely during the course of HBeAg-negative CHB, with long periods of biochemical inactivity [1,2,6], it follows that ALT should be serially assessed every 3 months for the first year to ensure correct identification of inactive disease and every 6 months thereafter to identify reactivation.

TABLE 27.1 Diagnostic criteria for the inactive carrier state of chronic HBV infection.

HBsAg: seropositive for at least 6 months
HBeAg: seronegative
Anti-HBe antibody positive
Persistently normal ALT (≤ 30 IU/mL for men, ≥ 19 IU/mL for women)
Undetectable or low-level HBV DNA (< 2000 IU/mL)
Liver biopsy* findings with minimal activity (necroinflammatory score < 4) and scant fibrosis

* Liver biopsy optional; may be beneficial in indeterminate cases or individuals at risk for progressive liver disease.
Source: adapted from Lok *et al.* [4] and Keeffe *et al.* [3].

Viral load testing

Multiple studies from Asia [7,8] and Europe [5,9–11] have unsuccessfully attempted to identify a baseline viral DNA that reliably distinguishes the inactive carrier state from HBeAg-negative CHB. In 2001, a serum HBV DNA level less than 10^5 copies/mL (20 000 IU/mL) was proposed at the National Institutes of Health workshop to differentiate these two phases of chronic HBV infection [2]. This value reflected the lower detection limit of early non-PCR-based assays rather than patient epidemiological data and has now been replaced by a more stringent value (< 2000 IU/mL) in the newest AASLD and US expert panel treatment guidelines [3,4]. Serial HBV DNA testing has been shown to improve the classification of inactive disease [7,8,11] and accordingly some guidelines advocate serial HBV DNA testing to ensure that the inactive state is maintained [3,12] and when ALT elevations are noted or clinical suspicion of reactivation is raised.

Prognosis

Longitudinal studies of the inactive carrier state are plagued by heterogeneity, both in the diagnostic criteria used to define the state and in the demographic features of the study population. Accordingly, the reported rates of progression to HBeAg-negative CHB or decompensated liver disease vary widely. Although the literature demonstrates that most individuals will have an excellent long-term prognosis, nearly one-third of individuals will progress to active chronic infection. Moreover, most studies demonstrate a small but significant risk of developing cirrhosis or HCC, validating the need for regular follow-up and monitoring.

The long-term outcome of a cohort of 283 Taiwanese patients with well-documented spontaneous HBeAg seroconversion has been described [13]. After a median follow-up of 8.6 years (range 1–18.4), 189 (67%) maintained a sustained remission of the inactive carrier state; 94 (33.2%) relapsed to active hepatitis: 12 (4.2%) reverted to HBeAg-positive CHB, 68 (24%) to HBeAg-negative CHB and 14 (5%) were indeterminate. Patients with pre-existing cirrhosis (4.9% of the total cohort) at time of seroconversion had a 10-fold increased risk of developing HBeAg-negative CHB and a 12-fold risk of reverting to HBeAg-positive CHB compared with patients without significant fibrosis on liver biopsy. Of the 269 patients without pre-existing cirrhosis, 21 (7.8%) developed cirrhosis after seroconversion: 5 of 9 (55%) with reversion to HBeAg-positive CHB, 14 of 62 (23%) with HBeAg-negative CHB, 1 of 14 (7%) with active hepatitis of indeterminate cause, and 1 of 184 (0.5%) with sustained maintenance of the inactive state. Six patients developed HCC 5.3–14.3 years after seroconversion, with an annual incidence of 0.2%: three cases (1.6%) were in long-term inactive carriers and three (4.4%) in patients who reverted to HBeAg-negative CHB.

The same group recently described the risk of relapse to active hepatitis and development of cirrhosis or HCC in a large study of 1965 'asymptomatic' HBsAg-positive blood donors in Taiwan [14]. Relapse to HBeAg-negative CHB occurred in 314 patients. The cumulative rate of relapse was approximately 22% after 25 years of follow-up, with more than 85% of relapse occurring in the first 10 years after enrolment and an annual relapse rate of 1.55%. Men were 2.5 times as likely to relapse as women ($P < 0.0001$). A total of 57 patients developed sonographic or clinical evidence of cirrhosis: 10 of 1651 inactive carriers (0.6%) and 47 of 314 relapsers (15.97%). The risk of developing cirrhosis was increased in those with advanced age at study entry, male gender, and reactivation to HBeAg-negative chronic hepatitis.

Recently, a cohort of 61 treatment-naive HBeAg-positive Italian patients followed prospectively for more than 20 years after seroconversion to HBeAg-negative CHB has been described [15]. The majority of individuals ($N = 40$, 66%) transitioned to the inactive carrier state with sustained normalization of ALT and undetectable HBV DNA by non-PCR-based detection methods; 21 individuals (34%) progressed to HBeAg-negative active hepatitis. Eleven patients in the cohort had pre-existing cirrhosis at the time of seroconversion. Among the cirrhotics, there was a higher prevalence of progression to HBeAg-negative CHB than transition to the inactive carrier state (50% vs. 17.5%; $P = 0.04$). After a median of 13.8 years (range 1.1–26.9), 18 (45%) of the inactive carriers lost their HBsAg, yielding an HBsAg loss rate of 2.1 per 100 person-years. The cumulative probability of survival at 25 years was significantly lower in the patients who progressed to chronic hepatitis (50%) compared with those who remained in the inactive carrier state (95%) ($P < 0.0001$), and the risk of orthotopic liver transplantation or liver-related mortality was 38-fold higher in those with reversion to CHB compared with those in sustained remission. Despite this excellent prognosis, two individuals (both with pre-existing cirrhosis) in the inactive carrier state developed HCC 7.7 and 9.4 years after seroconversion. Conversely, there were no cases of HCC or liver-related death in the 33 non-cirrhotic inactive patients. As seen in the Asian studies, male gender, older age, presence of cirrhosis and absence of sustained remission were all predictors of increased liver-related mortality.

Liver biopsy

The HBeAg-negative inactive carrier state is defined by ALT and viral load. Under current treatment guidelines (Table 27.1), liver biopsy is an optional assessment reserved for individuals at risk for progressive liver disease or in cases of indeterminate disease activity. However, it is well established that ALT and HBV DNA are imperfect surrogates for determining liver activity and fibrosis. Histological evaluation may therefore be a useful adjunct in selected individuals.

Nguyen *et al.* [16] demonstrated that up to one-third of patients with persistently normal ALT, particularly those over age 35, have significant liver activity on biopsy. Kumar *et al.* [17] evaluated 116 HBeAg-negative patients with

persistently normal ALT. Of the 58 patients who underwent liver biopsy, the median histological activity index (HAI) and fibrosis scores were 3.0 (1.0–10.0) and 1.0 (1.0–3.0), respectively. Overall, 13.8% had histological evidence of significant fibrosis (stage ≥ 2). Of the patients with a viral load less than 10^5 copies/mL (≤ 20 000 IU/mL), 21% had histologically active liver disease with HAI 3 or more and/or stage 2 or greater fibrosis. Only a small subset of patients with persistently normal ALT and low viral load (< 2000 IU/mL) underwent liver biopsy (9 of 52, 17.3%). However, two of these 'inactive' patients (22.2%) were subsequently found to have active liver disease on biopsy (HAI ≥ 3 and/or ≥ stage 2 fibrosis). Even when the data were reanalysed using the updated norms for ALT (30 IU/mL for men, 19 IU/mL for women), ALT and HBV DNA were inaccurate in distinguishing histologically active and inactive disease. Despite this cautionary report, there is insufficient evidence at this time to recommend routine liver biopsy for low-replicative chronic HBV infection, although it might be considered on an individual basis (e.g. based on ALT or other laboratory parameters or imaging suggesting progressive disease, closeness of HBV DNA to the cut-off of 2000 IU/mL, age). Further histological studies are needed to better define the risk of active disease in low-replicative HBV infection.

Hepatocellular carcinoma screening

The risk of HCC in patients in the inactive carrier state is small. Most, but not all, cases of HCC arise in patients with pre-existing cirrhosis at the time of diagnosing inactive disease [13,15,18,19]. Most published guidelines [3,4,12] do not directly address the issue of HCC screening in the inactive carrier state. In our practice, screening of all adult carriers with periodic abdominal imaging and alpha-fetoprotein is performed despite the absence of proven cost-effectiveness in those with the inactive carrier state. This approach would seem to be supported by the recent report from the REVEAL study in which HBsAg-positive individuals with undetectable (< 300 copies/mL) or low-level viraemia (300–9999 copies/mL) had hazard ratios of 3.0 (1.4–6.3) and 3.3 (1.7–6.6), respectively, for developing HCC compared with HBsAg-negative controls [20,21].

Treatment and surveillance

Currently, patients who meet criteria for the inactive carrier state are not considered candidates for antiviral therapy [3,4]. However, they should be monitored throughout their lives for progression to HBeAg-negative CHB and for development of progressive liver disease.

Determination of HBV genotype and assessment for the presence of precore or basal core promoter mutations may prove useful for long-term surveillance. It has been shown that genotype C is associated with increased risk of reactivation to HBeAg-negative CHB and progression to cirrhosis [22,23]. Similarly, it has recently been suggested that the addition of the precore (A1896) and basal core promoter (T1762/A1764) mutations into treatment algorithms might assist in the identification of patients at risk for developing HCC [24]. Studies demonstrate that the precore mutation can be detected in 38–99% of patients in the 'inactive state' with detectable virus [17,22,25] and further research is needed to determine if this imparts increased risk of HCC in this population.

Patients should be counselled on lifestyle modifications, including abstinence from alcohol, weight loss and glycaemic control where relevant. Seronegative individuals should be offered vaccination against hepatitis A virus. The risk of transmission should be routinely discussed, and family members and household contacts should be vaccinated against HBV, if not already immune, even if the index patient is HBV negative. Patients in the inactive carrier state should be counselled on the risk of reactivation in the face of immunosuppression (chemotherapy, systemic steroids, anti-TNF-α treatments) and appropriate prophylactic antiviral therapy should be administered.

Summary

- Diagnosis of the inactive carrier state requires repeated assessments of ALT and HBV DNA over at least a 1-year period using the most stringent ALT cut-offs (30 IU/mL in men, 19 IU/mL in women) to truly differentiate from HBeAg-negative CHB.
- ALT and HBV DNA are imperfect surrogates for assessing liver disease; however, liver biopsy is not part of the routine assessment of the inactive carrier state. Histological evaluation may be considered for selected individuals with risk factors for progression, such as male gender, Asian ethnicity, age over 35, genotype C and possibly the presence of precore or basal core promoter mutations.
- Lifelong serial monitoring for prompt diagnosis of viral relapse and initiation of antiviral therapy for individuals

with progression to HBeAg-negative CHB (HBV DNA > 2000 IU/mL, elevation in ALT and/or active necroinflammatory histology on liver biopsy).

- Given the small but significant risk of progressive liver disease, cirrhosis and HCC, the term 'inactive carrier state' should be reconsidered and replaced with 'low-replicative HBeAg-negative CHB' for patients with low-level rather than undetectable HBV DNA.

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28 HBeAg-negative chronic hepatitis B infection with abnormal transaminases and minimal changes on liver biopsy

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LEARNING POINTS

- HBeAg-negative chronic hepatitis B infection with minimal histological damage has an uncertain prognosis.
- The benefits of therapy in patients with HBeAg-negative chronic hepatitis B infection and minimal histological damage are uncertain.
- Discussion of the risks and benefits of therapy is required to reach the correct management decision.
- If therapy is not introduced, long-term monitoring with regular review is mandatory.

Introduction

Chronic infection with hepatitis B virus (HBV) is usually associated with different phases of disease that change over time. For patients with HBeAg-negative infection two phases of disease are recognized: (i) 'inactive carriers', individuals with low-level HBV DNA (usually defined as < 2000 IU/mL) and normal liver function tests; and (ii) HBeAg-negative disease, patients with higher levels of HBV DNA (> 2000 IU/mL) and abnormal liver function tests [1]. Since patients with HBeAg-negative disease often have fluctuating disease, it is important to monitor patients with HBeAg infection regularly to avoid diagnostic errors. Management of patients in the 'inactive carrier' phase of infection usually involves periodic review without further intervention. For patients with HBeAg-negative disease who have significant liver disease on liver biopsy, management usually involves antiviral therapy with either peg-interferon or oral antiviral agents. However, many patients with HBeAg-negative disease present with moderately high levels of HBV DNA, fluctuating mildly deranged liver function tests and minimal changes on liver biopsy. The most appropriate management of such patients is unclear.

Natural history of HBeAg-negative disease with minimal histological activity and effects of therapy

The natural history of HBeAg-negative disease has been evaluated in a number of studies, chiefly from the Far East [2,3], where cohorts of patients were followed up for many years without therapy. Patients were assessed at the start of the study with virological and serological assays but a liver biopsy was not usually performed. These studies showed that people with relatively low levels of HBV DNA at presentation had an increased risk of developing liver disease in the medium term. However, since these studies did not assess liver histology at enrolment, it is unclear whether the risk of liver disease relates to viral load *per se* or to liver damage, which is most often associated with high levels of viral replication. Although these pivotal studies have often been used to argue for a policy of early therapy in all patients with moderate to high levels of viraemia, it is unclear whether reducing the viral load in patients with minimal histological activity will reduce progression of liver disease. It is clear that antiviral therapy in patients with advanced liver disease reduces the risk of liver decompensation [4]

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but whether this extends to those with minimal histological lesions is less well defined. Thus the outcome of disease in patients with minimal histological activity remains unclear and the benefits of therapy are unproven.

The case for early therapy

The data from cohort studies indicate that persisting medium- to high-level viraemia in patients with HBeAg-negative HBV is associated with an increased risk of liver disease. Since studies of antiviral therapy have shown that therapy may improve liver histology and reduce the risk of developing complications in patients with severe disease, it seems reasonable to presume that therapy in patients with persisting viraemia and minimal liver damage will confer long-term benefits. These benefits are likely to include a reduction in the lifetime risk of developing severe liver disease. If patients with minimal histological disease are not offered antiviral therapy, the risks of disease progression are such that long-term follow-up with regular monitoring of liver function tests and viral load is required. Most physicians would agree that liver biopsy should be repeated at regular intervals (perhaps every few years) and therefore avoiding therapy requires extensive follow-up with regular histological assessment. Such an approach is often unpopular with patients and retention in long-term follow-up of untreated cohorts has never been assessed but is likely to be low. Furthermore, reduction in viraemia in patients with HBV may reduce the risk of onward transmission, and in countries where universal vaccination is not practised or where uptake of the vaccine is poor it might be argued that early therapy may have public health benefits. Thus it can be argued that early therapy for patients with minimal histological damage reduces the risk of long-term liver damage, avoids repeat liver biopsy assessment and facilitates compliance as well as potentially reducing the risk of inadvertent transmission.

The case for delaying therapy

As noted above the studies completed to date by no means show unequivocal evidence of benefit in treating patients with minimal disease. Therapy in minimal disease requires a long-term commitment by the patient to take medication regularly and undergo frequent monitoring. For patients who choose to take interferon-based therapies, the side effects may be considerable [5]; for patients who choose oral antiviral agents, regular review with repeated blood tests over many years is required. For patients who choose to take oral antiviral agents there is a risk that in the long term drug-resistant mutations will emerge and reduce the efficacy of therapy. Although the oral drugs that are currently available to treat patients with HBV (e.g. entecavir and tenofovir) have an excellent safety record in the short term [6,7], their long-term safety in patients with HBV has not been determined and their effects on the developing fetus are currently unknown, although the available data does not give rise to any concerns. Thus treating patients with minimal disease exposes them to therapy with no proven benefits and an unknown risk of long-term complications, including viral resistance.

Expert opinion

Two international groups have recently compiled guidelines for the management of chronic HBV infection [1,8]. In view of the lack of high-quality evidence relating to the management of patients with minimal histological disease, it is not surprising to find that the two groups have reached slightly different conclusions. The American guidelines produced on behalf of the American Association for the Study of Liver Diseases (AASLD) [1] suggest that 'These patients generally should not be initiated on treatment but a liver biopsy may be considered in patients with fluctuating or minimally elevated ALT levels, especially in those aged over 40 years of age'. The guidelines suggest that 'treatment may be initiated if there is moderate or severe necroinflammation or significant fibrosis on liver biopsy'. The European guidelines [8] adopt a subtly different approach, recommending that 'patients with slightly elevated ALT (less than 2 times ULN) and mild histological lesions (less than A2F2 with METAVIR scoring) may not require therapy. Follow-up is mandatory'. Thus there is no clear consensus as to the most appropriate management strategy.

Suggestions for management

All clinical decisions require a discussion between the patient and the clinician and this dialogue is of particular importance where the evidence base is weak or equivocal. Patients with minimal histological damage and persistent moderate/high-level viraemia should be advised that therapy is of unproven value but that it is likely to reduce the

risk of long-term liver damage. The side effects of therapy and the risks of resistance should be discussed along with the differing advantages and disadvantages of oral therapy and interferon-based treatment regimens. In general, I usually advise young fertile women who are considering starting a family to defer therapy but to continue to undergo regular monitoring. For patients with a family history of liver disease, particularly those with a history of liver cancer, I usually advocate early therapy. For patients who have other risk factors for progressive disease (e.g. men over the age of 40) early therapy is probably the most appropriate option but for patients who have no risk factors that predispose them to advanced liver disease a policy of careful observation is appropriate, provided that the patient is willing to consider regular liver biopsies to monitor disease progression.

The choice of therapy in patients with mild early HBeAg-negative disease is not yet clear. Interferon-based therapies have the advantage of a short fixed course of therapy without the risk of long-term viral resistance. A small proportion of patients will undergo HBsAg seroconversion (effectively a virological cure) and thereby avoid long-term follow-up. However, interferon-based therapies are associated with a wide range of side effects and are often unpopular with patients. Oral therapy is convenient, has few immediate side effects but requires long-term medication with regular clinical review. The optimal therapy is best determined by a careful discussion with the patient.

The future

The management of chronic HBV infection is evolving rapidly. For patients with mild disease it is likely that long-term cohort studies will continue to define the groups at greatest risk of long-term liver damage and, as more sophisticated stratification of risk becomes possible, it is probable that management decisions will be based on the probability of developing liver damage. Studies are currently in progress to determine factors that predict the response to interferon-based therapy in patients with HBeAg-negative disease and it is likely that in the near future it may be possible to identify those patients who are likely to undergo HBsAg seroconversion. Therapy for such patients is likely to be recommended regardless of the histological damage at presentation. Until such studies have been completed and ratified by repetition, clinicians and their patients will continue to balance the risks and benefits of early therapy to maximize the gains.

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29 Combination therapy for chronic hepatitis B virus infection: should we use it *ab initio* or sequentially?

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LEARNING POINTS

- HBV is highly mutable and with drugs that have low genetic barriers to resistance, combination therapy is important to prevent the development of drug resistance.
- For drugs such as entecavir and tenofovir that have high genetic barriers to resistance, it is not clear whether combination therapy is required at the outset or whether treatment initiation followed by careful monitoring and introduction of a second agent in the absence of a virological response is appropriate.
- It is generally agreed that in patients at high risk of resistance, combination therapy should be considered at the initiation of therapy.

Introduction

Combination therapy for the treatment of chronic hepatitis B virus (HBV) monoinfection has been a hotly debated topic since the licensing of lamivudine expanded the HBV formularly from interferon alfa-based treatment. Early studies looking at the combination of peginterferon and lamivudine showed no significant added value of combination therapy over monotherapy [1]. Since then, a further six drugs have become licensed or are in clinical use (adefovir, telbivudine, clevudine, tenofovir, entecavir and emtricitabine), and their utility in combination continues to be considered in a range of clinical settings. For example, following the development of resistance to lamivudine, Italian studies demonstrated the superiority of continuing lamivudine in combination with adefovir rather than switching to adefovir alone [2]. This chapter outlines the issues surrounding combination therapy and summarizes the arguments for and against its use *ab initio* versus sequential introduction of antiviral agents. The debate is informed by the biology of viral resistance, the evidence (in particular its paucity), health economic considerations and lessons from the management of other infectious diseases such as tuberculosis and HIV.

Aims of treatment

In chronic HBV infection the ideal outcome from therapy is eradication of HBV, yet surface antigen seroconversion (in so far as it correlates with viral clearance) remains a rare event. Therefore the effective goal of therapy is to control viral replication and to prevent (and, where possible, reverse) the complications of chronic HBV infection, while minimizing side effects of therapy and avoiding the emergence of resistance to antiviral therapy. The emergence of resistant species is associated acutely with hepatitis flares and episodes of decompensation and in the long term with the progression of chronic liver disease and the development of hepatocellular carcinoma [3–5]. Use of the term 'treatment failure' to describe the emergence of resistant species is therefore not unreasonable.

The key to this control is in deciding whom to treat and when to commence treatment. Maximal benefit is gained in patients at risk of progression (male sex, African ethnicity,

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age, family history, advanced disease) who are in either the immunoactive or immunoescape phases of infection. However, once the decision to treat has been made, the treatment strategy should be designed to minimize the long-term consequences of viral resistance.

Treatment strategy

The lack of proofreading capability of HBV polymerase as well as the very large number of virions produced on a daily basis are important factors in the emergence and propagation of resistance genes. The mantra 'no replication equals no resistance' underpins the strategy that irrespective of whether treatment is with single agents or combinations of drugs, the rapid reduction of HBV DNA levels to undetectable levels is a key goal. Once a treatment has been instigated, regular monitoring is required for early detection of treatment failure.

A rise in alanine aminotransferase (ALT) to greater than twice the upper limit of normal on therapy after normalization is considered biochemical resistance; however, this is preceded by virological breakthrough where viraemia increases, usually by several logs, many weeks before the emergence of overt biochemical resistance. Primary treatment failure is defined as a failure to reduce viral load by 1 log IU/mL after 3 months' therapy and secondary failure as a rebound of greater than 1 log IU/mL from nadir on two occasions at least 1 month apart [6]. The viral mutations associated with resistance to each drug have been studied and can be detected in the clinical setting. Knowledge of so-called genotypic resistance is key to selecting the most appropriate treatment strategy and some advocate HBV DNA sequencing in all cases both before and during therapy, although the value and cost-effectiveness of this approach has not been demonstrated.

