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Use and Outcome of Liver Transplantation in Acetaminophen-Induced Acute Liver Failure

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Once defined clinical criteria are fulfilled in acetaminophen-induced hepatotoxicity, prognosis without orthotopic liver transplantation (OLT) may be very poor. In the present study, we examined the application and outcome of OLT in 548 patients admitted to a single center between 1990 and 1996. Four hundred twenty-four (77%) of the patients studied did not fulfill transplantation criteria, and 396 of these (93%) survived. The majority of the 28 nonsurvivors (7%) in this group fulfilled two of three combined criteria, and the finding of a high APACHE III score could be used as an indicator for the need for OLT. Of the 56 patients (45%) not listed, in only a small proportion was this caused by psychiatric reasons, and in the majority, it was a consequence of the rapid development of multiple organ failure and cerebral edema. This also applied to 24 (35%) of the 68 listed patients in whom the rapidity of clinical deterioration, reflected in increasing APACHE III scores, was such that even with the prompt availability of donor organs, OLT was not possible. In the final event, only 44 (35%) of those who fulfilled criteria underwent OLT, of whom 33 (75%) survived to leave the hospital. Survival was greatest in those receiving unreduced grafts, and markers of early graft function differed significantly between survivors and nonsurvivors. Liver transplantation is an effective treatment in a relatively small number of patients with acetaminophen-induced hepatotoxicity, and for a substantial proportion, transplantation was never an option because of the rapidity of clinical deterioration. APACHE III scoring may be of value in decision making and in better defining patients in clinical trials. (HEPATOLOGY 1998;27:1050-1055.)

Acetaminophen-induced hepatotoxicity, usually as a result of deliberate overdose, is now the most common cause of acute liver failure (ALF) in the United Kingdom,[1] and has also recently become so in the United States.[2] Although the development of prognostic criteria[3] has enabled the accurate identification of patients in whom survival without liver transplantation is unlikely, emergency transplantation in this setting is associated with a significant mortality. Preoperatively, the patients are often critically ill with multiple organ failure and severe encephalopathy,[4] the clinical course being such that many deteriorate before grafts become available, allowing only a narrow "window of opportunity" for successful transplantation.[5] Rigorous pretransplantation assessment as undertaken before elective surgery is impossible. The extreme urgency for transplantation may also lead to the acceptance of suboptimal grafts. Furthermore, decisions to proceed with transplantation may have to be taken in the context of a deliberate suicidal attempt, often upon a background of significant mental illness or alcohol abuse.[6] To date, reports of successful transplantation[5,7] in this situation are based on a small numbers of patients. In this article, we describe the use and outcome of orthotopic liver transplantation (OLT) in 548 patients with severe acetaminophen-induced hepatotoxicity. The influence of preoperative clinical and psychiatric status, and intraoperative and graft factors, upon long-term survival is analyzed. We have also examined the clinical features of a subgroup of patients who failed to fulfill transplantation criteria and in whom the outcome proved fatal.[6]

PATIENTS AND METHODS

Five hundred forty-eight patients admitted to King's College Hospital with a diagnosis of severe acetaminophen hepatotoxicity during the period of January 1, 1990, to December 31, 1996, were identified from discharge summaries. The criteria for transfer included a progressive coagulopathy in which the prothrombin time in seconds exceeds the time in hours after overdose, or an international normalized ratio (INR) of >5 at any time, or evidence of metabolic acidosis, hypoglycemia, or renal failure. All patients were managed following a standard protocol as previously published,[8] including the use of intravenous *N*-acetylcysteine at a rate of 150 mg/kg for 24 hours until the INR was <2. Patients were considered for OLT if they fulfilled criteria previously defined[3] with either the concurrent finding of a serum creatinine >300 μmol/L, prothrombin time of >100 seconds, and grade III or IV encephalopathy in patients with a normal pH, or the single finding of a pH <7.3 after adequate fluid replacement. Evidence of irreversible brainstem dysfunction, major inotrope dependence, or culture-positive systemic sepsis resistant to 48 hours of antimicrobial therapy were considered medical contraindications to proceeding with transplantation, as was a history of severe chronic psychiatric disorder or of repeated suicide attempts, dependent on assessment by a psychiatrist and after consultation with the patient's family.

