Postexposure management of hepatitis A, B or C : Treatment, postexposure prophylaxis and recommendations

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Abstract

Although there is no consensus on the best management of acute hepatitis C or on optimal strategy of follow-up after potential contamination, certain guidelines can nevertheless be proposed for the care of these patients in practice. It is now recommended that acute hepatitis C be treated by interferon monotherapy in the presence of a C viremia, detectable by polymerase chain reaction, and an elevation of the transaminases. The earlier the treatment is started after appearance of symptoms, the more effective it is. Management of a potentially contaminated individual consists of screening for the C virus as early as the fifteenth day after the potentially contaminating act and, in the case of virus transmission, starting interferon treatment as soon as elevation of the transaminases appears. No special precautions are to be taken by the person potentially contaminated for avoiding possible secondary C virus transmission during the follow-up period.

In the case of acute hepatitis B, antiviral treatment should not be started, in view of the high percentage of spontaneous recoveries and the potentially negative effect of treatment on the chances of spontaneous recovery. Post-exposure prophylaxis by anti-hepatitis B immunoglobin injections and/or vaccination should be considered after evaluation of the hepatitis B surface antigen status of the source and of the vaccination and vaccine-response status of the exposed person. The classic scheme for selecting the most appropriate postexposure prophylaxis is reminded.

In post-exposure prophylaxis for hepatitis A virus, although there have been no studies comparing the effectiveness of vaccination with that of immunoglobin injections, it is at present proposed to provide only vaccination. The target groups eligible for post-exposure prophylaxis are evoked. (Acta gastroenterol. belg., **2003**, 66, **250-253**).

Key words : hepatitis C ; acute disease ; hepatitis ; prevention ; occupational exposure.

Hepatitis C

Acute hepatitis C, although rarely diagnosed on account of its generally asymptomatic nature, remains a relatively frequent affection. The number of new cases a year is estimated in the United States at 38,000 (1), in France at 5 to 6,000 (2). At present, the main transmission mode is by intra-venous drug-abuse. In practice, however, since few drug-addicts receive medical attention, most patients who consult for acute hepatitis C have been contaminated by more marginal transmission channels, essentially an invasive medical examination or an accidental needle-stick injury (3).

The questions to be answered by the clinician are as follows :

Should an acute hepatitis C be treated ?
If so, when should it be treated ?
What follow-up should be proposed after a potentially contaminating act ?
What recommendations should be made to the entourage ?

Should an acute hepatitis C be treated ?

It is at present considered that hepatitis C should be treated when diagnosed during the acute phase, although there are still insufficient data for drawing definite conclusions as to the best time to start therapy or as to the ideal therapeutic regimen to be recommended (5). Practical recommendations for the care of this affection can, however, be reasonably made.

The arguments in favour of treatment during the acute phase are the following :

It is known that acute hepatitis C can easily become chronic if left without treatment , roughly 50-90 % in adult cases (2,4,6), 55 % in children (7). Moreover, there is no clinical indicator or biological marker to predict, in any given patient, whether the acute infection will spontaneously recover or will develop into chronic affection. The most that is known is that there is statistically a better chance of spontaneous recovery when the hepatitis is icteric or clinically symptomatic. A long-term follow-up is moreover necessary before a diagnosis of spontaneous recovery can be made. It is known, indeed, that the viremia can be transiently undetectable in a consistent number of patients who ultimately will develop persistent viremia (6). Lastly, the strongest argument for treating the affection in its acute phase is the great effectiveness of treatment given at this stage, with a highly acceptable safety profile (4,8). The therapeutic regimen that is currently recommended is that proposed recently by Jaeckel *et al.* (8). In this multicentre German study, 44 acute hepatitis C patients, most of them symptomatic, were treated by interferon alfa-2b monotherapy, with a daily dose of 5 million units for 4 weeks, then 5 million units three times a week for 20 weeks. A sustained virological response was observed in 98 % of these patients. Tolerance was excellent ; only one patient had to interrupt the treatment on account of side-effects. The high rate of sustained viral response in case of treatment during the acute phase was confirmed by a Belgian study (4). In this study, the percentage of sustained viral response obtained in a group of 29 acute hepatitis C patients treated with 5 million units of interferon alfa-2b

a day for 2 months were compared with the percentage of spontaneous recoveries historically observed in a group of 16 patients not treated during the acute phase : the percentage of recovery under treatment was significantly higher in the group treated as against the group without treatment (84 versus 19%). In published studies, the safety profile of interferon given during the acute phase is similar to that observed in the treatment of chronic hepatitis C (5). The treatment is well tolerated even by icteric patients with a marked elevation of transaminases.

