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

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Abstract

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.

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).

Conclusion—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

Introduction

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 non-specific 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 (i.e. is indeterminate) in 49% of children [5] and death or LT can occur within days following initial hospitalization. As 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 as it is composed of children whose more specific diagnosis was not established for reasons such as an incomplete diagnostic evaluation due to 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. examined 703 PALF study participants and found only 55% had complete testing for autoimmune hepatitis.[5] 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 (NIDDK; 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 (PT) ≥ 20 seconds or international normalized ratio (INR) ≥ 2.0 (not correctable with vitamin K) **OR** by a PT ≥ 15 seconds or INR ≥ 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 (Supplemental 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 physician(s) 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 NIDDK provided a Certificate of Confidentiality. A Data and Safety Monitoring Board, appointed by the NIDDK, 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 seven days. The first outcome of death, LT, or hospital discharge with native liver within 21 days following enrollment was recorded. Participants discharged prior to 21 days following enrollment without undergoing LT received follow-up to confirm participant status of “alive”, “dead”, or “liver transplant” by day 21. Initial (e.g., 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 P3, enrolling sites decreased from 20 to 12 due to 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 (e.g, viral PCR) or lead to a more complete, focused diagnostic evaluation (e.g. lactate:pyruvate ratio, ceruloplasmin). Recommended AS-DT was incorporated into EMR-based order sets at all P3 sites easily accessed easily 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 upon 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 labs 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 25^{th} and 75^{th} 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’s 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. 21-day cumulative incidence rates for liver transplantation 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's test was used to compare the cumulative incidence functions among the phases. P-values less than 0.05 are considered statistically significant. The data were analyzed with SAS 9.4 and R 2013 was used to create figures.

Results

Twenty-four sites in the PALF consortium enrolled participants in at least 1 phase while 10 participated in all three phases (Supplemental Table 2). Demographic, diagnostic and laboratory data in the overall PALF cohort (n=1144) and the 10-site sub-cohort [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 phases 1&2. Differences in INR and creatinine are statistically different, but clinically similar. Assessable peak encephalopathy (EN) was less common in P3 than P1 and P2. The cohort deemed not assessable (e.g., on ventilator) likely included participants with EN stage III and IV.

Age-specific diagnoses reported in the combined P1 and P2 cohort (Supplemental 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 participants younger than 91 days of age were HSV, gestational alloimmune liver disease (GALD), and metabolic conditions including galactosemia, and mitochondrial/respiratory chain defects. No participant <91 days had a diagnosis of other causes of viral hepatitis (e.g., 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 years up to 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=0.006), enterovirus (p<0.0001), lactate (p=0.03), and pyruvate (p=0.02). Children over 90 days experienced a significant increase in diagnostic testing for all three autoantibodies, enterovirus, serum amino acids, acylcarnitine profile, lactate, pyruvate, and APAP (all with p<0.0001), ferritin (p=0.0001), ANA (p=0.0004), and HSV (p=0.006). While 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 (e.g., acetaminophen toxicity), was not captured.

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=0.0003. 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=0.004, Figure 1].

Cumulative incidence rate for LT at 21 days was significantly different (p=0.030) among P1 (34.6%), P2 (31.9%) and P3 (20.2%) (Figure 2). The hazard ratio for LT in P3 compared to the combined P1&2 is 0.59 (p=0.01) and remained similar after adjusting for participant age and clinical center with a hazard ratio of 0.60 (p=0.02). In contrast, 21-day cumulative incidence rate for death was not significantly different (p=0.20) 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 to P2 (36.1%) (p=0.07). (Supplemental 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, while percentage of both indeterminate diagnosis and LT decreased. LT utilization 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 1–20% when autopsy findings or simulated patients are anonymously evaluated.[17] Errors in diagnosis result from a failure in one 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, radiological or histopathological 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.

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 (e.g., indeterminate) among the risk factors associated with increased mortality in non-acetaminophen ALF.[22] Thus, it is not surprising that LT is more likely to occur in patients with an indeterminate vs 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 due to a greater percentage of participants with diagnoses of HSV, enterovirus, mitochondrial disease, HLH and GALD following integration of diagnostic recommendations. Early identification of HSV GALD, HLH, 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] While 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 which would potentially impact patient outcome.

