ACUTE LIVER FAILURE IN CHILDREN: THE FIRST 348 PATIENTS IN THE PEDIATRIC ACUTE LIVER FAILURE STUDY GROUP

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Objectives To determine short-term outcome for children with acute liver failure (ALF) as it relates to cause, clinical status, and patient demographics and to determine prognostic factors.

Study design A prospective, multicenter case study collecting demographic, clinical, laboratory, and short-term outcome data on children from birth to 18 years with ALF. Patients without encephalopathy were included if the prothrombin time and international normalized ratio remained ≥20 seconds and/or >2, respectively, despite vitamin K. Primary outcome measures 3 weeks after study entry were death, death after transplantation, alive with native liver, and alive with transplanted organ.

Results The cause of ALF in 348 children included acute acetaminophen toxicity (14%), metabolic disease (10%), autoimmune liver disease (6%), non-acetaminophen drug-related hepatotoxicity (5%), infections (6%), other diagnosed conditions (10%); 49% were indeterminate. Outcome varied between patient sub-groups; 20% with non-acetaminophen ALF died or underwent liver transplantation and never had clinical encephalopathy.

Conclusions Causes of ALF in children differ from in adults. Clinical encephalopathy may not be present in children. The high percentage of indeterminate cases provides an opportunity for investigation. *(J Pediatr 2006;148:652-8)*

Acute liver failure (ALF) is a dramatic clinical syndrome in which previously healthy children rapidly lose hepatic function and become critically ill within days.[1,2] Over the last 25 years, single center experiences[3-6] or general reviews[1,2,7] of pediatric ALF from Europe and North America identified a variety of infectious, metabolic, cardiovascular, and drug-related causes, as well as indeterminate cases.[4-6] These pediatric studies used the adult definition of ALF, which requires the presence of hepatic encephalopathy (HE) within 8 weeks of the development of clinical jaundice. Unfortunately, HE is difficult to assess in many infants and children and may not be essential to the diagnosis of ALF in children.[3,8]

The outcome for children with ALF remains poor for infants under 1 year of age,[3] patients with accidental acetaminophen overdose,[9] and Wilson's disease presenting with hepatic HE.[10] Spontaneous recovery (ie, survival without transplantation) remains between 15% to 20% for those with severe HE.[5,6] Given the ongoing shortage of donor livers,[11] development of a reliable prognostic score will be useful in allocating organs to the most needy patients.

The Pediatric Acute Liver Failure (PALF) study group was formed in 1999 to develop a database that would facilitate an improved understanding of the pathogenesis, treatment, and outcome of ALF in children. These data will also serve to identify factors that will help to predict the likelihood of death or need for liver transplantation.

AIH	Autoimmune hepatitis	INR	International normalized ratio
ALF	Acute liver failure	PALF	Pediatric acute liver failure
HE	Hepatic encephalopathy	TTMC	Tukey-type multiple comparison

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Supported by NIH grant RO1-DK58369-01; and by M01-RR00069, M01-RR00037, and M01 RR08084 from the General Clinical Research Center Program of the National Center for Research Resources of the NIH.

Submitted for publication Jul 17, 2005; last revision received Oct 3, 2005; accepted Dec 19, 2005.

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0022-3476/$ - see front matter

10.1016/j.jpeds.2005.12.051

Table I. Assessment of encephalopathy for young children: birth to age 3 years

Grade	Clinical	Asterixis/reflexes	Neurologic signs
Early (I and II)	Inconsolable crying, sleep reversal, inattention to task	Unreliable/normal or hyperreflexic	Untestable
Mid (III)	Somnolence, stupor, combativeness	Unreliable/hyperreflexic	Most likely untestable
Late (IV)	Comatose, arouses with painful stimuli (IVa) or no response (IVb)	Absent	Decerebrate or decorticate

Table II. Patient demographics

	Acetaminophen (%)	Indeterminate (%)	All Others (%)	χ^2 *P* value
Total (N = 348)	48 (14)	169 (49)	131 (38)	
Gender				.0002
Female (n = 181)	38 (79)	78 (46)	65 (50)	
Male (n = 167)	10 (21)	91 (54)	66 (50)	
Age				
< 3.0 (n = 127)	2 (4)	68 (40)	57 (44)	<.0001
⩾ 3.0 (n = 221)	46 (96)	101 (60)	74 (56)	
Race				.0275*
Black (n = 54)	5 (10)	32 (19)	17 (13)	
Asian (n = 30)	5 (10)	14 (8)	11 (8)	
Hispanic (n = 53)	3 (6)	32 (19)	18 (14)	
Native American (n = 4)	0 (0)	2 (1)	2 (2)	
Other (n = 21)	3 (6)	10 (6)	8 (6)	
White (n = 186)	32 (67)	79 (47)	75 (57)	

*Test of white versus nonwhite.