Once the decision for transplantation was made, the patients were registered with the United Kingdom Transplant Support Service and placed on the "super urgent" list. OLT was performed as previously published,[9,10] and, in the present analysis, the three cases who underwent auxiliary transplantation over this period are excluded.[11] With one exception, blood group compatibility was obtained, and, where possible, the organ was matched in size. The first available

Abbreviations: ALF, acute liver failure; OLT, orthotopic liver transplantation; INR, international normalized ratio; AST, aspartate transaminase.

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liver was not used without taking into account size, quality, or blood group compatibility. Livers with moderate steatosis and those requiring size reduction were accepted in patients whose clinical condition was deteriorating rapidly.

Immunosuppression over the period 1990 to 1994 consisted of the triple therapy regimen of corticosteroids, azathioprine, and cyclosporine (n = 28), and, from 1994, a Tacrolimus and low-dose corticosteroid regimen (n = 16). Episodes of acute rejection were treated initially with supplemental high-dose corticosteroids and, if refractory or recurrent, by conversion from cyclosporine to Tacrolimus (cases before 1994).

Variables Analyzed. In patients who fulfilled transplantation criteria, and in those who died without fulfilling criteria, APACHE III scores were determined both on admission to King's College Hospital and at the time OLT criteria were reached. The APACHE III score was also determined at the time of surgery or removal from the transplantation list. The APACHE III score was calculated as previously published,[12] with the additional adoption of a standardized scoring system[4] for the assessment of hepatic encephalopathy dependent on coma grade (grade 1: 3 points; grade 2: 8 points; grade 3: 13 points; grade 4 [without cerebral edema]: 24 points; grade 4 [with cerebral edema]: 33 points). In patients who were having mechanical ventilation, encephalopathy was graded as that present at the time when ventilation had been commenced, except where cerebral edema was present, upon which grade 4 encephalopathy was assumed.

The following parameters relating to the graft were recorded: donor age, sex, weight, cause of death, and graft quality as assessed by surgical inspection and by reperfusion biopsy. Grafts were considered as steatotic if more than 30% of hepatocytes were steatotic. Cold ischemic times were determined, as was the total operating time. Early graft function was assessed by INR value and serum aspartate transaminase (AST) measurements on days 1 and 2 postoperatively.

Statistical Methods. Comparison between groups was made by the Mann-Whitney *U*, χ^2, and Fisher's Exact tests. All tests were two-tailed, and results were considered significant if $P < .05$. Results of $P \leq .15$ are quoted to indicate trends. Data found significant on univariate analysis were entered into a stepwise logistic regression analysis to identify factors associated with diminished survival to hospital discharge. Data were analyzed using Statview, version 4.51 (Abacus Concepts, Berkeley, CA) and SPSS, version 6.1 (SPSS Inc., Chicago, IL).

RESULTS

Of the 548 patients, 424 patients did not fulfill transplantation criteria, and, of these, 396 (93%) survived and 28 (7%) died (Fig. 1). The 124 (23%) who fulfilled transplantation criteria did so because of severe acidosis alone in 75 cases and because of combined criteria in 49. Of these, 68 (55%) were listed for transplantation, and 56 were not listed for various reasons. Of the listed patients, 44 (65%) underwent transplantation, 33 (75%) of whom survived to leave the hospital. Of the 24 listed patients who did not undergo transplantation, 4 (17%) survived. Of the 56 patients who fulfilled criteria but were not listed, 5 (9%) survived.

TABLE 1. Analysis of Admission Clinical and Laboratory Findings in the Subgroup of 28 Patients Who Failed to Fulfill Transplant Criteria But Died, in Comparison With an Age- and Sex-Matched Group of Survivors

	Nonsurvivors	Survivors
n	28	28
Sex	10 M/18 F	10 M/18 F
Age (yr)	35 (16-68)	35 (17-59)
Admission		
APACHE III score	65 (27-113)	32 (24-71)*
pH	7.39 (7.0-7.54)	7.42 (7.3-7.5)
INR	7.35 (2.4-15)	4.25 (1.8-13)†
Bilirubin (μmol/L)	94 (17-311)	93 (35-270)
Creatinine (μmol/L)	179 (66-421)	117 (58-608)
Encephalopathy grade	3 (0-4)	0 (0-3)‡

NOTE: Data given are median (range).
*$P < .0001$; †$P < .006$; ‡$P = .006$.

