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The importance of orthotopic liver transplantation in acute hepatic failure

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Abstract Selection of patients with acute hepatic failure for liver transplantation remains difficult, and there is no definite proof of a survival effect. We therefore did a retrospective study in 75 consecutive patients referred over a 12-year period. In two-thirds we identified a cause, mostly viruses or drugs. Patients were grouped by the Clichy and King's College criteria. In 20 there was no indication for transplantation. Of the 5 with autoimmune hepatitis, 3 died, significantly differing from the other 15 ($P=0.009$). The remaining 55 met our criteria, except 1. All 9 patients with absolute contraindications died. Of the 46 enlisted, 7 died without transplantation. One-year survival after transplantation was 69%, compared with 58% by "intention to treat." For patients enlisted, transplantation reduced mortality by 78% ($P=0.069$). The Clichy and King's College criteria reliably predict survival without transplantation, except in autoimmune hepatitis. Our study strongly suggests that transplantation improves survival.

Keywords Acute hepatic failure · Liver transplantation · Survival

Introduction

Acute hepatic failure (AHF) is defined as a syndrome of severe hepatic dysfunction and hepatic encephalopathy in individuals with no evidence of preexisting liver disease. AHF is a medical emergency and the outcome can generally be determined in the first 12–24 h after admission. O'Grady, Schalm, and Williams [13] proposed to divide AHF into three groups, based on differences in clinical features and prognosis. Hyperacute hepatic

failure is the term used to describe patients who develop encephalopathy within 7 days after the onset of jaundice. The most frequent causes are acetaminophen intoxications and acute hemadsorption virus (HAV) or herpes simplex virus (HSV) infections. About one-third of the patients presenting with hyperacute hepatic failure survive without transplantation. AHF includes patients with an interval from jaundice to encephalopathy of 8–28 days. There is a high incidence of cerebral edema in this group, and survival without transplantation is less than 10%. Subacute hepatic failure describes those patients with an interval of 5–12 weeks between the appearance of jaundice and the onset of encephalopathy. Although the frequency of cerebral edema is low, the outcome is also poor, with a survival of approximately 15% [13].

The most frequent causes of AHF are hepatotropic viruses and drugs, but there is a large variety of other etiologic factors. In approximately 30% of all cases, no cause can be identified. Some conditions can be effectively treated by means other than liver transplantation, for instance *N*-acetylcysteine in cases of paracetamol intoxication or portosystemic shunting in Budd-Chiari syndrome. For most other causes of AHF, medical therapy is supportive only, aimed at prevention of complications such as infection and cerebral edema. In general, the mortality of patients with AHF treated without liver transplantation is high and ranges between 60 and 80% [10].

An early and accurate assessment of the individual patient is critical in deciding whether liver transplantation is indicated in the treatment of AHF. To identify patients with hepatitis B-induced AHF who die without liver transplantation, Benhamou and Bernuau have developed the Clichy criteria, which predict which patients could benefit from orthotopic liver transplant (OLT). Patients with hepatic encephalopathy (grade 3–4) and concentrations of coagulation factor V less than 20% in patients in the age group below 30 years and less than 30% in patients in the age group above 30 years die in 80% of all cases [2]. In a retrospective study, Pauwels et al. have found a low predictive value for these criteria in patients with AHF by nonviral causes [15].

O'Grady and Williams have analyzed 588 patients with AHF at King's College Hospital and proposed their criteria for liver transplantation. In acetaminophen-induced AHF, survival correlated with arterial blood pH, peak prothrombin time, serum creatinine, and grade of encephalopathy. In other patients, without hepatitis A or B or idiosyncratic drug reactions, aged less than 10 years or more than 40 years, jaundice for more than 7 days before the onset of encephalopathy, serum bilirubin more than 300 μmol/l, and a prothrombin time more of than 50 s were associated with a poor prognosis [12].

In this study we report the outcome in 75 patients with AHF referred for emergency liver transplantation. We also did a retrospective assessment of the applicability of the Clichy and the King's College criteria, and evaluated the effect of OLT on survival in patients put on the high-urgency waiting list.