METHODS

Organization

The PALF study group began as an adjunct to the National Institutes of Health–sponsored, adult-focused ALF Study Group (William Lee, MD, Principal Investigator). The PALF study group now consists of 24 active pediatric sites, 21 within the United States, 1 in Canada, and 2 in the United Kingdom. Working groups of pediatric hepatologists established definitions for ALF and various diagnostic categories. Representatives from all participating centers approved final recommendations from the working groups. Patient enrollment began in December 1999.

Data Collection

Following informed consent from a parent or legal guardian, demographic, clinical and laboratory information were recorded daily for 7 days. In most patients, an additional aliquot of serum or plasma was collected on each of the 7 study days, frozen at −70° C, and then shipped to the Data Coordinating Center located at the University of Texas Southwestern Medical Center in Dallas, Texas. Diagnostic evaluation and medical management were consistent with the standard of care at each site. As in the adult study, our primary outcome measures determined at 3 weeks after entry into the study included death, death after transplantation, alive with native organ, and alive with transplanted organ. Completed data forms were forwarded under code to the Data Coordinating Center for review by the principal investigator for the pediatric study. If discrepancies were identified, the site was queried, and on resolution, data were then entered into the PALF database. The National Institutes of Health provided a Certificate of Confidentiality to the study and IRB approval was secured at each site before patient enrollment.

Subjects of the Study

Patients from birth through 18 years of age were eligible for enrollment if they met the following entry criteria for the PALF study: (1) children with no known evidence of chronic liver disease, (2) biochemical evidence of acute liver injury, and (3) hepatic-based coagulopathy defined as a prothrombin time (PT) ≥ 15 seconds or international normalized ratio (INR) ≥ 1.5 not corrected by vitamin K in the presence of clinical HE or a PT ≥20 seconds or INR ≥2.0 regardless of the presence or absence of clinical HE. A standard adult clinical coma grade scale was used for older children, and a coma grade scale was adapted for infants and children < 4 years old (Table I).[12]

Diagnostic Categories

Diagnostic criteria for acute acetaminophen toxicity included a toxic serum acetaminophen level on the basis of the Rumack nomogram[13] or a history of an acute ingestion of 100 mg/kg within a 24-hour period. The diagnosis of autoim-

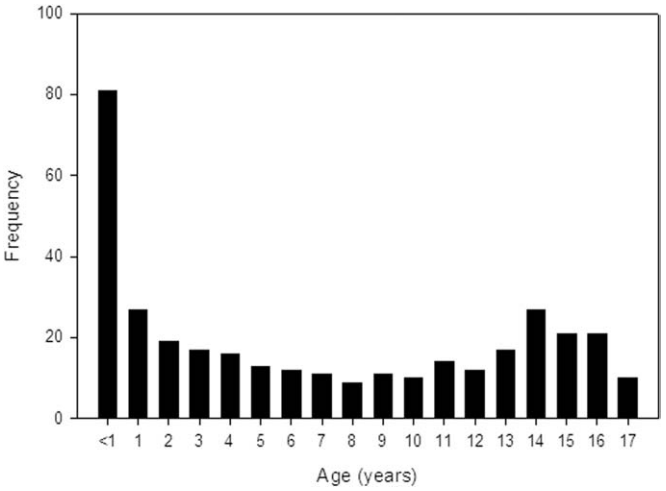

Figure 1. Age of the patient at entry into the PALF study.

