Chapter 8
Chronic Hepatitis B

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Key Learning Points

- To recognise that universal vaccination of newborns against HBV is effective to prevent CHB infections in the infants and bring down CHB prevalence in the post-vaccination era.
- To appreciate the viral structure and viral cycle of HBV.
- To understand and interpret different serological markers and viral markers in diagnosis and workup of CHB with regard to the phase of disease.

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- To learn the types of approved antiviral therapy, and the fact that newer drugs are being developed.
- To appreciate the indications of treatment and adjunct management in CHB patients and special populations.

Chapter Review Questions

1. What is the recommended immunisation protocol for infants born to HBsAg+ve mother?

   (a) HBV vaccine at 0, 1, 6 months.
   (b) HBV vaccine at 0, 1, 6 months + HBIg within 12–24 h.
   (c) HBV vaccine at 0, 1, 6 months + HBIg within 12–24 h + antiviral therapy for the mother if maternal serum HBV DNA level > 200,000.
   (d) HBV vaccine at 0, 1, 6 months + HBIg within 12–24 h + antiviral therapy for the mother if maternal HBeAg is positive.

2. Which of the following statement about HBV is true?

   (a) HBV is an RNA virus.
   (b) HBV enters the hepatocyte by sodium taurocholate cotransporting polypeptide.
   (c) HBV does not enter the nucleus of hepatocytes.
   (d) HBV is cytopathic and leads to robust inflammatory response within the liver.

3. HBsAg +ve, HBeAg −ve, ALT high, DNA high. Which of the following correctly describes the disease phase?

   (a) HBeAg-positive chronic hepatitis.
   (b) HBeAg-positive chronic infection.
   (c) HBeAg-negative chronic hepatitis.
   (d) HBeAg-negative chronic infection.

4. Which of the following is NOT an approved therapy for CHB?

   (a) Therapeutic vaccine.
   (b) Pegylated interferon.
   (c) Entecavir.
   (d) Tenofovir.

5. Which of the following patient does not require prophylactic antiviral therapy?

   (a) HBsAg–/anti-HBc + patient about to undergo haematopoietic stem cell transplantation.
   (b) HBsAg–/anti-HBc + patient about to receive rituximab.
   (c) HBsAg+/anti-HBc + patient about to receive high dose corticosteroid for newly diagnosed systemic lupus erythematosus.
   (d) HBsAg+/anti-HBc + patient about to receive a one-week course of prednisolone 20 mg daily for Bell's palsy.

Introduction

In 1965 Blumberg discovered the "Australia antigen" later to be known as hepatitis B surface antigen (HBsAg), the hallmark of chronic infection [1]. Several decades later chronic hepatitis B (CHB) remains a major public health challenge despite the availability of a vaccine since the early 1990s. Furthermore, despite access to established antiviral therapies, the currently available treatment strategies in CHB are non-curative, thus even treated patients require lifelong supervision in the majority of cases. This chapter summarises the diagnosis, natural history, virology, treatment, and management options in CHB for todays' physician.

Epidemiology

An estimated 292 million people are chronically infected globally [2]. In recognition of this in May 2016 the World Health Assembly released a target aim to significantly reduce the considerable morbidity and mortality found in individuals with chronic hepatitis B infections by the year 2030 [3]. Chronic infection remains highly prevalent in resource poor countries where it remains concentrated due to economical

and logistical limitations. Transmission of hepatitis B virus (HBV) is through exposure to infected blood or body fluids containing virus. In areas of endemic disease; Asia, Africa, and the Middle East, the principal mode of transmission is perinatal. In the western world prevalence is considered to be low, but as a consequence of global migration patterns prevalence in the UK has increased over recent years to reflect this.

Preventative Measures

Screening

CHB is the leading cause of primary liver cancer worldwide; the complications of chronic infection, cirrhosis, and HCC account for an estimated 890,000 deaths per year [4]. Efforts to reduce the morbidity and mortality of CHB start with case finding, screening of at-risk subjects and those from endemic areas. In addition to case finding, screening of family members, vaccination of household contacts, and referral to specialist care where appropriate are the mainstay of public health policy. However, it is estimated that only 9% HBV-infected subjects have been diagnosed and 8% of those who are eligible for treatment received appropriate therapy [4].