Patients and methods

From 1 April 1987 until 1 January 1999, 83 patients with acute liver failure were referred for OLT. Two patients died before the indication for transplantation could be established. Six other patients were not considered suitable candidates because of advanced age ($n=2$), ongoing chronic alcohol abuse ($n=2$), and liver failure secondary to severe nonhepatic disease ($n=2$). These 8 patients were not included in this analysis.

For the remaining 75 patients, emergency liver transplantation was considered. Diagnostic evaluation included routine hematological and biochemical tests, measurement of coagulation parameters, virological and immunological screening, toxicologic and metabolic tests, abdominal ultrasound, and a CT scan of the brain, to assess cerebral edema. Clotting factor V was determined by measurement of prothrombin time in plasma deficient of factor V. Arterial blood was used to determine pH values and lactate levels in patients with acetaminophen-induced AHF. The grade of encephalopathy was assessed using the Opolon criteria [14] and by spectral analysis of the electroencephalogram [16]. All patients with grade 3 or grade 4 encephalopathy were admitted to the ICU. According to protocol they were intubated, ventilated, received antibiotic prophylaxis, and if necessary were treated with intravenous glucose, vasopressive drugs, and mannitol. In each patient the indication for emergency liver transplantation was weighed against absolute or relative contraindications (i.e., extrahepatic infection, sepsis, malignancies, or HIV positivity). Prior to publication of the King's College and Cliichy criteria, the indication was based mainly on clinical judgement. Candidates for emergency liver transplantation were placed on the Eurotransplant high-urgency waiting list after consent was obtained from the nearest relative. Only blood group-compatible donors were accepted. Patients without an indication or not fit for liver transplantation received continuing conservative treatment according to protocol and were reevaluated twice daily until recovery or death.

Twenty patients met neither the Clichy nor the King's College criteria for enlistment (group 1), and in nine patients absolute contraindications for transplantation were present (group 2). Group 3 consisted of 46 patients who were enlisted for emergency liver transplantation, of whom 7 died while waiting for a transplant (group 3a) and 39 underwent orthotopic liver transplantation (group 3b). Three of the seven patients in group 3a were anhepatic at the moment of enlistment after total hepatectomy because of liver trauma. In 3 other group 3 patients, the Clichy criteria could not be applied because no factor V measurement was available. One patient with veno-occlusive disease met only one of the two Clichy criteria and two of the five King's College criteria, but was nevertheless accepted for emergency liver transplantation. Of the other 48 patients, two met only the King's College criteria and nine only the Clichy criteria, while the remaining 37 met both (Table 1). Grade III or grade IV encephalopathy was present in 49 of the 51 group 3 patients that could be evaluated.

Group 1 consisted of 4 men and 16 women with a median age of 41 years (range 17–57 years), group 2 of 6 men and 3 women with a median age of 45 years (27–62), group 3a of 4 men and 3 women with a median age of 40 years (16–55), and group 3b of 15 men and 24 women with a median age of 37 years (16–62). The largest diagnostic categories were acute viral hepatitis ($n=18$), drug-induced

Table 1 Indication for emergency liver transplantation according to the Clichy and King's College criteria. Of the 55 patients considered as candidates for emergency liver transplantation, six are not included. Three were anhepatic at the moment of enlistment and, in another three who did meet the King's College criteria, no factor V measurement was made

		Clichy criteria met	Clichy criteria not met
King's College criteria met	Total	$n=37$	$n=2$
	Hepatitis B	$n=5$	$n=0$
	Other causes	$n=32$	$n=2$
King's College criteria not met	Total	$n=9$	$n=1$
	Hepatitis B	$n=4$	$n=0$
	Other causes	$n=5$	$n=1$

hepatitis ($n=12$), acetaminophen intoxication ($n=11$), autoimmune hepatitis ($n=6$), and acute liver failure of unknown etiology ($n=19$). The other indications were irreparable liver trauma ($n=3$), Wilson's disease ($n=3$), Budd-Chiari syndrome ($n=2$), and acute fatty liver of pregnancy ($n=1$). These data are summarized in Table 2.

