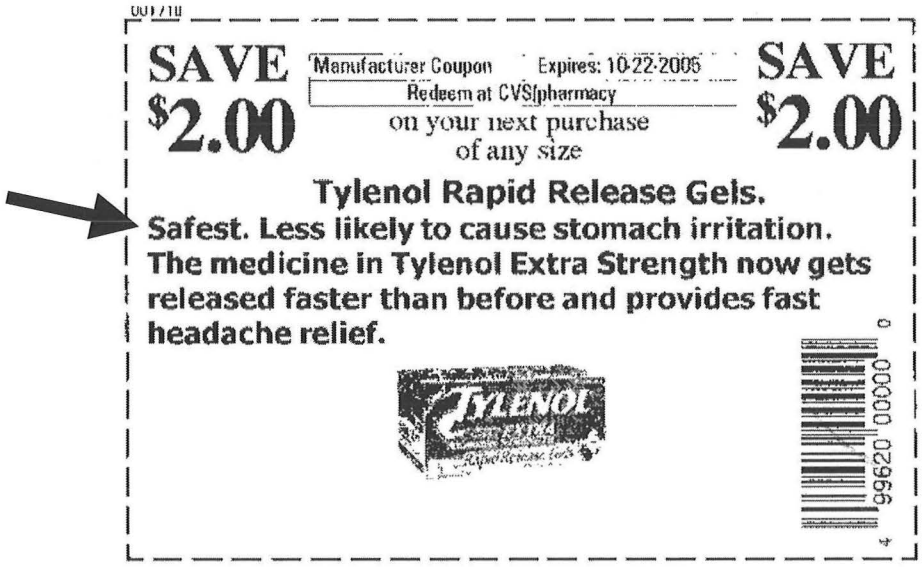
Acute Liver Failure 2006



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This is to acknowledge that William M. Lee, M.D. has not disclosed any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Lee will not be discussing off-label uses in this presentation.

Biographical sketch:
Dr. Lee was educated at Amherst College, Columbia University College of Physicians and Surgeons and completed his housestaff training at the Presbyterian Hospital in Nwq York City and Kings College Hospital, London. He holds the Meredith Mosle Chair in Liver Diseases and has been at UT Southwestern as Professor of Internal Medicine since 1990. His research and clinical interests center on hepatocyte injury, including acute liver failure, drug hepatotoxicity and viral hepatitis. He is one of 13 principal investigators in the HALT-C Trial and the Principal Investigator for the Acute Liver Failure Study Group (ALFSG) which has been based at UT Southwestern since 1998. The ALFSG is currently supported by U-01 058369 from the National Institute of Diabetes, Digestive and Kidney Diseases. Additional support is provided by the Tips Fund of Northwestern Medical Foundation and the Jeanne Roberts and Rollin and Mary Ella King Funds of the Southwestern Medical Foundation. He gratefully acknowledges the strong support of the ALF Study Group by these agencies as well as by staff at UT Southwestern including Carla Pezzia, Joan Reisch, Linda Hynan, Joe Webster, Julie Polson, Rehana Mohammed, Nahid Attar, Wendell King and Philip Pan and the countless investigators and coordinators at 23 study sites around the United States.

Introduction

Acute liver failure (ALF) is the most common term applied to an unusual clinical syndrome resulting from rapid loss in hepatocyte function. It occurs infrequently, affecting 2,000 patients annually in the United States, the culmination of severe liver cell injury from a variety of different causes. Because of its rarity, research in this area has been limited. However, in 1998 the Acute Liver Failure Study Group (ALFSG), based at UT Southwestern, began to collect detailed prospective information and bio-samples on patients from more than 20 US medical centers to more carefully delineate the condition and improve our understanding. Since that time, carefully collected data and samples have accrued on more than 1,100 patients with this condition. As a result, to date, more than 40 ancillary studies have utilized the serum and data bank and more than 17 original articles have been written describing aspects of this syndrome.

This Grand Rounds comprises our current knowledge of ALF, based in large part on the information gathered from the ALFSG. It represents the unstinting effort of a large number of collaborators and would not be possible without their assistance (see list of sites in the appendix—for more detailed information on ALFSG and on many aspects of ALF, visit www.acuteliverfailure.org).

Definition

Acute liver failure (sometimes referred to as fulminant hepatic failure) is most commonly defined as the onset of coagulopathy (International Normalized Ratio [INR] $\geq$1.5 and encephalopathy (any degree of altered mentation) in a patient without pre-existing liver disease or cirrhosis (1). The typical interval from onset of symptoms to onset of encephalopathy is 1-2 weeks, but cases evolving more slowly, up to 6 months, may still be included in the definition. A clinical feature that is virtually unique to ALF is cerebral edema, swelling of the brain that may produce herniation of the uncus through the falx cerebrum, yielding brain stem compression and death (2). The morbidity and mortality of ALF recorded in small case series in the pre-transplant era was extremely high, often exceeding 90%, the causes of death including multi-organ failure, hemorrhage, infection and cerebral edema. Fortunately, these dire outcomes have diminished somewhat due to a change in the causes of ALF to more benign etiologies over the past 40 years as well as to the introduction of liver transplantation (3,4). Patients have been designated as hyperacute, acute and subacute in presentation depending on the interval from onset of disease to onset of encephalopathy. Different etiologies typically have a specific time frame. For example, most acetaminophen cases are always considered hyperacute while those demonstrating a slower onset (acute or subacute) are typically the result of viral hepatitis, idiosyncratic drug reactions or indeterminate cause (5). Whether there is a distinct difference in outcome based on the length of disease itself remains unclear; however, the etiologic diagnosis *per se* is likely the strongest driver of outcomes.

