Management of acute hepatitis B and reactivation of hepatitis B

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Acute hepatitis B – Chronic hepatitis B – Hepatitis B reactivation – Antiviral drugs – Fulminant hepatitis – Hepatitis flare

Abstract
The natural course of hepatitis B virus infection and the resulting hepatic injury is determined by the degree of virus replication and the intensity of host immune response. Upon exposure to hepatitis B virus (HBV), individuals with a vigorous and broad immune response develop acute self-limited infection, which may result in acute hepatitis. However, with stringent testing for HBV and universal precautions, acute HBV is rather rare. Reactivation of HBV most often presents as acute hepatitis B (AVH-B) and clinically, it is difficult to differentiate AVH-B from reactivation of chronic hepatitis B (CHB) and it requires a high index of suspicion. In the presence of high HBV DNA (>2 x 10⁴ IU/ml) underlying liver disease should be investigated by liver biopsy, endoscopy and/or imaging. The degree of liver failure often depends on the severity of acute insult and the stage of underlying chronic liver disease. Mutations in the HBV genome, immunosuppressive therapy and viral or drug induced injury are common causes of reactivation. As most patients with AVH-B resolve the infection spontaneously, antiviral therapy is not indicated in them. However, the use of a potent oral nucleoside(tide) analogue is necessary as soon as possible in patients with CHB reactivation. Liver transplantation should be considered in patients who develop liver failure secondary to severe acute exacerbation. If this is not feasible, supportive therapy with the addition of granulocyte colony stimulating factor (GCSF) therapy could be beneficial.

Hepatitis B virus (HBV) infection is the tenth leading cause of death worldwide (1). Almost 30% of the world population has been exposed to HBV and an estimated 400 million of these are chronically infected (2). The natural course of HBV infection is determined by the interplay between viral replication and the host immune response. Upon exposure to HBV, individuals with a vigorous and broad immune response to the virus develop an acute self-limited infection, which may result in acute hepatitis. An aberrant response can lead to fulminant hepatitis. Individuals who do not have a broad and vigorous immune response do not clear the virus, but develop persistent chronic hepatitis B virus. The virus persists in the body even after serological recovery from acute hepatitis B; therefore, individuals who have been exposed to HBV are at risk for reactivation [flare or exacerbation] of hepatitis when an immune imbalance occurs (3). The severity of the flare depends on the state of underlying liver disease. As patients with severe acute exacerbation of chronic hepatitis B may not have underlying cirrhosis, they may recover to relatively normal liver function in contrast to those with end-stage cirrhosis. It is therefore important to recognize this clinical presentation of chronic hepatitis B.

Although there is no consensus definition of reactivation [flare or exacerbation] of hepatitis B is characterized by sudden elevation of serum ALT levels. It usually refers to an abrupt increase in serum ALT to >5–10 times the upper limit of normal or >3 times the baseline level (4). Reactivation of hepatitis in chronic HBV-infected patients is common and may be caused by a number of factors (Table 1). Reactivation of hepatitis B virus (HBV) replication is a sudden increase or reappearance of serum HBV DNA in a patient with chronic or past HBV infection (5).

This review will focus on management of acute hepatitis B and reactivation of hepatitis B (flare or exacerbation) spontaneous or that owing to superimposed hepatotropic viruses.

Acute hepatitis B
During acute hepatitis B, manifestations range from subclinical or anicteric hepatitis to icteric and, in some cases, fulminant hepatitis.
pathogenesis

An incubation phase lasting weeks or months with increasing and finally very high viraemia, but without clinical or biochemical signs of liver damage shows that replication and persistence of HBV is not cytopathic per se.

Analysis of the hepatocellular expression patterns in acutely HBV-infected chimpanzees showed that no host response to viral replication occurred during the incubation phase. HBV infection is a ‘stealth virus’ infection that does not stimulate the innate immune system, which recognizes pathogen-associated molecular patterns (6). In contrast, later during infection, most of the effector molecules associated with the adaptive cellular immune response are induced, followed by HBV antibodies. HBV elimination starts several weeks before the onset of the disease with T-cell-dependent noncytolytic mechanisms, but later cytolytic immune responses follow and generate the symptoms of acute hepatitis (7). During acute disease, high numbers of cytolytic CD8 (+) cells are present in the liver and they react with a multitude of HBV epitopes and eliminate the virus by destroying infected cells. The increased level of arginase in patients with acute hepatitis B suppresses the functions of activated CD8 (+) T cells. This mechanism might limit the amount of liver damage caused by activated CD8 (+) T cells in patients with acute HBV infection (8).

A recent study compared the intrahepatic transcriptional profiles of neonatal woodchucks with self-limiting woodchuck hepatitis virus (WHV) infection to woodchucks progressing to persistent WHV infection. Instead of early-acute stage (8 weeks) gene expression, a mid-acute phase (14 weeks) expression was seen and resolution was associated with induction of a prominent cytotoxic T cell signature (9).

