Therapy of Acute and Fulminant Hepatitis B

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Key Words

Hepatitis B virus · Acute hepatitis · Hepatitis B · Fulminant liver failure · Antiviral therapy

Abstract

Although new hepatitis B virus (HBV) infections are decreasing due to improving vaccination coverage, patients without vaccination coverage can still suffer from manifestation of acute hepatitis B with jaundice and (although rarely) liver failure. No treatment is indicated for mild acute hepatitis B; however, antiviral therapy should be initiated for patients showing signs of significant liver impairment as exemplified by deterioration of prothrombin time to an equivalent of 1.5 or 50% of the 'Quick test'. For fulminant hepatitis, there is no complete agreement on whether antiviral treatment would alter the course, but it should still be started, as it would reduce the risk of reinfection in case there is a need for liver transplantation. Patients in danger of progression towards acute liver failure should be referred to transplant centers as early as possible.

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Natural Course of Acute Hepatitis B Virus Infection

Hepatitis B virus (HBV) is highly contagious with an estimated 3–200 DNA copies being sufficient to cause infection, depending on the HBV strain [1, 2]. Newborns

with HBeAg-positive mothers have a high risk of HBV acquisition without vaccination and a very high rate of chronicity [3]. However, newborn infection can be prevented by active-passive vaccination in most; if mothers with a high viral load receive antiviral therapy during the last trimester of pregnancy, transmission can likely be prevented in all when combined with active passive vaccine [4]. Symptoms during acute infection can likely vary between asymptomatic infection to fatal disease. Acute hepatitis B is a vaccine-preventable disease. The introduction of universal newborn and risk group vaccination has led to a decline in the incidence of HBV infection in most countries [5, 6].

Infection with HBV frequently remains unnoticed, and might only be noticed by seroconversion to HBsAg-positive or anti-HBc-positive results, or mild-to-moderate elevation of transaminases [7]. Several vaccine trials comparing vaccine to placebo arms have indicated that the majority of patients contracting HBV actually will have some liver enzyme elevation [8]; however, jaundice was not mentioned in these publications, suggesting significant jaundice is indeed a relatively infrequent event.

After an incubation of 2–24 weeks, jaundice has been reported to develop in about 14–30% of infected individuals [9–11]. The likelihood of symptomatic disease following HBV infection is likely influenced by the infectious dose within an inoculum [12], the pathogenicity of the infecting strain, and the immune response of the host. In a study evaluating patients who received a serum-sta-

bilized yellow fever vaccine believed to be HBV contaminated, jaundice developed in 5–40% of the patients who received different vaccine lots [11].

In 2005, about 1% (24/2,452) of the patients reported to the Centers for Disease Control and Prevention (CDC) with acute HBV infection and information on their survival died from their hepatitis B infection [13]. In addition, a few patients were transplanted for fulminant hepatitis B [14]. Thus, HBV remains an important cause of fulminant hepatitis [15]. Similarly, of the 2,890 cases reported in 2011 to the CDC, 1,920 cases had some clinical information available, showing that 1,477 were jaundiced and 1,021 were hospitalized, with 22 reported to have died from the sequelae of acute HBV infection. The rates of hospitalization and jaundice in these reported cases are much higher than in cohorts prospectively evaluated for seroconversion.

In general, jaundice appears only in about 1 out of 3 individuals [16–18], but some HBV strains might be particularly virulent. In one recent outbreak attributed to an inadequately shared glucose-monitoring device, 6 out of 8 elderly patients contracting hepatitis B died from acute hepatitis B [19]. However, in a similar outbreak situation the outcome was intermediate [20] or rather benign [21].

