PEDIATRIC ACUTE LIVER FAILURE STUDY GROUP

Registry and Biological Samples Protocol

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Note: Items in quotes will be different for each treatment site.

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Design Synopsis

Primary Objective: To collect, maintain, analyze, and report clinical, epidemiological, and outcome data in children with ALF, including information derived from biospecimens.

Specific Aims:

- To identify cohorts of patients who have unique treatment requirements and outcomes.

- To test the hypothesis that variables useful for predicting spontaneous survival (survival without liver transplantation) in this population will vary with different patient age groups, but that diagnosis, multi-system organ failure, degree of encephalopathy and level of coagulopathy will be important regardless of patient age.

- To identify and define the various etiologies and outcomes of ALF in children on a national and international scale.

Inclusion Criteria:

- Evidence of acute liver injury: defined as severe liver dysfunction occurring within 8 weeks of onset of illness, with no known underlying chronic liver disease
- INR ≥ 1.5 or protime ≥ 15 seconds with encephalopathy OR
  INR ≥ 2.0 or protime ≥ 20 seconds with or without encephalopathy
- The patient is under 18 years of age at the time of enrollment
- Informed consent is obtained from the parent, or guardian, and patient assent is obtained when applicable

Exclusion Criteria:

- Known chronic underlying liver disease
- Coagulopathy corrected with Vitamin K

Duration of Follow-up
One year following the date of enrollment into the study.

Introduction

Acute liver failure (ALF) is a unique illness of multiple etiologies, unusual severity, and a rapid clinical course. Even when the etiology is known, the reasons for the fulminant nature of the disease in a given individual (hepatitis B, for example) remain unknown. The Adult Acute Liver Failure Study Group (ALFSG) was organized in 1997 around the idea that a disease this devastating and this infrequent (estimated 2,000 cases per year in the U.S.) can only be studied effectively by gathering data and evaluating treatments using multiple centers.

The Pediatric Acute Liver Failure (PALF) Study is a multi-center, multi-national collaborative study aimed at identifying, characterizing, and developing management strategies for infants, children, and adolescents who present with acute liver failure (ALF). It includes 20 clinical centers and a data coordinating center. Initial funding and support from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) came through the Adult Acute Liver Failure Study Group (NIH 1RO1-DK58369-01) with a Data Coordinating Center (DCC) at the University of Texas Southwestern in Dallas, TX. Due to the successful growth of this international pediatric network and the separate scientific questions posed by the pediatric investigators, PALF established its independence from the adult project with the Principal Investigator, Dr. Robert Squires, moving from Dallas, TX to the University of Pittsburgh. The registry is computerized and maintained by a Data Coordinating Center (DCC) which has moved to the Epidemiology Data Center (EDC) of the Graduate School of Public Health at the University of Pittsburgh.

The primary focus of the PALF study group is to collect, maintain, analyze, and report clinical, epidemiological, laboratory, and outcome data in children with ALF, including information derived from biospecimens. To accomplish this goal, a centralized registry has been created that includes detailed demographic, clinical, laboratory, and outcome data from over 400 children with ALF. The project was originally funded through August 31, 2010. An extension has been submitted to the NIH and is pending. It is estimated that 90-110 new patients will be enrolled each year. To date, the PALF study group has: (1) redefined acute liver failure in children, (2) identified acetaminophen as a cause of ALF in children who did not have a history of an acute ingestion, (3) demonstrated that the etiologies of ALF in children differ greatly from those seen in adults, particularly in relation to viral hepatitis, (4) described defects in fatty acid metabolism associated with ALF in children, (5) recognized that autoimmune hepatitis is a prominent cause of ALF in children and occurs more frequently in males.

1.0 Objective and Specific Aims

- To collect, maintain, analyze, and report clinical, epidemiological, and outcome data in children with ALF, including information derived from biospecimens.

- To identify cohorts of patients who have unique treatment requirements and outcomes.

- To test the hypothesis that variables useful for predicting spontaneous survival (survival without liver transplantation) in this population will vary with different patient age groups, but that diagnosis, multi-system organ failure, degree of encephalopathy and level of coagulopathy will be important regardless of patient age.

- To identify and define the various etiologies and outcomes of ALF in children on a national and international scale.