Strategies to lessen the risk of resistance include the use of interferon therapy (to which resistance does not develop) or an oral direct-acting antiviral agent that effectively suppresses viral replication and which has a high genetic barrier to resistance. To achieve these two aims many have proposed the use of *ab initio* combination therapy. However, common practice (and national/international society recommendations) has hitherto been to use a single agent and to add a second complementary drug when signs of treatment failure arise.

The logical combination of antiviral agents depends largely on the molecular biology of the resistance that develops to them. A viral mutation that confers resistance to one nucleotide analogue is likely to confer resistance to other drugs in that class, but unlikely to confer resistance to nucleoside analogues [7]. Therefore if resistance arises to a drug in one class, a drug from the other class (hence complementary) should be used and if *ab initio* combination is used, then the drugs should be complementary for the same reasons (see Chapters 33 and 38 for further details on complementary antiviral agents).

Sequential or *ab initio* combination?

The introduction of new direct-acting antiviral agents has been supported by a large body of evidence demonstrating safety and efficacy over existing therapeutic options. Unsurprisingly, most studies have been sponsored by pharmaceutical companies to address regulatory issues and, as such, most trials publish 1-year data with some subsequently extended up to 5 years. These data have informed our therapeutic choices but they do not answer the question as to whether treatment should start with monotherapy or combination therapy. Given the range of pharmaceutical companies involved and the very low rates of resistance with current agents, necessitating very large trials over very long periods of time, the studies needed to evaluate *ab initio* versus sequential combination therapy are unlikely to be conducted. In this era of evidence-based medicine, the absence of large randomized controlled trial data to support a management strategy can sometimes be taken as evidence for its ineffectiveness, although this is clearly not the case.

There are strong virological and economic arguments for initiating therapy with a single antiviral agent and only adding a complementary drug should treatment failure occur. Until the summer of 2007, lamivudine or adefovir were the only oral drugs available, and both are associated with high rates of resistance after 5 years' treatment (approximately 80% and 29%, respectively) [8]. However, sequential addition of adefovir to patients who have shown resistance to lamivudine results in effective suppression of viral load to undetectable in 72% of patients at 2 years [2]. This strategy also results in low rates of acquisition of new adefovir mutations (4% after 42 months) and this approach is the basis for the 'road-map' approach to therapy in which treatment is initiated with one drug and then changed to include additional agents if early virological control is not achieved. This concept is based on the fact that while resistance rates are high, treatment failure is not

universal and much evidence demonstrates that the addition of a nucleotide analogue usually rescues virological and biochemical breakthrough. The use of multiple drugs in series rather than in combination decreases the risk of adverse effects and if these do arise then the responsible agent is more readily identified. Although the road-map concept is theoretically attractive, it has never been tested in prospective studies and the definition of treatment failure is unclear.

The argument that supports the use of these drugs in combination *ab initio* is that combination therapy may achieve the goals of treatment more effectively than any single drug alone; in particular, combination therapy may be predicted to reduce the long-term risk from viral resistance. However, no randomized controlled trials have been conducted to test this hypothesis. In the absence of such evidence, many have turned to the lessons learned from HIV medicine over the past 25 years [9] and the management of tuberculosis over the past 50 years [10]. The development of resistance in HIV is rapid and the significant superiority of combination therapy over monotherapy was established very early after the drugs became available. However, HBV resistance occurs at a comparatively slow rate (over months and years versus days and weeks with HIV) and therefore the same rates of resistance have not been observed.

The results of a 2-year study comparing lamivudine monotherapy with lamivudine plus adefovir combination therapy in treatment-naive non-cirrhotic, predominantly Asian, patients demonstrate a degree of superiority of combination therapy over montherapy but are not as emphatic as advocates of combination therapy would have hoped [11]. HBV DNA levels were undetectable after 2 years' therapy in 26% of patients on combination therapy compared with 14% on lamivudine alone, and ALT normalized in 45% and 34% of patients respectively. However, after 52 weeks, more patients had normal liver function tests in the monotherapy arm than in combination (70% vs. 47%). Virological breakthrough was more frequently observed on monotherapy (44%) than on combination treatment (19%). Despite combination therapy, rtM204 mutations were detected in 9% and 15% at 52 and 104 weeks, respectively.

The nucleotide analogue tenofovir and the similarly effective nucleoside analogue entecavir have changed the landscape and expectations of antiviral therapy for HBV. Suppressing HBV DNA to undetectable levels in a minority of patients (such as the 26% in the above study) is no longer considered an adequate level of control and the third-generation drugs have viral suppression rates of greater than 80% for both HBeAg-positive and HBeAg-negative patients. For both of these drugs the medium-term resistance rates are low (well below 5% after several years) [12] and the arguments in favour of combination therapy are much reduced by these highly effective drugs. Nevertheless, the long-term resistance rates (i.e. over a patient's lifetime) with these drugs remains unclear and factors that predict the development of resistance are still unknown.

Consequences of treatment failure

The main advantages of sequential combination therapy – identification of side effects, cost and individualized therapy – are counteracted by the consequences of allowing treatment failure to one drug to develop; in other words, are we storing up problems for the future? The arguments for and against the use of combination therapy are based on the extrapolation of data from studies that report 1-year, 2-year or up to 5-year outcomes on these drugs. The natural history of chronic HBV infection both on and off treatment should be considered in terms of decades rather than years and, as far as we know, so should the intended duration of treatment. Therefore the durability of drugs should be measured over the same period of time.

Viral mutations that result in resistance to one drug will frequently lead to cross-resistance with agents from the same class. Therefore the use of lamivudine effectively precludes subsequent use of telbivudine. Similarly, prior use of adefovir is associated with a decreased response to tenofovir. Interestingly, even though entecavir is a structurally distinct (pentacyclic) nucleoside analogue and the viral mutations associated with resistance to it are not the same as those associated with resistance to lamivudine and telbivudine, prior use of lamivudine adversely affects response to entecavir such that after 4 years' therapy with entecavir 39.5% of lamivudine-resistant patients had also become resistant to entecavir [13]. In lamivudine-experienced patients who already have the rtM240V mutation, emergence of the entecavir-specific mutation rtM250V causes a marked drop in entecavir's effect, while in the absence of the lamivudine-resistance mutation rtM250V alone has minimal effect [14].

The emergence of mutations in suboptimally controlled patients with HBV infection can therefore have significant ramifications to future therapy and the consequences of early treatment decisions can have lifelong consequences

for patients. Given that suppression of viral replication is probably the most important determinant of the emergence of resistant strains, the proponents of *de novo* combination therapy argue that the most responsible management strategy is early and effective viral load suppression.

Conclusions

The ongoing debate that this chapter has summarized will continue but for today's patients decisions need to be made regarding their treatment options. Clearly this will be a two-way dialogue and different patients and their physicians will reach different conclusions. Our current approach is to recommend combination therapy with lamivudine and tenofovir in HBeAg-positive patients who either elect not to undertake interferon therapy or who have failed to respond to it. We use this approach as a proportion of patients will not achieve complete suppression of viral replication with montherapy. In patients with HBeAg-negative disease, the same combination therapy is considered although here the arguments for its use are much reduced as most patients achieve undetectable viraemia with monotherapy. For these patients we often employ entecavir or tenofovir unless we are concerned about resistance in which case we use tenofovir plus lamivudine. For patients who are intolerant of combination therapy we use entecavir monotherapy. It remains unclear as to whether this approach will lead to long-term benefits and emerging data over the next few years will decide whether this approach is necessary or is simply overprescribing. It is probable that as long-term resistance data emerges, pretreatment factors that predispose to long-term treatment failure will emerge and it will then become possible to reserve combination therapy for those patients in whom it is clearly indicated.

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30 Management of hepatitis B virus infection in pregnancy

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LEARNING POINTS

- The management of a pregnant woman who is HBsAg positive remains based on e-markers.
- There is convincing evidence available that one dose of hepatitis B-specific immunoglobulin as soon as possible after birth, along with a course of HBV vaccination, significantly reduces the chronic carrier rate in infants born to mothers who are HBeAg positive.
- HBeAg-positive women with an HBV DNA level above 10^7 copies/mL before 32 weeks require referral for specialist assessment for consideration of antiviral treatment, as this has been shown to further reduce transmission to their children.
- There is no major evidence to support the use of hepatitis B-specific immunoglobulin in the infants of anti-HBe-positive women. No chronic carriage appears to occur when these infants are treated with an accelerated course of HBV vaccination.
- Women who lack e-markers (i.e. are HBeAg and anti-HBe negative) should be managed in the same way as HBeAg-positive pregnant women.

Introduction

Mother-to-child (vertical) transmission of hepatitis B virus (HBV) accounts for approximately 35–40% of chronic infections worldwide [1]. Vertical transmission can occur in the prenatal period, during delivery or early after birth, although most transmissions occur during labour and delivery. Infections in this period from HBeAg-positive mothers usually result in chronic carriage of HBV.

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Management of the HBsAg-positive pregnant woman

The literature is in agreement that the management of a chronically infected pregnant woman is based on the presence of HBeAg or anti-HBe. As more experience accumulates on the routine use of quantitation of HBV DNA, this recommendation may become modified.

If the mother is HBeAg positive and no immunoprophylaxis is given, more than 85% of offspring will become chronically infected with HBV [2]. If the mother is anti-HBe positive and no immunoprophylaxis is given, less than 5% of offspring become chronically infected with HBV [3]. However, children of anti-HBe-positive mothers are also at risk of acute and fulminant HBV infection which, while rare, has a mortality rate of up to 75% [4].

Passive–active immunization administered to infants of HBeAg-positive women results in vertical transmission being reduced from 90% to between 1.1% [5] and 15% [6–8]. This variation is likely to reflect differing compliance with the recommended follow-up vaccination programme. When an accelerated course of HBV vaccination is started within 24 hours of birth for neonates whose mothers are anti-HBe positive, vertical transmission is reduced to less than 1% [6,8–11] with a significantly reduced risk of acute and fulminant hepatitis.

Immunization with hepatitis B immunoglobulin and HBV vaccine

The effect of passive immunization with hepatitis B immunoglobulin (HBIG) is immediate and lasts between 3 and 6 months [12], but it is expensive and there is limited availability in countries with low prevalence of HBV. As with all human blood derivatives, there is also a potential

risk of transmission of pathogens, both known (e.g. new-variant Creutzfeldt–Jakob disease) and those yet to be discovered. For infants born to HBeAg-positive mothers, administration of HBIG in addition to a course of vaccine reduces vertical transmission further than the use of vaccine alone [5,7,8]. However, despite active–passive immunoprophylaxis being employed in a timely manner, not all vertical transmission is prevented.

Of 235 Hong Kong infants of HBeAg-positive mothers, 20% of those in the group who received one dose of HBIG and vaccine were HBsAg positive at 3 years of age [7], and 35% of infants who received accelerated vaccine only were HBsAg positive at 3 years compared with 73% HBsAg positive in the placebo group. While some infections may not have been vertical, the benefit of HBIG at birth in infants of HBeAg-positive mothers is clear. A 10-year (1982–1992) neonatal HBV vaccination program in the Netherlands provides further evidence [5]. Of 705 infants born to HBeAg-positive women, eight (1.1%) became HBsAg positive despite passive–active immunoprophylaxis. No significant difference was found between the groups receiving one or two doses of HBIG. Of 140 infants born to HBeAg-positive mothers in Hong Kong, chronic carriage was 6.8% in children who received passive–active vaccination compared with 21.0% in those who received vaccine alone (with 73.2% chronic carriage in the control group) [8].

HBV DNA level determines consideration of antiviral treatment

In the Netherlands study discussed above (8 of 705 infants from HBeAg-positive mothers became chronic carriers despite passive–active vaccination), the only factor that was found to increase the risk of failure was the maternal HBV DNA level [5]. The protective efficacy rate was 100% if maternal HBV DNA was less than 150 pg/mL, but this was reduced to 68% for those with HBV DNA in excess of 150 pg/mL ($P = 0.009$). In an earlier paper based on the same cohort, median maternal HBV DNA was 314 pg/mL in the group which became chronic carriers in comparison with a median maternal HBV DNA of 4.5 pg/mL in the group which responded to passive–active immunoprophylaxis [13].

In a South Korean study, 17 of 144 (11.8%) children of HBsAg-positive mothers who received HBIG and vaccine suffered immunoprophylaxis failure [6]. Chronic carriage only occurred in children with a detectable maternal HBV DNA level (27% vs. 0% when maternal HBV DNA was undetectable). Chronic infection did not occur in children of HBeAg-positive mothers with undetectable HBV DNA. In one Chinese study, 7 of 95 infants (7.4%) became chronic carriers at 1 year despite passive–active immunization [14]. In mothers who transmitted the infection, mean HBV DNA was significantly increased ($P = 0.04$). In Taiwan, of 52 HBeAg-positive mothers, five had active–passive vaccination failure [15]. The high-infectivity group of 34 mothers with HBV DNA above 0.04 ng/mL contained all five cases of transmission. There was evidence of maternal–fetal haemorrhage in three cases.

Lamivudine taken in the third trimester by mothers with a high viral load reduces vertical transmission further than that achieved by passive–active immunization of the infant alone, but does not prevent all cases [16–18]. In one pilot study, eight women with HBV DNA in excess of 1.2×10^9 copies/mL were treated with lamivudine 150 mg from 34 weeks' gestation [18]. One of the eight (12.5%) children was HBsAg positive at 1 year in the lamivudine treatment group; in a historical control group, 7 of 25 (28%) were HBsAg positive at 1 year. All 33 infants received active–passive immunization. In China, lamivudine was provided throughout pregnancy for 38 women [16]. No complications were observed in the 38 children. Only 12 infants were tested for HBsAg at 1 year, none of whom were positive. Another study compared lamivudine treatment with HBIG administration for the prevention of intrauterine vertical transmission [17]. Both HBIG and lamivudine reduced intrauterine infection compared with the control arm (chronic carrier rate after HBIG prophylaxis 16.3%, chronic carrier rate after maternal lamivudine treatment 16.1%, control group 32.7%). No pregnancy-related complications were observed.

Because of evidence of an increased risk of chronic carriage in infants of HBeAg-positive women with a high HBV DNA level, we recommend that a conservative approach is taken in the rare case of an anti-HBe-positive women, previously known to have HBV DNA in excess of 10^7 copies/mL.

Use of HBIG in infants of anti-HBe-positive women

A Cochrane review did not identify any well-conducted trials which supported the addition of HBIG to vaccine for infants of anti-HBe carrier mothers. It identified no

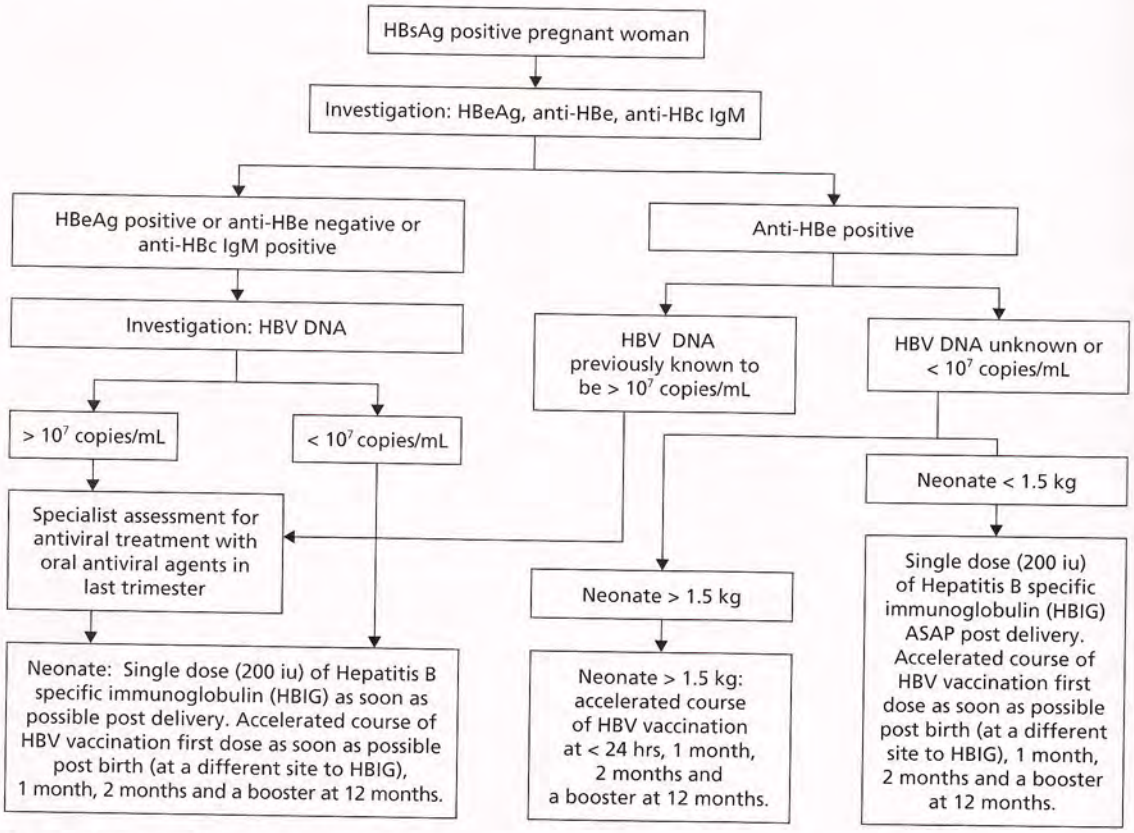

FIG. 30.1 Algorithm for the management of HBsAg-positive women. This algorithm was developed at a consensus meeting of the British Viral Hepatitis Group in summer 2008. It represents one approach to managing women who are HBsAg positive.

evidence for a role of higher viral level in anti-HBe carrier mothers that would support intervention beyond active vaccination [19]. In a study from Taiwan [9], 94 infants received one dose of HBIG and an accelerated course of vaccine; two infants were HBsAg positive at 2 months of age, but both children cleared the infection by 7 months of age. Another group of 122 infants received an accelerated course of vaccine only; one infant was HBsAg positive at 2 months of age, but once again the child cleared the infection by 7 months of age. None of the 122 infants who received vaccine alone became chronic carriers of HBV. In 125 Vietnamese infants born to anti-HBe-positive mothers who received vaccine alone, none became chronic carriers [10]. Of 88 infants born to HBeAg-positive mothers, 12 children became chronically infected despite active vaccination. Finally, in 125 British vaccinated infants born to anti-HBe-positive mothers, none became chronically infected. In 21 cases born to HBeAg-positive women, six infants became chronic carriers [11]. The use of HBIG in infants weighing less than 1.5 kg whose mothers are anti-HBe positive, while commonly included in guidelines, is not based on evidence.

Management of women who lack e-markers

Some 1% of HBsAg-positive mothers are both HBeAg and anti-HBe negative [8]. Currently, it is recommended to treat them in the same way as mothers who are HBeAg positive.

Conclusion

The approaches outlined above are evidence based. Although it is tempting to offer HBIG to all infants born to

HBsAg-positive mothers, it has to be understood there is little if any evidence to support such a stance. Further studies could be done to investigate the theoretical benefit of lamivudine prophylaxis for anti-HBe-positive mothers. It would be of interest to know if acute and fulminant hepatitis could be reduced by further management of the infant or if the maternal viral load is correlated with this outcome. Figure 30.1 presents a simplified algorithm for the management of women who are infected with HBV.

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31 Management of hepatitis B in children

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LEARNING POINTS

- Most individuals with chronic HBV acquired infection either perinatally or during childhood. Chronic HBV acquired during childhood may be associated with significant morbidity later in life, such as cirrhosis and hepatocellular carcinoma.
- Most children with chronic HBV are in the immune-tolerant stage. Treatment is not helpful or indicated during this stage, and indiscriminate use of nucleotide/nucleoside analogues may elicit resistance, with serious negative ramifications for later treatment.
- Some children with chronic HBV infection may be candidates for treatment. This includes those primarily in the immune activation stage, with persistently abnormal ALT values and histological chronic hepatitis.
- Therapeutic options for chronic HBV infection during childhood are limited.

When making treatment decisions, it is important to remember that the natural history of chronic hepatitis B virus (HBV) infection in children is variable, depending on age, mode of acquisition and ethnicity. These differences are likely due to the immune tolerance that is known to develop when infection occurs at an early age, although the exact mechanisms are unknown. Children from endemic countries in whom HBV is acquired perinatally are usually HBeAg positive with high levels of viral replication [1]. Rates of spontaneous seroconversion are less than 2% per year in children younger than 3 years of age, and 4–5% after age 3. In contrast, children in non-endemic countries are less likely to have acquired the disease perinatally. In this case, they frequently clear HBeAg and HBV DNA from serum during the first two decades of life [2]. In a 29-year longitudinal study of Italian children with chronic HBV who underwent HBeAg seroconversion, 95% of those without cirrhosis had inactive HBV infection at most recent follow-up and 15% cleared HBsAg [3]. Children who seroconvert spontaneously tend to have higher alanine aminotransferase (ALT) levels early in life. Although inflammatory changes are often mild in liver biopsies from children with chronic hepatitis B, fibrosis may be significant. In a recent study of 76 children with chronic HBeAg-positive HBV and elevated ALT (mean age 9.8 years), at least half had moderate to severe fibrosis, with 35% having either bridging fibrosis with lobular distortion or cirrhosis [4]. Cirrhosis is an infrequent complication of HBV infection during childhood, although precise incidence is uncertain. One of the largest studies included 292 consecutive children who were HBsAg positive and had an elevated serum ALT level [5]. Cirrhosis was found in 10 patients (3%) at a mean age of 4.0 ± 3.3 years. No child developed cirrhosis during follow-up (ranging from 1 to 10 years).

There are no data regarding treatment of acute HBV infection in children. Most children infected perinatally are asymptomatic, and the small percentage in whom acute, even fulminant, hepatitis develops rapidly clear HBsAg and viraemia. It has become apparent that some children with chronic HBV infection do require treatment in order to prevent serious sequelae, such as cirrhosis and hepatocellular carcinoma (HCC), in young adult life. Management of children with chronic HBV infection involves education and counselling, surveillance for HCC, and antiviral therapies in some cases.

