# Serious paracetamol poisoning and the results of liver transplantation

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**Abstract**

**Paracetamol poisoning is the most common cause of fulminant liver failure in the United Kingdom. An accurate assessment of prognosis at the time of referral will allow the appropriate application of liver transplantation in this setting. The outcome of 92 patients consecutively admitted to a specialist liver unit with severe poisoning has been examined. In patients who did not have a transplant, a fatal outcome was seen for 26/82 (32%), and was associated with late presentation, coma grade, prothrombin time prolongation, metabolic acidosis, and renal dysfunction. Cerebral oedema, and sepsis were responsible for most deaths. Prognostic criteria defined at King's College Hospital seemed to predict the outcome of patients who did not have a transplant managed on the Birmingham liver unit. Seventeen patients were listed for transplantation, 10 had liver transplantation, and seven of 10 survived. Seven were listed but not transplanted, and one of seven survived. Psychological rehabilitation of patients who had a transplant has not proved difficult. These results suggest a role for liver transplantation in the management of selected patients with paracetamol poisoning.**

(*Gut* 1994; 35: 809–814)

Paracetamol poisoning is the most common cause of fulminant liver failure in the United Kingdom.[1] Most patients present early after paracetamol poisoning,[2] and are effectively treated with N-acetylcysteine.[3] Late presentation is commonly associated with the development of liver damage, and may be complicated by significant nephrotoxicity. An analysis of patients presenting to King's College Hospital (KCH) liver unit (between 1973 and 1985)[4] suggested that the prognosis of patients with severe hepatotoxicity had improved, and that this improvement was independent of specific treatment used by that unit during this period. More recently, 'late' administration of N-acetylcysteine – that is, a period greater than 12 hours elapsed from poisoning to treatment – has been shown to improve the outcome of patients with paracetamol induced fulminant hepatic failure.[5 6]

Fulminant hepatic failure is now a common indication for liver transplantation,[7] and transplantation may also improve the prognosis of selected patients with paracetamol induced hepatotoxicity.[8] The appropriate application of liver transplantation in this setting requires an early and accurate assessment of prognosis. Factors predicting the outcome of patients treated at KCH have been defined.[1 9 10] Advanced coma grade, acidosis, severe and sustained coagulopathy, and renal dysfunction are features that identified patients with a poor prognosis. Potential problems with psychological rehabilitation should also be anticipated, and will influence the selection of patients for transplantation. Many patients have a history of impulsive and self-destructive behaviour. The longterm prognosis of such patients with respect to both repeated self-harm and compliance with treatment is uncertain.

We have undertaken a retrospective analysis of patients treated for paracetamol poisoning in the Birmingham Queen Elizabeth Hospital liver unit. The association of selected clinical features and laboratory results with patient outcome were examined. Prognostic criteria defined at KCH were assessed in non-transplanted patients treated on the Birmingham liver unit.

We report the short term results of liver transplantation for this indication. Successful longterm rehabilitation of survivors of transplantation is also described.

## Patients and methods

Ninety two patients (51 female) with serious paracetamol toxicity were admitted to the Queen Elizabeth Hospital liver unit between 1 September 1990 and 30 March 1992. These patients represent a few of those whose condition and prognosis had been discussed with physicians on the unit, and they were selected for transfer on the basis of the severity of liver dysfunction or associated complications, or both. Transfer to the liver unit was generally recommended (a) if the prothrombin time (measured in seconds) at the time of referral was numerically greater than the interval (measured in hours) from poisoning to the time of referral, (b) if the prothrombin time was in excess of 50 seconds, (c) if metabolic acidosis was confirmed at presentation, and (d) for all patients with established encephalopathy.

Referring units were generally advised to intubate and ventilate patients with advanced hepatic coma before transfer. Patients progressing to grade 3 coma after transfer were paralysed, seated, intubated, and ventilated. Central venous lines were inserted in all patients with significant hepatic or renal dysfunction. Pulmonary artery floatation

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Accepted for publication 11 October 1993