The CD4(+) Foxp3(+) regulatory T cells (Tregs) mitigate immunomodulated liver damage by down-regulating the antiviral activity of effector T cells but do not influence development of HBV-specific CD8 T cells or development of memory T cells. They may contribute to conservation of tissue integrity and organ function at the cost of prolonging virus clearance (10).

We have shown that CD4 + Tregs were more abundant and there was a higher expression of CCR1, CCR3, CCR4, CCR5 and CCR8 in patients with AVH-B. Effector T cells with a potential role in necro-inflammation accumulate during the acute infection and subsequent down-regulation occurs by T regulatory cells, favouring viral persistence during chronic infection (11).

High disease activity usually leads to clinical and serological resolution. However, even after serological resolution, small amounts of cccDNA persist in the liver for years, decades and possibly for life. T-cell immunity suppresses viral replication originating from these cccDNA copies to very low levels (12). Anti-HBs is formed during convalescence and later stage may enhance opsonization of HBsAg and block de novo infection of hepatocytes by released HBV. In contrast to the other HBV antibodies, anti-HBc induction is partially T-cell independent. This explains the presence of anti-HBc even in those patients who do not build up an efficient immune response. Serological resolution is defined by disappearance of HBsAg, which may take months after onset.

Diagnosis

The main differential diagnosis of HBsAg-positive acute hepatitis is reactivation of hepatitis in CHB virus patients.

Laboratory testing during the acute phase of acute hepatitis B reveals elevated alanine and aspartate aminotransferase levels (ALT and AST). Values up to 1000–2000 IU/l are seen during the acute phase with ALT higher than AST. Serum alkaline phosphatase and lactate dehydrogenase are usually only mildly elevated (less than three-fold). Bilirubin is variably increased, in both direct and indirect fractions. Serum bilirubin concentrations may be normal in patients with anicteric hepatitis. Serum albumin decreases especially in protracted severe
Acute hepatitis B

Jindal et al.

hepatitis. The prothrombin time can increase and is the most reliable marker of severity and prognosis. In patients who recover, normalization of serum aminotransferases usually occurs within 1–4 months. Persistently elevated serum ALT for more than 6 months may indicate progression to chronic hepatitis. Various autoantibodies can appear during acute hepatitis B, most smooth muscle.

The diagnosis of acute hepatitis B is based on the detection of HBsAg and IgM anti-HBc. During the initial phase, markers of HBV replication, HBeAg and HBV DNA, are present. Resolution of infection is accompanied by the disappearance of HBV DNA, HBeAg to anti-HBe seroconversion and then HBsAg to anti-HBs seroconversion. As acute hepatitis B resolves, anti-HBe appears after anti-HBc, but before anti-HBs. It usually disappears earlier than anti-HBs.

Patients rarely present during the window period when HBsAg has become negative, but anti-HBs is not yet positive. In this setting, which is more common in patients with fulminant hepatitis B with rapid clearance, IgM anti-HBc is the sole marker of acute HBV infection.

During acute infection, HBsAg concentrations rise exponentially for weeks to months from undetectable to typical final concentrations of 10 000–100 000 ng/ml with 2–4 days of doubling time (13). If acute HBV is resolved, HBsAg decreases with an initial half-life of 8 days until it has been disappeared completely from serum after weeks to months. In about 25% of cases of acute resolving hepatitis B, HBsAg disappears much faster, so that samples taken in the late acute phase may be HBsAg negative (14). A decrease in HBsAg concentrations by more than 50% within the first 4 weeks indicates resolving acute infection in >95% of cases (15). Hence, quantitative analysis of highly concentrated HBsAg is an excellent prognostic marker, indicating progression to chronicity if the values remain stable or increase.

Anti-HBc immunoglobulin [IgM anti-HBc] may be useful in two situations: (a) to distinguish acute hepatitis caused by HBV from a hepatitis of different aetiology in a patient with chronic HBV infection; and (b) to identify acute hepatitis in some hepatitis B patients, particularly those with fulminant hepatitis B or HDV coinfection, where HBsAg may have been eliminated very rapidly. Predominant TH1 immune response in AVH-B favours cell-mediating viral clearance, whereas TH2 mediated immune response in CHB favours antibody production. HBV antigens elicit immune mediated liver injury in a dose-dependent manner; therefore, low viral antigen load and subsequent resolution of infection in AVH-B compared to persistent viral antigenaemia in CHB leads to significantly increased production of HBV-specific antibodies (anti-HBe and anti-HBc) in CHB or exacerbation compared to AVH-B (16, 17). Tests should be quantitative because anti-HBc IgM is also positive in chronic hepatitis B and during convalescence. Levels >600 Paul–Ehrlich units/mL or IgM anti-HBc (>1:1000) suggest an acute HBV infection with high inflammatory activity (18, 19). In all other situations, concentrations are lower or undetectable. In one Greek study (20), low molecular weight (7–8S) IgM anti-HBc was observed more frequently in HDV superinfection and was related to low mortality. On the other hand, 19S IgM anti-HBc was observed more frequently in spontaneous reactivation of chronic hepatitis B and was related to a high mortality.

