

# Results of a Prospective Study of Acute Liver Failure at 17 Tertiary Care Centers in the United States

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**Background:** Because acute liver failure is rare, related data have been sparse. Studies have suggested that viral hepatitis is the most common underlying cause of this condition.

**Objective:** To describe the clinical features, presumed causes, and short-term outcomes of acute liver failure.

**Design:** Prospective cohort study.

**Setting:** 17 tertiary care centers participating in the U.S. Acute Liver Failure Study Group.

**Patients:** 308 consecutive patients with acute liver failure, admitted over a 41-month period.

**Measurements:** Detailed clinical and laboratory data collected during hospitalization, including outcome 3 weeks after study admission.

**Results:** 73% of patients were women; median age was 38 years. Acetaminophen overdose was the most common apparent cause of acute liver failure, accounting for 39% of cases. Idiosyncratic drug reactions were the presumptive cause in 13% of cases,

viral hepatitis A and B combined were implicated in 12% of cases, and 17% of cases were of indeterminate cause. Overall patient survival at 3 weeks was 67%. Twenty-nine percent of patients had liver transplantation, and 43% survived without transplantation. Short-term transplant-free survival varied greatly, from 68% for patients with acetaminophen-related liver failure to 25% and 17% for those with other drug reactions and liver failure of indeterminate cause, respectively. Coma grade at admission appeared to be associated with outcome, but age and symptom duration did not.

**Conclusions:** Acetaminophen overdose and idiosyncratic drug reactions have replaced viral hepatitis as the most frequent apparent causes of acute liver failure. Apparent cause and coma grade at admission were associated with outcome. Although transplantation may improve patient survival, it was unavailable or unnecessary for most patients.

*Ann Intern Med.* 2002;137:947-954.

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Acute liver failure is characterized by severe and sudden liver cell dysfunction leading to coagulopathy and hepatic encephalopathy in previously healthy persons with no known underlying liver disease (1). Sometimes termed *fulminant hepatic failure*, acute liver failure is thought to affect approximately 2000 persons per year in the United States (2). This catastrophic illness can rapidly progress to coma and death from cerebral edema and multiorgan dysfunction (2, 3).

Over the past 30 years, the most frequently identified cause of acute liver failure has been viral hepatitis, especially hepatitis B but also hepatitis A and, in tropical populations, hepatitis E (4–8). Smaller numbers of cases have been related to drug-induced liver injury and other causes (9). The frequency of identified causes of acute liver failure has varied greatly worldwide. A very high prevalence of suicidal overdoses of acetaminophen (73%) has been recorded in the United Kingdom (10), and no cases of acetaminophen-related disease have been observed in developing countries (7).

Until recently, only limited data have been available on the cause and outcome of acute liver failure in the United States, presumably because of the relative rarity of the condition, referral patterns in North America, and lack of a centralized data registry (11–14). The U.S. Acute Liver Failure Study Group was formed in 1997 as a consortium of liver centers interested in better defining causes and out-

comes of acute liver failure. The primary aim of the current study was to prospectively describe, with emphasis on the role of transplantation, the causes of acute liver failure and short-term outcomes of patients with this condition who presented to participating liver centers between 1998 and 2001. Our secondary aim was to compare presenting clinical features and liver transplantation in patients with acute liver failure related to acetaminophen hepatotoxicity, other drugs, indeterminate factors, and other causes.

## METHODS

Between January 1998 and May 2001, a 41-month period, 308 patients 15 years of age or older were enrolled from 17 tertiary care liver centers around the United States, all but one of which has a liver transplantation program. The local institutional review board of each center approved the study. All enrolled patients met entry criteria for acute liver failure: the presence of coagulopathy (prothrombin time > 15 seconds or international normalized ratio  $\geq$  1.5) and any hepatic encephalopathy within 26 weeks of the first symptoms without previous underlying liver disease (15). Informed consent was obtained from patients' next of kin before enrollment, according to the guidelines of local institutional review boards. On the basis of records of patients considered for enrollment but ex-

**Context**

Acute liver failure is a catastrophic condition affecting about 2000 persons in the United States each year.

