A Multi-Center Group to Study Acute Liver Failure

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A. SPECIFIC AIMS

Acute liver failure (ALF) is a dramatic syndrome in which previously healthy individuals rapidly lose hepatic function due to a variety of causes, develop hepatic encephalopathy, and become critically ill within days. The mortality is high, up to 94%. Even in the era of liver transplantation, more than 40% die, either due to complications of this devastating disease or because donor organs are not available. Since ALF occurs relatively infrequently, no one center in the US has a large enough experience to conduct important studies of this condition. The Acute Liver Failure Study Group had received funding from the National Institutes of Health (NIH) from September 1997 through August 31, 2005 under grants R03 DK52827 and R01 DK58369. In September of 2005, the study received funding through August 31, 2010 under a cooperative U01 agreement. ALFSG is currently funded by a continuation of this same U-01 cooperative research agreement through 2020, and currently involves 12 sites in the United States and Canada. Our initial goals were to develop a multi-center ALF study group initially at liver transplant centers around the United States, with the broad aims of 1) gathering data and serum on ALF patients, and 2) developing a pilot therapy trial of N-acetylcysteine (NAC) for ALF and these have largely been accomplished. Clinical data and serum collected since January 1, 1998 on over 2,500 carefully defined patients have yielded new insights into the natural history and outcomes of ALF. One important trend has been an apparent increase in the number of patients with drug-induced acute liver failure, which currently represents >50% of all cases. The unique availability of blood and tissue samples from a large number of patients with ALF has triggered more than 140 ancillary studies, generated over 70 original articles on all aspects of ALF. An addition in 2009 was the Acute Liver Injury (ALI) study, capturing earlier stage disease, prior to the onset of encephalopathy and advanced liver failure.

The specific aims of the study listed are below:

Specific Aim 1: To continue and extend the current highly successful registry tracking secular trends in ALF, with several added features: a tighter study group, continuation of the ALI study, more detailed data and specimen gathering on each case, electronic data capture, and use of detailed check lists for ICU management,. Emphasis will be placed on gathering tissue samples for mechanistic studies and detailed intensive care unit (ICU) data while improving prognostic scoring systems.

Specific Aim 2: To further elucidate the pathogenesis of liver injury and multi-organ failure. We continue to undertake studies of basic mechanisms of the innate and adaptive immune responses, the role of genetic predisposition, cytokines, coagulation, endothelial dysfunction and hepatic regeneration that initiate, sustain and resolve ALF.

Specific Aim 3: To evaluate the safety and efficacy of new prognostic and therapeutic agents in the management of ALF and ALI.

B. BACKGROUND AND SIGNIFICANCE

B.1. Introduction: Historical perspective. Acute liver failure (ALF) was first recognized as a specific and unique entity in the early 1950's. Defined as including coagulopathy and encephalopathy, cerebral edema is a unique feature of acute liver failure that frequently leads to death.[1],[2] Survival has improved in recent years from <10% to ~60% due in part to the use of liver transplantation and an evolution to more benign etiologies. Even now this catastrophic illness can progress within hours to coma and death due to multi-organ dysfunction.[3,4] We estimate that 24% of those listed for transplantation die because a liver graft cannot be found in time. Although ALF is truly an orphan disease affecting only about 2,000 persons per year,[5] its severity, its frequency among young adults, and its high resource utilization justifies the attention paid to it. In addition, ALF has captured the interest and attention of researchers because of its unique pathogenesis and extreme severity, encouraging us to understand the processes underlying all forms of liver injury, by focusing on this most lethal manifestation.

Acute Liver Injury (ALI), a milder form of ALF: Patients with ALF represent the most severe end of a spectrum of advanced liver injury. A second group of patients worthy of study are those with acute liver injury who have coagulopathy but do not reach the threshold of encephalopathy. Few studies have been performed on this less severe group; however, their morbidity and mortality may approach that of conventionally defined ALF.[6] It would be of value to study patients destined to possibly have ALF earlier in their illness for several reasons: first, we might be able to better predict who will progress to full liver failure; second, the current definition requiring encephalopathy limits the number of patients available for study at any site; finally, therapeutic trials might have greater efficacy if begun at earlier disease stages.

