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The new EASL guidelines for the management of chronic hepatitis B infection adapted for Swiss physicians

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Summary

Since the arrival of several new antivirals and due to the growing molecular and clinical knowledge of hepatitis B virus (HBV) infection, therapy of hepatitis B has become complex. Clinical guidelines aim at streamlining medical attitudes: in this respect, the *European Association for the Study of the Liver* (EASL) recently issued clinical practice guidelines for the management of chronic hepatitis B. Guidelines made by international experts need however to be adapted to local health care systems. Here, we summarise the EASL guidelines with some minor modifications in order to be compatible with the particular Swiss situation, while discussing in more detail some aspects. Chronic hepatitis B is a complex disease with several phases where host and viral factors interact: the features of this continuous interplay need to be evaluated when choosing the most appropriate treatment. The EASL guidelines recommend, as first-line agents, using the most potent antivirals available with the optimal resistance profile, in order to abate HBV DNA as rapidly and as sustainably as possible. Once therapy has been started, the infection evolves and resistant viral strains may emerge. Rescue therapy needs to be started early with more potent agents lacking cross-resistance.

Key words: hepatitis B virus; antiviral resistance; cirrhosis

Introduction

Over the last decades several guidelines for the treatment of chronic hepatitis due to the hepatitis B virus (HBV), or chronic hepatitis B (CHB), have been issued by many organisations and expert panels aimed at defining diagnostic criteria and guiding decisions regarding the management of CHB. These documents aim at streamlining the current attitude in dealing with HBV infection and disease, based on currently available evidence. The guideline-based approach to healthcare is relatively recent, its objectives being to standardise medical care, to improve its quality, reduce risks and achieve the best balance between cost and medical effectiveness. However, guidelines are often issued at international level and thus may need to be adapted to local healthcare systems [1]. In this review, we will summarise the consensus statements and algorithms of the recently issued EASL clinical practice guidelines for the management of chronic hepatitis B [2] with some adaptations due to the peculiar Swiss context.

HBV infection can cause chronic liver infection and hepatitis and is a global public health problem. Worldwide, about two billion people have been infected with HBV, of whom over 350 million are currently, chronically infected, accounting for about 700 000 deaths per year [3]. In Switzerland, about 6.5% of the population has been infected with HBV, with an estimated 20 000 cases presently suffering from CHB [4]. The annual incidence of HBV-related hepatocellular carcinoma (HCC) is high, i.e. between 2 and 5%, once cirrhosis is established [5]. In addition, the global and the local Swiss epidemiology of HBV is continually evolving, due to population migration, essentially from high to low endemicity countries.

When approaching HBV therapy, one should consider that CHB is a dynamic infection with five major phases (table 1), each of them potentially lasting for years or even decades. The correct appreciation of these phases is fundamental for the treatment of CHB. Schematically, HBV infection proceeds from a HBeAg-positive phase to a HBeAg-negative one. HBeAg-positive chronic

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Table 1

Phases of chronic HBV infection.

Phases of infection	HBsAg	HBV DNA	ALT levels	Histology	Comments
Immune tolerant	Positive	High levels	Normal	Mild or no necro-inflammation	Usually perinatally or early-in-life infected patients
Immune reactive	Positive	Low levels	Increased and/or fluctuating	Moderate to severe necro-inflammation	HBeAg is usually positive but seroconversion with HBeAg loss may occur. Progression to fibrosis is increased. Increased risk for HCC
Inactive carrier state	Positive	Very low or undetectable	Normal	Mild or no necro-inflammation	HBeAg is negative
HBeAg negative	Positive	Fluctuating levels	Increased, often fluctuating	Moderate to severe necro-inflammation	Lack of HBeAg secretion. Increased risk of cirrhosis and HCC
HBsAg-negative or past infection	Negative	Negative (minimal levels, i.e. <200 IU/ml, may indicate an occult infection)	Normal	No necro-inflammation	Anti-HBc with or without anti-HBs. Immunosuppression may reactivate viral replication

Table 2

Pre-treatment assessment of liver disease.

Biochemical markers: AST, ALT, γGT, AP, serum albumin prothrombin time, blood count
Full HBV serology: HBsAg, HBeAg, anti-HBe, anti-HBc and anti-HBs
Serum HBV DNA: quantitative measurement expressed in IU/ml
Screening for other causes of chronic liver disease: HDV, HCV, HIV, autoimmune, alcoholic and metabolic liver disease (steatosis)
Ultrasound examination of the upper abdomen
Liver biopsy: either if abnormal ALT or HBV DNA >2000 IU/ml (or both)

Table 3

Indication for the treatment of CHB.

