Guidelines for the management of chronic hepatitis C in patients infected after substance use

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Key words : hepatitis A, hepatitis B, hepatitis C, Chronic, substance abuse, drug therapy, interferons, ribavirin, depression, liver transplantation, vaccination.

Executive summary

These guidelines, from the Belgian Association for the Study of the Liver (BASL), contain evidence-based recommendations for the management of chronic hepatitis C (CHC) infection in substance users.

Statement of intent

This report is not intended to be construed or to serve as a standard of medical care for an individual patient. Standards of medical care are determined on the basis of all clinical data available and are subject to change as scientific knowledge and technology advance. These parameters of practice should be considered guidelines only. Adherence to them will not ensure a successful outcome in every patient, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the physician in light of the clinical data presented by the patient and the diagnostic and treatment options available.

It is expected that this guideline will be adopted after local discussion involving clinical staff. Significant departures from the national guidelines as expressed in a local guideline should be documented and the reasons for the differences explained. It is highly recommended that departures from the (local) guideline be documented in the patient's case notes at the time that the relevant decision is taken.

Copying of the guideline for the purpose of producing local guidelines will be consented upon simple request.

Dates

Date edited : January 2005
Date next stage expected : January 2007

Contact

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Intramural sources of support

None

Extramural sources of support

None

Description of development process

The clinical guideline development project is intended to assist clinicians in making decisions about appropriate and effective care for their patients. To avoid that this guideline would be liable to bias and not reflect current medical knowledge, the guidelines are based on a systematic review of the literature and not just on a consensus of expert opinion.

In principal, the methodology of the Scottish Intercollegiate Guidelines Network (SIGN) was used (see http ://www.show.scot.nhs.uk/sign/home.htm). Some modifications were necessary to adapt the SIGN methodology to the Belgian situation. The initial literature review was prepared by small working groups (see

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annex) and will separately be published. Of the different rounds needed to reach the final guideline, the first and the last were organised as a general meeting. In between two separate meetings were held first between hepatologists and second between physicians with expertise in substitution therapy and psychiatrists. The other consecutive developmental rounds were executed via e-mail exchange of the comments and suggested changes. This report is structured around the accepted criteria for validity of guidelines and based on the principles of the Appraisal of Guidelines for Research and Evaluation in Europe (AGREE) instrument.

This guideline was externally reviewed by clinical experts of the BASL, finally by the Steering Committee of the BASL. There was a close collaboration with clinical and methodological experts of the Belgian Center of Evidence-Based Medicine-CEBAM (for a detailed description of the methodology, see www.cebam.be). An open meeting was held on 17 12 2004 (IXth Winter Meeting of the Belgian Association for the Study of the Liver 2004).

Updating

This guideline should be re-evaluated in a period of 2 to 4 years if new evidence becomes available. In the meanwhile, all correspondence is welcome on *geert.robaeys@zol.be.*

Text of review

The literature reviews on which this guideline is based are described in articles published elsewhere in this Journal issue.

Objectives

The main objective of this project is the development of evidence-based practice guidelines for the diagnosis and management of chronic hepatitis C in patients infected after substance use. The implementation of these guidelines should avoid the evolution of chronic hepatitis C virus (HCV) infection to end-stage liver disease, prevent liver transplantation in those patients and reduce the spread of the viral infection to other people.

Subjects in long term complete remission (more than 12 months), subjects in long term partial remission, subjects with substance dependency or abuse and who are not in remission and some other subjects who fall not into the previous categories (e.g. subjects who experimented with substances for a very short period) are the main target population. Since those subjects can have a lot of personality disorders, may actively use illicit drugs and may not be under supervision or included in substitution programs, guidelines will also be formulated for those issues. Co-infection with human immune deficiency virus (HIV) will influence the evolution of chronic hepatitis C infection and the antiviral treatment of both diseases can influence each other. Drug users have been more frequently into contact with hepatitis A and B infections in comparison with other subjects in the Western society and may be very mobile. Therefore, guidelines will be developed for HIV/HCV co-infected patients and for the vaccination of HCV infected substance users.

Target audience

The target audience for these guidelines is all specialists in internal medicine, gastroenterology and hepatology involved in the treatment of chronic hepatitis C patients infected after intravenous drug use and other physicians, especially general practitioners, physicians participating in substitution maintenance therapy and psychiatrists, who care for such patients. The multidisciplinary guideline development group from both non-university and university hospitals consisted of specialists in general practice, substitution therapy for substance abuse, gastroenterology and hepatology, virology, epidemiology and psychiatry (the list is included at the end under the heading Guideline development group and conflict of interest).

These guidelines are at least applicable to Belgian and Benelux patients, since in the development process the results of the prevalence survey of the different hepatitis types in Belgian and the results of treatment of Benelux patients were taken into consideration. One can assume, however, that they may also be of interest for clinicians in other countries with similar problems.

