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TOPIC HIGHLIGHT

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# Potent antiviral therapy improves survival in acute on chronic liver failure due to hepatitis B virus reactivation

Cyriac Abby Philips, Shiv Kumar Sarin

Cyriac Abby Philips, Shiv Kumar Sarin, Department of Hepatology, Institute of Liver and Biliary Sciences, New Delhi 110070, India
Author contributions: Philips CA prepared the manuscript and designed the sections; Sarin SK edited the manuscript, revised the sections and prepared the final draft.
Correspondence to: Shiv Kumar Sarin, Professor, Head, Department of Hepatology, Institute of Liver and Biliary Sciences, D-1, VasantKunj, New Delhi 110070, India. shivsarin@gmail.com
Telephone: +91-11-46300000 Fax: +91-11-26123504
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## Abstract

Acute on chronic liver failure (ACLF) is a disease entity with a high mortality rate. The acute event arises from drugs and toxins, viral infections, bacterial sepsis, interventions (both surgical and non-surgical) and vascular events on top of a known or occult chronic liver disease. ACLF secondary to reactivation of chronic hepatitis B virus is a distinct condition; the high mortality of which can be managed in the wake of new potent antiviral therapy. For example, lamivudine and entecavir use has shown definite short-term survival benefits, even though drug resistance is a concern in the former. The renoprotective effects of telbivudine have been shown in a few studies to be useful in the presence of renal dysfunction. Monotherapy with newer agents such as tenofovir and a combination of nucleos(t)ides is promising for improving survival in this special group of liver disease patients. This review describes the current status of potent antiviral therapy in patient with acute on chronic liver failure due to reactivation of chronic hepatitis B, thereby providing an algorithm in management of such patients.



**Key words:** Acute on chronic liver failure; Chronic hepatitis B infection; Reactivation of hepatitis B; Flare of hepatitis B; Anti-viral therapy; Nucleoside analogue; Nucleotide analogue

**Core tip:** This topic highlight is an exhaustive review of acute on chronic liver failure (ACLF) secondary to reactivation of chronic hepatitis B virus (HBV) infection. It sheds light on current aspects of pathogenesis and definitions of reactivation of HBV and mechanisms of liver injury in acute on chronic liver failure in the wake of virus reactivation. The importance and effects of different nucleos(t)ide analogs in ACLF has been emphasized and an algorithm for management of this distinct condition has been provided.

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## ACUTE ON CHRONIC LIVER FAILURE

Acute on chronic liver failure (ACLF) was first described in 1995[1], with chronic and acute liver disease occurring simultaneously. ACLF has been defined variably by different working groups worldwide. In 2009, The Asia Pacific Association for the Study of Liver (APASL) Working Party Group defined it as an acute hepatic insult manifesting as jaundice and coagulopathy complicated within 4 wk by the development of ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease. APASL defined liver failure in ACLF as serum bilirubin > 5 mg/dL and international normalized ratio (INR) > 1.5 or prothrombin activity < 40%[2]. Another proposition at the European

**Table 1 Risk factors and causes of reactivation of chronic hepatitis B**

| Causes of HBV reactivation | Risk factors |
|---|---|
| | Male sex |
| Cancer chemotherapy | Genotypes B and D |
| Immunosuppressants | Pre-core and core promoter mutations |
| Corticosteroid withdrawal | Elevated ALT at presentation |
| Interferon therapy | |
| Hepatitis A/E virus superinfection | |
| Hepatitis C virus superinfection | |
| Hepatitis delta virus superinfection/co-infection | |
| Interaction with HIV infection | |
| Effect of immune reconstitution therapy | |

Modified from Jindal *et al*. Liver International (2011).

Association for the Study of the Liver/American Association for the Study of Liver Diseases single topic symposium defined ACLF as acute deterioration of pre-existing chronic liver disease usually related to a precipitating event and associated with increased mortality at 3 mo due to multiorgan failure. This definition was brought on with application of the Sequential Organ Failure Assessment scores and the APACHE Ⅱ scoring system[3]. The occurrence of organ failure in patients with cirrhosis with a defined severity of liver disease indicates a poor prognosis. A precipitating event generally culminates into ACLF due to an altered host response to injury resulting in aberrant and inappropriate inflammatory response and immune dysfunction increasing susceptibility to infections. Elevated levels of multiple pro- and anti-inflammatory cytokines have been extensively described in ACLF[4-6]. The inflammatory response is responsible for the immune dysregulation that predisposes to infection, which aggravates a proinflammatory response, resulting in a cycle of adverse events. ACLF can be considered to go through an initial systemic inflammatory response syndrome (SIRS) stage, a mixed inflammatory stage and then a compensated anti-inflammatory response[7]. The etiological agents precipitating the acute events in ACLF are diverse from East to West. Alcohol and drugs predominate in the West and infectious diseases predominate in the East. Among the infectious aetiologies, reactivation of hepatitis B virus (HBV) constitutes a major cause of ACLF in the Asian region. Other important infectious agents in these parts include hepatitis A and E viruses, mostly in the Indian subcontinent[8]. The noninfectious causes include alcoholism in the preceding 4 wk, hepatotoxic drugs, complementary and alternative medications, autoimmune hepatitis flare, acute Wilson's disease, surgical interventions, and variceal bleeding. The underlying chronic liver diseases are predominantly constituted by alcoholic cirrhosis in the western region (50%-70%), while hepatitis B constitutes only 10%-15% of cases. On the contrary, in the Asian region, hepatitis-B-related cirrhosis constitutes around 70% of all cases, and alcohol, only 15%[9-11]. HBV reactivation maybe either spontaneous or due to intensive chemotherapy or immunosuppressive therapy, immune restoration after highly active antiretroviral therapy for HIV[12] (Table 1), and reactivation of occult HBV infection by rituximab-based chemotherapy[13].

## PATHOPHYSIOLOGY OF ACLF

The mechanisms behind ACLF include mainly immune dysfunction, intestinal bacterial translocation, and circulatory dysfunction. Kupffer cell activation has been regarded as the main orchestrator of immune dysfunction in ACLF. This activation occurs most commonly through lipopolysaccharide or Gram-negative bacterial endotoxin. Binding of these leads to Toll-like receptor (TLR)-associated activation pathways that produce downstream signaling cascades. This leads to production of inflammatory mediators like cytokines, chemokines, oxygen-derived free radicals, eicosanoids, and lysosomal and proteolytic enzymes. Interleukin (IL)-1, IL-6, IL-7, IL-18 and tumor necrosis factor α culminate in SIRS. The phenomenon of immune paralysis in decompensated cirrhosis holds good for the pathophysiological manifestation in ACLF; thereby promoting a defect in compensatory anti-inflammatory response syndrome.

The natural killer cell component of innate immunity plays a role in ACLF pathogenesis. Thus, ACLF pathogenesis is considerably more sepsis-like. These changes occur at the microcirculatory level, which leads to perfusion abnormality and hepatocyte dysfunction. The pathophysiology of ACLF secondary to viral hepatitis is considered to be due to fibrin deposition and thrombosis within the microvasculature. The pivotal role in hepatocellular injury observed in this group of acute insults is considerably different from other acute insults. The generation of fibrin elicited is different from that of classical pathways of coagulation, such as that induced by mechanical trauma or bacterial lipopolysaccharide.

The pathophysiology of ACLF due to viral hepatitis is proposed to be through activated endothelial cells and macrophages that express distinct cell-surface procoagulants, including prothrombinase, and fibrinogen like protein 2 fibroleukin (Fgl2-fibrolekin), which are important for both initiation and localization of fibrin deposition. Fgl2-fibroleukin is critical in this aspect. In a study by Zhu *et al*[14], Fgl2-fibroleukin expression was detected in 91% of patients with severe ACLF secondary to HBV reactivation. This paved the way for a correlation between human Fgl2-fibroleukin expression and severity of liver disease (levels of bilirubin), and measurement of this expression in peripheral blood monocytes was proclaimed to be useful in monitoring the severity of ACLF-HBV and for therapeutic intervention at the needed time. Spontaneous or treatment-related inflammatory flares are seen in patients with chronic HBV. This corresponds to abrupt increases in serum levels of alanine transaminase which is a result of an increase in intrahepatic

| HBV status at Baseline | HBV status at Reactivation |
|---|---|
| HBsAg +<br>Anti HBe +<br>HBV DNA - | HBsAg +<br>Anti HBe +<br>HBV DNA + |
| HBsAg -<br>IgG anti HBc -<br>Anti HBs +<br>HBV DNA - | HBsAg +<br>HBV DNA + |
| HBsAg+<br>HBeAg -<br>Anti HBe + | HBsAg+<br>HBeAg +<br>Anti HBe + |
| HBsAg -<br>IgG HBc +<br>HBV DNA - | HBsAg +<br>IgG HBc +<br>HBV DNA + |
| HBsAg -<br>IgG HBc +<br>HBV DNA - | HBsAg +<br>IgG HBc +<br>HBV DNA - |
| HBsAg -<br>HBV DNA - | HBsAg -<br>HBV DNA - |

**Figure 1 Serological and virological profiles in reactivation of chronic hepatitis B.** HBV: Hepatitis B virus; HBeAg: Hepatitis B e antigen.

necroinflammatory processes associated with increases in intrahepatic lymphocytes, most commonly, cytotoxic T lymphocytes (CTLs). The reactivation of hepatitis B occurs in 14%-50% of patients following chemotherapy, and mortality rates can be in the range of 5%-12% even in the presence of timely antiviral treatment. The risk factors associated with HBV reactivation include treatment with corticosteroids, younger age, male gender and antiviral resistance[14].