While a specific diagnosis may be associated with a good (e.g., acetaminophen toxicity) or poor (e.g., neonatal HSV) outcome, diagnosis alone is insufficient to predict outcome, as survival with native liver, death, and liver transplantation occur within all diagnostic categories. We know other factors such as encephalopathy [29] as well as 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. While 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 > 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 non-

specific 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 due to 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 as well as 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 as well as 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. As 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 utilization of EMR-based AS-DT in PALF may improve outcomes in PALF and enhance the utilization of an invaluable limited resource, the donor liver.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

APAP	acetaminophen
ALF	acute liver failure
AS-DT	age-specific diagnostic testing
ALKM	anti-liver kidney Microsomal antibody
ANA	antinuclear antibody
ASMA	anti-smooth muscle antibody
AA	amino acids
CSF	cerebral spinal fluid
CIR	cumulative incidence rates
DNA	deoxyribonucleic acid
EMR	electronic medical record
EN	encephalopathy
EBV	Epstein Barr Virus
FAO	fatty acid oxidation defects
GALD	gestational alloimmune liver disease
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HSV	herpes simplex virus

HLH	hemophagocytic lymphohistiocytosis
HHV-6	human herpes virus-6
IL2R	interleukin-2 receptor
INR	international normalized ratio
IgG	Immunoglobulin G
IgM	Immunoglobulin M
LT	liver transplantation
MRI	magnetic resonance imaging
NIDDK	National Institute of Diabetes and Digestive and Kidney Disorders
P1	phase 1
P2	phase 2
P3	phase 3
PALF	pediatric acute liver failure
PCR	polymerase chain reaction
PT	prothrombin time
VCA	viral capsule antigen

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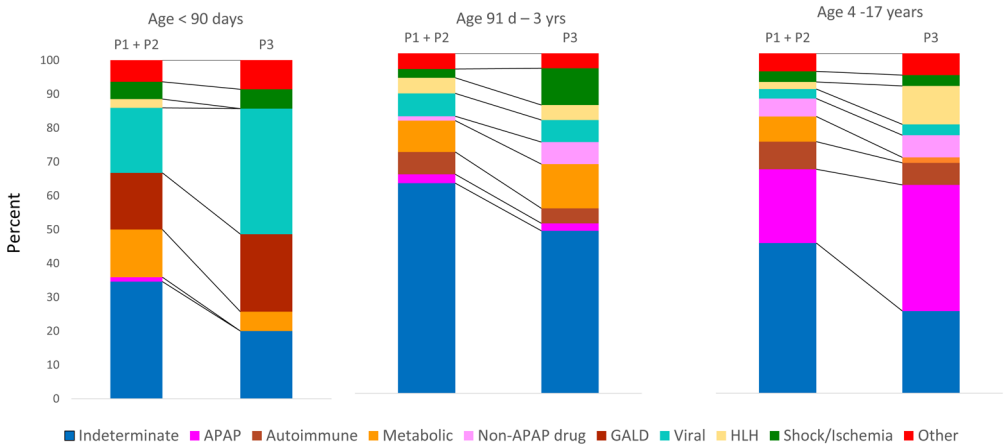

Figure 1.

Final diagnosis by age and phase before (P1+P2) and after (P3) age specific diagnostic testing.

