Treatment for hepatitis B virus (HBV) and hepatitis C virus (HCV) infection - Danish national guidelines 2011

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SUMMARY

The Danish Society of Infectious Diseases and Danish Society of Gastroenterology and Hepatology set up a committee in 2007 to produce national guidelines for treatment of viral hepatitis B and C. The 2011 version of the guidelines have been endorsed by the scientific societies and are presented below. Annual updates will be available at the websites of the societies. As this present English version has been written six months after the Danish 2011 version, it contains minor changes that will be integrated in the Danish 2012 version, available at the end this year.

Epidemiology: Viral hepatitis is not common in Denmark. The prevalence has not been determined by national surveys, but it is estimated that 10-15,000 patients are chronically infected with hepatitis B and 15-20,000 with chronic hepatitis C. The majority of patients with HBV infection in Denmark are emigrants from high endemic countries, probably infected at birth or early childhood in their country of origin, while the majority of patients with HCV infection have been infected by drug use. For both groups it is estimated that only half of the patients have been diagnosed, of whom only 20% attends specialized care for their chronic viral hepatitis.

Clinical Care: According to the Danish National Board of Health, patients with chronic viral hepatitis should be followed with regular intervals, at clinics specialized in either infectious diseases or gastroenterology/hepatology. The primary aim is to identify patients with significant liver disease to initiate treatment in order to prevent development of cirrhosis and death. This is primarily done by liver biopsy, but screening for fibrosis with non-invasive methods such as elastography may be sufficient in some patients. Patients with established cirrhosis should enter screening programs for complications such as esophageal varices and hepatocellular carcinoma.

The main treatment indications for hepatitis B are presence of fibrosis stage F2 and/or activity grade A2 according to the Metavir classification together with either HBV-DNA >2,000 IU/mL and/or Alanine Amino Transferase (ALT) > 50 IU/L for males and >35IU/L for females. In HBeAg positive patients with genotype A or B, low viral load, high ALT and no cirrhosis, treatment for 48 weeks of pegylated interferon-alpha-2a is suggested. For all other groups of HBV patients, treatment with a nucleos(t)ide analog (entecavir or tenofovir) is recommended.

The main treatment indication for chronic hepatitis C is the presence of fibrosis stage F2, regardless of ALT level. For genotypes 2 and 3 fibrosis evaluation by liver biopsy is not mandatory. Treatment is genotype dependent: For genotype 1 infection a combination of pegylated interferon, weight based ribavirin and a protease inhibitor (telaprevir or boceprevir) is recommended. Pegylated interferon alfa-2a and pegylated interferon alfa-2b are considered equally effective. Response guided therapy is suggested in patients without cirrhosis. Patients, who after a lead-in period of 4 weeks with pegylated interferon and ribavirin, become HCV-RNA negative, may be treated without the addition of a protease inhibitor. Patients with genotypes 2 and 3 should be treated with pegylated interferon and 800 mg ribavirin for 24 weeks. Shorter treatment duration is not recommended, but 48 weeks may be used in patients with cirrhosis. Patients, negative for HCV-RNA 24 weeks after end of treatment, are considered cured for hepatitis C and need no further follow-up except patients with cirrhosis who should continue surveillance for complications.

The diagnostic and therapeutic options for chronic viral hepatitis are rapidly developing and it is likely that the above recommendations change significantly in the near future with the prospect of cure for the vast majority of patients with hepatitis C and full control of the disease for patients with hepatitis B.

HEPATITIS B GUIDELINE

1. Epidemiology

The prevalence of hepatitis B in Denmark is unknown but presumed to be low. A study of the general population has never been performed and reporting of chronic hepatitis B has only been mandatory since year 2000. In Sweden, where HBV has been reported to the national health authorities since 1980, up

till 2007 30,000 cases with chronic hepatitis B have been identified [1]. This corresponds to 17,500 patients in Denmark. Among 140,000 pregnant women in Denmark 0.26% were positive for HBsAg during systematic screening 2005-2007 [2]. This corresponds to 13,500 persons in the general population. A conservative estimate is that 10-15,000 persons in Denmark have chronic hepatitis B, half of whom have not been diagnosed. The majority of HBV patients are not of Danish decent. Of the patients, half comes from the Mediterranean area and the Middle East, especially Turkey, while 1/3 comes from the Far East, predominantly Vietnam, Thailand and China [3]. These patients were presumably infected at birth or in early childhood. Among native Danes the most common route of transmission is by sexual exposure. Groups with increased prevalence are listed below.

2. Screening for Hepatitis B Virus

Groups listed below, are recommended to be tested for hepatitis B virus

- Immigrants from high endemic areas
- Men who have sex with men
- Drug users
- Sexual partners to persons with hepatitis B
- Household members to patients with chronic hepatitis B
- Persons with Down's syndrome, including those living outside institutions
- All persons living in institutions or homes for disabled persons together with chronic hepatitis B patients
- Patients undergoing renal dialysis
- Patients with hemophilia treated with clotting factor concentrates prior to implementation of heat inactivation (1984)
- Patients prior to treatment with an immunosuppressive agent (e.g. monoclonal antibodies, TNF-alpha- and interleukin-1 inhibition)
- Patients prior to treatment with chemotherapy
- Patients with elevated ALT (male >50IU/L, female >35IU/L)
- Patients infected with HCV
- Patients infected with HIV
- Patients with cirrhosis of the liver

3. Normal range of ALT with chronic viral hepatitis

In Scandinavia, the upper limit of normal (ULN) for ALT has recently been increased to 70 IU/L for males and 50 IU/L for females. This is not recommended in patients with liver disease. Large studies have shown that healthy persons and patients cured for viral hepatitis have an ULN of 30 IU/L for males and 19 IU/L for females [4, 5]. As most treatment studies have been based on a ULN for ALT of 50 IU/L for males and 35 IU/L for females, these limits have been used in our guidelines as well.