## PATHOPHYSIOLOGY OF HBV REACTIVATION

Chronic hepatitis B natural history is characterized by sessions of flares or exacerbations (Figure 1). Chronic HBV infection is staged into three phases (Figure 2): the first phase being that of immune tolerance [characterized by presence of hepatitis B e antigen (HBeAg), high serum DNA levels and normal transaminases, and no or minimal inflammation]. Two to three decades after the chronic infection, the second phase of immune clearance begins. Here, the replication becomes more intense and serum HBV DNA levels increase and there biochemical deterioration begins. Recurrent episodes of reactivation and remission leads to acceleration and progression of chronic HBV infection. The third phase is the low replicative phase, which is defined by the absence of HBeAg and the presence of anti-HBe, relatively normal transaminase levels, and low serum HBV DNA. Histologically, there could be mild hepatitis and fibrosis or even cirrhosis. This stage could persist indefinitely and it is in this phase that reactivation occurs, either spontaneously or under immunosuppressant use. The aminotransferase levels surges during this stage, associated with sudden emergence of viral replication. This is applicable to both HBeAg-positive and -negative patient groups[15,16]. Reactivation of chronic HBV infection could also occur in the immune clearance phase and is seen in 40%-50% of HBeAg-positive patients. This could lead to a prolonged course if the clearances are repeated and unsuccessful. Reactivation in HBeAg- negative patients (15%-30%) also leads to acute decompensation and is seen usually when there is HBeAg seroconversion[17]. Eight different HBV genotypes (A-H) have been described based on their genomic heterogeneity. In the Asia-Pacific countries, genotype B and C HBV are predominant with genotype C HBV associated with delayed HBeAg seroconversion and more aggressive disease activity as compared to other HBV genotypes. It is also associated with a higher risk of hepatocellular carcinoma. Genotype B HBV was found to be the predominant HBV strain among patients suffering from severe acute exacerbation. The HBV genotype B is associated with a 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. On the contrary, HBV genotype C is associated with less vigorous and more prolonged, abortive immune clearance, which is more likely to cause progressive liver damage and eventually liver cirrhosis and hepatocellular carcinoma[18]. The effect of different HBV genotypes on reactivation has been assessed in many studies. Yuen *et al*[19], Imamura *et al*[20] and Chauhan *et al*[21] undertook studies that revealed that genotype B was the predominant strain that caused reactivation in patients with chronic HBV. This genotype was also found to be associated with a greater surge in immune-mediated response, higher clearance, and higher risk of hepatic decompensation[22-24]. HBeAg functions to induce immune tolerance. In the absence of HBeAg, patients harboring pre-core mutant HBV may have a more rigorous immunological response. Chronic infection with pre-core mutants has been often associated with multiple flares with interspersed asymptomatic periods. Mutations at the basal core promoter regions lead to decreased HBeAg synthesis, active liver histology, and increased viral replication. These exacerbations are seen to lead to fulminant hepatic failure[20,25,26].

Reactivation processes in HBV are likely due to changes in the immunological control of viral replication. The liver injury is mediated by expanded numbers of T cells that react with HBeAg and hepatitis B core antigen (HBcAg). This cross-reaction leads to HBcAg/HBeAg-specific T cells that are immunologically overactive. The cellular infiltrates at areas of necroinflammation are mainly CD81 CTLs that are directed to HBcAg peptides on the surface of hepatocytes[21,27]. In the presence of ACLF, the inflammatory process seen at the immunological level is similar to that seen in severe sepsis. The monocyte activation is depressed and anti-inflammatory cytokine storm is exacerbated. Activation of TLRs oc-

| Parameter | Immune Tolerance | Immune Active | Inactive | Reactivation |
|---|---|---|---|---|
| Age | First to Second Decade | Third and Fourth Decade | Fifth and Sixth Decade | Second to Sixth Decade, mostly Third Decade |
| | (depends on different geographical regions) | (depends on different geographical regions) | (depends on different geographical regions) | (depends on different geographical regions) |
| | | | | Male Predominance |
| PNALT | DNA⩾ 5 logs in HBeAg+ve (60%) | DNA ⩾ 5 logs in HBeAg-ve (35%) | | ALT > 10 ULN |
| | Fibrosis ⩾ 2 (40%) | Fibrosis ⩾ 2 (14%) | | More in HBeAg +ve than in HBeAg -ve |
| | | Annual rate of flare 4.3% | | |
| PIEALT | DNA ⩾ 5 logs in HBeAg+ve (74%) | DNA ⩾ 5 logs in HBeAg-ve (76%) | | |
| | Fibrosis ⩾ 2 (65%) | Fibrosis ⩾ 2 (63%) | | |
| HBsAg | Higher in HBeAg+ve | Lower in HBeAg -ve | < 1000 IU/mL+ | |
| (Quantitative) | Lower the liver fibrosis | | < 2000 viral DNA copies/mL | |
| HBeAg | Present | Present | Absent | Present/absent |
| Anti HBe | Absent | Absent | Present | Absent/present |
| HBV DNA (Quantitative) | High | Moderate to Low | Low | High |
| Outcome | 90% go to HBeAg +ve immune active phase | 90% achieve seroconversion to anti HBe of which 20% to 40% revert back | 80% to 90% stay in this phase, 10% to 20% revert back to anti Hbe +ve immune active phase, 0.5% to 1% per year achieve HBsAg clearance | Depends on severity of hepatitis and underlying chronic liver disease, age, comorbidities, HBeAg status, DNA levels, ALT levels, Histologic activity index and presence of drug resistant mutants |