Diagnosis

The diagnosis of ALF must be considered in anyone presenting with the recent onset of an hepatic illness where the prothrombin time becomes prolonged. Mental alterations are part of virtually all definitions and the changes may be subtle, including, initially, agitation and confusion, followed by progression to deeper coma grades. With non-

descript presenting symptoms, the diagnosis is often missed by the initial medical contact. However, the combination of coagulopathy and encephalopathy is unique and is only seen in this setting. The presence of any degree of encephalopathy indicates a severe, life threatening condition that requires immediate hospitalization. Patients are best managed in an intensive care setting and specialty units devoted to acute liver failure are available in the United Kingdom (6). Rapid evaluation for transfer to a transplantation center and consideration for liver transplantation is mandatory once any degree of mental alteration occurs, since the outcome is uncertain and disease progression is often very rapid once this takes place (7).

Acute liver failure has a common clinical picture regardless of the etiology that represents the final pathway of acute organ failure, different from cirrhosis but specific to one organ, the liver. Patients appear to be relatively hypotensive and vasodilated with low systemic vascular resistance, and have a picture of multi-system failure that resembles in some ways that of gram-negative sepsis or end stage liver disease patients; however portal hypertension and ascites are usually absent. Renal failure resembling hepatorenal syndrome may develop and is reversible with return of hepatic function. Infection is unusually common in ALF, presumably signifying the role of the liver in the host's innate immune defenses, although gram-positive infections are the most commonly recognized ones, in part due to frequent invasive procedures (8,9).

Etiology

The causes of ALF are many and vary from country to country. In the era prior to transplantation, hepatitis B was very common and accounted for as many as 40-50% of US cases. Prior to 1990, although a well-recognized problem in the United Kingdom, acetaminophen did not account for more than a few US ALF cases. Current US figures provided by the ALFSG now show that acetaminophen-related acute liver failure accounts for ~50% of all cases, with hepatitis B responsible for only 7% (10). The etiologic breakdown in the US is similar to that found in Europe but is far different in the developing world, such as India, where drug-induced liver injury is limited solely to isoniazid, and acetaminophen injury is virtually unknown (11).

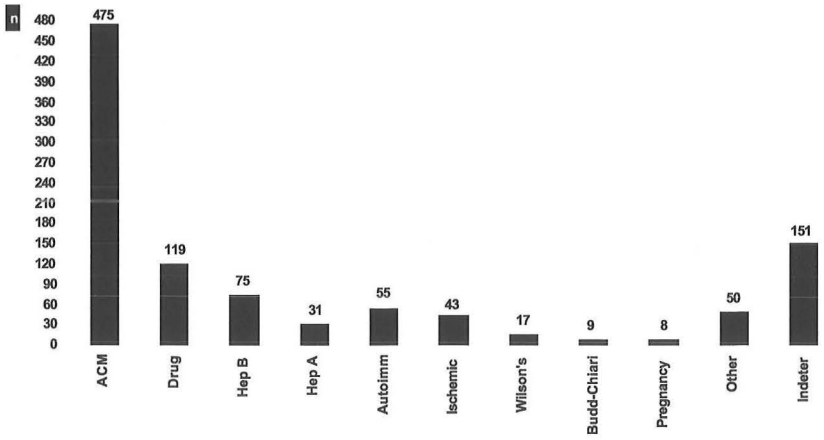


Figure 1. Etiologies of acute liver failure based on 1033 US cases.

After acetaminophen, the most common causes are drug-induced liver injury (comprising largely idiosyncratic reactions to prescription drugs), autoimmune hepatitis and a variety of smaller groups. In many instances (~15%), the etiology remains unclear despite extensive history taking and laboratory assessment and these cases are termed indeterminate. Regardless of the cause, the final common pathway is remarkably similar: worsening coma associated with a propensity for bleeding, infection and renal failure lead to poor overall survival without transplantation.

Acetaminophen-related liver injury

Although acetaminophen was approved for use in the 1950's, hepatotoxicity leading to liver failure was not recognized in significant numbers in the U.S. prior to 1980. With the linking of aspirin to Reyes syndrome in children around 1980, Americans began turning to acetaminophen as a safer alternative for children and adults. Cases were reported during the 1980's of 'therapeutic misadventures' and the association of unintended acetaminophen poisoning with alcohol was made (12). Although true incidence studies were (and are) not available, no large case series of acute liver failure patients included acetaminophen until a retrospective study from the ALF Study Group, covering the period 1994-96, found that 20% of cases were related to acetaminophen (13). Similar data were reported in 2000, in which 28% of transplant registry cases were believed related to acetaminophen during a 13-year retrospective study from the University of Pittsburgh (14). However, the U.S. ALF Study, in its first prospective series, recorded 39% of all ALF cases as due to acetaminophen between 1998 and 2001 (3), rising later to 51% in 2004. These figures represent the proportion of cases due to acetaminophen and may not be equated to actual incidence figures. Nevertheless, the increases are striking.

