



THE TARGET

TARGETING ACUTE LIVER FAILURE TO FIND A CURE IN THE 21ST CENTURY

A Word from the PI . . .

Less Is More: Why Study NAC?

Mies van der Rohe, the German-American architect who is famous for the simplicity of his designs of skyscrapers, is given credit for the statement: Less is more. His buildings lacked ornamentation and have stood the test of time and changing tastes. Sometimes simple solutions are the most effective. Currently, the N-acetylcysteine study is underway at most of our study sites and a few are still coming on line. NAC is the simple choice and maybe that is why it is hard to believe. How could such a simple solution be effective? There are many possible biochemical roles for NAC as glutathione repletter, apoptosis inhibitor; we just don't know where its influence within the hepatocyte stops.

The rationale for NAC is great: the drug is cheap, it is usable in any hospital setting, there is no fancy equipment needed and virtually no risk, since it has been used extensively for acetaminophen patients before. Nevertheless, enrollment in our study is lagging. From our recent review with the Data and Safety Monitoring Board, we find we have enrolled 41 percent of eligible patients at our sites. To improve enrollment, we must push our efforts in several directions: first, those sites not yet on board need to finish up IRB and contract issues. Second, we need to remain vigilant, reminding our colleagues who are on call to notify us about cases; keeping a list of substitute contacts when we are out of town; and speaking to ICU rounding teams, resident groups, and community colleagues. Finally, we need to SELL this study, not because we are pitching a second-rate product that would not make it on its own, but because we believe in it. Here are the answers to some frequently asked questions that may help you in your interchanges with patients' families and in your assessment of patients for the study:

- 1) "I found it hard to encourage a family to sign the consent for an experimental drug, when their loved one had experienced liver failure from one drug already. I cannot make them sign this consent." This is true, but it might be more understandable to them if you make it clear that NAC may serve as an *antidote* as it does in acetaminophen poisoning, where it is clearly universally life-saving if given in time. There is little downside since the drug has been used so often previously, just not in the present situation.
- 2) "We recently saw a patient with drug hepatotoxicity after nevirapine but she had hepatitis C so we did not enroll her because of her chronic liver disease." Hepatitis C is not a contraindication to enrollment, only the known presence of cirrhosis. If there is no evidence of cirrhosis, then the patient may be enrolled. We are avoiding "acute on chronic" when and only when the condition appears to be the worsening of cirrhosis, i.e., the development of encephalopathy in the setting of established cirrhosis.
- 3) "I have a post-transplant patient who comes in with a new liver-failure situation. Are they prohibited from being in the study?" We would not exclude a patient, say, with herpes hepatitis post-liver transplant, but we do not wish to include those with immediate primary non-function after transplantation.
- 4) "What about a bone marrow transplant recipient with drug-related toxicity?" As a rule, these patients have underlying malignant disease and thus, they probably should not be enrolled, since their overall outcome is to a great extent dependent on the success of the transplant and not the specific cause of the hepatotoxicity. The DSMB suggested we not enroll such patients.

(Continued on page 7)

Don't Forget About Long-Term Follow-up!

by Julie Polson, M.D.

Of the approximate 4,500 liver transplants performed in the United States each year, ALF accounts for about five percent. While several small studies (mainly in Europe) have shown less favorable outcomes in terms of patient and graft survival in transplanted ALF patients in comparison to transplanted cirrhotics, the US data is sparse, largely due to small study sizes and limited length of follow-up. Since transplant recipients from the ALFSG represent the largest group of ALF patients in whom blood samples and data have been prospectively collected, this study provides a unique opportunity to gather data on long-term outcomes of such patients. This data should yield valuable information about the overall outcome of transplant for treatment of ALF, and may identify prognostic factors that could potentially help to shape the criteria by which organs are allocated for transplant.