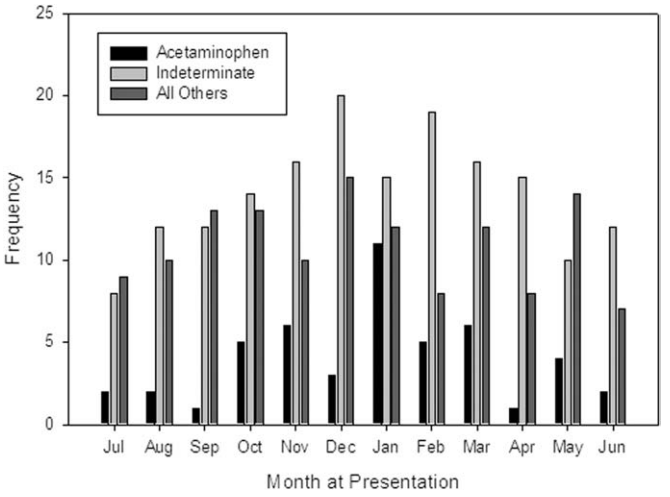

Figure 2. Calendar month when patients were entered into the PALF study. Patients were divided into three diagnostic cagtegories: acetaminophen toxicity, indeterminate, and all others with an established diagnosis.

mune hepatitis (AIH) was established if a patient had 1 or more positive autoantibody test results (anti-nuclear antibody $\geq$ 1:80, smooth muscle antibody $\geq$ 1:20, liver-kidney microsomal antibody $\geq$ 1:20) and no evidence of serologically defined viral hepatitis.[14] Non-acetaminophen drug-induced hepatitis was diagnosed if a temporal relationship between exposure to a suspected drug and the onset of ALF was established and other common causes were excluded. Hepatitis A, B, or C infection was confirmed serologically or by polymerase chain reaction. Evidence of other viral infections required a positive immunoglobulin M antibody, evidence of virus in liver tissue, or a positive polymerase chain reaction. Metabolic diseases were diagnosed by laboratory tests (eg, alpha-1-antitrypsin phenotype of ZZ), analysis of liver tissue (eg, mitochondrial enzyme defect), or analysis of cultured skin fibroblasts (eg, fatty acid oxidation defect). If the site investigator suspected an infection or metabolic disease but lacked supporting evidence or if a specific diagnosis could not be established, the final diagnosis was registered as indeterminate.

Statistical Methods

Diagnostic categories were defined as acetaminophen, indeterminate and all others in whom a specific diagnosis was determined. Age was dichotomized into patients younger than 3 years of age and those 3 years of age and older. Race was dichotomized into white versus non-white.

All associations between pairs of dichotomous or dichotomized variables (2-way tables) were conducted with χ^2 analyses. For those χ^2 analyses found significant, post hoc Tukey-type multiple comparison tests for proportions (TTMC) were performed.[15] The 2 independent samples proportions test with correction was used to compare proportions for two groups. Two different logistic regression models were used to predict death or transplantation in the 2 non-acetaminophen groups with data available at admission (coma grade, PT, and total bilirubin) and peak measures within the first 7 days of hospitalization or before transplantation (peak bilirubin, peak PT, maximum coma grade). These models also included sex (male vs female) and age ($<$3 vs $\geq$ 3 years). SPSS V12.0 and SAS V9.1 were used in all analyses. The assumptions for all statistical tests were checked for violations. Statistical significance was set at $P < .05$.

RESULTS

Between December 1999 and December 2004, 348 children were enrolled; patient demographics are outlined in Table II. The median dose of acetaminophen ingested was 183 mg/kg (range 19.2 to 734.1). There was an association between cause and sex ($P = .0002$), with the percentage of females significantly higher in the acetaminophen group compared with both non-acetaminophen groups (TTMC $P < .05$, 79% vs 46% or vs 60%, respectively). The association between the three etiologic categories and race (white vs non-white) was found to be significant ($P = .0275$) with more whites in the acetaminophen versus the indeterminate group (TTMC $P < .05$, 67% vs 47%; respectively). Children under 3 years of age accounted for 36.5% (127/348) of patients (Figure 1). ALF caused by acetaminophen and those of indeterminate cause appear to occur more commonly during the cooler months, but this did not reach statistical significance ($P = .2240$) (Figure 2).

HE at admission to the study and peak HE during the subsequent 7 days stratified by age and diagnosis is captured in Table III. HE was present more frequently in the combined non-acetaminophen groups than the acetaminophen group (56.6% [164/290] vs 39.6% [19/48]; $P = .0425$). In addition, the number of patients with development of HE during the 7-day study period was greater in those with non-acetaminophen ALF compared with the acetaminophen group (68.4% [203/297] vs 39.6% [19/48]; $P = .0002$). Patients in all diagnostic and age categories experienced worsening HE, although this occurred more commonly in older

Table III. Encephalopathy on admission and at peak during the 7-day study period stratified by age and diagnosis category