4. Natural history of Hepatitis B Virus infection

Chronic hepatitis B can be divided in the following phases [6, 7]:
Immune tolerant phase. Patients in this phase are HBeAg positive, have high serum HBV-DNA (≥ 10^8 IU/mL), normal or slightly elevated ALT (<50IU/L for males, <35 IU/L for females). Liver histology is with no or minimal activity (inflammation) and little or no fibrosis. The typical patient in this phase is a child infected at birth or early in life.
Immune active phase. Patients in this phase are HBeAg positive, HBV-DNA is lower (10^6-10^7IU/mL) and ALT is elevated or fluctuating. Liver histology is characterized by moderate to severe activity and fibrosis. This phase can persist from weeks to years. Typically, children in the immune tolerant phase may progress to the immune active phase as they become adults and patients infected in adult life may present directly in the immune active phase.
Latent phase (inactive carrier phase). Patients in this phase have seroconverted from HBeAg to anti-HBe, HBV-DNA is low (≤10^3 IU/mL) or undetectable, and ALT is normal. Liver histology shows minimal activity but fibrosis may vary from minimal to cirrhosis. Most patients in this phase are stable and have a good prognosis. Seroconversion from HBsAg to anti-HBs occurs in 0.5-3% per year in this group.
Reactivation phase (HBeAg negative chronic active hepatitis B). Patients in this phase have periodically or continuously active infection with elevated ALT, HBV-DNA ≥ 10^4 IU/mL, and may revert from an anti-HBe to HBeAg positive state. Liver histology shows active inflammation and fibrosis may progress to cirrhosis with a risk of decompensated liver disease and hepatocellular carcinoma (HCC). In order to distinguish between the latent and reactivation phase careful monitoring of the patients is required: ALT and HBV-DNA should be monitored every 3 months the first year and every 3-12 months hereafter depending of the activity of the disease.
Resolution. Patients in this phase have cleared the infection and are HBsAg and HBV-DNA negative with a normal ALT. If severe liver fibrosis/cirrhosis has developed during active infection, this may persist after cure. HBV-DNA may still be found in the liver as covalently closed circular DNA (cccDNA) and in case of severe immuno-suppression hepatitis B infection may become reactivated.
Occult hepatitis B. This is defined as patients HBsAg negative and HBV-DNA positive in serum. The clinical significance of this entity is uncertain but it has been associated with transfusion transmitted hepatitis B and cryptogenic cirrhosis [8].

5. Clinical care for patients with acute hepatitis B

The diagnosis is usually based on the clinical history, markedly elevated ALT and presence of HBsAg in serum. Supplementary test for anti-HBc IgM may be necessary in a few cases where acute hepatitis B is suspected and HBsAg is negative: these patients are in the "window phase" where HBsAg has become negative and anti-HBs not yet positive.

There are <30 reported cases of acute hepatitis B per year in Denmark and the mortality is <1%. Patients are monitored by their clinical appearance and INR/protrombin time; a liver biopsy is not indicated. If INR is above 1.7 the patient should be admitted to a ward specialized in viral hepatitis. Treatment is symptomatic but in case of incipient fulminant hepatitis (INR >2.5 or development of hepatic encephalopathy) the patient should be transferred to a liver transplant unit.

6. Clinical care for patients with chronic hepatitis B

All patients positive of HBsAg or HBV-DNA should be evaluated at a department specialized in viral hepatitis. At the first contact mode and time of transmission, drug and alcohol abuse, co-morbidity and social resources should be recorded.

Liver function is assessed by clinical examination together with the following laboratory analysis: ALT (and possibly AST), bilirubin, alkaline phosphatase, prothrombine time/INR, albumen and alpha-fetoprotein (AFP). Hematology should be evaluated by hemoglobin, platelets and leucocytes.

Testing for HBV-DNA is important for the diagnosis, indication for treatment, and the subsequent monitoring of the patient. This

should be done by a quantitative real-time PCR and the result expressed in IU/mL according to the WHO standard. The same analysis should be used for treatment monitoring in each patient.

Patients should be screened for HCV, HIV, HDV and previous HAV, as well as other significant liver diseases: alcoholic, autoimmune and metabolic. This includes measuring the levels of IgA, IgG, IgM, and testing for ANA, AMA, SMA and ferritin.

Liver biopsy is recommended for all patients with ALT >ULN (50 IU/L for males, 35 IU/L for females) and/or serum HBV-DNA >2,000 IU/mL in order to determine if the patients fulfill treatment indications. Liver biopsy is not indicated if clinical cirrhosis is present or if treatment will be initiated regardless of liver histology. Non-invasive test for fibrosis may in some cases replace liver biopsy.

Patients with a familial history of HCC, patients of African descent above 20-25 years of age and patients of Asian descent above 40-50 years of age have increased risk of HCC even without presence of cirrhosis [9]. For these groups screening for HCC with alpha-fetoprotein and ultrasonography of the liver as specified for patients with cirrhosis is recommended.

7. Clinical care for patients with Hepatitis B and cirrhosis

All hepatitis B patients with cirrhosis should be treated for hepatitis B (see below) [7, 9,10]. In addition to the clinical care offered to all HBV patients with blood tests for ALT, bilirubin, alkaline phosphatase, INR, albumen, hemoglobin, platelets and leucocytes (see above) cirrhotic patients should be screened for HCC with AFP every 6 month and ultrasonography of the liver every year. Screening for esophageal varices should be performed every second year.

Patients with decompensated cirrhosis should be evaluated for liver transplantation by a gastroenterologist/hepatologist.

8. Treatment for Hepatitis B

Evaluation, control, and especially treatment of patients for hepatitis B requires expertise and should take place at departments specialized in viral hepatitis.

The aim of treatment is to prevent development of cirrhosis, decompensated liver disease and HCC. This can to some extend be achieved by reducing serum HBV-DNA to <10-20 IU/mL, which leads to reduction in histological activity in the liver and normalization of ALT. However, total eradication of HBV has not yet been possible due to persistence of cccDNA in the liver.

Treatment indication

Treatment indication is identical for HBeAg positive and anti-HBe positive disease, and based on a combination of serum HBV-DNA level, ALT elevation, and liver histology:

Treatment should be considered if

- A liver biopsy shows activity ≥ A2 and/or fibrosis ≥ F2 according to the Danish modification of the METAVIR score [11];
- And either HBV-DNA >2000 IU/L or ALT >ULN.