Immunisation

At the heart of hepatitis B prevention is vaccination, which has been available since the mid-1980s. In 1992 the World Health Organisation (WHO) recommended global vaccination against hepatitis B, and a significant number of member states have integrated hepatitis B vaccination in to their infant vaccination schedules. Newborns to all HBsAg-positive women should receive a course of three doses of HBV vaccine (at birth, 1 and 6 months). Postvaccination testing occurs between 9 and 15 months. In addition, infants born to CHB mothers are recommended to receive hepatitis B immuno-

globulin (HBIg) in addition to the HBV vaccination course within 12–24 h [5]. Mothers with high viral load titres (defined as HBV DNA >200,000 IU/mL) will also be prescribed antiviral therapy at the beginning of their third trimester to further reduce the risk of vertical transmission of virus. Although vaccination uptake remains low in some countries, successful implementation of immunoprophylaxis has had a marked impact in reducing the rate of perinatal transmission in recognised endemic areas. In Taiwan and Hong Kong prevalence has fallen from 10% to 15% to less than 1% amongst children and young adults.

Diagnosis and Disease Work-Up

Persistence of hepatitis B surface antigen (HbsAg) in the blood for more than 6 months is the basis on which a diagnosis of CHB is made (Table 8.1). Following acute exposure, HbsAg can be detected within 6 weeks in the majority of cases. The resolution of acute infection, with the subsequent disappearance of HbsAg is accompanied by the emergence of antibodies to HBs (anti-HBs), but there may be a period during which neither HbsAg nor anti-HBs is detected; loss of HbsAg and the detection of anti-HBs signify resolution of acute HBV.

Anti-HBc IgM titres are elevated in acute HBV and are used to confirm acute infection in the clinic, but anti-HBc IgM can also be elevated during reactivation of CHB. Titres of anti-HBc IgG usually persist if there is chronic infection but are also present along with anti-HBs in individuals who have recovered from acute HBV and thus can experience reactivation during immunosuppression/chemotherapy.

Quantitative HBV DNA is a direct measure of replication activity of the virus. Although genotype testing is not widely implemented there is strong evidence it can influence the natural history of CHB and response of antiviral therapy. There are ten major genotypes (A to J) with distinct geographic distributions.

Table 8.1 Definition and interpretation of serological tests in hepatitis B virus

Marker	Clinical interpretation
HBsAg	Hallmark of infection Positive in early phase of acute infection Persistently positive in chronic infection
Anti-HBs	Recovery from acute infection (or chronic) Immunity following vaccination
HBeAg	"e" (envelope) antigen positivity Positive in HBeAg-positive chronic infection (formerly referred to as immune tolerant disease) and HBeAg-positive chronic hepatitis (formerly referred to as immune clearance phase) Initially positive in acute infection Associated with high viral load
Anti-HBe	Loss of "e" antigen—seroconversion to develop antibody against HBe Present in HBeAg-negative chronic infection (formerly referred to as inactive carrier or low replicative phase)—low viral load Present in HBeAg-negative chronic hepatitis (formerly referred to as immune escape)—higher viral load
Anti-HBc (IgM)	Positive in acute infection Positive during some exacerbations of chronic infection
Anti-HBc (IgG)	Exposure to infection Present in association with HBsAg in chronic infection Present in association with anti-HBs after recovery of infection Isolated presence may indicate seropositive occult HBV

Table 8.1 (continued)

Marker	Clinical interpretation
Tests	
HBsAg (−) Total anti-HBc (+) Anti-HBs (+)	Immune due to natural infection
HBsAg (−) Total anti-HBc (−) Anti-HBs (+)	Immune due to Hepatitis B vaccination
HBsAg (+) Total anti-HBc (+) Anti-HBc IgM (+) Anti-HBs (−)	Acute infection (or exacerbation of chronic infection)
HBsAg (+) Total anti-HBc (+) Anti-HBc IgM (−) Anti-HBs (−)	Chronic infection
HBsAg (−) Total anti-HBc (+) Anti-HBs (−)	Interpretation unclear; number of possibilities (a) Resolved infection (common) (b) False-positive anti-HBc (c) “Low level” chronic infection/ occult HBV (d) Resolving acute infection (e) Chronic infection with surface antigen mutation

Further laboratory investigations including serum alanine aminotransferase (ALT) and aspartate transaminase (AST) are used as surrogates for disease activity. Additional parameters such as platelet count, prothrombin time, serum bilirubin, and albumin are evaluated to assess synthetic liver function and the severity of liver disease.