When should acute hepatitis C be treated ?

The most effective strategy is to treat PCR-C positive acute hepatitis C patients as soon as possible after the elevation of transaminases. The Belgian study has shown that all the patients treated within the first six weeks after the appearance of symptoms recovered, while the results of delayed treatment were more uncertain (50% of sustained viral response) (4). The benefice to treat early was found as well as for icteric than for anicteric patients. The evolution from acute to chronic viral infection is effectively linked in part to the appearance of quasi-species allowing the virus to escape the host's immune system (9). It seems plausible that the high effectiveness of early treatment is linked to the eradication of the virus before the appearance of these quasi-species. It is however not at present recommended that patients be treated before the elevation of transaminases. Interferon being an immunomodulator, there is a theoretical risk that treatment started too early, before the host's immune response is activated, may lead to a lower sustained viral response (2). Although this point is under discussion, the excellent results of the German study (8) indicate that in any case there are no disadvantages, in term of therapeutic effectiveness, in waiting for elevation of transaminases.

If early treatment is a well-accepted strategy for anicteric patients, some authors, however, have recently advocated a wait-and-see strategy for icteric patients (18). Gerlach, indeed, showed than about half of icteric patients cleared the virus spontaneously, and that those who remained PCR positive twelve weeks after presentation could be treated efficiently at that time (with 80% of sustained viral response). Thus, the current dilemna for icteric patients is either to treat as soon as possible after presentation, with the risk of overtreating a significant proportion of patients, or to delay the treatment, with the risk of lowering the sustained response rate.

Immediate post-exposure treatment, before a viremia detectable by PCR becomes apparent, is clearly not recommended, in view of the low risk of transmission (between 3 and 10%) and the potential side-effects of the treatment.

Lastly, there is no effective prophylaxis by immunoglobin injection.

What follow-up treatment should be proposed after a potentially contaminating act ?

The immediate measures to be taken in case of accident or exposure include cleaning the wound with soap and water, followed by rinsing and prolonged antiseptic application, for at least 10 minutes, with Dakin or 12° bleach at 10% dilution (10).

No uniform recommendations at present exist concerning the ideal management of a potentially contaminated patient. In practice, however, the following recommendations can be proposed. An initial assessment is necessary in order to demonstrate the absence of previous chronic C virus infection (HCV antibodies and transaminases).The aim of management is then to detect early the appearance of possible infection in order to propose early treatment. The presence of the C virus is detectable in serum by PCR as early as one to two weeks after contamination (11). The viremia generally increases to reach a peak before decreasing, for either disappearing in the case of spontaneous recovery or stabilizing in case of progression to chronic infection (11). Attention must be paid to the fact that the viremia may occasionally become transiently undetectable for a few days or weeks before reappearing and reaching a stable level. Disappearance of the viremia following infection does not therefore necessarily mean spontaneous recovery from the infection (6). It can be deduced from these data that, if screening for the virus is delayed, it may produce a false negative result. It is thus advisable to carry out PCR viremia screening on the potentially contaminated individual as early as the fifteenth day after the risk of contamination. If this PCR is negative, the risk of infection in the patient becomes very low ; a check-up on transaminases and HCV antibodies 4 months later seems sufficient. If the PCR is positive, however, a regular transaminase check-up, every fortnight for example, is necessary, with treatment started as soon as elevation occurs.

Advice for avoiding secondary transmission

The potentially contaminated person is not advised to take any special precautions for avoiding possible secondary C virus transmission during the follow-up period. At the most, blood, plasma, organ, tissue or sperm donations should be avoided. The use of a condom for sexual intercourse during this period is not compulsorily recommended. A possible pregnancy should not be interrupted. Breast-feeding can be continued. Preventing the continuance of professional activities is not justified (12).

