A Learning Collaborative Approach Increases Specificity of Diagnosis of Acute Liver Failure in Pediatric Patients

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BACKGROUND & AIMS: **Many pediatric patients with acute liver failure (PALF) do not receive a specific diagnosis (such as herpes simplex virus or Wilson disease or fatty acid oxidation defects)—they are left with an indeterminate diagnosis and are more likely to undergo liver transplantation, which is contraindicated for some disorders. Strategies to facilitate complete diagnostic testing should increase identification of specific liver diseases and might reduce liver transplantation. We investigated whether performing recommended age-specific diagnostic tests (AS-DTs) at the time of hospital admission reduces the percentage PALFs with an indeterminate diagnosis.**

METHODS: **We performed a multinational observational cohort study of 658 PALF participants in the United States and Canada, enrolled at 10 medical centers, during 3 study phases from December 1999 through December 2014. A learning collaborative approach was used to implement AS-DT using an electronic medical record admission order set at hospital admission in phase 3 of the study. Data from 10 study sites participating in all 3 phases were compared before (phases 1 and 2) and after (phase 3) diagnostic test recommendations were inserted into electronic medical record order sets.**

Abbreviations used in this paper: ALF, acute liver failure; AS-DT, age-specific diagnostic testing; EMR, electronic medical record; EN, encephalopathy; GALD, gestational alloimmune liver disease; HSV, herpes simplex virus; LT, liver transplantation; P1, phase 1; P2, phase 2; P3, phase 3; PALF, pediatric acute liver failure.

Most current article

1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2018.04.050

RESULTS: **The percentage of subjects with an indeterminate diagnosis decreased significantly between phases 1–2 (48.0%) and phase 3 (to 30.8%) ($P = .0003$). The 21-day cumulative incidence rates for liver transplantation were significantly different among phase 1 (34.6%), phase 2 (31.9%), and phase 3 (20.2%) ($P = .030$). The 21-day cumulative incidence rates for death did not differ significantly among phase 1 (17.9%), phase 2 (11.9%), and phase 3 (11.3%) ($P = .20$).**

CONCLUSIONS: **In a multinational study of children with acute liver failure, we found that incorporating diagnostic test recommendations into electronic medical record order sets accessed at time of admission reduced the percentage with an indeterminate diagnosis that may have reduced liver transplants without increasing mortality. Widespread use of this approach could significantly enhance care of acute liver failure in children.**

Keywords: Management; Hepatic; Genetic Disorder; Early Detection.

Acute liver failure (ALF) is a rare syndrome in which abrupt liver injury severely impairs liver function in a previously healthy individual.[1] A preceding nonspecific prodrome may last days or weeks, but once features of ALF are established, the clinical course is dynamic, unpredictable, and sometimes rapidly progressive.[2,3] Interventions are largely supportive, although specific life-saving therapy is initiated if a treatable diagnosis is promptly identified.[4-6] A specific diagnosis may also suggest liver transplantation (LT) is contraindicated. Unfortunately, a diagnosis is not established (ie, is indeterminate) in 49% of children[5] and death or LT can occur within days following initial hospitalization. Because children with indeterminate pediatric acute liver failure (PALF) are more likely to receive LT than those with an established diagnosis, enhanced diagnostic specificity may impact LT decisions.[1]

The indeterminate cohort is heterogenous because it is composed of children whose more specific diagnosis was not established for such reasons as an incomplete diagnostic evaluation because of death, LT, or clinical improvement; an incomplete differential diagnosis; immune dysregulation defying discrete diagnostic testing; or novel metabolic or infectious conditions.[5] Narkewicz et al[5] examined 703 PALF study participants and found only 55% had complete testing for autoimmune hepatitis. Testing for other conditions, such as Wilson disease, fatty acid oxidation defects, and herpes simplex virus (HSV), was also incomplete with significant variations in diagnostic testing among sites.[5] Given evidence of incomplete diagnostic testing and a rapid clinical course for some participants, PALF investigators established a process to improve diagnostic testing frequency using a learning collaborative strategy[7] adopted by others to reduce clinical variability and improve outcome.[8,9]

Here, the PALF cohort is characterized before and after investigators incorporated age-specific diagnostic testing (AS-DT) recommendations into the electronic medical record (EMR) to determine if enhanced diagnostic testing occurred and whether this intervention was followed by a decrease in the frequency of an indeterminate diagnosis.

Materials and Methods

This observational cohort study was conducted by the PALF study group funded by the National Institute of Diabetes and Digestive and Kidney Diseases (UO1-DK072146). Patients <18 years of age were eligible for enrollment if they met the following criteria: (1) no prior evidence of chronic liver disease, (2) biochemical evidence of acute liver injury, and (3) hepatic insufficiency characterized by prothrombin time ≥20 seconds or international normalized ratio ≥2.0 (not correctable with vitamin K) or by a prothrombin time ≥15 seconds or international normalized ratio ≥1.5 in the presence of encephalopathy (EN). Two clinical EN grade scales were used depending on participant age,[1] the Whitington scale[10] for subjects up to 3 years of age (Supplementary Table 1) and West Haven score[11] for those 4 years and older. EN assignment was by the same investigator, if possible, throughout the data collection period. Diagnostic evaluation, medical management, and assigning the final diagnosis were directed by the attending physicians and consistent with the standard of care at each site as previously reported.[1] Participants were enrolled between December 1999 and December 2014 during 3 study phases determined by funding periods. Entry criteria were never altered. Study approval was by institutional review boards of all institutions and National Institute of Diabetes and Digestive and Kidney Diseases provided a certificate of confidentiality. A data and safety monitoring board, appointed by the National Institute of Diabetes and Digestive and Kidney Diseases, provided study oversight. Informed consent was obtained from parents or guardians.

Phase 1 (P1) began in December 1999. Demographic and clinical data were recorded daily for up to 7 days. The first outcome of death, LT, or hospital discharge with native liver within 21 days following enrollment was recorded. Participants discharged before 21 days following enrollment without undergoing LT received follow-up to confirm participant status of "alive," "dead," or "liver transplant" by Day 21. Initial (eg, at enrollment) and final diagnoses were determined by the site principal investigator based on study guidelines. A diagnosis of

neonatal iron storage disease was later revised to gestational alloimmune liver disease (GALD) to reflect pathophysiological advances.[12,13] An indeterminate diagnosis was registered in the absence of evidence for a specific diagnosis.