Outcome of acute hepatitis B

Fulminant hepatitis B is an atypical course for acute hepatitis B infection, occurring in less than 1% of icteric cases. Typically, in fulminant disease, HBV DNA and HBeAg become undetectable as hepatic failure supervenes. The reasons that HBV has a fulminant course in some patients are not well-understood. A case-control trial evaluated risk factors for a fulminant course in an outbreak among injection drug users. Compared with control patients, case patients were more likely to have used acetaminophen during their illness ($P = 0.08$), used more alcohol and methamphetamine, and lost more weight in the six months before illness. Furthermore, all nine isolates were genotype D (21).”

A more comprehensive study by the US Acute Liver Failure Study Group comparing 34 patients with HBV-related acute liver failure with a cohort of 530 patients with chronic HBV infection showed a higher prevalence of genotype D in the acute liver failure group (32% vs. 16%) even after matching for race and HBeAg status (22). These results indicate that HBV genotypes may play a role in the outcome of acute infection.

Profile and pattern of HBV mutations and their relevance

Precore and core promoter variants have been described in association with fulminant hepatitis (23, 24). It has been suggested that these variants result in a fulminant course because of enhanced HBV replication or a more aggressive immune response (25). The mechanism by which precore variants cause fulminant hepatitis in the new host, but an inactive liver disease in the original host remains unclear.

In a recent report from Japan, higher HBV DNA levels, subgenotypes B1/Bj, A1762T/G1764A, G1896A, G1899A and A2339G mutations were significantly more frequent in fulminant hepatitis B than in nonfulminant AVH-B. In multivariate analysis, G1896A mutations, serum HBV DNA (>5.23 log copies/ml) and total bilirubin (>10.35 mg/ml) were independently associated with a fulminant outcome by AVH-B (26). Subgenotypes B1/Bj HBV (HBV/B1) are known to frequently cause ALF in Japan. T1961V/C1962D mutations, which lead to S21 substitution in the core protein were found frequently in fulminant hepatitis B and may play important roles in the development of fulminant hepatitis B (27).

Because of the increased use of lamivudine (28), AVH-B caused by lamivudine-resistant strains is being
described. In one study from China, lamivudine-resistant mutations identified using direct PCR sequencing were found in 11 of the 234 (4.7%) AVH-B patients. Two patients infected with viruses with lamivudine-resistant mutations developed severe acute hepatitis, whereas one patient developed CHB (29).

Traces of HBV are often detectable in the blood using PCR for many years after a clinical recovery of acute hepatitis, despite the presence of serum antibodies and HBV-specific cytotoxic T cells, which can be present at high levels. Persistent histological abnormalities (including fibrosis and mild inflammation) were present as many as 10 years in another series in nine patients with a complete serological recovery after acute infection (30). These observations suggest that eradication of HBV rarely occurs after recovery from acute HBV infection and that latent infection can maintain the T cell response for decades following clinical recovery, thus keeping the virus under control. Immunosuppression in these patients can lead to reactivation of the virus.

The rate of progression from acute to chronic hepatitis B is mainly determined by the age at infection. The rate is approximately 90 per cent for a perinatally acquired infection, 20–50 per cent for infections between the age of 1 and 5 years old and less than 5 per cent for an adult-acquired infection.

Treatment

(Treatment for acute HBV is mainly supportive.) In addition, appropriate measures should be taken to prevent infection in exposed contacts. The decision to hospitalize patients should be individualized. Patients who have coagulopathy, are deeply jaundiced, or are encephalopathic should be hospitalized. Hospitalization may also be considered in patients who are older, have significant co-morbidities, or cannot tolerate oral intake.

There is no consensus on whether patients should be treated with non-nucleoside reverse transcriptase inhibitors (NNRTI) therapy because few studies have addressed the benefits of antiviral therapy during acute infection (31–35) (Table 2). As virus-specific antibody-producing B cells are enriched early after acute viral infection, the host immune system needs to be exposed to viral antigen during the early phase to induce production of neutralizing antibodies. Therefore, giving antiviral therapy early may inhibit the production of neutralizing antibodies to some extent. Nevertheless, it has also been reported that anti-HBs does not develop in 10% of untreated patients with AVH-B and long-term follow-up of these patients would help define the risk of reactivation of hepatitis B virus (HBV) in patients treated with antiviral therapy (36).