Hepatitis B

Prospective studies have shown that the risk of B virus transmission is linked to the presence or absence of HbeAg, an (imperfect) reflection of the extent of the viremia. The risk of developing a symptomatic hepatitis after an accidental needle-stick injury from an HbeAg-

positive patient is 22-31%, that of the appearance of serological markers showing contact with the virus is 37-62%. The respective figures for an accidental needle-prick from an HbeAg-negative patient are 1-6% and 23-37% (12). Studies carried out in the 70's showed that the prevalence of B virus infection in health workers was ten times greater than among the general population. These data amply justify the vaccination of health workers since the early 80's.

Post-exposure prophylaxis

The practical attitude recommended in post-exposure prophylaxis was laid down by the Centre of Disease Control in 2001 (12).

– Post-exposure prophylaxis is indicated for anyone who has not been previously vaccinated. This means both the injection of a single dose of anti-hepatitis B immunoglobins (HBIG) at 0.06 mL/kg I.M. (preferably within 24 hours) and a vaccination (preferably within 24 hours). The HBIG injection alone within one week of exposure gives 75% protection. Although not demonstrated by prospective studies, it seems likely that the administration of the vaccine in association with HBIG raises the protection percentage (this increased effectiveness has been shown in cases of perinatal exposure in children born of HBsAg-positive mothers : 75% protection with HBIG alone or vaccine alone ; 85-95% protection with HBIG + vaccination). The effectiveness of HBIG when administered > 7 days after exposure is unknown.
– For persons who are in the process of being vaccinated but have not completed the vaccination series, vaccination should be completed as scheduled, and a single dose of HBIG should be added.
– For persons previously vaccinated unsuccessfully (i.e. not having developed, 1 to 2 months after the last dose of vaccine, an anti-HBs antibody level > 10 mUI/ml), it is advisable to inject a single dose of HBIG and to proceed with a new series of 3 vaccines. It is known, indeed, that 30 to 50% of patients who have not responded to an initial series of vaccines respond to a second series of 3 injections. For those known to have totally failed to respond to B virus vaccination (i.e. having unsuccessfully received 3 injections and then another series of 3 injections), the administration of 2 HBIG doses is advised, the first as soon as possible after contamination and the second one month later.
– For vaccinated persons whose antibody response is unknown, it is recommended to test the exposed person and, when the antibody level is inadequate, to give 1 dose of HBIG and vaccine booster.

Adequate protection is provided by this prophylaxis plan. It is, however, recommended to test for the presence of HBsAg 6 months after exposure in order to detect the rare cases where infection has developed despite prophylaxis (13).

Treatment of acute hepatitis B

Antiviral treatment is not justified during the first six months of acute hepatitis B. Prospective studies have shown a spontaneous recovery percentage of 95%. Moreover, clearance of the virus being linked to a strong immune response against viral antigens, it is possible that inhibiting viral replication during the first week of infection may reduce the effectiveness of this immune response (13). Patients must however be followed until clearance of the virus. If the HBs antigen persists for over 6 months, treatment must be initiated, since the spontaneous recovery percentage then falls rapidly. There is at present no consensus on the preferred choice between the two available treatments, interferon or lamivudine.

Advice for avoiding secondary transmission

Advice is identical to that applying to C virus hepatitis (see above) (12).

HEPATITIS A

Hepatitis A remains the most frequently encountered disease among those preventable by vaccination. For this reason, vaccination is recommended not only for persons presenting increased risk of contracting the disease (travellers in highly endemic areas, homosexuals, drug-addicts, those presenting coagulation disorders, patients with chronic liver disease, children living in communities with high rates of disease), but also any person wishing to be protected against the virus.

Post-exposure prophylaxis

In the United States, the Centre for Disease Control today still recommends providing post-exposure prophylaxis by immunoglobin injection (14). The recommended dose is 0.02 mL/kg by intramuscular injection, as soon as possible but not later than 2 weeks after exposure. Because of the need to start post-exposure prophylaxis early for it to be effective, it is not recommended to carry out, before the immunoglobin injection, screening for acquired immunity (total HA antibodies) in order not to lengthen the time between exposure and the injection.