Phase 2 (P2) began in 2006. Data elements collected over the 7 days following enrollment were similar to P1. Modifications for the P2 protocol included outcome data extended from 21 days to 1 year from study entry. Data obtained 1 year following study entry were collected in clinic or by telephone and included vital status, change in diagnosis, and medical or surgical intervention including LT. All outcomes within 1 year of study entry were recorded in P2, not just by the first event as in P1.

In transition from P2 to phase 3 (P3), enrolling sites decreased from 20 to 12 because of factors that included enrollment targets, funding restrictions, site and consortium resources, data quality, and initiating broader and more detailed data collection; 10 of the 12 sites participated in all phases of PALF. Data elements collected in P1 and P2 were carried forward, including participant outcomes at 1 year. Daily data collection was extended to the entire enrollment hospitalization.

Enrollment into P3 was briefly delayed to adapt data collection tools to incorporate granular patient and management detail. Investigators also engaged in collaborative discussions to improve frequency of diagnostic testing using data collected during P1 and P2.[1,5,14,15] The product of this learning collaborative was to recommend AS-DT at the time of hospital admission with the goals of increasing the frequency of testing for age-appropriate diagnoses identified in P1 and P2, and reducing the frequency of indeterminate diagnosis, regardless of participation in the PALF study. Factors influencing test selection included blood volume restrictions; final diagnoses within age groups; availability of the test; and likelihood that a positive test would be clinically available in time to either establish the diagnosis (eg, viral polymerase chain reaction) or lead to a more complete, focused diagnostic evaluation (eg, lactate/pyruvate ratio, ceruloplasmin). Recommended AS-DT was incorporated into EMR-based order sets at all P3 sites easily accessed by the admitting physician by typing "acute liver failure" into the search function. Each test was within the standard of care at each site and defaulted to be ordered at hospital admission regardless of participation in the PALF study. Diagnostic testing and biochemical testing was performed by the local laboratory or its affiliate. Central testing was not performed. Diagnostic tests in the order sets were not incorporated into the research protocol, but served as a tool to promote safe, efficient, and evidence-based patient care. The attending physician was responsible for ordering individual tests, which could be selectively removed or added depending on the clinical circumstances. Diagnostic criteria for known diagnoses were outlined in the PALF Manual of Operations and served to guide the investigator in establishing the final diagnosis.

Statistical Analysis

Baseline demographic and laboratory data for all sites and for those included in all phases of PALF are reported. Study entry laboratory studies include measurements up to 3 days before enrollment with preference given to the enrollment day and then those closest to enrollment day. Etiology category and specifics within category are shown. If the category was suspected but the specific etiology within the category was not, etiology was categorized as indeterminate. Continuous variables are described by median and 25th and 75th percentiles. Categorical variables are described by frequencies and percentages. Comparative data analyses were performed from 10 study sites participating in all 3 phases before (P1 + P2) and after (P3) initiating testing recommendations. Wilcoxon rank sum statistics were used to test for differences in distributions of continuous variables between the study phases before and after AS-DT implementation (P1 + P2 vs P3) using data from the 10 clinical sites participating in all phases of PALF. Pearson or exact chi-square statistics were used to test for differences in percentages of categorical variables before and after AS-DT implementation and among the age groups in combined P1 + P2. The 21-day cumulative incidence rates for LT and death were calculated and reported for those sites included in all PALF phases. Death was considered a competing risk for LT. Post-LT death was excluded by treating LT as a competing risk for death. Gray test was used to compare the cumulative incidence functions among the phases. $P < .05$ was considered statistically significant. The data were analyzed with SAS 9.4 (SAS Institute Inc, Cary, NC) and R 2013 (R Foundation for Statistical Computing, Vienna, Austria) was used to create figures.

Results

Twenty-four sites in the PALF consortium enrolled participants in at least 1 phase and 10 participated in all 3 phases (Supplementary Table 2). Demographic, diagnostic, and laboratory data in the overall PALF cohort (n = 1144) and the 10-site subcohort (n = 658; P1 + P2 [n = 515] and P3 [n = 143]) are reported (Table 1). P3 participants were younger, more likely to be male, and had similar total bilirubin and alanine aminotransferase levels as those in combined P1 and P2. Differences in international normalized ratio and creatinine are statistically different, but clinically similar. Assessable peak EN was less common in P3 than P1 and P2. The cohort deemed not assessable (eg, on ventilator) likely included participants with EN stage III and IV.

Age-specific diagnoses reported in the combined P1 and P2 cohort (Supplementary Table 3) of all participants determined priorities for AS-DT recommendations for P3. In P1 + P2 (n = 986), indeterminate PALF was the most common final diagnosis (444/986; 45%), accounting for most children age 91 days through 3 years (162/274; 59%). The most common diagnoses among

Table 1. Demographic and Laboratory Data in the Overall PALF Cohort (N = 1144) and the 10-Site Subcohort (n = 658)

Characteristic	All sites (N = 1144)	Sites in all 3 phases, total (n = 658)	Phase 1 and 2 12/99–12/10 (n = 515)	Phase 3 5/12– 12/14 (n = 143)	Phase comparison *P* value
Age, *y*, median, Q1–Q3	4.5, 0.8–13.4	4.5, 1.0–13.9	5.0, 1.2–14.1	2.9, 0.3–13.7	.03
Age at enrollment, n %					
≤28 d	156 (13.6)	79 (12.0)	50 (9.7)	29 (20.3)	.003
29–90 d	64 (5.6)	34 (5.2)	28 (5.4)	6 (4.2)	
91 d to <1 y	99 (8.7)	54 (8.2)	44 (8.5)	10 (7.0)	
1–3 y	224 (19.6)	144 (21.9)	108 (21.0)	36 (25.2)	
4–12 y	297 (26.0)	153 (23.3)	132 (25.6)	21 (14.7)	
13–17 y	304 (26.6)	194 (29.5)	153 (29.7)	41 (28.7)	
Male, n %	585 (51.1)	332 (50.5)	249 (48.4)	83 (58.0)	.04
Race, n %					
White	812 (72.6)	463 (72.7)	368 (73.5)	95 (69.9)	.40
Nonwhite	307 (27.4)	174 (27.3)	133 (26.5)	41 (30.1)	
Unknown, n % of total	25 (2.2)	21 (3.2)	14 (2.7)	7 (4.9)	
Study entry laboratory studies (includes values up to 3 d before study entry)					
INR, median Q1–Q3	2.6, 2.1–3.8	2.6, 2.1–3.7	2.5, 2.0–3.7	2.7, 2.2–3.9	.02
Missing, n % of total	97 (8.5)	30 (4.6)	30 (11.3)	0 (0.0)	
Total bilirubin, *mg/dL*, median, Q1–Q3	9.1, 2.8–7.0	7.9, 2.7–16.3	8.7, 2.7–16.6	6.1, 2.5–14.2	.11
Missing, n % of total	103 (9.0)	81 (12.3)	58 (11.3)	23 (16.1)	
ALT, *IU/L*, median, Q1–Q3	1545, 386–3393	1735, 509–3932	1693, 513–3754	1858, 490–4708	.45
Missing, n % of total	94 (8.2)	12 (1.8)	10 (1.9)	2 (1.4)	
Creatinine, *mg/dL*, median, Q1–Q3	0.5, 0.3–0.8	0.5, 0.3–0.7	0.5, 0.3–0.8	0.4 0.2–0.7	.0001
Missing, n % of total	18 (1.6)	12 (1.8)	11 (2.1)	1 (0.7)	
Encephalopathy grade peak up to 7 d past enrollment, n %					.03
0	435 (39.9)	242 (38.7)	184 (36.8)	58 (46.0)	
1	238 (21.9)	133 (21.3)	100 (20.0)	33 (26.2)	
2	172 (15.8)	105 (16.8)	88 (17.6)	17 (13.5)	
3	134 (12.3)	73 (11.7)	64 (12.8)	9 (7.1)	
4	110 (10.1)	73 (11.7)	64 (12.8)	9 (7.1)	
Not assessable, n % of total	53 (4.6)	30 (4.6)	15 (2.9)	15 (10.5)	
Not done, n % of total	2 (0.2)	2 (0.3)	0 (0.0)	2 (1.4)	