Thus, antiviral therapy is not indicated in the most patients with acute hepatitis B, but may be indicated in certain subgroups of patients: (i) Patients with fulminant hepatitis B; (ii) Severe AVH-B: Individuals who fulfill any two of the following criteria: (a) hepatic encephalopathy; (b) serum bilirubin >10.0 mg/dl; and (c) international normalized ratio (INR) >1.6, especially if it is increasing; (iii) A protracted course (such as persistent symptoms or marked jaundice (bilirubin >10 mg/dl) for more than 4 weeks after presentation); and (iv) Those who are immunocompromised, have concomitant infection with hepatitis C or D virus, or have pre-existing liver disease.

These indications outline the limitations of differentiating AVH-B from reactivation of CHB. Interferon should be avoided because of the increased risk of hepatic necro-inflammation. Tenofovir, telbivudine and entecavir are acceptable options given as monotherapy because the treatment duration may be short. Treatment can be stopped when the patient’s clinical condition improves and HBsAg has been cleared.

Spontaneous reactivation (flare or exacerbation) of hepatitis B

The natural history of chronic hepatitis B is punctuated by spontaneous reactivation of the disease. The natural course of perinatally acquired chronic HBV infection has four phases, the first phase (immune tolerance) is characterized by the presence of HBeAg, high levels of serum HBV DNA, normal serum aminotransferases and minimal or no liver inflammation on histology. In patients with childhood-or adult-acquired HBV infection, the ‘immune-tolerant’ phase is short-lived or absent.

After two to three decades of chronic infection, patients enter the second phase of immune-clearance. In these patients, HBV replication intensifies, serum HBV DNA levels increase and biochemical deterioration occurs. Frequently, flares of hepatitis precede clearance of the virus and HBeAg-to-anti-HBe seroconversion. However, flares may also occur without subsequent loss of HBeAg (37). These episodes can be viewed as an abortive attempt at seroconversion. Some patients undergo multiple episodes in which flares precede HBeAg seroconversion only to have a second flare months later. Multiple episodes of reactivation and remission have been shown to accelerate the progression of chronic hepatitis B (38).

The next phase after immune-clearance is the low replicative phase, characterized by the absence of HBeAg, presence of anti-HBe, relatively normal AT levels and relatively low serum HBV DNA. Liver biopsy generally shows mild hepatitis and fibrosis, but significant liver injury or even cirrhosis in patients who have had severe liver injury during the preceding ‘immune-clearance’ phase. This phase may persist indefinitely, especially if this state is reached early. However, some patients have reactivation of HBV replication either spontaneously or as a result of immunosuppression. Most clinically recognizable reactivations occurs in patients who are in the low replicative phase of infection. During these episodes, serum aminotransferase
Reactivation of chronic HBV infection can occur in the immune-clearance phase affecting 40–50% of hepatitis B e antigen (HBeAg)-positive patients, and can be prolonged when there is repeated unsuccessful clearance of HBeAg (43). Reactivation of CHB at the HBeAg-negative phase, seen in 15–30% of HBeAg-negative patients, can also result in acute decompensation, and is occasionally associated with HBeAg seroreversion (44).

In Far Eastern regions, 23–38% of patients have been reported to develop jaundice and hepatic decompensation during biochemical exacerbation of CHB (44,45). These exacerbations are often associated with significant mortality. Influence of HBV Genotypes on reactivation has also been assessed. In case–control studies from Hong Kong (46, 47) and Japan (48) genotype B was found to be the predominant HBV strain among patients suffering from severe acute exacerbation as compared to control patients with various severities of liver diseases. Genotype B HBV may associate with more vigorous immune response that leads to a higher chance of successful immune clearance but also a higher risk of hepatic decompensation during the hepatitis flare.

Several HBV mutant strains, including mutations in precore, core promoter and deletion mutation in pre-S/S genes have been reported (49). Viral populations in the immune tolerance phase mostly consist of exclusively wild-type virus or HBeAg-positive strains with little or no precore/core promoter mutants or HBeAg-negative strains (50). Acute flares in chronic hepatitis B may also occur in response to HBV genotypic variation. Chronic infection with precore mutant is often associated with multiple flares interspersed with periods of asymptomatic infection (51, 52). A function of the HBeAg is to induce immunological tolerance. It is

levels increase in response to the sudden re-emergence of viral replication.

Thus, reactivation of hepatitis can occur in both HBeAg-positive and -negative patients (39, 40). A proportion of patients develop jaundice and hepatic decompensation during the hepatitis reactivation, namely, severe acute exacerbation, and may progress to acute-on-chronic hepatic failure (41, 42).