2.0 Background and Significance

2.1 Background

2.1.1 Acute liver failure

In adults, acute liver failure is best defined as the onset of altered mental status (hepatic encephalopathy) and coagulopathy (prolonged prothrombin time) occurring within 8 weeks of initial symptoms of a hepatitis-like illness. A broader definition is used by many investigators, that is, a maximum symptom to liver failure interval of 26 weeks. Many etiologies of ALF are recognized. Traditionally, the most frequent cause in the US has been viral hepatitis with drug-induced liver injury second, and smaller numbers of cases due to a variety of etiologies. In nearly 20%, no clear-cut cause can be determined [1-3]. Mortality figures in the range of 80-94% were observed in the pre-transplant era, but still are approximately 35%, even with liver transplantation. Prognosis in ALF has been thought to depend on a variety of factors including age, etiology, length of illness and the availability of specialized critical care facilities, but up-to-date studies and the development of better methods to predict outcome (need for transplantation) are needed.

In children, acute liver failure may be present without clinical evidence of encephalopathy [4]. Coagulopathy appears to be an important, consistent, and reliable finding in children with ALF. The incidence of acute liver failure in children is unknown, but likely approaches 100 cases per year. For those in whom a diagnosis is identified, the causes are typically related to infection, inherited metabolic defects, or drug-induced liver injury and treatment can be directed to the underlying condition. However, with over half of the cases of ALF in children found to be indeterminate, treatment strategies are primarily supportive [5, 6].

Orthotopic liver transplantation can be a life saving procedure for children with ALF [7]. Given the shortage of available organs, however, many will die prior to receiving

a liver transplant. For those fortunate to receive an organ, long term graft and patient survival is diminished when compared to those receiving liver transplants for other causes [8, 9].

2.1.2 Multiorgan Failure in ALF

ALF is not merely a disease involving the liver. The sudden loss of hepatocyte function sets in motion a complex process referred to as the multiple organ dysfunction syndrome (MODS), involving failure of kidneys, lungs, bone marrow, the circulatory system, and the brain [10]. A unique feature of ALF in comparison to other causes of MODS is cerebral edema [11]. Patients with ALF are also more susceptible to severe infections. Cerebral edema and systemic sepsis are the most frequent causes of death in ALF, but intractable arterial hypotension and the adult respiratory distress syndrome (ARDS) also account for significant morbidity and mortality in these patients. The pathogenesis of MODS in ALF is complex and not well elucidated. In addition to the loss of hepatocyte function, mediators including interleukin (IL)-1, endotoxin, IL-6, and tumor necrosis factor alpha (TNF-a), are involved [12]. The severe circulatory disturbance is characterized by a hyper-dynamic circulation and tissue hypoxia similar to the sepsis syndrome [13], with impaired tissue oxygen extraction or altered peripheral cellular metabolic pathways.

2.1.3 Other Studies of ALF

In adults, a focused research effort in ALF was conducted between 1972 and 1997 at Kings College Hospital, London which has a dedicated Acute Liver Failure Intensive Care Unit. Much of the information concerning etiology, pathogenesis, prognosis, and treatment modalities over the past 24 years has come from this unit. This unit pioneered use of activated charcoal perfusion columns (shown in a controlled trial to be of little efficacy), and most recently performed a pilot study using one of the early extracorporeal liver assist devices (ELAD). This same unit developed the prognostic criteria most commonly used around the world for determining the need for liver transplantation in ALF patients. The extensive experience at Kings has given this unit the edge in honing critical care skills, and their outcome figures, which have improved considerably over recent years, cannot be extrapolated to smaller, less experienced intensive care unit settings. Regional and world-wide differences in etiology are noted. For example, drug-induced acute liver failure is common in Europe and the US, but plays a very small role in developing countries. Recent reports from the US identify acetaminophen and other medications as accounting for over 50% of the cases of ALF while India, a developing country, reported no acetaminophen-related toxicity and only 5% of ALF cases related to medications with isoniazid being the most commonly identified. In contrast to developed countries, viral hepatitis, particularly hepatitis A in South America and hepatitis A and E in India, are dominant causes of ALF.

Fulminant hepatic failure in children has not received the attention it deserves. Published studies are few and the numbers of patients are small. Investigators from Los Angeles, London, and Chile in separate reports identified only 125 patients over many years time. Studies of children with liver failure that present to a transplant

center include patients with known chronic liver disease. We plan to focus upon causes of acute hepatic failure in children without known chronic liver disease.

The PALF Multi-Center Study Group addresses a definite need: lack of significant research in acute liver failure in the United States in children, due in part to different referral patterns in the US, resulting in fewer cases of ALF being seen at any one US center. Having established a widely-based multi-center study group through which information concerning the natural history, etiologies, and outcome of ALF in the United States, Canada, and the UK, can be drawn, we facilitate collection of clinically-derived samples, and use the group's strength in numbers to perform collaborative therapeutic trials in ALF.