Additional viral serology is indicated to exclude hepatitis type C and delta (HDV) in addition to HIV co-infection. HDV is a satellite virus that only exists in the presence of HBV. The latter can accelerate liver fibrosis and consideration for early antiviral therapy is mandated.

Basic imaging such as liver ultrasound is indicated as part of initial disease work-up and assessment, while more detailed cross-sectional imaging has a role in confirming chronicity, the severity of chronic liver disease and the presence of portal hypertension. Non-invasive modalities to assess liver fibrosis such as serum markers and transient elastography (TE) have largely replaced liver biopsy. APRI and FIB-4 scores have been most extensively studied and validated with evidence base substantiated in large meta-analyses. Acoustic radiation force impulse (ARFI) imaging and MR elastography have respective advantages and limitations. However, liver biopsy remains the only means and gold standard for the assessment of necro-inflammation and fibrosis stage, although procedural risks such as bleeding, pain, and perforation remain.

Establishing disease phase involves serial assessments of liver function in addition to viral parameters and due to the dynamic nature of HBV, newly diagnosed patients are seen three-monthly in the specialist clinic for the first year to confirm clinical phenotype. Quantitative HbsAg level has an emerging role when combined with HBV DNA and serum ALT levels for disease stratification. Serum HbsAg levels are perceived as a surrogate of intrahepatic transcriptionally active covalently closed circular (ccc) DNA and can provide complementary information to enhance disease assessment and evaluation of treatment response [6].

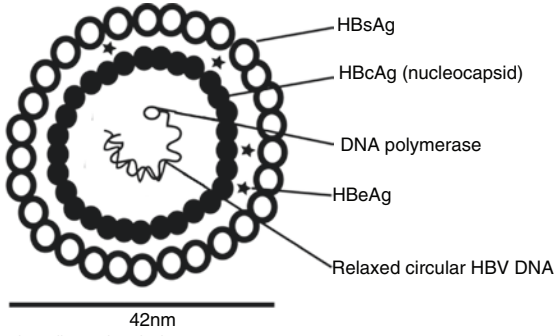
Virology

Structure

The HBV virion particle, also known as the Dane particle (Fig. 8.1), is approximately 42 nm in size and composed of an outer envelope (HbsAg), which surrounds a nucleocapsid containing a small DNA genome of 3.2Kb. The genome is circular, partially double stranded encoding four overlapping open reading frames (ORF). The activities of the major viral proteins (polymerase, core, envelope, X, and e antigen) are shown in Fig. 8.1.

Viral Replication

HBV belongs to the family of hepadnaviruses, where stealth infection of host hepatocytes, the major cell type in the liver, with HBV virions allows the HBV genome to be converted to covalently closed circular (ccc) DNA providing a template



There are four protein-coding regions in the genome:
(i) The first reading frame codes for the proteins making up Hepatitis B surface antigen (HBsAg)
(ii) The second for pre-core/core encoding the core protein (HBcAg), a structural unit of the nucleocapsid, and the non-structural pre-core protein, the secreted e-Antigen (HBeAg)
(iii) The third for the DNA viral polymerase 'pol' required for RNA encapsidation and DNA synthesis, and (iv) Fourthly the 'X ORF' encoding the small viral regulatory X protein (HBx), which is essential for viral replication. The function of the latter is not fully understood but appears to be associated with HCC.

FIGURE 8.1 Diagram of the Dane particle

for transcription of messenger RNA/ pre-genomic RNA and translation of all the viral proteins. The functional importance of persistence of cccDNA in the nucleus of infected hepatocytes is the basis of HBV chronicity.

A turning point in understanding the mechanisms of viral replication and the potential development of novel therapeutic interventions has been the recent identification of a liver bile acid transporter, the sodium taurocholate cotransporting polypeptide (NTCP), as a functional receptor for HBV [7].