As with ALF patients who undergo transplant, the outcomes of spontaneous survivors of ALF have not been well studied. In fact, while it has been suggested that a significant proportion of patients spontaneously surviving ALF from severe idiosyncratic drug toxicity may go

The primary aim of this study is to determine the long-term outcome of transplanted ALF patients within our study group. We will determine actuarial one- and two-year patient and graft survival, incidence and severity of post-transplant complications, and follow-up medical, lab, allograft, and functional status at year one and year two. We will then compare the results from ALF transplant patients with varying etiology of ALF and varying severity of illness on presentation and at time of transplant. One- and two-year patient and graft survival will also be compared with matched cirrhotics, and predictors of survival will be analyzed. Our secondary aim is to better define the long-term natural history of ALF in spontaneous survivors. Patient survival and follow-up medical, lab, and functional status at year one and two will be determined, and results will be compared to population controls. Comparison will also be made between spontaneous survivors with acetaminophen-related ALF and non-acetaminophen ALF.

Update forms have been developed to capture clinical, laboratory, and outcome information on all ALF patients enrolled in ALFSG since January 1, 1998. These forms should be completed at approximately one and two years post-ALF admission at a brief clinic visit or over the telephone. Blood samples will also be collected at the one- and two-year visits if possible (two 10ml red topped tubes) and frozen/shipped to UT Southwestern for storage. Serum samples will be used in the future to hopefully identify factors associated with the etiology and regenerative capacity of ALF patients.

For more detailed information regarding data collection for this study, please refer to the handbook from the ALFSG Annual Meeting, December 2001. The principal investigator for this study is Dr. Robert Fontana of the University of Michigan Medical Center, and he welcomes questions/concerns/suggestions. He can be reached by phone or e-mail:

(734) 936-4886
rfontana@umich.edu

Please do all you can to make this important part of the ALF study a success!



Kim Morton, adult coordinator at the University of Michigan, trains her fellow coordinators on the LTFU protocol.

on to develop chronic liver disease, there is nothing known about the long-term outcomes of spontaneous survivors of hepatotoxicity from acetaminophen, the most common cause of ALF in the US. Long-term follow-up data on spontaneous survivors in the ALFSG could thus provide additional important information on the natural history of ALF.

What We Look for During Monitoring Visits

by Annelise Thornton

The Goal

Much like what is done in pharmaceutical studies, the goal of our clinical research monitoring effort is to visit each site annually to verify information, and to further validate and confirm data in the patient registry. Once the NAC study is underway, we will also support and oversee its conduct.

We have twenty-five adult and twelve pediatric sites actively enrolling patients. With so many sites, it is important to maintain study standards and procedures.

How to Prepare

We will contact you well ahead of time to arrange a mutually agreeable date for the visit. The site has two primary responsibilities. One is to have the regulatory binder available for review. The initial IRB approval letters, continuing review letters, and approved consent forms are documents of particular interest to the monitor.

We will plan to review charts on approximately twenty percent of the subjects enrolled at each site. The site's second responsibility is to obtain the charts from medical records so that they are available for review during the visit. This part of the visit is crucial, and if your medical records department is like ours, you will need to begin the process plenty early!

The Visit

On average, the entire visit takes a half-day; a full day is needed for sites with high enrollment. Once at the site, a tour of the lab facility is helpful. We will take the opportunity to discuss pertinent study issues such as patient recruitment, serum collection, management and shipping, billing procedures, and case-report form completion.

We are always on the lookout for helpful hints that may be useful to other sites participating in the study. We value and appreciate the contribution each site makes to the ALF registry, and in many cases, the monitoring visit is an opportunity to put names and faces together. Visiting sites allows us the opportunity to glean information on how we can best improve our role as the coordinating center.



Dr. Schiødt (right) and Ezmina Lalani (left), Study Coordinator Central Site, review charts with Tamara Bernard (center), Study Coordinator at the University of Nebraska.



Monitoring visit to the University of Nebraska.

Summer 2002

Acute Liver Failure at Digestive Disease Week

by Frank V. Schiødt, M.D.

