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(Consensus conference organised with the participation of ANAES)

Consensus conference

Indications for liver transplantation

19-20 January 2005
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ACHBT

AFEF

About these guidelines[1]

This consensus conference was held on 19-20 January in Lyon, France. It was conducted in accordance with the method recommended by the *Agence nationale de l'Accréditation et de l'Evaluation en Santé (ANAES*). Since January 2005, ANAES has become part of the *Haute Autorité de santé (HAS).* The conclusions and guidelines were drawn up by an independent conference jury. HAS is not responsible for their content. Names of sponsors and supporting organisations are given in the Acknowledgements section.

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[1] The guidelines are taken from a full-length report in French available from the *Haute Autorité de santé* (French National Authority for Health) website: www.has-sante.fr.

QUESTIONS PUT TO THE JURY

Question 1. What is the best way of managing patients undergoing transplantation for viral hepatitis?

Question 2. When is alcoholic cirrhosis an indication for liver transplantation?

Question 3. When should liver cancer be treated by liver transplantation?

Question 4. When is living donation an alternative?

Question 5. What are the developments with regard to indications for liver transplantation?

Introduction

Liver transplantation (LT) matured between 1984 and 1993, and was perfected from 1993 to 2003. This consensus conference focused on whether to extend the indications for LT and thus also addressed organisational aspects and living donation.

To expand or optimise resources?

A number of contrasting observations can be made:
- there is a shortage of available organs, yet the demand for them is increasing due to advances in screening and imaging, and to the increased prevalence of chronic viral and/or malignant liver disease;
- treatment is based on predefined protocols, yet patients are treated as individuals;
- there is a temptation to extend the indications of LT, yet these should be based on a high level of evidence.

As there is a shortage of organ donations, the indications for the increasingly widespread use of LT have to be based on:
- more precise epidemiological data: the number of patients needing LT and the true requirements for organs are not known;
- better expression of outcomes after LT, to improve comparisons between indications and treatment strategies in terms of efficacy and economic data;
- better coordination among French centres and with European centres - the current problems in using split livers is a striking illustration of this need;
- better organisation to reduce disparities in access to care and waiting list times;
- a more energetic policy throughout France for harvesting organs from individuals in a state of brain death in order to reduce current regional disparities. It should motivate the teams harvesting donor organs and should improve information and education of the general public on the subject of organ donation.

Discussion about indications for LT cannot ignore:
- the anticipated rise in the incidence of hepatitis C and hepatocellular carcinoma (HCC), mainly due to advances in screening and diagnostic tools;
- the anticipated negative effects of the marked decrease in vaccination against hepatitis B in children and infants in France;

- social and medical indifference to alcohol dependence, and shortcomings in its psychological, social and medical management, which is still too hidebound by moralising judgemental attitudes;
- the inadequacy of primary prevention policies against risk of infection from parenteral drug use;
- the increased requirement for LT due to an ageing population;
- the increase in hepatitis B and C in immigrants.

Chronic liver disease related to alcohol or viral hepatitis takes a long time to develop and its course often fluctuates. Management requires early collaboration between general practitioners and hepatologists in order to assess the patient's condition and coordinate management long before the question of LT is raised. This type of cooperative and patient-centred strategy should help improve and standardise clinical outcomes.

These issues were addressed by the consensus conferences of 1983 and 1993, which recommended that care and practice should be assessed, and that there should be a restricted number of LT centres with a high level of activity, to improve the competence of the teams involved. These recommendations have not been widely adopted, particularly in France where the number of centres, often with a low level of activity, has risen.

QUESTION 1 - What is the best way of managing patients undergoing transplantation for viral hepatitis?

LT must be considered in patients with viral hepatitis if they develop fulminant hepatitis, decompensated cirrhosis and/or HCC.

Viral hepatitis currently accounts for 20% of indications for LT in France, i.e. about 200-250 LTs per year (not counting LTs for HCC; see question 3). However, as there are no precise epidemiological data, the proportion of patients progressing to end-stage liver failure and/or HCC who are currently offered LT is not known.