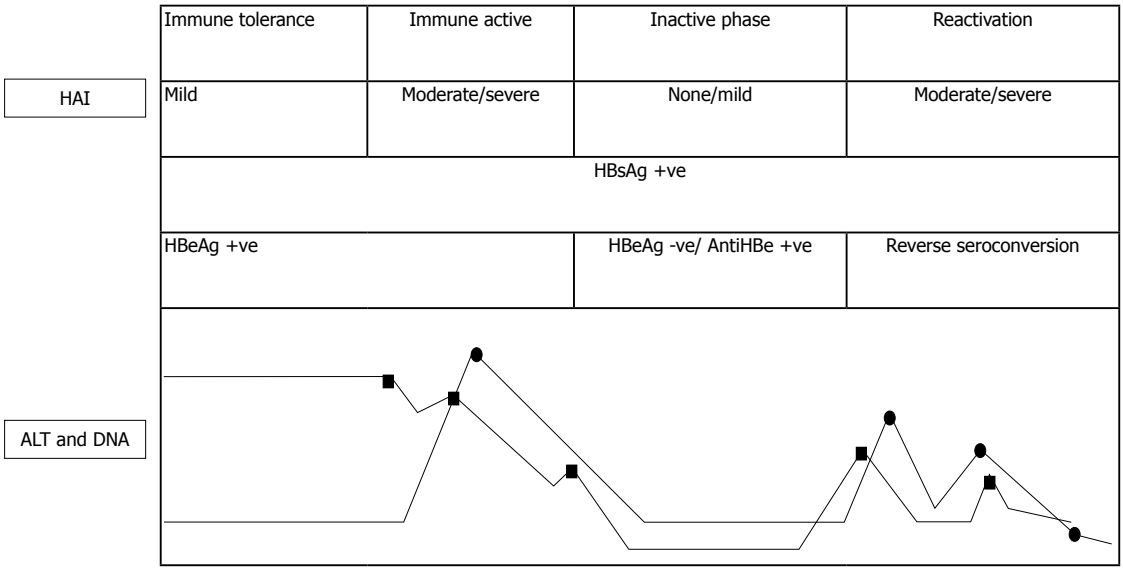


**Figure 2 Natural history of chronic hepatitis B virus infection and phases of reactivation.** The variations in alanine aminotransferase (ALT) and DNA levels are shown in relation to histological activity index (HAI) (also shown in the inset). ALT (circles) and HBV DNA (squares). PIEALT: persistently or intermittently elevated ALT [defined as ⩾ 3 ALT values in the year prior to baseline liver biopsy, and all values were > 40 IU/L and had remained so until the start of treatment or last follow-up if not treated (persistently elevated) or if they had ⩾ 3 ALT values and ⩾ 1 > 40 IU/L in the year prior to baseline biopsy or anytime until the start of treatment or last follow-up, if not treated (intermittently elevated)]. PNALT: Persistently normal ALT (defined as ⩾ 3 ALT values in the year prior to baseline liver biopsy, and all values were < 40 IU/L and had remained so until the start of treatment or last follow-up if not treated). HBeAg: Hepatitis B e antigen.

curs, which are associated with recognition of specific pathogen-associated molecular patterns. TLR2-5, 7, 9 and 10 are expressed highly during ACLF related to HBV reactivation. It has also been shown that B lymphocytes activity and peripheral glucocorticoid receptor expression (which is increased) are also involved in the pathogenesis of ACLF related to HBV reactivation. Massive accumulation of plasma cells secreting IgM and IgG targeting HBcAg has been demonstrated. Lai *et al*[28] investigated the dynamics and clinical significance of serum HBV DNA levels during the terminal phase of ACLF with different HBeAg status. They found that the serum levels of HBV DNA in patients with HBeAg positivity were higher than those in patients with anti-HBe positivity as the disease phase of ACLF nears fatality. Following the deterioration to liver failure, the HBV DNA load in HBeAg(+) patients remained stable, while that in anti-HBe(+) patients decreased[29].

Previously, chronic hepatitis was classified into chronic active hepatitis, chronic persistent hepatitis, chronic lobular hepatitis, and non-specific reactive hepatitis. Nair and Perrillo, in 2001, defined a flare as an increase in alanine aminotransferase (ALT) of at least twice the upper limit of normal (ULN) compared with baseline values, while Yuen and colleagues defined a flare as elevated transaminases above twice the ULN. Chu *et al*[30] defined acute

**Table 2 Factors to differentiate severe acute exacerbation of chronic hepatitis B from acute hepatitis B**

| Parameters | | AVH-B | HBV-R |
|---|---|---|---|
| IgM anti-HBc | > 600 Paul Ehrlich units/mL | Yes (7 s and 8 s forms) | Yes (19 s form) |
| | > 1:1000 titer | Yes | No |
| HBV DNA | > $2.25 \times 10^4$/mL (121 000 copies/mL) | No | Yes |
| Liver biopsy: evidence of chronic hepatitis such as lymphocytic portal inflammation with interface hepatitis, spotty lobular inflammation, portal expansion, periportal fibrous strands, bridging fibrosis, and/or cirrhosis | | No | Yes |
| Basal core promoter mutation | | No | Yes |
| Pre-core stop codon mutation | | No | Yes |

Jindal *et al*. Management of acute hepatitis B and reactivation of hepatitis B. Liver International 2013. HBV: Hepatitis B virus.

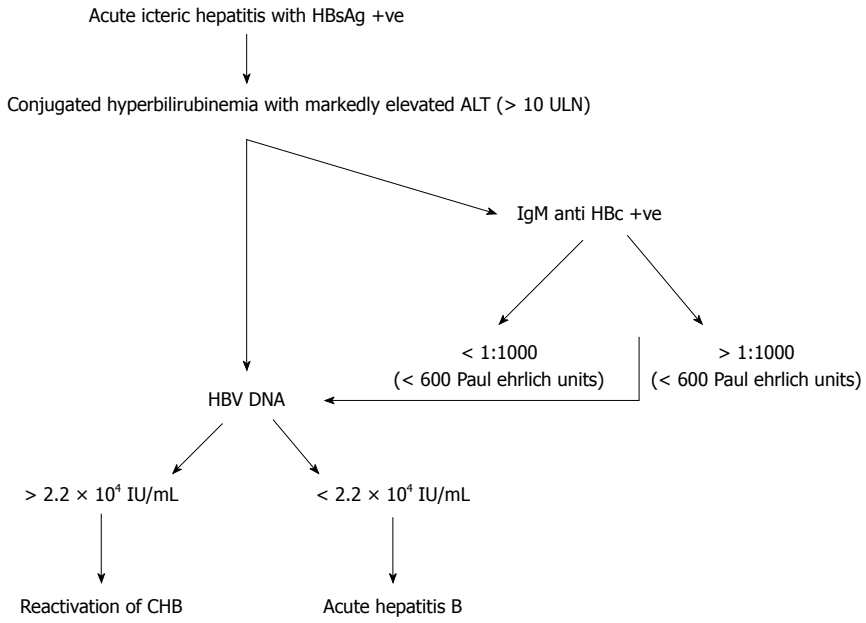


**Figure 3 Algorithm for diagnosis of acute viral hepatitis B *vs* hepatitis B reactivation.** HBeAg: Hepatitis B e antigen; ALT: Alanine aminotransferase.

exacerbation or hepatitis flares as "an abrupt elevation of ALT over 300 U/L in patients with a baseline ALT level below 200 U/L or fivefold the ULN"[31,32]. Lok *et al*[24] arbitrarily defined acute exacerbation or hepatitis flare as "an abrupt elevation of serum ALT to beyond 200 U/L (over fivefold the ULN) or a greater than threefold increase in ALT, whichever is higher". More recently, a definition of "intermittent elevations of aminotransferase activity to more than 10-fold the ULN and more than twice the baseline value" was adopted at the National Institute of Health workshop on management of hepatitis B, 2000. All of the above definitions agree that an ALT elevation > 200 U/L or fivefold the ULN is the minimum criterion. Currently, a safe definition of hepatitis flares or acute exacerbations is an abrupt elevation of serum ALT to over fivefold the ULN, and for reactivation, more than 10 times the ULN. This is also suggested by the increase or reappearance of serum HBV DNA in a patient with chronic or past HBV infection[33-35]. This is also suggested by the increase or reappearance of serum HBV DNA in a patient with chronic or past HBV infection[30-33].

The main challenge in diagnosing reactivation of chronic HBV infection is to differentiate it from acute hepatitis B (Table 2 and Figure 3). Patients with severe acute reactivation can have positive IgM anti-HBc which again creates dilemma with diagnosis of acute hepatitis B. Levels of more than 600 Paul-Ehrilch units/mL or IgM anti HBc > 1:1000 suggest an acute infection with high inflammatory activity. Kumar *et al*[38] suggested that a low titer of anti HBc IgM (< 1:1000) and high HBV DNA (> 0.5 pg/mL or $2.2 \times 10^4$ IU/mL, which is equivalent to 141500 copies/mL) are useful in identifying severe acute reactivation of HBV from acute hepatitis B. In Japanese studies, the presence of basal core promoter mutation and pre-core stop codon mutations have been suggested to differentiate severe acute exacerbations of chronic HBV infection from acute HBV-related hepatitis[36-39]. Previous history of chronic hepatitis B or a positive family history suggests possibility of reactivation, whereas

**Table 3 Independent prognostic factors for mortality (and liver transplantation) in severe acute exacerbation of chronic hepatitis B[22]**

| Parameters | Chan *et al*[40] 2002, *J Viral Hepatol* | Yuen *et al*[19] 2003, *Clin Infect Dis* | Chien *et al*[49] 2003, *J Hepatol* | Tsubota *et al*[45] 2005, *J Gastroenterol Hepatol* | Kumar *et al*[38] 2006, *Dig Dis Sci* |
|---|---|---|---|---|---|
| Age | N/A | N/A | N/A | N/A | N/A |
| Sex | N/A | N/A | N/A | N/A | N/A |
| Albumin | N/A | N/A | Low | N/A | N/A |
| Bilirubin | High | High | High | High | High |
| Prothrombin Time | N/A | Prolonged | Prolonged | Prolonged | Prolonged |
| ALT | N/A | N/A | N/A | N/A | High |
| Platelet count | Low | Low | Low | N/A | Not studied |
| HBeAg | N/A | N/A | N/A | N/A | High |
| HBV DNA | Not studied | N/A | N/A | N/A | High |
| Creatinine | N/A | N/A | N/A | Not studied | Not studied |
| AFP | Not studied | N/A | N/A | N/A | Not studied |
| Cirrhosis | Not studied | Present | N/A | Present | Not studied |
| Ascites | Not studied | Not studied | Present | N/A | Not studied |
| CTP | Not studied | Not studied | High | High | Not studied |

AFP: α-fetoprotein; N/A: Not applicable; HBeAg: Hepatitis B e antigen; ALT: Alanine aminotransferase; HBV: Hepatitis B virus; CTP: Child-Turcotte-Pugh.

historic receipt of high-risk blood, or percutaneous or sexual exposure also suggests acute hepatitis B. The outcome of acute severe exacerbation of chronic hepatitis B depends on the underlying severity of liver disease.