**Contribution**

Among 308 consecutive patients with liver failure admitted to 1 of 17 referral centers between 1998 and 2001, acetaminophen overdose (39%) and idiosyncratic drug reactions (13%) were the most common cause of disease. Sixty-seven percent of patients were still living 3 weeks after presentation (44% without liver transplantation and 23% after transplantation). Survival was associated with cause of liver failure (persons with acetaminophen overdose fared best) and depth of coma at presentation.

**Implications**

Drug toxicities cause most cases of acute liver failure in the United States. Cause and depth of coma at presentation predict patient outcomes.

—The Editors

cluded because of lack of informed consent or other reasons, more than 65% of eligible patients were enrolled.

Under code to protect confidentiality, each center provided detailed demographic, clinical, laboratory, and outcome information for all enrolled patients. Hepatic coma was graded on a standard scale of I to IV, as described elsewhere (1, 2). Etiologic diagnoses, which were made at each study center, were based on accepted diagnostic criteria circulated to all investigators. These criteria involved history; laboratory values; imaging studies; and, in some cases, histopathologic characteristics. Acute liver failure was considered to be of indeterminate cause when extensive clinical, radiographic, and laboratory evaluation (including toxicology screens and serologic markers for viral hepatitis A, B, and C and antinuclear and anti-smooth-muscle antibodies) was inconclusive. Investigators tested and searched for other viruses by using RNA methods as clinically indicated, but these results were not uniformly available. Clinical guidelines for patient management, although determined at each site, were uniform (16).

Candidacy for liver transplantation was determined at individual centers according to the guidelines of the United Network of Organ Sharing. Shortly after patients were admitted to the study, an initial case report form was completed and forwarded to the central study site (University of Texas Southwestern Medical Center, Dallas, Texas). In addition, an outcome case report form detailing the hospital course and final laboratory results not available at admission was completed within 3 weeks of discharge, death, or transplantation. Outcome end points, which were determined 3 weeks after study admission, included liver transplantation, death, and survival without transplantation. Case report forms were checked for missing

values and inconsistencies; queries were sent to the participating centers, and corrections were made at the data coordinating center. All data were then entered into an Access database (Microsoft Corp., Redmond, Washington). Annual site visits by researchers from the data coordinating center confirmed the accuracy of the data.

**Statistical Analysis**

Results are expressed as medians and ranges. Statistical significance was not used in the analysis because the data were descriptive.

**Role of the Funding Sources**

The funding sources had no specific role in the design, conduct, or reporting of the study.

**RESULTS****Demographic Characteristics and Clinical Data**

Of the 308 patients with acute liver failure, 224 (73%) were women. The median age of the group was 38 years (range, 15 to 78 years); women were older than men (39 years vs. 32.5 years). Two hundred twenty-seven patients (74%) were white, 31 (10%) were Hispanic, 29 (9%) were African American, 10 (3%) were Asian, 5 (2%) were Native American, and 6 (2%) were of other ethnic backgrounds. Extensive variation was seen in the median duration of symptoms (6 days [range, 0 to 74 days]) and jaundice (2 days [range, 0 to 61 days]) before encephalopathy onset. Coma grade at study admission was relatively equally distributed (Table 1). Forty percent of patients had a serum creatinine concentration of 177  $\mu\text{mol/L}$  or greater ( $\geq 2.0$  mg/dL), and 14% had acidosis (arterial pH < 7.30). Nearly half of patients (44%) acquired a culture-proven infection. Most patients (260 [84%]) were referred from other hospitals, and the remainder were admitted directly to the tertiary care centers.

**Causes of Acute Liver Failure**

The Figure displays the presumed cause of acute liver failure and the outcome data for all study patients. Acetaminophen overdose was the most commonly implicated reason for acute liver failure, accounting for 120 patients (39%). The median dosage of acetaminophen ingested was 13.2 g/d (range, 2.6 to 75 g/d), and 99 of 120 patients (83%) had ingested more than 4 g/d (the maximum package recommendation). Among these 120 patients, 44 (37%) were considered to have ingested acetaminophen with suicidal intent (single ingestion with suicide attempt admitted) and 68 (57%) had accidental toxicity (many ingestions for pain relief without suicidal intent). In 8 patients (7%), the reason for overdose could not be determined.