For comparisons between groups, Fisher's exact test was used. The effect of liver transplantation on survival in patients put on the high-urgency waiting list was investigated using Cox regression, with transplantation as time-dependent variable. Calculations were done using the Logxact program (1993; CYTEL Software Corporation, Cambridge, Mass., USA).

Results

Follow-up in group 1 patients (no indication, $n=20$), most of whom were sent back to the referring clinician after recovery, is limited to a median of 14 days (range 2–1,859 days). Three of the five patients with autoimmune hepatitis in this group died: one at day 14 after uncontrollable bleeding from a duodenal ulcer, one at day 25 of sepsis as a complication of immunosuppressive treatment, and one at home, at 91 days from admission and after successful treatment of her liver disease, of an unknown cause. No deaths were observed in the 15 patients with other diagnoses ($P=0.009$, Fisher's exact test). All patients in group 2 (absolute contraindictions, $n=9$) died at a median of 2 days (range 0–11) after admission. The main causes of death in this group were irreversible shock and multiorgan failure.

In group 3 (enlisted, $n=46$), 7 patients, including the 3 anhepatic patients, died whilst waiting for transplants at a median of 2 days (range 0–7) after enlistment. Causes of death were cerebral edema in three cases, uncontrollable bleeding in two, and irreversible shock and sepsis in one each. The median stay on the waiting list for the 39 transplanted patients was 1 day (range 0–5 days). The median follow-up in the 27 survivors of transplantation was 2 years and 6 months (range 6 days to 9 years and 6 months), with 23 patients followed up for at least 1 year, 17 for at least 2 years, and 9 for at least 5 years. All but one of the 12 deaths after transplantation occurred within 6 months, at a median of 14 days (range 2–159 days) after enlistment. Death after transplantation was caused by sepsis in 3 patients, by cerebral edema in 2 patients, and by a variety of other causes in 6 patients. The one remaining patient died of a pulmonary malignancy after 6 years and 3 months. The causes of death in the different patient groups are listed in Table 3. The actual survival of transplant patients at 1 years, 2 years, and 5 years was 69% compared with 58% when calculated according to the intention-to-treat principle. Cox regression, comparing mortality of transplanted patients with that of those still on the waiting list, showed a relative death rate of 0.22 (95% confidence interval 0.03–1.47, $P=0.069$).

Discussion

OLT has changed the prognosis of patients with AHF and is recommended when spontaneous recovery appears unlikely. A large US series from the late 1980s and early 1990s showed a 63% 1-year survival after liver transplantation for AHF [4], with a 68% survival at 2 months reported in the largest contemporary European study [5]. In a more recent US multicenter study, the 1-year survival had increased to 76% [17], while in Europe it remained at about 70% [6, 11]. Auxiliary liver transplantation, originally advocated as an alternative therapy for end-stage chronic liver disease [19], has theoretical advantages over the conventional orthotopic procedure and results in an approximately 60% survival [3, 18], but is an accepted treatment for acute liver failure in selected cases only. Other therapies such as artificial hepatic support systems and hepatocyte transplantation are still at an experimental stage or only serve as a bridge to OLT [7, 9].

We describe our single-centre experience with acute liver failure over a 12-year period, which differs from other reports in at least one important aspect. Recently 295 cases seen in 13 centers were reported from the USA [12], with acetaminophen-induced acute liver failure as the most frequent diagnosis. In the UK, acetaminophen even accounts for the majority of cases [1, 14]. Acetaminophen intoxication was the cause of acute liver failure in only 11 of our 75 patients (15%), with only 2, both with an absolute contraindication, meeting the criteria for transplantation.

In our series the Clichy and King's College criteria accurately predicted survival without transplantation for all patients, with the exception of three out of five presenting with acute autoimmune hepatitis, who died of causes not directly related to the primary liver disease. The chance of finding a difference like the one in this study, when in fact the survival in these two subgroups is equal, is less than 1%.