Serum ALT levels > upper level of the norm
HBV DNA >2000 IU/ml (except in patients in the immune tolerant phase)
Moderate to severe active necro-inflammation (≥A2) and/or fibrosis (≥F2 in the METAVIR score) at liver histology
Compensated cirrhosis and detectable HBV DNA: treatment should be considered even in case of normal ALT levels and/or low HBV DNA (≤2000 IU/ml)
Decompensated cirrhosis: rapid, profound suppression of HBV DNA is mandatory independently of other parameters

HBV infection presents usually with high levels of viral replication and infectivity: liver disease can be mild or nil, reflecting host immune tolerance. Then, spontaneous seroconversion from HBeAg to anti-HBe may occur, usually accompanied by a hepatitis flare-up. This is characertised by increased serum transaminases and inflammatory infiltrates of liver lobules and decreasing viraemia levels, signalling the attempt of the host immune response to eliminate HBV-infected hepatocytes. If efficacious, this immune elimination may evolve towards a phase of inactive HBV carriage, with stably normal transaminases, no or minimal liver damage, and low to undetectable HBV DNA. HBeAg seroconversion is a commonly accepted, surrogate end-point of treatment outcome, since it is associated with improved prognosis. However, evolution towards a distinct entity, namely HBeAg-negative chronic hepatitis B, is also possible. This is associated with mutations in the HBV genome, preventing the virus from secreting HBeAg, and is characterised by fluctuating transaminases, lower HBV DNA levels and sometimes progressive disease. The choice of treatment differs according to the phase of infection, and will be discussed below. Recently, moreover, eight genotypes of HBV have been identified (A through H). Growing evidence shows that the natural history and treatment response may differ depending on the infecting HBV genotype. In general, genotype A is associated with better response to interferon treatment, with higher HBeAg seroconversion rates (47%) than genotype B (44%), genotype C (28%) or D (25%) [7]. Also disease progression seems to vary according to genotypes, since it appears to be slower in genotype B than in C [8], whereas genotype C and certain subtypes of B appear to be associated with a higher risk of developing cirrhosis and HCC [9]. However, further data are warranted before HBV genotyping can be recommended for clinical decision making.

Indication for treatment: who needs to be treated and why?

Chronic infection with HBV does not necessarily mean chronic liver disease. Thus, the accurate assessment of the appropriate markers over an appropriate time period (at least two laboratory tests over 12 months) is fundamental to establish a correct diagnosis and the indication for treatment. Thus, prior to starting antiviral therapy, the severity of liver disease should be assessed, and any potential co-morbidity should be ruled out (table 2). A complex and still controversial issue is the role of the liver biopsy in CHB. Liver biopsy is an invasive procedure primarily aimed at determining the degree of inflammation and fibrosis. The EASL guidelines recommend performing a biopsy

either when ALT levels are abnormal or when serum HBV DNA levels are above 2000 IU/ml. Moreover, a liver biopsy is not deemed necessary if treatment is indicated regardless of liver histology or in case of clinical evidence of cirrhosis. However, it remains an open question, whether patients in the "immune tolerant" phase (e.g. perinatally infected patients) should undergo biopsy. Such patients present with no or only mild necro-inflammation without fibrosis [6]. Thus, a liver biopsy is unlikely to change the treatment decision in patients who might not be eligible for treatment anyway.

Indication for therapy is based on the combination of three criteria: 1) serum HBV DNA levels; 2) serum aminotransferase levels and 3) histological grade and stage (table 3). Thus, treatment is indicated when serum ALT levels are above the upper limit of normal (ULN) and/or liver biopsy shows moderate to severe necro-inflammation and/or fibrosis (≥A2 and/or ≥F2 in the METAVIR score) and/or HBV DNA is above 2000 IU/ml (or 10 000 copies/ml), with the notable exception of patients in the immune tolerant phase. Decision making co-factors for therapy are the patient's age and health status and whether the patient will have continuous access to the anti-viral agents (problematic are patients without stable residency or immigrants from developing countries without legal status).

The objective of therapy is to suppress HBV replication in a sustained manner to prevent progression towards cirrhosis and HCC. Thus, the main goal of the therapy is HBV DNA reduction below the limit of detection (10 IU/ ml). As known from the HIV field, sustained viral abatement is necessary to avoid the risk of antiviral resistance. However, the expected end-points of treatment depend on the selected therapy (interferon versus nucleos(t)ide analogues: NUCs) and accordingly, three levels of therapy goals in CHB are obtainable: 1) complete and definitive remission of CHB characterised by HBsAg loss (± anti-HBs seroconversion) 2) seroconversion to anti-HBe in HBeAg positive CHB with loss of HBeAg and 3) sustained undetectable HBV DNA while on treatment.