ALT, alanine aminotransferase; PALF, pediatric acute liver failure.

participants younger than 91 days of age were HSV, GALD, and metabolic conditions including galactosemia and mitochondrial/respiratory chain defects. No participant <91 days had a diagnosis of other causes of viral hepatitis (eg, Epstein-Barr virus; hepatitis A, B, C, or E) or autoimmune hepatitis. Thus, AS-DT in these youngest participants included selected viruses, metabolic disease, and GALD, but did not include autoantibody testing or viral diseases not previously identified, other than confirming maternal hepatitis B serology to identify newborns at-risk for vertical transmission. For participants, older than 90 days old, autoimmune hepatitis and acetaminophen or other drug-related liver diseases were identified. Metabolic diseases, including mitochondrial, were distributed throughout older participants, but Wilson disease was diagnosed only in participants older than 3 years. Recommended AS-DT for children ≤90 days, 91 days through 3 years, and 4–18 years are in Table 2.

Changes in the pattern of diagnostic testing before implementing the recommendations (P1 + P2) and after (P3) are depicted in Table 3. In concordance with AS-DT recommendations, participants ≤90 days demonstrated an increase in diagnostic testing for HSV ($P = .006$), enterovirus ($P < .0001$), lactate ($P = .03$), and pyruvate ($P = .02$). Children >90 days experienced a significant increase in diagnostic testing for all 3 autoantibodies, enterovirus, serum amino acids, acylcarnitine profile, lactate, pyruvate, and acetaminophen (all with $P < .0001$), ferritin ($P = .0001$), antinuclear antibody ($P = .0004$), and HSV ($P = .006$). Although ferritin was not recommended for older participants, its inclusion in diagnostic criteria for hemophagocytic lymphohistiocytosis, more frequently diagnosed in P3, likely influenced testing. Modification of AS-DT recommendations for individual circumstances, such as having an established diagnosis at hospital admission (eg, acetaminophen toxicity), was not captured.

Table 2. Recommendations for Minimal Diagnostic Evaluation by Age in Pediatric Acute Liver Failure

Recommended tests	Indication	Recommended age of diagnostic testing			
		<3 mo	3 mo to 3 y	3 mo to 18 y	4–18 y
Blood and urine tests					
Herpes blood PCR	Systemic herpes infection	X		X	
Serum amino acid profile	Urea cycle; other metabolic defects	X		X	
Ferritin	GALD screen	X			
Lactate, pyruvate	Mitochondrial screen	X		X	
Plasma acylcarnitine profile	FAO defects	X		X	
Urine succinylacetone	Tyrosinemia	X			
Enterovirus blood PCR	Systemic enterovirus infection	X	X		
Acetaminophen level	Acetaminophen exposure			X	
Hepatitis A virus IgM	Hepatitis A			X	
Hepatitis B surface antigen	Hepatitis B			X	
EBV VCA IgM or PCR	EBV infection			X	
Antinuclear antibody	Autoimmune disease screen			X	
Anti–smooth muscle ab	Autoimmune disease screen			X	
Liver kidney microsomal ab	Autoimmune disease screen			X	
IgG	Autoimmune disease screen			X	
Ceruloplasmin	Wilson disease screen				X
24-hour urine copper	Wilson disease screen				X
Historical information					
Drug history	APAP other drug or HDS exposure	X		X	
Confirm newborn screen results	Galactosemia and tyrosinemia	X			
Confirm maternal hepatitis B serology	Hepatitis B in newborn	X			
Procedures					
Abdominal ultrasound with Doppler	Vascular anomalies	X		X	
Echocardiogram	Cardiac dysfunction	X		X	
Optional diagnostic screening					
Blood culture	Sepsis				
Viral testing for adenovirus, enterovirus, HHV-6, parvovirus, influenza	Viral infection				
Hepatitis E IgM	Hepatitis E				
Soluble IL2R, ferritin, triglyceride level	HLH				
Liver copper, Wilson gene mutation analysis	Wilson disease				
MRI for extrahepatic iron deposition	GALD				
Urine orotic acid	Urea cycle defects				

Ab, antibody; APAP, acetaminophen; EBV, Epstein-Barr virus; FAO, fatty acid oxidation defects; GALD, gestational alloimmune liver disease; HDS, herbal dietary supplement; HHV-6, human herpes virus-6; HLH, hemophagocytic lymphohistiocytosis; IL2R, interleukin-2 receptor; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; VCA, viral capsule antigen.