Idiosyncratic drug reactions were deemed responsible for another 40 cases of acute liver failure (13%). Hepatitis A and B infection led to 14 cases (4%) and 22 cases (7%), respectively. Presumptive diagnoses of ischemic hepatitis ("shock liver"), autoimmune hepatitis, Wilson disease, and

**Table 1. Characteristics of Patients at Admission according to Presumed Cause of Acute Liver Failure\***

Variable	Presumed Cause of Acute Liver Failure			
	Acetaminophen	Other Drugs	Indeterminate	All Others
Patients, <i>n</i>	120	40	53	95
Median age (range), <i>y</i>	36 (19–76)	41 (20–65)	38 (15–76)	43 (15–78)
Women, <i>n</i> (%)	95 (79)	29 (72)	32 (60)	68 (72)
White ethnicity, <i>n</i> (%)	108 (90)	23 (58)	35 (66)	61 (64)
Survived without transplant, <i>n</i> (%)	82 (68)	10 (25)	9 (17)	31 (33)
Survived with or without transplant, <i>n</i> (%)	87 (73)	28 (70)	34 (64)	58 (61)
Received transplant, <i>n</i> (%)	7 (6)	21 (53)	27 (51)	34 (36)
Coma grade at study admission, <i>n</i>				
I	33	8	14	21
II	27	15	14	29
III	35	14	15	21
IV	25	3	10	24
Maximum coma grade, <i>n</i>				
I	18	7	14	17
II	35	10	10	24
III	31	20	14	22
IV	36	3	15	32
Mean symptom duration (range), <i>d</i>	3 (0–32)†	15.5 (2–74)	23 (0–67)	10 (0–64)
Mean jaundice duration (range), <i>d</i> ‡	1 (–3 to 12)	12 (–1 to 59)	12 (0–61)	4 (–5 to 42)
Mean value of mean arterial pressure, <i>mm Hg</i>	87 (41–130)	92 (67–118)	84 (34–133)	88 (52–133)
Mean platelet count (range), × 1000 <i>cells/mm</i> <sup>3</sup>	125 (16–699)	154 (36–376)	129 (14–462)	148 (28–424)
Mean prothrombin time (range), <i>s</i>	28.5 (15.0–135)	22.5 (15.2–86.6)	23.7 (15.1–151.4)	26.8 (15.0–106)
Mean INR (range)	2.8 (1.5–44.4)	2.4 (1.5–10.9)	2.7 (1.5–24.8)	2.7 (1.5–26.1)
Mean serum bicarbonate level (range), <i>mmol/L</i>	21 (2–35)	23 (7–37)	23 (9–31)	23 (7–36)
Mean ALT level (range), <i>U/L</i>	4310 (136–17 670)	574 (88–5380)	947 (32–10 660)	1060 (3–12 533)
Mean AST level (range), <i>U/L</i>	4333 (59–28 870)	636 (127–3673)	858 (93–14 626)	1003 (50–21 925)
Mean bilirubin level (range)				
μmol/L	74 (5–592)	345 (127–852)	419 (17–742)	215 (22–1026)
mg/dL	4.3 (0.3–34.6)	20.2 (7.4–49.8)	24.5 (1.0–43.4)	12.6 (1.3–60.0)
Mean creatinine concentration (range)				
μmol/L	168 (44–928)	88 (27–460)	106 (35–619)	133 (35–2210)
mg/dL	1.9 (0.5–10.5)	1.0 (0.3–5.2)	1.2 (0.4–7.0)	1.5 (0.4–25.0)
Mean arterial pH	7.41 (6.94–7.65)	7.48 (7.26–7.63)	7.46 (7.10–7.59)	7.44 (7.12–7.81)

\* ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio.