There are few large trials in children to guide treatment decisions. Treatment is generally considered in patients

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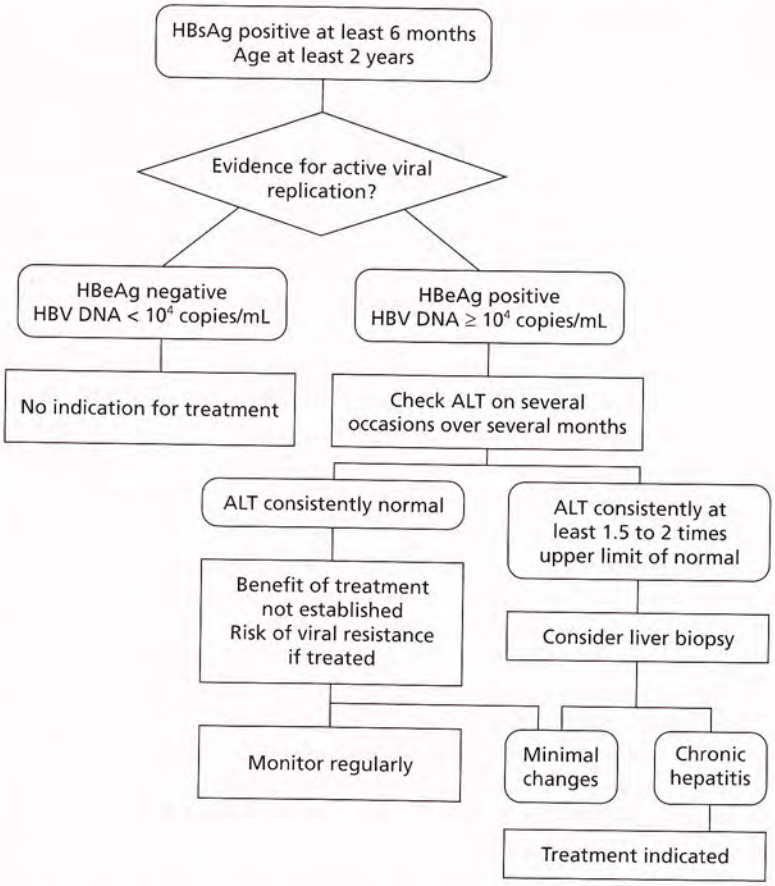

FIG. 31.1 Selection of paediatric patients with chronic hepatitis B for treatment.

who are in the immune active phase, usually defined as ALT more than twice normal and HBV DNA more than 20 000 IU/mL for at least 6 months [6] (Figure 31.1). Almost all children with chronic HBV are HBeAg positive, but therapy can also be considered for the few who are HBeAg negative, provided that viraemia above 10^4 IU/mL is documented and other diseases are excluded. None of the available treatments are highly efficacious. Therefore, the choice of whether to treat depends on patient-specific characteristics that predict the efficacy of treatment, including persistently abnormal ALT levels and active disease on liver biopsy, as well as considerations regarding the likelihood of achieving appropriate therapeutic goals.

The likelihood of response to any of the currently available drugs very much depends on the degree of elevation of serum aminotransferases [7–9]. ALT levels less than 1.5–2 times the upper limit of normal (ULN) generally indicate that the patient is in the immune-tolerant phase of HBV infection. Such children are not typically candidates for treatment, because treatment with any of the currently available drugs does not result in higher rates of HBeAg seroconversion compared with no treatment. Prolonged treatment with nucleoside or nucleotide analogues at this stage are associated with little benefit, but impose the important risk of viral resistance, both to the agent chosen and similar drugs. An exception may be those immune-tolerant children who will be undergoing immunosuppression, such as those who will have chemotherapy or stem-cell or solid organ transplantation. Just as in adults, HBV suppression should be considered during these critical periods to avoid activation of hepatitis. Children with ALT values greater than 10 times ULN may be in the process of spontaneous HBeAg seroconversion, and should be observed for several months before treatment is begun. There may be several other considerations in deciding on treatment in individual patients, such as co-infection with

hepatitis C virus (HCV), hepatitis D virus or HIV, or other comorbidities.

A number of drugs are currently approved for treatment of chronic HBV infection in adults. However, in the USA, only lamivudine and interferon alfa are licensed for use in children, and adefovir dipivoxil is available for use in those over 12 years of age. Interferon alfa leads to a beneficial response in 30–40% of patients. However, it is expensive and may be accompanied by frequent and unpleasant side effects. Success rates of interferon alfa treatment in children have varied significantly in different regions of the world. Response rates have been highest in Western countries, where treatment with interferon alfa results in loss of HBV DNA or HBeAg seroconversion in 20–58% compared with 8–17% in untreated controls. In contrast, only 3–17% of children treated with interferon alfa in Asian countries clear HBV DNA or seroconvert from HBeAg to anti-HBe. However, if aminotransferases are elevated, there may be no difference in response rates between children born in Asian countries (22%) and those from Europe and North America (26%) [10]. Children most likely to respond to interferon alfa, regardless of ethnicity, are of younger age with elevated aminotransferases and low HBV DNA levels. A large, multinational, randomized controlled trial of interferon alfa was performed in 144 children with chronic HBeAg-positive infection and ALT greater than twice ULN [8]. Serum HBeAg and HBV DNA became negative in 26% of treated children compared with 11% of untreated controls. In addition, 10% of treated children lost HBsAg compared with 1% of controls.

Interferon is not a good option in children with an underlying autoimmune disorder, organ transplant or serious neuropsychiatric disease. An advantage of interferon is that it has a finite duration of treatment and is not associated with the development of resistant HBV mutants. For children with HBeAg-positive chronic HBV infection, interferon alfa is given at a dose of 6 MU/m^2 (maximum 10 MU) three times a week for 24 weeks, followed by an observation period of 6–12 months. A year of treatment may be preferable in those with HBeAg-negative chronic HBV infection, based on data in adults. Patients should be monitored regularly for hepatitis flares during the first few months after the drug is discontinued. The efficacy of peginterferon alfa in children with chronic HBV infection has not been investigated. However, based on efficacy in adults and experience in children with HCV, it may be a reasonable choice for children with HBV, using a 48-week course and HCV doses, as recommended for adults.

Lamivudine is the only oral nucleoside analogue approved in the USA for treatment of children younger than 12 years with chronic HBV. In 2002, a multicenter, randomized, double-blind, placebo-controlled trial in HBeAg-positive children with ALT greater than 1.3 times ULN demonstrated clearance of HBeAg and HBV DNA at 52 weeks in 23% of treated children compared with 13% of controls [7]. In children whose baseline ALT was at least twice normal, this response rate increased to 35%. Subsequently, open-label lamivudine given to non-responders showed a cumulative 3-year virological response rate of 35%. HBsAg loss occurred in 3% of patients. HBeAg seroconversion from the first year was durable in 88% of patients at 3 years [11]. However, viral resistance developed in 64% of children who received lamivudine for 3 years. Of the children who participated in this trial, 151 were then followed for two more years [12]. Subjects were divided into two groups for analysis: those who had already achieved virological response by the end of the 3 years of therapy, and those who had not. In those who had achieved virological response, long-term durability of HBeAg seroconversion was 82% and greater than 90% in those who had received lamivudine for 52 weeks and at least 2 years, respectively. This compares with 75% for those who had achieved seroconversion after placebo. In those who had not already achieved virological response, an additional 11% did so during the next 2 years; they had all received lamivudine in the previous trial and none had received further treatment. Eight more children lost HBsAg; all had received lamivudine at some point during the previous trials. Although these findings are consistent with a recent study in Korean children where long-term treatment with lamivudine led to significant improvement in the seroconversion rates of HBeAg and HBsAg [13], results of several other small studies of children receiving long-term lamivudine have reported low rates of HBeAg seroconversion and no clearance of HBsAg.

Lamivudine is safe for children with hepatitis B and is well tolerated. Serious side effects were not reported after 3 years of continuous treatment. In comparison to treatment with interferon alfa, decreased height velocity and weight loss were not observed [11]. Children with higher pretreatment ALT and histological activity index scores on liver biopsy were more likely to respond to lamivudine. Other factors such as HBV DNA levels, age, gender, race, ethnicity, body weight and body mass index did not appear to significantly influence response to lamivudine treatment in

children [14]. Initial data suggested that continued treatment of patients who develop resistance might be beneficial in those in whom HBV DNA continues to be suppressed. However, long-term follow-up of such patients suggests that the disease continues to progress. Thus, it may be prudent to discontinue lamivudine in children who develop lamivudine-resistant HBV. Patients should be monitored regularly for hepatitis flares during the first few months after the drug is discontinued. For those who require additional therapy, options are limited at this time.

A double-blind placebo-controlled trial of adefovir dipivoxil (ADV) has been recently reported [15]; 173 children with HBeAg-positive chronic HBV were stratified by age and prior treatment. In the 12–18 year age group, as had been noted in adults, significantly more ADV-treated subjects achieved the primary efficacy end-point (serum HBV DNA < 1000 copies/mL and normal ALT at the end of blinded treatment) compared with placebo-treated subjects (23% vs. 0%; $P = 0.007$). In the younger groups, the differences between ADV and placebo at the end of blinded treatment were not statistically significant. The HBeAg seroconversion rate was 16% compared with 5% in the placebo group. No subject developed an ADV-associated mutation that has been linked to resistance. Each group achieved ADV concentrations in the target range. ADV treatment was well tolerated by all subjects, and no safety issues were identified. An open-label Phase 2 pharmacokinetic and dose-finding study of entecavir in children is underway. A randomized placebo-controlled trial of tenofovir in adolescents is currently enrolling subjects. Telbivudine has not yet been tested in children with chronic HBV.

The only treatments currently approved for chronic HBV infection in children are standard interferon and lamivudine. ADV is available for patients 12 years and older. However, these are less than ideal for the reasons discussed, and some practitioners have begun to use peginterferon in children without contraindications. In my own practice, we use peginterferon in some, and we are enrolling children in the entecavir trial. The adolescent tenofovir trial is in progress. For these reasons, at this time initiation of treatment should be reserved for those children with histological evidence of significant chronic hepatitis or fibrosis. At present, there are no recommendations regarding the best treatment of children co-infected with HCV or HIV, since these co-infections are rare in paediatric patients.

Children with chronic HBV in the immune-tolerant stage (normal ALT, HBeAg positive) need to be monitored carefully for activation. ALT should be determined twice yearly, and HBeAg and anti-HBe yearly. Patients who are in the inactive phase of HBV infection (HBeAg negative, anti-HBe positive, persistently normal ALT, serum HBV DNA $< 10^4$ copies/mL) should undergo monitoring of ALT every 6–12 months. The infection may reactivate even after years of quiescence; 4–20% of inactive 'carriers' have one or more reversions to HBeAg, and approximately 20–25% will develop HBeAg-negative chronic HBV. Periodic measurement of serum alpha-fetoprotein levels and hepatic ultrasound for HCC surveillance have been recommended in adults based on observational data and expert opinion, even after HBeAg seroconversion, either spontaneous or after treatment. The risk of HCC increases with increasing age, but childhood cases have been well described. Currently, there are no guidelines as to when this surveillance should be initiated, and how often testing should be done.

Children with HBV infection should be allowed to participate in all regular activities of childhood. There is no need to exclude infected children from regular school and sports participation [16]. HBV-infected children should receive hepatitis A vaccine. Household contacts should receive HBV immunization and be tested to ensure vaccine efficacy. They should be counselled not to share items that may be contaminated with blood and to carefully dispose of such items. Adolescents need to be informed of the risks of transmission of HBV by sexual activity and needle sharing.

Optimal treatment for children with chronic HBV infection should be individualized, depending on clinical and histological status, comorbid conditions, ability to take medications, contraindications and family concerns. The goal of treatment should be suppression of HBV DNA and durable HBeAg seroconversion, indicating cessation of active viral replication, to prevent the long-term consequences. Appropriate patient selection and understanding of the strengths and limitations of each of the therapeutic options are key to successful treatment.

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32 Hepatitis B infection in surgeons and healthcare workers: what should we do to protect patients?

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LEARNING POINTS

- Healthcare workers with chronic HBV infection can transmit the virus to their patients.
- The risk of transmission is related to viral load, with HBeAg-positive individuals being at greater risk of inadvertent transmission. However, HBeAg-negative patients can transmit HBV to their patients.
- Effective antiviral therapy can reduce the risk of transmission but the optimal treatment regimen and the definition of a 'safe' viral load remains unclear.

Chronic infection with hepatitis B virus (HBV) may be associated with very high levels of circulating viraemia. Transmission of the virus by blood to blood contact is well recognized and infection by contact with other contaminated bodily fluids is established. It is therefore not surprising to find that infected healthcare workers have occasionally and inadvertently infected their patients, sometimes with catastrophic results [1,2]. The risks of transmission are inevitably greater in those who perform prolonged, open surgical procedures but healthcare workers who take part in any invasive procedure may also pose a risk to their patients. The recognition that healthcare workers who are HBeAg positive have high levels of viral replication and pose the greatest risk has led most countries to insist that all those who perform high-risk interventional procedures should be tested for HBV and those who are HBeAg positive are usually barred from performing such high-risk procedures [1]. The definition of a high-risk procedure is not universally agreed: in the UK the definition of an 'exposure-prone procedure' is one in which the operator's hands are in a body cavity with a sharp instrument. This definition includes surgical operations, dental procedures and obstetric interventions but does not include endoscopic procedures or venesection. In some units concern has been expressed that this definition does not prevent laparoscopic procedures that may escalate rapidly to open surgery and some units have redefined exposure-prone procedures to include 'procedures that may progress to a procedure where the operator's hands are in a body cavity with a sharp instrument'. Similar definitions have been adopted in many other jurisdictions. Unfortunately, excluding healthcare workers at greatest risk of transmitting chronic HBV infection has not completely prevented inadvertent HBV transmission to patients and detailed studies have shown that healthcare workers with HBeAg-negative HBV may also transmit the virus to patients, particularly if the healthcare worker has high-level viraemia [3]. The recognition that some people with HBeAg-negative disease can transmit the virus to other patients led to the introduction of amended guidelines in many countries, whereby patients with HBeAg-negative disease were barred from high-risk procedures if they had high levels of circulating viraemia [4]. The level of viraemia deemed 'safe' varies from country to country but in the UK a value of less than 10^3 genome equivalent per ml is regarded as safe and healthcare workers with viral loads below this level are permitted to operate freely. Other countries have adopted slightly higher viral loads.

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The introduction and widespread use of potent antiviral agents has led to calls for a re-evaluation of the guidelines on infected healthcare workers and many authorities have argued that surgeons and other healthcare workers receiving antiviral therapy should be allowed to operate provided that their viral load is reduced to an acceptable, very low, level [5]. However, a policy whereby surgeons are allowed to operate if their viral load is reduced by antiviral therapy is potentially hazardous: the viral load may rise rapidly if a drug-resistant mutation develops and the prospect of an infected healthcare worker with a drug-resistant viral mutation infecting a patient with a resistant virus led many authorities to impose strict limits on healthcare workers undergoing therapy. The UK has one of the most rigorous policies and current UK policy is to allow infected healthcare workers to perform exposure-prone procedures only if their pretreatment viral load is low ($< 10^5$ genome equivalents per mL) and only if they are undergoing therapy that is carefully monitored by a named physician [4]. In view of the variation in different laboratories testing HBV viral loads, the tests need to be performed in one of two designated laboratories in the UK. The rationale for allowing only healthcare workers with low pretreatment viraemia to operate is based on the assumption that people with low pretreatment viraemia are least likely to develop on-treatment mutations and, in the unlikely event of a resistant mutation developing, it is reasonable to presume that the viral load will not rise rapidly to very high levels, thereby providing an opportunity for early detection of resistance and intervention to prevent transmission from healthcare worker to patient.

The optimal approach to managing healthcare workers with HBV is fraught with difficulty. On the one hand, experienced operators are a scarce resource and are expensive to train and banning healthcare workers from performing exposure-prone procedures may reduce the number of procedures that can be performed. Many HBV-infected healthcare workers have become infected during their work as medical practitioners and preventing them from continuing to work because of a work-related accident seems punitive. This is clearly of particular concern in areas where income is related to the number of procedures performed. On the other hand, patients have a right to expect that they will not be exposed to unnecessary risk while receiving healthcare and placing restrictions on healthcare workers to protect patients from harm is a well-established principle that is widely respected by healthcare professionals. The UK guidelines are among the most restrictive in the world and are generally regarded as reasonable. However, a small number of infected individuals have argued that the restrictions are unnecessary and unduly restrictive.

For healthcare professionals infected with HBV there is an established principle, exemplified by current guidelines, that activity should be restricted when the viral load is very high but there should be few or no restrictions on clinical practice when the viral load is low or when effective therapy is being taken. Some restrictions have been imposed to protect patients from unexpected increases in viraemia caused by viral resistance. Given that the current generation of oral antiviral agents (particularly entecavir and tenofovir) are very potent, have a very low rate of resistance and reduce the viral load in the majority of patients to almost undetectable levels [6,7], it is reasonable to ask whether all infected healthcare workers should be allowed to operate if they are receiving one of these potent antiviral agents. Such a policy has the advantage of restoring experienced professionals to the workplace, of simplifying the management of infected healthcare workers and is highly likely to protect patients because surgeons with viraemia reduced by potent drugs are highly unlikely to transmit virus to their patients. On the other hand, there is a small, but not zero, risk of virological relapse due to either non-compliance or resistance and if a healthcare worker were to infect a patient at a time when his or her viral load was raised it is probable that there would be serious repercussions for all those involved.

Discussion relating to the optimal management of HBV-infected healthcare workers has been led by high-quality studies evaluating the risks of transmission and the effectiveness of antiviral therapies. In many countries the majority of the population are further protected by universal vaccination programmes and hence inadvertent transmission is unlikely. However, policies to protect patients from HBV infection will inevitably establish a precedent that may be used to determine policies for healthcare workers infected with HIV and hepatitis C virus (HCV) and these infections cannot currently be prevented by vaccination and carry a greater stigma than infection with HBV. Thus policies around HBV transmission need to be reviewed in the light of other blood-borne viruses.

The optimal management of healthcare workers with chronic HBV remains controversial. The procedures that

carry the highest risk of transmission to patients are well recognized and it seems reasonable to place some restrictions on infected healthcare workers who perform such procedures. At present, most countries prevent those at greatest risk of transmitting virus from performing such procedures but a case could be made for relaxing these restrictions provided that the healthcare worker is taking antiviral medication that can be shown to be effective. Many countries have now introduced complex management algorithms that allow those who have modest levels of viraemia to perform exposure-prone procedures but preclude those with high-level viraemia from performing high-risk procedures. As experience with the new antiviral agents accumulates, it is probable that the current restrictions will be relaxed further and more and more infected healthcare workers will be allowed to return to performing high-risk invasive procedures. It will be important to ensure that all such individuals are very closely monitored to ensure that accidental transmission does not take place: the 'relaxations' in the current restrictions may be rapidly reversed in response to the public pressure that may follow a high-profile inadvertent transmission of viral hepatitis to a patient.

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33 HBV in the poorly compliant patient: dare we start oral drugs?

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LEARNING POINTS

- The prevention and treatment of antiviral resistance is a major clinical problem in the management of chronic hepatitis B.
- The emergence of antiviral resistance is dependent on the interplay of viral, host and antiviral drug factors.
- The common pathways of antiviral drug resistance are predictable, and application is advantageous to the treating physician in planning salvage treatment options.
- Non-adherence to therapy is a risk factor for the emergence of antiviral resistance, which can in turn result in virological rebound and clinical progression of disease.
- Ongoing patient counselling and education is a critical component in the management of chronic hepatitis B.

HYPOTHETICAL CLINICAL SCENARIO

Mr T. was a 57-year-old Asian man with HBeAg-negative disease and advanced fibrosis on histology. He was started on lamivudine (LMV) 1 year ago and achieved an on-therapy biochemical and virological response, with normalization of serum alanine aminotransferase (ALT) and an undetectable hepatitis B virus (HBV) load. Unfortunately, Mr T. did not take LMV on a recent 3-month overseas trip, during which he was unwell with a non-specific illness. Upon recommencement of LMV on his return, Mr T. subsequently developed an on-treatment hepatic flare with severe hepatic decompensation. Virological rebound and genotypic resistance to LMV was confirmed, but despite aggressive supportive measures, including attempts at rescue add-on antiviral therapy, Mr T. unfortunately died.

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Introduction

In the past decade, the development of safe and efficacious oral nucleos(t)ide analogue (NA) therapy for chronic HBV has advanced considerably. However, clinical experience with agents such as LMV, adefovir dipivoxil (ADV) and telbivudine highlight the emerging problem of antiviral resistance. The prevention and treatment of antiviral resistance is a major clinical problem in the management of chronic hepatitis B. The clinical impact of antiviral resistance is associated with multiple negative outcomes, including progression of liver disease, an increased risk of hepatocellular carcinoma (HCC), graft failure in post-transplant patients, reduced HBeAg seroconversion rates, and public health concerns including the potential for selection of vaccine escape mutants and transmission of multidrug-resistant virus.

In clinical trials of chronic HBV therapy, medication non-adherence accounts for up to 30% of virological breakthrough [1]. The intensity of monitoring is clearly more rigorous in clinical trials, and there are few published data available on the impact of non-adherence in chronic HBV treatment in everyday clinical practice. Furthermore, although clinical trials often employ an 80% compliance and drug dosing rule as acceptable inclusion in final data analysis (intention to treat versus off-protocol assessment), the applicability of this in the day-to-day post-registration phase of chronic hepatitis B treatment is unclear. While the hypothetical scenario of Mr T. represents the most severe spectrum of potential complications, the increased development of drug-resistant mutants and clinical deterioration in patients non-adherent to therapy is no doubt seen in everyday clinical practice.

This chapter addresses the factors involved in antiviral resistance, specific pathways of resistance to oral NA

agents, potential consequences of non-adherence to therapy, and prevention of antiviral resistance.