2.2 Significance

This research will allow investigators to:

- Perform in-depth analysis of specific disease entities such as autoimmune hepatitis, metabolic disorders, drug-induced liver injury, and established or novel infectious agents.
- Define the clinical parameters that encompass the spectrum of ALF in children.
- Explore diagnostic or pathophysiological mechanisms of disease beyond the clinical description.
- Study disease processes in a patient population with fewer co-morbidities than adults and with a unique physiology that may predispose them to different susceptibilities, presentations and outcomes than adults with respect to ALF.
- Enhance the ability to identify those children likely to survive without transplantation and those too sick to survive despite transplantation.

3.0 Research Design and Methods

3.1 Study Procedures

This research will not impact the standard of care, as determined by each clinical site that is provided to the patient. The principal investigator, co-investigator, or clinical research coordinator determine eligibility and obtain informed consent from the patient's parent or guardian. A decision to obtain assent from the child to participate in the study will be made by each site and will be based upon local criteria for obtaining assent as well as the child's developmental and cognitive abilities at the time assent is obtained. The principal investigator, co-investigator, or clinical research coordinator collects in-depth information, via case report forms, concerning risk factors, causes of illness where known, clinical and laboratory features, and outcome with and without liver transplantation.

Eligible patients who die during the hospitalization prior to obtaining consent are considered to be enrolled so that in-hospital information may be obtained via a retrospective chart review.

Biospecimens

The biospecimens collected for this study are blood, urine, liver tissue, bile, and skin.

At the time of routine blood draw, additional blood samples will be collected on the 1st or 2nd day following study enrollment, or as soon as possible following enrollment. Samples will be collected, processed, and then batch shipped to a NIDDK-funded repository for use in future studies or shipped directly to a designated testing laboratory. The samples will be stored in the repository indefinitely. If consent has been provided for collection of a DNA specimen (see Section 4.4.1 below), one of the blood samples will be sent directly to the NIDDK supported laboratory where the DNA will be extracted from the blood sample. If consent for the collection of a DNA specimen is not provided, the cumulative whole blood volume taken over the study period will be 5.2cc less in children under 50 kilograms and 20.0cc less in children 50 kilograms or over. If a patient is discharged before the genetics sample is obtained, the sample may be collected during a routine blood draw performed at a clinical follow up visit.

The amount of blood taken for research purposes is dependent upon the weight of the patient and the amount of blood taken for clinical purposes. Center specific guidelines will be followed in regard to the maximum amount of whole blood taken during a single draw and the cumulative amount taken over the study period. Whole blood volumes in the following table will be used as a guide:

Patient Weight	Maximum Whole Blood Volume Over the Study Period for Research Purposes
Less than 5 kgs	9.2 cc (1.9 teaspoons)
≥5 and <10 kgs	19.2 cc (3.9 teaspoons)
≥10 and <20 kgs	21.7 cc (4.4 teaspoons)
≥20 and< 50kgs	26.7 cc (5.4 teaspoons)
50 kgs and over	41.5 cc (8.4 teaspoons)

Urine samples (5 to 20 ml) will be collected on days 1 and 2 of study participation. When a urinary catheter is not in place as a result of standard clinical care, urine samples will be collected via sterile collection cup or bag. A urinary catheter will not be placed solely for the purpose of obtaining a sample for the study. Urine samples will be collected, frozen on site, and then batch shipped to a NIDDK-funded repository for use in future studies. The samples will be stored in the repository indefinitely.

In addition, when a liver biopsy is performed for clinical purposes or in the event of liver transplantation or autopsy, a liver tissue sample will be obtained when available. The sample will be processed according to study guidelines and stored in the NIDDK sponsored repository.

At the time of liver transplantation or autopsy, bile will be extracted from the gall bladder. The sample will be processed according to study guidelines, and stored in a NIDDK-funded repository.

At the time of an open liver biopsy performed for diagnostic purposes or liver transplantation a skin biopsy will be performed. At autopsy a skin or tendon biopsy will be performed. A sample measuring approximately 2-4mm X 2-4mm will be removed from the incision site and placed into growth media. The sample will be shipped directly to the designated testing laboratory for processing, then shipped to a NIDDK-funded repository for storage.

Samples collected at the time of autopsy will require a separate consent. Samples will be collected only when the parent or guardian has provided consent to obtain samples at the time of autopsy.

Repository samples may be used by secondary investigators if sponsored by a member of the PALF Study group and if the investigators have a protocol approved by the PALF Steering Committee.