### Table 2. Major studies on antivirals in acute viral hepatitis B.

<table>
<thead>
<tr>
<th>Author, year, Country</th>
<th>Type of study</th>
<th>Treatment</th>
<th>Patients [n]</th>
<th>Severe AVH-B [n]</th>
<th>ALF [n]</th>
<th>Bilirubin</th>
<th>INR</th>
<th>Treatment duration</th>
<th>Mortality/LT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schmilowitz Weiss et al. 2004 Israel (31)</td>
<td>Cases series</td>
<td>Lamivudine 100 mg/days</td>
<td>15</td>
<td>15</td>
<td>5</td>
<td>18 ± 6.8</td>
<td>4.5 ± 6.4</td>
<td>3–6 mo</td>
<td>14.4</td>
</tr>
<tr>
<td>Tillman HL et al. 2006 Germany (32)</td>
<td>Historical cohort</td>
<td>Lamivudine 100–150 mg/ days</td>
<td>17</td>
<td>17</td>
<td>7</td>
<td>14.44 ± 7.77</td>
<td>4.15 ± 2.19</td>
<td>Till HBsAg</td>
<td>17.6</td>
</tr>
<tr>
<td>Kumar et al. 2007 India (33)</td>
<td>RCT</td>
<td>Lamivudine 100 mg/ days Placebo</td>
<td>20</td>
<td>20</td>
<td>0</td>
<td>19.18 ± 12.04</td>
<td>3.91 ± 1.59</td>
<td>negative</td>
<td>80</td>
</tr>
<tr>
<td>Miyake et al. 2008 Japan (34)</td>
<td>Retrospective cohort</td>
<td>Lamivudine 100–150 mg/ days</td>
<td>31</td>
<td>22</td>
<td>2</td>
<td>10.9 ± 5.7</td>
<td>2 ± 0.86</td>
<td>3 mo</td>
<td>0</td>
</tr>
<tr>
<td>Yu et al. 2010 China (35)</td>
<td>RCT</td>
<td>No antivirals Lamivudine 100 mg/days Placebo</td>
<td>23</td>
<td>23</td>
<td>23</td>
<td>10.7</td>
<td>–</td>
<td>–</td>
<td>73.9</td>
</tr>
</tbody>
</table>

### Table 3. Differences between acute viral hepatitis B and spontaneous reactivation of hepatitis B [Modified From: (90)]

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Serum bilirubin median (range); mg/dl</td>
<td>8.2 (2.7–72.9)</td>
<td>9.8 (3.0–37.2)</td>
<td>0.264</td>
</tr>
<tr>
<td>ALT levels median (range); IU/ml</td>
<td>1085 (400–6920)</td>
<td>923 (400–2900)</td>
<td>0.103</td>
</tr>
<tr>
<td>PT prolongation median (range); s</td>
<td>3.0 (0–32)</td>
<td>4.4 (0–16)</td>
<td>0.689</td>
</tr>
<tr>
<td>Serum albumin median (range); g/dl</td>
<td>3.70 (2.9–4.6)</td>
<td>3.75 (2.7–4.5)</td>
<td>0.887</td>
</tr>
<tr>
<td>Albumin/globulin ratio median (range)</td>
<td>1.20 (0.94–1.85)</td>
<td>1.09 (0.77–2.00)</td>
<td>0.070</td>
</tr>
<tr>
<td>Anti-HBe-positive, n (%)</td>
<td>10 (20.4)</td>
<td>25 (83.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IgM anti-HBc &gt;1:1000</td>
<td>38 (77.5)</td>
<td>9 (30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HBV DNA &lt;0.5 pg/ml</td>
<td>47 (95.9)</td>
<td>4 (13.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
possible that the absence of HBeAg in patients harbouring precore mutant HBV may permit a more vigorous immunological response to core peptides expressed on the surface of hepatocytes. Episodic flares have been attributed to increases in the concentration of precore mutants and changes in the proportion of precore to wild-type HBV (53). It has been suggested that disease exacerbations remain uncommon during the earliest phase of chronic HBV at a time when wild-type HBV predominates and that flares become common with the gradual emergence of the precore variant. These flares have been thought to subside with time as the genetic heterogeneity disappears and patients become exclusively infected with precore HBV (53). Mutations at the basal core promoter region are associated with decreased HBeAg synthesis, active liver histology and increased viral replication. Sometimes these exacerbations have been fatal, presenting as fulminant liver failure (54).

Pathogenesis of spontaneous reactivation of hepatitis B virus infection

Spontaneous reactivation (flare or exacerbation) of hepatitis B virus infection are likely explained by changes in the immunological control of viral replication. Reactivation seems to occur more commonly in male homosexuals, patients who are infected with human immunodeficiency virus (HIV), concurrent with bacterial infections or surgery and when there is emotional or physical stress (55). Pregnancy and postpartum may also be a risk factor (56). Liver injury during these spontaneous flares appears to be mediated by expanded numbers of T cells that are reactive to hepatitis B e antigen (HBeAg) and HBCAg that are crossreactive at the T-cell level (57). Increased T-cell responses occur in the early phase of acute flares and subside after recovery from acute exacerbation and HBeAg seroconversion (57). T-cell responses do not diminish if the patient does not enter a clinical remission and low-level responses to S gene products are noted throughout all phases of the flare, indicating that HBCAg/HBeAg-specific T cells play an important role in acute exacerbations. Immunopathological studies during acute exacerbations have shown that the cellular infiltrates at the site of necroinflammatory reaction are mainly CD81 cytotoxic T lymphocytes (CTL), which are generally considered to be directed to HBCAg peptides that reside on the surface of hepatocytes (58).