Patients Who Did Not Reach Transplantation Criteria. Causes of death in the 28 patients who died although not fulfilling criteria were cerebral edema within 5 days of admission in 10 cases, and multiple organ failure related to sepsis in the remainder, occurring at a median of 11 days after admission (range, 3-28 days). On admission, 21 of the 28 patients who died concurrently had two (encephalopathy and prothrombin time) of the three findings required to fulfill the combined criteria for OLT selection. To ascertain whether this subgroup could be identified within the total group of 396 patients who never fulfilled transplantation criteria, the 28 patients were compared with a group of 28 age- and sex-matched patients from within the same series who similarly also failed to meet OLT criteria but who survived (Table 1). Median admission APACHE III scores were significantly higher in the nonsurvivors compared with survivors (median, 65 [27-113] vs. 32 [24-71]; $P = .0001$), and nonsurvivors had higher INR values (7.35 [2.4-15] vs. 4.25 [1.8-13]; $P < .006$) and were more encephalopathic (median, 3 [0-4] vs. 0 [0-3]; $P < .006$). In a stepwise logistic regression of survival to discharge from the hospital, the admission APACHE III score remained an independent determinant ($r = .39$). A cut-off value for an

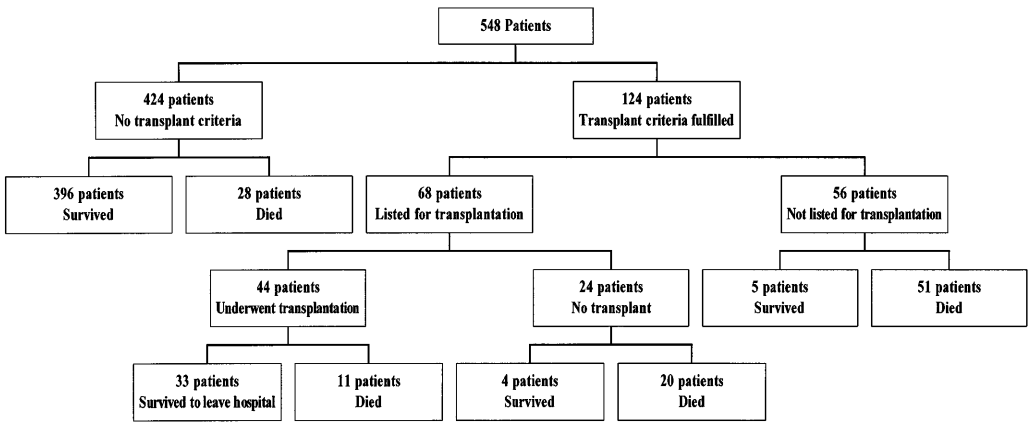

FIG. 1. Outcome of patients admitted with severe acetaminophen-induced hepatotoxicity from 1990 to 1996.

admission APACHE III score of greater than 60 identified 16 of 28 nonsurvivors and 3 of 28 survivors, giving a sensitivity of 57%, specificity of 89%, and positive predictive value of 84%.

Patients Fulfilling Criteria But Not Listed for Transplantation. In 37 (66%) of the 56 patients in this category, the reasons for not listing were a rapidly deteriorating clinical state and hemodynamic instability. This was reflected in a higher median APACHE III score at admission compared with those who were listed: 86 (range, 38-141) versus 71 (35-121) in those listed ($P < .002$), and at the time of fulfilling criteria 92 (52-141) versus 76 (35-121) ($P = .001$). Another reflection of the severity of hepatic and multiple organ failure in these patients was the finding that the majority (30 cases) had fulfilled OLT criteria on a basis of acidosis rather than combined criteria. Indeed, 12 of the 37 patients already had evidence of cerebral edema on admission as compared with 11 of 68 patients who were listed.

Of the other 19 patients fulfilling criteria, 4 were not listed because of advanced age (median age, 70 years) and significant comorbid medical conditions. None of these patients survived.

The remaining 15 patients (27%) were not listed for predominately psychiatric considerations. Median APACHE III scores and encephalopathy grade at admission and at the time of fulfilling criteria were comparable with the 68 cases who were listed (Table 2) (median criteria APACHE III score 79 [53-128] vs. 76 [35-121]) and encephalopathy grade 3 [0-4] vs. 3 [0-4]). Thirteen of the 15 patients had a background of documented psychiatric illness, compared with 19 of 68 listed ($P < .0001$), and 11 of 15 versus 19 of 68 were receiving psychotropic medication. Two of the 15 patients had a history of schizophrenia, and 11 had a history of severe depression. Nine had at least one documented previous inpatient admission for psychiatric illness, compared with 2 of 68 listed ($P < 10^{-6}$), and 12 had a history of one or more previous suicide attempts, compared with 19 of 68 listed ($P < .0005$). Six patients had taken their overdose while undergoing in-patient psychiatric treatment. One of the 15 patients in this subgroup survived to leave the hospital.