† Some patients with accidental acetaminophen overdose had symptoms for a long period.

‡ Jaundice developed after onset of encephalopathy in some patients.

the Budd–Chiari syndrome accounted for 17 (6%), 13 (4%), 8 (3%), and 5 (2%) cases, respectively. Six patients with pregnancy-associated acute liver failure were listed as having acute fatty liver (*n* = 2), the HELLP (Hemolysis, Elevated Liver enzymes, Low Platelets) syndrome (*n* = 3), or eclampsia (*n* = 1). Acute liver failure was attributed to cancer (metastatic carcinoma or lymphoma) in 4 patients and to another cause (heat stroke, sepsis, or giant-cell hepatitis) in 6 patients. Fifty-three cases (17%) of indeterminate cause were equally divided among the 12 centers (median cases per center, 4.5 [range, 1 to 9]).

#### Comparison of Clinical and Laboratory Features by Presumed Cause

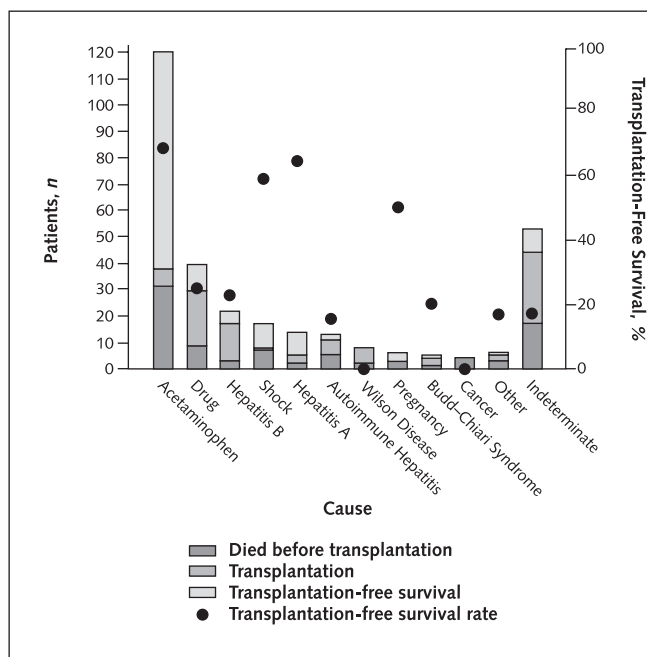
Table 1 shows between-group differences in clinical and laboratory data at admission, based on presumed cause of acute liver failure. All groups had a similar preponderance of women. Patients with acetaminophen-related liver failure and those with indeterminate liver failure were younger than patients with liver failure that was drug induced or related to other causes. White persons were over-represented in the acetaminophen group compared with the other three groups. Patients with acetaminophen-

related disease had shorter disease duration; higher serum alanine aminotransferase, aspartate aminotransferase, and creatinine levels; and lower bilirubin levels and arterial pH. The drug-induced and indeterminate groups had longer disease duration, lower alanine aminotransferase levels, and higher bilirubin levels. The groups did not differ significantly in other measures of disease severity at presentation (for example, coma grade, mean arterial pressure, prothrombin time, or international normalized ratio).

#### Outcomes

Short-term outcomes were assessed 3 weeks after study admission (Figure). Most patients (286 of 308 [93%]) had a definitive outcome (death, transplantation, or hospital discharge) at 3 weeks. Overall survival was 67% (207 of 308 patients). One hundred thirty-two patients (43%) survived without transplantation. One hundred thirty-five patients were listed for transplantation, and 89 (66% of listed patients, 29% of the total study group) received a liver graft. Seventy-five patients who received transplants survived for at least 3 weeks (short-term survival, 84%). Causes of death for the 101 patients who died were cere-

**Figure.** Presumed causes and outcomes in 308 patients with acute liver failure.



bral edema, multiorgan failure, sepsis, cardiac arrhythmia or arrest, and respiratory failure. Thirty patients died awaiting a graft, and 47 died but had not been listed for transplantation. The median time from transplantation listing to actual transplantation was 3.5 days (range, 1 to 42 days), and median time to death after admission was 5 days (range, 2 to 21 days).