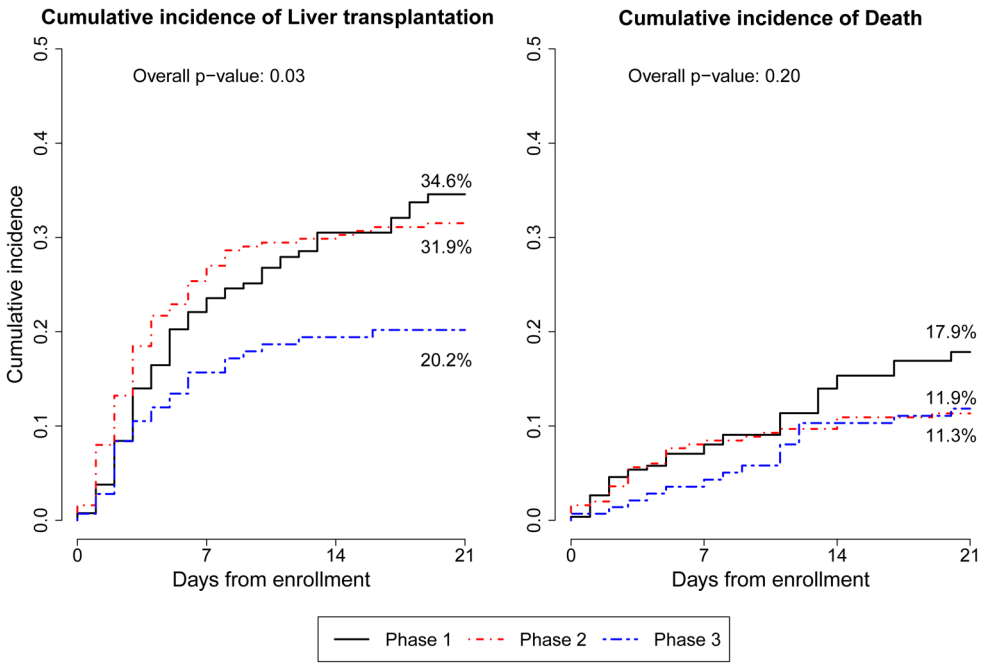

Figure 2.

Comparing the cumulative incidence of liver transplantation and death among the 3 phases of PALF.

Table 1

Demographic and laboratory data in the overall PALF cohort (n=1144) and the 10-site sub-cohort (N=658).

Characteristic	All Sites (n = 1144)		Sites in all 3 phases Total (n=658)		Phase 1 & 2 12/99–12/10 (n=515)		Phase 3 5/12 – 12/14 (n=143)		Phase comparison p-value
Age(yrs),									0.03
median,	4.5,		4.5,		5.0,		2.9,		
Q1–Q3	0.8 – 13.4		1.0 – 13.9		1.2 – 14.1		0.3 – 13.7		
Age at enrollment, n %									
≤ 28 days	156	13.6	79	12.0	50	9.7	29	20.3	0.003
29–90 days	64	5.6	34	5.2	28	5.4	6	4.2	
91 days to < 1 year	99	8.7	54	8.2	44	8.5	10	7.0	
1–3 years	224	19.6	144	21.9	108	21.0	36	25.2	
4–12 years	297	26.0	153	23.3	132	25.6	21	14.7	
13–17 years	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	0.04
Race, n %									
White	812	72.6	463	72.7	368	73.5	95	69.9	0.40
Non-White	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 Labs (includes values up to 3 days before study entry)									
INR,									0.02
Median	2.6,		2.6,		2.5,		2.7,		
Q1–Q3	2.1 – 3.8		2.1 – 3.7		2.0 – 3.7		2.2 – 3.9		
Missing, n % of total	97	8.5	30	4.6	30	11.3	0	0.0	
Total Bilirubin (mg/dL),									0.11
median,	9.1,		7.9,		8.7,		6.1,		
Q1–Q3	2.8 – 17.0		2.7 – 16.3		2.7 – 16.6		2.5 – 14.2		
Missing, n % of total	103	9.0	81	12.3	58	11.3	23	16.1	
ALT (IU/L)									0.45
median,	1545,		1735,		1693,		1858,		
Q1–Q3	386 – 3393		509 – 3932		513 – 3754		490 – 4708		

Characteristic	All Sites (n = 1144)		Sites in all 3 phases Total (n=658)		Phase 1 & 2 12/99–12/10 (n=515)		Phase 3 5/12 – 12/14 (n=143)		Phase comparison p-value
Missing, n % of total	94	8.2	12	1.8	10	1.9	2	1.4	
Creatinine (mg/dL)									0.0001
median,	0.5,		0.5,		0.5,		0.4		
Q1–Q3	0.3 – 0.8		0.3 – 0.7		0.3 – 0.8		0.2 – 0.7		
Missing, n % of total	18	1.6	12	1.8	11	2.1	1	0.7	
Encephalopathy Grade peak up to 7 days past enrollment, n %									0.03
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	

Table 2

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

Recommended Tests	**Indication**	**Recommended Age of Diagnostic Testing**			
Blood and Urine Tests		**<3 mo.**	**3 mo. to 3 yrs.**	**3 mo. to 18yr.**	**4 to 18 yr.**
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	
Immunoglobulin G	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				