Treatment should also be considered

- In all patients with cirrhosis, regardless of HBV-DNA level
- In patients with a family history of HCC
- In pregnant women with HBV-DNA ≥10^6IU/mL

Aims of treatment

- Undetectable HBV-DNA (<10-20 IU/mL)
- HBeAg seroconversion to anti-HBe
- ALT <ULN
- Normalization of liver histology
- HBsAg seroconversion to anti-HBs

Predictors of response

Baseline predictors for HBeAg seroconversion are

- HBV-DNA <10^7IU/mL
- ALT ≥ 3 x ULN
- Liver histology with activity ≥A2

Treatment strategy

Treatment can be of finite duration or continuous. Only with interferon the duration can be determined at treatment start (48 weeks). HBV genotype A and B are more sensitive to interferon than genotype C and D, whereas there is no difference in response to nucleoside treatment between genotypes. Treatment with nucleoside analogs for HBeAg positive disease may be terminated 48 weeks after seroconversion to anti-HBe, but this cannot be predicted at treatment initiation. Patients with cirrhosis and patients anti-HBe positive at treatment initiation, who start treatment with nucleoside analogs, are expected to receive lifelong treatment, unless HBsAg seroconversion is achieved.

Laboratory tests during treatment

Patients treated with interferon should be monitored with: hematology, renal function, ALT, bilirubin, alkaline phosphatase, INR, albumen, TSH and HBV-DNA. Hematology, liver tests and renal function should be monitored after 1, 2, 4 weeks and every 4 weeks hereafter until end of treatment. TSH and HBV-DNA should be measured every 3 months during treatment.

Patients treated with nucleoside analogs should be monitored with hematology, renal function, phospate, ALT, bilirubin, alkaline phosphatase, INR, albumen and HBV-DNA 4 weeks after treatment initiation and every 3 months hereafter during treatment.

Treatment failure

If treatment failure is observed, patient compliance must be evaluated. Among compliant patients receiving nucleoside/nucleotide analogues failure can be divided into three classes [6]:

1. Primary non-response: HBV-DNA unchanged (decreased < 1 log) after 12 weeks of treatment. In this case treatment should be changed or supplemented with a more potent drug.
2. Partial virological response: HBV-DNA declined but still detectable after 24 weeks of treatment. In this case treatment should also be changed or supplemented with a more potent drug. Patients who experience a substantial drop in HBV DNA while treated with entecavir or tenofovir may continue this treatment for 48 weeks before a change is considered.
3. Virological breakthrough: An increase in HBV-DNA >1 log from nadir after initial treatment response. By frequent monitoring of HBV DNA development of resistance can be identified before biochemical breakthrough is detected as a continuous rise in ALT during treatment.
   By genotypic resistance a mutation, that has been associated with decreased drug sensitivity, is detected by sequencing the polymerase gene. By phenotypic resistance decreased sensitivity to the drug is demonstrated by in vitro test of HBV from a patient sample.
   By virological breakthrough adding on a new drug without cross resistance is the only effective strategy. To avoid fur-

ther development of resistance it is important to modify treatment as soon as resistance has been detected.

Selection of therapeutic regime

Interferon	
Pegylated interferon-alpha2a	180 µg/week for 48 weeks
Nucleos(t)ide analogs	
Entecavir	0.5-1 mg qd
Tenofovir	245 mg qd
Adefovir	10 mg qd
Lamivudin	100 mg qd
Telbivudin	600 mg qd

Pegylated interferon-alpha2a has the advantage of finite treatment duration. Development of resistance has not been observed. HBeAg seroconversion is seen in up to 30% of treated patients and is stable after treatment cessation [7]. Interferon should not be used for patients with cirrhosis. As mentioned above, genotypes A and B respond better to treatment with interferon than genotypes C and D. However, drug selection should not be solely based on HBV genotype.

Entecavir is a very potent drug with few side effects and very limited development of resistance in naïve patients [12, 13]. Most patients will become HBV-DNA undetectable (<10-20 IU/mL) during treatment. Patients with prior resistance to lamivudine must be treated with 1 mg qd, however patients still face a relatively high risk of development of resistance. Therefore, entecavir is not the drug of choice for patients with lamivudine resistance.

Tenofovir is related to adefovir, but, due to less nephrotoxicity, tenofovir may be given at a higher dose. It has a high potency (comparable to entecavir) and most patients will become undetectable for HBV-DNA (<10-20 IU/mL) during treatment [14]. Resistance development is very low and HBV strains resistant to lamivudine are susceptible to tenofovir [15]. Therefore, tenofovir is the drug of choice for patients with lamivudine restistance. Side effects are few, but renal function and serum phosphate should be monitored during treatment.

Adefovir treatment should not be initiated *de novo*. The drug has been used for a decade, but due to nephrotoxicity the dose has been low, leading to lack of response and development of resistance. Partial response has been observed in >30% of treated patients [16]. The drug has few side effects, but renal function should be monitored carefully.

Lamivudine has been the most frequently used drug for hepatitis B, but it is no longer recommended as the drug of first choice [17]. Up to 70% will become HBV-DNA undetectable (<10-20 IU/mL) during treatment, but with prolonged treatment the majority of patients will develop resistance [18, 19]. By short term prophylactic treatment (e.g., during immunosuppressive treatment), as well as in combination with other drugs, lamivudine may still be indicated. The drug has very few side effects.

Telbivudine has not been used in Denmark. It is more potent than lamivudine and adefovir, but due to significant resistance problems and cross-resistance with lamivudine the drug will have a limited role in treatment [20, 21].

9. Treatment conclusions

HBeAg positive patients without cirrhosis
Treatment with entecavir 0.5mg qd or tenofovir 245mg qd for at least one year or until 6-12 month after HBeAg seroconversion is recommended. Alternatively, pegylated interferon-alpha2a 180 µg/week for 48 weeks may be used, if the patient has genotype A or B and ALT >2 x ULN.

HBeAg negative patients without cirrhosis
Tenofovir 245 mg qd or entecavir 0.5mg qd. There are no data to suggest duration of treatment and this should not be discontinued unless seroconversion from HBsAg to anti-HBs is observed in which case treatment can be stopped 6 months after seroconversion.
Pegylated interferon-alpha2a 180 µg/week for 48 weeks may be used prior to nucleoside treatment especially if the patient has genotype A or B.