Short-term outcomes varied according to the presumed cause of acute liver failure (Figure, Table 1). For patients with acetaminophen overdose, hepatitis A virus infection, shock liver, or pregnancy-related acute liver failure, short-term survival without transplantation was 50% or greater. Patients whose liver disease was of indeterminate cause or was presumed to be related to drugs other than acetaminophen, hepatitis B virus infection, autoimmune hepatitis, Wilson disease, the Budd–Chiari syndrome, or cancer had lower rates of short-term transplant-free survival (<25%) (Figure). Transplantation was performed in only 6% of the acetaminophen group compared with 53% of the drug-induced group, 51% of the indeterminate group, and 36% of the “other cause” group. Fifty-six of 120 patients with acetaminophen-related liver failure (47%) fulfilled transplantation criteria. However, only 32 (57%) were listed for transplantation; the remaining patients were excluded for psychosocial reasons (for example, psychiatric disease or substance abuse) or because of medical contraindications (for example, sepsis or cerebral edema). While short-term survival without transplantation was lower in the drug-induced and indeterminate groups, overall survival was similar in all groups (acetaminophen group, 73%; drug-induced group, 70%; indeterminate

group, 64%; “other cause” group, 61%) (Figure, Table 1). Rates of overall survival, transplant-free survival, and transplantation were independent of sex (data not shown).

### Age Comparisons

Because age is thought to affect the outcome of acute liver failure, we analyzed outcomes by decades of life. The peak age group for patients with acute liver failure was 26 to 35 years, and the number of patients in each age group gradually decreased with increasing age. Overall survival remained relatively unchanged for all age groups (between 63% and 77%) except for those older than 65 years of age. These patients had poor survival (33%), but the group was relatively small ( $n = 15$ ).

### Symptom Duration

Since symptom duration has also been used to predict outcome, we used the methods described by O’Grady and colleagues (15) to stratify patients with non-acetaminophen-related liver failure. Hyperacute failure was classified as 7 or fewer days of symptoms before onset of hepatic encephalopathy, acute failure was classified as 8 to 28 days of symptoms, and subacute failure was classified as more than 28 days of symptoms. Information on symptom duration was available for 178 of the 188 patients with non-acetaminophen-related liver failure (95%). As shown in Table 2, transplantation was used more frequently and transplant-free short-term survival was lower in the subacute group. Serum aminotransferase levels were highest and bilirubin levels were lowest in the hyperacute group.

### Role of Coma Grade at Admission

At study admission, 161 patients (52%) presented with grade I or II hepatic coma. Among these patients, 84 (52%) survived without transplantation for 3 weeks. In contrast, of 147 patients who presented with grade III or IV hepatic coma, 48 (33%) survived 3 weeks without transplantation. The transplantation rate was 29% for patients with grade I or II coma and those with grade III or IV coma, whereas overall rates of short-term survival in these groups were 77% and 56%, respectively. Short-term transplant-free survival was 87%, 35%, 18%, and 38%, respectively, for patients with presumed acetaminophen overdose, drug reactions, liver failure of indeterminate cause, or liver failure of other causes who presented with grade I or II coma and was 50%, 12%, 16%, and 27%, respectively, for patients who presented with grade III or IV coma. The corresponding overall rates of short-term survival were 88%, 70%, 79%, and 66% and 57%, 71%, 48%, and 56%.