Antiviral drug resistance

The development of antiviral resistance is dependent on the interplay of multiple factors. These include factors related to the virus (viral replication rate, the error-prone reverse transcriptase/polymerase, replication fitness of viral quasi-species), host (compliance with therapy, prior drug experience, genetic factors such as drug metabolism to active moiety), drug (potency of antiviral agent, genetic barrier of drug to viral resistance, pharmacokinetic properties) and hepatocyte (available replication space). Furthermore, antiviral therapy may not reach potential sequestered sites/sanctuaries of viral replication, and does not eradicate covalently closed circular DNA, which is a crucial HBV replicative intermediate within the hepatocyte.

Specific pathways of resistance to oral NA agents

Antiviral resistance occurs because of the development of adaptive mutations under the selective pressure of antiviral therapy, with the consequence of diminished susceptibility of mutant virus to the inhibitory effect of a drug. The currently available NA agents can be classified according to chemical structure: L-nucleoside analogues such as LMV, telbivudine, emtricitabine and clevudine; acyclic phosphonates such as ADV and tenofovir (TDF); and the cyclopentane ring group such as entecavir (ETV). This chemical classification of oral NA agents is useful as patterns of antiviral resistance are predictable and generally structure specific (Table 33.1).

L-nucleoside pathway

LMV is the most well-characterized L-nucleoside and is associated with 80% genotypic resistance rates following 5 years of use. Treatment with LMV can lead to the resistant mutation rtM204V/I/S (which is found in the YMDD location in the C domain of HBV polymerase) with or without rtL180M (B domain). Mutations conferring resistance to LMV decrease *in vitro* sensitivity to LMV 100–1000 fold.

Once antiviral resistance to an L-nucleoside occurs, the effect of salvage 'switch' therapy with other agents within the group is attenuated due to cross-resistance, and thus ideally should not be instituted. Furthermore, add-on therapy of drugs within a class is also not recommended, because these drugs may compete for cellular activation mechanisms and viral targets. It should be noted that the rtM204V/I mutation also reduces susceptibility to ETV [2]. In a very small minority of cases, primary LMV resistance can also be observed with the emergence of rtA181T [3].

Acyclic phosphonate pathway

Genotypic resistance rates with ADV occur less frequently than resistance to LMV (Table 33.2). Treatment with ADV can select out rtN236T (D domain) with or without rtA181T/V (B domain). TDF is a nucleotide analogue that is structurally similar to ADV. TDF has much higher potency than ADV, in part because it can be given at a

TABLE 33.1 Pathways of antiviral resistance in chronic HBV infection.

Pathway	Mutation	Associated resistance
L-nucleoside	rtM204V/I/S ± rtL180M rtA181T	Lamivudine Emtricitabine Telbivudine
Acyclic phosphonate	rtN236T rtA181T/V	Adefovir Tenofovir
'Shared'	rtA181T/V	L-nucleosides (see above) Acyclic phosphonates (see above)
Naive entecavir resistance	rt180M + rtM204V with changes at one of rtT184, rtS202 or rtM250 codons	Entecavir
Multidrug resistance	Complex patterns, e.g. rtA181T + rtN236T + rtM250L	Multidrug

TABLE 33.2 Annual resistance rates for oral antiviral agents in chronic HBV infection.

Drug	Cumulative resistance rate (%)				
	1 year	2 years	3 years	4 years	5 years
Treatment naive					
Lamivudine [8,9]	23	46	55	71	80
Adefovir dipivoxil (HBeAg negative) [10]	0	3	11	18	29
Entecavir [11]	0.2	0.5	1.2	1.2	1.2
Emtricitabine [12,13]	13	18	–	–	–
Telbivudine [14]					
HBeAg positive	4.4	21.6	–	–	–
HBeAg negative	2.7	8.6			
Tenofovir fumarate [15]	0	–	–	–	–
Previous lamivudine resistance					
Adefovir dipivoxil (LMV resistant) [16]	0–18	38.3	–	–	–
Adefovir/LMV (LMV resistant) [17]	1	2	4	4	–
Entecavir (LMV resistant) [18]	6	15	35	43	51

much higher dosage because of less nephrotoxicity [1]. Cross-resistance exists between ADV and TDF *in vitro*, and longer-term studies with TDF are required to determine other mutations that may arise in the clinical situation.

Shared pathway

Most patients with antiviral resistance to LMV have rtM204V/I, and thus a salvage option is to add on ADV therapy. However, the shared pathway which selects out rtA181T/V confers resistance to acyclic phosphonates (e.g. ADV), and partial cross-resistance to LMV. rtA181T/V is seen in 40% of ADV treatment failures and 5% of LMV treatment failures [4]. The development of rtA181T/V has also been shown to have a dominant inhibitory effect on wild-type virion secretion, and could challenge the traditional case definition of virological breakthrough ($\geq 1.0 \log_{10}$ IU/mL increase from nadir) [5].

Naive entecavir resistance pathway

ETV is the most potent oral antiviral agent, with *in vitro* studies demonstrating 100–300 times greater potency than LMV [6]. Resistance to ETV was first noted in patients with pre-existing LMV resistance (Table 33.2). Virological breakthrough to entecavir requires at least three substitutions, including two lamivudine-resistant mutations (rtM204V and rtL180M), and an additional substitution at either rtS202I, rtT184G and/or rtM250V [7]. Thus, in treatment-naive patients, ETV has a high genetic barrier to resistance, and the 5-year cumulative genotypic resistance rate is only 1.2% (Table 33.2).

Clinical consequences of non-adherence and antiviral resistance

The impact of non-adherence to therapy in chronic HBV infection on healthcare is difficult to quantify. However, it is likely a significant cause of additional usage of healthcare resources, including repeated visits to clinic, requirement for additional investigations and changes to therapeutic regimens. Furthermore, non-adherence can hasten the emergence of antiviral resistance. The development of antiviral resistance can in turn result in virological breakthrough, reduced HBeAg seroconversion rates (in HBeAg-positive HBV), on/off treatment hepatic flares, histological progression of disease, and hepatic decompensation [1].

Prevention of antiviral resistance

There are multiple factors involved in the prevention of antiviral resistance to oral antiviral therapy. Patient counselling and education regarding the natural history of HBV infection, potential complications, and indications for antiviral therapy are essential (refer to published AASLD, EASL and APASL guidelines) [1,19,20]. Furthermore, given that treatment may be long term, and possibly indefinite in the setting of HBeAg-negative disease and

cirrhosis, it is imperative that adherence to therapy is encouraged to minimize the emergence of antiviral resistance.

In chronic hepatitis B, it is not possible to directly measure adherence to therapy by measurement of serum or urinary drug levels. Furthermore, such measures would be both problematic and costly. Thus, general measures that may improve adherence include involvement of a dedicated liver nurse, regular education of both patient and family, provision of written information, empowerment of patients to take ownership of their treatment, monitoring of pill counts, and the development of a strong therapeutic relationship between the treating physician and patient/family.

Once therapy is indicated in treatment-naive patients, careful selection of initial antiviral agent is required. Highly potent drugs with low rates of resistance should be used where possible. Much interest has surrounded the concept of combination therapy for HBV, similar to the highly active antiretroviral therapy used in HIV medicine. Ideally, combination therapy with synergistic drugs with different mechanisms or sites of action should be employed. However, the drugs that comprise the current oral therapeutic arsenal against HBV all have similar mechanisms of action. Furthermore, the combination of immunomodulators such as interferon with oral agents has not shown definitive superiority over monotherapy. As of 2008, there are still insufficient data to recommended initial combination therapy for the management of chronic HBV infection if starting with the newer, more potent NA agents such as ETV or TDF.

On-therapy monitoring includes 3-monthly quantitative serum HBV and ALT measurements. Regular 3-monthly testing facilitates the assessment of antiviral efficacy as indicated by response, durability and development of virological breakthrough. If viral load rises on therapy, compliance needs to be assessed, and in patients adherent to therapy virological breakthrough usually equates with antiviral resistance. At this juncture, genotype testing should ideally be performed to confirm resistance and identify known mutations associated with antiviral resistance (Table 33.1). This in turn allows the appropriate initiation of add-on salvage therapy, which can be determined by understanding the aforementioned pathways of resistance. Clinical experience thus far has shown add-on therapy to be more efficacious than sequential monotherapy. It is emphasized that for optimal suppression of viral replication, salvage therapy should be commenced as soon as resistance is detected. Clearly, it is too late to wait for clinical signs of antiviral resistance such as hepatic flare or hepatic decompensation, particularly in patients with already compromised hepatic reserve.

A critical question is whether a target viral load threshold exists below which the emergence of antiviral resistance does not occur. Ideally, complete suppression to undetectable levels by polymerase chain reaction is preferable, although this may not always be achievable in clinical practice. In clinical practice, consistent and durable suppression of viral replication to less than 3 $\log_{10}$ copies/mL (equivalent to approximately 2.2 $\log_{10}$ IU/mL) may be a reasonable viral threshold target to minimize emergence of resistance, providing a highly potent drug with a high genetic barrier to resistance is used.

Conclusion

The emergence of antiviral resistance in the treatment of chronic HBV infection not only results in virological and biochemical breakthrough, but can lead to histological progression, hepatic decompensation and even death. The combination of a limited spectrum of available drugs and often long-term treatment means that the problem of antiviral resistance will continue to pose a major clinical challenge. Adherence to drug therapy is a critical component in the prevention of antiviral resistance. Strategies for minimizing antiviral resistance include patient education and support from both the physician and liver nurse, careful timing and selection of initial therapy, regular viral load monitoring, and understanding of current pathways for antiviral resistance to determine salvage options.

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Summary of resistance pathways.

34 Acute liver failure and HBV: is there a role for HBV therapy?

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LEARNING POINTS

- Acute liver failure secondary to HBV infection remains a significant problem worldwide.
- Most patients with acute HBV will recover spontaneously.
- Treatment with oral nucleoside/nucleotide analogues may be initiated in cases of severe acute HBV infection with severe jaundice, coagulopathy and/or encephalopathy, but definitive data are lacking that it improves clinical outcomes.
- Further studies on viral genotypes, host immune factors and more potent therapies are needed to determine the true indication of treatment.

The aetiology of acute liver failure (ALF), characterized by coagulopathy and encephalopathy in a patient without pre-existing cirrhosis [1], varies by geography. In the USA and the UK, paracetamol toxicity remains the leading cause of ALF, while acute hepatitis B virus (HBV) infection constitutes 7–19% of all cases [2]. In Asia, HBV remains an important cause of ALF, accounting for 21–38% of all cases based on various studies from different countries [3].

The clinical spectrum of acute HBV infection varies from subclinical asymptomatic hepatitis to fulminant hepatic failure. Age at the time of infection, as well as host immune status, are key determinants of the clinical outcome of acute infection. Perinatally acquired HBV is usually associated with a more benign asymptomatic hepatitis but leads to high rates of chronicity. This is in contradistinction to adult-acquired HBV, which has a more symptomatic clinical presentation with a constitutional prodrome and icterus in approximately 30% of adults, but a more benign course as ultimate clearance of HBsAg occurs in approximately 95% of infected individuals [4].

The natural history of patients with ALF due to acute HBV who do not undergo liver transplantation is poor, with a published survival rate thought to range between 19 and 33% [5]. Moreover, ALF due to acute HBV is generally considered to have a worse prognosis than ALF due to most other aetiologies as reported in a large study involving 17 tertiary care centres in the USA [2]. Liver transplantation, the only therapeutic treatment shown to prevent death, is associated with a greater than 80% survival in patients with ALF due to acute HBV [6]. However, its use is exceedingly limited by timely availability of donor organs within a short interval from diagnosis to death. In patients who do undergo transplantation, the recurrence rate of HBV infection is estimated to be 20% [6]. In general, studies on the prevalence of acute HBV as a cause of ALF have been limited by a lack of consistency in the serological diagnosis of acute HBV.

While no randomized controlled trials have evaluated the efficacy of medical treatment in patients specifically with ALF due to acute HBV, studies in acute HBV infection suggest that antiviral therapy may be beneficial in the treatment of ALF due to HBV. Importantly, nucleoside analogue antiviral therapy has been shown to be extremely well tolerated and to have an excellent safety profile in both patients with chronic HBV [7] and in patients with decompensated liver disease [8]. Moreover, the use of antiviral therapy in ALF due to acute HBV also reduces the risk of HBV recurrence should the patient undergo liver transplantation. In contrast to the oral therapies, interferon therapy may actually accelerate the course of liver disease in

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TABLE 34.1 Summary of available studies evaluating nucleoside analogue therapy for HBV-induced acute liver failure.

Reference	Methods and inclusion criteria	Drug	Serological status prior to therapy	Serological response	Clinical response
Schmilovitz-Weiss *et al.* [10]	Prospective study 15 patients with HBV ALF defined by two of the following: (i) HE; (ii) serum bilirubin ≥ 10.0 mg/dL; (iii) INR ≥ 1.6	Lamivudine 100 mg daily for 3–6 months	15/15 HBsAg positive 13/15 HBeAg positive 15/15 IgM HBcAb positive	11/11 HBsAg negative 11/13 HBeAg negative 9/13 HBeAb positive within 6 months of follow-up	13/15 survived without transplant 2/15 required liver transplantation
Tillman *et al.* [11]	Prospective study 17 patients with HBV ALF defined by INR > 2.0 or HE	Lamivudine 100 or 150 mg daily until HBsAg cleared	17/17 HBsAg positive 5/17 HBeAg positive 17/17 IgM HBcAb positive	17/17 HBsAg negative within 6 months of follow-up	14/17 survived without transplant 2/17 required liver transplantation 1/17 died from herniation
Kumar *et al.* [12]	Randomized controlled trial 71 patients randomized to treatment (31) or placebo (40) with HBV ALF defined by two of the following: (i) HE; (ii) serum bilirubin ≥ 10.0 mg/dL; (iii) INR ≥ 1.6	Lamivudine 100 mg or placebo daily for 3 months	31/31 HBsAg positive 26/31 HBeAg positive 31/31 IgM HBcAb positive	30/31 HBsAg negative 26/26 HBeAg negative 22/31 HBeAb positive within 18 months of follow-up	31/31 survived without transplant No significant biochemical or clinical improvement seen between placebo and treatment groups
Seremba *et al.* [13]	Retrospective study 57 patients with HBV ALF of whom 32 received a nucleoside analogue	Lamivudine ($N = 29$) Adefovir/lamivudine ($N = 1$) Entecavir ($N = 2$) Median use 9 days	Not available	Not available	20/32 who received a nucleoside analogue survived (14 were transplanted) 20/25 who did not receive a nucleoside analogue survived (9 were transplanted)

HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; IgM HBcAb, immunoglobulin M antibody to hepatitis B core antigen; HBeAb, hepatitis B e antigen antibody; HE, hepatic encephalopathy; INR, International Normalized Ratio.

ALF because of its immunomodulatory effect [9] and is not recommended in the setting of acute disease.

In 2004, Schmilovitz-Weiss *et al.* [10] published the first pilot study evaluating lamivudine treatment (100 mg daily for 3–6 months) for severe acute HBV infection (Table 34.1). They enrolled 15 patients who fulfilled at least two of the following criteria for severe acute HBV: hepatic encephalopathy, serum bilirubin 10.0 mg/dL or greater, or INR 1.6 or greater. Thirteen patients (86.7%) responded to treatment with resolution of hepatic encephalopathy within 3 days and coagulopathy within 1 week. Serum HBV DNA was undetectable within 4 weeks and serum liver enzymes normalized within 8 weeks. Two patients in whom lamivudine administration was delayed by 6 weeks developed fulminant hepatitis and underwent urgent liver transplantation. No adverse events were reported [10].

Based on this initial study, and on case reports of successful lamivudine use in patients with fulminant reactivation of chronic HBV after chemotherapy for hepatocellular carcinoma, Tillman *et al.* [11] sought to evaluate lamivudine therapy (100 or 150 mg daily) in patients with acute (INR > 2.0) or fulminant (hepatic encephalopathy) HBV

in an attempt to prevent HBV reinfection following potential liver transplantation. Instead, they found that 14 of 17 (82.4%) lamivudine-treated patients survived without liver transplantation at all. All these 14 patients cleared HBsAg on lamivudine therapy within less than 6 months. In addition, prothrombin time normalized and bilirubin decreased in 12 of these 14 patients within a week of therapy, while the other two patients had normalization of prothrombin time and a decline in bilirubin after 2 weeks of therapy. No drug-related adverse events were recorded. Furthermore, of the three patients who progressed to transplant despite lamivudine therapy, one became HBsAg negative after 3 days of therapy allowing transplantation without hepatitis B immunoglobulin therapy after transplantation. These three patients included patients with the most severe liver disease (as indicated by severe coagulopathy) or concomitant paracetamol ingestion (> 5 g). In contrast, only 4 of 20 historical control patients not receiving lamivudine antiviral therapy survived without transplantation. The study also included 20 other patients with ALF treated with lamivudine referred to the authors for inclusion; only 5 of 20 (25%) required transplantation in this subgroup [11].

In contrast to these non-randomized studies, Kumar *et al.* [12] recently reported results of a randomized controlled trial comparing lamivudine 100 mg daily for 3 months versus placebo in the treatment of acute HBV infection and found no differences in clinical or biochemical improvement between the two groups. While the study included all patients with acute HBV, the majority of patients in both the lamivudine-treated group (22 of 31 patients, 71%) and in the placebo group (25 of 40 patients, 62.5%) had severe acute viral hepatitis as defined by the presence of any two of three criteria: hepatic encephalopathy, serum bilirubin 10.0 mg/dL or greater, and INR 1.6 or greater. Two patients in the lamivudine-treated group and one patient in the placebo-treated group had encephalopathy, thus suggesting ALF. While HBV DNA levels were significantly lower in the lamivudine group compared with placebo at week 4, thereafter no differences in HBV DNA levels were seen between the two groups. Furthermore, no differences in clinical or biochemical tests, including serum bilirubin, alanine aminotransferase (ALT) and INR, were seen up to 1 year after therapy. Interestingly, the rate of development of protective anti-HBs in the lamivudine-treated group after 1 year was lower than in the placebo-treated group (67.7% vs. 85%; $P = 0.096$) [12].

Additionally, a retrospective study (reported as an abstract) examined whether use of nucleoside analogues favourably influenced outcomes in HBV-induced ALF using the ALF Study Group registry [13]. In total, the authors identified 57 patients with HBV ALF, 32 (56.1%) of whom received a nucleoside analogue (29 lamivudine, one adefovir/lamivudine and two entecavir). The median duration of nucleoside analogue use was 9 days (range 1–36). The group that received a nucleoside analogue was older (51 vs. 38 years; $P = 0.03$), had greater bilirubin levels (23.4 vs. 15.2 mg/dL; $P = 0.01$) and lower ALT (1234 vs. 2416 IU/L; $P = 0.06$) and aspartate aminotransferase (AST) levels (676 vs. 1347 IU/L; $P = 0.03$). Overall survival was 20 of 32 (62.5%) for the nucleoside analogue treatment group and 20 of 25 for the non-treatment group ($P = 0.15$). From this retrospective non-randomized study, no benefit for therapy was identified in HBV ALF though selection bias and differences in treatment duration likely confounded presented results [13]. Indeed, in a study published by Wai *et al.* [14] evaluating the clinical features and prognostic factors in patients with HBV ALF, the authors found that advanced age was the only independent factor associated with a poor outcome while no laboratory test predicted outcome.

Virological factors have not been shown to affect overall survival or the rate of recovery among patients with ALF due to acute HBV; however, a number of viral factors are thought to increase the likelihood of development of ALF [14]. From several Asian studies, the presence of precore stop codon (G1896A) and core promoter dual (T1762A, A1764T) variants is associated with a greater rate of HBV ALF, suggesting that these factors may portend a worsened prognosis [14]. In addition, HBV genotype D has also been found to have a greater association with HBV ALF compared with chronic HBV infection, suggesting that this genotype may also be associated with a more aggressive disease course. Further studies are needed to determine the effect of antiviral therapy in acute HBV ALF in these subgroups of patients with possible markers of a more aggressive disease course.

Based on the above clinical information weighing the risks of therapy with nucleoside/nucleotide treatment (few) with the potential benefit of initiating therapy in a patient with severe acute HBV presenting with signs of liver failure (many), most clinicians and guidelines, despite a lack of robust randomized controlled studies showing efficacy, will initiate therapy on presentation, and we agree with this

strategy [15]. Future studies should be aimed at evaluating more potent antiviral drugs, including entecavir and tenofovir in patients with ALF due to HBV, host immune responses to HBV, and viral predictors of liver failure.

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35 High-risk needle exposure in hepatitis B vaccine failures: what are the options?

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LEARNING POINTS

- Protective immunity after completion of the HBV vaccination schedule is defined as an anti-HBs titre of ≥ 10 mIU/mL.
- Protective immunity is achieved in 90–95% of healthy individuals after completion of the HBV vaccination series. However, up to 50% of people with chronic medical conditions and/or specific HLA haplotypes fail to respond to the vaccination series.
- Predictors of non-response include age, male gender, obesity, tobacco use, alcoholism, chronic medical conditions, immunocompromised states and genetic predisposition.
- The algorithm for post-exposure prophylaxis must take into account the adequacy of the host's vaccination response.

Background

Infection with hepatitis B virus (HBV) has long been regarded as an occupational hazard for those employed as healthcare workers (HCWs). While HBV may be transmitted through a myriad of routes, parenteral or mucosal exposure to hepatitis B surface antigen (HBsAg)-positive blood or body fluids is clearly the largest threat to HCWs [1]. Prior to the discovery and formulation of a vaccine against HBV, HCWs exposed to HBsAg-positive/hepatitis Be antigen (HBeAg)-positive blood had a 37–62% chance of developing serological markers of infection. A 20–40% seroconversion rate was observed if the exposure in question was to HBsAg-positive/HBeAg-negative blood [2].