Acute severe exacerbation of chronic hepatitis B can occur in the immune clearance phase affecting 40%-50% of HBeAg-positive patients and can be prolonged when there is repeated unsuccessful clearance of HBeAg. Reactivation of chronic hepatitis B 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. HBV DNA level that can differentiate whether HBeAg-negative patients would remain inactive carriers or develop exacerbations is currently unknown. The first prospective study by Lok *et al*[34], investigating the natural history of acute exacerbations in chronic hepatitis B found that 15%-47% of patients developed exacerbations after 4 years follow-up. In patients with flares, up to 8% of patients developed decompensation. The mortality rates associated with ACLF-HBV are in the range of 65%-93% and 30%-70% in the absence of liver transplantation. Yuen *et al*[19] evaluated the prognostic factors in severe exacerbation of chronic hepatitis B. The parameters independently associated with an adverse outcome included pre-existing cirrhosis, high Child-Turcotte-Pugh (CTP) class scores, hypoalbuminemia, high total bilirubin levels, prolonged prothrombin time (PT), and thrombocytopenia. Furthermore, in hospital, peak bilirubin, duration of peak PT, development of encephalopathy, and presence of ascites were also found to be poor prognostic indicators. Chan *et al*[40] from a series in Hong Kong found that the only independent factors that led to a poor outcome in ACLF related to acute HBV reactivation were thrombocytopenia and high serum bilirubin. In the presence of both risk factors, the mortality in that series was 69%.

Jeng *et al*[41] in their study from Taiwan on HBeAg-positive, non-cirrhotic patients with acute exacerbation, found that about 5% of exacerbations resulted in hepatic decompensation, and serum HBV DNA levels was the only significant risk factor. A DNA level cut off of $1.55 \times 10^9$ copies/mL predicted decompensation with a sensitivity of 85%, with a negative predictive value of 99% and a positive predictive value of 24%. Once the disease reached the stage of ACLF, the prognosis was poor with high 3-mo mortality. Among the models used in predicting survival in ACLF in chronic hepatitis B, the MELD score was found to be more objective as compared to the CTP score[41-43]. Scores that were found to be better than MELD in predicting survival in ACLF-HBV patients found variables of hepatorenal syndrome, positive HBeAg, hypoalbuminemia, and prolonged PT to be more reassuring. Another model based on the presence of hepatic encephalopathy, hepatorenal syndrome, positive HBeAg and prolonged PT was also found to be better than MELD and CTP score. Before the advent of lamivudine, the prognostic model for ACLF-HBV consisted of the presence of hepatorenal syndrome, liver cirrhosis, HBeAg positivity, hypoalbuminemia, and low prothrombin activity. With the arrival of lamivudine therapy for ACLF-HBV patients, the prognostic model changed, with hypoalbuminemia, INR and HBV DNA levels becoming forerunners. Furthermore, studies from South East Asian countries reported that MELD scores of 30-40, low HBV load, and rapid declines in HBV DNA were good predictors of mortality in patients with ACLF-HBV treated with lamivudine. HBV replication hence became the key factor in predicting mortality in this group of patients (Table 3)[44].

## ANTIVIRAL TREATMENT OF ACLF-HBV

The aim of antiviral treatment for ACLF-HBV is to reduce viral load at an appreciably high rate, thereby promoting reduction in hepatocyte cell death and improved survival outcomes by prevention of decompensation-related multiorgan complications in this group of severely ill patients. Several studies have delineated the fact that low pretreatment HBV DNA load and a rapid decrement in viral load improves outcomes in ACLF-

HBV[44], whereas a study from India reported that a 2 log decrease in HBV DNA at week 2 improved survival benefit in patients with ACLF-HBV[15]. Antiviral therapy also promotes chances of stabilization to liver transplant time and improves transplant outcomes. Although liver transplantation significantly improves survival rates, it is limited by many factors, and most importantly by donor shortages. Studies have debated on the issue of antiviral therapy related improvement in the long term[8]; lamivudine decreased viral load significantly, but did not result in significant biochemical or clinical improvement compared with those patients given placebo. Mortality of patients receiving nucleoside analog therapy was significantly lower than the placebo group, which indicated that antiviral therapy improved prognosis of patients with ACLF-HBV if implemented as soon as possible[44]. Even in the age of effective antiviral therapy, early transfer to a transplantation facility should be considered before managing conservatively by medical means. The APASL consensus guidelines on ACLF describe the value of early and prompt institution of antiviral therapy in ACLF-HBV. Patients who were detected to have chronic hepatitis B infection and in whom chemotherapy or immunosuppression modalities need to be started were suggested to undergo prompt antiviral prophylaxis for prevention of reactivation-related serious consequences. As per AASLD and EASL recommendations, although lamivudine or adefovir may be adequate for short-term prophylaxis, antiviral nucleoside analogs with a higher barrier to resistance should be considered for patients in whom long-term prophylaxis is likely, particularly if high levels of HBV DNA are present before immunosuppressive therapy. HBV DNA levels are now not an indication for commencement of antivirals in ACLF HBV reactivation, as earlier starting of such therapy, even prophylactic, has been found to have great survival benefit in the long run. A detailed discussion on antiviral therapy follows.

## LAMIVUDINE

Chan *et al*[40] investigated the role of lamivudine in treatment of severe hepatitis-B-related acute exacerbations leading to ACLF in 28 patients as against 18 controls. It was concluded that lamivudine conferred no survival benefit to conventional treatment in severe exacerbations of chronic hepatitis B and that patients with thrombocytopenia and high bilirubin should be considered for liver transplantation. Tsubota *et al*[45] studied 25 patients with spontaneous severe acute exacerbation treated with lamivudine, and found that lamivudine monotherapy did not significantly prevent progression to hepatic failure. Multivariate analysis identified baseline serum bilirubin $\geqslant$ 6 mg/dL, pre-existing cirrhosis and baseline PT < 40% as independent determinants of the event. It was then shown that lamivudine monotherapy conferred no significant protection against rapid progression of the disease to hepatic failure, but it resulted in long-term benefits, and that lamivudine combined with other drugs could be more beneficial for patients with the aforementioned risk factors. The same group similarly analyzed prospectively 116 consecutive lamivudine-naïve patients who had received long-term lamivudine therapy (> 1 year). They stated that severe acute exacerbation tended to reduce or delay development of biochemical breakthrough. Eventually the group concluded that the study provided important information for the development of more effective and rational long-term lamivudine therapy for HBeAg-positive, chronic hepatitis B patients infected exclusively with genotype C[46]. Wong *et al*[25] treated 45 patients with severe acute exacerbation and 31 controls with lamivudine for a median of 2.8 (range 1.0-7.1) years and 3.8 (range 3.5-8.4) years, respectively. They found that compared with controls, patients with severe acute exacerbation had higher HBeAg seroconversion rates and lower risk of virological breakthrough. However, 33% of patients with severe acute exacerbation still developed lamivudine resistance and virological breakthrough by 5 years. HBV DNA levels at week 4 and prolonged baseline PT were independent factors associated with virological breakthrough. It was then concluded that among patients with severe acute exacerbation of HBeAg-positive chronic hepatitis B treated with lamivudine, virological breakthrough and post-treatment relapse were common despite a high rate of HBeAg seroconversion[47]. In their study from Taiwan, Chen *et al*[48] for a period of 10 mo, studied a total of 60 consecutive acute exacerbation of HBV-related ACLF patients and treated with 150 mg/d lamivudine. They concluded that lamivudine may prevent fatality in chronic hepatitis B patients with hepatic decompensation if therapy was started early enough or before serum bilirubin levels rose over 20 mg/dL, and that it helped less if serum level had already risen over that level[49]. Sun *et al*[50] studied the influential factors of prognosis in lamivudine treatment for patients with acute-on-chronic hepatitis B liver failure. They found that the cumulative survival rates of patients in the lamivudine group were higher than those of the control group and the low virus load group. For patients with a MELD score of 20-30 by week 4, the mortality of those with HBV DNA that was undetectable or declined for > 2 log10 was lower than that of those with < 2 log10 decline. The group concluded that lamivudine could significantly decrease the 3-mo mortality of patients with a MELD score of 20-30, and that a low pretreatment viral load and rapid decline of HBV DNA load were good predictors for the outcome of treatment (Table 4)[50].