Table 3. Frequency of Diagnostic Tests Performed Before and After Age-Specific Testing Recommendations

Test performed, n %	All PALF participants (N = 1144)	Total (n = 658)	Phases 1 and 2 (n = 515)		Phase 3 (n = 143)		Age ≤90 d *P* value	Age >90 d *P* value
			Age ≤90 d (n = 78)	Age >90 d (n = 437)	Age ≤90 d (n = 35)	Age >90 d (n = 108)		
ANA	678 (59.3)	380 (57.8)	8 (10.3)	282 (64.5)	*1 (2.9)*	**89 (82.4)**	.27	.0004
ASMA	667 (58.3)	378 (57.4)	5 (6.4)	288 (65.9)	*2 (5.7)*	**83 (76.9)**	1.00	.03
ALKM	614 (53.7)	341 (51.8)	3 (3.9)	251 (57.4)	*1 (2.9)*	**86 (79.6)**	1.00	<.0001
AI all 3	559 (48.9)	309 (47.0)	2 (2.6)	227 (52.0)	*1 (2.9)*	**79 (73.1)**	1.00	<.0001
HSV[a]	426 (37.2)	306 (46.5)	36 (46.2)	183 (41.9)	**26 (74.3)**	**61 (56.5)**	.006	.006
Enterovirus[a]	155 (13.5)	138 (21.0)	12 (15.4)	49 (11.2)	**29 (82.9)**	**48 (44.4)**	<.0001	<.0001
Serum AA	412 (36.0)	265 (40.3)	45 (57.7)	127 (29.1)	**27 (77.1)**	**66 (61.1)**	.047	<.0001
Acylcarnitine profile	358 (31.3)	247 (37.5)	37 (47.4)	111 (24.4)	**23 (65.7)**	**76 (70.4)**	.07	<.0001
Urine succinylacetone	249 (21.8)	154 (23.4)	42 (53.9)	69 (15.8)	**24 (68.6)**	*19 (17.6)*	.14	.65
Hepatitis A	785 (68.6)	465 (70.7)	35 (44.9)	330 (75.5)	*9 (25.7)*	**91 (84.3)**	.054	.052
Hepatitis B	893 (78.1)	525 (79.8)	43 (55.1)	374 (85.6)	*14 (40.0)*	**94 (87.0)**	.14	.70
Ferritin	476 (41.6)	256 (38.9)	43 (55.1)	133 (30.4)	**26 (74.3)**	*54 (50.0)*	.054	.0001
Ceruloplasmin[a]	538 (47.0)	332 (50.5)	5 (6.4)	257 (58.8)	*2 (5.7)*	**68 (63.0)**	1.00	.43
Urine copper	195 (17.0)	99 (15.0)	0 (0.0)	74 (16.9)	*0 (0.0)*	**25 (23.1)**	—	.13
Lactate	751 (65.6)	398 (60.5)	54 (69.2)	218 (49.9)	**31 (88.6)**	**95 (88.0)**	.03	<.0001
Pyruvate	254 (22.2)	213 (32.4)	31 (39.7)	93 (21.3)	**22 (62.9)**	**67 (62.0)**	.02	<.0001
Lactate/pyruvate on same day	225 (19.7)	187 (28.4)	27 (34.6)	77 (17.6)	**20 (57.1)**	**63 (58.3)**	.03	<.0001
Acetaminophen level	487 (42.6)	325 (49.4)	8 (10.3)	231 (52.9)	*4 (11.4)*	**82 (75.9)**	1.00	<.0001

NOTE. Bold text: expected to increase based on recommended age-specific diagnostic tests. Italic text: expected to decrease based on recommended age-specific diagnostic tests.

AA, amino acids; AI, autoimmune; ALKM, anti-liver-kidney microsomal antibody; ANA, antinuclear antibody; ASMA, anti–smooth muscle antibody; HSV, herpes simplex virus; PALF, pediatric acute liver failure.

[a]There was less viral and ceruloplasmin testing in phase 1 than in phase 2.

Change in distribution of diagnoses after implementing AS-DT recommendations in P3 is reflected in Table 4. The difference in the percentage of participants with an indeterminate diagnosis decreased significantly between P1 + P2 (48.0%) and P3 (30.8%); $P = .0003$. The percentage with an indeterminate diagnosis declined in each age group, but most significantly in the oldest age group (P1 + P2 [44.2%] vs P3 [24.2%]; $P = .004$) (Figure 1).

Cumulative incidence rate for LT at 21 days was significantly different ($P = .030$) among P1 (34.6%), P2 (31.9%), and P3 (20.2%) (Figure 2). The hazard ratio for LT in P3 compared with the combined P1 + P2 is 0.59 ($P = .01$) and remained similar after adjusting for participant age and clinical center with a hazard ratio of 0.60 ($P = .02$). In contrast, 21-day cumulative incidence rate for death was not significantly different ($P = .20$) among P1 (17.9%), P2 (11.9%), and P3 (11.3%). Outcomes 1 year following enrollment were available only in P2 and P3. The cumulative incidence for LT did not differ significantly in P3 (26.1%) compared with P2 (36.1%) ($P = .07$) (Supplementary Figure 1).

Discussion

Using principles of collaborative learning, PALF investigators implemented recommendations that impacted diagnostic testing, final diagnosis, and outcome.[7,8] Following integration of AS-DT into admission EMR-based order sets, diagnostic testing increased and percentage of participants with specified diagnosis increased, whereas percentage of both indeterminate diagnosis and LT decreased. LT use was reduced without increasing mortality. These efforts affirm the report from the Institute of Medicine on "Improving Diagnosis in Health Care" that asserted errors in establishing the correct diagnosis occur and may have lasting consequences, and efforts to improve the diagnostic process should be implemented.[16]

An established diagnosis enables caregivers to focus on the child's disease, it's treatment, and associated outcome. Yet efforts to confirm a correct diagnosis remain imperfect. Diagnostic error rates have never been reported in ALF in children or adults, but can range from 1% to 20% when autopsy findings or simulated patients are anonymously evaluated.[17] Errors in diagnosis result from a failure in 1 or several steps including incomplete or incorrect interpretation of medical records or history; inaccuracies in physical findings; deficient diagnostic considerations; flawed communication or clinical reasoning skills; and misinterpreting results of clinical, radiologic, or histopathologic tests.[18-21] Mild to moderate patient harm resulted as a consequence of diagnostic delay or additional diagnostic testing in up to 50% of diagnostic errors in adults with cancer.[21] Improved diagnostic accuracy in PALF may yield opportunities for disease-specific therapy, identify contraindications to LT, and prevent the harmful consequences of unnecessary LT.