In order to address risk and benefit of treatment in the setting of acute hepatitis B, it is important to first discriminate between different severities of acute hepatitis B infection:

1. Mild HBV infection without clinical manifestation.
 - a. Asymptomatic HBV infection without transaminase elevation or jaundice.
 - b. Asymptomatic HBV infection with transaminase elevation, but no jaundice.
2. Moderate-to-severe acute hepatitis B infection with clinical manifestation.
 - a. HBV infection with jaundice, but no or only mild impairment of coagulation.
 - b. Severe acute hepatitis: acute hepatitis and the presence of coagulopathy with international normalized ratio (INR) increased to >1.5.
 - c. Acute liver failure/fulminant hepatitis: acute hepatitis and the presence of coagulopathy and hepatic encephalopathy [22]; acute liver failure can be differentiated depending on the interval from onset of jaundice to onset of hepatic encephalopathy as follows: hyperacute (<7 days), acute (7–28 days), and subacute (<26 weeks, but more than 4 weeks); a more acute presentation might be associated with slightly better prognosis [23].

In general, for management of severe acute hepatitis it is important to act quickly – ideally prior to onset of he-

patic encephalopathy. As for some other types of fulminant hepatitis, an earlier intervention is more likely to prevent fatal outcome. Ideally, prior to onset but certainly once signs of hepatic encephalopathy emerge, evaluation for transplant benefits and transfer to a transplant center should be achieved.

Treatment to Prevent Chronicity of Acute Hepatitis B

In contrast to the high rate of chronicity in newborns, the progression from acute HBV infection to chronicity in immunocompetent adults is low and varies between 0.2 and 15% in various studies (table 1), and is somewhat higher in immunocompromised or elderly patients.

The low rate of chronicity in immunocompetent patients makes prevention of chronicity an unlikely indication of antiviral therapy in the setting of acute hepatitis B. Pursuing a study concerning prevention of chronicity would be further complicated by the large variation in progression to chronicity. However, a concept could be to initiate treatment for preventing chronicity in patients who show signs of failure to achieve spontaneous clearance, such as lack of HBsAg reduction by more than 50% within 4 weeks [24–26]. Still the feasibility of such a study is questionable; however, in contrast to treating all patients with acute hepatitis, where the window to recruitment would be only days, a study targeting prevention of chronicity in patients with evidence towards failure of spontaneous clearance might allow weeks from onset to recruitment.

Risk Factors for Disease Severity and Treatment Consideration for Acute Hepatitis B

There are no well-established algorithms to predict severity of acute hepatitis B, but age has been reported to be relevant [27, 28], with jaundice occurring more frequently among older individuals. In addition, factors associated with decreased or absent HBeAg expression might lead to more severe disease such as with viruses harboring basal core promotor and/or precore mutations [precore (*G1896A*, *G1899A*), core promotor (*T1753A/C*, *T1754C/G*, *A1762T/G1764A*)] [29]. In a small study among American Indians, alcohol abuse and methamphetamine abuse was associated with worse outcome [30].

Table 1. Different chronicity rates after acute hepatitis B reported in various studies

Chronicity rate	Population studied	95% CI	Study
0.2% (1/507)	Greek patients	0.04–1.1	Tassopoulos et al. [52]
0.5% (1/392)	US Veterans	0.6–1.4	Seeff et al. [53]
1% (3/301)	Japanese patients	0–2.1	Ozasa et al. [54]
2.6% (1/30)	Taiwanese students	0–7.5	Beasley et al. [55]
4.6% (11/240)	Turkish patients	2.4–12.1	Kuruüzüm et al. [56]
6.3% (5/80)	German patients	2.5–14.4	Möller et al. [57]
8.5% (25/294)	Shanghai patients	5.31–11.69 ^a	Zhang et al. [58]
9.7% (13/134)	US patients	5.8–15.9	Redeker [59]
13.3% (25/188)	Alaskan Natives	8.5–18.2 ^b	McMahon et al. [60]
13.4% (11/82)	Japanese patients	6.0–20.8 ^c	Suzuki et al. [61]
15.9% (34/214)	Japanese patients	11.6–21.4 ^d	Ito et al. [62]
27% (19/70)	Korean patients	18.1–38.6	Lee et al. [63]

^a Genotype dependent [C2 20/50 (40%, CI: 26.4–53.6), B2 5/36 (13.9%, CI: 2.6–25.2)].