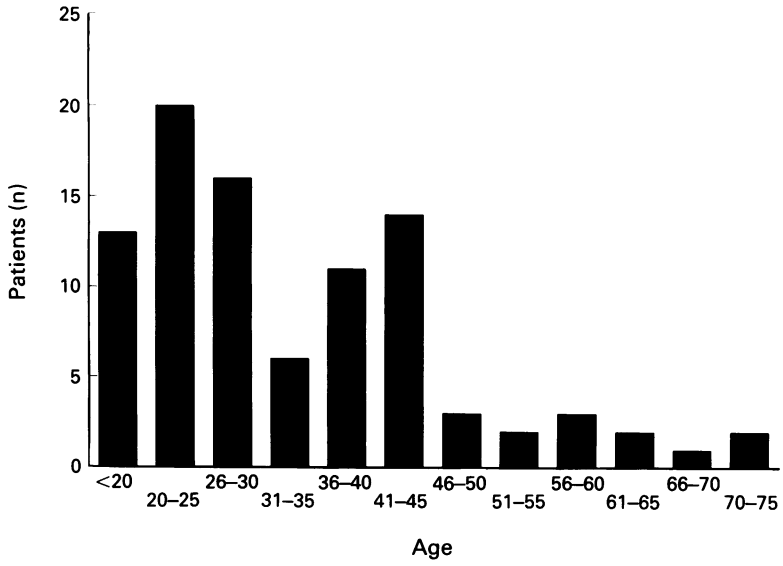


*Figure 1: Age of patients at presentation showing bimodal distribution*

catheters were inserted if arterial hypotension persisted despite adequate blood volume expansion, and continuous arteriovenous haemodialysis (CAVHD) by a peripheral shunt was established immediately in oliguric patients. Episodes of raised intracranial pressure were treated by hyperventilation and intravenous mannitol. Thiopentone infusion was used for patients with refractory intracranial hypertension. All patients received $H_2$ receptor blockers. Antibiotic prophylaxis was not routinely used. When sepsis was either proved or suspected, antibiotics were started immediately after sampling of specimens for microbiological culture. Treatment with N-acetylcysteine was not started on the liver unit, but in many cases infusion had been commenced at the referring hospital. In these cases, the recommended infusion schedule was completed on the liver unit.

The median age of the 92 referred patients was 29 years (range 14–74, 51 female) with a bimodal distribution (Fig 1). Thirteen patients had a history of previous parasuicide, and five of multiple previous suicide attempts. Sixteen had serious premorbid psychiatric disease (including longstanding depression and alcoholism). In 36 cases the paracetamol overdose was clearly an impulsive act, precipitated most commonly by relationship or financial problems. In most cases, however, no clear single precipitating event could be identified.

*Statistical analysis* – data are expressed as median (range). Statistical comparison between groups was made by Wilcoxon rank sum test and $\chi^2$ test with Yates's correction where appropriate.

## Results

### CONDITION AT PRESENTATION AND MANAGEMENT BEFORE REFERRAL

The median interval from the time of poisoning to presentation for the 92 patients was 19 hours (range 9–59). The median interval from poisoning to presentation in 10 patients who subsequently had liver transplantation was 27 hours (17–43), and in non-transplanted patients was 18 hours (9–59). Non-transplanted patients who subsequently died presented significantly later than those who survived to be discharged from hospital ($p=0\cdot01$) (Table I).

Seven patients presented early (within 12 hours of poisoning), but four of these were not treated with N-acetylcysteine. The three treated patients experienced significant hepatotoxicity but survived. Two untreated patients subsequently died, and two survived. Two of four untreated patients had measured plasma paracetamol concentrations below the recommended treatment threshold (at five and nine hours respectively) and one subsequently died. There was trend towards improved outcome in those patients treated at presentation with N-acetylcysteine (mortality in treated patients 24%, in untreated patients 42%, $p=0\cdot1$).

Table I shows the laboratory results at the time of presentation. Many patients had established liver failure with encephalopathy at the time of presentation, and prothrombin time prolongation at the time of presentation was significantly associated with ultimate patient outcome ($p<0\cdot05$).

Arterial pH was measured in only 24 patients at the time of initial presentation. Four of these 24 patients subsequently had liver transplantation, and all were severely acidotic at the time of presentation. The presence of acidosis directly influenced their candidature for transplantation. The prognosis of the 20 non-transplanted patients is possibly related to arterial pH at presentation ($p=0\cdot1$). In this group of 20 patients, an arterial pH<7·30 had a predictive value (for subsequent death) of about 90%.