	Acetaminophen (%)		Indeterminate (%)		All Others (%)	
Admission coma grade	Age < 3.0	≥ 3.0 yr	Age < 3.0	≥ 3.0 yr	Age < 3.0	≥ 3.0 yr
0 (N = 155)	0 (0)	29 (63)	27 (42)	38 (38)	30 (55)	31 (44)
1–2 (N = 138)	0 (0)	12 (26)	34 (53)	45 (45)	20 (36)	27 (38)
3 (N = 31)	1 (50)	4 (9)	2 (3)	12 (12)	5 (9)	7 (10)
4 (N = 14)	1 (50)	1 (2)	1 (2)	5 (5)	0 (0)	6 (8)
Peak coma grade	<3.0	≥ 3.0	< 3.0	≥ 3.0	< 3.0	≥ 3.0
0 (N = 123)	0 (0)	29 (63)	21 (31)	25 (25)	26 (46)	22 (30)
1–2 (N = 134)	0 (0)	12 (26)	36 (54)	40 (40)	21 (38)	25 (34)
3 (N = 39)	1 (50)	1 (2)	4 (6)	15 (15)	8 (14)	10 (14)
4 (N = 49)	1 (50)	4 (9)	6 (9)	21 (21)	1 (2)	16 (22)

Table IV. Clinical characteristics by diagnostic category and age category

	Diagnosis				Age group		
	Acetaminophen (%) n = 48	Indeterminate (%) n = 169	All others (%) n = 131	χ^2 *P* value	<3 yr (%) n = 127	≥3 yr (%) n = 221	χ^2 *P* value
Ascites (n = 78)	2 (4)	35 (21)	41 (31)	.0004	42 (33)	36 (16)	.0003
Seizure (n = 23)	0 (0)	13 (8)	10 (8)	.1394	6 (5)	17 (8)	.2833
Ventilation Support (n = 145)	8 (17)	75 (44)	62 (47)	.0007	62 (49)	83 (38)	.0402
Pressor Support (n = 82)	5 (10)	33 (20)	44 (34)	.0012	33 (26)	49 (22)	.4198
Hemofiltration (n = 33)	3 (6)	11 (7)	19 (15)	.0457	8 (6)	25 (11)	.1244
Plasmapheresis (n = 35)	3 (6)	21 (12)	11 (8)	.3301	8 (6)	27 (12)	.0772
Red cell transfusion (n = 146)	7 (15)	81 (48)	58 (44)	.0002	79 (62)	67 (30)	<.0001
Fresh frozen plasma (n = 221)	20 (42)	122 (72)	79 (60)	.0003	90 (71)	131 (59)	.0306

patients (24.0% [29/121] vs 34.6% [75/217]). Other clinical and management features stratified by diagnosis and age are listed in Table IV. Development of ascites, need for ventilator and blood pressure support, and requirement for red blood cell and plasma infusions were more likely to develop in patients within the 2 non-acetaminophen groups than in the acetaminophen group. In comparisons by age category, those in the younger age group were more likely to have development of ascites, require ventilator support, and infusions of red blood cells and fresh frozen plasma.

Overall, a specific cause of ALF was not identified in 49% of patients and 54% of children less than 3 years of age. (Table V; available at www.jpeds.com) acetaminophen toxicity accounted for only 14% of all patients, with 96% of these cases occurring in older patients. Specific viruses, drugs, toxins, and metabolic disorders are also listed in Table V. Interestingly, only 3 patients with acute hepatitis A infection, 1 patient with hepatitis C, and no patients with hepatitis B were identified in this cohort.

The short-term outcome for each diagnostic category is described in Table VI. When all cases are considered, the association between outcome and sex was significant (P = .0428) with spontaneous recovery for females higher than for males (60% vs 46%, respectively), but this association disappears when the acetaminophen group is removed from the analysis. Survival and need for liver transplantation varied depending on the diagnosis. Spontaneous recovery was greatest in children with acetaminophen toxicity (45/48; 94%), worst for those with non-acetaminophen drug-induced liver injury (7/17; 41%) and with indeterminate cause (73/169; 43%). Patient outcomes on the basis of admission and peak HE are outlined in Table VII. Patients who never had HE were more likely to experience spontaneous recovery than those who did (78.9% vs 40.1%; $P < .0001$). In contrast, patients with development of stage III or IV HE had a spontaneous recovery rate of only 33% and 22%, respectively. Logistic regression analysis (Table VIII) to predict death or liver transplantation identified total bilirubin ≥ 5 mg/dL, INR ≥ 2.55, and HE to be risk factors if present on admission. The logistic regression model with peak values was similar to that for admission, with increasing predictive values (odds ratios) for all variables.