^b Age dependent (7.7–28.6%).

^c Some difference depending on the genotype: genotype A 7/31 (22.6%, CI: 11–40), genotype B 1/9 (11%, CI: 2.5–44.5), genotype C 3/42 (7%, CI: 2.6–19.1).

^d With 9/105 (8.5%, CI: 4.6–15.5) nongenotype A vs. 25/107 (23.3%, CI: 16.3–32.2) genotype A ($p = 0.003$).

Treatment to Ameliorate Course of Acute Hepatitis B

Treatment of Acute Asymptomatic Hepatitis B

As with influenza virus infection, treatment could be used to ameliorate the course of disease rather to prevent chronic infection. Only a minority of patients with acute hepatitis B will even come to medical attention due to the mostly relatively indolent course for most patients; however, a few may develop more serious to even fatal disease. It is also important to note that anyone with evidence of HBV exposure might be at risk of HBV reactivation in situations of immunosuppression such as therapy with biologics or chemotherapy [31].

For nonicteric patients with mild acute hepatitis B, there seems to be no indication for antiviral therapy to ameliorate the course, as these patients are asymptomatic, and antiviral therapy would unlikely be of any benefit as amelioration would not be needed. There is currently no clear understanding why some patients progress towards chronicity, but it is likely related to the immune response being too weak compared to the required immune response. Therefore, one could speculate whether an immunomodulatory therapy such as interferon could increase HBsAg clearance rates in patients with slow HBsAg decline and/or prolonged HBsAg persistence who are likely to become chronic carriers. As outlined above, chronicity in patients with acute hepatitis B is relatively rare, but in cases of failure to reduce viral load spontane-

ously as a sign of chronicity, one could consider antiviral therapy, preferentially with interferon for its immunomodulating properties.

Treatment of Acute Symptomatic Hepatitis B with Mere Jaundice

In the absence of coagulopathy, antiviral therapy is currently not recommended in the AASLD or EASL guidelines outside of studies [32, 33]. However, patients with jaundice may get hospitalized for several days and may benefit from antiviral therapy. A recent study from Germany found a trend towards earlier decline of bilirubin, ALT normalization, and HBsAg clearance in treated patients, but failed to demonstrate a significant benefit due to lack of power. We calculated 140 patients would have been needed, which we presume would have been possible to recruit within 18 months based on the annual reported incidence of 1,400 cases per year in Germany at that time. However, likely due to the majority of such reported cases being less severely ill than anticipated, only 40 patients could be recruited over a 25-month period, leading to early termination of the trial [34].

Treatment of Severe Acute Hepatitis B

There have been several cases series which indicated efficacy of antiviral therapy. In addition, there are two randomized studies in patients with severe acute hepatitis B. One underpowered study from India evaluated the

benefit from lamivudine in acute hepatitis B, including patients with severe acute hepatitis B defined as fulfilling 2 of the following 3 criteria: hepatic encephalopathy, serum bilirubin >10.0 mg/dl, and INR of coagulopathy >1.6. Although the authors of the study concluded a lack of efficacy, the study suggested faster recovery in 31 lamivudine-treated patients compared to 40 patients who received placebo. The difference, however, was not significant, possibly due to being underpowered in light of the small number of patients [35]. A statistically significant result was found in a Chinese study which recruited 80 patients with severe acute hepatitis B with bilirubin about 9 times the upper limit of normal (171 μ mol/l) and an INR between 1.4 and 1.6. The study found a higher mortality rate in the patients of the control group (10/40, 25%) versus the lamivudine-treated group (3/40, 7.5%) [36]. Thus, overall there is good evidence to support antiviral therapy in patients with severe acute hepatitis B as indicated by signs of impaired liver function. Antiviral treatment should be continued at least until HBsAg clearance.