Chronic hepatitis B patients with cirrhosis
All patients with cirrhosis and positive HBV-DNA should be treated, regardless of HBV-DNA and ALT levels. The drugs of choice are entecavir 0.5mg qd or tenofovir 245mg qd. In case of previous treatment with lamivudine, tenofovir should be used. Treatment should not be stopped unless seroconversion from HBsAg to anti-HBs is observed. In these cases treatment can be stopped 6 months after seroconversion.

10. Treatment of special populations

Patients co-infected with HCV

The dominant virus should be treated according to its treatment indications. The dominant virus is identified by comparing HBV-DNA and HCV-RNA levels and in most cases HCV will be the dominant virus. Treatment results for hepatitis C in patients co-infected with HBV are comparable to results for HCV mono-infected patients [22, 23]. After treatment for HCV, flair in hepatitis B may be seen, and this should be monitored closely and possibly treated with nucleoside(t)e analogs according to guidelines for HBV mono-infection. However HBV seroconversion may also be seen after treatment for HCV or the patient may remain in the inactive carrier state.

Patients co-infected with HDV

Co-infection with HDV is diagnosed by presence of HDV-RNA. Only interferon treatment is effective against HDV and treatment should be monitored as in HBV mono-infected patients except that the patient should also be tested for HDV RNA. Treatment prolongation beyond one year may be indicated and HDV-RNA will often become undetectable (<100 IU/mL) during treatment [24]. Nucleoside analogs used for hepatitis B do not affect HDV replication [25].

Patients co-infected with HIV

HBV patients co-infected with HIV have an increased risk of developing cirrhosis [26]. The indication for HBV treatment is the same as for HBV mono-infected patients [27]. Patients should start treatment for HBV and HIV simultaneously at the same time. A combination of tenofovir/emtricitabin (Truvada) together with a third drug for HIV is recommended [28, 29]. Entecavir has activity against both HBV and HIV and is therefore contraindicated as mono-therapy due to the risk of drug resistance [30].

Treatment of pregnant women and pregnancy during treatment

Some studies indicate that vertical transmission of HBV is increased if the pregnant woman has a high level of HBV-DNA (>10^6IU/mL) despite hepatitis B vaccination of the newborn [31,

32]. If the woman is not already on treatment for HBV this should be considered with start at the beginning of the third trimester and continued until 12 weeks after delivery, in order to decrease the risk of flair after end of treatment.

There is amble experience with treating HIV infected pregnant women with lamivudine and tenofovir and it is recommended that tenofovir is used as drug of choice in pregnant women. The FDA lists tenofovir as category B drug; it has the highest potency and a low risk of resistance.

The FDA lists lamivudine, adefovir and entecavir as category C drugs.

Prophylactic treatment prior to immunesuppression

- Patients, planned to undergo immunosuppressive therapy, should be screened for ongoing or prior hepatitis B infection with HBsAg, anti-HBc and anti-HBs. Patients not previously immunized should be vaccinated.
- HBsAg positive patients should start treatment for hepatitis B prior to immune suppression therapy.
- Patients who are anti-HBc positive, but negative for HBsAg and anti-HBs ("core only") should be monitored by frequent HBV-DNA measurement (initially every month). Patients who become HBV-DNA positive should initiate HBV treatment.
- Patients who are anti-HBc and anti-HBs positive may be followed by loss of anti- HBs/appearance of HBsAg.

There is a considerable experience using Lamivudine as prophylactic treatment, but due to the risk of resistance entecavir or tenofovir is recommended if treatment for more than 6 months is planned or HBV-DNA levels are high [33].

11. Treatment of drug-resistant hepatitis B

- Lamivudine or telbivudine resistance: Add tenofovir
- Adefovir resistance: change to tenofovir plus lamivudine
- Entecavir resistance: change to tenofovir
- Resistance to several nucleoside analogs: A combination of entecavir and tenofovir may be tried. However, there is no published evidence for this combination and the long-term effects are unknown.

HEPATITIS C GUIDELINE

1. Epidemiology

The prevalence of hepatitis C in Denmark is unknown but presumably low. In Norway, Sweden, and Germany the prevalence of hepatitis C has been found to be 0.5% in the adult population with maximum at age 40-50 [34-37]. Applying these figures to the Danish population corresponds to 21,000 persons infected. Accordingly, the current estimate is that Denmark has a population of 15-20,000 with chronic hepatitis C, half of whom have been diagnosed, and out of these 20% attend specialized clinical care.

Hepatitis C is almost exclusively transmitted by exposure to HCV infected blood, and the vast majority of Danish patients with hepatitis C have been infected by injection drug use (IDU). Among IDUs the prevalence exposure is 70% (anti-HCV positive) and 50% have chronic hepatitis C (HCV-RNA positive). Apart from IDUs, patients with hemophilia, patients undergoing renal dialysis, multi-transfused, and patients originating from highly endemic areas have an increased prevalence of hepatitis C.

2. Screening for hepatitis C

Groups, listed below, are recommended to be tested for hepatitis C virus

- Current and former drug users
- Patients who received blood products or organ transplants prior to the introduction of anti-HCV screening (1991)
- Patients undergoing renal dialysis
- Children born of hepatitis C infected mothers
- Health-care workers exposed to needle stick injuries
- Patients with persistently elevated ALT (>50 IU/L for males and >35 IU/L for females)
- Patients infected with HBV
- Patients infected with HIV
- Patients with cirrhosis of the liver

For patients undergoing hemodialysis, and patients infected with HIV, the anti-HCV test may be negative despite chronic infection. Thus, such patients with elevated ALT should be tested for HCV-RNA despite negative HCV serology.

Persons, who live in a monogamous sexual relation with a HCV infected partner, according to most studies have a very low risk of hepatitis C infection [38]. However, persons with multiple sexual partners have an increased risk and should be offered testing for hepatitis C.

Screening for hepatitis C should be done with anti-HCV by ELISA technique, and positive samples should be tested by PCR for HCV-RNA. Persons who are positive for anti-HCV but negative for HCV-RNA should be retested by PCR after 3-6 months.

3. Natural history of hepatitis C Virus infection

The risk of infection is related to the route of transmission, and transfusion with blood from a hepatitis C infected donor causes the highest risk - probably reflecting the size of the inoculum. The average risk of chronic infection after transmission is 50-80% [39]. Risk of transmission and the natural history of the infection have been difficult to establish as the acute infection is subclinical or with few symptoms in 80% of the cases [40]. Therefore, the following numbers are uncertain estimates.