Lamivudine therapy for ACLF-HBV became less enthusiastically received once drug resistance set in. This was then followed by setting up of studies that evaluated other options for management of patients with liver failure and ACLF with HBV reactivation.

## ADEFOVIR

Use of adefovir for ACLF-HBV has been rare. In two case reports, adefovir dipivoxil failed to salvage cases of

**Table 4 Studies that have provided long-term data on lamivudine treatment for severe acute exacerbation of chronic hepatitis B**

| Characteristics | Chan *et al*[40] 2002, *J Viral Heapt* | Wong *et al*[25] 2009, *J Gastroenterol Hepatol* | Tsubota *et al*[45] 2005, *J Gastroenterol Hepatol* | Kumar *et al*[38] 2006, *Dig Dis Sci* |
|---|---|---|---|---|
| Location | Hong Kong | Hong Kong | Japan | India |
| Follow up (median, yr) | 2.5 | 2.8 | 2.9 | 1.5 |
| ALT (median, IU/L) | 1758 | 1325 | 816 | 1658 |
| Bilirubin (median, mg/dL) | 31.6 | 19.6 | 14.4 | 10.1 |
| PT/INR (median) | 1.63 | 1.60 | 1.58 | 2.0 |
| HBeAg +ve (%) | 0 | 100 | 70 | 83 |
| HBV DNA (median, log copies/mL) | 6.76 | 8.08 | 8.69 | 5.135 |
| SVR | 21/26 | 21/29 | 18/21 | 21/31 |

SVR defined by Chan and Wong as < 10000 copies/mL; Tsubota as undetectable by bDNa assay (Chiron) and by Kumar as < 600 copies/mL. SVR: Sustained virological response.

lamivudine resistance after jaundice and liver failure developed. Adefovir has a relatively weak antiviral activity and the onset of action is slow. It is hence not advisable to use adefovir as a first-line drug in the treatment of acute severe exacerbation. High-dose entecavir and tenofovir are alternative agents for lamivudine resistance[51,52].

## ENTECAVIR

Chen and his group treated 55 patients with severe acute exacerbation of HBV leading to decompensation with entecavir, comparing them with 74 other patients who were not treated with nucleoside analogs. Entecavir greatly reduced HBV replication in different periods of therapy ($P < 0.001$), but the MELD score and liver function (ALT, albumin, bilirubin and PT) showed no significant change. However, the MELD score and parameters of liver function (albumin, bilirubin and PT) were different between the two groups ($P < 0.05$). These results suggested that short-term suppression of HBV replication may not slow down the progression of liver failure in patients with chronic severe hepatitis B[53].

A brief summary of studies related to ACLF-HBV and treatment with entecavir, or in comparison with lamivudine, is given in Table 5.

In 2013, Lai *et al*[54] analyzed the data from 182 HBeAg-negative patients with ACLF in China, and found that 93 were treated with entecavir 0.5 mg/d orally and 89 with lamivudine 100 mg/d orally. HBV DNA level decreased within 3 mo in both groups ($P < 0.05$), regardless of the pretreatment MELD score. In patients with the same range of pretreatment MELD scores, treatment duration, post-treatment HBV DNA levels, percentage of HBV DNA level < 2.7 log copies/mL, biochemical parameters, MELD scores, and 3-mo mortality were similar in the two groups (all $P > 0.05$). Thus, in HBeAg-negative patients with ACLF, the short-term efficacy of entecavir *vs* lamivudine was similar and the degree of pretreatment liver failure significantly affected the outcome of treatment. Liu *et al*[55] studied entecavir and lamivudine therapy for severe acute chronic hepatitis B and compared the efficacy at 4 wk with that of entecavir or lamivudine therapy in patients with severe acute exacerbation caused by chronic hepatitis B. The groups received 0.5 mg entecavir or 100 mg lamivudine daily. They found no significant differences between the virological and biochemical responses or the deterioration rates of the two groups[57]. These results suggested that short-term treatment with lamivudine markedly alleviated the increased bilirubin levels in patients with severe acute exacerbation of chronic hepatitis B, and that there was no significant difference in the deterioration rate between patients treated by the two types of medication. Entecavir did not show any superiority over lamivudine, particularly in its ability to reduce bilirubin levels. However, entecavir also did not lead to the elevation of short-term mortality rates. In a recent study by Chen *et al*[59], 21 consecutive patients with ACLF-HBV were treated with either telbivudine or entecavir. During the initial 2-wk period, the change in bilirubin was -1.2 mg/dL in the survivors, but was +8.05 mg/dL in those that died ($P = 0.009$), and by combining the baseline and on-treatment bilirubin levels, a positive predictive value of 80% and a negative predictive value of 100% were achieved. During the course, deterioration of estimated glomerular filtration rate was significant in the entecavir-treated group ($P = 0.028$), but not in telbivudine-treated patients. Additionally, the patients treated with telbivudine had a significant increase in serum α-fetoprotein (27.9-191.9 ng/mL, $P = 0.046$) in the first 2 wk, whereas the corresponding increase was not found in those treated with entecavir ($P = 0.139$). This prospective observational study concluded that the baseline and on-treatment bilirubin levels should be combined to achieve a better predictive value, and that telbivudine might have renoprotective effects in addition to its efficacy in viral suppression in patients with severe acute exacerbation[59]. Recent studies by Chen *et al*[60] on entecavir *vs* lamivudine in chronic hepatitis B patients with severe acute exacerbation and hepatic decompensation revealed that the choice between entecavir and lamivudine was not an independent factor for mortality in chronic hepatitis B patients with acute exacerbation and hepatic decompensation, and that patients with ascites, hepatic encephalopathy, and MELD scores ⩾ 24 were associated with poor outcome, and should be considered for liver transplantation. The pros and cons of lami-

**Table 5 Summary of older studies that dealt with role of entecavir and entacavir *vs* lamivudine in patients of hepatitis B virus-related acute on chronic liver failure[52-55]**

| Study | Patient No. | Drug used (no. of patients treated) | Clinical implications | Salient features | Conclusion |
|---|---|---|---|---|---|
| Chen *et al*[53] | 55 | Entecavir | ALT, albumin, bilirubin, PT; no significant change between groups | No difference in mortality rates below 3 mo and after 3 mo, MELD not affected between groups | Short-term suppression of HBV replication offers no benefit on survival |
| Wong *et al*[56] | 124 | Entecavir | Treatment achieved < 3 logs HBV DNA; significantly higher survival rate; prevention of liver or renal dysfunction | Tongji prognostic predictor model is better than MELD in prognostication in HBV-ACLF | Entecavir prevents disease progression and increases the survival of patients with HBV-ACLF |
| Shouval *et al*[61] | 36 *vs* 117 | Entecavir (36); Lamivudine (117) | Prolonged jaundice, encephalopathy, ascites in Entecavir group | More liver-related mortality in entecavir group, faster virological response | Short-term mortality high in entecavir group, but faster reduction in viral load |
| Cui *et al*[58] | 33/34/37 | Entecavir (33); lamivudine (34); placebo (37) | Liver function and MELD scores did not improve significantly | No significant difference in 3-mo survival was observed, levels of HBV DNA and rates of recurrence of HBV-associated ACLF were lower | Nucleoside analog treatment did not improve the short-term prognosis of patients with HBV-associated ACLF although it was efficacious and safe in the management of HBV DNA levels |
| Imamura *et al*[20] | 34 | Entecavir and lamivudine consecutively | No reduction of < 1 log IU/mL in HBV DNA after 1 or 3 mo of treatment. Initial virological response, with lamivudine and entecavir, respectively, was 83.3% and 100% | Twelve months after treatment, 41.6% of 24 lamivudine group patients switched to another drug or added adefovir to their treatment due to the emergence of lamivudine-resistant mutants | Entecavir appears to be as effective as lamivudine in the treatment of patients with acute exacerbation of chronic hepatitis B |

HBV: Hepatitis B virus; ACLF: Acute on chronic liver failure.

vudine *vs* entecavir in decompensated or severe acute exacerbation of chronic hepatitis B can be summarized as entecavir being more effective in promoting faster viral load decrement, albeit its hepatic and extrahepatic adverse effects. It was also stated that the available clinical evidence suggests that clinicians treating chronic hepatitis B patients with acute HBV exacerbation or decompensated liver disease should use the most potent nucleoside analogs available[61].