Treatment of Acute Liver Failure Due to Hepatitis B

No placebo-controlled trial has been published in the setting of established acute liver failure, but several case series have suggested lower mortality in patients with fulminant hepatitis B compared to case series of patients who did not receive antiviral therapy. Most of these studies recruited patients before they had progressed to more advanced hepatic encephalopathy (HE stages 3 or 4). In a study recruiting patients with more advanced liver failure, no benefit of nucleoside on survival was observed [37], but those authors still concluded that nucleos(t)ide analogues would be indicated in such patients to reduce viral load prior to potential liver transplantation. It is likely that early intervention is crucial. N-acetyl cysteine, which is highly effective in preventing death from liver failure from paracetamol/acetaminophen overdosing, has limited efficacy once hepatic encephalopathy is present. While early antiviral intervention is likely to be more effective when given early, we suggest that it should also be given at later time points, as it at least diminishes the risk of HBV reinfection should liver transplantation be required. In case of transplantation, it is unclear whether antiviral therapy can be stopped soon after or if long-term antiviral treatment is required. If transplantation can be avoided, antiviral treatment should be continued at least until HBsAg clearance.

Treatment of Acute-on-Chronic Hepatitis B

In the absence of a history of positive or negative HBV serology, there is limited possibility to discriminate ‘acute

hepatitis B’ from ‘acute-on-chronic hepatitis B’. Both can present with a similar clinical picture, and hepatitis B core antibody (anti-HBc) IgM can be positive in both acute hepatitis B and acute-on-chronic liver failure due to HBV. However, anti-HBc IgM titers are usually higher in acute hepatitis B compared to exacerbations of chronic hepatitis B [38].

In case of doubt, it might be worth considering preexisting chronic hepatitis B, and antiviral treatment should be initiated promptly. Nucleos(t)ide analogues with a high barrier to resistance should be used, given that a long duration of treatment is likely needed in such cases compared to true acute HBV infection.

In a study of 27 patients from India with reactivation of HBV and acute-on-chronic liver failure randomized to tenofovir or placebo, 3-month mortality was 6/14 (42.8%) and 11/13 (84.6%, $p = 0.03$), respectively, and survival was related to fast reduction of HBV DNA within 2 weeks [39].

While the ethics of placebo control in such a population is questionable, the results of that study were clear: early treatment intervention has the potential to reverse the course of a disease in patients with an otherwise very poor prognosis. Therefore, the 2009 APASL guideline recommended antiviral therapy in all patients with acute-on-chronic liver failure due to hepatitis B. One can discuss whether a threshold of viral load should be required to initiate antiviral therapy, but given the safety of current oral antiviral therapy, we would favor to treat in case of doubt – even if HBV DNA may be undetectable but HBsAg is detectable.

Treatment for Acute Hepatitis B-Associated Extrahepatic Manifestations

Acute HBV infection has in the past been associated with a number of extrahepatic manifestations. Most of these are believed to be related to immune complex formation with either HBeAg or HBsAg. Therefore, one might consider interferon-based therapies to be potentially more effective than purely antiviral therapies; interferon also has been associated with stronger reduction of HBeAg and HBsAg than pure antivirals. Some recent papers, however, have also reported success with direct antiviral therapy, which remains the only option for interferon intolerant patients.

Interestingly, as acute HBV infections decrease, patients presenting with extrahepatic manifestations due to acute HBV infection are also seen less frequently [40]. In our experience, we do not recall any patient with acute hepatitis and significant extrahepatic manifestations such

are renal disease of polyarteritis nodosa. Still, it is important to be aware that HBV may be associated with extrahepatic diseases.

Interestingly, while HCV is associated with membranoproliferative glomerulonephritis, glomerulopathies associated with HBV were found to be dominantly membranous glomerulopathy (MGN) [41].