The first vaccine against HBV became commercially available in 1982 [1]. This vaccination, a series of three intramuscular injections administered at baseline, 30 days and 180 days, is highly effective at preventing chronic HBV infection [3]. Since the advent of clinical guidelines mandating vaccination for HCWs, the incidence of HBV seroconversion has declined by 95% [4].

As appropriate vaccine administration for HCWs has been undertaken, other high-risk groups have emerged whose seroconversion rates surpass that of HCWs. Currently, despite the continued targeting of high-risk groups for HBV vaccination, there are still instances where vaccination fails to provide protective immunity. Vaccination failure in those exposed to HBV may result in chronic HBV infection, with its inherent risk of cirrhosis, liver failure, hepatocellular carcinoma and even death. This chapter discusses strategies for the post-exposure management of high-risk exposures in the setting of HBV vaccination failures.

Identification of high-risk populations for vaccination

The Centers for Disease Control and Prevention (CDC) recommend that in addition to the vaccination of all infants and children previously not vaccinated, all adults at high risk for HBV infection should undergo vaccination. The high-risk groups targeted for vaccination include HCWs,

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inmates of long-term correctional facilities, injection drug users, men who have sex with men, those with high-risk heterosexual practices, household contacts of HBV-positive patients, haemodialysis patients, recipients of clotting factor concentrates, and long-term international travellers. Estimates obtained by the CDC from the 2004 National Health Interview Survey indicate that only 45.4% of these high-risk populations are actually vaccinated against HBV [5]. Although vaccination is required of HCWs, surveys show that only about 75% complete the full vaccination series [6].

HBV vaccination and characteristics of failure

Current anti-HBV vaccines consist of single-antigen formulations of recombinant HBsAg. The two commercially available vaccine preparations, Recombivax HB and Engerix-B, are administered in typical doses that contain 10–40 μg/mL of the HBsAg protein. With administration of the three-aliquot series, the accepted protective serum antibody level is defined as a detectable titre of 10 mIU/mL (or 10 IU/L) or greater. Seroconversion with protective serum titres of anti-HBs is achieved in 90–95% of healthy individuals after completion of the vaccination series [1,7].

Non-response is defined as an anti-hepatitis B surface antigen (anti-HBs) titre below 10 mIU/mL, typically measured 1–6 months after the last dose of a full immunization schedule. Hyporesponse is defined as an anti-HBs titre greater than 10 and less than 99 mIU/mL. Predictors of non-response include age 30 years, male gender, obesity, tobacco use, alcoholism, diabetes, chronic renal disease, chronic liver disease and immunocompromised states (such as HIV or medication-induced immunomodulation) (Table 35.1) [3,7]. Additionally, studies have demonstrated that genetics may play a role in the degree of response to vaccination. Data have shown that individuals who are homozygous for two extended major histocompatibility complexes (MHCs) of HLA haplotypes (HLA-B8, DR3, SC01 and HLA-B44, DR7, FC31) are likely to be non-responders while heterozygous individuals tend to be hyporesponders [8].

The true non-responder is not protected against HBV infection if exposure occurs. Several strategies have been employed to address those who, after a full vaccination schedule, are deemed non-responders. The CDC recommends revaccination of non-responders with one or more additional vaccine doses. In the case of three or more additional booster injections, as many as 30–50% of recipients respond with appropriate production [3]. For individuals with risk factors for non-response, some clinicians also advocate using higher doses of vaccine, specifically 40-μg dosing for the initial three injections instead of the standard adult dosing of 10–20 μg.

TABLE 35.1 Predictors of non-response to HBV vaccination.

Vaccine administration
Site of injection (gluteal >> deltoid)
Length of needle
Depth of injection (intradermal >> intramuscular)
Incomplete vaccination series
Host characteristics
Male gender
Age > 30 years
Obesity
Genetic predisposition
Habits
Tobacco
Alcohol
Disease states
HIV/AIDS
Chronic liver disease
Chronic renal disease

Along with changing the dose and/or dosing schedule of the HBV vaccine, the use of adjuvant therapy with vaccination has been explored. This has included the use of various antigen delivery systems and immunomodulators intending to increase the rate of immune response (Table 35.2). For instance, various cytokines, including interferon alfa, have been studied in HBV vaccine non-responders and hyporesponders. Unfortunately, these agents have been unsuccessful in decreasing vaccine failure rates [9]. Hence there are no current recommendations for the use of adjuvant delivery systems.

Although the use of adjuvant delivery system for HBV vaccines has been disappointing, newer more immunogenic vaccines have shown promising results in increasing vaccine response rates. Most recently, a third-generation HBV vaccine containing PreS1, PreS2 and S antigens, surface proteins of HBV that play a role in immunogenicity, has shown an increase in antibody titres when used in non-responders compared with conventional vaccination (S antigen alone). Several studies have examined use of this vaccine in high-risk populations [10].

TABLE 35.2 Adjuvant strategies for HBV vaccination in healthy non-responders/hyporesponders.

Immunization strategy	Intervention group response rate*	Control group response rate*	*P*-value
Rendi-Wagner *et al.* [10] PreS/S vaccination, non-responders	81.7%	49.1%	< 0.001
Goldwater *et al.* [9] Interferon alfa			
Non-responders	53.0%	41.0%	NS
Hyporesponders	87.5%	70.0%	NS
Kim *et al.* [12] GM-CSF†, non-responders	55.2%	53.3%	0.60
Goldwater *et al.* [13] SRL 172, non-responders	41.7%	45.4%	NS

* Response is defined as anti-HBs titres > 10 mIU/mL after vaccination.
† Studies in haemodialysis and HIV-infected patients have established efficacy of GM-CSF [7,14].

In addition, there is a growing body of evidence that the use of granulocyte/macrophage colony-stimulating factor (GM-CSF) may enhance the immune response to HBV vaccination. However, the exact mechanism by which GM-CSF may improve the response in HBV vaccination remains unclear. Proposed mechanisms for the action of GM-CSF have included macrophage activation, an increase in MHC class II antigen expression, enhancement of cell maturation, migration, T- and B-cell activation, and induction of localized inflammation. A recent meta-analysis published in 2007 reviewed 13 randomized studies evaluating GM-CSF as an adjuvant to HBV vaccination and found a more favorable rate of response compared to conventional vaccination (RR 1.54, 95% CI 1.04–2.27) [7]. GM-CSF has been found to be beneficial for inducing seroconversion in both healthy non-responders and groups of high-risk non-responders such as haemodialysis patients [7]. Because additional research into the role of GM-CSF needs to be explored, there are no current recommendations for its clinical use at this time.

High-risk exposure in non-responders

High-risk exposures for HCWs include blood splashes to mucous membranes or open cuts/abrasions, needle or sharps injury with hollow-bore needles contaminated with blood, or direct introduction of blood or body fluids into an open cut. In these settings, the addition of inadequate vaccination or hyporesponse or non-response to a full vaccination schedule results in a high risk of infection, ranging from 4 to 30% in those with inadequate vaccination and up to 100% in non-responders [11]. Further complicating the matter is that at the time of their exposure, HCWs are unlikely to know that they may have had an inadequate response to vaccination.

Algorithm for management of high-risk needle exposures in HBV vaccination failures

Hepatitis B immunoglobulin (HBIG) is a human immune globulin extracted from the plasma of healthy donors with high levels of HBsAb. In addition to an exhaustive process to eliminate donors who have serological markers of other viral infections (e.g. HIV, hepatitis C virus), the multistep process utilized for its preparation also targets such viruses for deactivation.

HBIG provides passive immunity against HBV. After an intramuscular injection of 0.06 mL/kg, the mean half-life of the immune globulin is 17.5–25 days. Given the long half-life of this antibody in the blood, we recommend that all known non-responders and hyporesponders to the full HBV vaccination series receive HBIG after a high risk HBV exposure. The initiation of a revaccination series in this group may also be performed if this has not already been undertaken. If the quality of the prior anti-HBs response is unknown in an individual with a

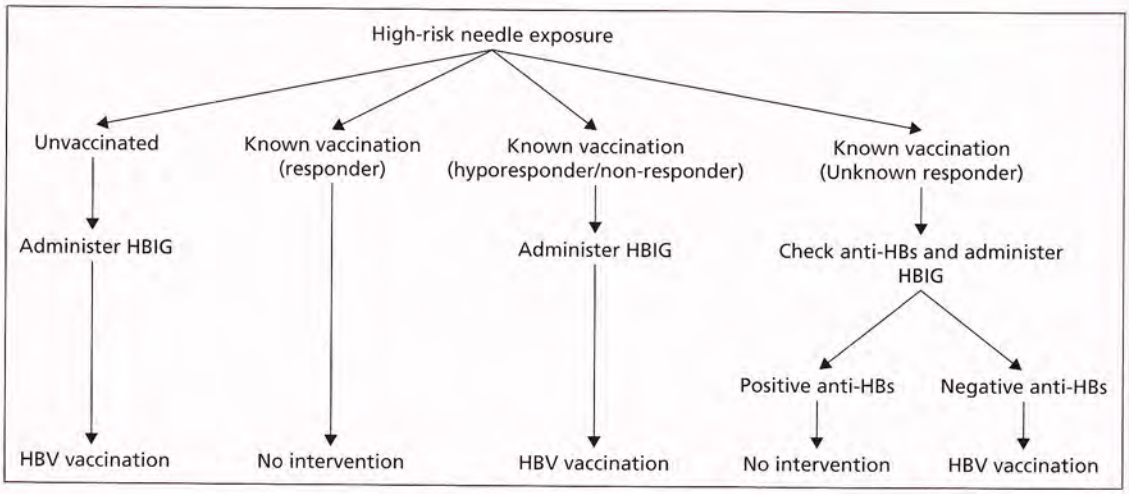

FIG. 35.1 Algorithm for post-exposure prophylaxis in high-risk needle exposures.

reported history of HBV vaccination, anti-HBs titres should be assessed and HBIG administered. If anti-HBs titres are inadequate, revaccination may be attempted although the yield may be low. If intermediate anti-Hbs titres are found, a booster injection is not required given a documented amnestic immune response.

Revaccination may certainly play a role in boosting the immunity of hyporesponders, although this role may be limited in those individuals who are truly non-responders. Regardless, revaccination has been suggested in the algorithm of the post-prophylaxis therapy for high-risk exposures in non-responders and hyporesponders as noted above (Figure 35.1).

Conclusion

HCWs remain at high risk for the acquisition of HBV in the setting of high-risk needle or sharps exposures. Although vaccination against HBV has decreased the transmission rate of HBV in healthcare settings, vaccination non-adherence or hyporesponse/non-response may still leave providers and patients cared for by those providers at risk. While some risk factors for non-response are modifiable, such as obesity, tobacco use and alcoholism, some are non-modifiable host factors or comorbidities. In this case, aggressive post-exposure prophylaxis with HBIG and potentially HBV revaccination are of the utmost importance. In the future, immune response primers such as GM-CSF may be added to traditional HBV vaccination in order to boost the immune response in traditional non-responders or hyporesponders.

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36 Antiviral prophylactic treatment of chronic hepatitis B to prevent viral reactivation during cytotoxic chemotherapy

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LEARNING POINTS

- HBV reactivation, characterized by an increase in serum HBV DNA levels in individuals with chronic or resolved HBV infection, occurs at increased rates in patients undergoing cytotoxic chemotherapy.
- Although few have been definitively authenticated, numerous risk factors for reactivation have been suggested. These include, but are not limited to, HBsAg seropositivity, detectable pre-chemotherapy HBV DNA levels, male gender, younger age, and treatment with glucocorticoids, anthracyclines or rituximab.
- Lamivudine prophylaxis has been shown to effectively reduce the risk of HBV reactivation, with the only noteworthy drawback being the selection for lamivudine-resistant mutant HBV strains.
- Newer and more potent antivirals with better resistance profiles are likely to be successful as prophylactic strategies, although specific data are lacking and clinical trials are needed.

Chronic hepatitis B virus (HBV) infection, a disease defined by the presence of hepatitis B surface antigen (HBsAg) in the circulation for longer than 6 months, afflicts approximately 350 million individuals worldwide. The prevalence of the infection varies from highly endemic regions such as sub-Saharan Africa and East Asia (≥ 8%) to areas of relatively low prevalence such as North America and northern Europe (< 2%) [1]. HBV is transmitted both vertically or perinatally, and horizontally, often as a result of sexual exposure or intravenous drug use. The development of chronic infection is closely associated with the mode of transmission, such that vertical transmission leads to chronicity in up to 90% of infected patients whereas horizontal transmission during adulthood does not progress beyond the acute stage in 95% of infected patients [2]. It is estimated that 15–40% of HBV carriers will develop liver failure, cirrhosis or hepatocellular carcinoma during their lifetimes [1].

One of the current clinical dilemmas encountered in the management of chronic HBV individuals with resolved or inactive infection revolves around the increased risk of viral reactivation during or following cytotoxic chemotherapy. HBV reactivation has been somewhat vaguely defined as an increase in HBV viral replication in individuals with chronic or resolved HBV infection. Although there are no standardized diagnostic criteria for this condition, a recent study proposes the following: an increase in serum HBV DNA level to above 1 log higher than baseline, an absolute increase greater than 6 $\log_{10}$ copies/mL, or transition from negative to positive serum HBV DNA [3]. Reactivation may occur in an average of up to 50% of chronic HBV cases undergoing cytotoxic chemotherapy while not on antiviral prophylaxis. Such a development may pose a significant health challenge by impairing overall survival and obligating delays and interruptions in chemotherapeutic treatment regimens as a result of associated liver complications such as icteric hepatitis flares [4]. Studies have reported delays as long as 100 days and direct mortality rates between 4 and 60% due to HBV reactivation [5].

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It is believed that the risk of viral reactivation is subject to variance depending on the aggressiveness and duration of the chemotherapy, the types of drugs administered, the type of malignancy, and a patient's gender, age and serological profile. Important surveys of the literature by Kohrt *et al.* [5], Lalazar *et al.* [6] and Yeo and Johnson [7] inform much of the following summary of the suspected key risk factors involved in HBV reactivation. However, it is important to note that small sample sizes and heterogeneity in factors such as malignancies studied, treatment regimens and baseline serological status prevent definitive elucidation of risk stratification for HBV reactivation.

Univariate analysis in a study of 78 HBsAg-positive cases with various malignancies has shown an increased risk of viral reactivation associated with male gender and younger age. Use of corticosteroids, due perhaps to their interaction with a glucocorticoid response element in HBV DNA that may lead to increased viral replication, and of anthracyclines, which have been shown to increase viral DNA secretion *in vitro*, have also been identified as risk factors in a multivariate analysis of 138 HBsAg-positive individuals with various malignancies. It is important to note here that although corticosteroids confer a greater risk of reactivation, steroid-free chemotherapy should not necessarily be considered a better alternative given that studies have shown a significantly decreased rate of remission and overall survival as a result of this potentially weaker treatment regimen. Use of CD20 monoclonal antibody therapy with rituximab has also been suggested in multiple reports to be a risk factor. In a recent study of a homogeneous population of 46 HBsAg-negative/anti-HBc-positive patients with diffuse large B-cell lymphoma undergoing chemotherapy (CHOP therapy) with or without rituximab, it was found that rituximab was significantly associated with HBV reactivation [8]. Univariate analysis in a study of 46 HBsAg-positive patients with lymphoma also suggested that treatment using second- or third-line chemotherapy led to an increased incidence of reactivation.

In terms of risk factors related to the patient's serological profile, it has been determined that the greatest risk of reactivation exists in patients positive for HBsAg and the lowest risk in patients with hepatitis B surface antibody (anti-HBs) levels above 10 IU/L. Detectable anti-HBc in the absence of positive HBsAg or anti-HBs has also been suggested to confer a risk, though lower, for reactivation. Seropositivity for HBeAg has been identified as a risk factor, but the absence of HBeAg does not preclude the possibility of reactivation given the existence of HBeAg-negative precore and core promoter mutations preventing production of HBeAg. A recent multivariate analysis that examined predictors of viral reactivation in 133 patients who had undergone HBeAg seroconversion found that genotype C (compared with genotype B), male gender and alanine aminotransferase (ALT) levels above five times upper limit of normal during the HBeAg-positive phase, and age older than 40 years at the time of HBeAg seroconversion were all significantly associated with greater incidence of reactivation [9].

A detectable pre-chemotherapy HBV DNA level has been associated with increased risk in a univariate analysis of 41 breast cancer patients (viral load $> 3 \times 10^5$ copies/mL) and a multivariate analysis of 138 patients with various malignancies (viral load $> 2.9 \times 10^5$ copies/mL). Kohrt and colleagues suggest that this may be the strongest indicator of reactivation risk.

The highest reported risk of reactivation (67%) was found in patients undergoing glucocorticoid-containing therapy for haematological malignancies. The lowest overall risk ($\leq 40\%$) was observed in patients undergoing glucocorticoid-free chemotherapy for solid tumours. It is not yet clear whether differences in reactivation risks in varying malignancy types are due to variation in tumour histology or variation in the form and drugs used in their respective chemotherapy treatments. A summary of many of the above-mentioned risk factors is provided in Table 36.1.

Given the significant risk of viral reactivation and the chances of life-threatening sequelae occurring, prophylactic treatment of HBV has been suggested for preventing reactivation of HBV during and after chemotherapeutic

TABLE 36.1 Risk factors associated with an increased risk of HBV reactivation in patients undergoing cytotoxic chemotherapy.

Detectable pre-chemotherapy HBV DNA level
HBsAg seropositivity
HBeAg seropositivity
Male gender
Younger age
Corticosteroid and anthracycline use
Rituximab/CD20 monoclonal antibody therapy
Second- or third-line chemotherapy

TABLE 36.2 Summary of the meta-analyses by Loomba *et al.* and Ziakas *et al.*[*]

Study	Patients	Serological profile	Malignancy	Chemotherapy regimen	Prophylactic strategy	HBV reactivation risk reduction	HBV-related mortality risk reduction
Loomba *et al.* [10]	275 treatment 485 control	HBsAg positive	Various	Varied	Lamivudine	9/240 vs. 156/424 RR 0.00–0.21	4/208 vs. 27/394 RR[†] 0.00–0.20
Ziakas *et al.* [11]	127 treatment 269 control	HBsAg positive	Lymphomas	Varied	Lamivudine	11/127 vs. 136/269 RR 0.21	2/117 vs. 15/254 RR 0.68

* Loomba *et al.* studied patients with a variety of malignancies including lymphomas, hepatocellular carcinoma, breast cancer, leukaemia, nasopharyngeal carcinoma and solid tumours, whereas Ziakas *et al.* studied only lymphoma patients. Lamivudine administration was highly variable in both studies, ranging widely from 28 days to 1 day before and from 1 to 12 months after chemotherapy.

† For simplicity, this RR range does not include the one conflicting study, published only as an abstract, from the Loomba survey that showed three deaths in the treated group and none in the control group.

treatment. Although hepatitis B is relatively uncommon in developed Western countries, except within subsets of immigrant communities from highly endemic regions, there is an increasingly large number of individuals expected to develop cancer and subsequently undergo chemotherapy. This calls for serious consideration of prevention of chemotherapy-induced HBV reactivation, in both hypoendemic and hyperendemic regions, given the important clinical and public health implications [10]. Most studies of antiviral prophylaxis have focused exclusively on the use of lamivudine, a nucleoside analogue used in conventional treatment of chronic hepatitis B to curtail HBV replication, reduce viral loads and improve liver injury while maintaining a highly favourable side-effect profile [10]. A variety of different studies with small datasets have analysed the efficacy of lamivudine prophylaxis, leading to the recent publication of several meta-analyses. Table 36.2 summarizes the relevant findings of the two recent meta-analyses discussed below.

Loomba *et al.* [10] reviewed published literature until June 2007 and conducted a meta-analysis of two randomized controlled trials, eight prospective controlled studies and four retrospective studies in order to assess the risk of HBV reactivation, HBV-related morbidity and HBV-related mortality in HBsAg-positive patients receiving chemotherapy with or without lamivudine prophylaxis. The authors did not pool the data of these smaller studies due to inconsistencies in their experimental designs and patient populations and instead reported their results as patterns based on study-specific estimates. A total of 485 control patients were administered deferred or no lamivudine treatment while 275 patients were administered lamivudine prophylactically. All studies showed a relative risk ratio (RR) in favour of prophylactic lamivudine ranging from 0.00 to 0.21 in assessments of both viral reactivation and HBV-related hepatitis. No patient undergoing prophylactic lamivudine suffered HBV-related hepatic failure in the seven studies reporting this outcome as opposed to a total of 21 patients from the control groups (RR 0.00). Nine of ten studies reporting HBV-related death showed decreased numbers of this outcome associated with prophylaxis (RR 0.00–0.20) while the remaining study, published only as an abstract, cited three deaths among the 26-patient prophylactic group and no deaths in the 25-patient control group. No harmful side effect was seen as a result of lamivudine prophylaxis and a smaller percentage of prophylaxis patients experienced chemotherapy interruptions (27 of 156 patients, 17.3%) relative to the control group (127 of 322 patients, 39.4%) in the six studies reporting this outcome. Cancer-related mortality (34.9% or 15/43 vs. 26.2% or 11/42) and all-cause mortality (36.3% or 57/157 vs. 17.8% or 21/118) were also reduced in the group receiving lamivudine prophylaxis. In summary, this meta-analysis determined that lamivudine prophylaxis for HBsAg-positive patients undergoing chemotherapy results in fewer interruptions, confers a 79% or greater risk reduction for viral reactivation and HBV-related hepatitis, and reduces the risk of HBV-related death and HBV-related

hepatic failure. The limitations of this meta-analysis include the heterogeneity of the patient populations, treatment regimens and cancer type as well as the overall weak experimental methodology of the incorporated studies. These limitations may potentially have resulted in some bias.