TABLE I *Clinical and laboratory data of 92 consecutive admissions with paracetamol poisoning*

| | *All patients (92)* | *Transplants (10)* | *Non-transplants* | | |
|---|---|---|---|---|---|
| | | | *Alive (56)* | *Dead (26)* | |
| Interval (h) | | | | | |
| OD-presentation | 19 (9–59) [48] | 27 (17–43) [6] | 17 (9–59) [31]* | 24 (16–54) [11]* | *p=0·01 |
| OD-liver unit | 62 (24–107) [53] | 53 (26–70) [7] | 62 (24–107) [33] | 56 (29–91) [13] | NS |
| Presentation | | | | | |
| PT | 52 (14–180) [45] | 54 (29–120) [7] | 47 (14–101) [23]* | 80 (24–180) [15]* | *p<0·05 |
| pH | 7·29 (6·90–7·47) [24] | 6·90–7·16 [4] | 7·37 (7·12–7·47) [8] | 7·26 (6·90–7·46) [12] | p=0·1 |
| Creatinine | 196 (65–517) [21] | 156–304 [3] | 316 (65–157) [9] | 172 (90–379) [9] | NS |
| QE admission | | | | | |
| PT | 61 (18–180) [87] | 71 (48–125) [10] | 58 (18–159) [54] | 56 (33–180) [23] | NS |
| pH | 7·47 (7·18–7·58) [32] | 7·18–7·38 [3] | 7·47 (7·32–7·58) [23] | 7·45 (7·38–7·48) [6] | p=0·08 |
| Creatinine | 147 (62–933) [83] | 274 (78–446) [10] | 115 (62–933) [52]* | 263 (85–593) [21]* | *p=0·001 |

*For non-transplanted alive *v* dead; [ ] number of observations; OD=overdose; PT=prothrombin time.

TABLE II *Association of peak prothrombin time (PT) and peak serum creatinine with outcome in non-transplanted patients*

| Peak PT | <50 | 50–100 | 100–150 | >150 |
|---|---|---|---|---|
| Dead | 0 | 7 | 11 | 8 |
| Alive | 9 | 28 | 14 | 5 |
| Peak creatinine (mcmol/l) | | <150 | 150–300 | >300 |
| Dead | | 0 | 3 | 21 |
| Alive | | 25 | 10 | 17 |

Twelve (60%) of these 20 non-transplanted patients died. The overall mortality of the 82 non-transplanted patients was only 32% (26/82), which is significantly less than the mortality seen in these 20 patients who had arterial pH measured at presentation. It is probable that arterial pH is more likely to be measured at the time of presentation in those patients with a poorer prognosis.

CONDITION ON TRANSFER AND MANAGEMENT IN THE LIVER UNIT

The median interval from presentation (at the referring centre) until arrival on the liver unit in Birmingham was 36 hours (range 2–71), and from poisoning to arrival was 62 hours (range 24–107).

Sixty three (68%) achieved hospital discharge, and 29 died. Seventeen patients were 'listed' for, and 10 of these subsequently had liver transplantation. Seven transplanted patients survived (median follow up 16 months, range 13–35 months on 1 May 1993). Six patients died on the waiting list, and one patient recovered to be withdrawn from the list (and was eventually discharged). Seventy five patients were not listed for transplantation, and 20 died. Nine of these 20 were excluded from consideration for liver transplantation because of premorbid psychopathology, which we considered would prejudice successful rehabilitation after transplantation. Five patients were considered unfit for transplantation at the time of their arrival on the liver unit (aspiration pneumonitis 4, irreversible cerebral oedema 1), two patients had improving prothrombin times (transplantation felt to be inappropriate), and one patient (74 years of age) was too old to be considered for grafting.

*Non-transplanted patients*

Hepatic coma grade at the time of admission to the liver unit was significantly associated with patient outcome. The mortality of non-transplanted patients admitted with grade 4 coma was in excess of 60% (16/26), and no deaths were seen in 26 patients who were not encephalopathic at the time of admission.

Most patients with severe coagulopathy were given fresh frozen plasma after presentation, before arrival on the liver unit. Admission prothrombin time values were not statistically associated with the outcome of the 82 non-transplanted patients. Peak prothrombin time (measured at any time between presentation and death or discharge) was strongly associated with patient outcome. Stratification of peak prothrombin time values (Table II) shows this association. No deaths were seen in the group with peak prothrombin time <50 seconds, and 62% mortality (8/13) was associated with peak values greater than 150 seconds. Peak prothrombin time >100 seconds was associated with 50% mortality.