Chronic hepatitis C is usually associated with few or no symptoms, but may lead to cirrhosis of the liver. Young age at transmission and female gender are associated with slow development of fibrosis, but alcohol consumption above 50g/day (and in some studies lower quantities), co-infection with HIV, immune suppression and other concomitant liver disease increases the speed of fibrosis development [41-43]. The development of fibrosis may not be linear, as some studies have reported an exponential increase with age [44].

The reported risk of cirrhosis spans from 4-20% in 20 years of follow up [40, 45, 46].Once cirrhosis has developed a strong increase in morbidity and mortality has been observed [47, 48]. The 5-year risk of hepatocellular carcinoma (HCC) is 7% and the risk of decompensated liver disease (portal hypertension with ascites, esophageal varices, and hepatic encephalopathy) is 18%. When a patient progresses to decompensation the 5-year survival decreases to 50% [47, 49].

4. Clinical Care for patients with acute hepatitis C

Infection with HCV becomes chronic in 2/3 of cases [50]. The acute infection is seldom symptomatic and therefore only rarely diagnosed. Symptomatic infection results in cure more often than subclinical infection. Several case series of treatment in the acute phase with non-pegylated interferon have been published;

however, randomized studies are not available. Results from these case series demonstrate effect of treatment in the acute phase, and after a major German study [51] it is recommended to observe the patient for three months and to proceed to treatment if HCV RNA is still positive at this point in time. Pegylated interferon is recommended although this has not been evaluated by any study. There are no randomized trials to guide duration of therapy, the largest study used 6 months and this is recommended. It is unknown whether addition of ribavirin will improve the response in this situation.

5. Clinical Care for patients with chronic hepatitis C

At the first contact mode and time of transmission, drug and alcohol abuse, co-morbidity, and social resources should be recorded.

Liver function is assessed by clinical examination, and the following laboratory analysis: ALT (and possibly AST), bilirubin, alkaline phosphatase, prothrombin time/INR, albumen, and alpha-fetoprotein (AFP). Hematology should be evaluated by hemoglobin, platelets and leucocytes including differential count.

The ALT upper limit of normal for patients with hepatitis C is the same as for patients with hepatitis B: 50IU/L for males and 35 IU/L for females.

Unless test results are already available a quantitative HCV-RNA and HCV genotype should be performed at the first clinical visit to be used as part of later treatment evaluation. HCV-RNA should be tested by a quantitative real-time PCR and the result expressed in IU/mL according to the WHO standard. The same analysis should be used for treatment monitoring in each patient.

Patients should be screened for HBV, HIV and previous HAV infection, as well as for other significant liver diseases: alcoholic, autoimmune and metabolic. This includes test for IgA, IgG, IgM, ANA, AMA, SMA and ferritin.

After initial clinical examination and testing evaluation of liver fibrosis/cirrhosis is usually performed. This can be done by liver biopsy unless clinical cirrhosis is present or if treatment will be initiated regardless of liver histology. Non-invasive tests for fibrosis are in development and may replace liver biopsy in some cases. The non-invasive tests perform better predicting cirrhosis (F4) than significant fibrosis (F2-F3)

If elastography (Fibroscan) is used for detection of fibrosis, an ULN of 7.0 kPa is suggested. By abnormal values the scan should be repeated after 1-3 months (preferably in the fasting state). A reproducible measurement between 7 and 17 kPa must be further evaluated, usually by liver biopsy. When other causes of increased stiffness have been eliminated (liver inflammation, congestive heart disease etc.) patients with values ≥ 17 kPa are highly likely to have cirrhosis [52]. These patients should be cared for, and treated, as cirrhotics and liver biopsy will often not be necessary.

Patients, for whom treatment is not indicated, should have their liver tests and hematology performed at intervals of 6-12 months. Some patients may require evaluation with shorter time-intervals. Until now, progression of fibrosis has required a new liver biopsy with 3-5 years interval, but this will probably be evaluated by non-invasive methods in the future.

6. Clinical care for patients with hepatitis C and cirrhosis

In addition to clinical care offered to all HCV patients with blood tests for ALT, bilirubine, alkaline phosphatase, INR, albumen, hemoglobin, platelets and leucocytes (see above), cirrhotic patients should be screened for HCC with AFP every 6 months and ultrasonography of the liver every year. Screening for esophageal varices should be performed every second year.

Patients with decompensated cirrhosis should be evaluated for liver transplantation by a gastroenterologist/hepatologist.

7. Treatment for hepatitis C

The purpose of treatment for hepatitis C is to prevent cirrhosis and HCC by eliminating the causal virus. A successful treatment is defined as persistent loss of HCV-RNA (sustained virological response - SVR). Patients who have undetectable virus in plasma 6 months after end of treatment are considered cured for hepatitis C.

The treatment has gradually improved over the last 15 years, first by addition of ribavirin and later by fusion of polyethylene glycol (PEG) to interferon-alpha-2a and interferon-alpha-2b. Peg-interferon-alpha-2a is used in a fixed dose of 180µg/week and Peg-interferon-alpha-2b is used weight-based at a dose of 1.5µg/kg/week.

In autumn 2011 the first direct acting antivirals (DAAs) for hepatitis C treatment were introduced. The NS3protease-inhibitors telaprevir (Incivo®) and boceprevir (Victrelis®) have been marketed in Denmark for treatment of hepatitis C genotype 1 infection. Additional DAAs have entered phase 3 trials and are expected to become available within the coming years.

Baseline factors associated with SVR are genotype 2 and 3 (compared to 1 and 4), IL28B genotype CC, low HCV-RNA level, female gender, low fibrosis score, and young age.

Indication for treatment

Treatment should be considered if a patient fulfills the following two criteria

- Positive HCV-RNA
- Liver biopsy or Fibroscan compatible with moderate to severe fibrosis

Treatment may be indicated with less advanced stages of fibrosis if the infection is a considerable burden to the patient or in the presence of co-morbidity which may be influenced by the treatment of hepatitis C.