Table 4. Changes in the Distributions of Diagnoses Between Each PALF Among the 10 Sites Participating in All Phases of PALF

Characteristic	All participants (N = 1144)	Sites in all 3 phases total (n = 658)	Phases 1 and 2 12/99–12/10 (n = 515)	Phase 3 5/12– 12/14 (n = 143)	Phase comparison *P* value
Final diagnosis, n %					.002[a]
Indeterminate	491 (42.9)	291 (44.2)	247 (48.0)	44 (30.8)	
APAP	152 (13.3)	91 (13.8)	67 (13.0)	24 (16.8)	
AutoAB(+)/Autoimmune	75 (6.6)	39 (5.9)	33 (6.4)	6 (4.2)	
Metabolic					
Wilson disease	36 (3.2)	21 (3.2)	21 (4.1)	0 (0.0)	
Mitochondrial disease	17 (1.5)	9 (1.4)	4 (0.8)	5 (3.5)	
Galactosemia	15 (1.3)	6 (0.9)	4 (0.8)	2 (1.4)	
Other metabolic	42 (3.7)	19 (2.9)	17 (3.3)	2 (1.4)	
Non-APAP drug	37 (3.2)	24 (3.7)	17 (3.3)	7 (4.9)	
Gestational alloimmune liver disease	37 (3.2)	21 (3.2)	13 (2.5)	8 (5.6)	
Viral					
Herpes/enterovirus	53 (4.6)	31 (4.7)	18 (3.5)	13 (9.1)	
Other viral	43 (3.8)	20 (3.0)	15 (2.9)	5 (3.5)	
Hemophagocytic lymphohistiocytoisis	34 (3.0)	24 (3.6)	15 (2.9)	9 (6.3)	
Shock/ischemia	40 (3.5)	26 (4.0)	17 (3.3)	9 (6.3)	
Other	72 (6.3)	36 (5.5)	27 (5.2)	9 (6.3)	
Indeterminate final diagnosis	491 (42.9)	291 (44.2)	247 (48.0)	44 (30.8)	.0003

APAP, acetaminophen; PALF, pediatric acute liver failure.
[a]*P* value for final diagnoses listed in bold text.

PALF participants with an indeterminate diagnosis are without a reliable distinguishing clinical feature.[5] Uncertainties regarding treatment and clinical course embedded in the indeterminate cohort may influence management decisions to err on the side of LT to avoid death or irreversible morbidities. In fact, Kings College Criteria include non-A, non-B hepatitis (eg, indeterminate) among the risk factors associated with increased mortality in nonacetaminophen ALF.[22] Thus, it is not surprising that LT is more likely to occur in patients with an indeterminate versus specific established diagnosis.[5] Given these unique clinical circumstances associated with PALF, the importance and urgency to establishing a diagnosis is apparent.

PALF investigators were successful in decreasing the percentage of participants with an indeterminate diagnosis in part because of a greater percentage of participants with diagnoses of HSV, enterovirus, mitochondrial

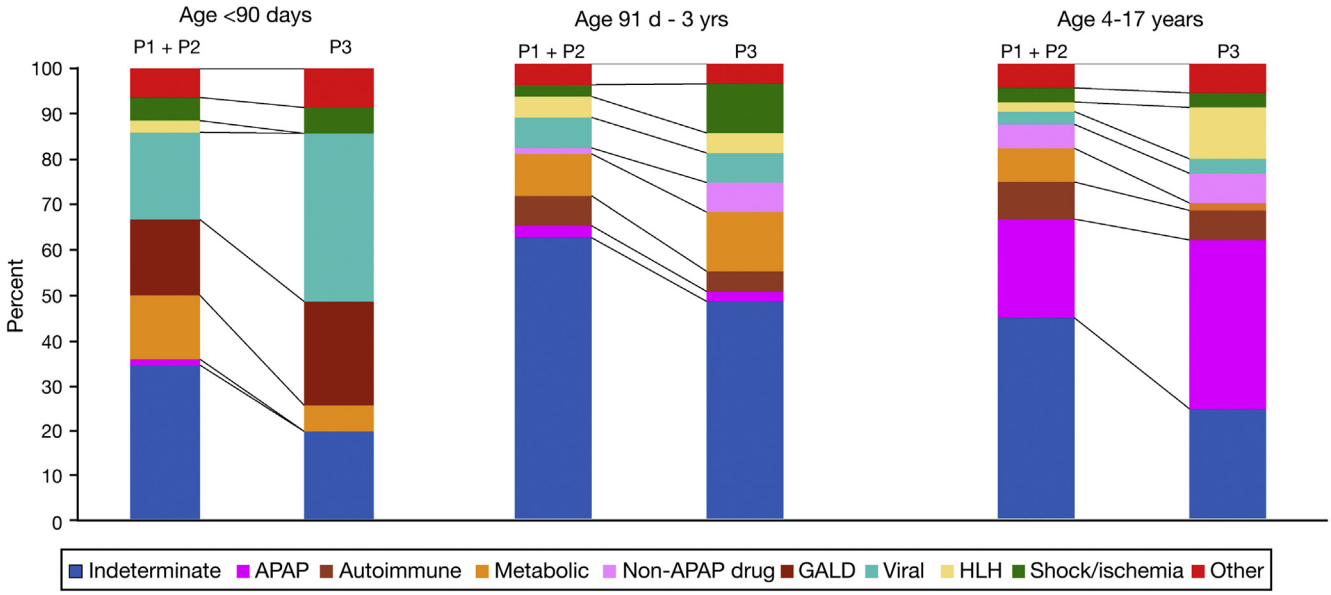

Figure 1. Final diagnosis by age and phase before (P1 + P2) and after (P3) age-specific diagnostic testing. APAP, acetaminophen; HLH, hemophagocytic lymphohistiocytosis.