Scientific review

Using this methodology, the published studies used to create recommendations were categorised according to study design and quality ; then, the recommendations developed from these studies were graded according to the strength of evidence behind them. For particular recommendations and statements, the strength of the supporting evidence and quality of the data were rated by use of the SIGN-grading system (table 1).

Criteria for considering studies for this review

Types of studies

The evaluation of the management of chronic hepatitis C is based on existing evidence-based guidelines, the results of meta-analyses and systematic reviews, or of randomised, controlled studies. For methadone maintenance treatment for diagnosis and for epidemiology, which were because of obvious reasons seldom studied in randomised controlled trials, also cohort types of studies were evaluated. A lower level of evidence and lower grade of recommendation in this review will identify them as such.

Table 1. — **The SIGN-Scottish Intercollegiate Guideline Network grading system**

Levels of evidence	
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1	Meta-analyses, systematic reviews or RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies or High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2	Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion
Grades of recommendations	
A	At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+

Types of participants

Patients described as infected after intravenous drug use (IVDU) were defined as having used at least once intravenous illicit drugs.

Types of interventions

Search strategy for identification of studies

1. *Existing guidelines*

Searching all available Internet guideline clearinghouses Medline, Pub Med, the following guidelines on the treatment of CHC in IVDUs were retrieved :

– American Association for the Study of Liver Diseases (AASLD) (1)
– British HIV Association (BHIVA) guidelines (2)

2. *Pub Med search (Medline)*

Both the primary terms and the related Mesh's (Medical Subject Headings) were searched for separately. The following limits were used to restrict the search :

Hepatitis viral, human, hepatitis A, hepatitis B, hepatitis C , Chronic, microbiology - virology ; prevention & control, substance abuse, substance addiction, substance abuse, treatment centres, drug therapy, interferons, ribavirin, depression, liver transplantation, vaccination , [MESH] ; 1985 to 2004.

3. *Cochrane Library/Database of abstracts of Reviews of Effectiveness (DARE) registry*.

All these databases were searched with the primary term : Hepatitis C, Chronic, substance abuse, substance dependence, substance use disorders, drug therapy, interferons, ribavirin, depression, liver transplantation, Vaccination

Methods of the review

Using Pub Med, the Cochrane Library, DARE and CCT, studies were retrieved using the above mentioned search strategy. In a first step the abstracts of all articles were scanned to extract the relevant articles. Studies already present in a 'higher' category (e.g. a randomised controlled trial (RCT), which is already presented in a selected meta-analysis, or a study identified as clinical trial, which is also a RCT) were omitted at the lowest level.

The searches were performed by the guideline development group manager and could be reviewed by the members of the development group. The publications that were selected as potential source of evidence were critically appraised guided by checklists. Evidence tables were then compiled to summarise all the validated studies. These instruments were prepared by the guideline developing managers and subsequently reviewed and adapted by the guideline developing group members in consecutive rounds.

Description of studies

The literature was reviewed and summarised in different papers included in this Journal issue.

Reviewers' conclusions

Implications for practice

Definition and classification

1. Substance users are defined as persons who have used illicit drugs at least once in their life. Comment : It is almost impossible to know for certain whether a patient has ever used drugs intravenously or not. Therefore we included all patients who ever used illicit drugs in a broad operational definition. Obviously we were especially interested in those patients who used drugs intravenously, as they are at a higher risk to be infected with HCV.

2. Substance users can be classified according to DSM-IV criteria *(***http ://mysite.verizon.net/res7oqx1/id8.html***)*.

Patients

Therefore, subjects infected with HCV after substance use can be divided in 4 categories (according to DSM IV criteria) :

Category 1 : Former drug users : subjects in long- term complete remission (more than 12 months)

Category 2 : Subjects in long-term partial remission : they may be on agonist therapy and/or in a controlled environment. This can include the occasional use of illicit drugs.

Category 3 : Subjects with either substance dependence or substance abuse and who are not in remission.

Category 4 : 'Other' subjects : those who do not fall into the previous categories (e.g. subjects who experimented with substances for a very short period).

Recommendations for treatment of Chronic Hepatitis C (CHC) in substance users

1. *Diagnosis and staging of CHC and co-infection (HAV, HBV, HIV)*

1. In all substance users without a known positive anti-HCV testing the following tests have to be performed :
   Yearly screening for HCV infection by determination of serum anti-HCV antibodies and determination of level of serum transaminases (3-6,9-10) (level 4, grade D) for category 2-3. In category 1 and 4 only once a screening has to be performed.
   If anti-HCV is positive : determination of qualitative HCV-RNA and genotype (1). Correct manipulation and transport of serum samples is mandatory (7-8).
   If HCV-RNA is negative : those patients have presumably been exposed to hepatitis C virus but have eliminated the virus spontaneously. HCV-RNA must be tested on at least two separate occasions 6 months apart since low-level, fluctuating viraemia may confound the diagnosis (10-12) (level 4, grade D).
   If HCV-RNA is positive : further option for treatment should be taken.
2. A liver biopsy may be obtained to provide information on prognosis (13-15).