## TENOFOVIR

In a seminal study by Garg *et al*[62], consecutive patients with ACLF due to spontaneous reactivation of chronic hepatitis B were randomized to receive either tenofovir or placebo. The primary endpoint was survival at 3 mo. The cumulative survival of two groups of ACLF-HBV patients treated with tenofovir *vs* placebo is shown in the Kaplan-Meier graph in Figure 4. More than 2 log reduction in HBV DNA levels at 2 wk was found to be an independent predictor of survival. The authors concluded that tenofovir significantly reduced HBV-DNA levels, improved CTP and MELD scores, and reduced mortality in patients with severe spontaneous reactivation of chronic hepatitis B presenting as ACLF, and that reduction in HBV-DNA levels at 2 wk should be considered a desirable goal and a good predictor of survival. However, genotype D was the predominant HBV genotype in the Indian patients (85.2%), but genotype B or C is the main HBV genotype in China. Also, it is still unknown whether HBV genotype may affect the results of antiviral treatment in ACLF. As mentioned earlier, the Wong *et al*[47] study shed light on the problem of lactic acidosis or an exaggerated immune response due to rapid virological suppression, which may lead to and exacerbate liver injury among patients with severe acute exacerbation of chronic hepatitis B. However, the latter explanation is contradictory to the opinion of Garg *et al*[62] who proposed that rapid reduction in HBV DNA levels independently predicted a good short-term survival rate. Thus, larger prospective and multicenter studies are encouraged to evaluate further the effect of tenofovir and entecavir on short-term mortality of patients with HBV-associated ACLF.

## REVIEW OF META-ANALYSIS

In a meta-analysis of antiviral therapy in ACLF-HBV by Xie *et al*[63], the core issue of effectiveness of nucleoside analogs on patients with chronic-hepatitis-B-associated liver failure was considered. They searched 11 randomized controlled trials that included 654 patients with chronic-hepatitis-B-associated liver failure. Three hundred and forty patients adopted nucleoside analogs, such as lamivudine, entecavir, telbivudine or tenofovir, and the remaining 314 patients adopted no nucleoside analog or placebo. In this meta-analysis, examination of survival, HBeAg seroconversion, and reduction in serum

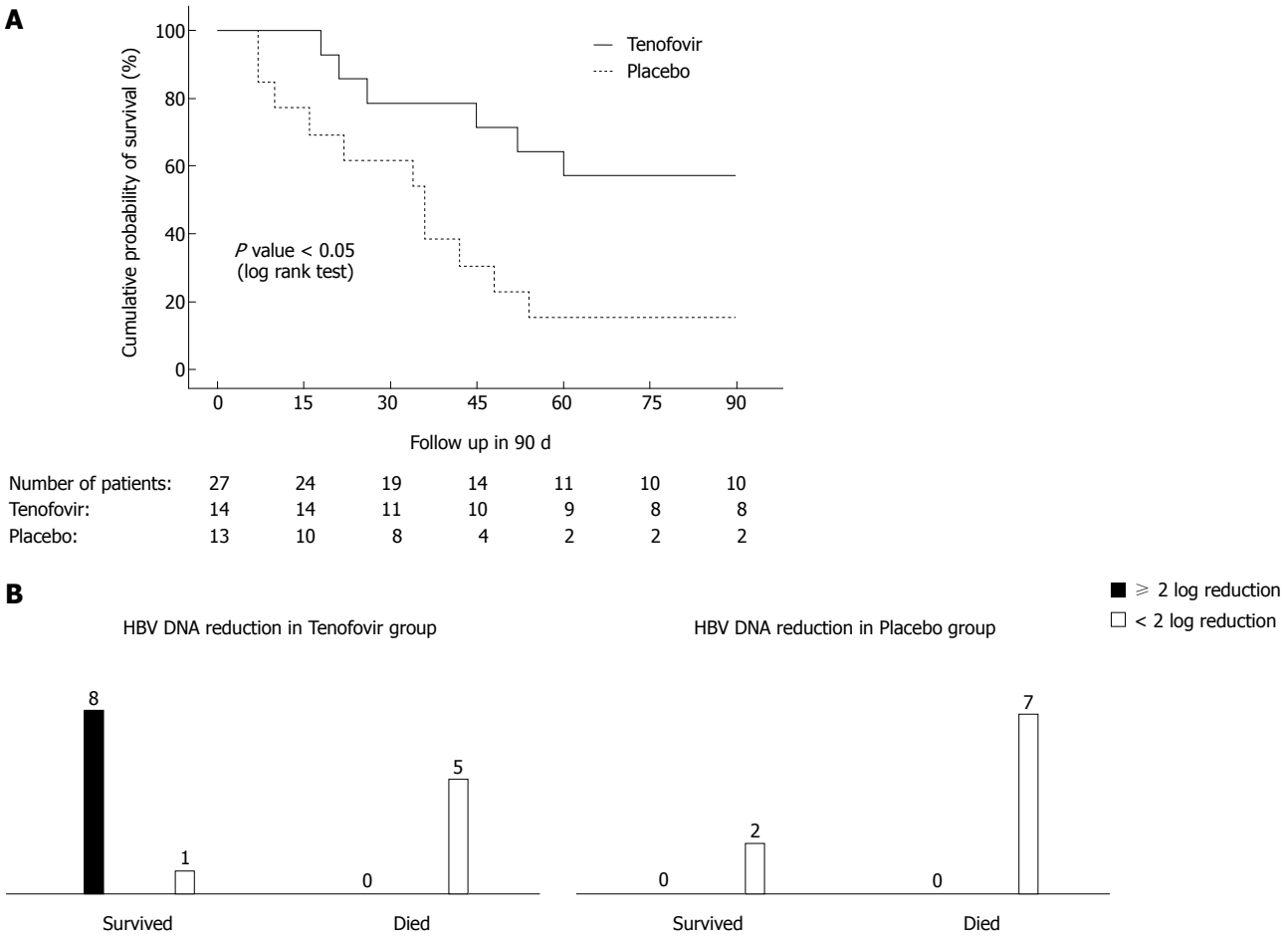


**Figure 4 Cumulative survival of two groups of acute on chronic liver failure-hepatitis B virus patients treated with tenofovir *vs* placebo is shown in the Kaplan-Meier graph below.** A: Cumulative survival of acute on chronic liver failure-hepatitis B virus (ACLF-HBV) group of patients who were randomized to receive tenofovir *vs* placebo. Of the 90 patients with ACLF of different etiologies, 27 (26%) were due to reactivation of chronic hepatitis B. The median baseline HBV DNA level was $9 \times 10^5$ IU/mL. Fourteen patients received tenofovir and 13 placebo. At 3 mo the probability of survival was higher in the tenofovir than the placebo group [8/14 (57%) *vs* 2/13 (15%), respectively; $P < 0.03$]. The cause of death in the 15 patients was progressive liver failure leading to multiorgan failure. In the surviving patients, there was a significant improvement in the Child-Turcotte Pugh (CTP) and model for end-stage liver disease (MELD) scores and significant decline in the HBV DNA levels in the tenofovir group, whereas these parameters did not change significantly in the placebo group. B: A 2-log reduction in HBV DNA level at 2 wk predicted survival benefit. Garg *et al*[61] 2011 (Hepatology). HBV: Hepatitis B virus.