The annual Digestive Disease Week was held in San Francisco, at the Moscone Center. Traditionally, hepatology is not as strongly represented at DDW as compared with the AASLD meeting. The acute liver failure abstracts were not given the opportunity for oral presentations this year. However, fifteen ALF posters were presented; three of them from our ALF group (see below). Other posters included iNOS and eNOS expression, the value of MELD score in ALF, and plasma exchange studies. However, to be honest, very limited new and significant data was presented. Hopefully, better luck at the Boston AASLD meeting.

Wednesday, May 22, Will Lee and Andy Blei chaired a Combined Clinical Symposium on fulminant hepatic failure. All four speakers are investigators with our group. Titles included: 'Acetaminophen and drug toxicity' (Bob Fontana), 'A systematic approach to management' (Eileen Hay), 'Infections in acute liver failure' (Frank Schiødt), and 'Artificial and bioartificial liver support' (Andy Blei). One follow-up of the talks will be a special article in *Hepatology* on controversies in ALF.

The Abstracts from the ALF Group

ACETAMINOPHEN HEPATOTOXICITY IN ACUTE LIVER FAILURE: VALIDATION OF A SCORING SYSTEM FOR THE CERTAINTY OF THE DIAGNOSIS. Schiødt FV, Larson AM, Lee WM, and the Acute Liver Failure Study Group.

Background: Acetaminophen (ACM)-induced acute liver failure (ALF) has a more favorable outcome than all other ALF etiologies but is still the leading cause of ALF deaths in the US. In most instances the diagnosis is clear, but in certain patients, it remains unclear due to missing data points. We aimed to test a model for assessing the degree of certainty of an ACM etiology.

Methods: A model for the diagnosis of ACM-induced ALF was set up:

	Possible Max:
History of intake (> 4 gram/day: +3; ≥ 10 gram/day: +5)	5
ACM level (Detectable: +2; ≥ 50 mg/L: +3)	3
Peak ALT/AST (>3,500: +3; >7,000: +5)	5
Admission creatinine (≥ 2 mg/dL: +1)	1
Admission arterial pH (≤ 7.30: +1)	1
Other possible causes (yes: -3; no: 0)	0
Centrilobular necrosis in biopsy (yes: +2; no -2)	2
	17

Sum: The model was tested in 285 patients with ALF, enrolled in the US ALF Study Group trial, including 108 patients who were considered having ACM hepatotoxicity.

Results: Overall, patients with ACM-induced ALF had a median score of 10 (range 0-15) compared to the score of -2 (-5 to +8) for the 177 non-acetaminophen patients (p<0.0001).

Score	ACM	Non-ACM	ACM%	Category
≥9	70	0	100%	Definite
6-8	26	2	92.8%	Probable
3-5	11	18	37.9%	Possible
≤2	1	157	0.6%	Unlikely

The model score in *ACM patients* with known type of overdose (not determined in 7):

	Accidental (n=57)	Suicidal (n=44)	
>9	29 (50.9%)	36 (81.8%)	
6-8	19 (33.3%)	6 (13.6%)	
3-5	8 (14.0%)	2 (4.5%)	
<2	1 (1.8%)	0	
Mean Score:	8.4	10.6	p<0.001

Conclusions: Most ACM patients (especially those with suicidal overdose) had a definite diagnosis according to the proposed model. We suggest using the model for determining the certainty of a diagnosis of ACM toxicity in ALF.

AUTOIMMUNE HEPATITIS-INDUCED ACUTE LIVER FAILURE IN THE UNITED STATES. Schiødt FV, Fontana RJ, Larson AM, McGuire BM, McCashland TM, Satyanarayana R, Schilsky M, Han S, Weinstein J, Lee WM, and the Acute Liver Failure Study Group.

Background: Autoimmune hepatitis (AIH) rarely causes acute liver failure (ALF). We aimed to characterize clinical and biochemical features and outcome of patients with ALF due to AIH.

Methods: 353 consecutive patients enrolled in the US ALF multi-center registry over a 46-month period were screened for possible AIH etiology and scored according to the International AIH Group scoring system.