The treatments: how to treat

At the time of writing, seven drugs are available for treatment of CHB in Switzerland (table 4): pegylated interferon-α_{2a} (PEG-IFN-α_{2a}) (Pegasys®) and three classes of nucleos(t)ide analogues (NUCs): 1) L-nucleosides analogues, comprising lamivudine (Zeffix®) and telbivudine (Sebivo®), 2) deoxyguanosine analogues, represented by entecavir (Baraclude®) and 3) acyclic nucleoside phosphonates, such as adefovir dipivoxil (Hepsera®) and tenofovir disoproxil fumarate (Viread®), the latter also available in combination with emtricitabine in a single pill (Truvada®).

The long-term efficacy of these drugs diverges because of the different drug-resistance patterns. Based on the available drugs, the treatment approach can be divided into two categories: treatment of finite duration with PEG-IFN-α_{2a} and long-term treatment with NUCs.

In Switzerland the licensed indication for NUCs differs from drug to drug and also from other countries (hence the need to adapt international guidelines). At the time of writing lamivudine, telbivudine and entecavir are approved as first-line therapy for treatment-naïve CHB, whereas adefovir is a second-line treatment, i.e. approved – so far – only for CHB with previous treatment failure under a NUC. Tenofovir is for the moment licensed only in case of human immunodeficiency virus (HIV) infection and in HIV-HBV co-infected patients for the treatment of HIV infection. Tenofovir cannot be prescribed in HBV monoinfected patients unless a specific permission from the patient's health insurance has been granted. PEG-IFN-α_{2a} is approved without limitations: its use is more favourable in HBeAg-positive patients, who have the best chance of seroconversion to anti-HBe. PEG-IFN-α_{2a} should be used with caution in patients with cirrhosis, and is even contraindicated in those with decompensated cirrhosis (see below). HBeAg-negative chronic hepatitis B may also be treated with PEG-IFN-α_{2a} if histologically-proven, moderate-to-severe necro-inflammatory activity or fibrosis are present. However, the chances of response in this form are lower.

The HBeAg seroconversion rate after one year of treatment for all NUCs is around 20%, increasing to up to 33% with PEG-IFN-α_{2a} [2]. In HBeAg-negative patients, the on-treatment virological response (suppression of HBV DNA) can be obtained in 60-90% at one year, irrespectively of the regimen. The ultimate goal of HBsAg loss can be achieved only in about 8% with PEG-IFN-α_{2a} and only in some very rare cases with NUCs. Lamivudine has the lowest barrier to viral resistance followed by telbivudine. Adefovir has an intermediate efficacy (barrier to resistance) and is

Table 4

Available drugs to treat CHB in Switzerland as of June 2009.

Active substance	Trade name	Registered indication in CH
Pegylated interferon-α_{2a}	Pegasys®	All stages of CHB
Lamivudine	Zeffix®	Treatment-naïve CHB
Telbivudine	Sebivo®	Treatment-naïve CHB
Entecavir	Baraclude®	Treatment-naïve CHB
Adefovir	Hepsera®	Only if treatment failure with NUC
Tenofovir	Viread®	HIV infection and/or HIV/HBV co-infection
Tenofovir+Emtricitabine	Truvada®	HIV infection and/or HIV/HBV co-infection

Table 5

Pre-treatment and on-treatment predictors.

	Pre-treatment predictors for HBe seroconversion	On-treatment predictors for treatment response
Pegylated interferon-α_{2a}	Low HBV viraemia (<10^7 IU/ml) High serum ALT (>3 times ULN) High activity score in histology HBV genotypes A and B may respond better than genotypes C and D	HBV DNA decrease to <20,000 IU/ml at 12 weeks Kinetics of serum HBsAg might be useful but is not sufficiently studied
NUCs	Low HBV viraemia (<10^7 IU/ml) High serum ALT (>3 times ULN) High activity score in histology	Undetectable HBV DNA

the most expensive drug. The most potent antivirals with the highest barrier for resistance mutations are tenofovir and entecavir: both may be the ideal candidates for first-line treatment of CHB and are also the treatment of choice whenever resistance occurs, in which case, however, the specific resistance profile of each drug should be taken into consideration for adjusting the regimen (table 6).