At present, advances and limitations in LT for viral hepatitis are mainly governed by advances and limitations in antiviral therapy to control blood viral load.

I. What treatment should be offered to reduce the risk of recurrence of viral hepatitis B in the transplant?

There is no doubt that LT is appropriate in hepatitis B. Medium- and long-term survival is good (75% at 5 years, 63% at 10 years in the European Liver Transplant Registry (ELTR)) (grade C; see Annex 1). The main problem is preventing recurrence in the transplant. The risk of recurrence was about 80% before preventive measures were started and increased with pretransplantation viral load.

I.1. Before transplantation

An attempt should be made to reduce blood viral load to at least $< 10^5$ copies/ml, using lamivudine or adefovir (interferon is contraindicated in decompensated cirrhosis) in all patients with detectable blood viral load (experts' opinion). If blood viral load is $\geq 10^5$ copies/ml, LT may not be appropriate.

Lamivudine or adefovir may improve liver function and avoid LT in some patients, but there is a risk of induction of viral resistance and of escape which is greater with lamivudine than with adefovir (grade C).

Antiviral hepatitis B therapy should be discussed with an LT team before being given to a cirrhotic patient who is a candidate for LT. Long-term antiviral therapies, particularly adefovir, should not be started too early in patients with minor hepatic lesions so as not to induce viral resistance before LT.

I.2. During and after transplantation

Routine administration of high doses of anti-HBs immunoglobulins (HBIg) reduces the risk of recurrence (defined by reappearance of the HBs antigen) (grade C). However, the risk remains high in patients with a blood viral load $>10^5$ copies/mL before LT (grade C) and justifies adding an antiviral. Such preventive treatment should be prescribed in the event of viral replication and considered in its absence (grade C).

Treatment with HBIg and an antiviral should continue for the rest of the patient's life, except when spontaneous anti-HBs seroconversion is suspected (no fall in anti-HBs antibody titre between 2 injections of HBIg).

Discontinuing or reducing HBIg under cover of continued antiviral therapy should not be considered outside randomised trials of sufficient size and duration. The jury recommended that such trials should be carried out as soon as possible because of the very high cost of lifetime treatment with HBIg.

II. What treatment should be offered to reduce the risk of recurrence of viral hepatitis C in the transplant?

The indication for LT in hepatitis C is not compromised by current poor medium- and long-term outcomes compared to better recent short-term results. The poor outcomes are due to:

- relatively early reinfection of the transplant with hepatitis C virus (HCV);
- accelerated development to cirrhosis (10-40% at 5 years), with a subsequent very high risk of progression to decompensated cirrhosis (40% 1 year after diagnosis), and a 10-20% increase in mortality after 5-10 years' follow-up compared with other indications for LT. Survival at 5 years in the ELTR is 62% when cirrhosis is present and 89% in the absence of cirrhosis;
- increasingly old patients and donors.

II.1. Before liver transplantation

Eradication of HCV should be attempted, particularly in patients who have not previously received optimum antiviral therapy.

LT is indicated even in patients who still have a blood viral load after antiviral therapy. There is no upper limit to the acceptable number of copies in patients undergoing LT, but transplant and patient survival are lower when viral load is above rather than below 10^6 copies/ml. Indications for LT are not restricted by viral genotype.

II.2. After liver transplantation

Regular histological examination of the liver is essential.

The best time to treat recurrence of viral hepatitis C seems to be after 1 year (experts' opinion) when lesions with a score $\geq$ A1F1 appear, i.e. lesions that are predictive of a high risk of progression to cirrhosis (grade C). Although no increased risk of rejection has been observed during antiviral therapy, immunosuppression should not be reduced too much during treatment for recurrence of viral hepatitis C (experts' opinion).

The combination of pegylated interferon (IFNp) and ribavirin (at optimum dose with growth factors) achieves a lasting viral response (PCR-confirmed zero blood viral load) in about a third of patients (grade C). If possible, antiviral therapy should be continued for at least 6

months after PCR tests for HCV are negative. If test results are not negative, treatment should be discontinued. Any benefit from adding amantadine has not been assessed after LT.