Identifying the failure of previous meta-analyses to distinguish between antiviral prophylactic effect on lymphoma versus solid tumours, Ziakas *et al.* [11] conducted a meta-analysis focusing solely on HBsAg-positive lymphoma patients undergoing chemotherapy or immunotherapy. They reviewed published literature until December 2008 and selected one randomized controlled trial, three prospective cohorts and five retrospective cohorts comprising a total of 396 participants, 269 in the control group and 127 in the lamivudine prophylaxis group. The RR was pooled and calculated according to the fixed effects method and statistical heterogeneity between studies was evaluated using the chi-squared Q test and the I^2 statistic. The authors found no evidence of statistical heterogeneity and identified a significant reduction in the risk of HBV reactivation (RR 0.21, 95% CI 0.13–0.35) in the prophylaxis group (11 of 127, 8.6%) compared with the control group (136 of 269, 50.6%). There was also a trend, though not statistically significant (RR 0.68, 95% CI 0.19–2.49), for reduced risk of HBV-related mortality in the prophylaxis group (2 of 117, 1.7%) compared with the control group (15 of 254, 5.9%).

An economic analysis of prophylactic lamivudine use demonstrates that prophylaxis used until 6 months after chemotherapy cessation is a cost-effective strategy (incremental cost-effective ratio $33 514) compared with use of lamivudine after hepatitis is evident [12]. Despite the evidence of HBV reactivation risk reduction using antiviral prophylaxis, quite alarmingly a recent survey of oncologists in Washington, DC showed that only 56% knew of the existence of prophylactic therapy and 48% were doubtful of which antiviral agent to use [13].

One drawback to lamivudine therapy is that extended use of lamivudine allows the selection of lamivudine-resistant HBV strains with mutations in the YMDD (tyrosine-methionine-aspartate-apartate) motif. A cohort study of 58 patients undergoing conventional (non-prophylactic) lamivudine treatment of chronic HBV infection showed that 12–20% of patients developed mutations after 1 year and 67% developed mutations after 4 years [5]. The risk of viral resistance with prophylactic lamivudine is not well established, nor is the clinical significance of such an occurrence. Given the possibility of this complication, more trials investigating the efficacy of non-lamivudine antiviral prophylaxis are greatly needed, as data are currently very limited.

In a recent case report, three HBsAg-positive patients undergoing cytotoxic chemotherapy with steroids for solid tumours were given entecavir prophylaxis until 6 months after completion of chemotherapy [14]. None of the patients developed HBV reactivation. Another case report mentioned an HBsAg-positive lymphoma patient who received adefovir prophylaxis while undergoing chemotherapy with rituximab but who developed HBV reactivation after 3 months of treatment [15]. Despite the limited data on prophylactic use of non-lamivudine drugs, their success in conventional treatment of chronic HBV makes them reasonable candidates for prophylaxis as well. As a result, the 2007 AASLD guidelines propose that newer antiviral drugs such as adefovir and entecavir should be considered for prophylaxis that is expected to be maintained over a long duration (> 12 months) rather than lamivudine [16]. The more recently approved drug tenofovir may also be considered for prophylactic therapy. Although these newer antiviral drugs may prove efficacious, their use may be limited in certain parts of the world by their higher costs.

Summary

It is suggested that clinicians administer prophylactic treatment with lamivudine or other antiviral agents prior to chemotherapy to reduce the risk of viral reactivation in HBV carriers. For this purpose, a therapeutic model adapted from Kohrt and colleagues is proposed in Figure 36.1. A full serological work-up for HBV markers is recommended for all at-risk patients prior to chemotherapy, especially those from highly endemic regions. Prophylactic treatment is recommended for those testing positive for HBsAg and risk assessment should be performed on HBsAg-negative patients. The duration of treatment is not yet clearly established but reasonable guidelines are as follows: a minimum of 6 months after cessation of conventional chemotherapy and 12 months or longer for patients with high pre-chemotherapy HBV DNA levels or immunosuppression regimens involving monoclonal antibodies such as rituximab [3].

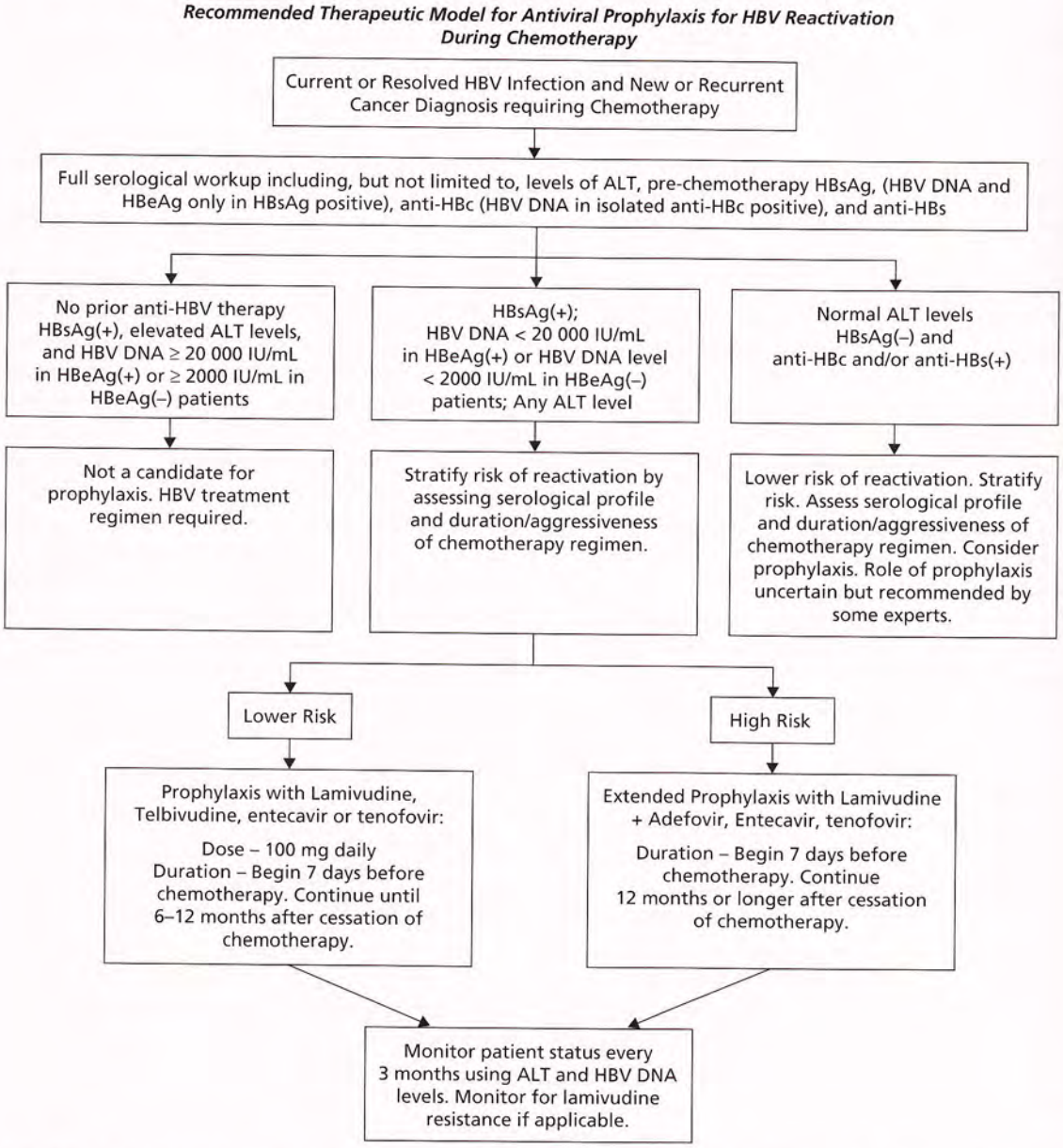

FIG. 36.1 A model adapted from the work of Kohrt *et al.* [5] that summarizes the treatment strategies to be employed in the management of chemotherapy patients with resolved or current HBV infection. Note that although most data exists with the use of lamivudine, other antiviral HBV drugs (entecavir and tenofovir) can be considered because of a better resistance profile. However, the cost-effectiveness of lamivudine versus other strategies has not been studied.

37 Management of hepatitis B in HIV-infected and other immunosuppressed patients

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LEARNING POINTS

- Hepatitis B has an aggressive course in patients co-infected with HIV, with increased risk of development of chronicity after acute HBV infection, persistence of HBeAg with high levels of HBV viraemia, and accelerated progression to cirrhosis.
- Therapy for HBV in HIV/HBV co-infected patients should preferably be administered as part of HAART to prevent emergence of drug-resistant HIV strains. In those co-infected with HIV, drugs with antiretroviral activity (lamivudine, tenofovir, entecavir) should be avoided as monotherapy for HBV in the absence of HAART is likely to lead to HIV resistance.
- Immunosuppression administered after renal or other organ transplantation in patients with chronic HBV infection leads to enhanced HBV replication and progressive liver disease that can be effectively prevented by nucleos(t)ide analogues.
- Patients with rheumatological diseases and inflammatory bowel disease being considered for treatment with biological agents should be screened for HBV and administered antiviral prophylaxis if HBsAg positive.

Introduction

Hepatitis B virus (HBV) is widely prevalent and it is not uncommon to encounter patients who have active or inactive HBV infection and develop immunosuppression because of a disease state (i.e. HIV) or who require immunosuppressive therapy for management of an unrelated disorder (i.e. chemotherapy for haematological or other malignancy, immunosuppression after organ transplantation). Patients with chronic kidney disease on dialysis are also intrinsically immunosuppressed and a significant proportion have associated HBV infection. Another group of patients recently recognized are those receiving biological agents for rheumatic disorders or inflammatory bowel disease. Patients with chronic HBV infection, under these conditions, have a substantial risk of reactivation of HBV that may lead to liver-related morbidity, liver failure and death. In this chapter we discuss the natural history, clinical presentation and diagnosis of chronic HBV infection in the above patient subgroups, followed by the essential role of antiviral therapy to suppress viral replication and prevent progressive liver disease.

HIV/HBV co-infection

Co-infection with HBV is common in HIV-infected individuals since both viruses are transmitted predominantly by percutaneous and sexual routes. In areas of low HBV endemicity, about 5–7% of HIV-positive individuals are co-infected with HBV, whereas this figure is 10–20% in areas of high HBV prevalence [1]. Men who have sex with men have higher co-infection prevalence rates (9–17%) than heterosexual individuals and intravenous drug users [2]. Although the effects of HBV on the natural history of treated and untreated HIV infection is debatable, there is well-documented evidence that HIV adversely affects all phases of the natural history of HBV. Following acute HBV infection, HIV-infected individuals are more likely to progress to chronic HBV infection rather than clear the virus. The risk of progression to chronic HBV is higher in patients with low CD4 T-cell counts [2]. Chronic co-infected patients who are HBeAg positive are less likely to have HBeAg seroclearance. HBV DNA levels are higher in

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co-infected patients compared with HBV monoinfected patients. Alanine aminotransferase (ALT) levels tend to remain normal in co-infected patients and thus do not reflect ongoing hepatic inflammation [3]. HIV-positive patients who have evidence of resolved past HBV infection (anti-HBc positive with or without anti-HBs positivity), although not shown to be at risk for progressive liver disease, are at risk for subsequent reactivation of HBV when CD4 T-cell count decreases or when administered chemotherapy for malignancies, especially lymphoma [4]. Although hepatocyte injury is immune mediated in HBV, there is accelerated progression of chronic hepatitis to cirrhosis in co-infected patients, despite the existence of an immunosuppressed state. The rate of progression is in fact faster in patients with low CD4 T-cell counts [5]. With regard to hepatocellular carcinoma (HCC), it is unclear whether HIV/HBV co-infected patients have an increased risk compared with HBV monoinfected patients. Recent studies suggest that the incidence of HCC is higher than the population average in HIV-positive patients co-infected with HBV or hepatitis C virus (HCV) and receiving highly active antiretroviral therapy (HAART). Underlying cirrhosis and increased longevity has been suggested as the principal reason for this phenomenon [6]. Overall, HIV/HBV co-infected individuals are more likely to die of liver-related causes than those infected with HBV alone. An eightfold risk of liver-related mortality has been shown in the Multicentre AIDS Cohort Study among HBV/HIV co-infected individuals compared with HIV monoinfected individuals, particularly in patients with low CD4 nadir counts [7]. Similarly, a large European study (EuroSIDA) has also reported a 3.6-fold higher risk of liver-related deaths in co-infected patients [8]. However, there are reports that effective suppression of HBV with potent antiviral agents, particularly tenofovir, may halt progression of liver fibrosis and prevent development of decompensated liver disease [9].

Diagnosis of HBV infection in HIV/HBV co-infected patients

Diagnosis of HBV in HIV-infected patients is similar to individuals not infected with HIV. Screening should be performed in all patients, with tests for HBsAg, anti-HBs and anti-HBc. Standard HBV vaccination is recommended for those who are negative for HBsAg and anti-HBs. Adequate antibody titres are achieved in only 17–56% of HIV patients; vaccine failures are therefore common and periodic testing is necessary in patients who continue to show high-risk behaviour [9]. Those who are diagnosed with chronic hepatitis B (evident by presence of HBsAg for at least 6 months) should have further evaluation with liver chemistries, imaging and testing for HBeAg, anti-HBe and HBV DNA. Liver biopsy is often necessary to stage the disease and occasionally to differentiate from other causes of hepatitis. The significance of isolated anti-HBc positivity in patients with HIV infection is not known. It may represent either resolved past infection or an occult HBV infection. The latter may be diagnosed by performing a sensitive assay for HBV DNA (lower limit of detection 10–20 IU/mL). Positive HBV DNA by such assays has been variably reported (2–89%) [2]. Although liver disease has not been associated with occult HBV infection, such patients may be at risk for reactivation during periods of further immunosuppression such as administration of chemotherapy for haematological malignancies. Reactivation with spontaneous disappearance of anti-HBs and reappearance of HBsAg can also occur, especially if CD4 T-cell counts are less than 200×10^6/L [2]. Therefore, even in HBsAg-negative patients with prior positive anti-HBs and/or anti-HBc, extended evaluation with all HBV-related serologies and HBV DNA should be performed in the presence of unexplained liver disease.

Management of chronic HBV in HIV/HBV co-infected patients (Figure 37.1)

The goal of antiviral therapy in HIV/HBV co-infected patients is suppression of HBV replication to prevent development of end-stage liver disease. Drug regimens should be carefully designed, since including agents effective against both HIV and HBV can promote drug resistance if either virus is inadequately suppressed. Most patients require therapy for both viruses and usually patients are initiated on HAART containing tenofovir in combination with either emtricitabine or lamivudine as the nucleoside backbone [2,9,10]. In co-infected patients it has been shown that using two drugs effective against HBV (including tenofovir) is more effective in reducing HBV DNA levels to less than 100 IU/mL than tenofovir, emtricitabine or lamivudine therapy alone [2]. Most importantly, a combination of two drugs effective against HBV prevents development of drug resistance. Patients with prior lamivudine-resistant HBV can also be adequately suppressed with tenofovir and

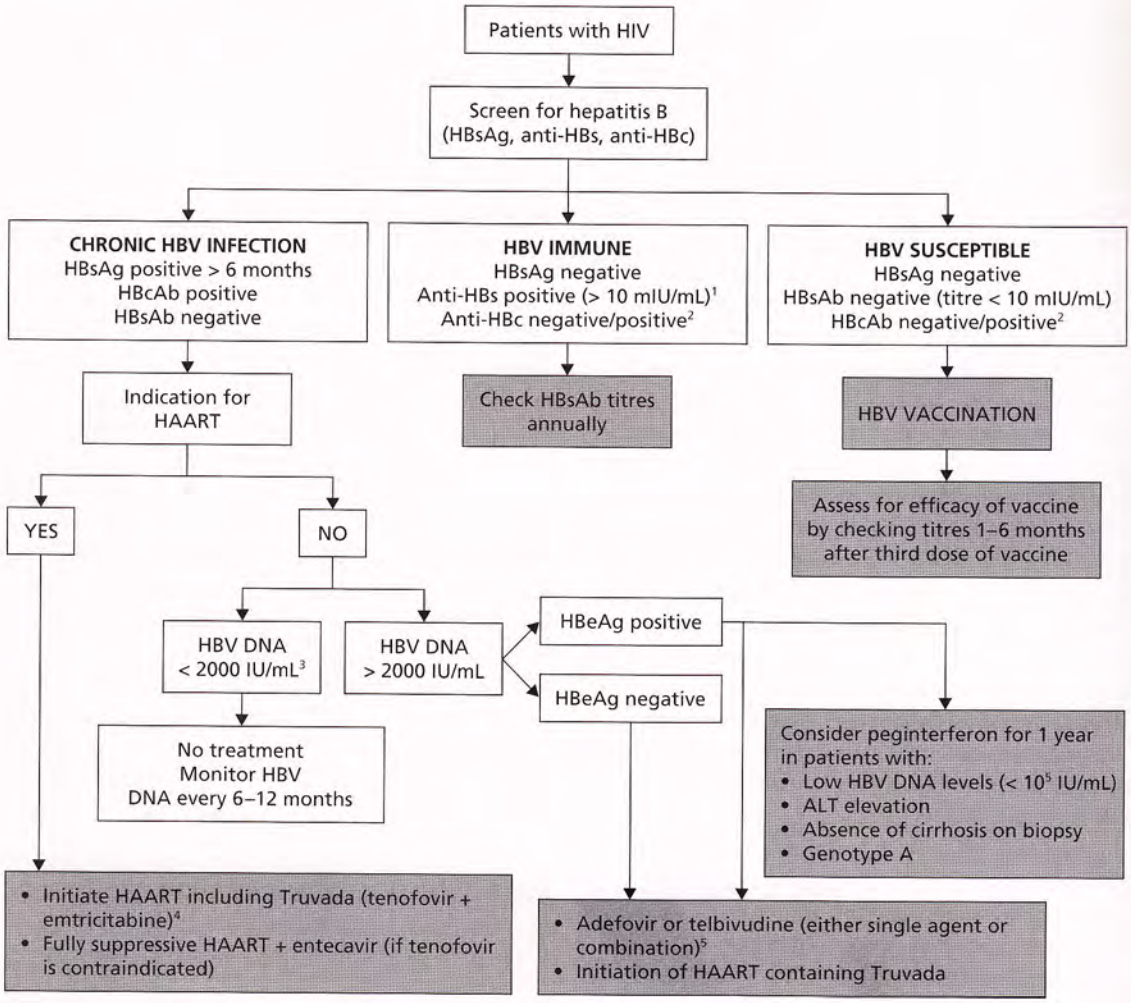

FIG. 37.1 Approach to evaluation and management of HBV infection in HIV-infected patients. 1, Anti-HBs titres must be checked annually; titres may fall with progression of HIV disease. 2, Anti-HBc-positive patients (with or without anti-HBs positivity) are at risk for HBV reactivation especially during periods of severe immunosuppression (organ transplantation, treatment of lymphoma, fall in CD4 T-cell counts). 3, Patients with cirrhosis and any level of detectable HBV DNA need nucleos(t)ide therapy. 4, Patients with lamivudine-resistant HBV also respond well to Truvada. 5, Patients who do not reach undetectable serum HBV DNA at week 24 of single-agent therapy should have add-on therapy with the other nucleos(t)ide.

emtricitabine combination. If tenofovir cannot be used as part of the initial regimen in patients with or without lamivudine resistance, alternatives include adefovir and entecavir. Compared with adefovir, entecavir is more potent and has a high genetic barrier to resistance. However, even though entecavir is effective in lamivudine-resistant HBV, resistance develops more rapidly. Moreover, since entecavir inhibits HIV replication, it should be used only with a fully suppressive HAART.

If there is no indication to treat HIV, use of nucleos(t)ide analogues for HBV treatment alone may result in development of HIV drug resistance mutations. Therefore it is important to assess the replication status of HBV as well as the stage of liver disease to guide treatment decisions. There are no established cut-off values of HBV DNA for initiation of treatment in co-infected patients. Patients with levels of 2000 IU/mL or more should preferably be treated [9,10,11]. Biopsy is ideal for assessing inflammatory

activity and fibrosis stage since aminotransferase levels tend to be low in patients with HIV. The presence of more than mild inflammation should be a consideration for therapy. Patients with advanced fibrosis and established cirrhosis should be treated in the presence of any detectable HBV DNA. Patients who need treatment for HBV without therapy for HIV should ideally be treated with agents that have no activity against HIV [10]; adefovir and telbivudine are two such drugs. Adefovir is unable to achieve complete HBV suppression due to its low potency, while telbivudine has been shown to manifest rapid development of resistance in HBV monoinfected individuals when used alone. Peginterferon can be considered for HBeAg-positive patients, although data are limited. Ideal patients for peginterferon treatment are those with low HBV DNA levels, elevated transaminases, genotype A and absence of significant fibrosis/cirrhosis on biopsy. A 1-year course of peginterferon can be expected to lead to HBeAg seroconversion in 20–30% patients [9,11]. Another option is to initiate HAART earlier than recommended by HIV treatment guidelines. Many clinicians prefer this approach, since this allows treatment of HBV with more potent drugs, allowing complete suppression of HBV replication and preventing long-term consequences of progressive liver disease.

It is important to monitor both HIV and HBV infections during therapy. HBV DNA and ALT levels should be monitored every 3 months to detect emergence of drug-resistant virus. Patients who are HBeAg positive should be monitored every 6 months for HBeAg loss and anti-HBe seroconversion. Patients who do not meet criteria for HIV therapy and who have low HBV viral load (< 2000 IU/mL) with no or minimal inflammation and absence of fibrosis on biopsy do not need treatment [11]. However, they need monitoring with HBV DNA and ALT levels every 6 months. If a HAART regimen containing anti-HBV agents needs to be discontinued, there is a risk of HBV reactivation in up to one-third of patients [12]. This is manifested by elevation in ALT and HBV DNA levels. Reactivation hepatitis can occasionally lead to severe hepatitis and liver failure, especially in patients with underlying cirrhosis [12]. Reactivation can be prevented by treating with an agent effective only against HBV (and not HIV) when HAART is discontinued.

HAART can lead to a rapid decline in HIV RNA levels and rise in CD4 T-cell counts. Reconstitution of the immune system is usually seen within the first 4–8 weeks of initiating HAART. This may lead to immune-mediated damage of HBV-infected hepatocytes that may cause worsening of the liver disease and occasionally hepatic decompensation and liver failure. Since HIV suppression occurs earlier than HBV suppression, it may be logical to initiate anti-HBV therapy before HAART therapy especially in patients with high HBV DNA levels. Such an approach is not universal and has not been studied to prove its effectiveness in preventing immune reconstitution hepatitis.