Results: Fourteen patients were listed as 'autoimmune hepatitis' by the site investigator; however, one case (a male patient with an IAIHG score of 6) was excluded from analysis, leaving 13 patients (all women) with AIH-induced ALF (3.7% of all ALF cases). The median (range) age was 55 (28 – 68) years in AIH patients vs. 37 (15 – 78) years in patients with other etiologies ($p=0.004$). Six patients had a medical history of other autoimmune diseases. Symptom duration prior to encephalopathy was 18 (9 – 43) days, whereas jaundice had been present for 17 (1 – 37) days. ANA was positive in 11 of 12 studied patients (92%), SMA in 4/12 (33%), and anti-LKM was negative in 4/4 patients. The IAIHG score was 16 (12 – 18) and 9 of the patients (69%) had a 'definite' diagnosis of AIH. On admission, ascites and/or splenomegaly were present in 5 and 3 patients, respectively. Nine patients (69%) had peak coma grade III or IV. Treatment with prednisolone and/or azathioprine was initiated in 4 patients prior to development of hepatic encephalopathy, one of whom survived spontaneously. Two patients survived spontaneously, 6 patients were transplanted, whereas 5 patients died before transplantation could be performed. Histology was available in 9 patients: massive hepatocyte necrosis and collapse was present in 6 patients whereas 3 patients had more chronic features with cirrhosis or fibrosis.

Conclusions: Patients with fulminant presentation of autoimmune hepatitis were much older at presentation than other ALF patients. The course of illness was very short despite evidence in some patients of underlying chronic liver disease, and steroid treatment was initiated in less than half of the patients prior to encephalopathy. Two-thirds reached grade III or IV encephalopathy and spontaneous survival was very low, emphasizing the need for early transplantation in these patients.

EARLY PROGNOSTIC MARKERS IN ACUTE LIVER FAILURE: A NEW OUTCOME MODEL BASED ON U.S. DATA. Schiødt FV, Hynan L, Rakela J, Blei A, Lee WM, and the ALF Study Group.

Background: Many liver centers assess prognosis in acute liver failure (ALF) based on King's College criteria; however, several studies suggest that these criteria that were developed more than a decade ago from U.K. patients in the pre-transplant era do not apply to current U.S. ALF patients. We aimed to develop a new prognostic model for outcome in U.S. ALF patients.

Methods: 353 patients with ALF prospectively included in the ALFSG Registry were studied. We analyzed spontaneous (transplant-free) survival vs. non-spontaneous survival. The following variables were analyzed using univariate testing for possible inclusion in multivariate models: etiology, age, gender, ethnicity, symptoms of illness prior to onset of hepatic encephalopathy, coma grade on admission (I/II vs. III/IV), and admission values of mean arterial pressure, heart rate, temperature, creatinine, INR, and arterial pH. Also, INR increase/decrease from day 1 to day 3 was studied.

Results: All significant variables from univariate testing were available in a total of 340 patients. The spontaneous survival rate was 43.8% (149 of 340), and the transplantation rate was 27.1% (92 of 340). The spontaneous survival rate was 70% for 140 patients with acetaminophen hepatotoxicity, 67% for hepatitis A ($n=15$), 59% for ischemic hepatitis ($n=17$), and 50% for pregnancy-induced ALF ($n=6$). The spontaneous survival rate was less than 25% for all other etiologies. The following variables were included by forward logistic regression analysis in the final model: 1) *favorable etiology* (acetaminophen, hepatitis A, shock liver, or pregnancy), odds ratio 10.8, 2) *coma grade I/II*, OR 3.8, 3) *short symptom duration before coma*, OR 1.026 per day, and 4) *low INR*, OR 1.179 per unit. Sensitivity and specificity were 75.2% and 79.1%, respectively.

Conclusions: The proposed model offers new information on the factors that influence prognosis in ALF. Acetaminophen toxicity, hepatitis A, shock liver, and pregnancy-induced ALF may be considered 'favorable' etiologies. In addition, lower admission coma grade and INR and short symptom duration prior to coma were major determinants of spontaneous survival. The outcome of ALF depends on many features and a discrete scoring system with high predictive capacity still eludes us.

Fatty Acid Oxidation in ALF Children

by Ben Shneider, M.D.