Arterial pH values affected by the administration of bicarbonate solutions and by the use of mechanical ventilation have not been included in the following analyses.

Arterial pH values at the time of admission to the liver unit were significantly higher than those recorded at the time of presentation (median 7·47 *v* 7·29, p=0·02) (Table I). Paired values – that is, at presentation and at time of admission to liver unit – were available for eight patients, and pH increased during this interval in 7/8 (Table III).

At least one arterial pH measurement was made for 48/82 non-transplanted patients. An examination of the first arterial pH measurement for each of these patients confirmed that the presence of metabolic acidosis was strongly associated with outcome – mortality 11/13 when pH<7·35. The exact interval from poisoning to measurement of arterial pH was known in only 34 of 82 non-transplanted patients. Most measurements (21/34) were performed at least 48 hours after poisoning. Only four measurements were made within 18 hours of poisoning. Two of these four patients survived – both were acidotic at presentation, and both were treated with N-acetylcysteine.

Renal dysfunction (reflected by raised serum creatinine) at the time of admission to the liver unit was strongly associated with subsequent mortality of non-transplanted patients. Peak serum creatinine was also associated with patient outcome, an association shown by stratification of peak creatinine values (Table II). Fifty per cent mortality was associated with peak serum creatinine greater than 300 mcmol/l, and no mortality was seen when serum creatinine did not exceed 150 mcmol/l.

Thirty one non-transplanted patients required haemodialysis and 18/31 (58%) subsequently died. The mortality among 51 patients who did not require dialysis was only 16% (p<0·01).

Cerebral oedema was the predominant cause of death in non-transplanted patients. Sixteen of 20 patients who died within 10 days of poisoning had cerebral oedema, which was refractory to treatment with mannitol, hyperventilation, and thiopentone. Sepsis, most often pulmonary, was an important

TABLE III *Eight patients had arterial pH measured at both the presenting hospital and on arrival in the liver unit (excluding patients who were ventilated or given bicarbonate)*

| *Patient (age/sex)* | *Presenting pH* | *Liver unit pH* | *Interval* | *Outcome* |
|---|---|---|---|---|
| 28/F | 7·33 (47) | 7·45 (65) | 18 | Dead/non-transplanted |
| 17/M | 7·32 (12) | 7·46 (62) | 50 | Alive/non-transplanted |
| 43/F | 7·35 (38) | 7·50 (74) | 36 | Alive/non-transplanted |
| 21/F | 7·12 (14) | 7·32 (24) | 10 | Alive/non-transplanted |
| 48/M | 6·99 (36) | 7·18 (42) | 6 | Dead/transplanted |
| 50/F | 7·45 (16) | 7·42 (54) | 38 | Dead/non-transplanted |
| 27/F | 7·44 (NK) | 7·48 (NK) | 10 | Dead/non-transplanted |
| 19/F | 6·90 (24) | 7·21 (26) | 2 | Alive/transplanted |

Hours after overdose shown in parentheses; NK=time of overdose not known.

TABLE IV *Sensitivity, specificity, and positive predictive value (PPV) (for the identification of patients who will die of paracetamol poisoning) of KCH prognostic criteria (see reference 1)*

| | *Sensitivity (%)* | *Specificity (%)* | *PPV (%)* |
|---|---|---|---|
| Arterial pH<7·30 (irrespective of coma grade) | | | |
| King's College Hospital | 49 | 99 | 95 |
| Birmingham liver unit | 44 | 97 | 89 |
| Prothrombin time >100 s and creatinine >300 mcmol/l and coma grade 3 or 4 | | | |
| King's College Hospital | 45 | 94 | 67 |
| Birmingham liver unit | 58 | 96 | 87 |

contributory factor to the deaths of six patients who died 10 or more days after poisoning. These six patients died with improving prothrombin times. One patient died (20 days after poisoning) of cerebral haemorrhage complicating intracranial pressure monitor placement.