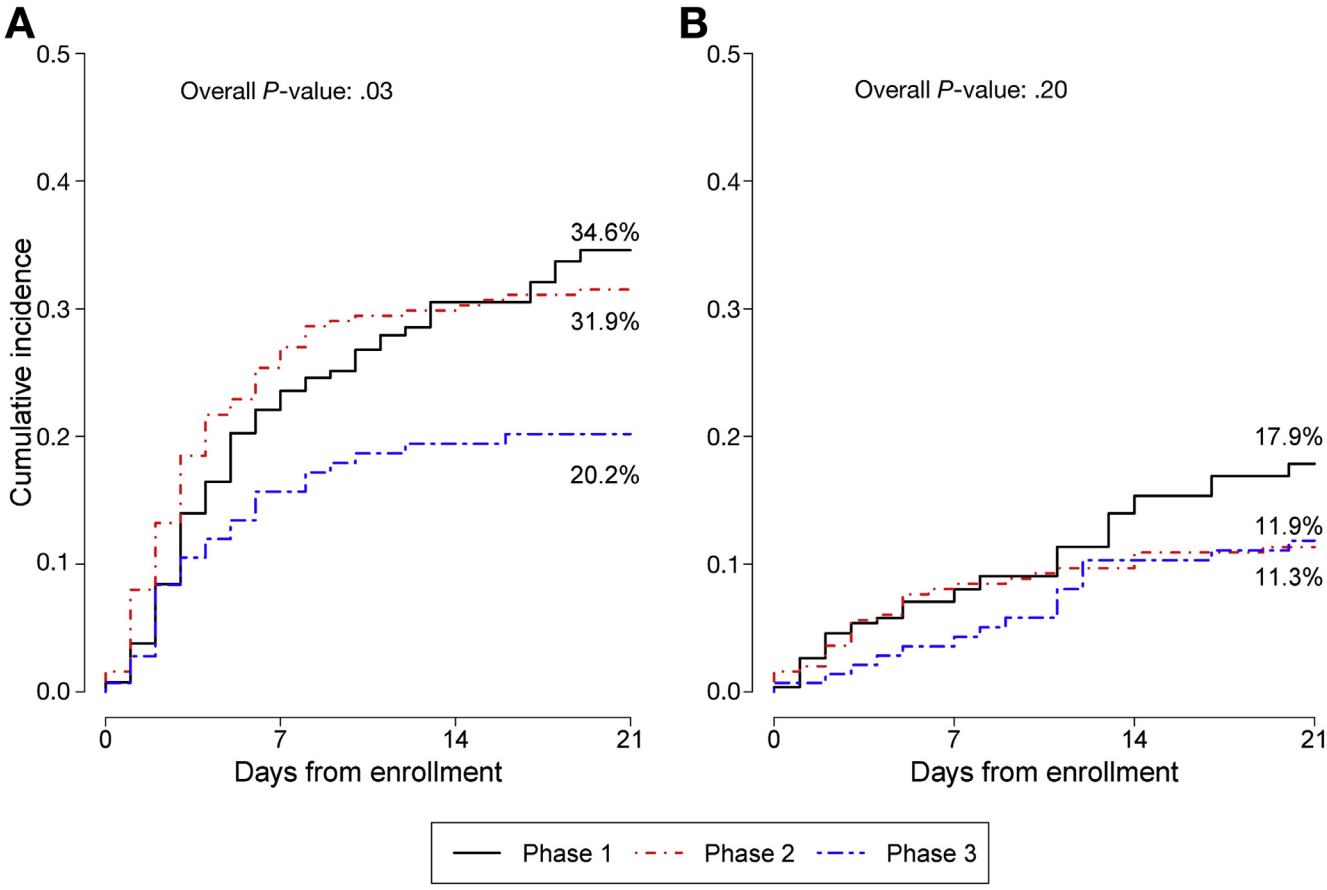

Figure 2. Comparing the cumulative incidence of (*A*) liver transplantation and (*B*) death among the 3 phases of PALF.

disease, hemophagocytic lymphohistiocytosis, and GALD following integration of diagnostic recommendations. Early identification of HSV GALD, hemophagocytic lymphohistiocytosis, or acute acetaminophen toxicity leads to potentially life-saving targeted medical interventions and treatments.[14,23-26] Conversely, a diagnosis of mitochondrial hepatopathy with systemic manifestations, currently a relative contraindication to LT, represents proper stewardship of a scarce resource.[27,28] Although our data cannot confirm a change in treatment or intervention followed the increase in known diagnoses, we assume the investigator would initiate specific treatment for an established diagnosis that would potentially impact patient outcome.

Although a specific diagnosis may be associated with a good (eg, acetaminophen toxicity) or poor (eg, neonatal HSV) outcome, diagnosis alone is insufficient to predict outcome, because survival with native liver, death, and LT occur within all diagnostic categories. We know other factors, such as EN[29] and immune and inflammatory responses provoked by inciting events,[30,31] participate in determining outcomes. Differences in patient management, variability of LT decisions, and organ availability also impact outcome.[32] On June 18, 2013, United Network Organ Sharing policy entitled "Share 35" was implemented to improve access to deceased donor organs. The brief overlap of 18 months between implementation of Share 35 and the end of PALF follow-up precludes assessment of its impact on outcome. However, this policy should have made deceased donor organs more available with the potential to increase LT among the sickest patients, yet the percentage who underwent LT in P3 was less than in earlier phases. Although changes in outcome identified in this analysis cannot be solely attributed to implementing AS-DT recommendations, reducing the prevalence of an indeterminate diagnosis may have made some impact on LT, without adversely affecting mortality.

A prioritized approach to diagnosis is a core principle in clinical medicine.[33,34] However, as knowledge and experience evolve, modifying and interpreting what constitutes best clinical practice is expected; interpreting early diagnostic testing is no exception.[34] For example, subsequent to initiating AS-DT elements, positive tests for autoantibodies were determined to be not specific for autoimmune hepatitis in PALF.[35] This is not to say autoantibody testing should be abandoned. Rather, in the absence of a gold standard diagnosis for autoimmune hepatitis in the setting of PALF, results need to be placed into clinical context that might include histologic findings or elevated immunoglobulins. An elevated serum lactate $\geq$2.5 mmol/L or, more specifically, a molar ratio of lactate/pyruvate of at least 25 were established screening tests for mitochondrial hepatopathies when

AS-DT was implemented.[36-38] However, an increased lactate/pyruvate ratio was also found to be nonspecific for mitochondrial disorders among PALF participants.[39] Possible reasons for this finding include secondary disruption of respiratory chain function in the setting of ALF, presence of an undiagnosed mitochondrial disorder concomitant with development of ALF caused by another known pathogenic condition, or altered fluid status and tissue perfusion associated with critically ill patients. In addition, integration of genetic testing using targeted next-generation sequencing into AS-DT algorithms will be transformational as cost and turn-around time for results decrease.[40] Therefore, AS-DT of children with ALF must not be static or inflexible, but should adapt to changes and improvements in diagnostic testing and assessed in the context of clinical expertise that may defy characterization by algorithms.