HBV DNA level were studied. The overall analysis revealed that nucleoside analogs significantly improved 1-, 3- and 12-mo survival. Comparison of 3-mo HBV DNA showed a significant reduction in use of nucleoside analogs, and comparison of 3-mo HBeAg seroconversion showed a highly significant increase in HBeAg loss in patients receiving antiviral therapy. This analysis concluded that nucleoside analogs in patients with chronic-hepatitis-B-associated liver failure significantly improved patient survival, HBeAg seroconversion, and rapidly reduced HBV DNA levels. A second meta-analysis by Yu *et al*[64] investigated the application of nucleos(t)ide analogs in HBV-related ACLF, and examined their efficacy and safety. In this study, the 3-mo mortality was defined as the primary efficacy measure. ACLF reactivation and HBV-DNA inhibition were considered secondary efficacy measures. The study found a total of five eligible studies that showed that antiviral treatment with nucleos(t)ide analogs significantly reduced HBV DNA (HBV DNA reduction > 2 log). ACLF patients receiving nucleos(t)ide analogs had significantly lower 3-mo mortality, as well as incidence of reactivation compared to those who did not. There was no significant difference in the prognosis of patients treated with entecavir or lamivudine. The findings of this meta-analysis suggested that nucleos(t)ide analog treatment reduced short-term mortality as well as reactivation of HBV-related ACLF. Nucleos(t)ide analogs were well-tolerated during therapy (with no adverse outcomes documented) and evidence indicated that entecavir and lamivudine conferred comparable short-term benefits in these patients. The important studies on antiviral therapy for patients with acute severe hepatitis B and decompensation of cirrhosis are shown in Table 6.

## PROGNOSTIC MODELS FOR ACLF-HBV

Fan *et al*[65] identified the risk factors for predicting the outcome of acute-on-chronic hepatitis B liver failure (ACHBLF). Their study included 113 patients (87 men

**Table 6 Important studies on antiviral therapy in hepatitis-B-related acute on chronic liver failure**

| Ref. | Country | Study design | Drugs/dose | No of patients treated | End events | Follow up | Remarks |
|---|---|---|---|---|---|---|---|
| Yang *et al*[79] | China | RCT | Entecavir (0.5 mg) | 55 | Liver function, HBV DNA | 1 mo | Useful |
| Sun *et al*[50] | China | Retrospective cohort | LAM (100 mg) | 130 | Mortality, DNA, YMDD mutation | 3 mo | Not useful |
| Qiu *et al*[80] | China | RCT | Telbivudine (600 mg) | 30 | Liver function, HBV DNA | 1 mo | Useful |
| Cui *et al*[58] | China | Retrospective cohort | LAM (100 mg) or EVT (0.5 mg) | 67 (LAM) *vs* EVT (37) | Mortality, MELD, HBV DNA, recurrence | 12 mo | Similar |
| Zhang *et al*[72] | China | Observational study | LAM (100 mg) plus Dexamethasone (10 mg/d, 5 d) | 56 | Liver function, MELD, Survival | 1 mo | Useful |
| Garg *et al*[62] | India | RCT | Tenofovir (300 mg) *vs* placebo | 14 *vs* 27 | Mortality, MELD, HBV DNA | 3 mo | Useful |
| Chen *et al*[60] | China | Retrospective cohort | LAM (100 mg) or EVT (0.5 mg) | 72 (LAM) *vs* 34 (EVT) | Mortality, recurrence, HBV DNA, YMDD mutation | 7 mo | Similar |
| Chen *et al*[47] | China | RCT | LAM (100 mg) or EVT (0.5 mg) | 42(EVT) *vs* 30(LAM) | HBV DNA, YMDD mutation, MELD Na | 7 mo | Evt more useful |
| Qin *et al*[81] | China | RCT | Telbivudine (600 mg) | 12 | Mortality, liver function, HBV DNA | 3 mo | Useful in renal dysfunction |
| Lai *et al*[54] | China | RCT | LAM (100 mg) or EVT (0.5 mg) | 93(EVT) *vs* 89(LAM) | HBV DNA, MELD, HBeAg -ve | 3 mo | Evt useful |
| Chen *et al*[82] | China | RCT | Entecavir (0.5 mg) plus Dexamethasone (10 mg/d, 3 d) | 31 | Liver function, MELD, Mortality | 3 mo | Useful |

HBV: Hepatitis B virus.

and 26 women) with a mean age of 49.84 years. Fifty-two patients survived, and 61 died. Liver failure (85.2%), sepsis (34.4%), and multiple organ failure (39.3%) were the main causes of death. Multivariate analyses showed that APACHE Ⅱ scores ⩾ 12 and positive blood culture on the day of diagnosis and MELD scores ⩾ 28 after the first week of treatment were independent predictors of mortality. Zheng *et al*[66] investigated the dynamic patterns of the natural progression as well as their impact on the outcomes of ACHBLF. In this study, the baseline characteristics showed that there were significant differences in only HBV DNA levels and platelet count between the deceased and surviving patients. Furthermore, the dynamic state of the MELD score gradually increased from an initial hepatic flare until week 4 of ACHBLF progression, and there were notable changes in the dynamic state of the MELD score at two time points (weeks 2 and 4) during ACLF-HBV progression. The MELD scores were significantly greater in the dead group (24.80 ± 2.99) than in the survival group (19.49 ± 1.96, $P < 0.05$) during the clinical course of ACHBLF, and the MELD scores of the survival group began to decrease from week 4, while they continued to rise and eventually decreased as more patients died. The gradients of the ascent and descent stages predicted exactly the severity and prognosis of ACLF-HBV. It was concluded that the natural progression of ACLF-HBV could be divided approximately into four stages including ascent, plateau, descent, and convalescence stages, according to different trends in liver failure progression. Thus, the special patterns of the natural progression of ACLF-HBV could be regarded as a significant predictor of the 3-mo mortality of ACLF-HBV. He *et al*[67] compared four prognostic models and a new logistic regression model to predict short-term prognosis of ACHBLF. In their study, the 3-mo mortality was 43.6%. The largest concordance statistic predicting 3-mo mortality was MELD score at 2 wk after admission, followed by MELD scores: sodium and integrated MELD (iMELD) scores, ΔMELD, ΔMESO and MELD plus sodium (MELD-Na) scores (Figure 5). In multivariate logistic regression analysis, the independent factors predicting prognosis were found to be hepatic encephalopathy, serum creatinine, INR, and total bilirubin at 2 wk after admission and cholinesterase upon admission. This regression model had a greater prognostic value compared to the MELD score at 2 wk after admission.

## NEW FRONTIERS

Di Campli *et al*[68] in 2007 utilized for the first time, granulocyte colony-stimulating factor (G-CSF) treatment in patients with ACLF (alcoholic liver failure). They found out that this therapy was able to induce CD34 mobilization in patients with ACLF. The expression pattern of chemokine CXC receptor 4, very late activation antigen 4, and vascular endothelial growth factor receptor suggested that these molecules are involved in G-CSF-induced stem cell mobilization, which eventually led to liver regeneration and repair. However, they did not show the effect of G-CSF on survival benefit. Similarly, Spahr *et al*[69] investigated the efficacy of G-CSF in patients with alcoholic steatohepatitis, and observed an elevated peripheral $CD34^+$ cell count and proliferating hemopoietic cells in the liver tissues, but they failed to demonstrate improvement of liver function.

Garg *et al*[70] studied the efficacy of G-CSF in ACLF patients. The first report of G-CSF therapy in ACLF-HBV was by Duan *et al*[71] in 2013. They observed that G-CSF therapy increased the peripheral neutrophil count

| Parameters | AUC | 95%CI | | Cutoff | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|---|---|
| | | Lower | Upper | | | |
| MELD_2 | 0.800 | 0.733 | 0.866 | 27.5 | 61.3 | 85.6 |
| MESO_2 | 0.796 | 0.729 | 0.864 | 1.986 | 70.7 | 76.3 |
| iMELD_2 | 0.758 | 0.687 | 0.829 | 45.57 | 74.7 | 64.9 |
| ΔMELD | 0.752 | 0.679 | 0.825 | 0.5 | 58.7 | 77.3 |
| ΔMESO | 0.729 | 0.653 | 0.805 | 0.902 | 73.3 | 57.7 |
| MELD-Na_2 | 0.728 | 0.653 | 0.803 | 29.65 | 74.7 | 67.0 |

**Figure 5 Sensitivity, specificity, and 95%CI for the four model for end-stage liver disease-based prognostic models used to predict mortality with the best predictive cut offs at 3 mo[67].**

and $CD34^+$ cell count in patients with HBV-associated ACLF, and that G-CSF treatment demonstrated improved liver function compared to the control group, as demonstrated by the CTP and MELD scores. After 3 mo follow-up, the survival rate in the treatment group (48.1%) was found to be significantly higher than that in the control group (21.4%). G-CSF therapy could be a potential tool for management of such a sick cohort of patients.