Finally, predictors of response to treatment should be taken into consideration when choosing a therapy for HBeAg-positive CHB (PEG-IFN-α_{2a} versus NUCs) (see table 5). The choice whether to treat with PEG-IFN-α_{2a} or NUCs is certainly not easy. PEG-IFN-α_{2a} should be considered as first-line treatment because of its higher chance of inducing HBeAg and even HBsAg seroconversion (table 8 compares pros and cons of PEG-IFN-α_{2a} versus NUCs).

Table 6

Viral mutations and cross-resistances to the different anti-viral agents (S: sensitive; I: intermediate; R: resistant). Adapted from [1].

HBV variant	Levels of susceptibility				
	LAM	LdT	ETV	ADV	TDF
Wild type	S	S	S	S	S
M204I	R	R	I/R	S	S
L180M + M204V	R	R	I	S	S
A181T/V	I	S	S	R	S
N236T	S	S	S	R	I
L180M + M204V/I ± I169T ± V173L ± M250V	R	R	R	S	S
L180M + M204V/I ± T184G ± S202I/G	R	R	R	S	S

Treatment failure

Three types of treatment failure can be identified: 1) primary non-responders (<1 $\log_{10}$ drop of HBV DNA at week 12 of therapy), 2) partial virological responders (with slow decline of viraemia towards still detectable levels) 3) virological breakthrough (initial response and reappearance of serum HBV viraemia while still on treatment).

In all patients with treatment failure the most important initial step is to check for treatment compliance, as this is the major reason for treatment failure. If compliance is certain and true resistance is suspected, genotypic resistance testing should be carried out and rescue therapy initiated with the most effective antiviral agent, in order to avoid the risk of selecting multiple drug-resistant viral strains. The rescue therapy may be a switch or add-on of a more potent NUC. Resistant viral strains can present with cross-resistance between drugs (table 6). As an example, the resistance pattern of lamivudine is similar to telbivudine, and therefore the chances of success when treating lamivudine resistance with telbivudine are low. In Switzerland, the licensed rescue drugs comprise adefovir and entecavir, however, based on the resistance profile of lamivudine and telbivudine, the most potent, ideal agent is tenofovir (table 6 and table 7).

Table 7

Treatment adjustment in case of resistance to antivirals.

If resistance to:	Treatment Adjustment:
Lamivudine (LAM)	Switch to Adefovir or Tenofovir
Adefovir (ADF)	If a N236T mutation is present add LAM or ETV or LdT or switch to Tenofovir combined with Emtricitabine (Truvada®); if a A181V/T mutation is present, add ETV or switch to Tenofovir
Telbivudine (LdT)	Add Tenofovir
Entecavir (ETV)	Add Tenofovir
Tenofovir (TDF)	Add LAM or ETV or Emtricitabine (Truvada®)

Treatment of special patients groups

Cirrhosis

Fibrosis (≥F2) or cirrhosis constitute a definite indication for treatment. Patients with compensated or decompensated cirrhosis must be treated with NUCs. Although PEG-IFN-α_{2a} can be used for the treatment of compensated cirrhosis, albeit with some caution, it is definitely contraindicated in cases of decompensated cirrhosis. In cirrhotics it is reasonable to use one of the most potent anti-

Table 8

Advantages and disadvantages of PEG-IFN-α_{2a} and NUCs for the treatment of chronic hepatitis B.

	Pegylated Interferon-α_{2a}	Nucleos(t)ide analogues
Tolerability	Side effects may be important and can lead to dose reduction or treatment discontinuation	Usually well tolerated and rare side effects
Treatment duration	48 weeks	Unlimited
HBeAg seroconversion	33%	20%
HBsAg seroconversion	Up to 8%	Very rare
Antiviral resistance	Absent	Significant with lamivudine; less important with adefovir or telbivudine; very rare with entecavir and so far not described for tenofovir
Use in cirrhosis	Limited use (only in compensated cirrhosis)	Ideal indication, because they can prevent decompensation

viral drugs (entecavir or tenofovir) to avoid hepatic decompensation due to hepatic flare when a resistant strain is selected. Patients need to be closely followed, because HBV DNA should be suppressed as early as possible and in a sustained manner.

Liver transplant patients

Patients with CHB and end-stage liver disease, for whom an indication to liver transplant has been established, should be treated with NUCs, regardless of ALT and HBV DNA levels. It is of enormous importance that patients do not present an active HBV infection at the moment of transplantation because the risk of re-infection of the grafted liver is high. Ideally, serum HBV DNA must be undetectable at transplantation. After transplantation, long-term combination treatment with NUCs and anti-HBs immunoglobulins (HBIG) reduces the risk of HBV re-infection of the graft virtually to nil. Because of the high costs of HBIG, there is a trend today to withdraw them at one point post-LT and treat either with a potent antiviral alone or a NUCs combination therapy. However, after discontinuation of HBIG, i.e. in cases with NUCs prophylaxis alone, the re-infection rate at 4 years is 9% [10], which is fairly high compared to 0% that could be reached with the combined therapy.