In patients with genotype 2 or 3 and without evidence of advanced liver disease a liver needle biopsy is not mandatory to start a treatment (1).

In patients with co-morbidity such as HIV co-infection and alcohol abuse a liver needle biopsy is strongly advised (16) (level 4, grade D).

3. If cirrhosis is suspected surveillance for portal hypertension and hepatocellular carcinoma should be performed (17-20, 23) (level 2++, grade B).
4. Co-infection is determined by serum anti-HAV, anti-HBs, HBsAg, anti-HBc and anti-HIV (21, 22) (level 4, grade D).

2. *Who can be treated ?*

Substance users from category 1, 2 and 4 : may be eligible for antiviral treatment (24-35) (level 2++, grade B).

Subjects who are on a methadone maintenance program and who occasionally use illicit drugs can be treated, provided they understand the need for and actively want HCV treatment, are able and willing to maintain close monitoring and take the necessary measures for birth control (contraception) (1). (Level 4, grade D).

Patients from category 3 : as a general rule these patients will not be eligible for antiviral treatment. However, decisions about antiviral treatment should be made by a multidisciplinary treatment team together with the patient based on individualized risk-benefit assessments (32) (level 4, grade D).

3. *Management of the HCV infected patient and risk of reinfection*

3.1. Pre-treatment evaluation (level 4, grade D)

Patients from all categories :

Have to be educated and informed on all aspects of epidemiology of hepatitis C and its treatment (e.g. additional risk of liver damage due to alcohol and co infection and risk of HCV re-infection (35-37).
Drug use counselling and relapse prevention support should be available (1).
In case of a history of psychiatric disorders psychiatric services should be easily accessible (30,33)

Patients from category 1 and 4 :

Have to be assessed for current level of depression and psychiatric disease. Well-established questionnaires can be used in cooperation with a psychiatrist. A score above a certain cut off point can be used to refer to a psychiatrist (39).

Patients from category 2 and 3 :

Have to be evaluated by a physician with expertise in treating substance users.
Have to be evaluated by a psychiatrist concerning the risk for depression or other psychiatric disorders.
Have to agree to be followed up in a multidisciplinary setting (38).
Patients in category 3 have to be advised and referred to start a substitution therapy. Their social situation needs to be stabilised as well before interferon treatment can be started (39).

3.2. Treatment for Chronic hepatitis C (Level 2+, grade C)

Peginterferon alfa-2a 180 µg SC (Pegasys®) once weekly regardless of weight or Peginterferon alfa-2b 1.5 µg/kg SC (PegIntron®) once weekly + ribavirin (Copegus®, Rebetol®) (800-1200 mg po daily in two divided doses), dose depending on genotype (genotype 2,3 : 800 mg ; genotype 1 :1-1,2 g), and patient weight (41,42).

Patients with genotype 2 and 3 should be treated for 24 weeks ; patients with genotype 1, 4 and 5 should be treated for 48 weeks (41).

Only in patients with genotype 1, there is evidence to stop treatment after 12 weeks if there is no decline of more than 2 log or more from baseline HCV-RNA (Early Viral Response) (1,46). In genotypes 2 and 3, testing for early viral response is not necessary, as almost all patients respond. In the other genotypes insufficient data on the predictive values of early viral response are currently available.

If one decides not to treat a patient a new liver biopsy should be performed after 3-5 years (1,40) (level 2+, grade C).

In patients with acute hepatitis C after illicit drug use the need for antiviral treatment should be assessed on a case-by-case basis by a hepatologist. No definitive recommendations can be made regarding timing, treatment regimen and duration of treatment (43-45).

Substance users with CHC and decompensated liver disease (category 1, 2, 4) may be candidates for orthotopic liver transplantation (47,48,50,51) (level 4, grade D).

Type and frequency of side effects of interferon treatment are the same in substance users as in other patients with CHC (35). The same measures can be used to treat these side effects (1,35). Methadone and buprenorphine do not influence the effects/side effects of antiviral treatment (38).

3.3. Care organisation and consequences of substitution therapy (level 4, grade D)

It is possible for patients to learn injecting interferon subcutaneously themselves. There are no contraindications for substance users to learn this technique (30) (level 4, grade D).

Patients from category 2 to 4 need to be followed up in a multidisciplinary setting (27). The different aspects of their care (medical, psychological, social) have to be translated in the different disciplines that need to be present in the multidisciplinary network. Regional differences may exist in the way this care is practically organised (e.g. social function can be with a nurse or a social worker, psychological function may be with psychologist, psychiatrist or psychiatric nurse, provision of substitution therapy may be organised in different ways) (33,37,38) (level 4, grade D).