3.2 Data Collection and Statistical Considerations

3.2.1 Study Data Collection

Data regarding the initial hospital admission, medical history, and current condition of patient will be obtained at the time of enrollment in the registry. A daily log of clinical measurements, tests, and procedures will be recorded. A minimal amount of follow-up data will be obtained at 6 and 12 months following entry into the registry. Follow-up data will include outcome status (alive, transplantation, or death) and changes to final diagnosis. These data may be collected at the time of a clinical follow-up visit or via telephone contact with the patient or patient's parent or guardian.

A parent or guardian may withdraw consent for participation at any time in the course of this research study. Any research or medical information recorded for, or resulting from, the child's participation in this research study prior to the date that consent for child's participation was formally withdrawn may continue to be used by the investigators for the purposes described above.

A site principal investigator may withdraw a child from the study in circumstances related to either the parent or child's failure to cooperate fully with the conduct of the study, or the recognition of significant medical risks associated with the child's continued participation in this study. If a child's participation in this study is stopped, the reasons will be discussed with the parents and the child. Any research or medical information recorded for, or resulting from, the child's participation in this research study prior to the date that the child's participation was formally withdrawn may continue to be used by the investigators for the purposes described above.

Data may be used by secondary investigators if sponsored by a member of the PALF Study group and if the investigators have a protocol approved by the PALF Steering Committee.

3.2.2 Statistical Analysis

To test the main hypothesis that survival without liver transplantation (i.e., spontaneous survival) of children with ALF varies by age, survival models will be used. Covariates will include diagnosis, an indicator of multi-system organ failure, degree of encephalopathy, and level of coagulopathy. We will utilize stepwise modeling to determine whether these, or other, variables are independently associated with spontaneous survival. If the p-value associated with the coefficient for a variable is less than 0.05, then that variable will be considered to be associated with spontaneous survival and included in the model. An advantage of having an ongoing registry is that results of this exploratory analysis can be confirmed by testing whether the models identified in this manner also fit newly diagnosed cases. The ongoing registry will provide the opportunity for numerous investigations, descriptive and inferential. Appropriate statistics (e.g., measures of central tendency, variability) and analytical techniques will be employed by having the study statistician involved in all analyses.

4.0 Human Subjects

4.1 General Characteristics – Minority Inclusion and Non-Discriminatory Statements

In general, ALF patients comprise somewhat more females than males, but there is no preponderance of any racial group, other than that expected on the basis of geographic differences. No exclusion will be made on the basis of race, ethnic group or gender. Criteria for inclusion of females and minorities will be those established in the NIH guidelines.

4.2 Inclusion of Children in Research

This research is restricted to children.

4.3 Inclusion/Exclusion Criteria – Pregnancy and Birth Control Statements

There are no entry criteria regarding pregnancy since the registry is an observational study, with the exception of the biospecimen collection as part of the routine blood draw.

4.4 Recruitment Procedures

Each clinical center must submit timely applications to its institutional review board, including renewals and amendments to current protocols. Failure to do so will disqualify a center from participation until the process is completed. Each site must send a copy of the current IRB approval letter to the DCC, citing the study and its approval date. Copies of the approved informed consent document should also be submitted to the DCC.

All patients from birth through 17 years of age presenting with evidence of acute liver failure will be considered for participation in the Registry. An estimated 90-110 patients will be enrolled across all sites each year.

Inclusion Criteria:

- Evidence of acute liver injury: defined as severe liver dysfunction occurring within 8 weeks of onset of illness, with no known underlying chronic liver disease
- INR ≥ 1.5 or protime ≥ 15 seconds with encephalopathy OR
  INR ≥ 2.0 or protime ≥ 20 seconds with or without encephalopathy
- Patient is under 18 years of age at the time of enrollment
- Informed consent is obtained from the parent, or guardian, and patient assent is obtained when applicable

Exclusion Criteria:

- Known chronic underlying liver disease
- Coagulopathy corrected with Vitamin K

In some instances, the physician caring for the child with PALF may not be a listed investigator. In this situation, the treating physician may introduce this study to the parent, and should the parent be interested in meeting with a PALF study investigator, the treating physician will document the parent's interest in the study and permission for the treating physician to pass the parent's name and contact information to a study investigator.

4.4.1 Informed Consent

The principal investigator/co-investigator will inform the parent/guardian about the purpose of the study, the type of information to be collected, including blood samples, a liver tissue sample when clinically indicated, and measures taken to protect confidentiality. The parent/guardian will be informed of the risks and potential benefits of the study and of the child's rights as a research subject. Each site will follow their respective state laws regarding the definition of a legal guardian and the right of the legal guardian to provide consent for research. All questions will be answered prior to obtaining their signature on the informed consent document.