DISCUSSION

This report of the first 348 children in the PALF data set highlights a number of important observations: (1) HE is not an absolute requirement to establish the diagnosis of ALF in children; (2) a specific diagnosis was not made in almost half of all infants and children; (3) the causes of ALF in children differ from those seen in adults,[16] with children

Table VI. Short-term (21 days) outcome of children with ALF

	Not transplanted		Transplanted		χ^2
	Alive	Dead	Alive	Dead	p-value
Age					.2141
< 3.0 (n = 127)	67 (53)	24 (19)	33 (26)	3 (2)	
≥ 3.0 (n = 221)	119 (54)	25 (11)	72 (33)	5 (2)	
Sex					.0428
Female (n = 181)	109 (60)	19 (10)	50 (28)	3 (2)	
Male (n = 167)	77 (46)	30 (18)	55 (33)	5 (3)	
Diagnosis					<.0001
Acetaminophen (n = 48)	45 (94)	1 (2)	1 (2)	1 (2)	
Other Dx Categories (n = 300)	141 (47)	48 (16)	104 (35)	7 (2)	
Dx details					
Acetaminophen (n = 48)	45 (94)	1 (2)	1 (2)	1 (2)	
Indeterminate (n = 169)	73 (43)	18 (11)	71 (42)	7 (4)	
Autoimmune (n = 22)	12 (55)	3 (14)	7 (32)	0	
Infectious (n = 20)	10 (50)	5 (25)	5 (25)	0	
Non-APAP drug induced liver disease (n = 17)	7 (41)	5 (29)	5 (29)	0	
Metabolic (n = 36)	16 (44)	8 (22)	12 (33)	0	
Other (n = 20)	10 (50)	6 (30)	4 (20)	0	
Shock (n = 16)	13 (81)	3 (19)	0	0	
For the Non-APAP patients					
Age					.0884
< 3.0 (n = 125)	66 (53)	23 (18)	33 (26)	3 (2)	
≥ 3.0 (n = 175)	75 (43)	25 (14)	71 (41)	4 (2)	
Sex					.2274
Female (n = 143)	74 (52)	18 (13)	49 (34)	2 (1)	
Male (n = 157)	67 (43)	30 (19)	55 (35)	5 (3)	

Table VII. Patient outcome based on admission and peak encephalopathy

	Not transplanted		Transplanted		χ^2
	Alive (%)	Dead (%)	Alive (%)	Dead (%)	*P* value*
Admission Coma Grade					
0 (n = 155)	102 (66)	14 (9)	35 (23)	4 (3)	.0002
1–2 (n = 138)	59 (43)	20 (14)	57 (41)	2 (1)	
3 (n = 31)	11 (35)	9 (29)	10 (32)	1 (3)	
4 (n = 14)	8 (57)	3 (21)	2 (14)	1 (7)	
Peak Coma Grade					
0 (n = 123)	97 (79)	9 (7)	16 (13)	1 (1)	<.0001
1–2 (n = 134)	65 (49)	12 (9)	55 (41)	2 (1)	
3 (n = 39)	13 (33)	8 (21)	18 (46)	0 (0)	
4 (n = 49)	11 (22)	18 (37)	15 (31)	5 (10)	

*Test compares spontaneous recovery (alive–not transplanted) to the other 3 groups combined.

having more indeterminate cases and fewer acetaminophen and viral-induced cases; and (4) short-term outcome varied among diagnostic groups.

HE is difficult to assess in children and, in fact, may never become clinically apparent in the setting of ALF.[3] However, coagulopathy is an independent risk factor for death or need for liver transplantation in ALF.[17] Therefore we chose to include children without HE in our study, but only when a significant uncorrectable coagulopathy was present. HE remains an important predictor of outcome[18] and, similar to other studies in the post-liver transplantation era, only 25% of our children with a peak HE of grade 3-4 had a spontaneous recovery. However, it is equally important to note that of 79 children with non-acetaminophen ALF who never had clinically detectable HE, death (8/79) or liver transplant (8/79) occurred in 20%. Our data support a definition of pediatric ALF that does not require HE.