### DISCUSSION

This study is one of the first to prospectively characterize a large number of patients with acute liver failure from several U.S. tertiary care centers, all but one of which perform liver transplantation. Earlier studies have been small, retrospective, or limited to single academic centers

**Table 2. Characteristics of Patients with Non-Acetaminophen-Related Acute Liver Failure according to Symptom Duration before Onset of Hepatic Encephalopathy\***

Variable	Hyperacute Liver Failure	Acute Liver Failure	Subacute Liver Failure
Patients, <i>n</i>	53	83	42
Mean age (range), <i>y</i>	39 (15–78)	42 (15–72)	41.5 (17–65)
Women, <i>n</i> (%)	40 (75)	51 (61)	31 (74)
White ethnicity, <i>n</i> (%)	33 (62)	55 (66)	28 (67)
Cause of liver failure, <i>n</i>			
Autoimmune disorder		10	3
Budd–Chiari syndrome	1	3	1
Drugs	6	21	11
Hepatitis A	4	7	3
Hepatitis B	11	8	1
Indeterminate	12	20	16
Cancer	1	1	2
Other	1	2	2
Pregnancy	5	1	
Shock	11	5	1
Wilson disease	1	5	2
Survived without transplant, <i>n</i> (%)	16 (30)	27 (33)	6 (14)
Survived with or without transplant, <i>n</i> (%)	27 (51)	57 (69)	27 (64)
Received transplant, <i>n</i> (%)	16 (30)	32 (39)	25 (60)
Mean platelet count (range), $\times 1000$ cells/mm <sup>3</sup>	119 (14–386)	155 (19–452)	132 (24–462)
Mean prothrombin time (range), <i>s</i>	24.3 (15.3–100)	26.1 (15.0–106)	23.7 (15.2–151)
Mean INR (range)	2.3 (1.5–15.5)	2.9 (1.5–15.5)	2.5 (1.5–15.5)
Mean ALT level (range), <i>U/L</i>	1753 (3–12 533)	972 (11–7603)	373 (26–6430)
Mean AST level (range), <i>U/L</i>	1569 (52–20 000)	863 (50–21 925)	430 (127–8850)
Mean bilirubin level (range)			
$\mu\text{mol/L}$	183 (17–920)	373 (31–1026)	416 (26–992)
$\text{mg/dL}$	10.7 (1.0–53.8)	21.8 (1.8–60.0)	24.3 (1.5–58.0)
Mean creatinine concentration (range)			
$\mu\text{mol/L}$	150 (27–557)	106 (35–2210)	106 (44–583)
$\text{mg/dL}$	1.7 (0.3–6.3)	1.2 (0.4–25.0)	1.2 (0.5–6.6)

\* Hyperacute liver failure = 0–7 days of symptoms before encephalopathy onset; acute liver failure = 8–28 days of symptoms before encephalopathy onset; subacute liver failure = >28 days of symptoms before encephalopathy onset. Laboratory values reported are those at admission. ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio.

over many years (11–14, 17). Our previous study, which included 295 patients who developed acute liver failure from 1994 to 1996, was limited because it provided only minimal retrospective information on demographic features, presumed cause, and outcome (18). Our present study was also limited because it provided detailed information only from tertiary care centers. In that sense, our data set does not represent U.S. patients overall and is subject to biases regarding referral for transplantation. Patients who were elderly, had underlying malignant disease, may have had milder disease, or may have had other issues precluding transplantation were probably underrepresented. Because our selection criteria were coagulopathy and encephalopathy, only the most severely ill patients were included. The overall outcome for the conditions studied would have been considerably better if all hospitalized patients had been included.

We observed a much higher frequency of presumed acetaminophen overdose–related hepatotoxicity (39%) than have previous reports. We included all cases evaluated at the tertiary care centers as long as informed consent could be obtained. It is likely that the proportion of acetaminophen-related cases in our earlier retrospective study (20%) was an underrepresentation; that study included only data from transplantation databases, and many pa-

tients with acetaminophen toxicity are not listed for transplantation. No acute liver failure attributed to acetaminophen had been reported in three small U.S. series, totaling 129 cases, before the advent of transplantation in the early 1980s (11–13). In one more recent study from a single large transplantation center in 1983 to 1995, acetaminophen was listed as the presumed cause of injury in 19% of cases (14). The apparent increase in the proportion of acetaminophen cases in our study might be partly explained by a decreasing incidence of other diseases, such as viral hepatitis. Nevertheless, our findings may represent a real increase in the incidence of acetaminophen-related acute liver failure as observed in U.S. transplantation centers.