Natural History and Immunology

Acute HBV Infection

Age of viral acquisition and immune status of the host are critical to the successful clearance of infection. The majority of healthy adults (>90%) will recover from acute infection and develop long lasting immunity. Previous animal studies have demonstrated that resolution of HBV infection is largely mediated by the adaptive immune response but there is growing recognition of the role of the innate immune response in viral control [8].

Phases of Chronic HBV Infection

The disease course of established HBV infection remains unpredictable, although our understanding of hepatitis B immunopathogenesis and virology has improved in recent years.

Traditionally CHB is thought to progress through four distinct disease phases (Fig. 8.2) and this terminology has been updated within guidelines to be based on the description of the two main characteristics of chronicity; infection versus hepatitis [9, 10]. Better disease stratification is central to improve disease outcomes [11].

Perinatal or early infection in childhood is typically associated with high levels of virus, normal ALT, minimal inflam-

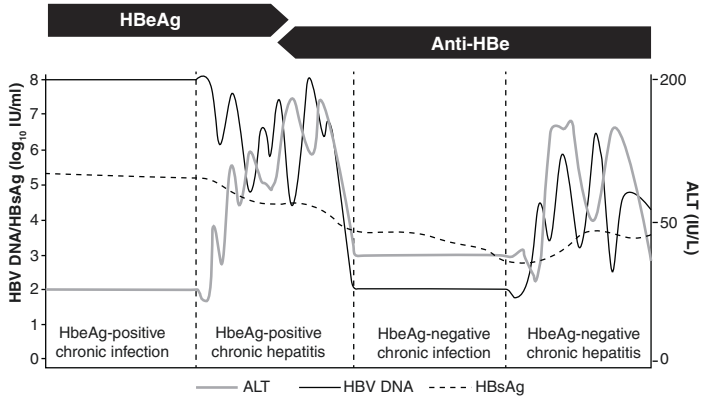


FIGURE 8.2 Clinical parameters during disease phases of Chronic Hepatitis B

mation, and mild or no fibrosis on liver biopsy. Historically defined as the "immune tolerant" (IT) disease phase, there was emerging data challenging this clinical phenotype with features of a signature immune profile of these patients to be more compromised than traditionally viewed [12] and this is now defined as "HbeAg-positive chronic infection". This is an important development in the field, as the classical disease phases have been the premise on which treatment decisions are made.

The immune active (previous nomenclature of "immune clearance") phase is now defined as "HbeAg-positive chronic hepatitis" thought to represent an awakening of the immune response with more marked immune activity reflected in perturbation of the serum ALT. Persistence of this disease phase is thought to result in progressive liver damage and thus treatment is indicated to avert the development of fibrosis and cirrhosis. HbeAg seroconversion marks the end of this phase and combined with low HBV DNA and normal serum ALT represents immune control. Classically this immune control phase, often referred to as the inactive or asymptomatic carrier phase, now renamed as "HbeAg-negative chronic infection" marks the end of immune mediated liver damage

and therefore in the majority is associated with minimal or no fibrosis. This phase is characterised by the presence of anti-Hbe, HBV DNA is <2000 IU/mL, and normal serum ALT. HbeAg seroconversion and progression to this phase of disease before the age of 30 is associated with reduced risk for the development of HCC [13, 14].

A proportion of these patients will develop disease reactivation with the emergence of viral escape mutants, reflected in elevated HBV DNA levels and changes in serum ALT. HbeAg is not expressed owing to mutations in the pre-core or core promoter areas of the virus, thus this clinical picture is referred to as "HbeAg-negative chronic hepatitis". This phase is associated with low rates of spontaneous remission and prognostically is associated with a poor outcome.

Management of Hepatitis B

In line with national and international guidelines, CHB patients should be under long-term specialist follow-up to monitor disease progression. Spontaneous HbsAg seroclearance in untreated CHB patients occurs in <1% per year. Persistence of HbsAg—a risk factor for disease progression and the development of HCC—mandates lifelong specialist supervision [15].

The major challenge in CHB is the lack of curative therapies to achieve eradication of cccDNA representing a complete cure, let alone eradication of integrated HBV DNA which represents sterilising cure. Previously, the therapeutic goal in CHB was viral suppression and normalisation of serum ALT but today the "gold standard" treatment endpoint is HbsAg loss defined as "functional cure", which is associated with favourable clinical outcomes including lower risks of liver decompensation, liver transplantation, HCC, and death [16–18]. Current treatment strategies in CHB are aimed at avoiding the complications of disease and reducing liver-related morbidity and mortality. Approved antiviral agents broadly fall into two categories; nucleos(t)ide analogs (NUCs) or pegylated-interferon (Peg-IFN).