HBV-associated panarteritis nodosa/polyarteritis nodosa is a severe disease in which antiviral therapy has been reported to be beneficial, but not always able to prevent a fatal outcome [42]. In addition, given the importance of viral load for polyarteritis nodosa, it is more likely to present with ongoing HBV replication, and thus in a phase where acute HBV infections transition to a chronic phase of disease.

Another manifestation reported with HBV is Gianotti-Crosti syndrome. This is a syndrome of skin eruption described as papular acrodermatitis. It is mostly limited to children and not limited to HBV, but reported with acute HBV infection [43].

In summary, current treatment for extrahepatic manifestations may include antiviral therapy, but has not completely been established as beneficial. In addition, plasma exchange and intravenous immunoglobulin also need to be considered.

How to Treat?

Is Interferon an Option?

There is evidence for an overwhelming immune response in the pathogenesis of fulminant hepatitis B; therefore, an immune-stimulant such as interferon- α could be dangerous. However, it was explored as an option for acute hepatitis B in the past, without obvious deleterious effects, but also without evidence of benefit [44]. Still interferon might be an option for cases that are not too severe, but prolonged without significant HBsAg decline during the early weeks of infection. Such patients could be more likely to benefit from an immune-stimulating agent in order to achieve HBsAg seroconversion. HBsAg seroconversion during chronic HBV infection is more frequently observed with interferon than with direct antivirals.

Non-Interferon-Based Therapies?

In contrast to interferon, oral nucleoside analogues immediately inhibit HBV replication with a rapid decline of serum HBV DNA. In principle, all nucleosides [lamivudine, telbivudine, clevudine (where available), enteca-

vir, adefovir, and tenofovir] can be used, though adefovir due to its slower action on viral decline might be the least favored. Concerning which one to choose, there are no good head-to-head data available, and given the difficulties of studies in acute hepatitis B, it is unlikely there ever will be any.

The first reports of successful use of an antiviral were obtained with lamivudine, whereby death was successfully prevented in a few patients who had developed acute life-threatening reactivation of hepatitis B. Likewise, lamivudine was observed to be effective in ameliorating HBV reactivation in a series of renal transplant recipients. In these studies it was found that an early start of lamivudine therapy is crucial, and delayed initiation might be deleterious.

The same appears to hold true for severe acute hepatitis B infection in immunocompetent patients: several case series have reported low mortality in patients treated with lamivudine for severe acute or fulminant hepatitis B. Two case series showed significantly better survival in lamivudine-treated patients compared to historic controls [45, 46]. In multivariate analysis in one of these and another study it was found that age over 45 years and presence of systemic inflammatory response syndrome was detrimental, while lamivudine therapy was positively associated with improved survival [46, 47]. Thus, given the efficacy and safety of nucleosides, they would be the preferred treatment choice in the setting of severe acute or acute liver failure, while interferon could be dangerous.

The AASLD practice guideline for HBV notes the lack of sufficient data and recommends lamivudine, telbivudine, or entecavir as options; lamivudine and telbivudine could be considered if the anticipated duration of treatment is short [32]. The 2012 EASL clinical practice guideline on hepatitis B recommends entecavir or tenofovir only [33].

Hepatitis Delta Virus/Hepatitis D Virus

Specific Therapy for Acute Hepatitis Delta Virus Infection

Since the start of vaccination against HBV, a decline in the incidence of acute hepatitis delta virus (HDV) infection has been observed in many regions [48]. HDV requires ongoing expression of HBV surface genes to be able to infect a host, but it does not require HBV replication. Simultaneous coinfection with both HBV and HDV is associated with more severe disease and higher risk for fulminant hepatitis than acute HBV alone; however,

HDV superinfection may also present as acute hepatitis [49]. In general, coinfection is more likely to lead to severe acute presentation, but rarely leads to chronicity, while superinfection of HDV usually leads to chronicity [50]. For example, 2 of 218 HDV coinfecting patients but none of 128 HDV superinfected patients died from consequences of acute hepatitis [48, 49].