HBV in chronic kidney disease and renal transplantation

Universal screening, vaccination and strict infection control measures have reduced the prevalence of HBV in chronic kidney disease patients on long-term haemodialysis to between 0 and 7% in the developed world, although the prevalence may be higher in developing countries (5–20%) [13,14]. The course of HBV infection in patients on long-term dialysis is variable with only a few studies reporting excess liver-related morbidity and mortality. Patients usually have normal ALT levels and stable low levels of HBV DNA. Studies documenting histological evolution of liver disease are lacking in this patient population. However, HBV does have a detrimental effect on outcome after renal transplantation [15]. HBV DNA levels rise after renal transplantation and this may be related to immunosuppression and use of corticosteroids. A study evaluating serial liver biopsies after renal transplantation has shown histological deterioration in more than 80% of patients [16]. Accelerated progression to cirrhosis occurs in one-quarter of patients and survival is markedly reduced in patients who develop cirrhosis. Annual risk of development of HCC is 2.5–5% [13].

In patients with chronic kidney disease, antiviral therapy is indicated in chronically infected HBsAg-positive patients with detectable serum HBV DNA. Although controversial, even patients with low HBV DNA levels (< 2000 IU/mL) are being treated at many centres. Patients with undetectable HBV DNA (< 100 IU/mL) do not usually warrant treatment, unless they receive immunosuppression or chemotherapy [13]. Reports of interferon treatment are anecdotal and the mainstay of therapy has been the nucleoside analogue lamivudine. The dose of lamivudine has to be adjusted according to creatinine clearance and doses of 50–100 mg after each dialysis session or 10–20 mg daily have been used [14]. Although there are no published data on the use of entecavir and tenofovir in patients with

TABLE 37.1 Modification of entecavir dose in patients with renal impairment and in those on haemodialysis.

Creatinine clearance (mL/min)	Lamivudine-sensitive HBV	Lamivudine-resistant HBV
> 50	0.5 mg once daily	1.0 mg once daily
30–49	0.25 mg once daily *or* 0.5 mg every 48 hours	0.5 mg once daily
10–29	0.15 mg once daily *or* 0.5 mg every 72 hours	0.30 mg once daily *or* 0.5 mg every 48 hours
< 10	0.05 mg once daily *or* 0.5 mg every 7–10 days (administer after haemodialysis)	0.10 mg once daily *or* 0.5 mg every 72 hours

Oral solution (0.05 mg/mL) is recommended for doses less than 0.5 mg.
No dose adjustment is recommended based on age or for patients with hepatic dysfunction.

chronic kidney disease, these drugs are being preferred for the treatment of chronic HBV infection considering their favourable resistance profile. Patients with creatinine clearance below 50 mL/min as well as those on haemodialysis need reduced doses of entecavir and tenofovir (Tables 37.1 and 37.2). All patients, irrespective of HBV DNA levels require ongoing surveillance for HCC as well as serial ALT and HBV DNA to monitor for spontaneous HBV reactivation. Biopsy is desirable especially in patients being evaluated for renal transplantation to stage fibrosis and detect cirrhosis, since the presence of cirrhosis adversely affects post-transplant outcome. Presence of decompensated cirrhosis necessitates assessment for combined liver and kidney transplantation. Isolated renal transplantation in patients with well-compensated cirrhosis is controversial. With the availability of several nucleos(t)ide analogues that are quite potent at suppressing HBV replication and thereby preventing progression of cirrhosis, patients with stable well-compensated cirrhosis who have undetectable HBV DNA on treatment may be considered for isolated renal transplantation [13]. For renal transplant patients, nucleos(t)ide analogues should be started at least 4–6 weeks prior to transplantation in those with detectable HBV DNA. Patients with undetectable HBV DNA may be started on treatment at the time of transplantation. Choice of nucleos(t)ide analogue should consider long-term risk of resistance since treatment is required for prolonged periods. Entecavir or tenofovir may be preferred over lamivudine, although published experience on these drugs in post-transplant settings is limited. Regular monitoring of ALT and HBV DNA should be done every 3 months to detect reactivation. HCC surveillance should be continued especially in patients with cirrhosis. Risk of reactivation in HBsAg-negative HBcAb-positive patients is negligible and prophylaxis is not recommended routinely. HBV vaccination has been suggested prior to transplantation in the subgroup of HBsAg-negative HBcAb-positive patients with a low titre of HBsAb (< 100 IU/mL) who are at a higher risk for reactivation [13].

TABLE 37.2 Modification of tenofovir dose in patients with renal impairment and in those on haemodialysis.

Creatinine clearance (mL/min)	Tenofovir dose
> 50	300 mg once daily
30–49	300 mg every 48 hours
10–29	300 mg twice weekly
< 10, or patients on haemodialysis	300 mg once a week (administer after three dialysis sessions)

HBV in rheumatic diseases

Although most of the published literature on HBV reactivation is from the fields of oncology and transplantation, an increasing number of cases are being reported in patients with rheumatic diseases on immunosuppressants. Not uncommonly, patients with rheumatic diseases receive long-term low-dose immunosuppression (with or without corticosteroids). Corticosteroids specifically enhance HBV replication and this is related to the presence of a glucocorticoid responsive element in the HBV genome. HBV reactivation has been reported after brief interruption of immunosuppression as well as during chronic therapy [17]. There have been several recent reports of patients developing HBV reactivation while on therapy with

biological agents such as tumour necrosis factor (TNF)-α inhibitors and anti-B-cell therapy (rituximab) [18]. All patients developing HBV reactivation were HBsAg positive prior to initiation of treatment with infliximab. Prophylaxis with lamivudine has been shown to prevent HBV reactivation in HBsAg-positive patients on infliximab in a few case reports [18]. Although there are no guidelines for HBV screening in rheumatology patients, those being considered for corticosteroids, TNF-α inhibitors or rituximab therapy should be screened for HBV. HBV prophylaxis should be given to patients who are HBsAg positive irrespective of HBV DNA levels. Currently, HBsAg-negative and anti-HBc-positive patients may not receive preventive treatment, although periodic monitoring of HBV status is desirable.

HBV in inflammatory bowel disease

There have been reports of HBV reactivation following infliximab therapy for Crohn's disease. Death from HBV reactivation-induced liver failure has also been reported [18]. Similar to rheumatic diseases, it may be prudent to screen patients prior to initiation of infliximab and offer lamivudine prophylaxis to all HBsAg-positive individuals. Since infliximab is administered intermittently, lamivudine should be given continuously and at least until 6 months after the last infusion. There have been no reports of HBV reactivation with other TNF-α inhibitors (adalimumab, etanercept), although this is likely to occur in these patients as well and therefore prophylaxis appears prudent.

Conclusion

Approximately 10% of HIV-infected individuals have chronic hepatitis B. Liver disease is a leading cause of morbidity and mortality in patients with HIV infection, despite adequate control of HIV with HAART. HIV affects both the natural history and treatment of chronic HBV infection. HIV/HBV co-infected patients have higher HBV DNA levels, lower rates of spontaneous HBeAg loss, increased risk of progression to cirrhosis and possibly an increased risk of HCC. The management of hepatitis B in HIV infection is complicated by the dual activity of several nucleos(t)ide analogues against both HIV and HBV, which can lead to rapid development of drug resistance of either virus if single agents are used and viral suppression is incomplete. Patients with other forms of immunosuppression such as after renal transplantation, where the prevalence of chronic HBV is higher, are also at risk of HBV reactivation and progressive liver disease. More recently, patients with chronic HBV infection and rheumatological disease or inflammatory bowel disease receiving immunosuppression with high-dose steroids, infliximab or rituximab have also been reported to manifest HBV reactivation. Screening of all immunosuppressed patient groups followed by antiviral prophylaxis with nucleos(t)ide analogues in HBsAg-positive patients can effectively prevent HBV reactivation and associated liver-related morbidity.

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38 Lamivudine and adefovir resistance: what should we do?

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LEARNING POINTS

- Resistance to the original oral antiviral agents (lamivudine and adefovir) is common but appropriate use of targeted 'rescue' therapies allows resistance to be managed.
- For patients with lamivudine resistance it is important to add on adefovir because resistance to adefovir is common if the drug is substituted for lamivudine in patients with lamivudine resistance.
- For patients with adefovir resistance add-on strategies are probably appropriate and consideration should be given to using the third-generation antiviral agents.
- In the future the newer more potent antiviral agents (such as tenofovir and entecavir) may reduce resistance rates appreciably.

Introduction

Considerable progress has been made in the development of potent and safe inhibitors of hepatitis B virus (HBV). However, nucleoside analogues may lead to the development of antiviral resistance, diminishing their efficacy. Thus choices of therapy depend on a number of factors predictive of treatment response, including clinical circumstances and stage of disease, potency of different agents, and the likelihood and consequences of resistance to treatment. HBeAg-positive disease is typically associated with high levels of HBV replication for a prolonged period of time. In anti-HBe-positive chronic hepatitis B, HBV DNA concentrations are typically in excess of 10^5 copies/mL but less than 10^8 copies/mL.

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Lamivudine and adefovir in HBV infection

Lamivudine (2′,3′-dideoxy-3′-thiacytidine or 3TC) is a cytidine analogue. Lamivudine competes with cytosine in the synthesis of viral DNA. It is a (−)enantiomer and a phosphorylation step is required for transformation to active drug. The drug has a strong safety record, and reliably reduces HBV DNA concentrations in serum by 2–4 $\log_{10}$. Elevated serum alanine aminotransferase (ALT) levels have likewise been shown to predict a higher likelihood of HBeAg loss in patients with chronic HBV treated with lamivudine. Lamivudine is a relatively inexpensive drug, and the lack of side effects in patients with advanced disease is attractive. As a result, lamivudine has become a widely used first-line drug for the treatment of HBeAg-positive and anti-HBe-positive disease. The major disadvantage of lamivudine treatment is the high rate of resistance observed in both HBeAg-positive and anti-HBe-positive patients.

Adefovir dipivoxil is a phosphonate acyclic nucleoside analogue of adenosine monophosphate [1]. Adefovir diphosphate acts by selectively inhibiting the reverse transcriptase/DNA polymerase of HBV by directly competing with the binding of the endogenous substrate deoxyadenosine 5′-triphosphate (dATP) [2]. A variable proportion of patients, particularly HBeAg-positive patients with higher body mass index (BMI) and high viral load, have slower and poorer primary responses; in one analysis, 25% of patients had less than 2.2 $\log_{10}$ reduction. These effects may be seen in routine clinical practice where worse compliance and a higher BMI may affect susceptibility to adefovir, resulting in poor primary responses. In anti-HBe-positive patients [3], adefovir-treated group show significant improvement when compared with placebo. Thus adefovir is an agent that has low rates of resistance and good

long-term viral suppression, which is of particular benefit in HBeAg-negative HBV infection.

Lamivudine

What are the characteristics of lamivudine-resistant HBV?

Lamivudine resistance is conferred through acquired selection of HBV with mutations of the YMDD motif of the HBV DNA polymerase gene [4,5]. The incidence of lamivudine resistance is 15–20% per year, with 70% of patients becoming resistant after 5 years of treatment. Variants emerging during lamivudine therapy display mutations in the viral polymerase, within the catalytic domain (C domain), which includes the YMDD motif (e.g. M204V or M204I), and within the B domain (e.g. L180M or V173L). These mutants have a reduced replicative capacity compared with wild-type virus. The commonest mutation is the substitution of methionine to isoleucine or valine (rtM204V/I) at the highly conserved YMDD motif of the reverse transcriptase. Four major patterns have been observed: L180M + M204V; M204I; L180M + M204I; V173L + L180M + M204V; and occasionally L180M + M204V/I. Although viral 'fitness' may be reduced, as lower levels of HBV DNA occur, recent studies have suggested that the disease may progress [6]. Resistance to lamivudine emerges at higher rates in HIV/HBV co-infection [7] and more rapidly in patients with HBV genotype A than in those with genotype D. Lamivudine resistance is accompanied by breakthrough of HBV DNA levels and a subsequent rise in ALT, but this is variable. In patients with decompensated cirrhosis undergoing lamivudine monotherapy, early detection of viral breakthrough is critical.

How should lamivudine resistance be managed?

Adefovir and tenofovir (and to a degree entecavir) are active against lamivudine-resistant HBV, but it is advisable to continue lamivudine in combination in these patients rather than replacing lamivudine with adefovir. Nonetheless, the clinical course after the development of resistance is complex and variable. Hepatitis is common, but is not always severe. Most patients generally experience worsening of liver disease [6]. Adefovir has been an important drug for the treatment of lamivudine-resistant HBV infection. There are a number of reports of successful treatment of lamivudine-resistant patients with adefovir, particularly for recurrence of HBV before or after transplantation [8–11]. The wisdom of discontinuing lamivudine has been challenged, given the rates of resistance or non-response observed with adefovir monotherapy in some centres [12]. A 1 $\log_{10}$ rise in previously undetectable HBV DNA levels is taken as indicative of phenotypic resistance; adding a rescue therapy before waiting for an increase in ALT levels is advisable for these patients (see below). Thus the early addition of adefovir at the time of detection of a log rise in HBV DNA is advocated, as subsequent resistance (and adverse clinical events) are reduced if adefovir is added at lower concentrations of HBV DNA [13,14]. In the future, tenofovir will replace adefovir for the treatment of lamivudine resistance. In our current state of knowledge it is reasonable to suggest that tenofovir should be added to therapy for patients with lamivudine resistance.

Entecavir shows some efficacy against lamivudine-resistant HBV, but the effect is partial and higher doses of entecavir (1.0 mg) are required. Virological rebound and resistance have been reported in 43% of lamivudine-resistant patients after 4 years of switching treatment to entecavir. Lower rates of HBV suppression were reported in this group when using 1.0 mg of entecavir. Entecavir resistance is thus common in lamivudine-resistant patients and is not the preferred therapy.

Telbivudine cannot be used for the treatment of lamivudine-resistant patients. The magnitude of early HBV suppression (24 weeks) is linked to clinical efficacy and resistance at 1 year.

How should lamivudine be used?

The efficacy of lamivudine monotherapy is offset by the development of resistance, restricting its use as a first-line monotherapy, although monotherapy will suffice for 3–5 years in about 15–20% of anti-HBe-positive patients with low levels of replication. After emergence of resistance, the clinical benefit of continuing lamivudine is doubtful, and resistance can be taken to imply treatment failure.

The value of lamivudine monotherapy is being questioned because of the likelihood of subsequent resistance to a lineage of drugs including entecavir, telbivudine and possibly adefovir. Lamivudine resistance has typically been managed by sequential treatment with adefovir, and more recently tenofovir, but the disadvantage of sequential treatment strategies has been highlighted. If forced to use lamivudine, it is ideal to restrict it to patients likely to benefit, i.e. those with high ALT concentrations and low

HBV DNA concentrations. Early viral suppression, in particular HBV DNA levels below 200 copies/mL or less than 3 $\log_{10}$ after 6 months of treatment, predicts a lower risk of resistance after 1 year of treatment [15,16]. Long-term lamivudine therapy can prevent the complications of HBV-related liver disease as long as viral suppression is maintained [17]. Thus progression of liver disease can be prevented with a prolonged viral response, but this response is attenuated in those with virological breakthrough (i.e. resistance). In summary, lamivudine is not recommended as a single agent but could form the backbone of maintenance combination therapies.

Recurrent HBV infection in the transplanted liver has previously been a major problem. Lamivudine for pre-transplant prophylaxis, in combination with hepatitis B immunoglobulin (HBIG), reduces the risk of graft infection to less than 10%, as long as HBV is suppressed before transplantation. With the advent of lamivudine and adefovir, outcomes have improved further [18,19]. Currently, both HBIG and lamivudine and/or adefovir are used prophylactically and recurrent HBV is now rare. Other licensed and more potent nucleosides could also be considered. For patients with high levels of replication, or with cirrhosis, many experts would consider initiating treatment concurrently with lamivudine and adefovir, or preferably using drugs with high genetic barriers to resistance (i.e. tenofovir or entecavir).

Adefovir

What are the characteristics of adefovir resistance?

Sequencing of the RT domain of the HBV polymerase has suggested that mutations rtA181V/T in the B domain and rtN236T in the D domain confer resistance to adefovir [20]. The reported mutations correlate with HBV DNA rebounds of more than 1 log above nadir, suggesting phenotypic resistance. Life-table analysis has suggested a cumulative incidence of 3.9–5.9% (in naive patients) after 3 years of treatment. A figure of 18% at 4 years of therapy has been reported. However, in clinical practice, higher rates than this are being reported [21]. Patients with prior lamivudine resistance are at greater risk of adefovir resistance [22]. HBV DNA levels at week 48 predict rate of resistance. Suppression to less than 3 $\log_{10}$ was associated with a 4% rate of adefovir resistance at week 144, but an HBV DNA concentration of greater than 6 $\log_{10}$ was associated with 67% resistance at week 144. Adefovir resistance is apparently uncommon in treatment-naive patients treated with adefovir and emtricitabine or adefovir and lamivudine in combination.

How should adefovir resistance be treated?

Adefovir mutants remain sensitive to lamivudine, emtricitabine, telbivudine and entecavir [23,24]. The A181V mutation has a greater effect on subsequent sensitivity to lamivudine than N236T; this compares with observed *in vitro* effects on fold sensitivity.

How should adefovir be used?

It is important to identify patients with high levels of replication, or host factors, for whom adefovir monotherapy will not suffice. Anti-HBe-positive patients could be treated with adefovir monotherapy, as first-line treatment is effective in this group. Long-term therapy is required, and resistance has been reported but at lower rates than with lamivudine therapy. In other groups such as HBeAg-positive patients or anti-HBe-positive patients with decompensated cirrhosis or high viral loads, rapid suppression of HBV DNA replication with a low risk of primary non-response or resistance is important, and combination therapies could be advantageous. Tenofovir will supplant adefovir shortly.

What about newer agents for the treatment of HBV?

Tenofovir

Tenofovir and adefovir are related molecules with a similar mechanism of action. Tenofovir disoproxil fumarate is the prodrug of tenofovir. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate dATP and, after incorporation into DNA, causing DNA chain termination. There is strong clinical evidence of the efficacy of tenofovir in chronic hepatitis B, with less nephrotoxicity. The drug is active against wild-type and precore mutant HBV, as well as lamivudine-resistant HBV *in vitro* [25–31].

Thus tenofovir is a far more consistent and potent suppressor of HBV replication than adefovir. Levels of suppression in both HBeAg-positive and anti-HBe-positive patients are similar to those observed with other newer potent nucleosides such as entecavir, although these two drugs have not been compared. Tenofovir is effective against lamivudine-resistant strains of HBV as well as the

A181T strain of adefovir-resistant HBV. Tenofovir shows intermediate activity against the N236T variant associated with adefovir resistance and is effective against entecavir-resistant HBV. Tenofovir will also be more useful than adefovir for the treatment of lamivudine resistance. Tenofovir has proven useful for the management of delayed or suboptimal responses to adefovir. A rapid switch to tenofovir or entecavir for these latter patients is recommended.

Entecavir

Entecavir is a cyclopentyl guanosine analogue. Early studies in animals and humans indicated that entecavir is a potent inhibitor of viral replication. Entecavir has been licensed for the treatment of chronic hepatitis B. Entecavir inhibits all three activities of the HBV polymerase/reverse transcriptase: base priming, reverse transcription of the negative strand from the pregenomic mRNA and synthesis of the positive strand of HBV DNA. Phase III trials have been completed.

In Phase III trials in HBeAg-positive patients, HBV DNA was suppressed to less than 300 copies/mL in 67% and 36% of entecavir- and lamivudine-treated patients, respectively [32]. The mean change from baseline was −6.9 log and −5.4 log respectively. HBeAg seroconversion occurred in 21% and 18% of entecavir- and lamivudine-treated patients, respectively. In HBeAg-negative patients, HBV DNA suppression to less than 300 copies/mL occurred on treatment in 90% of entecavir-treated and 72% of lamivudine-treated patients. The mean change of HBV DNA from baseline was −5.0 log and −4.5 log. ALT normalized in 78% and 71% respectively. Rebound to levels detectable by polymerase chain reaction (PCR) occurs in the majority of patients after cessation of treatment [33].

Entecavir resistance

A complex picture of entecavir resistance is emerging, suggesting a requirement for new reverse transcriptase changes in combination with those conferring lamivudine resistance to reduce susceptibility to entecavir. Entecavir resistance requires M204V/I plus L180M mutations and T184, S202 or M250 mutations [34]. After 4 years of follow-up, a cumulative resistance rate of approximately 1.2% of a subset of naive treated and monitored patients has been reported. At 5 years, resistance rates remain low in virological responders on continued treatment; entecavir thus confers a high genetic barrier to resistance in naive patients.

How can resistance be avoided?

Avoiding resistance should take into account the appropriate indications for treatment and the optimization of therapy to avoid resistance. This is particularly applicable to therapy with agents such as lamivudine and adefovir, which can lead to high rates of resistance. The disadvantages of using a single drug with high-frequency resistance are:

- treatment failure is likely;
- failure is frequently associated with exacerbation of disease;
- an increase in the population with resistant strains will result;
- resistance to lamivudine may increase precedent for resistance or deleterious mutations with other agents;
- resistance represents and the drug may become unusable.

Newer potent agents capable of suppressing HBV in most patients to levels undetectable by current PCR assays (< 10–15 IU/mL) are preferred.

Resistance can be prevented by adhering to the following recommendations.

- There should be a clear indication for starting therapy.
- Encourage patient compliance.
- Maximize antiviral activity.
- Suppress HBV DNA to the lowest possible level.
- Maximize genetic barriers.
- Avoid sequential treatment.
- Avoid treatment interruptions.
- Increase pharmacological barriers.

Table 38.1 shows the cross-resistance data for the most frequently resistant HBV variants and Table 38.2 shows the appropriate management strategy when resistance is encountered.

Who should be treated?