Once acute-on-chronic liver failure (ACLF) develops, the immunological changes seen in the inflammatory process are very similar to that of severe sepsis (59). There is reduced monocyte activation, which is associated with an exacerbated production of anti-inflammatory cytokines, including interleukin (IL)-6, IL-10, IL-12 and interferon-gamma. Cytokine production is associated with activation of toll-like receptors (TLR), an important component of the innate immune system in recognizing specific pathogen-associated molecular patterns. TLR2/3/4/5/7/9/10 shows an increased expression during ACLF because of reactivation of HBV (60, 61). IL-17-producing CD4+ T (Th17) cells have also been shown to be involved in liver injury in CHB patients with ACLF (62). However, Th-17 is not specifically involved in ACLF because of reactivation of CHB, but is also involved in ACLF of different aetiologies. B cells may also be involved, as shown in a study demonstrating a massive accumulation of plasma cells secreting immunoglobulin (Ig)M and IgG targeting the hepatitis B core antigen in liver tissues of CHB patients who required liver transplantation because of ACLF (63). Peripheral glucocorticoid receptor expression is also increased in CHB patients with ACLF (64). As the ACLF progresses, the resulting inflammatory responses in the liver and its associated cellular immune dysfunction can result in multiorgan failure.

Diagnosis

The typical presentation of severe reactivation is a short onset of jaundice and very high ALT level, sometimes preceded by prodromal constitutional symptoms, in a patient with chronic hepatitis B. If signs of chronic liver disease are present, the diagnosis could be easy, however, most patients presenting with severe acute reactivation of chronic hepatitis B may not have been earlier diagnosed as chronic HBV infection. In countries with intermediate and high endemicity, the possibility of reactivation of chronic HBV infection is high, which may be the first presentation of chronic hepatitis B or compensated cirrhosis, which was asymptomatic before exacerbation. Hence, a possibility exists that the large proportion of patients with suspected acute hepatitis B might actually be suffering from chronic hepatitis B and manifesting clinically for the first time during a period of severe reactivation (flare or exacerbation) (19). In areas of intermediate to high HBV endemicity, endemic for CHB, reactivation (flare or exacerbation) accounts for 27–70% of presumed acute hepatitis B (19, 65). The symptoms and biochemical parameters of severe acute reactivation of chronic hepatitis B can be very similar to those of acute hepatitis B (19). Hence, severe acute reactivation of chronic hepatitis B might be misdiagnosed as acute hepatitis B in some cases. Patients with severe acute reactivation of CHB can have positive IgM anti-HBc, which may again be confused with the diagnosis of acute hepatitis B. Levels >600 Paul–Ehrlich units/ml or IgM anti-HBc (>1:1000) suggest an acute HBV infection with high inflammatory activity. In all other situations, concentrations are lower or undetectable (18,19) (Table 3).

An Indian study suggests that a low titer of IgM anti-HBc (<1:1000) and high HBV DNA level (>0.5 pg/ml, which equals 141 500 copies/ml) are useful to identify
severe acute reactivation of CHB from acute hepatitis B (19). However, HBV DNA may sometimes become undetectable at the peak of the biochemical exacerbation because of vigorous immune-clearance. The presence of basal core promoter mutation and precore stop codon mutations have been suggested to differentiate severe acute exacerbation of chronic hepatitis B from acute hepatitis B in Japanese series, but its use in clinical practice needs further validation (66).

A previous history of chronic hepatitis B or a positive family history of chronic hepatitis B may suggest reactivation; whereas recent history of at risk blood, percutaneous or sexual exposure may suggest AVH-B. Liver biopsy showing evidence of chronicity may suggest chronic infection.

In uncertain cases of acute hepatitis B vs. severe reactivation of CHB, one should manage these patients as severe reactivation and hepatitis B surface antigen should be retested after 6 months. In over 95% of AVH-B acquired in adulthood, HBsAg will be cleared on the follow-up testing; however, a small percentage of patients with acute reactivation of CHB may also clear HBsAg.

As CHB infected patients can still acquire other viral infections that cause acute hepatitis, other sources of viral hepatitis (A, C, D and E) must be excluded by serological assays. If suspected, other aetiologies should also be excluded before a diagnosis of severe acute exacerbation of chronic hepatitis B is made.

Outcome
The clinical presentation of acute reactivation of chronic hepatitis B infection depends on the underlying severity of liver disease and other factors.