There is no established treatment for acute hepatitis D infection. The only treatment really affecting chronic hepatitis D is interferon, which has limited efficacy. Combining interferon with a nucleos(t)ide analogue does not confer any overall benefit [51]. There is no data on the use of interferon with or without a nucleos(t)ide analogue in patients with acute liver failure due to HBV/HDV coinfection or acute-on-chronic liver failure due to HDV superinfection. These patients should be evaluated for liver transplantation and receive prophylaxis to prevent HBV reinfection as that would also prevent HDV reinfection. The majority of the patients with HBV/HDV coinfection will have a self-limiting course and do not require antiviral therapy.

Prognosis and Indication for Liver Transplantation

Acute and severe acute hepatitis is not an indication for liver transplantation. However, patients may progress to fulminant hepatitis/acute liver failure. Thus, patients must be monitored for signs of recovery versus deterioration.

Basically, the prognosis of fulminant hepatitis depends on halting further cell damage and on the ability of the hepatocytes to replicate, thereby resulting in liver regeneration. Regeneration is likely to decrease with age and history of prior damage to liver cells. This explains, why a higher risk of death is observed in older patients with acute hepatitis and in those with a preexisting underlying liver disease. Prognosis deteriorates dramatically once hepatic encephalopathy sets in.

Conventional orthotopic liver transplantation is the only proven therapy for patients with severe fulminant hepatitis when they progress to liver failure indicated by hepatic encephalopathy and fulfil King's College Criteria: INR >6.5 or 3 of the following 4 criteria: (1) patient age <11 or >40 years, (2) serum bilirubin >300 µmol/l, (3) time from onset of jaundice to the development of coma of >7 days, and/or (4) INR >3.5.

However, correct timing is crucial for liver transplantation in fulminant hepatitis. On the one hand, transplantation should be avoided in patients with a realistic pos-

sibility of hepatic regeneration and eventual survival without transplantation. On the other hand, transplantation has to take place before irreversible complications such as development of brain stem herniation, and further intervention would be futile. To prevent unnecessary delay, every patient with fulminant hepatitis should be referred to a specialized center for evaluation for liver transplantation. Transplantation is indicated in patients with an estimated mortality above 80%. Contraindications are irreversible brain damage, uncontrolled sepsis, AIDS (as uncontrolled HIV infection opposed to controlled HIV infection), advanced comorbidities, or a malignant disease. Patients with fulminant hepatitis have a higher priority for liver transplantation than those with chronic liver disease, resulting in short waiting periods of just a few days.

Conclusion

Acute hepatitis ranges from asymptomatic liver injury only identified by elevated liver transaminases to severe acute hepatitis and finally liver failure. Acute hepatitis usually does not require specific treatment with the exception of hepatitis C. For severe acute hepatitis, treatment appears reasonable when a specific intervention is feasible, e.g. nucleos(t)ide analogue for severe acute hepatitis B. Fulminant hepatitis/acute liver failure will require, in addition to specific therapies, management of its complications and monitoring and evaluation for liver transplantation if indicated.

The main viral agents are the classical hepatitis viruses (A, B, D, E, and rarely C). Common extrahepatic complications include cerebral edema, coagulopathy with risk of bleeding, bacterial and fungal infections, changes in metabolism, and multiorgan failure (especially renal failure). Because these complications dictate survival, therapy should be aggressive and begin early. However, despite significant improvements in intensive care medicine, mortality remains high. The prognosis of patients with acute liver failure can be predicted by clinical scores, but these scores have a low sensitivity. In patients with an estimated high probability of a fatal course, liver transplantation represents the treatment of choice. Therefore, early referral to a transplantation center is mandatory.

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