For patients with genotype 1 and 4 the decision to treat has been based on the degree of fibrosis due to the lower treatment response (50% SVR), longer treatment duration (48 weeks), and significant side effects associated with pegylated interferon and ribavirin. With the new DAAs the SVR rate for genotype 1 patients has increased to 70-80%, which should be considered in the treatment decision.

For patients with genotype 2 and 3 liver biopsy may be omitted at the discretion of the treating physician, due to the high SVR rate (70-80%) and shorter duration of treatment (24 weeks). However, it should be acknowledged that an accurate staging of fibrosis has implications for the long-time follow-up: presence of cirrhosis means that the patient must enter a surveillance program for complications (even after the virus has been successfully eradicated).

Contraindications for treatment

Absolute contraindications are: Severe uncontrolled psychiatric disease, decompensated cirrhosis, advanced cardiac or pulmonary disease, autoimmune liver disease, insufficiently controlled epilepsy, untreated severe anemia and poorly controlled diabetes.

Ribavirin is teratogenic in animal experiments. Pregnancy, or insufficient use of contraceptives, is a contraindication to treatment. Contraception must be used until 4 months after treatment for women and 7 months for men.

Ribavirin is contraindicated in patients with renal insufficiency (creatinine clearance <50mL/min). However treatment with low dose ribavirin and frequent monitoring of hemoglobin and plasma-ribavirin concentration may be considered in some cases.

Precautions must be taken when treating cirrhotic patients with prior decompensation, by neutrophils $<0.75x10^9$/L or platelets $<50\ x10^9$/L and when treating patients with dysregulated diabetes.

Patients with alcohol overconsumption and/or ongoing drug abuse will often have considerable problems with compliance. Alcohol may decrease the chances of SVR and injecting drug users have a risk of repeated infection. Therefore, it is recommended that the problems of abuse should be managed first, and that treatment for hepatitis C is postponed until the patient has stabilized. Treatment with methadone, buprenorfin or disulfiram is not a contraindication for treatment.

Treatment-naïve patients

Patients with genotype 1:

- Standard of care is currently pegylated interferon-alpha and ribavirin combined with a DAA drug, as addition of a DAA increases the likelihood of SVR from 45 -70%, as well as allowing a shorter treatment duration for a significant proportion of patients [53-56].
- Treatment may be started with a "lead-in" phase of 4 weeks with pegylated interferon-alpha and ribavirin prior to the addition of boceprevir or telaprevir as this will identify a group of patients with a rapid virological response (RVR), i. e. patients negative for HCV-RNA after 4 weeks of "lead-in" treatment, who may not need the addition of DAAs to obtain SVR.
- This response is primarily seen in patients with favorable baseline predictors for SVR (younger age, low HCV-RNA, IL28B CC genotype and no cirrhosis) who can be treated for 24 weeks with a high chance of SVR.
- Pegylated interferon-alpha is administered as weekly injections of either pegylated interferon-alpha2a at a fixed dose of 180 µg/week or pegylated interferon-alpha2b at a weight-based dose of 1.5 µg/kg/week.
- Ribavirin is administered as oral tablets b.i.d. (weight based 15mg/kg/day, minimum 1000mg/day maximum 1400mg/day, rounded up to whole tablets).
- Telaprevir and boceprevir are administered as tablets t.i.d. (every 7-9 hours) together with food (not low-fat) and may be used with both types of pegylated interferon and ribavirin.
- Telaprevir is administered as tablets containing 375mg: 2 tablets 3 times daily.
- Boceprevir is administered as tablets containing 200mg: 4 tablets 3 times daily.
- Telaprevir and boceprevir are considered equally efficient, but in case of co-morbidity with increased risk for anemia during treatment telaprevir may be preferred. By skin disease boceprevir may be preferred.
- It is recommended to reduce ribavirin and pegylated interferon instead of using erythropoietin to treat anemia and GCSF (granulocyte colony stimulating factors) to treat leucopenia.

Patients with genotypes 2, 3, 4, 5, 6

- Patients with genotype 2 and 3 are treated for 24 weeks with the same dose of pegylated interferon as in genotype 1, but with a fixed dose of 800 mg ribavirin daily [57]. Preliminary data suggest that treatment with pegylated interferon-alfa2b, 1.0µg/kg/week is equivalent to 1.5µg/kg/week at least in combination with weight based ribavirin [58] [59].
- For genotype 4 current data suggests that duration of treatment should be 48 weeks
- For genotype 5 and 6 there is no available data for optimal treatment dose and duration. Treatment as genotype 1 is suggested.

Monitoring during treatment

Patients with genotype 1

- For patients with genotype 1 treated with pegylated interferon-alpha/ribavirin/telaprevir HCV-RNA should be measured after 4, 8, and 12 weeks of treatment. Telaprevir is administered for 12 weeks. For patients without cirrhosis, who have undetectable HCV-RNA at both 4 and 12 weeks of treatment, pegylated interferon-alpha and ribavirin can be stopped after 24 weeks.
- For patients with HCV-RNA >1000 IU/mL at either 4 or 12 weeks of treatment, and/or detectable HCV-RNA after 24 weeks, treatment must be stopped as it is unlikely to lead to SVR.
- For patients with genotype 1 treated with pegylated interferon-alpha/ribavirin/boceprevir after a lead-in phase of pegylated interferon-alpha/ribavirin HCV-RNA should be measured after 4, 8, 12, and 24 weeks of treatment. If HCV-RNA is negative at these measurements, treatment can be stopped after 28 weeks (4 weeks of lead in with pegylated interferon-alpha/ribavirin and 24 weeks of pegylated interferon-alpha /ribavirin/boceprevir). Patients who are HCV-RNA positive at week 8 and negative week 24 should continue tipple therapy until week 36 and receive an additional 12 weeks of pegylated interferon-alpha/ribavirin (total treatment duration 48 weeks).
- If HCV-RNA is > 100 IU/mL after 12 weeks of treatment or positive after 24 weeks, treatment must be stopped, as it is unlikely to lead to SVR.
- If lead-in is used and the patient has a RVR, then treatment with pegylated interferon-alpha/ribavirin, without DAAs, is continued for a total of 24 weeks. HCV-RNA should be measured after 4, 12, and 24 weeks.
- If HCV-RNA has not decreased by 2 log after 12 weeks or is detectable after 24 weeks of treatment, treatment must be stopped as the likelihood to obtain SVR is <2%.
- All patients negative of HCV-RNA 24 weeks after end of treatment are cured for hepatitis C.