B.2. Prior studies in ALF: Specific Etiologies. Early reports of acute liver failure were limited to small series from individual centers over many years. The lack of specific serologic tests led to most cases being attributed on clinical grounds to viral hepatitis,[2,5] with hepatitis B as the most common cause. Early on, no hepatitis A or acetaminophen toxicity cases were recognized. In the 60's through the 1980's, the etiologic makeup of ALF was unclear, in part because of lack of accurate diagnoses, but also because there was no central ALF registry. Our

initial report of 295 patients seen between 1994 and 1996 at the 14 initial Acute Liver Failure Study Group (ALFSG) centers was the first systematic multi-center review of etiologies and outcomes. That study identified acetaminophen toxicity as present in 20% of ALF patients.[7] The etiologies associated with ALF have continued to change further over the years with an apparent decline in viral hepatitis, and a remarkable increase in acetaminophen toxicity to its current level of ~44-50% of cases.[8,9] A further problem in studying ALF is that the number of cases of a specific etiology observed at any one institution are vanishingly small. The earliest goals of the ALF Study then were to more carefully define the etiologies of ALF on a national scale, and to finally allow in-depth study of specific ALF causes such as autoimmune ALF, viral hepatitis and Wilson disease (WD).

B.3. Outcome in Acute Liver Failure and the Role of Transplantation: Despite the diverse etiologies recognized, the final clinical common pathway of acute liver failure is remarkably similar across all patient groups. Coagulopathy, encephalopathy and cerebral edema constitute a hallmark triad, but hypotension and renal insufficiency, susceptibility to infection and other multi-organ system failure are typically observed as well. Causes of death include cerebral edema, multi-organ failure, sepsis, cardiac arrhythmia or respiratory failure. Factors associated with prognosis, scoring systems and analysis of intensive care prior to transplant—all these features of ALF have been exceedingly difficult to study at a single institution. The short-term survival of patients after transplantation is said to be less than that of patients with cirrhosis, presumably due to the severity of illness and the emergent nature of the surgery performed, but specific studies of post-transplant outcomes have not been available previously. In the US, under the authority of the United Network of Organ Sharing (UNOS) criteria, acute liver failure remains the only criterion for the most urgent listing category, status 1. However, data regarding ALF provided by the UNOS registry have been limited since UNOS' focus is directed toward transplantation and not to the underlying diseases prior to transplantation. We have recently published an analysis of the outcomes of patients with ALF listed for transplantation, indicating that etiology of ALF governs outcomes both with and without transplantation.[10]

B.4. Therapeutic Trials: Prior to 1998, therapeutic trials in ALF were limited to those performed at a single center, Kings College Hospital in the United Kingdom (UK). Only one multi-center US therapy trial in ALF had taken place: steroid therapy was tested for fulminant hepatitis B in the 1970's and its negative results finally reported in 1991.[11] A multi-center trial using a bio-artificial assist machine (BAL) sponsored by the manufacturer was published in 2004.[12] While the BAL study yielded negative results and has flaws, the authors encountered many of the difficulties inherent in the design and execution of a controlled trial for this rare condition.

B.5. Summary of the Past: Research in acute liver failure in the US prior to the ALFSG remained limited due to lack of a coordinated effort. Much of the data concerning ALF came either from London or from single US sites over many

years time, were not necessarily representative of the overall United States' experience and few therapy trials were performed.

C. STUDY MECHANICS

The virtue (and difficulty) in studying acute liver failure is that the syndrome evolves rapidly and the outcome is known quickly (either death, survival, or transplantation occur within one to three weeks in most cases). Most study patients will be cared for in an intensive care unit setting. The key to accurate and complete data collection is rapid accession of all eligible patients into the study. Both for data and bio-sample collection purposes, and particularly for therapeutic trials, late study entry will skew results, and may preclude inclusion of patients.

C.1. Study monitors/site visits/marketing. Monitoring visits to the sites are undertaken by the Clinical Coordinating Center PI and coordinator at intervals of about one and a half years, providing support for the investigators and coordinators and quality control with regard to data collection and the therapeutic trial. Source documents are reviewed for accuracy and further data queries submitted. The study has a Website, acuteliverfailure.org, as well as providing patient information brochures in lay language.