Acetaminophen is the most widely used nonprescription analgesic in the United States. In the Third National Health and Nutrition Examination Survey (19), 76% of Americans reported using a nonprescription product in the previous month, and 36% specified acetaminophen. There is very little evidence of liver injury when acetaminophen is used according to package recommendations. Nevertheless, acetaminophen is a common putative cause of severe liver injury because of its recognized dose-related hepatotoxicity; its easy availability; and possibly other cofactors, such as alcohol use and starvation (20–22). Unlike in the United Kingdom, more than half of our patients with presumed

acetaminophen overdose were believed to have overdosed accidentally rather than during a suicide attempt. However, most of our patients (83%) exceeded the daily maximum recommended dose, and the median dose in our series was more than three times that value. It should be stressed that only the most severely ill patients, those who have usually taken the largest overdoses or who have had a long delay before initiation of antidote treatment, develop acetaminophen-related liver failure (23).

Our patients with acute liver failure related to acetaminophen were as ill as those with failure related to other causes. However, many more patients in the former group survived (73%), and very few received liver transplants (6%). Patients with acetaminophen-related liver failure have the best chance of spontaneous recovery with supportive care; however, 43% in our study were not considered for transplantation because of medical contraindications and psychosocial reasons (alcohol or other substance abuse; repeated suicide attempts; and, in two cases, lack of funding). Despite the relatively good outcome of patients with acetaminophen-related liver failure, 33 of our patients with this type of disease died (28% of all patients in the acetaminophen group and 11% of patients admitted to the study). The even higher proportion of acetaminophen-related cases in Europe (24–26) has led to legislation limiting the quantity of acetaminophen available without a prescription (27–29). In light of these findings, our observation of an apparent increase in prevalence of severe liver injury due to acetaminophen overdose bears close scrutiny.

Idiosyncratic drug reactions appeared to cause 13% of cases of acute liver failure. Two of the drugs prominently implicated, bromfenac and troglitazone (four cases each), have been withdrawn by the U.S. Food and Drug Administration (30, 31). Isoniazid was thought to be responsible for five cases of acute liver failure in our study. However, despite its toxicity, it remains first-line therapy for tuberculosis worldwide (7).

The importance of idiosyncratic drug reactions is reflected in the overall poor outcome for patients with this type of liver failure; only 25% recover spontaneously once hepatic encephalopathy is present. Patients with acute liver failure of indeterminate cause made up 17% of our study group and were equally represented across the study sites. Whether another hepatotropic virus or unknown drug exposures were present in these patients remains to be determined. No specific features suggest that these cases had a unique cause. It is likely, however, that some patients ingested a toxin but had no history to suggest this and that others contracted a virus that may have acted as the etiologic agent.

A striking finding in our study is that nearly three quarters of U.S. patients with acute liver failure are women. The proportion increased from 54% in our previous retrospective study (18) to 73% in the present study. In earlier U.S. studies of acute liver failure, between 56% (13) and 63% (11, 14) of cases occurred in women. The

reasons for the preponderance of women in our series have not been elucidated. A real increase over an interval of less than 4 years seems unlikely. Causes of acute liver failure that are specific to women, such as those related to pregnancy or breast cancer, were involved in only a small number of our cases. Female preponderance was present in all groups in our study, so a simple increase in the total number of acetaminophen-related cases, in which women predominate, cannot account for these differences. The possibility of a selection bias related to greater availability of relatives for informed consent was not borne out by our records of patients for whom consent could not be obtained. Whether women are innately more susceptible to acute liver failure or are taking more kinds of prescription and nonprescription drugs and are therefore at higher risk remains to be determined (19).

The overall short-term survival in our study (67%) is much higher than that previously observed in the United States. In the three small studies done in the pretransplantation era, survival rates were between 3% and 18% (11–13). Two more recent studies, our retrospective study (18) and the large single-center study (14), yielded short-term survival rates of 25% and 14% without transplantation and 49% and 41% with transplantation, respectively. By comparison, our current series yielded a short-term transplant-free survival rate of 43%, and only 29% of our patients received a liver graft. These more favorable results seem to reflect both an increase in patients with acetaminophen-related disease, who are more likely to have survived 3 weeks without transplantation, and a substantial role for liver transplants in management of acute liver failure.