Health care workers

EASL guidelines suggest that healthcare workers, especially those involved in invasive procedures, should be treated with a potent NUC, if HBV viraemia ≥2000 IU/ml. Undetectable HBV DNA is a requirement to minimise the risk of HBV transmission to patients.

Acute hepatitis B

In immunocompetent individuals, acute HBV infection recovers spontaneously with HBsAg seroconversion in more than 95% of cases. Treatment with antivirals is not indicated.

Coinfection with hepatitis delta virus (HDV)

Interferon is the only efficient drug for replicative HDV infection and sometimes therapies longer than one year are necessary. HDV clearance and even HBsAg seroconversion can be obtained with PEG-IFN-α_{2a}.

Coinfection with hepatitis C virus (HCV)

In HCV/HBV co-infected patients, usually one virus dominates over the other, often with predominance of HCV. If HCV is viraemic, treatment with PEG-IFN-α_{2a} and ribavirin should be given. If HCV is cleared (sustained virological response), HBV can reactivate and thus needs to be closely monitored and eventually treated with NUCs.

Coinfection with HIV

HIV-HBV coinfected patients are at higher risk for cirrhosis and HCC than HBV mono-infected patients. The indications of therapy are the same as in HBV mono-infected patients. If a highly active retroviral therapy or an anti-HBV therapy is necessary, treatment should always target both viruses to avoid the development of viral resistance, as some NUCs (lamivudine, entecavir, tenofovir, emtricitabine) act on both viruses to different degrees [11, 12]. If, however, there is need to treat HBV without interacting with HIV, adefovir and telbivudine are agents without activity on HIV replication and are the treatment of choice.

Children

The majority of children presents with CHB in an immune tolerant phase and should not be treated. Only conventional interferon-α, lamivudine and adefovir have been evaluated for safety and efficacy, which are comparable to adults.

Pregnancy

Telbivudine and tenofovir are characterised by the FDA as category B drugs, whereas lamivudine, adefovir and entecavir are listed as category C. Antiviral treatment is to be avoided until the third trimester of pregnancy. Studies show that in patients with high viraemia lamivudine reduces the risk of intra-uterine and perinatal transmission of HBV if given in addition to passive and active vaccination by HBIG and HBV vaccination [13].

Immunosuppressed patients

Patients undergoing immunosuppressive treatment or chemotherapy, even for short-term courses, should be screened for HBsAg, anti-HBc, and anti-HBs (and HBV DNA if HBsAg is already positive) because of the high risk of viral reactiva-

tion with hepatic flares [14]. In HBV naïve patients (all serum markers negative), vaccination should be given prior to immunosuppressive treatment. HBsAg-positive patients (inactive carriers) should be tested for HBV DNA levels and treated with lamivudine, probably the best candidate because due to its low price and negligible side effects. This pre-emptive therapy should be maintained for up to 12 months after cessation of immune suppression or chemotherapy. Anti-HBc positive carriers (HBsAg negative ± anti-HBs, past infection) should only be closely followed without pre-emptive anti-HBV treatment. HBV viraemia and ALT levels should be tested bimonthly and in case of HBV DNA reactivation (even without ALT elevation) a potent NUC should be urgently added to avoid hepatic flares.

Patients with chronic renal failure

Patients with chronic renal failure and undergoing dialysis can be treated with NUC but dosage needs to be adapted to renal function. Consistent data are available for lamivudine and may be the safest choice in patients with impaired renal function. Adefovir and tenofovir should be used with caution due to possible effects on renal function. For kidney transplant recipients the best drugs may be lamivudine or entecavir.

In conclusion, HBV is a dynamic infection with different phases, which determine the different attitude towards antiviral therapy. HBV viraemia, ALT levels and liver histology are crucial parameters for treatment indication. However, due to the increasing availability of antivirals and concomitant growing emergence of drug resistance strains the management of CHB has become complex. The most potent antiviral drugs are the best choice to start therapy but, due to registration issues, in Switzerland only few drugs for first-line treatment are available. Therefore, even if the new EASL guidelines help to facilitate the management of CHB, it may be idealistic to believe that a "one-size-fits-all algorithm" could exist. The situation may change in the future, of course, depending on the evolution of the Swiss official recommendations.

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