*Liver transplantation for paracetamol poisoning*

Patients were listed for transplantation when laboratory tests reflected severe hepatic dysfunction in the presence of advanced (grade 3 or 4) or rapidly advancing encephalopathy. Our selection of patients for liver transplantation has been influenced by the published KCH analyses, which examined the outcome of non-transplanted patients with paracetamol poisoning. In addition, patients with a history of repeated self-destructive behaviour were not considered for liver transplantation, but instead received aggressive conservative management. The decision to proceed with liver transplantation was only made when a suitable liver became available. ABO blood group compatible organs were used for all transplanted patients.

In the absence of psychiatric or physical contraindications, 17 patients were thought, at the time of admission, to be suitable candidates for liver transplantation. Ten ultimately underwent transplantation (Table IV), with a median interval from poisoning to transplantation of 79 hours (range 64–98), and from liver unit admission to transplantation of 24 hours (range 10–60). Seven patients were listed but not transplanted, and six of these died (median 98 hours from poisoning to death, 58 hours from admission to death) (Fig 2).

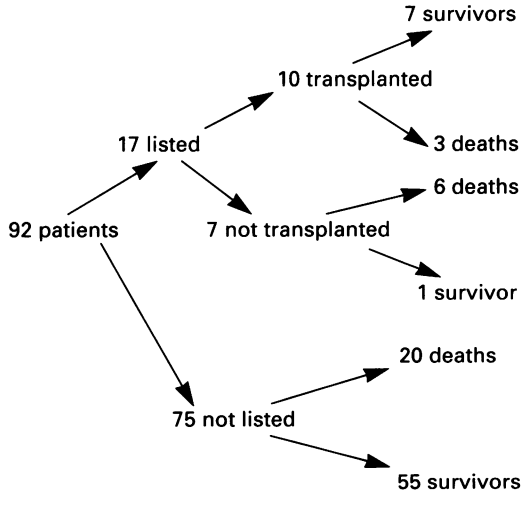


*Figure 2: Management and outcome of 92 consecutive patients admitted to the liver unit with paracetamol poisoning*

Patients listed for transplantation first cleared the psychiatric hurdle. Of 10 transplanted patients, only one had significant premorbid psychiatric disorder (a stable depressive illness treated with lithium, which had been inappropriately discontinued). Paracetamol poisoning in these patients was usually the result of deliberate overdose performed as an impulsive act in response to an identifiable crisis. Although follow up of the seven surviving patients has been brief (range 13–35 months), psychological rehabilitation has not presented unusual difficulty, and none has attempted suicide since transplantation.

Seven of the 10 patients had established renal failure (creatinine greater than 150 mcmol/l) and required haemodialysis before transplantation. CAVHD was initially used in all dialysed patients. Intermittent haemodialysis was later used when patients had become haemodynamically stable in the postoperative period. Five of seven surviving patients required postoperative dialysis for a median period of 26 days (range 5–74 days) until recovery of renal function was seen. No survivor has persisting neurological sequelae to perioperative cerebral swelling.

## Discussion

Paracetamol poisoning is associated with serious hepatotoxicity when patients who have taken a significant overdose are not treated early. Early treatment (before 12 hours have elapsed) with N-acetylcysteine is almost completely successful in averting significant liver damage.[2 3] Increasingly severe toxicity is associated with delayed treatment. Retrospective analysis,[5] then prospective controlled evaluation[6] of patients treated at KCH liver unit suggested that late treatment may also reduce paracetamol induced hepatotoxicity. Analysis of non-transplanted patients in this Birmingham series suggested some benefit from 'late' treatment with N-acetylcysteine. An improved outcome might, however, be related to the timing of presentation with respect to overdose (median interval only 18 hours in treated patients, 24 hours for untreated patients). Conclusions regarding the efficacy of 'late' N-acetylcysteine treatment need not be drawn from this type of retrospective analysis. Based on prospective work performed at KCH,[6] we believe that 'late' treatment is beneficial, and that all patients should be treated at presentation.

Patients receiving early treatment after paracetamol poisoning rarely require referral to a specialist liver unit. Only seven of these 92 consecutive admissions presented within 12 hours of poisoning, and the three treated at presentation with N-acetylcysteine survived to be discharged from hospital. Failure to give this antedote despite early presentation was probably responsible for the subsequent deaths of two patients. N-acetylcysteine is a safe and effective treatment, and such reports

would support a policy of 'treatment for all', at least until the development of significant hepatotoxicity has been excluded (invariably present within 48 hours of poisoning). Such a policy would also provide an opportunity for psychological counselling and intervention.