3.4. Psychiatric aspects

Always assess current level of depression before starting interferon treatment. Preventive antidepressant treatment is not indicated, unless depression is present or when a past psychiatric history indicates a risk for depression relapse (39).

Continue to monitor the level of depression during the first weeks of treatment (the highest risk for development of depression exists within first 8 weeks of interferon treatment) (52,53) (level 2++, grade C). If depression develops during antiviral treatment start Selective Serotonin Reuptake Inhibitor (SSRI) (33, 39) (level 4, grade D).

In case of former depression under interferon treatment (previous attempt to treat chronic hepatitis C infection) an SSRI has to be started before retreating with antiviral medication (39,54) (level 4, grade D). In case of severe psychiatric pathology continuation of therapy should be considered in a multidisciplinary setting.

In case of craving, the methadone dose can be increased (35) (level 2++, grade B).

3.5. Re-infection rate (level 4, grade D)

The re-infection rate of HCV after successful treatment of CHC in illicit drug users seems lower than in naïve infected substance users. This may be due to safer injection routines in experienced substance users or to a partial protective immunity (25,32,56,57).

3.6. Vaccination against HAV-HBV (level 4, grade D)

First, determine the immune status by blood testing.

Vaccinate against HAV (0, 6 to 12 months) all HCV-infected patients without HAV IgG antibodies.

Vaccinate against HBV (0, 1, 6 months) all HCV-infected patients in absence of HBsAg or anti-HBs antibodies (i.e. in absence of levels < 10 mU/ml) (58-61).

4. *HIV co-infection* (2, 16, 62-67)

- Vaccination against HAV and HBV in all HIV-HCV co-infected patients found non-immune is recommended (level 4, grade D).
- Because of the rapid disease progression and the possibility of co-morbidity in hepatitis C co-infected patients) (level 2++), a liver biopsy is strongly advised and HCV-treatment should always be strongly considered. If for whatever reason treatment is not performed, a new liver biopsy is advised after 2 years, in view of the rapid progression of fibrosis. HIV-HCV co-infected patients with markers of advanced liver cirrhosis should be monitored closely during interferon-based therapy for risk of hepatic decompensation (64,65) (level 2++, grade B).
- Patients having CD4+ cells > 350/µL are good candidates for anti-HCV therapy, with higher rate of response for higher count of CD4+ cells ; patients with CD4+ counts of 200-350/µL may also benefit, and decision should be taken on an individual basis, taking into account the severity of HCV infection (degree of fibrosis) and the risk of HIV diseases progression (high if HCV-RNA > 50,000-100,000 copies/µL) ; in patients with CD4+ counts < 200/µL anti-HCV therapy is relatively contra-indicated (short-term risks of opportunistic infections and low rate of response), antiretroviral therapy has priority (level 4, grade D).
- Active substance abuse must be addressed before anti-HCV therapy ; candidates should not be active

intravenous drug or alcohol users ; patients under stable maintenance substitution therapy are candidates for hepatitis C treatment (level 4, grade D).

- HCV treatment should not be initiated in the presence of active opportunistic infection (level 4, grade D).
- Patients who require Highly Active Antiretroviral Therapy (HAART) should be stable under anti-HCV treatment (CD4 > 350/µL and undetectable HIV-RNA for more than 3 months), before initiating HCV therapy (level 4, grade D).
- HCV therapy should be the same as the regimen recommended in HIV-negative individuals (level 2++, grade B). Pending further data, it could be wise to prolong the treatment during at least 48 weeks for all genotypes, in view of the higher relapse frequency in HIV-HCV co-infected patients after discontinuing therapy (62) (level 2++, grade B). In case of absence of early viral response in treatment with peginterferon plus ribavirin, defined as less than 2 log decline of HCV RNA level after 12 weeks compared to baseline, treatment discontinuation should be considered in patients with genotype 1 (66) (level 2++, grade B).
- If anti-HCV therapy has to be started, didanosine (ddI) should be avoided in HAART regimen (16, 64) (level 2+, grade B) and patients taking zidovudine (AZT) or stavudine (d4T) should be carefully followed for possible increased ribavirin toxicity every two weeks during the first two months, afterwards monthly till the sixth month, afterwards every six weeks until the end of therapy and during follow-up.
- If patients on HAART initiate HCV therapy, careful monitoring of blood cell counts, including CD4 cells, liver and pancreas enzymes, and serum lactate is necessary.
- HIV-infected patients with decompensated liver disease may be candidates for orthotopic liver transplantation (level 4, grade D).
- There should be close collaboration between hepatologists and infectiologists to improve the management of HIV-HCV co-infected patients (level 4, grade D).

Guideline development group and potential conflict of interest

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