An indeterminate cause of ALF was assigned to 54% of children < 3 years of age and 49% overall. Factors that may influence the intensity of the diagnostic evaluation in children

Table VIII. Logistic regression results predicting death or liver transplantation at 3 weeks Based upon Admission and Peak Measures

	Odds Ratio	95.0% C.I. for OR		Wald p-value
		Lower	Upper	
Admission values				
Overall Test - Coma				.0012
Coma Grade 1–2 versus rest	2.83	1.55	5.16	.0007
Coma Grade 3–4 versus rest	2.96	1.22	7.16	.0160
INR ≥ 2.55	2.04	1.15	3.62	.0150
Total Bilirubin ≥ 5.0 mg/dL	10.69	5.49	20.85	<.0001
Model fit statistic: Hosmer-Lemeshow $P = .30$				
Peak values				
Overall Test for Max Coma				<.0001
Max Coma 1–2 versus rest	3.60	1.95	6.66	<.0001
Max Coma 3–4 versus rest	6.92	3.40	14.07	<.0001
Max INR ≥ 2.55	3.36	1.91	5.91	<.0001
Max Total Bilirubin ≥ 5.0 mg/dL	8.62	4.28	17.34	<.0001
Model fit statistic: Hosmer-Lemeshow $P = .91$				

with ALF include prioritization of the etiologic possibilities, blood volumes required for diagnostic studies, and the rapid evolution of disease to transplant or death. Thus all potential diagnostic studies were not performed on each patient. The indeterminate group may include patients who were "under-evaluated" for known causes of ALF, as well as those with novel infectious, immune, autoimmune, metabolic, or genetic disorders.

An infectious agent was identified in only 6% of patients in this series. Herpes simplex virus and Epstein Barr virus were the most common identifiable infections in children <3 years and ≥3 years, respectively. Hepatitis A and B are commonly associated with ALF in adults[19]; however, we identified only 3 cases of hepatitis A, one case of hepatitis C, and no cases of hepatitis B. Nevertheless, these infections are common causes of ALF in children living in endemic areas where hepatitis A can represent up to 40% of ALF cases.[20] Respiratory viruses, enterovirus, or perhaps medications used for symptomatic treatment of these conditions might be implicated given the surge of cases in the winter months; however, these viruses were rarely identified.

AIH presenting as ALF accounted for 6% of patients, occurred in all age groups and should therefore be considered early in the diagnostic evaluation to enable timely initiation of corticosteroid treatment.[21] A metabolic cause for ALF was established in 18% of children <3 years of age. Unfortunately, diagnostic criteria for several conditions are not well established, and special attention to proper collection and transport of biological specimens to specialized research laboratories is needed. Wilson disease and defects or deficiencies in mitochondrial function and metabolism (ie, mitochondrial hepatopathy) were the most common metabolic conditions identified in our study.

Acute acetaminophen toxicity is the most common identifiable cause of ALF in children ≥3 years old (21%), but the frequency is even higher in adults (40%).[22] Instances involving prolonged or inappropriate dosing, so-called "therapeutic misadventures,"[23] are not easily captured by this study. Acetaminophen-protein adducts are formed when the usual mechanisms of acetaminophen metabolism and excretion are exhausted, and the reactive acetaminophen metabolite binds to important intracellular proteins, resulting in cell death. Detection of these adducts in serum may serve as a biomarker of acetaminophen toxicity.[24]

Non-acetaminophen drug-related ALF was recognized only in the older age group in our series. Drug-related hepatotoxicity is relatively common in children, particularly those taking neuroleptic medications, yet ALF is rare.[25,26] The mechanism of injury leading to ALF is believed to be an idiosyncratic reaction in most cases; however, children with ALF related to valproic acid should be evaluated for an underlying mitochondrial disorder.[27] In addition, polymorphisms of genes associated with drug detoxification or cytokine expressions may enhance a patient's susceptibility to liver injury.[28,29]

Patient outcome was influenced by a number of factors including age, diagnosis, the degree of HE, and severity of the coagulopathy. The risk of death or liver transplantation was highest among children <3 years of age. Although the numbers are relatively small, patients with grade IV HE at enrollment experienced a higher rate of spontaneous recovery than those who progressed to grade IV during the course of the study (50% vs 20%). At the same time, 20% of children who never experienced clinical HE either died or received a liver transplant. Logistic regression analysis identified total bilirubin ≥ 5 mg/dL, INR ≥ 2.55, and HE to be risk factors to predict death or liver transplantation.