TABLE 2. Comparison of Patients Listed for Transplantation With Those Not Listed Because of Psychiatric Illness

	Not Listed	Listed
n	15	68
Sex	5 M/10 F	21 M/47 M
Age (yr)	41 (28-56)	29 (14-51)*
Previous psychiatric illness (n)	13	19*
Previous psychiatric hospitalization (n)	9	2†
Previous overdoses (n)	12	19‡
Current psychotropic medication (n)	11	19*
Alcohol (units/wk)	40 (0-120)	20 (0-120)
Criteria		
APACHE III score	79 (53-128)	76 (35-121)
Encephalopathy grade	3 (0-4)	3 (0-4)

NOTE: Data given are patient numbers or median (range).
*$P < .0001$; †$P < 10^{-6}$; ‡$P < .0005$.

Patients Listed But Not Transplanted. Of the 68 patients listed for transplantation, 24 were not transplanted. In 22 of the latter subgroup, this was due to clinical deterioration with one or more major medical contraindications being present. Four (17%) of these patients survived. Median time from listing to removal from the transplantation list was 26 (10-100) hours compared with 24 (6-63) hours ($P = .27$) to transplantation in those who underwent OLT. In a further 2 patients who were not transplanted, clinical improvement occurred, as evidenced by the cardiorespiratory parameters and a falling INR; 1 of these patients survived. At the time of fulfilling transplantation criteria, the median APACHE III score in the 22 cases who deteriorated was similar to those who underwent OLT (78 [54-115] vs. 73 [35-121]; $P = .33$), although the increase was greater in those cases who were not transplanted. At the time of removal from the list, the median score in the 24 cases was 103 (68-136) compared with 82 (35-121) ($P < .002$) immediately before surgery in the 44 patients transplanted (Fig. 2).

Of the 24 patients who fulfilled criteria and were listed but not transplanted, 4 (17%) survived, and of the 56 not listed after fulfilling criteria, 5 (9%) survived. In those patients who fulfilled OLT criteria but were not transplanted, there were 71 deaths, 33 as a result of cerebral edema with or without multiple organ failure at a median of 4 days following admission, and multiple organ failure alone in 34 cases at a median of 5 days. Four cases had abrupt dysrhythmias with cardiac arrest within 1 day of admission.

To examine those factors influencing outcome in patients who met OLT criteria but were not transplanted, we analyzed possible factors influencing survival in the group of 65 patients made up of those who were not listed because of clinical deterioration (n = 41), and those who were listed but did not undergo OLT for the same reason (n = 24) (Table 3). The 8 survivors were less acidotic on admission ($P < .005$) than the 57 (88%) who died, and admission APACHE III scores were lower (median, 64 [37-109] vs. 86 [25-141]; $P < .04$). More survivors fulfilled combined rather than acidosis criteria ($P < .02$), and at time of fulfilling criteria, APACHE III scores tended to be lower in survivors than nonsurvivors (median, 77 [55-109] vs. 93 [52-141]; $P = .066$).