Nucleos(t)ide Analogs (NUCs)

NUCs achieve viral suppression by inhibiting reverse transcription of the pre-genomic RNA into HBV DNA. Rates of HbsAg seroclearance in e-antigen negative patients on oral antiviral treatment are equivalent to spontaneous seroclearance and thus treatment in the majority is lifelong. Despite this, NUCs are perceived as advantageous owing to their good tolerability profile and high genetic barrier to resistance. Furthermore, they are considered first-line therapy in specific patient subgroups, such as those who have decompensated disease, or patients who are intolerant to Peg-IFN or have poor predictors of response and/or co-morbidities that preclude the use of Peg-IFN. There have been some reports of renal toxicity, hypophosphatemia, Fanconi-like syndrome, and reduced bone mineral density have been reported with use of adefovir (now no longer recommended) and tenofovir disoproxil fumarate (TDF), but this appears largely restricted to those with pre-existing renal risk factors [19]. Moreover, tenofovir alafenamide (TAF), another prodrug of tenofovir, has been approved by the U.S. Food and Drug Administration (FDA) for use since year 2015 which demonstrated improved renal and bone safety with same efficacy as TDF [20, 21]. Recent studies have demonstrated histological reversal of fibrosis with long-term NUC therapy [22, 23]. Emerging data suggest the potent first-line NUCs (i.e. entecavir or tenofovir) are associated with reduction in HCC risk [24, 25].

Pegylated-Interferon (Peg-IFN)

Peg-IFN has an immune modulatory effect such that off-treatment immune control can be achieved; however, its use in clinical practice is limited due to systemic effects and the fact that patients with decompensated cirrhosis are contraindicated for PEG-IFN. Although it can be used in both e-Antigen positive and negative phases with compensated disease, appropriate patient selection is central to achieving

Table 8.2 Stopping rules for HBeAg negative and positive patients treated with Peg-IFN

	HBeAg negative	HBeAg positive
Week 12	Genotype D: No decline in qHBsAg and < $2\log_{10}$ IU/mL decline in HBV DNA	Genotypes A and D: No decline in qHBsAg Genotypes B and C: qHBsAg levels >20,000 IU/mL
Week 24	Not applicable	Genotypes A-D: qHBsAg >20,000 IU/mL

sustained immune control. Peg-IFN represents a finite treatment option and the utility of early stopping rules (Table 8.2) has optimised treatment in Peg-IFN treated patients leading to an early switch strategy to NUC therapy in those with an unfavourable response.

Patient Selection/Who to Treat

Due to the dynamic nature of CHB, the timing of antiviral therapy is critical and treatment decisions should be made on an individual basis.

Although International guidelines lack uniformity in their recommendations for first line-therapies, this allows flexibility and physician discretion. Various treatment algorithms have been proposed, and therapy is currently recommended for those with evidence of chronic active disease. Treatment criteria focus specifically on age; as the development of fibrosis, cirrhosis, and HCC increases significantly with advancing age; the level of HBV DNA and perturbation in serum ALT. Antiviral therapy is recommended in adults aged >30 years with HBV DNA >2000 IU/mL and abnormal ALT, on two consecutive tests 3 months apart; or if aged <30 years with HBV DNA >2000 IU/mL, abnormal ALT and evidence of necro-inflammation or fibrosis on liver biopsy or a TE

score of >6 kPa (fibrosis F2 or higher). HBV DNA level of >20,000 IU/mL is a clear indication for treatment, irrespective of age and this recommendation is consistent across all international guidelines (AASLD, EASL, and APASL) [9, 10, 26]. There has been some debate as to what constitutes a normal ALT level and historical data have revised these thresholds on a number of occasions, initially favouring Prati criteria (an abnormal ALT is defined as >30 U/L in an adult male and > 19 U/L in an adult female) with more recent updated guidelines adjusting these limits again (AASLD; >25 U/L women and >35 U/L in men).

e-Antigen Positive

In hepatitis B e-Antigen (HbeAg) positive disease, patients completing 48 weeks of Peg-IFN demonstrated a favourable response with 25–30% achieving HbeAg seroconversion (tested 24 weeks post-treatment), and a proportion of these patients went on to achieve HbsAg loss [27]. Predictors of response are similar in both groups; younger age, female gender, higher serum ALT, and lower HBV DNA levels are considered more favourable factors for response to Peg-IFN. Genotype A and B patients have historically been reported to be more responsive to Peg-IFN therapy.