Patients with genotype 2 and 3

- If HCV-RNA has not decreased by 2 logs after 12 weeks, treatment must be stopped as it is unlikely to lead to SVR.
- In contrast to patients with genotype 1 where duration may be shortened by "response-guided therapy" several studies have shown that for patients with genotype 2 and 3 who obtain RVR, treatment duration should generally not be shortened to 12-16 weeks as this has been associated with decrease in SVR [60]. For patients with favorable baseline

factors (see above) and severe side effects treatment shortening may be considered [61].

Prolonging treatment duration for more than 48 weeks (genotype 1/4) or 24 weeks (genotype2/3) in patients with slow response (HCV-RNA at week 12 decreased > 2 log but still positive) does not seem to improve SVR.

In exception to this it may be considered to treat cirrhotic patients with genotype 2/3 and cirrhosis for 48 weeks. However, this has not been demonstrated in controlled trials.

Patients with genotypes 4, 5, 6

- Treatment for 48 weeks with pegylated interferon and ribavirin is recommended. HCV-RNA should be measured after 4, 12, 24, and 48 weeks of treatment, and 3 and 6 months after end of treatment.

Clinical management of all treatments

At treatment initiation the following tests should be performed:

- Hematology, renal function, ALT (AST), bilirubin, alkaline phosphatases, protrombin time/INR, albumen, TSH and quantitative HCV-RNA.
- Hematology and renal function are monitored after 1, 2, and 4 weeks and every 4 weeks hereafter until end of treatment.
- TSH should be monitored monthly
- HCV-RNA should be measured after week 4, 8 (if receiving boceprevir), 12, (16 optional), 24, and at end of treatment. Hereafter at 12 and 24 weeks post-treatment, (48 weeks post-treatment, optional).

In case of significant side effects the dose of pegylated interferon-alpha may be reduced to 2/3 without loss of effect. Pegylated interferon should be reduced if neutrophils decrease to < 0.75×10^9/L or platelets to < 50×10^9/L and paused at neutrophils < 0.50×10^9/L or platelets < 25×10^9/L.

Ribavirin reduction is recommended at hemoglobin <6.5mmol/L (10.5g/dL), usually stepwise by 200 mg (one tablet), and paused at 5.5 mmol/L (8.9g/dL).

8. Treatment of special populations

Treatment of patients with previous treatment failure

A proportion of patients have previously been treated with standard interferon with or without ribavirin. The result of repeated treatment depends on whether the patient had a null, partial, or relapse response to prior treatment.

Standard of care for treatment experienced patients with genotype 1 with previous relapse or partial response is pegylated interferon-alpha, ribavirin and a DAA drug, either telaprevir or boceprevir. Previous null responders may be considered for treatment with pegylated interferon-alpha, ribavirin and telaprevir [62, 63].

Response-guided treatment as used for naïve patient (see above) may be considered for patients with previous relapse and partial response to pegylated interferon-alpha and ribavirin but not for patients with null response.

Experienced patients treated with pegylated interferon-alpha, ribavirin and telaprevir treatment should be stopped if HCV-RNA is >1000 IU/mL at either 4 or 12 weeks as it is unlikely to lead to SVR.

For treatment experienced patients treated with pegylated interferon-alpha, ribavirin and boceprevir treatment should be stopped if HCV-RNA >100 IU/mL after 12 weeks as it is unlikely to lead to SVR.

Treatment of patients with chronic hepatitis C and cirrhosis

Experience with treatment of patients with chronic hepatitis C and cirrhosis is limited. In general the antiviral treatment of HCV-related cirrhosis has less effect and more pronounced side effects. In patients with compensated cirrhosis (Child-Pugh score A), treated with pegylated interferon-alpha and ribavirin, SVR is achieved in 50-70% of patients with genotype 2 and 3, and in 20-30% of patients with genotype 1. By adding DAAs SVR increases, but the experience is limited. However, combination therapy with pegylated interferon-alpha, ribavirin and DAA is first choice, also for this group of patients. Especially hematological side effects (anemia, neutrocytopenia and thrombocytopenia) are frequently seen and will often lead to dose reduction or discontinuation of treatment. Patients with cirrhosis and affected hematology prior to treatment may benefit from starting with reduced dose of interferon (e.g. 2/3 of standard dose) and then titrated up if this is tolerated. Apparently, such dose reduction does not reduce SVR significantly.

Few studies have addressed treatment response to pegylated interferon-alpha and ribavirin in patients with decompensated cirrhosis (Child-Pugh B). The treatment is associated with pronounced and often serious side effects and SVR is only obtained in 50% of genotype 2 and 3 and 10 % of genotype 1 patients. Treatment of patients with Child-Pugh C cirrhosis has only been reported as case series and only for patients on the waiting list for liver transplantation.

Treatment of patients co-infected with HIV

In patients co-infected with HIV the development of fibrosis is accelerated if the CD4 counts is below 500 /mm^3 and the patient does not receive antiretroviral therapy [43]. Among HIV patients with controlled viremia this is probably not the case. Thus, it is important to monitor this group of patients with repeated liver biopsy or fibroscans, during follow-up in patients where treatment has not been implemented. There is no conclusive evidence if treatment of HIV has any influence on the development of fibrosis but available data suggest that this might be the case.

Usually it is an advantage to start treatment for hepatitis C in patients with a high CD4 count. In patients with CD4 <200 /mm^3 the treatment indication must be balanced against an increased risk of treatment complications. In genotype 1 infected patients the treatment indication is primarily based on the demonstration of significant fibrosis in the liver (as in HCV monoinfected patients), and by ≥F2 treatment is indicated in the absence of contraindications. Published results indicate that HIV patients with genotype 1 have lower SVR than mono-infected patients [64].

No randomized trials of HIV/HCV co-infected patients with the new DAAs have yet been published. There are significant interactions between telaprevir and lopinavir/ritonavir and efavirenz. So far atazanavir is the protease inhibitor with least interaction demonstrated. The recommendation is to switch HIV treatment away from lopinavir/ritonavir and efavirenz prior to treatment with telaprevir. Preliminary data suggest that boceprevir may be combined with atazanavir, darunavir and lopinavir/ritonavir. There are no data on interaction between non-nucleoside reverse transcriptase inhibitors and boceprevir.