Increasingly poor outcomes have been observed over the last 3 decades for LT in viral hepatitis C. The reason is not known for certain. It may be related to the higher age of donors, the use of living donors or increased immunosuppressive therapy. Current recommendations are avoiding anti-OKT3 and bolus doses of corticosteroids, reducing corticosteroids slowly, and limiting immunosuppressive therapy to one anticalcineurin (experts' opinion).

Any factors that could aggravate development to cirrhosis (alcohol consumption, smoking, metabolic syndrome) must be reduced (experts' opinion).

III. Can liver transplantation be offered to patients co-infected with human immunodeficiency virus (HIV)?

Viral hepatitis B and C are currently the main cause of death in HIV-infected patients. These patients should be offered preventive measures, screening and treatment.

III.1. Treatment of concomitant infection

Development of hepatitis B lesions may be slowed down with anti-HBV antivirals (interferon, lamivudine, adefovir, tenofovir). The likelihood of a lasting viral response in these patients is lower than in those without concomitant infection. Anti-HBV antiviral use should be warranted and agreed by both the infectious disease consultant and the hepatologist on the basis of the stage of development of both infections, in order to administer each treatment – anti-HBV or anti-HIV antiviral – at the most appropriate time.

Hepatitis C can be cured with a combination of pegylated interferon and ribavirin in about one-third of patients (grade B). In view of current infection patterns and of the much faster development of hepatitis C to cirrhosis in HIV-infected patients (grade C), using LT in co-infected subjects has become a major issue of debate.

III.2. Liver transplantation in patients with concomitant infection

The only available data on LT are from small case series totalling about 200 patients. The main indication for LT was decompensated cirrhosis in rigorously selected patients whose HIV was controlled by highly active anti-retroviral therapy (HAART). Follow-up was short, generally 2-3 years.

For hepatitis B or C, short-term survival does not appear to be any worse in patients with than without concomitant HIV infection (grade C).

In patients infected with both HIV and HCV, HCV viral load and especially the speed of progression of fibrosis are much higher than in non co-infected patients. Hepatitis C is more difficult to treat, and treatment is less effective, than when there is no HIV infection. Specific complications (mitochondrial cytopathies in particular) should be anticipated and tested for. Immunosuppressive therapy should be very carefully adjusted because of major drug interactions with protease inhibitors.

In short, LT seems feasible in very carefully selected patients whose HIV infection is stable, for the same indications as in patients without HIV infection (grade C), provided specific arrangements are available in transplant services, together with increased support and rigorous prospective assessment (experts' opinion). Treatment and follow-up are particularly demanding and make compliance harder. Rehabilitation within the community is likely to be even more difficult than for non co-infected patients.

QUESTION 2 – When is alcoholic cirrhosis an indication for liver transplantation?

In France, alcoholic cirrhosis is the main cause of LT (270 of 850 LTs performed in 2003). According to the ELTR, survival was 83% at 1 year, 72% at 5 years, and 59% at 10 years.

In spite of these results, controversy persists on whether LT is indicated in alcoholic cirrhosis because of the risk of alcoholism relapse after transplantation, and on the duration of abstinence before transplantation. However, existing guidelines all tend to agree that:

- like other forms of cirrhosis, alcoholic cirrhosis is an indication for LT;
- alcoholism should be managed by a multidisciplinary team.

Unless HCC is present, the indications for LT remain limited to complicated cirrhosis (Child-Pugh class C patients) (grade B). LT is not recommended in Child-Pugh class B patients.

Patients should be included on the waiting list for LT on condition that:

(i) pretransplantation tests look for extrahepatic lesions related to alcoholism (or alcoholism and smoking) such as cancer and precancerous states of the ENT, lungs or oesophagus, and such as cardiovascular or respiratory disease;

(ii) alcoholism is managed as early as possible by a specialist team. The team may help the patient withdraw from alcohol, which may improve liver function sufficiently to avoid LT.

Alcohol withdrawal is essential. The pretransplantation period should be used to motivate the patient to give up alcohol. The patient needs to be committed to receiving treatment for alcoholism, which should help to protect them from relapse after transplantation. Six months abstinence before LT (grade B) should no longer be regarded as an inviolable rule and as the mandatory condition for access to LT.