C.2. Governance. The Clinical Coordinating Center PI provides overall supervision with a multiple PI leadership team, an Executive Committee, Ancillary Studies and Publications committees actively participating. We have face-to-face meetings at AASLD, DDW and, most important, a 1-1/2 day fly-in meeting each year to review study progress, and aspects of ALF. We have monthly teleconferences to update coordinators and site investigators and encourage enrollment.

C.3. Eligibility Criteria: Our present system provides that when a patient with suspected acute liver failure arrives at a study site, the local site investigator or his coordinator is promptly notified. The patient is evaluated and a determination is made as to whether he or she qualifies for the data and serum collection portion of the study. Criteria for ALF to enter a patient to the study must include altered mentation of any degree, evidence of moderately severe coagulopathy (INR ≥ 1.5) and a presumed acute illness onset of less than 26 weeks. No patients with cirrhosis should be included in the study.

C.4. A separate category of patients may also be enrolled that have Acute Liver Injury (ALI) and meet the following criteria:

1) Hospitalized patient
2) If presumed acetaminophen etiology: acute hepatic illness < 2 weeks, with INR ≥ 2.0, alanine aminotransferase (ALT) of ≥ 10X ULN.

3) If presumed non-acetaminophen etiology: acute hepatic illness of < 26 weeks, with INR ≥ 2.0, ALT of ≥ 10X ULN, total bilirubin of ≥ 3.0 mg/dL.

C.5. Screening. A screen failure log is entered monthly into WebDCU^{TM} at each enrolling site, documenting demographic information and the reasons for failure to enroll. These are principally related to inability to obtain informed consent (or refusal presence of liver failure without evident encephalopathy lack of available next of kin or 'other'—transplanted before patient could be enrolled, for example.

C.6. Informed Consent: When a patient is identified at a study site, the site Principal Investigator (PI) obtains separate informed consents for the data/blood and urine/tissue registry and DNA (up to 2 consents total). Informed written consent from the patient's next of kin (since by definition, patients enrolled in the study will not have normal mental functioning) is required for data and specimen collection (7 days of serum, first day urine and plasma samples and liver tissue where available). A separate consent is required for collection of a DNA specimen. A copy of the consent(s) shall be given to the person signing the form. The consent form must embody the legally required elements of informed consent. The site investigator shall give the patient's representative adequate time to read the form prior to signature. The subject or the next of kin can withdraw the subject from the study at any time, and this decision will not influence the treatment otherwise offered. A copy of the data and serum collection consent must be placed in the medical chart and the original securely kept in the study files. The DNA consent should not be filed in the medical chart but stored securely in the study files.

C.6.a. Patients meeting criteria for ALI, by definition, do not have encephalopathy and can therefore sign their own consent forms. If any doubt exists about mental status, then they are considered to have ALF and require consent by next of kin. Patients that meet criteria for ALI and subsequently become encephalopathic are considered to have consented for the entire study. If this occurs, the subject becomes enrolled in the ALF study. The first day that ALF criteria are reached becomes day 1 for ALF enrollment.

It is not anticipated that any special groups will be enrolled in the study in any proportion other than those representative of the US population. However, vulnerable groups such as prisoners may be enrolled under special circumstances if approval has been sought and obtained by the site and its Institutional Review Board (IRB). In the case of cognitively impaired individuals, the next of kin or guardian will serve as the responsible party for consent purposes. The NIH guidelines on the inclusion of women and minorities as patients in clinical research will be observed. Emergency consent procedures will be invoked, if prior approval for such is obtained from the site's IRB.

C.7. Overall Subject Management: A detailed standardized management protocol is available at each site (see reference 13). This protocol has been

approved by the principal investigators at each site as representing best current practice for patients with ALF. Several additional articles have outlined established expert opinion in this orphan disease area regarding management.[14,15] In addition, ALFSG has performed clinical trials of the use of N-acetylcysteine for non-acetaminophen acute liver failure,[16] and is currently undertaking a trial of OCR-002, ornithine phenylacetate, for the treatment of elevated ammonia levels in the ALF setting.

C.8. Data collection: Every effort has been made to streamline data accession and entry. Data is entered electronically into the study database at the enrolling sites. The study database, called WebDCU™, is developed and maintained by the Data Coordination Unit at the Medical University of South Carolina (MUSC). As data is submitted, the principal investigator or designee and data managers review the data, and generate queries to resolve discrepancies.