In a Chinese study on the evaluation of prognostic factors in severe reactivation (flare or exacerbation) of CHB, the following parameters were independently associated with adverse outcome at admission: pre-existing cirrhosis, high Child–Pugh score, low albumin level, high bilirubin level, prolonged prothrombin time (PT) and low platelet count (47). For the subsequent stay in the hospital, these factors were as follows: high peak bilirubin level, long peak prothrombin time, long duration to reach the peak prothrombin time, development of encephalopathy and presence of ascites (47).

In a study from Hong Kong reporting 46 chronic hepatitis B patients who developed severe reactivation, but without hepatic encephalopathy at presentation, 24% patients died or received liver transplantation during hospital admission. The only independent factors that could predict in-hospital mortality were low platelet count and high serum bilirubin. The mortality of patients who had both risk factors (low platelet and high bilirubin) was 69%. On the other hand, the mortality of patients who had either thrombocytopenia or elevated bilirubin alone was much lower (11% and 13%, respectively), and the mortality of patients who had none of the two risk factors was zero in this series (67). Because of the limited hepatic reserve, patients with cirrhosis recover more slowly and are more prone to complications, including sepsis, gastrointestinal bleeding and acute renal failure.

Many other studies from Hong Kong, Taiwan and Japan, have found that patients with pre-existing cirrhosis and more serious hepatic dysfunction (prolonged prothrombin time, elevated serum bilirubin and high Child–Pugh score) have a higher risk of mortality (68, 69, 70).

In one study from Taiwan on HBeAg-positive non-cirrhotic patients with acute exacerbation, 5.1% of the exacerbation episodes resulted in hepatic decompensation, and serum HBV DNA level was the only significant risk factor ($P = .003$). A serum HBV DNA cut-off value of $1.55 \times 10^9$ copies/ml predicted decompensation with a sensitivity of 85.7%, a specificity of 85.5%, a negative predictive value of 99.1% and positive predictive value of 24.0% (71). Once the disease reaches the stage of ACLF, the prognosis is extremely poor, with 3-month mortality rates without liver transplantation around 50% (72). Different predictive models have been used in predicting acute-on-chronic liver failure in chronic hepatitis B. MELD score has been found in many studies to be more objective score compared to Child–Pugh score in predicting survival in CHB patients with ACLF (73, 74).

One regression model, using the presence of hepatorenal syndrome, cirrhosis, positive HBeAg, low albumin and prolonged PT, was found to be better than the MELD score in predicting 3-month mortality (72). Another model based on the presence of hepatic encephalopathy, hepatorenal syndrome, positive HBeAg, cirrhosis and prolonged PT was also found to be better than both the MELD and Child–Pugh score (75). Additional studies to externally validate these models are needed.

Treatment
Patients need intensive supportive care including close monitoring and treatment of complications.

In severe reactivation of chronic hepatitis B when immune activity is already excessive, IFN-based treatment may aggravate the hepatic decompensation and is thus contraindicated. Oral nucleos(t)ide analogues are the treatment of choice.

In one initial case series from Japan, three patients with cirrhosis who presented with severe acute exacerbation and hepatic encephalopathy responded dramatically to lamivudine treatment (76). However, many later case series or case-control studies did not demonstrate any benefit in survival of lamivudine treatment (67, 69, 77).

The high mortality rate of these patients despite lamivudine treatment was probably related to the delayed beginning of lamivudine and viral suppression. In patients with liver failure, the main determinant for recovery is liver regeneration and rapid cessation of
ongoing necro-inflammation. Neither factors are directly dependent on HBV replication. Thus, complications including sepsis and multiorgan dysfunction develop in patients in whom treatment is delayed (78). A study from Taiwan suggests that the beneficial effect of antiviral therapy on short-term survival depends on the timing of treatment. In a group of consecutive CHB patients with severe acute exacerbation treated with lamivudine, all 25 patients who had baseline bilirubin below 20 mg/dl survived. In patients with low (<20 mg/dl) baseline serum bilirubin levels, lamivudine treatment definitely improves survival compared to historic controls who did not receive lamivudine (5/20 patients died, 20%, P = 0.013). On the other hand, the mortality rate of patients who received lamivudine when bilirubin was above 20 mg/dl (23/35, 67%) was similar to that in untreated historical controls (9/11, 82%) (68). A more recent study found improved survival in lamivudine-treated patients compared to controls in patients with a MELD score of 30 or less. However, those treated with lamivudine still had a 3-month mortality of 50.7%. A low pretreatment HBV DNA and a rapid decline in viral load were predictors of good outcome (79).