Preventing relapse of alcoholism before and after LT has been neglected too long, and should be a constant concern of the multidisciplinary team. It may be possible to predict relapse from factors such as earliness of onset of alcoholism, family history and difficult socio-economic conditions (grade B). One episode of alcohol resumption does not necessarily constitute relapse. If this happens, a psychiatrist, psychologist or specialist in addiction medicine should assess the episode in order to avoid relapse.

Concomitant hepatitis C (30-40% of alcoholic patients have hepatitis C) is not a contraindication to LT. In such circumstances, LT would require simultaneous care and monitoring for HCV and for alcoholism. The alcoholism needs to be managed, particularly as alcohol is a known factor furthering the development of cirrhosis in patients with hepatitis C.

Drinking plus smoking requires special attention as patients who abstain from alcohol may increase their smoking. Nicotine replacement therapy should be used in these circumstances.

To sum up:

- alcoholic cirrhosis is a good indication for LT;
- it is strongly recommended that patients should be managed by specialists in alcohol addiction as a matter of routine, as the pretransplantation period should be used to establish an alcoholism management plan;
- the post-transplantation period in patients with alcoholic cirrhosis should include supportive care from the whole monitoring team, as for patients with other forms of cirrhosis. It is strongly recommended that a team specialising in alcohol addiction be involved during this period;
- the attitude of society and of health professionals towards alcoholic cirrhosis must change. A patient with alcoholic cirrhosis who is a candidate for LT should systematically be regarded as having two diseases, alcoholism and liver disease, and should therefore routinely be offered treatment for both diseases by a specialist team.

QUESTION 3 – When should liver cancer be treated by liver transplantation?

I. Hepatocellular carcinoma

HCC accounts for 15% of indications for LT in Europe. LT is contraindicated if there are metastases, adenopathy or vascular invasion.

Liver biopsy is not contraindicated in candidates for LT, provided the track of the biopsy needle is protected and patients are carefully selected (experts' opinion):

- single small tumour: Biopsy may provide information on the nature of an isolated small nodule and so reduce false positives. However, there may be difficulty in interpreting findings on the tumour sample and inter-observer variation;
- bulkier tumour: A biopsy can detect poor differentiation or microvascular invasion, which might suggest a poor prognosis. Their presence leads some teams to question the indication for LT. However, this attitude is controversial. The jury suggested that specific studies be carried out in this area.

HCC consisting of a single tumour of <5 cm or 2-3 nodules of <3 cm ("Milan criteria") is the best-validated indication for LT (grade B).

Although LT is the most effective long-term treatment, a single HCC of <2 cm (TNM1) should no longer be regarded as a routine indication for LT other than in a patient with Child-Pugh class C cirrhosis (experts' opinion). The reasons for this are the availability of alternative treatments (i.e. LT as immediate rescue therapy), the risk of false positives, and the shortage of donor organs at a time when the number of patients with a single <2 cm HCC is expected to increase.

In France, 28% of LTs for HCCs are outside the "Milan criteria". It has been estimated that the 5-year survival rate after LT might be 50% in patients with one nodule <6.5 cm or with several nodules with the largest <4.5 cm in diameter and the sum total of all diameters <8 cm (UCSF criteria). The jury recommended that a study be performed to confirm this survival rate and identify any prognostic factors, particularly histological and biological factors. Because of the current shortage of donor organs, this type of LT should only be performed as part of a trial.

The efficacy of treatments habitually given whilst waiting for a LT has not been proven and needs to be assessed.

II. Other cancers

The role of LT in managing malignant tumours other than HCC is unclear because of the large number of histological types, the stages at which management is initiated, and the inadequate design of published studies.

As 5-year survival is at least 50%, LT may be perfomed in the few patients who have hepatoblastoma, epitheloid haemangioendothelioma or metastases of carcinoid tumours (grade C).