The pretransplantation hospital stays of those who received a liver graft (median, 3.5 days) and those who died while on the waiting list (median, 5 days) were very similar, indicating the limited time span in which transplantation is possible. In all, 30 patients (10%) died awaiting a graft despite being listed in the top recipient category (United Network of Organ Sharing Status 1). Accurate prognostic tests for determination of outcome are lacking. Another 16 patients, 35% of those who were listed for but did not receive transplants, recovered after being placed on the transplantation list. Given the shortage of available organs and the high cost of transplantation, new therapies for acute liver failure are urgently needed.

Previous European studies have suggested that acute liver failure is more likely to be fatal in patients older than 40 years of age and those younger than 10 years of age (24). We confirmed that most cases of acute liver failure were in younger patients (26 to 45 years). However, the rate of overall survival was not worse for adult patients through age 65 years, and only a few of our patients were older than 65 years of age. The spontaneous survival rate was highest for patients 26 to 35 years of age and 36 to 45 years of age; however, because these age groups also had the highest numbers of acetaminophen-related cases, this higher rate was not unexpected (data not shown). Our

study does not suggest that age was an important determinant of outcome. However, because of a selection bias toward fitness for transplant candidacy, many older patients are probably excluded from referral to liver transplantation centers.

Symptom duration is considered to be a major variable in determining the prognosis of patients with acute liver failure (15). Paradoxically, patients with hyperacute onset of hepatic encephalopathy ( $\geq 8$  days of symptoms before coma) have been considered to have a better prognosis than those with acute (8 to 28 days of symptoms) or subacute ( $> 28$  days of symptoms) onset (15, 32). However, when we excluded patients with acetaminophen-related disease from the hyperacute group (Table 2), the results did not differ from those of the acute group. The subacute group still had the lowest likelihood of spontaneous survival. Overall survival did not differ among the groups, possibly because the rate of transplantation was higher (60%) in the subacute group. In addition to the predicted poorer survival in the subacute group, which led to earlier listing for transplantation, the slower disease evolution may have increased the likelihood of receiving a liver graft (33). In keeping with previous studies (24), our results suggest that coma grade at admission may be an important determinant of outcome and emphasize the importance of early transfer to an intensive care setting. Better prognostic models are needed to more accurately predict outcome, preventing transplantation in those who will survive without it and allowing the procedure in those who otherwise have no hope of survival.

Acute liver failure, although rare, remains a rapidly progressive and frequently fatal condition. Estimates of overall incidence cannot be derived from our study. Treatment is generally supportive (in the absence of an antidote such as *N*-acetylcysteine for acetaminophen overdose), and infection and cerebral edema remain the leading causes of death. In the United States, most liver injury is presumably due to medications (acetaminophen overdose and idiosyncratic drug reactions) and may therefore be preventable. Clinicians should be aware of the rapidity with which liver injury evolves and the possible dire consequences for patients who develop any degree of coagulopathy and encephalopathy. Since outcome is unpredictable, early transfer to a transplantation facility should be considered before the onset of advanced grades of coma, after which transfer becomes impossible. Further understanding of the pathophysiologic characteristics of this multisystem condition and the development of better support therapies should improve the outcome of patients with acute liver failure.

## APPENDIX: U.S. ACUTE LIVER FAILURE STUDY GROUP, 1998–2001

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**Acknowledgment:** The authors thank the site coordinators and nurses for their support.

**Grant Support:** By the National Institutes of Health (RO3 DK52827, RO1 DK58369) and the U.S. Food and Drug Administration Orphan Products Program (FD-R-001661). Dr. Schiødt was supported by a Schering Research Fellowship from the American Association for the Study of Liver Diseases.

**Potential Financial Conflicts of Interest:** *Consultancies:* W.M. Lee.

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