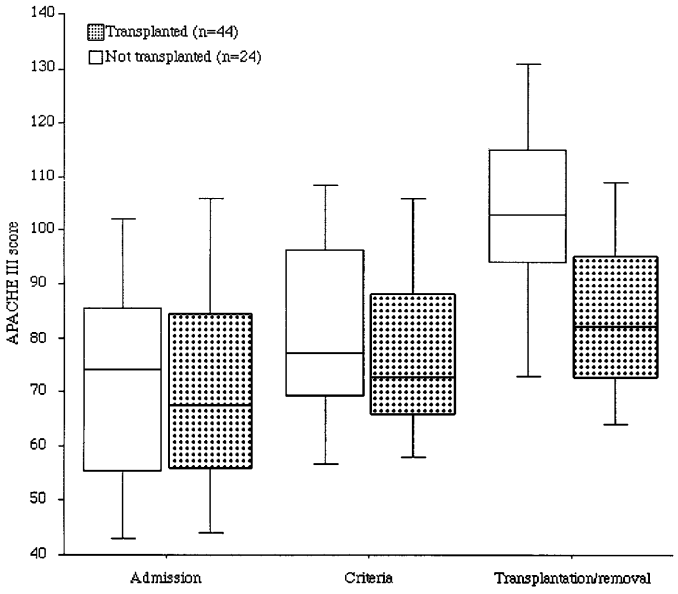

FIG. 2. APACHE III scores in patients listed for transplantation. Box plot shows 10th, 25th, 50th (median), 75th, and 90th centiles of APACHE III scores determined in patients listed for transplantation at admission, at the time transplantation criteria were fulfilled, and at the time of surgery or removal from the transplantation list.

Cases Transplanted and Outcome. The 44 patients who underwent liver transplantation (35 women and 12 men) had a median APACHE III score immediately before surgery of 83 (35-121), and the median encephalopathy grade was 4. Twenty (45%) had exhibited signs of cerebral edema immediately before surgery. Thirty-six patients received a whole graft, 8 received a reduced graft, and all but one graft was ABO-compatible.

Thirty-three patients survived to leave the hospital (75%). The median duration of hospital stay was 40 days (22-76 days). Twenty-nine (66%) are currently alive with a median follow-up of 37 months (range, 1-72 months). Seven died within 2 weeks of transplantation: one of brain death caused by intraoperative cerebral edema, one of multiple organ failure following primary graft nonfunction, two of sepsis and multiple organ failure, two following intracranial hemorrhage, and one following a catastrophic intra-abdominal hemorrhage. Three died of sepsis between 2 weeks and 3 months following transplantation. One patient died at 120 days following retransplantation for chronic rejection.

Comparison between survivors and nonsurvivors showed no significant differences in terms of age or sex, median APACHE III scores at the time of admission, or when fulfilling OLT criteria, or immediately before surgery (Table 4), or in the time from listing to transplantation (Table 5). Patients receiving reduced-size grafts had poorer survival ($P < .03$), while poor graft quality (n = 7), as assessed by intraoperative inspection or reperfusion biopsy, was not associated with a poorer outcome (Table 5). Measures of early graft function showed nonsurvivors of transplantation to have significantly higher serum AST (day 1: $P < .03$; day 2: $P < .04$) and INR (days 1 and 2: $P < .03$) (Table 5).

Three (6%) patients underwent retransplantation, one at 15 days after the original transplantation for graft nonfunction, one for intractable chronic rejection at 110 days, and the third patient at day 165 following hepatic artery thrombosis. The first two patients died at days 35 and 10, respectively, post–second transplantation from sepsis-related complications, and the third is alive and well at time of writing (follow-up, 36 months).

Psychiatric Follow-up. Four (12%) of the 33 transplanted patients who survived to leave the hospital died as a result of deliberate self-harm at a median of 8 months following transplantation. Two took further overdoses, 1 committed suicide by violent means, and 1 died as a result of graft failure secondary to deliberate noncompliance. Only one of the patients who committed suicide had a history of severe depression preoperatively, and none had previously had psychiatric hospitalization. Following discharge from the hospital, 2 patients have had recurrent psychiatric hospitalizations, and 10 remain under long-term psychiatric or psychotherapeutic follow-up. Sixteen patients are currently employed or in full-time education, 9 are unemployed, 3 are homemakers, and 1 patient is lost to follow-up.

TABLE 3. Analysis of Admission Findings of the 65 Patients Who Fulfilled Transplant Criteria But Were Not Transplanted, in Relation to Eventual Outcome

	Survivors	Nonsurvivors
n	8	57
Sex	6 F/2 M	30 F/27 M
Age (yr)	28 (18-36)	35 (14-76)
Hours to referral	33 (22-62)	48 (20-100)
APACHE III score	63 (37-109)	85 (25-141)*
pH	7.44 (6.96-7.5)	7.25 (6.96-7.46)†
INR	6.5 (2.3-11.6)	8.5 (2.2-15)
Bilirubin (μmol/L)	79 (29-203)	81 (23-236)
Creatinine (μmol/L)	203 (97-507)	298 (57-721)
Encephalopathy grade	3 (1-4)	3 (0-4)
Cerebral edema (%)	2 (25)	18 (31)
Number fulfilling acidosis transplant criteria (n)	2	41‡

NOTE. Data given are patient numbers (n) or median (range).
*$P < .04$; †$P < .005$; ‡$P < .02$.