Defects in fatty acid oxidation (FAO) are the result of enzymatic deficiencies in the complex process involved in the catabolism of fatty acids. At least 20 different specific fatty acid oxidation disorders have been described. These disorders are protean in their manifestations and can include sudden death, skeletal and cardiac myopathy, seizures, and acute liver disease. Typically, they become apparent in times of fasting and/or stress when fat is utilized as an energy source. The pathophysiology of this group of disorders is related to both energy deficiency and accumulation of toxic intermediate metabolites of fatty acid oxidation.

At present it is suspected that four of the over twenty different FAO defects are associated with acute onset of severe liver disease. Diagnosis is often suggested by the finding of nonketotic hypoglycemia and characteristic dicarboxylic aciduria. These characteristic features may be transiently present, and thus many cases may not be clinically recognized. Accurate diagnosis of FAO defects may lead to life-saving metabolic therapy, genetic counseling for siblings and identification of systemic diseases that may not be amenable to liver transplantation.

The current analysis of FAO defects seeks to comprehensively characterize these disorders in a cohort of children with acute liver failure. The study will prospectively examine liver, bile, and fibroblasts from children enrolled in the acute liver failure study who undergo either liver transplantation or autopsy. These samples allow a more comprehensive and accurate assessment of potential fatty acid oxidation defects. The primary goals of the investigations are to determine the prevalence and outcome of FAO defects in children with life-threatening acute liver failure.

Selected References

Rinaldo P, Raymond K, Al-Odaib A, Bennett MJ. Fatty acid oxidation disorders: Clinical and biochemical features. *Curr. Op. Pediatr.* 1998; 10:615-621.

Boles RG, Buck EA, Blitzer MG, Platt MS, Cowan TM, Martin SK, Yoon H, Madsen JA, Reyes-Mugica M, Rinaldo P. Retrospective biochemical screening of fatty acid oxidation disorders in postmortem liver of 418 cases of sudden death in the first year of life. *J. Pediatr.* 1998; 132:924-933.

Al Odaib A, Shneider BL, Bennett MJ, Pober BR, Reyes-Mujica M, Friedman AL, Suchy FJ, Rinaldo P. A defect

in the transport of long-chain fatty acids associated with acute liver failure. *N. Engl. J. Med.* 1998; 339:1752-1757.

Current Progress of Study

To date, 16 study subjects have been enrolled in the study of fatty acid oxidation in acute liver failure. Twelve are from Mount Sinai, two from Dallas, and one each from Denver and Cincinnati. Six of the analyses are suspicious for abnormalities and further investigations are underway.

We are hopeful that more centers will participate in the study. I have listed the entry criteria for the study below. These include an additional method of entry that was not previously available (C).

Accurate diagnosis of FAO defects may lead to life-saving metabolic therapy, genetic counselings for siblings and identification of systemic diseases that may not be amenable to liver transplantation.

Entry Criteria

1. Enrollment in the acute liver failure study group
2. A. Liver transplantation [submission of liver, bile +/- skin fibroblasts]
- B. Autopsy [submission of liver, bile +/- skin fibroblasts]
- C. High index of suspicion of fatty acid oxidation defect (i.e., characteristic urine organic acids) in a patient who did not undergo transplantation or autopsy [submission of skin fibroblasts]

The analyses that are available include

1. urine organic acids
2. blood spot analysis for acylcarnitines.
3. Liver/bile metabolic profiles
4. Skin fibroblast fatty acid oxidation (new assay: see attached file).

Shipping materials, shipping costs, and test costs are covered by the study.

In addition, a \$500 administrative fee will be paid to each center for each patient enrolled.

Attached you will find descriptions of the study, the new fibroblast assay and a relevant reference for that assay.

Please email me at Benjamin.Shneider@mssm.edu if you have any questions and/or if you would like to participate.

A Time for Farewells and Welcomes



FRANK V. SCHIØDT, M.D.