After informed consent, the site investigator must detail all aspects of study admission, history, physical exam, lab data and clinical course, including the presumed diagnosis, applying standard criteria. The details of patient history are often lacking in these very ill referral patients where, by definition, mental changes must have occurred to be included in the study.

A defined set of clinical measurements will be available to the site investigator largely done as standard of care for acute liver failure: complete blood count, chemistry profile including aminotransferases, alkaline phosphatase and bilirubin; coagulation studies including prothrombin time and activated partial thromboplastin time, electrolytes, calcium, magnesium, phosphorus and acetaminophen levels. Serologic studies for acute hepatitis A, B, C and HIV, ceruloplasmin levels, and a drug screen to include cocaine, opiates and barbiturates will be performed. Demographic data, medical history and data influencing etiology including drug and alcohol intake, all pharmaceutical agents, herbals and other xenobiotics ingested in the prior six months will be recorded.

Data collection for cases of ALF or ALI related to acetaminophen poisoning includes a two-part questionnaire that the subject may be asked to respond to, once they begin to recover. Once medically stable, these patients may be approached by study personnel and asked to provide informed consent to answer a detailed questionnaire regarding use of acetaminophen prior to hospitalization, a diagnostic screen for psychiatric illnesses, symptom severity score for depression, and a short impulsivity scale. There will be no additional collection of bio-samples for these patients.

Data will be collected through Day 7 unless the patient undergoes transplantation, dies or is discharged from the hospital. At Day 21, patients will be contacted by study personnel to determine vital status.

C.9. Bio-sample collection:

C.9.a. Serum: Daily serum samples (two 10 ml serum separating tubes) are

collected starting on the first day of study for up to 7 days, aliquoted in 500 µL aliquots and stored at -80^0 for later shipment to the central repository. If there is difficulty collecting samples, existing serum that has been refrigerated for clinical purposes can be used. The serum is aliquoted to provide multiple samples for each time point. If an ALI subject develops encephalopathy (qualifies as having ALF) then collection begins again as study day 1 of ALF study, continuing for a total of no more than 14 days.

C.9.b. Plasma: A single 10 ml blood sample will be obtained on study admission in EDTA and / or citrated tubes, and the plasma separated, aliquotted in similar fashion to serum, marked clearly as plasma, and stored at -80^o prior to shipment to the Repository. However, if an ALI subject develops encephalopathy (qualifies as having ALF) a second plasma sample will be collected.

C.9.c. Urine: Ten ml of urine is to be collected on the day of study admission or the following day, to be aliquotted in 1 ml aliquots stored at -80^o and shipped with other samples to the Repository. However, if an ALI subject develops encephalopathy (qualifies as having ALF) a second urine sample will be collected. These samples (serum, plasma and urine) are labeled with sample specific pre-printed labels containing: the NIDDK site number, the ALF site number, subject EDC ID number (generated by WEBDCU upon enrollment), and collection date. They are stored at -80º and batch shipped Monday thru Wednesday to the NIDDK Repository at approximately 3-month intervals depending on the quantities involved.

C.9.d. Tissue: Liver tissue samples in the form of stained /unstained slides, frozen tissue, and blocks are to be sent to the NIDDK Repository from all patients who have a liver biopsy, liver transplant or autopsy. Frozen tissue should be accessioned where possible at the time of explantation.

In the case of an explant, we suggest that 10-20 g of liver tissue be collected for storage at -80º and sectioned in special 10 ml cryovials provided by the NIDDK repository. The liver tissue should be shipped frozen with other bio-samples or separately as needed on dry ice to the NIDDK Repository.

C.4.f. DNA: Samples are to be collected only after the special separate DNA consent has been signed. The separate consent is necessary because of the more complex issues surrounding archiving DNA. Only a single time point draw is necessary to collect the blood for extraction of DNA that can be archived for future DNA tests. This should be collected on all patients when possible; however, those of particular interest include suspected drug toxicity, indeterminate cases and acetaminophen toxicity cases. Archiving DNA samples provides a unique source of information regarding ALF that can only be obtained from DNA - many of the tests for this aspect of the study are only now being developed, but should provide totally different body of knowledge in the future.