TABLE 4. Analysis of Preoperative Clinical and Laboratory Findings in the 44 Patients Transplanted With Respect to Successful Outcome

	Survivors	Nonsurvivors
n	33	11
Sex (M/F)	10 M/23 F	1 M/10 F
Age (yr)	29 (14-50)	24 (716-37)
On admission		
APACHE III score	67 (31-121)	68 (38-111)
pH	7.34 (7.05-7.383)	7.27 (7.09-7.45)
Creatinine (μmol/L)	290 (57-563)	253 (131-709)
INR	8.5 (3.3-15)	8.6 (5-15)
Cerebral edema (%)	4 (12)	1 (9)
Immediately before OLT		
APACHE III	81 (35-121)	82 (53-108)
pH	7.35 (7.094-7.47)	7.34 (7.08-7.45)
Creatinine (μmol/L)	332 (77-570)	264 (112-700)
Bilirubin (μmol/L)	106 (30-364)	94 (43-121)
Cerebral edema (%)	16 (48)	5 (45)

DISCUSSION

The majority of patients in this series admitted with severe hepatotoxicity from acetaminophen overdose did not fulfill transplantation criteria, and 93% of these patients survived with medical management alone. In contrast, of those who did fulfill OLT criteria, a substantial proportion (30%) were already too ill from multiple organ failure at the time criteria were fulfilled for transplantation to be considered, and, not surprisingly, survival in this group was poor. The rapidity of clinical deterioration in those patients who were listed for transplantation was such that, even with the availability of appropriate grafts for most patients within 24 hours, 30%

TABLE 5. Analysis of Operative and Postoperative Clinical and Laboratory Findings in the 44 Patients Transplanted With Respect to Successful Outcome

	Survivors	Nonsurvivors
n	33	11
Time from listing to OLT (hr)	24 (6-63)	24 (6-40)
Donor age (yr)	46 (14-67)	42 (14-52)
Cold ischemic time (hr)	8.5 (4-13)	11 (2-13)
Whole graft (n)	30	6
Reduced graft (n)	3	5*
Steatotic graft (n)	4	3
Day 1 postoperative		
AST (IU/l)	896 (258-2,976)	2,119 (498-4,760)*
INR	1.7 (1.1-2.7)	2.1 (1.4-4)*
Day 2 postoperative		
AST (IU/l)	350 (104-1,363)	991 (116-3,450)†
INR	1.44 (0.9-2)	2.1 (1-6.2)*

*$P < .03$; †$P < .04$.

became too ill for transplantation, and, in the event, only 35% of those fulfilling criteria were finally transplanted. The factors responsible for the more rapid progression of multiple organ failure in some of the patients listed remain unclear. At the time criteria were fulfilled, there appeared little to distinguish this group from those whose disease course was such that transplantation remained an option.

This study confirms the previously reported sensitivity (72%), specificity (98%), and positive predictive value (89%) of the criteria[3] used to identify those patients with a poor prognosis who need transplantation. The particularly poor prognosis of cases with a systemic acidosis was also confirmed. In the patients in whom criteria were not fulfilled, survival was 97%, but identification of the small subgroup (28 cases) who did badly proved difficult. A significant proportion fulfilled two of the three combined criteria for OLT, but few reached the cut-off value of a serum creatinine >300 μmol/L for the third criterion.

By using APACHE III scores with a cut-off value of >60, 16 of 28 nonsurvivors would have been identified with a sensitivity of 57%, specificity of 89%, and positive predictive value of 84%, and its additional use in those cases fulfilling two but not three criteria may be of significant benefit. Although the APACHE III scoring system has not been widely applied in liver disease, its adoption in general intensive care systems has the potential to considerably improve the accuracy of clinical judgments on likely patient mortality. Recent studies in chronic[13] and acute[4] liver failure have demonstrated its usefulness in the assessment of severity of illness and prediction of mortality. Although the APACHE III system does not include direct measures of hepatic function such as INR or factor V levels as variables in its determination, in acetaminophen-induced ALF, the effects of the associated multisystem illness may have a more important influence on prognosis than the severity of liver failure itself.[4] Indeed, patients with a significant isolated coagulopathy may require only a short period of supportive intensive care before recovery, and in those patients who fulfill transplantation criteria, some specific measures of liver damage (e.g., prothrombin time) may even be improving at the time of transplantation.[4] As shown in the present series, serial estimation of APACHE III scores can provide a quantitative estimate of the rate of clinical deterioration, and may be of value in the difficult decisions of listing and appropriateness for transplantation. In acetaminophen-induced ALF, as with critical illness of other etiologies, scoring systems such as the APACHE III also have potential uses in clinical research including the stratification of patient groups in clinical trials, and in further defining the relationship between multiple organ failure and the clinical manifestations and severity of the underlying liver injury. The application of pretransplantation hepatectomy,[14] or the use of bioartificial liver-assist devices,[15] might be best targeted to those patients in whom a particularly rapid progression of multiple organ failure has been identified in this way.