In summary, this multicenter, multinational database has confirmed that acetaminophen-induced ALF has an excellent outcome when HE is absent,[30] demonstrated that the causes of ALF in children are age-dependent and differ from those in adults, and identified AIH as an important cause of

ALF in all ages of children. Unfortunately, most cases of ALF in children are indeterminate. Therefore improvement in diagnosis will require a focused search for treatable causes that prioritizes diagnostic conditions known to cause ALF. Newer techniques to identify children with an underlying metabolic disease, acetaminophen toxicity, and immune dysregulation will likely improve our ability to establish a diagnosis in these seriously ill children.

Acknowledgments available at www.jpeds.com.

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Table V. Final diagnosis in children with ALF

Diagnosis	Age category < 3 (%)	Age category ≥ 3 (%)	Total (%)
Acetaminophen (n = 48)	2 (2)	46 (21)	48 (14)
Indeterminate (n = 169)	68 (54)	101 (46)	169 (49)
Autoimmune (n = 22)	6 (5)	16 (7)	22 (6)
Infectious (n = 20)	9 (7)	11 (5)	20 (6)
Adenovirus (n = 2)	1 (1)	1 (0)	2 (1)
Cytomegalovirus (n = 1)	1 (1)	0 (0)	1 (0)
Epstein-Barr virus (n = 6)	1 (1)	5 (2)	6 (2)
Enterovirus (n = 1)	1 (1)	0 (0)	1 (0)
Hepatitis A (n = 3)	0 (0)	3 (1)	3 (1)
Hepatitis C (n = 1)	0 (0)	1 (0)	1 (0)
Herpes simples virus (n = 6)	5 (4)	1 (0)	6 (2)
Non-APAP drug induced liver disease (n = 17)	1 (1)	16 (7)	17 (5)
Mushroom (n = 2)	0 (0)	2 (1)	2 (1)
Anesthetic (n = 1)	0 (0)	1 (0)	1 (0)
Bactrim (n = 1)	0 (0)	1 (0)	1 (0)
Cylert (n = 1)	0 (0)	1 (0)	1 (0)
Cytoxan/Dilantin (n = 1)	0 (0)	1 (0)	1 (0)
Dilantin (n = 1)	0 (0)	1 (0)	1 (0)
INH (n = 2)	0 (0)	2 (1)	2 (1)
Iron (n = 1)	0 (0)	1 (0)	1 (0)
Methotrexate (n = 1)	0 (0)	1 (0)	1 (0)
Minocycline (n = 1)	0 (0)	1 (0)	1 (0)
Pravastatin (n = 1)	0 (0)	1 (0)	1 (0)
Valproate (n = 3)	1 (1)	2 (1)	3 (1)
Metabolic (n = 36)	23 (18)	13 (6)	36 (10)
Alpha-1 antitrypsin (n = 1)	1 (1)	0 (0)	1 (0)
Fatty acid oxidation defect (n = 4)	4 (3)	0 (0)	4 (1)
Galactosemia (n = 2)	2 (2)	0 (0)	2 (1)
Fructose intolerance (n = 1)	1 (1)	0 (0)	1 (0)
Mitochondrial disorder (n = 4)	2 (2)	2 (1)	4 (1)
Niemann-Pick type C (n = 1)	1 (1)	0 (0)	1 (0)
Respiratory chain defect (n = 7)	7 (6)	0 (0)	7 (2)
Reyes syndrome (n = 1)	0 (0)	1 (0)	1 (0)
Tyrosinemia (n = 4)	4 (3)	0 (0)	4 (1)
Urea cycle defect (n = 2)	1 (1)	1 (0)	2 (1)
Wilson disease (n = 9)	0 (0)	9 (4)	9 (3)
Other (n = 20)	11 (9)	9 (4)	20 (6)
Budd-Chiari (n = 2)	0 (0)	2 (1)	2 (1)
Hemophagocytic syndrome (n = 4)	2 (2)	2 (1)	4 (1)
Leukemia (n = 2)	1 (1)	1 (0)	2 (1)
Neonatal iron storage disease (n = 6)	6 (5)	0 (0)	6 (2)
Veno-occlusive disease (n = 6)	2 (2)	4 (2)	6 (2)
Shock (n = 16)	7 (6)	9 (4)	16 (5)
Total	127 (36)	221 (64)	348 (100)