The Central Site would like to say farewell to Frank V. Schiødt, M.D., Post-Doctoral Research Fellow who worked closely with the ALF project. Dr. Schiødt will be returning to his home in Denmark. He has been working with the Central Site for the past year by helping with monitoring visits, interpreting ALF data, and publishing collected data. This is Frank's second year being with us at UT Southwestern. Frank will be greatly missed, and we wish him all the best.

JULIE POLSON, M.D.



In addition, the Central Site would also like to welcome Drs. Julie Polson and Ponsiano Ocama.

Dr. Julie Polson is beginning a fellowship in gastroenterology/hepatology and will be with ALF for the next two years. She will be taking over some of Dr. Schiødt's ALF responsibilities. Dr. Polson will be obtaining a Master's in Public Health here at UT Southwestern. She just finished her residency in internal medicine.



PONSIANO OCAMA, M.D.

Dr. Ocama Ponsiano is a visiting research fellow from Uganda, Africa for the next year. His main interest is working with hepatitis B and C, both acute and chronic. Ocama obtained a Bachelor of Medicine and Bachelor of Surgery from Makerere University, Kampala, Uganda, in 1994. He then attained a Master's of Medicine in Internal Medicine in 2001.

We look forward to their contributions to the ALF Study Group.

A Word from the PI (Continued from Page 1)

- 5) "Our IRB demands a durable power of attorney specifically for research before a patient can allow his/her next of kin to participate." This has been encountered in California and New York, but not in every hospital. We think this is unreasonable and precludes patients from possible life-saving intervention. Protection from research is not always healthy for the patient! We will deal with individual IRBs and contact them directly if you are having difficulties.

I hope that these vignettes/questions will help raise your consciousness about the study and that this will translate to greater enrollment. I know we can do it if we try. Thanks again to all you who are working so hard to fulfill the promise of NAC.

Congratulations Are In Order!



Congratulations to Grace Samuel, Study Coordinator for the Acute Liver Failure Study at the Central Site, and her baby Annika Samuel. Annika was born in April. She weighed 7 pounds, 10 ounces, and her height was 20 inches. Grace will be working on a part-time basis, since the birth of Annika, and taking over her full-time position will be Ezmina Lalani. From all of us at UT Southwestern, we wish Grace and Annika all the best.

Annika Samuel



Another congratulations and a farewell to Annelise Thornton. She has decided to pursue a graduate degree in International Public Health at John Hopkins University in Baltimore. Annelise's contributions to the Acute Liver Failure Study, such as implementation of *The Target*, the development of patient databases, the strategic marketing of the ALF protocol, and much more, will be sorely missed. All of us at the Central Site sincerely thank Annelise for all her efforts and wish her the best of luck in her endeavors.

Save the Date...

Ideas for Increasing Enrollment

Enrollment has really slowed down. The following are a few pointers that might help you to increase enrollment at your site.

1. TALKS - Present the study and our findings to date to your colleagues. Slides are available from the Central Site.
2. POSTERS - Post notices about the study in the ICUs at your hospital.
3. TRAINING - Gather the ER and internal medicine residents for a training on how to identify ALF. Pass out cards with your contact information and study criteria.
4. ARTICLE REPRINTS - *Clinical Perspectives in Gastroenterology* published this article, "Acute Liver Failure," by Dr. William M. Lee. Reprints are available for you to distribute at your site.

August

22nd-23rd: Monitoring Visit at Washington University in St. Louis

September

25th: Monitoring Visit at Albert Einstein Medical Center

26th: Monitoring Visit at the University of Pennsylvania

26th: Monitoring Visit at University of Medicine and Dentistry in New Jersey

Visit Us on the Web!

Take a few moments to check out our website for the Clinical Center for Liver Diseases at UT Southwestern Medical Center at Dallas. You can also view the online version of *The Target* in Adobe Acrobat® PDF format.

www3.utsouthwestern.edu/liver

*Acute Liver Failure Study Group
UT Southwestern Medical Center
5323 Harry Hines Blvd.
Dallas, Texas 75390-9151*

Tel: 214 648 2665

Fax: 214 648 2070

acuteliverfailure@utsouthwestern.edu