Limitations associated with studying a long-term observational cohort such as this one are unavoidable. Clinical, procedural, and LT decisions and designation of the final diagnosis were site and investigator dependent and subject to differences in clinical practice, patient referral patterns, consultant recommendations, organ availability, and other factors. Decisions to exclude, include, or expand elements of the recommended minimal age-specific diagnostic evaluation were site- and investigator-dependent and not protocol-driven. Improvements in, or availability of, diagnostic tests and maturation of clinical reasoning likely occurred over the study period, which may contribute to an ascertainment bias. Changes in practice at the enrolling sites may have an impact on the nature of the cohort including baseline demographics and changes in the duration of follow-up may impact outcome determinates. Because the comparative study was limited to participants in North America, these findings may not be generalizable to other regions of the world.

In conclusion, within this cohort of PALF participants, integrating EMR-based AS-DT at hospital admission was associated with enhanced diagnostic specificity and a commensurate reduction in indeterminate diagnoses. The percentage of participants undergoing LT within 21 days decreased without a change in mortality. Widespread use of EMR-based AS-DT in PALF may improve outcomes in PALF and enhance the use of an invaluable limited resource, the donor liver.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2018.04.050.

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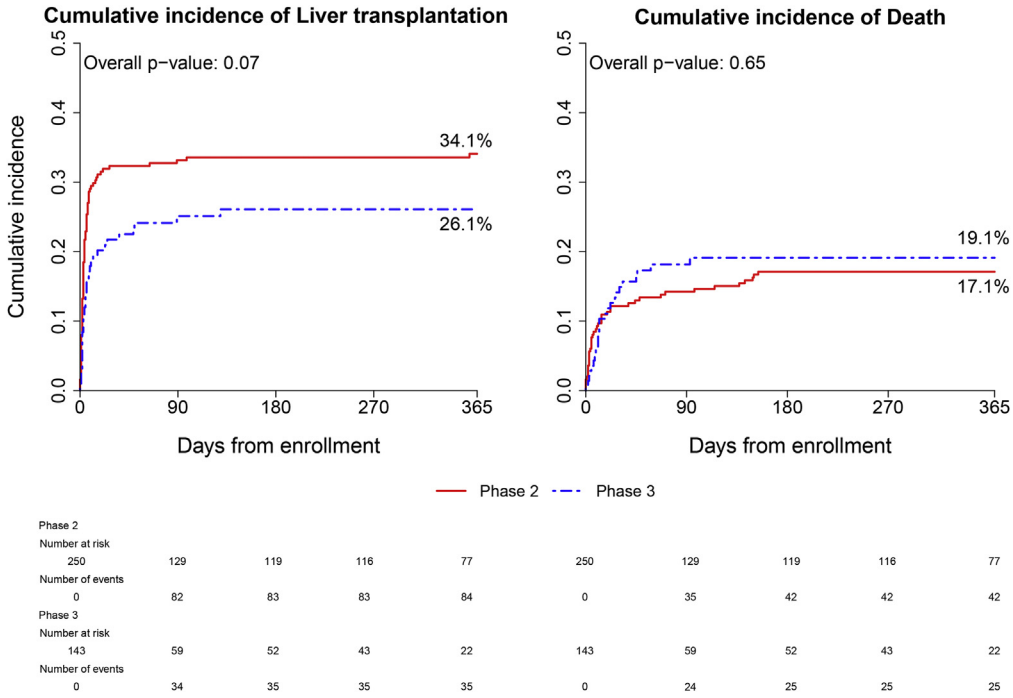
Acknowledgments
Key individuals who have actively participated in the PALF studies by site are listed next. *Current Sites, Principal Investigators and Coordinators*: Robert H. Squires, MD, Kathryn Bukauskas, RN, CCRC, Madeline Schulte, RN, BSN, Clinical Research Coordinator (Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania); Michael R. Narkewicz, MD, Michelle Hite, MA, CCRC (Children's Hospital Colorado, Aurora, Colorado); Kathleen M. Loomes, MD, Elizabeth B. Rand, MD, David Piccoli, MD, Deborah Kawchak, MS, RD, Christa Seidman, Clinical Research Coordinator (Children's Hospital of Philadelphia, Philadelphia, Pennsylvania); Rene Romero, MD, Saul Karpen, MD, PhD, Liezl de la Cruz-Tracy, CCRC (Emory University, Atlanta, Georgia); Vicky Ng, MD, Kelsey Hunt, Clinical Research Coordinator (Hospital for Sick Children, Toronto, Ontario, Canada); Girish C. Subbarao, MD, Ann Klipsch, RN, Sarah Munson, Clinical Research Coordinator (Indiana University Riley Hospital, Indianapolis, Indiana); Estella M. Alonso, MD, Lisa Sorenson, PhD, Susan Kelly, RN, BSN, Katie Neighbors, MPH, CCRC (Lurie Children's Hospital of Chicago, Chicago, Illinois); Philip Rosenthal, MD, Shannon Fleck, Clinical Research Coordinator (University of California San Francisco, San Francisco, California); Mike A. Leonis, MD, PhD, John Bucuvalas, MD, Tracie Horning, Clinical Research Coordinator (University of Cincinnati, Cincinnati, Ohio); Norberto Rodriguez Baez, MD, Shirley Montanye, RN, Clinical Research Coordinator, Margaret Cowie, Clinical Research Coordinator (University of Texas Southwestern, Dallas, Texas); Simon P. Horslen, MD, Karen Murray, MD, Melissa Young, Clinical Research Coordinator, Heather Nielson, Clinical Research Coordinator, Jani Klein, Clinical Research Coordinator (University of Washington, Seattle, Washington); David A. Rudnick, MD, PhD, Ross W. Shepherd, MD, Kathy Harris, Clinical Research Coordinator (Washington University, St. Louis, Missouri). *Previous Sites, Principal Investigators and Coordinators*: Saul J. Karpen, MD, PhD, Alejandro De La Torre, Clinical Research Coordinator (Baylor College of Medicine, Houston, Texas); Dominic Dell Olio, MD, Deirdre Kelly, MD, Carla Lloyd, Clinical Research Coordinator (Birmingham Children's Hospital, Birmingham, United Kingdom); Steven J. Lobritto, MD, Sumerah Bakhsh, MPH, Clinical Research Coordinator (Columbia University, New York, New York); Maureen Jonas, MD, Scott A. Elifoson, MD, Roshan Raza, MBBS (Harvard Medical School, Boston, Massachusetts); Kathleen B. Schwarz, MD, Wikrom W. Karnsakul, MD, Mary Kay Alford, RN, MSN, CPNP (Johns Hopkins University, Baltimore, Maryland); Anil Dhawan, MD, Emer Fitzpatrick, MD (King's College Hospital, London, United Kingdom); Benjamin L. Shneider, MD, Nanda N. Kerkar, MD, Brandy Haydel, CCRC, Sreevidya Narayanappa, Clinical Research Coordinator (Mt. Sinai School of Medicine, New York, New York); M. James Lopez, MD, PhD, Victoria Shieck, RN, BSN (University of Michigan, Ann Arbor, Michigan). The authors are also grateful for support from the National Institutes of Health (Edward Doo, MD, Director Liver Disease Research Program, and Averell H. Sherker, MD, Scientific Advisor, Viral Hepatitis and Liver Diseases, DDDN-NIDDK) and for assistance from members of the Data Coordinating Center at the University of Pittsburgh (directed by Steven H. Belle, PhD, MScHyg).