Nevertheless, although there have been no clinical studies comparing the effectiveness of vaccination carried out soon after exposure with that of immunoglobin injections, it is now increasingly considered that post-exposure prophylaxis can be effected by vaccination alone, without immunoglobin injection. It is known that vaccination protects against the virus within an average of 15 days (54 to 62% and 94 to 100% of those vaccinated show neutralising antibodies 15 days and 1 month respectively after the first vaccine dose), while the incubation period before onset of the disease is 30 days on

average (15 to 45 days). It has also been demonstrated during epidemics in different countries that these epidemics could be effectively controlled by vaccination (15,16,17).

Target groups for post-exposure prophylaxis

These recommendations, drawn up in 1999 by the Centre of Disease Control (14) concerned immunoglobin injection. They can also be applied to post-exposure vaccination.

Target groups requiring post-exposure prophylaxis are as follows :

– Persons having been in close personal contact with the patient : members of family living under the same roof ; sexual partner ; drug-addict sharing a needle… Also included in this non-exhaustive list are all those (for example, a regular baby-sitter) who have had any other form of close contact with the patient.
– Day care centres : where there is a case of hepatitis A in a child or employees, or two or more households of centre attendees, it is advisable to vaccinate all unvaccinated employees and the other babies of the classroom. If an epidemic is declared (1 case in over 3 families), it is advisable to vaccinate all members of households that have children in diapers as well.
– In primary and secondary schools, offices and places of work : it is unnecessary to vaccinate the other children or colleagues if a single case of hepatitis A is declared and if the person has been contaminated outside the school or occupational area. Nor is post-exposure prophylaxis necessary in hospitals for non-vaccinated hospital staff or other patients on the arrival of a hepatitis A patient. Only careful hygienic practices (e.g. hand-washing) are required. If, however, an epidemic sets in (i.e. transmission of the virus to other schoolchildren, patients or hospital staff), it is necessary to start a vaccination programme.
– If hepatitis A is diagnosed in a food handler, all other food-handlers in the same place of work must be vaccinated. As to persons who have been customers of the establishment at the time when there was risk of contamination, prophylaxis is not recommended except if these customers can be identified and vaccinated within two weeks of potential contamination.

Evaluation of the exposed person and the source after occupational exposition

An organisation should be set up to ensure effective follow-up during working hours, even at night or during holidays, of a worker potentially contaminated by a medical act : the effectiveness of prophylactic measures can depend on how soon these measures are taken (12).

A medical file must be opened and show the following points : date and time of the accident ; details of the medical act in question ; nature of infection in the source patient ; risk of infection in the exposed person (e.g. hepatitis B vaccination and vaccine-response status).

The nature of the source patient's infection (HBs antigen, HCV and HIV antibodies) must be identified from the file. If this data is unknown, the source patient must be informed of the accident and must, with his/her consent, undergo serological screening for B, C and HIV virus. If an infection is confirmed, the patient must be advised to consult and be treated by a specialist. Confidentiality must be guaranteed. If the patient is HIV positive, it is important to establish the development stage of the disease and the existence of previous or ongoing anti-viral treatment, as well as the virus count.

The risk of infection in the worker exposed must be estimated by detecting the HCV antibody, HIV antibody, HBs antigen and HBs antibody and by finding out if the worker has had a B virus vaccination.

No detection of the presence of the virus on the needle or object that caused the potential contamination should be carried out by reason of the unreliability of the data resulting from such an analysis and the risk of this procedure to the person manipulating the object in question.