Enrolled patients who turn 18 years of age during the course of the study but after they are discharged from the hospital, will be contacted via telephone by the principal investigator, co-investigator, or clinical research coordinator to request their permission for continued participation in the study. The study staff will review the details of the study, including measures taken to protect confidentiality, their rights as a research subject, and the risk of a breech of confidentiality. All questions will be answered prior to obtaining the subject's verbal consent for continued participation. The principal investigator, co-investigator, or clinical research coordinator will document, the date/time of contact with the patient, the patient's response to the request for continued participation, and the name of the person making contact.

When an enrolled patient turns 18 years of age while still in the hospital, the principal investigator, co-investigator, or clinical research coordinator will review the details of the study and answer all questions prior to obtaining the subject's signature on the consent document for continued participation in the study.

Blood samples

- Information on the collection of blood samples is on the main registry consent.

DNA specimens

Information on the intent to conduct genetic testing is provided on the main registry consent form or a separate consent document, per the guidelines at each clinical center. The patient's parent or guardian is asked to consent to the use of the patient's blood sample for genetic testing by initialing one of the following statements.

- I give permission for my child's blood samples to be used for genetic testing. Specimens may be stored for as long as they can be used. Specimens can be used for genetic research that is not yet planned and may be performed after the completion of the PALF study.

- I **do not** give permission to collect or store my child's blood as described above for genetic research.

4.5 Risk/Benefit Ratio

The only risk associated with the collection of clinical data is the unlikely risk of a breach of confidentiality. To protect patients' confidentiality, patients' names will be used only for the informed consent form and medical chart reviews. Patients will be given unique study identifiers, which will be written on all data collection forms. In addition, documents that link the study IDs with patient names will be kept in secured, locked files at the clinical center.

Plasma samples collected involve removal of small quantities of blood at the time of a routine blood draw, for basic clinical care, and thus do not require special phlebotomy procedures. The risks of venipuncture at the time of the blood draws are pain, bruising, and superficial phlebitis. The total quantity of blood withdrawn per day for the purposes of the study is based upon the child's weight and amount of blood drawn for clinical purposes. The combined volume drawn for clinical and research purposes will not exceed the volume specified by the clinical center IRB for daily volume or total volume over a week's time.

Liver tissue samples taken at the time of a liver biopsy performed for clinical purposes, or at the time of liver transplantation or autopsy do not require special study procedures.

Collection of urine from a catheter that is already in place or via a sterile cup or bag does not require special study procedures.

There will be no added risk to the patient when a sample of skin is taken from the open incision at the time of an open liver biopsy, liver transplantation, or autopsy as the sample is taken from the incision line which will be approximated when the skin is closed. There will not be an additional scar as a result of taking this small skin sample.

Subjects are unlikely to receive any personal benefit from being in this study. However, a study to delineate the nature of acute liver failure in the United States has not been performed previously due to the logistical difficulties of coordinating many centers. This study has the potential to bring to light new information concerning this serious and usually fatal condition, which often affects young people.

4.6 Data and Safety Monitoring

A Data and Safety Monitoring Board (DSMB), with members appointed by the NIDDK, consists of individuals who are independent of the institutions and investigators participating in the PALF study and who have no financial ties to the outcome of the study. The ongoing review of the data by this independent committee assures the investigators and the NIDDK that the study can continue. The roster and charter of the DSMB members have been provided to investigators participating in the study for submission to their IRB.

The DSMB charter was developed by the NIDDK. The DSMB reviewed the study protocol and recommended recruitment continuation. It will monitor all aspects of the study (e.g., recruitment, protocol deviations, breeches of confidentiality, site visit summaries, data quality, attrition, descriptive characteristics), and recommend protocol modifications, including early study termination. Quarterly reports will be prepared by the DCC. Tables showing study progress will be presented by clinical center and overall. These will include recruitment, protocol deviations, attrition, breeches of confidentiality, data quality, and descriptive characteristics of the study sample. The DCC will maintain a cumulative summary of breeches of confidentiality to be forwarded to the DSMB for their semi-annual meetings via conference call or in person. Based on the data presented, the DSMB will recommend continuation or termination of the study. A summary of the DSMB findings will be forwarded to all investigators for submission to their respective IRBs.

5.0 Costs and Payments

5.1 Research Study Costs

The patient's insurance provider will not be billed for any procedures performed solely for the purpose of this research study. Expenses resulting from standard care for medical problems are the responsibility of the patient, patient's guardian, or the patient's insurance provider or government program. There are no funds available to pay for lost time away from work and other activities, lost wages, or child care expenses.

5.2 Research Study Payments

There are no payments or other remunerations to the research subjects.

6.0 Appendices

6.1 Bibliography and References

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