The logistics for obtaining the DNA sample necessitate drawing the blood at only one time point, on a Monday, Tuesday or Wednesday, using at least two 10 ml lavender top (EDTA) tubes which must be shipped overnight at ambient temperature, by Fed Ex to UTSW ALFSG DNA processing core. A shipment notification email must be sent to: ALFDNA@UTSouthwestern.edu
on the day of shipment to notify UTSW. DNA samples can be collected at any time and need not be drawn on the first hospital day. The extracted DNA will be shipped from UTSW to the central NIDDK repository in batch shipments.

C.10. Subject Withdrawal: It is the right of the subject's family or next of kin or the physicians caring for each subject to discontinue from the study at any time. Data and samples collected before discontinuation should be maintained if there is no objection. Progression to liver transplantation, intubation, placement of intra-cerebral pressure monitoring devices or other standard of care procedures should be unaffected by study participation.

D. INSTITUTIONAL REVIEW BOARD

The Institutional Review Board (IRB) at the Clinical Coordinating Center and at each study site must provide a current approval for the study to proceed. No subject enrollment can occur before IRB approval has been obtained at that site. The Clinical Coordinating Center and the Principal or Site Investigator will assure that an appropriately constituted IRB, that complies with the requirements of 21 CFR 56, will be responsible for the initial and continuing review approval of the clinical study at each individual site. A photocopy of the site's IRB approval and consent form must be forwarded to the Clinical Coordinating Center.

The Clinical Coordinating Center will also assure that the sites will promptly report to the IRBs concerned all changes in the research activity, all unanticipated problems involving risks to human subjects or others, and that he/she will not make any changes in the research without IRB approval except where necessary to eliminate apparent immediate hazards to the human

subjects. For minor changes to previously approved research, it may be possible for the site investigator to obtain an expedited review by IRBs as allowed for under 21 CFR 56.110.

As part of the IRB requirements for continuing review of approved research, the Clinical Coordinating Center and Site Investigator will be responsible for submitting periodic progress reports to the IRBs at intervals appropriate to the degree of patient risks involved but no less than once per year. Copies of all correspondence between the site investigator and the site IRB indicating its continued approval of this study or the withdrawal of such approval must be forwarded immediately to the Clinical Coordinating Center.

E. CONFIDENTIALITY

E.1. Each subject is automatically assigned a unique subject ID number by WebDCU™ at the time of enrollment. All electronic CRF data is housed on secure servers at the Data Coordinating Center located at the Medical University of South Carolina in Charleston, SC. Every effort is made to protect the identity of the subject and his samples.

E.2. The ALFSG has obtained a Certificate of Confidentiality to provide special privacy protection for each subject enrolled. A copy of the certificate should be on file at your site. This privacy protection means that the subject will not be identified as participating in the study, unless he or she consents, or if it is necessary to reveal the information in order to protect the subject or another from serious harm, as in cases of child abuse.

Data that are protected by a Certificate of Confidentiality may be disclosed under the following circumstances:

- Voluntary disclosure of information by study participants themselves to physicians or other third parties, or authorization by study participants of release of information to insurers, employers, or other third parties.
- Voluntary reporting by the investigator of information, such as child abuse or threat of other potential violence by the study participant to the participant or others, provided such intention is specified in the informed consent document.
- Voluntary compliance by the researcher with reporting requirements of other state laws such as knowledge of a communicable disease, provided such intention is specified in the informed consent document.
- Release of information by investigators to Department of Health & Human Services (DHHS) as required for audits of research records or to the Food and Drug Administration (FDA) as required under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 301 et seq.).

F. INCLUSION OF WOMEN AND MINORITIES

Acutely ill ALF patients are not amenable to conventional recruitment methods. They are evaluated on admission in the ICU setting without consideration of race or gender. In our retrospective study, patients were nearly equally divided between the sexes, although there are more women (74%) than men in the current prospective study. There is no preponderance of any racial group, other than that represented by specific hospital populations. No exclusion will be made on the basis of race, ethnic group or gender. Criteria for inclusion of women and minorities will be those established in the NIH guidelines.