Interferon therapy is contraindicated because it exacerbates hepatic decompensation. Corticosteroids, based on their anti-inflammatory activity, have been used in a recent study, wherein intravenous dexamethasone 10 mg/d was given for 5 d, together with continuous lamivudine to 56 patients. When compared with controls, dexamethasone treatment was an independent factor influencing survival, with a rapid decline in serum bilirubin in the first 5 d being predictive of survival. Another study showed no impact on survival of dexamethasone therapy along with entecavir standard treatment in patients of ACLF-HBV[72].

## ACLF-HBV AND LIVER TRANSPLANTATION

Orthotopic liver transplantation remains the only definitive therapy for patients with ACLF-HBV who do not stabilize on medical management. Chan *et al*[73] concluded that live donor liver transplantation using the right lobe is an effective therapeutic option for patients with ACLF due to hepatitis B. It results in satisfactory survival outcomes comparable with those in patients undergoing living donor liver transplantation for elective conditions.

The APASL consensus experts have agreed to the use of standard King's College Hospital criteria for liver transplantation in patients with ACLF and the need for earlier intervention for type 1 hepatorenal syndrome or spontaneous bacterial peritonitis. Liver transplantation in patients with ACLF has been retrospectively analyzed by Bahirwani *et al*[74]. They showed that the group with ACLF had 26% mortality compared with 17% in the non-ACLF group. The difference was significantly different in univariate analysis, but when only single organ transplants were analyzed, the results were not significant. On multivariate analysis, ACLF was not an independent predictor of post-transplant mortality, arguing strongly that this is a good indication for transplantation. The timing of transplantation is crucial because patients with ACLF may provide a window of opportunity. Living-donor transplantation is an attractive option; the experience of which has been reported extensively in South-East Asia, mainly in patients with ACLF resulting from HBV reactivation. Chen *et al*[75] suggested that although the patients with ACLF and hepatorenal syndrome had a more difficult postoperative course, living donor transplantation could be performed safely, and overall, there were no significant differences in 5-year survival of about 80%. Similar observations have been made by Chok *et al*[76] in similar cohorts of patients.

Finkenstedt *et al*[77] investigated the feasibility of transplantation and determined the postoperative outcomes of patients with ACLF. They found that multiorgan failure was the most common cause of death. Patients who developed infectious complications (particularly pneumonia and/or sepsis) and patients who received renal replacement therapy or mechanical ventilation were less likely to undergo transplantation. The 1- and 5-year survival rates of 87% and 82% were comparable to the rates for non-ACLF patients. This study showed that liver transplantation remains the only therapeutic option for the vast majority of patients with ACLF. However, transplantation was feasible in < 25% of the patients with a 5-year survival rate > 80%.

Duan *et al*[78] studied 100 consecutive patients with pathologically confirmed ACLF who underwent liver transplantation. The preoperative data showed that all patients were in a serious condition with a median high MELD score of 32. The patients underwent either deceased donor or living donor liver transplantation with an overall mortality of 20%. The 1-, 3- and 5-year cumulative survival rates were 76.8%, 75.6% and 74.1%, respectively, and graft 1-, 3- and 5-year accumulative survival rates were 73.3%, 72.1% and 70.6%, respectively. It was concluded that both deceased and living donor liver transplantation were effective therapeutic options for pa-

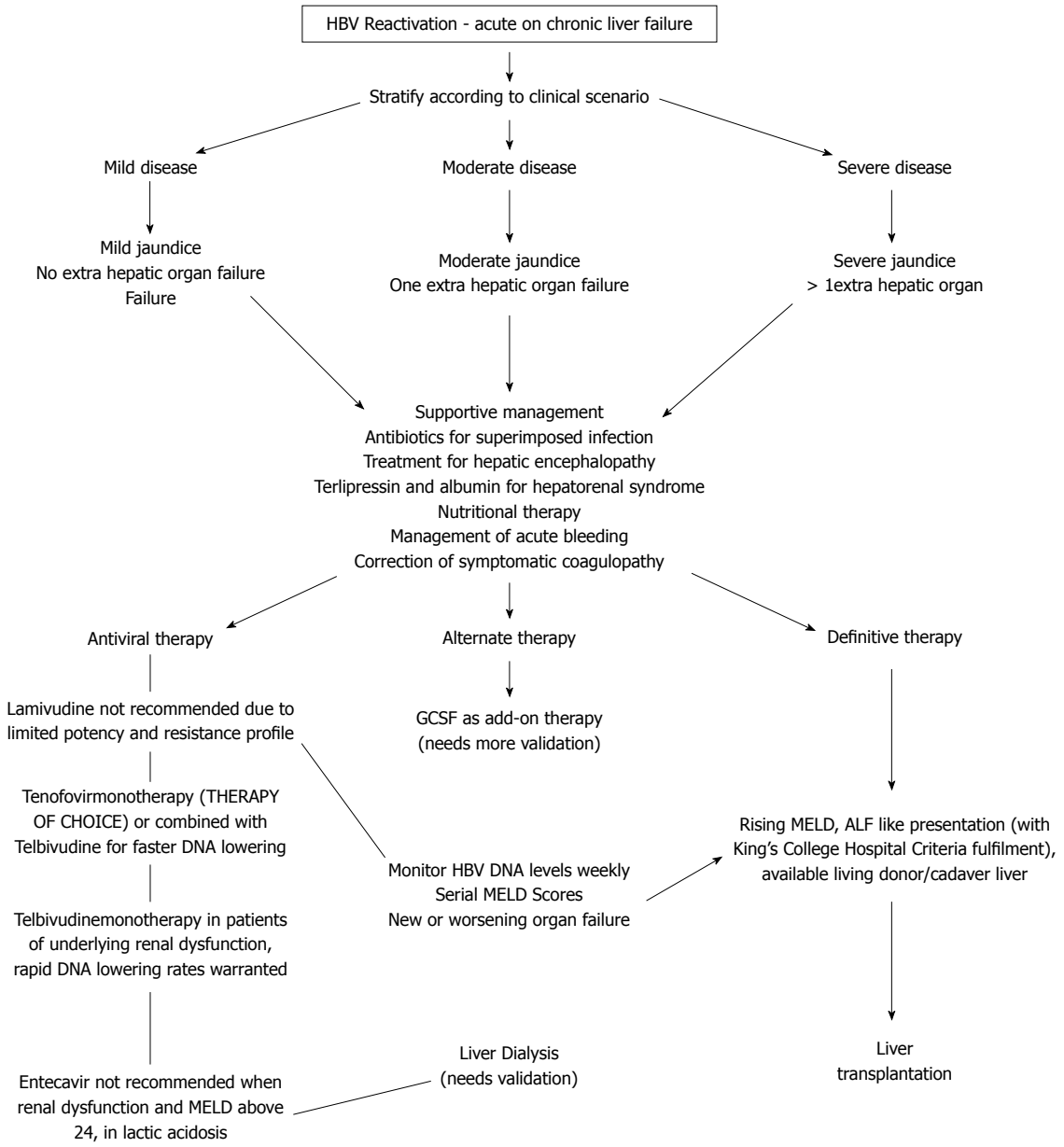


**Figure 6 Algorithm for management of acute on chronic liver failure secondary to reactivation of chronic hepatitis B.** HBV: Hepatitis B virus.

tients with ACLF and the short- and long-term survival rates were encouraging.

In the era of more technically astute liver transplantation methodology, it is important to conduct more prospective and multicenter studies to define preoperatively which patients would benefit from transplantation in this group of patients.

A possible algorithm for management of ACLF-HBV is given in Figure 6.

The use of highly potent antiviral therapy has been shown to improve outcomes in ACLF-HBV patients. Lamivudine and entecavir showed similar rates of improvement, but definite short-term survival benefits. Adefovir is not particularly helpful in a serious disease such as ACLF-HBV. Tenofovir, even though used in a small subset of study patients, still showed greater benefit than that achieved by other antiviral agents. Telbivudine has been shown in a few studies to be useful in the presence of renal dysfunction, due to its renoprotective effects.

The current concepts in management of HBV-related ACLF have come a long way, but several issues remain to be addressed before standardized protocols can be recommended. The use of nucleoside and nucleotide analogs is warranted, and has clear survival benefits. Larger, challenging and well-designed studies to compare the many available high-potency antiviral agents in ACLF-HBV patients need to be undertaken to clarify and produce standardized management protocols. The goals in this cohort of patients who have high mortality rates in the absence of effective drug intervention need to be defined.

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