The European Association for the Study of the Liver (EASL) has recently published guidelines for therapy [35]. Serum aminotransferase levels, serum HBV DNA levels and histological grade and stage are taken into account. Thus these guidelines suggest that patients should be considered for treatment when serum ALT levels are above the upper limit of normal for the laboratory and/or HBV DNA levels are above 2000 IU/mL (~ 10 000 copies/mL), and liver biopsy shows moderate to severe active

TABLE 38.1 Cross-resistance data for the most frequently resistant HBV variants.

HBV variant	Lamivudine	Telbivudine	Entecavir	Adefovir	Tenofovir
Wild type	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive
M204I	Resistant	Resistant	Intermediate	Sensitive	Sensitive
L180M + M204V	Resistant	Resistant	Intermediate	Sensitive	Sensitive
A181T/V	Intermediate	Sensitive	Sensitive	Resistant	Sensitive
N236T	Sensitive	Sensitive	Sensitive	Resistant	Intermediate
L180M + M204V/I ± I169T ± V173L ± M250V	Resistant	Resistant	Resistant	Sensitive	Sensitive
L180M + M204V/I ± T184G ± S202I/G	Resistant	Resistant	Resistant	Sensitive	Sensitive

Source: European Association for the Study of the Liver [35].

TABLE 38.2 Appropriate management strategy when resistance is encountered. The safety of some combinations in the long term is unknown.

Drug resistance	Second drug addition
Lamivudine resistance	Add tenofovir
Adefovir resistance	If N236T substitution, add lamivudine, entecavir or telbivudine or switch to tenofovir plus emtricitabine If A181T/V substitution, add entecavir or switch to tenofovir plus emtricitabine
Telbivudine resistance	Add tenofovir
Entecavir resistance	Add tenofovir
Tenofovir resistance (not yet described)	Entecavir, telbivudine, lamivudine or emtricitabine could be added

necroinflammation and/or fibrosis using a standardized scoring system (e.g. at least grade A2 or stage F2 by Metavir scoring). Patients with mild disease and normal ALT levels may not require immediate treatment and should be monitored carefully at appropriate intervals.

The guidelines suggest that therapy with nucleosides should aim to reduce HBV DNA concentrations in serum to as low a level as possible, ideally below the lower limit of detection of real-time PCR assays (10–15 IU/mL), to ensure virological suppression that will then lead to biochemical remission, histological improvement and prevention of complications and reduce the risk of resistance [35]. Prolonged continuous HBV DNA reduction to undetectable levels is necessary to reduce the risk of resistance to nucleosides. It also increases the chance of HBeAg seroconversion in HBeAg-positive patients and the possibility of HBsAg loss in the mid to long term in HBeAg-positive and HBeAg-negative patients.

The recently formulated EASL guidelines suggest that because entecavir and tenofovir are potent HBV inhibitors and have a high barrier to resistance, they can be confidently used as first-line monotherapy. The role of monotherapy with entecavir or tenofovir could be modified if higher rates of resistance become apparent with longer treatment duration. In a compliant patient with a primary non-response, identification of possible HBV resistance mutations can help formulate a rescue strategy that must reasonably be based on an early change to a more potent drug that is active against the resistant HBV variant. Although there are no data that any combinations tested to date are synergistic, proof of principle exists to suggest that, for example, resistance to lamivudine and adefovir are reduced when used in combination.

There is some urgency to establish the efficacy of potent and appropriate combination therapies, but these will need necessarily large and hence expensive trials. Thus we may need to glean the efficacy of potent monotherapies and combination therapies from direct clinical experience and learning in the next few years.

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39 HBV therapy following unsuccessful interferon therapy: how do you see the role for oral therapies?

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LEARNING POINTS

- Interferon is a well-accepted therapy for chronic HBV, particularly HBV genotypes A and B.
- Combination therapy with interferon and an oral nucleos(t)ide analogue has not been shown to be superior to interferon alone.
- In interferon non-responders, oral therapy appears to be the best option.
- Strategies of sequential therapy or single or multiple combination therapies in interferon non-responders need to be evaluated.

Introduction

The two broad treatment options for chronic hepatitis B virus (HBV) infection are the interferon alfas (conventional and pegylated) and oral antivirals (nucleotide and nucleoside analogues). Interferon has a dual mechanism of action involving both immunomodulatory and antiviral actions. Compared with the conventional or standard interferons, pegylated interferons have lower potency *in vitro* but a more favourable pharmacokinetic profile with a half-life that allows weekly dosing. Findings from a Phase II dose-finding study showed that in HBeAg-positive patients, peginterferon alfa-2a had better outcomes than interferon alfa-2a and was more convenient with weekly dosing [1]. Interferon was the first therapy approved for chronic HBV in 1992, with peginterferon approved in 2005. Advantages of interferon therapy are a finite duration of treatment, absence of resistance, and immune-mediated viral suppression even after the dosing period. The side-effect profile and subcutaneous administration have limited its use in this era of oral antiviral therapies. Furthermore, the majority of patients treated with interferon do not achieve a response and will require further therapy. This chapter discusses the initial and subsequent efficacy of interferon therapy and treatment options for those who fail.

Interferon efficacy

HBV treatment end-points include HBV DNA suppression, HBeAg seroconversion, and HBsAg loss with or without seroconversion to anti-HBs. Pretreatment factors that are predictors of seroconversion with interferon therapy are low viral load, high serum alanine aminotransferase (ALT) levels and high activity scores on liver biopsy [2,3]. When treated with conventional interferon for 16–24 weeks or peginterferon for 48 weeks, roughly one-third of patients respond with HBeAg seroconversion. The results of two large multicentre trials with peginterferon therapy are summarized in Table 39.1. In HBeAg-positive patients, 25% and 14% of patients achieved HBV DNA below 400 copies/mL at the end of 48 weeks of peginterferon alfa-2a (week 48) and after 24 weeks of follow-up (week 72), respectively. Because of the immunomodulatory effects of interferon, HBeAg seroconversion continues to occur weeks to months after the end of therapy. HBeAg seroconversion occurred in 27% of patients at week 48 and in 32% at week 72 while HBsAg seroconversion occurred in 3% of

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TABLE 39.1 Outcomes of studies comparing peginterferon with lamivudine.

	End of treatment (week 48)		End of follow-up (week 72)	
	Peginterferon alfa-2a (%)	Lamivudine (%)	Peginterferon alfa-2a (%)	Lamivudine (%)
HBeAg-positive patients				
Normalization of ALT	39	62	41	28
HBeAg seroconversion	27	20	32	19
HBV DNA < 400 copies/mL	25	40	14	5
HBsAg seroconversion	–	–	3	0
HBeAg-negative patients				
Normalization of ALT	38	73	59	44
HBV DNA < 400 copies/mL	63	73	19	7
HBsAg loss	–	–	4	0
HBsAg seroconversion	–	–	3	0

patients [4]. The results of the study confirmed the efficacy of peginterferon in HBV DNA suppression and seroconversion of HBsAg and HBeAg. In HBeAg-negative patients, 63% and 19% of patients achieved HBV DNA below 400 copies/mL at week 48 and week 72, respectively. HBsAg loss and seroconversion occurred in 4% and 3% of patients [5].

There are few studies with long-term follow-up of patients treated with interferon. Lau *et al.* [6] reviewed the long-term outcomes in both conventional interferon responders and non-responders. Response was defined as HBeAg seroconversion. Interestingly, even beyond the dosing period, seroconversion continued to occur, as did HBsAg loss, particularly in those with initial response. After a mean follow-up of 6.2 years, 100% of initial responders and 65% of non-responders became HBeAg negative while 86% of responders and 11% of non-responders lost HBsAg. In a study by Moucari *et al.* [7], 14 years of follow-up in 97 HBeAg-positive patients treated with interferon revealed continued yearly loss of HBsAg up to 29% by the end of follow-up. Similarly, in HBeAg-negative patients treated with peginterferon, HBsAg loss occurred after the dosing period, reaching 8.7% by 3 years [8]. These studies suggest that there are potential benefits even beyond the dosing period when patients are treated with interferon, especially if they show an initial response.

Not all genotypes of HBV respond well to interferon. Higher responses to interferon have been reported for genotype A than D and for genotype B than C. A study conducted by Hou *et al.* [9] reported response to interferon in 33% of genotype A patients and 11% of genotype D patients, a difference that was statistically significant. Flink *et al.* [10] found that loss of HBsAg occurred in 14% of genotype A and 2% of genotype D patients. Kao *et al.* [11] found that interferon was more efficacious in genotype B than C, with 41% and 15% responding, respectively. Difference in response by genotype may be explained by the differences in molecular characteristics of each genotype. Given that these differences in outcome based on genotype have been noted in several studies, most recommend considering interferon therapy for genotype A and perhaps B.

Retreatment of interferon non-responders

Therapy options for interferon non-responders are limited to retreatment with interferon, oral antivirals or a combination of both. The role of interferon retreatment in interferon non-responders is limited. In a small pilot study conducted by Janssen *et al.* [12], 18 patients who had failed prior interferon therapy were retreated with 16 weeks of dose-escalating interferon. Although all patients experienced a decrease in their HBV DNA level by 80%, only two of the 18 patients (11%) became HBV DNA negative and had HBeAg seroconversion. None of the patients experienced HBsAg loss. Combination therapy with interferon and an oral antiviral has also not been proven to be of benefit [13].

Because of the lack of efficacy in retreating interferon non-responders with another course of interferon or a combination regimen, monotherapy with oral antivirals appears to be the preferred treatment option. In a small

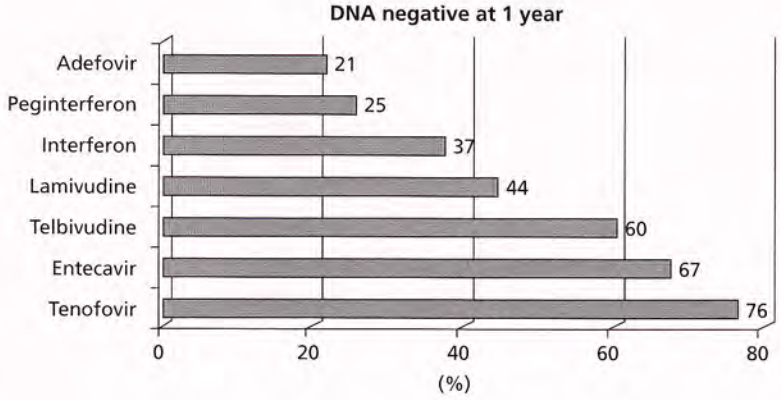

FIG. 39.1 Efficacy of approved therapies for chronic HBeAg-positive hepatitis B.

dose-finding study, Dienstag *et al.* [14] treated 32 chronic HBeAg-positive patients with lamivudine (25, 100 or 300 mg) or placebo for 12 weeks. Of this group, 17 had previously failed interferon. While the majority had viral suppression, only six maintained suppression and five of them were the interferon non-responders, four of whom seroconverted. In a larger study conducted by Schiff *et al.* [13], interferon non-responders were treated for 52 weeks with lamivudine or placebo. Although the study failed to show a significant difference in HBeAg seroconversion, more patients experienced HBeAg loss at week 52 with lamivudine compared with placebo (33% vs. 13%; $P = 0.013$). Comparison of liver biopsies at baseline and at week 52 did not show significant changes in fibrosis but did show greater improvement in necroinflammatory activity in the lamivudine group compared with the placebo group.

Oral antivirals

No large datasets have compared nucleoside/nucleotide treatment of interferon non-responders and interferon-naive patients. However, there is little to suggest that efficacy would be lower in the interferon-experienced patients. Indeed, as the apparent benefits of interferon therapy appear to extend beyond the treatment period, oral therapy may further enhance this benefit. This requires further study. As for the choice of oral antiviral, the two preferred compounds are the two most potent with the lowest barriers to resistance, namely entecavir and tenofovir. Further study comparing the two in a post-interferon setting is required before any firm recommendations can be made. Figure 39.1 shows the relative potency of the compounds with 48–52 weeks of therapy (12–24 weeks with conventional interferon) [15]. These data are not from head-to-head comparisons and patient demographics and trial designs varied considerably. Lamivudine has the largest breadth of data and is well characterized. It does have a weak barrier to resistance and, like telbivudine, the resistance profile has limited its usefulness. Adefovir is a weak antiviral and although there is little early resistance, its lack of efficacy leads to high rates of late resistance.

Conclusions

Interferon remains a viable first-line therapeutic option for genotypes A and B, with potential benefits extending beyond the dosing period. Nevertheless, the majority of these patients will fail therapy and will need an oral agent. At that point, they should be treated in the same way a treatment-naive patient would be. Future studies need to further explore the utility of interferon and antivirals in various schemata in the treatment of chronic HBV infection. Now that there are five oral compounds, conventional interferon and two peginterferons, many permutations exist that can be explored in an effort to optimize therapy. Sequential therapy, priming with one agent followed by another, combination therapies and even alternating therapies can all be explored. One must remain cautious, however, as novel adverse events may occur when drugs are combined. The combination of peginterferon alfa-2a and telbivudine led to several cases of peripheral neuropathy in a clinical trial setting. It is best to study all potential combinations in a rigorous systematic way to minimize toxicity while addressing the aim of the study.

40 Hepatitis B and hepatitis C co-infection

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LEARNING POINTS

- HBV/HCV co-infection is a common phenomenon, particularly in areas where both infections are endemic.
- Viral interaction may result in fluctuating HBV/HCV dominance and frequently leads to apparent suppression of HBV replication.
- Peginterferon and ribavirin combination therapy for HCV is as efficacious and safe in HBV/HCV co-infection as in monoinfection.
- Few data are available to guide therapy in patients with dually active co-infection, although addition of a nucleos(t)ide may be appropriate.
- Antiviral therapy may alter the viral dynamics and reverse the suppression of HBV replication. This should be actively sought and nucleos(t)ide therapy instituted as appropriate.

Introduction

The globally high prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV), in association with the shared routes of transmission of these viruses, explains the inevitable common finding of HBV/HCV co-infection. Such interactions were first described when HCV infection was known as non-A, non-B hepatitis [1]. It is difficult to accurately determine the number of HBV/HCV co-infected individuals and there is considerable geographical variation; it is estimated that 3–22% of chronic HBV-infected patients are HCV antibody positive and that 2–10% of anti-HCV-positive patients are HBsAg positive [2]. Outside endemic areas, HBV/HCV co-infection most frequently occurs in specific high-risk populations, particularly intravenous drug users, HIV-positive individuals and patients on haemodialysis [2]. Reports of occult HBV infection (HBsAg negative, HBV DNA positive) suggest it is likely we underestimate the true prevalence of co-infection and implies that co-infection should be actively sought by HBV DNA testing, particularly in anti-HBcAb-positive individuals [2,3]. Dual viral infection may occur rarely by simultaneous acute infection with both viruses or more commonly by a second acute infection in an individual already chronically infected with one hepatitis virus (superinfection). Typically, particularly in areas with high HBV prevalence, acute HCV will be superimposed on chronic HBV [4]. Acute superinfection may provoke a fulminant hepatitis [5] or may lead to a chronic dual hepatitis with sequelae including cirrhosis and hepatocellular carcinoma (HCC). Rarely, superinfection with HCV may result in clearance of HBV [6]. Despite the relatively large disease burden, knowledge regarding the virological interactions, clinical consequences of co-infection and optimum therapy remains incomplete.

Viral interaction in HBV/HCV co-infection

Laboratory and clinical studies demonstrate that HBV and HCV may interact with each other and affect the host immune response. Typically, HBV/HCV co-infection is associated with both lower HBV viraemia *and* lower HCV viraemia than control monoinfected subjects [7]. Cross-sectional studies suggest that many co-infected cases have detectable HCV viraemia but significantly reduced levels of HBV DNA, possibly indicating a dominance of HCV over HBV [2]. In chronic infection, HBsAg/anti-HBs seroconversion occurs at a higher rate in co-infected individuals

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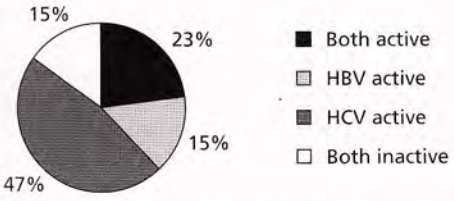

FIG. 40.1 Pattern of viral activity among HBV/HCV co-infected patients ($N = 103$). (Based on data from Raimondo *et al.* [12].)

(2.08% per annum) than monoinfected individuals (0.43%), which may contribute to the development of so-called occult HBV co-infection [4]. This is despite evidence that proliferative responses in peripheral blood mononuclear cells are more reactive against HCV than HBV [8]. This relative lack of immune selective pressure on HBV may result in the observed reduced prevalence of HBV precore mutations in co-infected HBV patients [9].

In vitro evidence indicates that HCV core protein is able to directly interact with HBV X-protein, pol protein and pregenomic RNA and that it may also indirectly affect Enh1 and Enh2/basal core promoter to suppress HBV transcription [10,11]. However, the primacy of HCV over HBV remains controversial, with a number of observational studies reporting the opposite effect. This apparent discrepancy may be explained by the findings of an Italian longitudinal study in a cohort of HBV/HCV co-infected patients which shows that while HCV is the dominant viral infection in the majority, a more complex spectrum of virological profiles with evidence of a dynamic relationship and fluctuating co-dominance occurs in up to one-third of patients [12] (Figure 40.1).

Fibrosis progression and HCC in HBV/HCV co-infection

Cross-sectional studies report that HBsAg-positive patients with active HCV infection show more severe hepatic fibrosis and faster progression to cirrhosis than patients with sole HCV infection [13]. A multicentre Italian study of 59 co-infected patients demonstrates that coexisting HBV and HCV infection is associated with a higher cirrhosis prevalence than in HBV monoinfection (28.8% vs. 15.1%) [14].

Epidemiological data from a large meta-analysis indicates that there may be a synergistic carcinogenic effect between the two viruses, with an odds ratio for HCC of 35.7 (95% CI 26.2–48.5) in individuals with active co-infection compared with 14.1 (95% CI 10.6–18.8) in HBV monoinfection and 4.6 (95% CI 3.6–5.9) in HCV monoinfection [15]. Even when HBV is inactive (HBsAg negative, anti-HBc positive) and apparently does not contribute to inflammation, it still increases the risk of developing HCC by 2–2.5 fold [11].

Treatment of HBV/HCV co-infection

Established guidelines for the treatment of HBV/HCV co-infected patients have been hampered by the lack of high-quality evidence of treatment efficacy as co-infection has been an exclusion criterion in the majority of large clinical trials. In addition, many patients with HCV/HBV co-infection in Western countries have not been suitable for clinical trials, either because of additional HIV infection or due to chaotic lifestyles associated with injecting drug use in some patients with recent acquisition of hepatitis. Based largely on evidence of HCV dominance over HBV infection, recent European guidelines suggest that initial treatment should be targeted at HCV [16]. As HCV is cleared, there is a risk of reactivation of latent HBV that may necessitate subsequent treatment with nucleos(t)ide analogues [16].

Two randomized trials have examined the efficacy of standard HCV treatment (peginterferon alfa-2a/2b and ribavirin) in HCV/HBV co-infection [17,18]. HCV-infected patients (serum alanine aminotransferase > 1.5 times upper limit of normal, RNA > 10^5 copies/mL) with ($N = 161$) or without ($N = 160$) detectable HBsAg were studied in Taiwan. Patients received standard 24/48 weeks therapy according to genotype with peginterferon alfa-2a 180 mg/week plus ribavirin 800–1200 mg daily. Follow-up 6 months after completion of therapy showed that sustained virological response (SVR) rates were no different in those with co-infection compared with HCV alone: 72.2% in co-infected genotype 1 patients compared with 77.3% in genotype 1 monoinfected patients, and 82.8% versus 84% in genotype 2 and 3 patients. Of patients with HBV DNA above 1000 IU/mL at the start of treatment, 45% achieved an HBV virological response at 24 weeks; 19 patients with previously undetectable HBV DNA experienced an increase in HBV DNA load.

The smaller European HEP-NET prospective multicentre trial of peginterferon alfa-2b and ribavirin that enrolled 19 patients (10 genotype 1, 9 genotype 2/3) has been published in full [17]. A total of 15 patients completed

treatment and 24 weeks' post-treatment follow-up. At 24 weeks after therapy, SVR was observed in 86% of genotype 1 and 100% of genotype 2/3 patients. Two of six patients who initially had detectable HBV DNA were cleared of detectable HBV virus and four patients with initially undetectable HBV load experienced a reactivation of HBV replication. The frequency of serious adverse events was in line with previous monoinfection trials.

Both studies demonstrate that standard HCV therapeutic protocols may be applied to HBV/HCV co-infected individuals; however, close monitoring of HBV viral load is advised, even in patients with undetectable HBV DNA at the start of treatment. Similar conclusions were made after treatment with non-pegylated interferon and ribavirin in 42 co-infected patients in a study by Chuang *et al.* [19]. Only 1 of 42 had simultaneous clearance of HCV and HBV with interferon and ribavirin, although five (11.9%) developed HBsAg seroconversion during follow-up (to 72 weeks). HBV clearance correlated negatively with HCV SVR. Potthoff *et al.* [20] reported a case of HBV/HCV co-infection treated with peginterferon and ribavirin where the combination of antiviral therapy and active HBV immunization achieved successful clearance of both viruses with development of high-titre anti-HBs.

None of these studies examined the role of nucleos(t)ides in the treatment of co-infection. Data in this area are particularly limited, being confined to a single study of eight patients given standard interferon plus lamivudine; HCV SVR was achieved in 50% and HBeAg clearance was observed in three patients [21]. There have been no studies examining the use of more potent nucleos(t)ides in co-infection.

Summary

HBV/HCV co-infection is a common but insufficiently studied condition, particularly in endemic areas. Interactions occur between the two viruses both at a virological level and, importantly, at a pathogenic level, where co-infection appears to promote accelerated disease progression and increased risk of HCC. HCV treatment response to peginterferon and ribavirin appears to be similar in co-infection to monoinfection, although the possibility of rebound activation of suppressed HBV mandates surveillance. Studies examining the use of combination therapy with interferon, ribavirin and potent nucleos(t)ides are urgently needed.

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