Although acetaminophen overdose may be an impulsive act, a recent study has indicated that there is often a background of severe mental illness or alcohol or drug dependency. In the majority of severely poisoned patients, this represents a true suicidal attempt.[6] It has been assumed that such a psychiatric background would lead to poor compliance with postoperative drug regimens and the risk of further suicide attempts. Considerable difficulties are encountered in the psychiatric assessment of these patients given the rapid progression of their illness and the fact that the majority are encephalopathic from the time of admission. Thus, much of the decision making must involve difficult subjective judgments by the clinicians involved in the patient's care. The present findings show that the proportion of patients considered to have psychiatric contraindications is small, and that in the group that was transplanted, many of the patients clearly had significant psychiatric illness. The occurrence of further and successful suicide attempts is also shown, though its rate remains relatively low. The majority of those patients transplanted are now either in work or education, but the frequency of significant long-term psychiatric problems in this patient group means that planned psychiatric follow-up in these patients is essential.

A previous study in 21 patients who underwent OLT at King's College Hospital as a result of acetaminophen overdose during the period between 1984 and 1992 examined the effects of immediate pretransplantation clinical status on 2-month mortality[4] and demonstrated that pretransplantation APACHE III scores and total serum bilirubin differed significantly between survivors and nonsurvivors, with the pretransplantation APACHE III score remaining significant on multivariate analysis in determining survival. This is in contrast to our study, in which there were no significant differences between survivors and nonsurvivors in any of these preoperative variables at the time of transplantation. The most likely explanations for this apparent inconsistency include the influence of graft factors, including graft reduction, in determining outcome, and more frequently, the removal from the waiting list of those patients with a deteriorating clinical condition, in whom transplantation is judged to be inappropriate in the light of increased experience of such patients.

In elective transplantation, the use of steatotic grafts[16] or grafts from elderly donors,[17] and, in emergency transplantation, reduced-size grafts,[18] has been associated with diminished early patient and graft survival, and the same is likely to apply to emergency transplantation in acetaminophen-induced ALF. Our practice is to avoid the use of suboptimal livers whenever possible; however, livers with moderate steatosis or those requiring size reduction were accepted in 16 patients whose clinical condition necessitated immediate transplantation. This is in contrast to the recent experience of Hôpital Paul Brousse[18] of 116 patients who underwent transplantation for fulminant hepatitis of varying etiologies using the first available graft, regardless of the above factors. Patients with ALF from acetaminophen hepatotoxicity have a more severe and rapidly progressive multiorgan illness than those whose ALF is caused by other etiologies,[4] but our practice resulted in a survival rate similar to that of the Paul Brousse series in those who are transplanted (1-year survival [including suicides] 66% vs. 68%) and with a lower retransplantation rate (7% vs. 18%). However, over a comparable time period, an increased proportion of our patients died while awaiting a graft; 25 (36%) of 68 listed patients died compared with 22 (19%) of the 116 Paul Brousse patients. In common with the French group, we have found that the use of reduced grafts was associated with lower patient survival, but that no effect of using steatotic grafts was detectable, probably as a consequence of the small numbers involved. Postoperatively, the serum AST and INR differed significantly between survivors and nonsurvivors; these data emphasize

the importance of early graft function on patient survival. In such critically ill patients, early graft dysfunction after the use of inferior organs is likely to predispose to the development of sepsis and be associated with a substantially increased mortality. A difficult balance must therefore be struck between the risk of delaying transplantation until an appropriate graft is available, with the likelihood of further deterioration before that time, and the acceptance of suboptimal grafts that may be associated with a poorer outcome.

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