LT is contraindicated for metastases of colorectal cancer, pancreatic endocrine tumours and peripheral cholangiocarcinoma as results are poor. Either these tumours can be resected and LT is not relevant, or they cannot be completely removed by partial hepatectomy and LT gives poor results. Hilar cholangiocarcinoma seems to belong to this group. Most teams consider that LT is contraindicated because of the high recurrence rate and the frequency of sepsis-related complications, combined with a shortage of donor organs. A recent paper by the Mayo Clinic has addressed the issue. It concerned a very carefully selected subgroup of patients (n= 28; 2%). LT was used in combination with intensive adjuvant therapy.

QUESTION 4 – When is living donation an alternative?

I. Living donor liver transplantation

Living donor liver transplantation (LDLT) has been developed over recent years as a response to cultural issues (organ donation is not acceptable in some countries because of attitudes to body integrity) and to problems of supply (shortage of donor organs and long waiting lists, leading to some patients dying while on the list).

LDLT accounted for 2.7% of transplantations in Europe (5% in France in 2003). Half of all centres are involved (12 out of 24 in France with an average of 40 LTs/year over the last 3 years).

Owing to differences in context, improved techniques and increasing experience, it is not possible to give a final opinion on LDLT outcomes. The procedure is becoming reliable with survival figures similar to those for cadaver donor liver transplantation (CDLT) in adults, and probably better than CDLT results in children.

There are no specific indications for LDLT. The jury was concerned by high donor morbidity and mortality in Europe. Morbidity is 27% and mortality 0.27% (0.46% when the right liver is harvested, i.e. the part used for LT in adults). It suggested that the activity should be limited to certain centres that have adequate and regular experience.

Contraindications other than those for CDLT are mainly inadequate functional liver volume, in either donor or receiver, and certain anatomical features.

For the donor, liver integrity should be verified (absence of fibrosis or steatosis), together with absence of concomitant morbidity, psychological vulnerability or disabling psychiatric problems. This requires a very rigorous medical examination and a series of interviews to provide complete and well understood information to the prospective donor, in order to obtain his or her freely-given informed consent, in compliance with the provisions of the French bioethics law of 6 August 2004.

The jury emphasised that it is essential to plan long-term medical, psychological and social follow-up for the donor. The Registry kept by the *Établissement français des greffes* (which has become the *Agence de biomédicine* since the consensus conference) in compliance with the law satisfies this requirement and will help establish a long-term estimate of the risks incurred. Such information is currently not available. In the unusual event of the donor experiencing complications, nationwide help should be sought.

In the current state of knowledge, the jury felt that recourse to LDLT should not mean extending the indications for LT, even though it was aware that some teams were eager for extension to HCC.

LDLT is likely to stabilise as a procedure, provided staff and equipment resources are made available to develop or initiate other techniques. For example, the jury regretted that the split and domino methods had not been adequately evaluated. They require better coordination and cooperation between centres with rationalisation of resources, and should be used more widely. The technique of non-heart beating organ donation should be introduced as soon as possible in France in the footsteps of other European countries.

Finally, the jury emphasised its key point, ie resources must be allocated to the provision of information and education for the public and doctors on how to make best use of the possibilities afforded by cadaver organs, which are still clearly underexploited.

II. What other surgical resources are available to alleviate the shortage of liver transplants?

- *Split liver* requires very highly trained surgical teams with full mastery of the technique. It requires sophisticated surgical management and a close collaboration among teams used to working together. Adults who are to receive a left liver graft should be very carefully selected, particularly in relation to weight.
- *Sequential or domino transplantation* is currently used in familial amyloid polyneuropathy, where LT has become the treatment of choice. Explanted livers have caused no symptoms over a period of more than 10 years. Careful monitoring is required as medium- and long-term follow up is insufficient.
- The use of livers from *marginal donors* cannot be accepted in routine practice, but may be useful for transplantation into patients in immediate danger.
- *Non-beating heart organ donation* is not currently permitted in France. It involves restrictive procedures and requires major equipment that can be mobilised rapidly. Despite these problems, the jury recommended that the procedure should be introduced in France as early as possible.

QUESTION 5 – What are the developments with regard to the indications for liver transplantation?