Recommended Tests	Indication	Recommended Age of Diagnostic Testing			
Blood and Urine Tests		**<3 mo.**	**3 mo. to 3 yrs.**	**3 mo. to 18yr.**	**4 to 18 yr.**
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, HHV-6: Human Herpes Virus-6, HLH: hemophagocytic lymphohistiocytosis, HDS: herbal, dietary supplement, IgM: immunoglobulin M, IL2R: interleukin 2 receptor, MRI: Magnetic resonance imaging, PCR: polymerase chain reaction, VCA: viral capsule antigen

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Table 3

Frequency of diagnostic tests performed before and after age-specific testing recommendations

Test performed	All PALF participants (N=1144)		Total (N=658)		Phases 1 & 2 (N=515)				Phase 3 (N=143)				Age ≤ 90 days p-value	Age > 90 days p-value
					Age ≤ 90 days (n=78)		Age > 90 days (n=437)		Age ≤ 90 days (n=35)		Age > 90 days (n=108)			
ANA, n %	678	59.3	380	57.8	8	10.3	282	64.5	*1*	*2.9*	**89**	**82.4**	0.27	0.0004
ASMA, n %	667	58.3	378	57.4	5	6.4	288	65.9	*2*	*5.7*	**83**	**76.9**	1.00	0.03
ALKM, n %	614	53.7	341	51.8	3	3.9	251	57.4	*1*	*2.9*	**86**	**79.6**	1.00	<0.0001
AI all 3, n %	559	48.9	309	47.0	2	2.6	227	52.0	*1*	*2.9*	**79**	**73.1**	1.00	<0.0001
HSV *, n %	426	37.2	306	46.5	36	46.2	183	41.9	**26**	**74.3**	**61**	**56.5**	0.006	0.006
Enterovirus *, n %	155	13.5	138	21.0	12	15.4	49	11.2	**29**	**82.9**	**48**	**44.4**	<0.0001	<0.0001
Serum AA, n %	412	36.0	265	40.3	45	57.7	127	29.1	**27**	**77.1**	**66**	**61.1**	0.047	<0.0001
Acylcarnitine profile, n %	358	31.3	247	37.5	37	47.4	111	24.4	**23**	**65.7**	**76**	**70.4**	0.07	<0.0001
Urine succinylacetone,	249	21.8	154	23.4	42	53.9	69	15.8	**24**	**68.6**	*19*	*17.6*	0.14	0.65
Hepatitis A, n %	785	68.6	465	70.7	35	44.9	330	75.5	*9*	*25.7*	**91**	**84.3**	0.054	0.052
Hepatitis B, n %	893	78.1	525	79.8	43	55.1	374	85.6	*14*	*40.0*	**94**	**87.0**	0.14	0.70
Ferritin, n %	476	41.6	256	38.9	43	55.1	133	30.4	**26**	**74.3**	*54*	*50.0*	0.054	0.0001
Ceruloplasmin *, n %	538	47.0	332	50.5	5	6.4	257	58.8	*2*	*5.7*	**68**	**63.0**	1.00	0.43
Urine copper, n %	195	17.0	99	15.0	0	0.0	74	16.9	*0*	*0.0*	**25**	**23.1**	--	0.13
Lactate, n %	751	65.6	398	60.5	54	69.2	218	49.9	**31**	**88.6**	**95**	**88.0**	0.03	<0.0001
Pyruvate, n %	254	22.2	213	32.4	31	39.7	93	21.3	**22**	**62.9**	**67**	**62.0**	0.02	<0.0001
Lactate/Pyruvate on same day, n %	225	19.7	187	28.4	27	34.6	77	17.6	**20**	**57.1**	**63**	**58.3**	0.03	<0.0001
Acetaminophen level, n %	487	42.6	325	49.4	8	10.3	231	52.9	*4*	*11.4*	**82**	**75.9**	1.00	<0.0001

* There was less viral and ceruloplasmin testing in Phase 1 than in Phase 2.

BOLD: Expected to increase based on recommended age-specific diagnostic tests. ***ITALICS***: Expected to decrease based on recommended age-specific diagnostic tests

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 & 2 12/99–12/10 (N=515)		Phase 3 5/12 – 12/14 (N=143)		Phase comparison p-value
Final Diagnosis, n %									0.002 *
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 lymphohistiocytosis	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	0.0003

* p-value for final diagnoses listed in bold