For HIV/HCV patients, co-infected with genotype 2 and 3, fibrosis evaluation is recommended prior to treatment. Treatment results in this group seem to be comparable to those obtained in

mono-infected genotype 2 and 3 patients (co-infected treated for 48 weeks).

Treatment with pegylated interferon-alpha results in an average drop in CD4 count of 100 cells /mm^3. This is the result of interferon induced lymphopenia and is equally distributed between CD4 and CD8 positive cells. It is not clear whether the risk of infections in this situation is comparable to the risk of a spontaneous drop in CD4 count of the same magnitude. Taking this into account treatment for HCV may be initiated in HIV untreated patients with a CD4 count above 500 /mm^3.

Some antiretroviral drugs interfere with pegylated interferon-alpha and ribavirin treatment. The intercellular concentration of phosphorylated didanosine is increased to toxic levels and may lead to mitochondrial toxicity and lactate acidosis. Therefore, this drug is contraindicated during ribavirin treatment. Stavudine may possibly also lead to mitochondrial injury, and zidovudine may worsen the anemia caused by ribavirin, so both drugs should be avoided during hepatitis C treatment. Co-infected patients should receive 48 weeks of treatment with either pegylated interferon-alpha2a 180µg/week or pegylated interferon-alpha2b 1.5µg/kg/week supplemented with ribavirin 1,000 -1,200 mg for genotype 1 and 800 mg for genotype 2 and 3. There are no solid data suggesting that duration of treatment can be reduced to 24 weeks, as in mono-infected patients, and pegylated interferon-alpha2b has only been studied in the dose of 1.5 µg/kg/week. There are no data available for genotypes 4, 5 and these are suggested to be treated as genotype 1. Treatment control is not different from mono-infected patients and the same stopping rules apply: if HCV-RNA has not declined by 2 log after 12 weeks of treatment or HVCRNA >50 IU/mL after 24 weeks of treatment, this should be terminated.

Treatment of patients with renal failure

In patients with decreased renal function the dose of pegylated interferon should be reduced. Approximately 30% of pegylated-interferon-alpha2b is excreted by the kidneys. The dose should be reduced by 25% if creatinine clearence is reduced to 30-50 mL/min, and by 50% in the interval 15-29 mL/min. By a creatinine clearance below 15mL/min pegylated-interferon-alpha2b should not be used.

Pegylated-interferon-alpha2a is less influenced by renal function. The dose should be reduced to 135 µg/week by a creatinine clearance <10mL/min.

Ribavirin is predominantly excreted by the kidneys and the drug should normally not be used in patients with a creatinine clearance <50mL/min. On an individual basis ribavirin may be administered cautiously to patients with renal failure. This requires careful monitoring of hemoglobin and plasma ribavirin levels and this treatment should be centralized at few centers.

Side effects

Both interferon-alpha and ribavirin have a number of side effects. Some of these (e.g., bone marrow suppression) are more pronounced in patients with advanced liver diseases.

For interferon-alpha the most important side effects are: Fever, muscle/joint pain, nausea, diarrhea, psychic instability, depression, fatigue, bone marrow depression, visual disturbance, hyper- and hypothyroidism dermatitis, alopecia, dry mucosa and aggravation of preexisting epilepsy.

Ribavirin induces a dose-dependent anemia and may cause dyspepsia and rash. Birth defects have been produced in animal experiments and contraception should be used during treatment and until 4 month after (female)/7 month after (males) end of treatment.

The most important side effects of boceprevir are anemia and dysgeusia, of telaprevir anemia and itching/rash.

Bone marrow depression may to some extent be treated with growth factors such as G-CSF and erythropoietin or blood transfusion. However available data do not suggest that these drugs improve treatment outcome (SVR).

Conflicts of interest

Peer Brehm Christensen has participated in clinical trials as investigator for Roche, Bristol-Meyers Squibb, Janssen-Cilag, has given lectures for Roche, and arranged scientific meeting for Janssen-Cilag. Mette Rye Clausen has been a member of advisory boards for GlaxoSmithKline and Merck Sharp & Dohme. Henrik Krarup has participated in clinical trials as investigator for Schering-Plough and Roche and given lectures for Gilead, Roche, Schering-Plough, and Swedish Orphan. Alex Lund Laursen has participated in clinical trials as investigator for Bristol-Meyers Squibb, received grants from Abbott and is advisory board member for Gilead, GlaxoSmithKline, Janssen-Cilag, Merck Sharp & Dohme and Bristol-Meyers Squibb. Poul Schlichting: nothing to declare. Nina Weis has participated in clinical trials as investigator for Bristol-Meyers Squibb, Presidio, and Roche, advisory board member for Bristol-Meyers Squibb, Gilead, , Janssen-Cilag, Medivir and Merck, Sharp & Dohme, arranged scientific meetings/given lectures for Bristol-Meyers Squibb, Gilead, Janssen-Cilag, Merck Sharp & Dohme and Roche.

Abbreviations and acronyms

ADF	adefovir
AFP	alpha-fetoprotein
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
AST	aspartate aminotransferase
Anti-HBc	hepatitis B core antibody
Anti-HBe	hepatitis B e antibody
Anti-HBs	hepatitis B surface antibody
ART	antiretroviral therapy
AST	aspartate aminotransferase
cccDNA	covalently closed circular DNA
DNA	deoxyribonucleic acid
F2	septal fibrosis (Metavir stage)
F4	cirrhosis (Metavir stage)
FDA	Food and Drug Administration (USA)
G-CSF	granulocyte colony stimulating factors
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis delta virus
HIV	human immunodeficiency virus
IDU	injecting drug user
IFN	interferon
INR	international normalized ratio
IU	international unit
MSM	men who have sex with men
PCR	polymerase chain reaction
PEG	polyethylene glycol

PEG-IFN	pegylated interferon
PI	protease inhibitor
RNA	ribonucleic acid
RVR	rapid virological response
SVR	sustained virological response
TDF	tenofovir
TSH	thyroid stimulating hormone

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