The aim of treating HbeAg positive disease is to achieve HbeAg seroconversion as delayed HbeAg clearance increases the risk of progression to fibrosis, cirrhosis, and HCC. Achieving HbeAg loss or seroconversion with NUC monotherapy can be achieved in 30–40% of patients but this can take up to 3–5 years in some patients.

At present, there are no data to suggest a clinical benefit in treating patients in the HbeAg-positive chronic infection phase, formerly referred to as the IT phase, however, there is growing evidence that not all patients designated IT are truly tolerant [12]. Therefore a proportion of these patients may benefit from earlier intervention or at the very least closer supervision and monitoring [28].

e-Antigen Negative

In this cohort the response rate to Peg-IFN (<25%) is lower than in HbeAg positive disease, however, this still remains higher than HbsAg seroclearance with NUC therapy alone. A decision to start a young patient on NUC therapy will require a discussion of the pros and cons of the prospect of lifelong therapy. Guidelines recommend that at lower thresholds of HBV DNA (>2000 or >20,000 IU/mL) additional factors should be taken into account such as patient age, family history of HCC, and family planning. The subgroup of patients who have a normal ALT, but persistent fluctuations in HBV DNA (between 2000 and 20,000 IU/mL) may have evidence of significant fibrosis and treatment may be warranted in these patients [28].

Special Populations

Cirrhotic

AASLD and EASL recommend treatment with NUC in cirrhotic patients with any detectable HBV DNA and ALT in addition to six-monthly ultrasound surveillance for HCC. Furthermore, NUC therapy in the cirrhotic patient should be lifelong to prevent the risk of reactivation, decompensation, and the development of HCC.

Immunosuppressed

In HbsAg positive (HBsAg+) patients or HBsAg negative (HbsAg-) but anti-HBc positive (anti-HBc+) patients on immunosuppressive agents, chemotherapy or undergoing haematopoietic stem cell transplantation, the risk of HBV reactivation is variable and therefore NUCs maybe mandated during treatment for a period of 6 months, and in some instances, to up to 2 years after completing chemotherapy or discontinuing immunosuppression. If the anticipated risk of reactivation is high (i.e., >10%), such as patients receiving B cell depleting therapy or HbsAg+ patients receiving anthra-

cycline derivatives, prophylactic NUCs are required. Where the anticipated risk of viral reactivation is moderate (i.e., 1–10%), such as patients receiving anti-tumour necrosis factor or tyrosine kinase inhibitors, these patients may either be started on prophylactic antiviral or be carefully monitored with frequent serum ALT and DNA levels. Patients who receive traditional immunomodulators (e.g., azathioprine, 6-mercaptopurine, methotrexate) or low dose (<10 mg prednisolone or equivalent) corticosteroids for any duration do not need routine antiviral prophylaxis due to a low risk of HBV reactivation (i.e., <1%) [29]. Therefore, patients with any history of HBV exposure should be risk-stratified during immunosuppression to decide on the management strategy.

Pregnancy

Based on safety data from Tenofovir treated HIV-infected mothers and the low risk of teratogenicity, Tenofovir is recommended as the NUC of choice in CHB mothers with high levels of HBV DNA in the last trimester of pregnancy. HBIg is administered to newborns of CHB mothers (in addition to vaccination) regardless of whether NUC was taken to prevent vertical transmission.

Biomarkers

Loss of HbsAg or functional cure is the desired treatment endpoint in studies of novel HBV therapies. Thus, a reduction in qHBsAg levels is a measure of efficacy of new therapies, be that through an antiviral effect or as a result of immune-mediated clearance of infected hepatocytes. Levels have been shown to correlate with HBV DNA and cccDNA in HbeAg positive patients [30]. In addition, studies have demonstrated a role for qHBsAg levels to identify patients who may be suitable for treatment discontinuation (qHBsAg levels <100 IU/mL) and higher HbsAg levels correlate with HCC risk [31].