Table 2 Etiology of liver disease and demographics in 75 patients with acute hepatic failure (*AHF*) according to indication and contraindications for liver transplantation. Group 1, criteria not met ($n=20$); group 2, absolute contraindications ($n=9$); group 3a, listed, died on list ($n=7$); group 3b, listed, transplanted ($n=39$) (*NSAID* nonsteroidal anti-inflammatory drug)

Group	Total	1	2	3a	3b
Indication		No	Yes	Yes	Yes
Contraindication			Yes	No	No
Death on waiting list				Yes	No
Total number	75	20	9	7	39
Male/female	29/46	4/16	6/3	4/3	15/24
Age (years)					
Median	39	41	45	40	37
Range	16–62	17–57	27–62	16–55	16–62
Acute viral hepatitis	18	2	4	2	10
Acute hepatitis B	12	1	4		7
Acute hepatitis A	2	1			1
Acute EBV hepatitis	2			1	1
Acute HSV hepatitis	1			1	
Acute hepatitis E	1				1
Drug-induced hepatitis	23	10	3	2	8
Acetaminophen	11	9	2		
NSAID	2			1	1
Ecstasy	2				2
Other drugs	8	1	1	1	5
Other causes	15	6		3	6
Autoimmune hepatitis	6	5			1
Wilson's disease	3				3
Liver trauma	3			3	
Budd-Chiari syndrome	2				2
Acute fatty liver in pregnancy	1	1			
Cause unknown	19	2	2		15

The outcome in the 39 patients who received transplants most probably would have been worse without transplantation than the 69% 1-year survival observed in this group, given the results of our Cox regression analysis and the results of medical treatment reported in the pretransplantation era [8]. Mortality among the patients on the waiting list for emergency liver transplantation and in the postoperative period does, however, remain a serious problem. Most deaths are due to irreversible complications already present at or shortly after enlistment, such as cerebral edema or infection. Of our 46 patients enlisted for emergency liver transplantation, 18 (39%) died on the waiting list ($n=7$) or in the postoperative period ($n=11$). As expected, death in these patients was mainly caused by infections ($n=6$) and by cerebral edema ($n=5$). Various other causes accounted for the remaining 7 deaths. A totally different pattern is seen in patients with contraindications for transplantation, most of whom died of irreversible shock or multiorgan failure.

Our study confirms that, in patients that do meet either the Clichy or the King's College criteria, emergency liver transplantation improves survival, although due to the small number of end points the difference to the patients that died on the waiting list was only of borderline significance. In the group of patients enlisted for emergency liver transplantation, the short-term mortality remains relatively high, but might be improved by measures aimed at preventing cerebral edema and infections. Of special interest might be the outcome in the five patients with acute autoimmune hepatitis without an indication, three of whom died. In acute autoimmune hepatitis, the selection criteria for emergency liver transplantation currently in use appear not be appropriate. In these patients treatment with immunosuppressive drugs seems to be a hazardous course, and a different approach may be warranted. From this retrospective study in a relatively modest number of patients, we conclude that the combined King's College and the Clichy criteria are useful in deciding which patients with acute liver failure will or will not benefit from emergency liver transplantation in most diagnostic categories.

Table 3 Causes of death in 21 patients with acute hepatic failure according to indication and contraindications for liver transplantation. *MOF* multiorgan failure, *MRSA* methicillin-resistant *Staphylococcus aureus*

Group	Total	1	2	3a	3b
Total number	75	20	9	7	39
Number of deaths	31	3	9	7	12
Causes of death					
Irreversible shock/MOF	10		8	1	1
Sepsis	6	1	1	1	3
Cerebral edema	5			3	2
Uncontrollable bleeding	3	1		2	
Aorto-enteral fistula/MRSA	1				1
Veno-occlusive disease	1				1
Primary nonfunctioning graft	1				1
Pneumonia (Legionella)	1				1
Cardiac tamponade	1				1
Unknown	1	1			
Bronchuscarcinoma (late)	1				1

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