Recently, studies have been performed with more potent antivirals. A study from China compared entecavir (n = 33), lamivudine (n = 34), or no nucleoside analogues (n = 37). Both nucleoside analogues achieved significant viral suppression after 3 months, but there was no improvement in survival; 3-month survival rates were 48.5, 50.0 and 40.5% respectively (80). In one Japanese study, 34 patients with acute exacerbation were consecutively treated with lamivudine or entecavir and all patients in both groups survived. Twelve months after treatment, 41.6% of 24 lamivudine patients developed lamivudine-resistant mutations. On the other hand, patients receiving entecavir did not need to change drugs (81). Another study from Hong Kong found entecavir (n = 36) to be associated with increased short-term mortality compared to lamivudine (n = 117), perhaps caused by lactic acidosis (82, 83). This finding must be confirmed.

A randomized trial from India (84) found improved 3-month survival with tenofovir (57%) compared to placebo (15%) in patients with acute exacerbation of CHB presenting as acute-on-chronic liver failure. A reduction in more than 2 log in HBV DNA levels at 2 weeks was found to be an independent predictor of survival.

The definitive treatment for severe reactivation (flare or exacerbation) with ACLF is liver transplantation. A study from Hong Kong retrospectively analysed 149 patients presenting with ACLF who received liver transplantation including 50 with severe exacerbation of CHB. The 5-year survival rates exceeded 90% (85).

A lot of research is being undertaken to improve the poor outcome of ACLF due to CHB reactivation. One randomized placebo-controlled trial found the administration of granulocyte-colony stimulating factor improved survival after 2 months (86). Use of bioartificial liver support systems is controversial and the results of a randomized controlled multicentre study in ACLF patients failed to identify any benefit in survival (87). Corticosteroids, based on their anti-inflammatory activity, have been used in CHB with ACLF. In a recent study, intravenous dexamethasone 10 mg daily was given for 5 days with continuous lamivudine in 56 patients. Dexamethasone was an independent factor influencing survival compared to controls, and a rapid decline in serum bilirubin in the first 5 days was predictive of survival (88).

**Reactivation (flare or exacerbation) of hepatitis B caused by infection with other viruses**

Patients with chronic HBV infection may exhibit reactivation (flare or exacerbation) of hepatitis when superinfected with other hepatotropic viruses, such as hepatitis A virus (HAV), hepatitis E virus (HEV), hepatitis C virus (HCV) and hepatitis delta virus (HDV). The severity of hepatitis flare depends on the severity of the underlying hepatitis B.

Excess mortality has been reported by several investigators when hepatitis A is superimposed on chronic hepatitis B (89). HEV has also been described as a cause of acute exacerbation of CHB. In one Indian study, HEV super-infection contributed to 20% of acute exacerbation episodes and, in particular, 36% of episodes in initially HBeAg (−) patients (90). Severe hepatitis flare frequently occurs when delta virus super-infection is superimposed on chronic hepatitis B (91). Should infection with delta virus become chronically established, as is often the case, this frequently leads to an increase in disease activity and accelerated progression to cirrhosis, during which time multiple fluctuations in serum aminotransferase levels are common (91).

Acute hepatitis C may also lead to severe hepatitis flares in patients with chronic hepatitis B (92). Similar to delta infection, infection with HCV frequently becomes chronic, and the subsequent course may be characterized by frequent fluctuations in ALT and AST values (93).

Super-infection with another virus on chronic HBV infection is not uncommon. In one study, in 55% of the patients, acute flares in serum aminotransferase levels in anti-HBe-positive patients had delta superinfection, and only 24% were considered to have reactivation of HBV (94). In an Indian study (90), only 9.5% of exacerbations in the HBeAg-positive patients were owing to superinfection with other hepatitis viruses, whereas 90.5% had spontaneous exacerbation of HBV per se; whereas in the HBeAg-negative patients, superinfection, and acute exacerbation of HBV both were equally common.

Patients with chronic hepatitis B who become infected with other hepatotropic viruses may be found to be HBeAg–negative and serum HBV DNA negative.
by molecular hybridization tests due to a process of viral interference (95). In some instances, these super-infections may result in HBsAg and HBeAg seroconversion (96).

Conclusions

The presentation of acute hepatitis caused by reactivation of chronic hepatitis B is quite common and is often difficult to clinically and biochemically differentiate from AVH-B. The presence of high serum HBV DNA and evidence of underlying chronic liver disease by imaging techniques, liver biopsy, endoscopy or raised hepatic venous pressure gradient are helpful in differentiating the two conditions. As most patients with acute HBV resolve this infection spontaneously, treatment with an oral anti-HBV agent is not necessary. However, the use of an oral anti-HBV agent may be indicated in certain subgroups of patients. Spontaneous reactivation (flare or exacerbation) of hepatitis during the course of chronic HBV infection is a common phenomena in areas where HBV infection is moderately or highly endemic. Reactivation may sometimes be confused with acute viral hepatitis B. The severity of the reactivation depends on the severity of underlying liver disease, but can progress to liver failure and death. Antivirals should be started as early as possible and should be continued. Liver transplantation should be considered in patients with severe disease.

Disclosure

The authors have no disclosure.

References

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