G. DATA ANALYSIS

The collected registry data is analyzed for various study-wide papers as well as ancillary studies. Each study/paper proposal goes through a formal review process by the ancillary studies committee that includes a detailed plan of the objectives, necessary registry data, analysis plans and timeline. All publications are approved by the ALFSG publication committees prior to submission.

G. SITE REIMBURSEMENT

Site reimbursement is a flat yearly rate based on past performance and will be disbursed quarterly throughout the year dependent on time worked on study for that quarter and after invoicing by the sites to the central site.

H. REFERENCES

1) Trey C, Davidson CS. The management of fulminant hepatic failure. In: Popper H, Schaffner F, eds. Progress in liver diseases. New York: Grune & Stratton; 1970: 282-98.
2) Ritt DJ, Whelan G, Werner DJ, Eigenbrodt EH, Schenker S, Combes B. Acute hepatic necrosis with stupor or coma. An analysis of thirty-one patients. Medicine. 1969;48:151-72.
3) Lee WM, Schiødt FV. Fulminant hepatic failure. In: Schiff ER, Sorrell MF, Maddrey WC, eds. Schiff's Diseases of the Liver. 8th ed. Philadelphia: Lippincott-Raven Publishers; 1999: 879-95.
4) Benhamou J-P. Fulminant and subfulminant liver failure: definition and causes. In: Williams R, Hughes RD, eds. Acute liver failure. Improved understanding and better therapy. London: SmithKline Beecham Pharmaceuticals;1991:6-10.
5) Hoofnagle JH, Carithers RL, Shapiro C, Ascher N. Fulminant hepatic failure: summary of a workshop. Hepatology. 1995;21:240-252.
6) Elinav E, Ben-Dov I, Hai-Am E, Ackerman Z, Ofran Y. Predictive value of admission and follow-up Factor V and VII levels in patients with acute hepatitis and coagulopathy. J Hepatol 2005;42:82-6.

7) Schiødt FV, Atillasoy E, Shakil O, Lee WM, et al. Etiology and outcome for 295 patients with acute liver failure in the United States. Liver Transplant Surg, 5:29-34, 1999.
8) Ostapowicz GA, Fontana RJ, Schiodt FV, Larson A, Davern TJ, Han SBH, Lee WM, et al., Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med 2002;137:945-54.
9) Larson AM, Fontana RJ, Davern TJ, Polson J, Lalani EK, Hynan LS, Reisch JS, Shakil OA, Schiødt FV, Ostapowicz GA, Lee WM and the ALFSG. Acetaminophen-induced acute liver failure: Results of a United States multicenter, prospective study. Hepatology 2005:42:1367-72.
10) Reddy KR, Ellerbe C, Schilsky M, Stravitz RT, Fontana RJ, Durkalski V, Lee WM, Acute Liver Failure Study Group. Determinants of Outcome Among Patients with Acute Liver Failure Listed for Liver Transplantation in the US. Liver Transpl 2015 Sep 30. [Epub head of print].
11) Rakela J, Mosley JW, Edwards VM, and the Acute Hepatic Failure Study Group. A double-blinded, randomized trial of hydrocortisone in acute hepatic failure. Dig Dis Sci. 1991;36:1223-8.
12) Demetriou AA, Brown RS Jr, Busuttil RW, Fair J, McGuire BM, Rosenthal P, et al. Prospective, randomized, multicenter, controlled trial of a bioartificial liver in treating acute liver failure. Ann Surg 2004;239:660-7.
13) Stravitz RT, Kramer AH, Davern T, Shaikh AOS, Caldwell SH, Mehta RL, Blei AT, Fontana RJ, McGuire BM, Rossaro L, Smith AD, Lee WM and the Acute Liver Failure Study Group. Intensive care of patients with acute liver failure: Recommendations of the U.S. Acute Liver Failure Study Group. Crit Care Med. 2007;35:2498-2508.
14) Polson J, Lee WM. AASLD Position Paper: Acute Liver Failure. Hepatology 2005,41:1179-97.
15) Lee WM, Stravitz RT, Larson AM. Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver failure 2011. Hepatology 2012;55:965-7.
16) Lee WM, Hynan LS, Rossaro L, Fontana RJ, Stravitz RT, Larson AM, Davern TL III, Murray NG, McCashland T, Reisch J, Robuck PR and the ALFSG. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. Gastroenterology 2009; 137:856-864.