Most cases of poisoning result from deliberate overdose. Some patients have premorbid psychiatric disturbance, but in most cases the overdose is precipitated by relationship or financial problems. All potential treatment options, including liver transplantation, should be considered for these patients. The mortality seen in patients not undergoing liver transplantation was 32% (26/82). Twenty one patients did not develop hepatic encephalopathy. The mortality seen in patients with fulminant hepatic failure (which by definition requires the presence of encephalopathy) was 41% (25/61). The mortality seen in patients progressing to advanced coma (grade 3 or 4) was 61%. Outcome was clearly related to grade of encephalopathy, both at presentation, and at the time of admission to the liver unit. O'Grady *et al* saw a death rate of 66% in a comparable group of patients with advanced coma admitted to KCH liver unit during a 12 year period.[1]

In an attempt to define those patients who might benefit from the application of innovative treatment, prognostic factors have been defined for patients presenting with paracetamol poisoning. The severity of coagulopathy as reflected by peak prothrombin time,[1] prothrombin time rising on day 4,[9] and admission factor VIII/V ratio[10] were all found to have prognostic value in patients with hepatic coma treated at KCH after paracetamol overdose. Admission factor V values less than 10% of normal also predicted outcome in the same setting.[10]

In patients referred to the Birmingham liver unit, prothrombin times (both presentation and peak values) were significantly higher in non-transplanted patients who subsequently died when compared with those who survived (Tables I and II). Liver unit admission prothrombin time values were frequently affected by the administration of fresh frozen plasma in the referring hospital before transfer, and did not distinguish fatal from non-fatal poisoning. Despite the enthusiasm of some liver units for its measurement,[10 11] factor V values are not routinely measured in patients with fulminant liver failure managed in the Birmingham liver unit.

O'Grady *et al* found that admission (to the liver unit) arterial pH provides important prognostic information irrespective of coma grade.[1] In that retrospective analysis, metabolic acidosis (pH<7·30) had a 95% predictive value for subsequent death. We have seen a fatal outcome for 9/10 patients with an arterial pH<7·30 measured at some time after presentation. Our analysis highlights potential problems in the use of arterial pH measurements to predict outcome. We have shown that arterial pH was more likely to be measured in patients with a bad outcome. The prognostic value of prospectively collected data, with respect to both sensitivity and predictive value, will probably be different. Unfortunately, arterial pH measurement lacks sensitivity (for prediction of subsequent death), and many patients with admission arterial pH>7·30 will subsequently die. Metabolic acidosis seems to be an early and transient phenomenon after paracetamol poisoning. Table III clearly shows the propensity of metabolic acidosis to correct without treatment as illustrated by the paired measurements.

The prognostic value of arterial pH measurement is dependent on the timing of that measurement with respect to the time of poisoning. Because of greater awareness of its prognostic value, arterial pH will be measured more commonly at the time of initial presentation. The extrapolation of the KCH criterion to this early period is probably not justified. For example, arterial pH was recorded within 18 hours of admission in only four of 82 non-transplanted patients in the Birmingham series. Two of these four were acidotic (pH< 7·35) but survived. Both were treated at presentation with N-acetylcysteine. The predictive value of early arterial pH measurements may be significantly less than that defined by O'Grady, and may be influenced by treatment with N-acetylcysteine. Despite these criticisms, persisting – that is, 48 hours – and severe metabolic acidosis has important prognostic value, and may provide an opportunity for early listing for liver transplantation (before the onset of hepatic encephalopathy).

O'Grady *et al* have proposed criteria that can be applied to the selection of patients with paracetamol poisoning for liver transplant-