Conflicts of interest
These authors disclose the following: Phil Rosenthal has consulted for Gilead, Abbvie, Roche/Genentech, Intercept, Alexion, Retrophin, Albireo, and Audentes; received research grants from Gilead, Abbvie, BMS, and Roche/Genentech; and served on the speakers' bureau for Retrophin. Rene Romero has consulted for Gilead. Robert H. Squires received royalties from Up-To-Date. The remaining authors disclose no conflicts.

Funding
Supported by the National Institutes of Health (National Institute of Diabetes and Digestive and Kidney Diseases, U01 DK072146).



Phase 2									
Number at risk									
250	129	119	116	77	250	129	119	116	77
Number of events									
0	82	83	83	84	0	35	42	42	42
Phase 3									
Number at risk									
143	59	52	43	22	143	59	52	43	22
Number of events									
0	34	35	35	35	0	24	25	25	25

Supplementary Figure 1. Cumulative incidence of liver transplantation and death in phases 2 and 3 when outcome at 1 year following enrollment was recorded.

Supplementary Table 1. Whitington Scale for Encephalopathy in Children Less Than 3 Years of Age

Stage	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

Supplementary Table 2. Pediatric Acute Liver Failure Study Group Clinical Sites

[a]Children's Hospital Colorado
[a]Children's Hospital of Philadelphia
[a]Hospital for Sick Children, Toronto
[a]Lurie Children's Hospital of Chicago
[a]University of California, San Francisco
[a]University of Cincinnati
[a]University of Pittsburgh
[a]University of Texas Southwestern
[a]University of Washington
[a]Washington University in St. Louis
Baylor College of Medicine
Birmingham Children's Hospital, Birmingham, UK Columbia University
Drexel University Emory University Harvard University Indiana University
Johns Hopkins University King's College Hospital Mt. Sinai
University of Alabama, Birmingham University of California, Los Angeles University of Michigan
University of Nebraska

[a]Site participated in all 3 phases of PALF.

Supplementary Table 3. Summary of Diagnostic Categories By Age Group

Diagnosis[a]	All n = 986	0–90 d n = 181	91 d–3 y n = 274	4–17 y n = 531	*P* value
Indeterminate	444 (45)	64 (35)	162 (59)	218 (41)	<.001
APAP	123 (12)	1 (1)	12 (4)	110 (21)	
Metabolic	100 (10)	31 (17)	30 (11)	39 (7)	
Tyrosinemia	9 (9)	3 (10)	6 (20)	0 (0)	
Wilson disease	36 (36)	0 (0)	0 (0)	36 (92)	
Fatty acid oxidation	5 (5)	0 (0)	5 (17)	0 (0)	
α_1-Antitrypsin	2 (2)	0 (0)	2 (7)	0 (0)	
Mitochondrial	20 (20)	9 (29)	10 (33)	1 (3)	
Galactosemia	13 (13)	13 (42)	0 (0)	0 (0)	
Niemann-Pick type C	4 (4)	4 (13)	0 (0)	0 (0)	
Urea cycle defect	8 (8)	2 (6)	5 (17)	1 (3)	
Glycosylation defect	1 (1)	0 (0)	1 (3)	0 (0)	
Reye syndrome	1 (1)	0 (0)	0 (0)	1 (3)	
Fructose intolerance	1 (1)	0 (0)	1 (3)	0 (0)	
Viral hepatitis	77 (8)	36 (20)	14 (5)	27 (5)	
Hepatitis A	5 (6)	0 (0)	0 (0)	5 (19)	
Hepatitis B	3 (4)	0 (0)	1 (7)	2 (7)	
Hepatitis C	1 (1)	0 (0)	0 (0)	1 (4)	
Hepatitis E	2 (3)	0 (0)	0 (0)	2 (7)	
Epstein-Barr virus	8 (10)	0 (0)	3 (21)	5 (19)	
Cytomegalovirus	3 (4)	2 (6)	1 (7)	0 (0)	
Herpes simplex	31 (40)	28 (78)	1 (7)	2 (7)	
Enterovirus	8 (10)	6 (17)	1 (7)	1 (4)	
Adenovirus	5 (6)	0 (0)	2 (14)	3 (11)	
Human herpes virus 6	2 (3)	0 (0)	1 (7)	1 (4)	
Parvovirus	1 (1)	0 (0)	0 (0)	1 (4)	
Influenza/parainfluenza	5 (6)	0 (0)	3 (21)	2 (7)	
Paramyxovirus	3 (4)	0 (0)	1 (7)	2 (7)	
Autoimmune	68 (7)	0 (0)	20 (7)	48 (9)	
Shock/ischemia	31 (3)	6 (3)	8 (3)	17 (3)	
Non-APAP drug induced	29 (3)	27 (15)	2 (1)	27 (5)	
GALD	27 (3)	6 (3)	0 (0)	0 (0)	
HLH	25 (3)	2 (1)	10 (4)	9 (2)	
Multiple	20 (2)	0 (0)	5 (2)	13 (2)	
Veno-occlusive disease	12 (1)		6 (2)	6 (1)	
Other	30 (3)	8 (4)	5 (2)	17 (3)	
Budd-Chiari	3 (10)	0 (0)	0 (0)	3 (18)	
Mushroom toxicity	5 (17)	0 (0)	0 (0)	5 (29)	
Leukemia	3 (10)	1 (13)	0 (0)	2 (12)	
Sepsis	4 (13)	2 (25)	1 (20)	1 (6)	
Other	15 (50)	5 (63)	4 (80)	6 (35)	

NOTE. The *P* value compares the distributions of the bold diagnostic categories across the 3 age groups in PALF phases 1 and 2 combined (n = 986).
APAP, acetaminophen; GALD, gestational alloimmune liver disease; HLH, hemophagocytic lymphohistiocytosis.
[a]Summarized by frequency (column %).