References

1. ORLAND J., WRIGHT T., COOPER S. Acute hepatitis C. *Hepatology*, 2001, **33** : 321-327.
2. PAWLOTSKY J. The pros of antiviral therapy in acute hepatitis C virus infection and use of antivirals for postexposure prophylaxis. In : SHOUVAL D. (ed.). EASL postgraduate course : Prevention and intervention in liver disease. Kenes International, 2002 : 83-89.
3. DELWAIDE J., GERARD C., VAIRA D., MAGGIPINTO G., RENTIER B., BELAÏCHE J. Hepatitis C virus infection following invasive medical procedures. *J. Intern. Med.*, 1999, **245** : 107-108.
4. DELWAIDE J., BOURGEOIS N., GERARD C., DE MAEGHT S., MOKADDEM F., WAIN E., BASTENS B., FEVERY J., GEHENOT M., LE MOINE O., MARTINET J.P., ROBAEYS G., SERVAIS B., VAN GOSSUM M., VAN VLIERBERGHE H., and the BASL. Icteric and Anicteric acute hepatitis C : early treatment is more effective (submitted 2003).
5. ALBERTI A., BOCCATO S., VARIO A., BENVEGNÙ L. Therapy of acute hepatitis C. *Hepatology*, 2002, **36** : S195-S200.
6. VILLANO S., VLAHOV D., NELSON K., COHN S., THOMAS D. Persistance of viremia and the importance of long-term follow-up after acute hepatitis C infection. *Hepatology*, 1999, **29** : 908-914.
7. VOGT M., LANG T., FROSNER G. *et al.* Prevalence and clinical outcome of hepatitis C infection in children who underwent cardiac surgery before the implementation of blood donor screening. *N. Engl. J. Med.*, 1999, **341** : 866-870.
8. JAECKEL E., CORNBERG M., WEDEMEYER H., SANTANTONIO T., MAYER J., ZANKEL M., PASTORE G., DIETRICH M., TRAUTWEIN C., MANNS M. Treatment of acute hepatitis C with interferon alfa-2β. *N. Engl. J. Med.*, 2001, **345** : 1452-1457.
9. FARCI P., SHIMODA A., COIANA A., DIAZ G., PEDDIS G., MELPOLDER J.C. The outcome of acute hepatitis C can be predicted early by the evolution of quasispecies. *Science*, 2000 , **288** : 339-344.
10. Conférence de Consensus.- Hépatite C : dépistage et traitement. *Gastroenterol. Clin. Biol.*, 1997, **21** : 45-49.
11. PAWLOTSKY J.M. Use and interpretation of virological tests for hepatitis C. *Hepatology*, 2002, **36** : S65-S73.
12. UPDATED U.S. public health service guidelines for the management of occupational exposures to HBV, HCV, and HIV and recommendations for postexposure prophylaxis. *MMWR*, 2001, **50** (RR-11) : 1-52.
13. THOMAS H.C. Post-exposure prophylaxis after exposure to HBV or HCV. The arguments against. In : SHOUVAL D. (ed.). EASL postgraduate course : Prevention and intervention in liver disease. Kenes International, 2002, 90-93.

14. Centers for Disease Control and Prevention- Prevention of hepatitis A through active and passive immunization : recommendations of the advisory committee on immunization practices. MMWR, 1999, **48** (RR-12) : 1-37.
15. MC MAHON B., BELLER M., WILLIAMS J., SCHLOSS M., TANTILLA H., BULKOW L. A program to control an outbreak of hepatitis A in Alaska by using an inactivated hepatitis A vaccine. *Arch. Pediatr. Adolesc. Med.*, 1996, **150** : 733-739.
16. IRWIN D., MILLERSHIP S. Control of a community hepatitis A outbreak using hepatitis A vaccine. *Commun D Public Health*, 1999, **2** (3) : 184-187.
17. ZAMIR C., RHISPON S., ZAMIR D., LEVENTHAL A., RIMON N., BEN PORATH E. Control of a community-wide outbreak of hepatitis A by mass vaccination with inactivated hepatitis A vaccine. *Eur. J. Clin. Microbiol. Infect. Dis.*, 2001, **20** (3) : 185-187.
18. GERLACH J., DIEPOLDER H., ZACHOVAL R., GRUENER N., JUNG M., ULSENHEIMER A. *et al*. Acute hepatitis C: high rate of both spontaneous and treatment-induced viral clearance. *Gastroenterology*, 2003, **125** : 80-88.