Another marker Hepatitis B core related antigen (HbcrAg) has been found to correlate well with cccDNA. Whilst on antiviral therapy, HbcrAg declines at a slower rate than HBV DNA, and as such, it can be regarded as a marker of persistence of HBV and correlates with intrahepatic cccDNA in liver biopsy studies [32]. Independently levels have been found to predict hepatocarcinogenesis in untreated and treated patients, however, currently there are no published risk models that incorporate this as there is not yet a consensus on a cut-off level to help inform the decision.

HBV RNA has emerged as a novel biomarker, which is detectable in the serum as encapsidated virion-containing pre-genomic RNA [33]. HBV RNA has been shown to mirror levels of HBV DNA (1–2 logs higher than RNA) in untreated subjects and demonstrated a distinct profile depending on the phase of infection [34, 35]. In treated subjects, HBV RNA has been shown to predict off-NUC virological relapse [36] and HCC development [37]. HBV RNA is also commonly measured in drug trials to prove target engagement. Standardisation of assays for HBV RNA are needed prior to its acceptance more broadly as a biomarker in clinical practice.

HCC Surveillance

International guidelines are fairly consistent in their approach to initiate oral antivirals in cirrhotic patients and 6-monthly HCC surveillance with ultrasound with or without serum alfa-feto protein measurement. In non-cirrhotics, HCC surveillance is recommended if there is a family history of HCC and using risk calculators such as REACH-B (validated in Asian CHB cohort) and PAGE-B score (good predictability for HCC in Caucasian CHB cohort) which incorporate non-modifiable risk factors such as age and ethnicity, as well as widely available parameters such as platelets. However, metabolic syndrome is emerging as an important co-aetiology with CHB and current early risk stratification scores do not yet incorporate this when evaluating HCC risk. In particular, diabetes mellitus is being increasingly recognised as a risk

factor for HCC, and thus the CAMD scoring system (incorporating cirrhosis, age, male gender, diabetes mellitus) has been derived [38] and early validation studies have been published [39].

Future Therapies

Eradicating HBV and achieving a sterilising cure is the ultimate treatment goal but remains an elusive outcome. Novel strategies to maximise the efficacy of currently available treatments (NUCs & Peg-IFN), including the combination of these agents or their use in sequence has also been investigated, but without demonstrating superior treatment outcomes [40]. The discovery of the HBV entry receptor, NTCP, has been an important development in the field such that cell culture systems can provide an accessible platform to study new therapeutic targets. Novel agents in clinical phase of development are designed to inhibit viral replication by alternative mechanisms (other than inhibition of DNA polymerase) or antigen reduction, which include viral entry inhibitors, core protein allosteric modulators, RNA interference-based therapy, and nucleic acid polymers that prevent surface antigen export. Another approach is to boost or restore the host immune response against HBV using toll like receptor agonists, immune checkpoint inhibitors, soluble bispecific fusion molecules, therapeutic vaccination, and engineered monoclonal antibodies are also under investigation [41, 42]. The majority of these strategies have had proven efficacy in suppression of viral protein and/or nucleic acids, but the durability of therapeutic effects is unknown. Despite these advances in HBV therapy, the question arises whether such agents will be affordable in areas where HBV is endemic. Moreover, long-term safety data is awaited, and together with this, it is also likely these strategies will be combined with NUCs and/or Peg-IFN in the short term, therefore, the therapies used in today's clinic are likely to constitute a central component of treatment strategies for the foreseeable future [43].

Conclusion

There is renewed focus on treatment and management of CHB in light of the recent advances in the hepatitis B field. A better understanding of the complex HBV life cycle, clinical phenotypes as well as the host–virus interplay will lead to the development of curative treatment strategies in the future and hopefully, novel therapeutic approaches that are able to achieve sustained off-treatment responses in the majority of cases.

Chapter Review Questions

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   (d) HBsAg+/anti-HBc + patient about to receive a one-week course of prednisolone 20 mg daily for Bell's palsy.

Answers

1. (c)
2. (b)
3. (c)
4. (a)
5. (d)

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