I. How should age affect liver transplantation?

Donors and receivers have become older. In 2003, 15% of patients receiving a liver transplant were over 60 and 4% were over 65. Most of the LTs were performed for cirrhosis (69%) and cancer (20%). The age of patients reaching LT stage for hepatitis C is increasing.

There do not seem to be any problems in using organs from donors aged over 60, except possibly in the case of LT for hepatitis C.

In the absence of concomitant morbidity confirmed by a very thorough medical examination (with particular emphasis on cardiovascular and oncological diseases), it is legitimate to allow transplantation up to the age of 70 (except for patients admitted to intensive care units). There is an approximately 10% excess mortality in the 10 years following LT in patients over 60 compared to those under 60. This is probably due to increased post-transplant morbidity, mainly related to immunosuppressive therapy.

The indications should not be any different from those for younger patients.

II. Liver retransplantation

In France, 10% of LTs are retransplantations.

- Retransplantation is required in acute emergency or emergency situations if the transplanted liver fails to function or malfunctions. Outcomes are 20% poorer than for initial LT.
- Late or “elective” transplantation is required generally for recurrence of the initial disease. In this case, teams have to choose between primary transplantation and retransplantation. The contraindications to retransplantation therefore need to be defined in a flexible manner. The decision to perform retransplantation should be based first on a detailed analysis of the patient’s own wishes, and should include consideration of the patient’s age and the available treatment options for the causes

underlying retransplantation. This is particularly true when the transplant is infected with HCV, where results after retransplantation are not fully known and where the indications should be examined on a case-by-case basis.

III. Indications for multiple organ transplant

Multiple organ transplants, mainly liver and kidney transplants, account for 5% of CDLTs. In France, regional priority is given to patients awaiting a double transplant. However, such routine allocation of priority was criticised in favour of a case-by-case discussion.

LT has a protective effect on the kidney transplant in terms of immunity but the reason for this is not known. There is undoubtedly an indication for liver and kidney transplant in conditions such as primary hyperoxaluria type I or hepatic and renal polycystosis. The issue is less clear for double transplants in cirrhosis. In the case of alcoholic cirrhosis combined with chronic pre-end stage nephropathy, the indication has not been clearly defined. In the context of viral cirrhosis, global survival appears to be no different than for CDLT alone. Hepatorenal syndrome is not an indication for liver and kidney transplant because the renal disorder can be reversed after LT alone.

There is insufficient data to allow proper assessment of the indications for heart-liver, lung-liver or intestine-liver transplants. International cooperation and comprehensive submission of such data to a registry is needed before any recommendations can be made.

Conclusion

The shortage of organ donations and the expansion in indications should not lead to research being directed exclusively to solutions which replace CDLT by ever more complex or restrictive techniques.

Increasingly bold medical and surgical solutions are being proposed, which have reinforced links between people everywhere. This ought to encourage organ donation by individuals in a state of brain death not only out of generosity and compassion but to meet the challenge of "ecological solidarity" between human beings.

We do not have to resign ourselves to a situation where there are not enough organs available for transplantation. French and European examples demonstrate the efficacy of regional and national initiatives in maximising donations. It is only then that extending the indications for liver transplantation can be considered. Using living or non-beating heart donors and split livers could certainly improve the situation, but will never replace the pool of available but unused cadaver organs. A major initiative should be launched to address this issue, with no hesitation in confronting cultural obstacles. The most serious of these obstacles is the paradox of an individualistic society which demands reparative medicine but is hostile to organ harvesting.

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Annex 1.

Table 1. ANAES grading used for clinical trials

Level of published scientific evidence	Grade
Level 1 - Randomised controlled trials of high power - Meta-analyses of randomised controlled trials - Decision analyses based on properly conducted studies	**A:** Established scientific evidence
Level 2 - Randomised controlled trials of low power - Properly conducted non-randomised controlled trials - Cohort studies	**B:** Presumption of scientific foundation
Level 3 - Case-control studies	**C:** Low level of evidence
Level 4 - Comparative studies with major bias - Retrospective studies - Case series	