TABLE V *Characteristics of 10 transplanted patients on admission to the liver unit and before liver transplantation (worst values* recorded at either QE or presenting hospital)*

| | | *Intervals* | | | *QE admission* | | | | *Worst value** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Age/sex* | *Outcome* | *OD-presentation* | *OD-QE* | *QE-transplantation* | *Coma* | *PT* | *pH* | *Creatinine* | *Coma* | *PT* | *pH* | *Creatinine* |
| 38/F | A | 34 | 50 | 48 | 1 | 76* | 7·38 | 319 | 4 | 100 | 7·38 | D |
| 32/M | A | 17 | 68 | 22 | 4 | 102 | Vent | 134 | 4 | 172 | Vent | 154 |
| 19/F | A | 18 | 65 | 14 | 3 | 95 | 7·34 | 114 | 4 | 140 | 7·34 | 114 |
| 31/F | A | NK | NK | 20 | 4 | 66* | Vent | 446 | 4 | 123 | Vent | D |
| 20/F | A | 24 | 53 | 11 | 4 | 88* | Vent | 284 | 4 | 160 | Vent | D |
| 29/M | A | 43 | 70 | 20 | 4 | 48* | Vent | 263 | 4 | 92 | 7·35 | D |
| 19/F | A | 24 | 26 | 43 | 1 | 59 | 7·21 | 126 | 3 | 300 | 6·90 | D |
| 29/M | D | NK | NK | 35 | 4 | 125* | Vent | 423 | 4 | 136 | 7·08 | D |
| 47/M | D | 36 | 41 | 27 | 3 | 62* | 7·18 | 331 | 4 | >120 | 6·99 | D |
| 23/F | D | NK | NK | 60 | 4 | 49* | Vent | 113 | 4 | >120 | 7·16 | 158 |

D=Haemodialysis commenced before liver transplantation; *fresh frozen plasma given by referring hospital before transfer; vent=patient ventilated; NK=time of overdose not known.

ation.[1] We have examined the sensitivity and predictive value of these criteria in forecasting the outcome of the 82 non-transplanted patients admitted to the Birmingham liver unit (Table IV). Both KCH criteria are highly predictive of the outcome of patients managed in the Birmingham liver unit. Seven of 10 transplanted patients also fulfilled these criteria (Table V).

The prospective definition of prognostic criteria and improved patient selection for liver transplantation remain important challenges for hepatologists. The prospective collection of clinical and laboratory data, and a time dependent analysis of these data, may improve the sensitivity and predictive value of patient selection criteria. Transplanted patients (selection usually based on existing criteria) should be excluded from these analyses, as their inclusion simply reinforces, and cannot improve existing prognostic formulas.

Most liver transplant units are convinced that liver transplantation has significantly improved the outcome of selected patients with fulminant hepatic failure. Despite calls for a controlled trial,[12] it seems unlikely that liver transplantation will be submitted to controlled evaluation in the management of patients with life threatening paracetamol toxicity. In the absence of controlled evaluation, the validity of patient selection policies is possibly best reflected by the outcome of those patients who are 'listed' but not transplanted. These patients may either die, or show signs of recovery before the availability of a donor organ. Seventeen patients admitted to the Birmingham liver unit with severe paracetamol poisoning were listed for transplantation. Seven of 10 transplanted patients survived, but only one of seven non-transplanted patients survived to be discharged from hospital ($p<0.05$). Importantly, the interval from listing to death in non-transplanted patients (median 58 hours) was not less than the interval from listing to transplantation (median 24 hours).

The KCH liver unit criteria were prospectively applied in that centre to the selection of suitable transplantation candidates.[8] Twenty nine of 66 consecutive patients had indicators of a poor prognosis. Six of 29 ultimately had liver transplantation, and 4/6 survived. Twenty three were not given a transplant, and only four (17%) survived.

These comparisons indirectly support selection criteria (for liver transplantation) applied to patients referred to Birmingham and KCH with severe paracetamol poisoning.

Some patients are clearly unsuitable for liver transplantation. Patients with serious premorbid psychiatric disease should be managed conservatively. Successful longterm rehabilitation of the patient with a history of repeated self-injury seems unlikely.

Other patients have developed complications that would mitigate against recovery after transplantation. Some complications of liver failure, such as aspiration pneumonitis, are possibly preventable. Patients with advanced hepatic coma should undergo endotracheal intubation before transfer, and should be accompanied by a senior anaesthetist. Liver transplantation could not be considered a treatment option for four patients with aspiration pneumonitis. Three of these four aspirated during transfer from the referring hospital to the liver unit. Experienced liver units should be consulted early, permitting patient transfer before the development of encephalopathy and incipient cerebral oedema.

Liver transplantation is now an important treatment option for selected patients with fulminant liver failure secondary to paracetamol poisoning.

The authors wish to acknowledge the contribution made to the care of these patients by the junior medical and surgical staff, and by the nursing staff working on the liver unit.

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