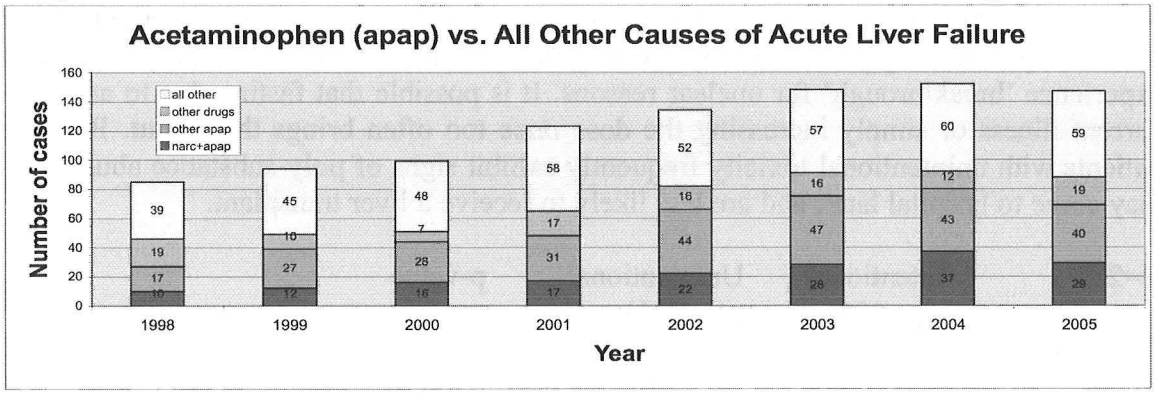


Figure 2. Incidence of acetaminophen alone and with narcotics causing acute liver failure.

It is important to distinguish between considering all cases entering the hospital with presumed acetaminophen overdose and that smaller subset that experiences acute liver failure. Of 71 acetaminophen overdose patients admitted to Parkland Hospital over a 39-month period, 50 were considered suicidal with only 1 of 50 resulting in ALF and death, whereas 6 deaths occurred among 21 unintentional overdoses (15). Only the 7 patients who died had developed acute hepatic failure, and only 10 of 50 suicidal patients had aminotransferase levels $\geq$ 1,000 IU/L. These data confirmed that most suicidal patients typically receive medical care within 4 hours of ingestion, and are therefore reliably protected by the acetaminophen antidote, N-acetylcysteine (NAC). By contrast,

overdoses that are called accidental, or more accurately unintentional, are associated with ingestion over several days, a specific cause of pain and denial of suicidal intent. Late presentation is characteristic of the unintentional group since there is no understanding of possible harm; medical attention only is sought after symptoms of toxicity have developed. Previous studies have suggested a strong association with excess alcohol in this group, however, this remains controversial (16-18). It is important to note that data from the Acute Liver Failure Study Group differs from that described above in terms of severity of disease, because it pertains only to those developing coagulopathy and encephalopathy, and not to the whole spectrum of potential or actual toxicity.

Unintentional acetaminophen-related acute liver failure

The U.S. ALF Study has provided a more detailed snapshot of all acetaminophen-related cases (19), and in particular the unintentional group. In a series of 275 patients, 38% of the unintentional group took more than one acetaminophen-containing preparation and 62% were taking a narcotic combination such as hydrocodone and acetaminophen (Vicodin® and others; Figure 2). The total quantity consumed over several days approximated that used in the suicidal cases (median ~24 gms), the apparent result of repeated overdosing when pain relief is not forthcoming. In many instances, individuals are using alcohol, hypnotics or illicit drugs in combination, undoubtedly clouding judgment and often delaying hospitalization. In a small number of cases, excessive use of the narcotic compounds, (up to 40 or more tablets per day) appears to build up gradually over days or weeks prior to onset of liver injury, suggesting addiction to the narcotic component with development of tolerance to the narcotic and to the acetaminophen, and subsequent exhaustion of the compensatory mechanism. Tolerance has been observed in animals fed increasing acetaminophen doses (20). The events prior to presentation are often unclear but the biochemical picture (AST/ALT elevations/ bilirubin levels) in these 'chronic' patients is just as acute, suggesting that patients may tolerate both drugs, then experience 'breakthrough' for unclear reasons. It is possible that fasting due to an inter-current illness or simply increasing the dose once too often brings this about. Because patients with unintentional toxicity frequently exhibit signs of poly-substance abuse they may come to hospital later, and are less likely to receive a liver transplant.

N=253	Intentional (n=122)	Unintentional (n=131)	p-value
Female (%)	74	73	NS
ACM dose (g)	25	20	NS
Dose per day	25	7.5	0.001
Coma (%≥3)	39	55	0.026
ALT (IU/L)	5326	3129	0.001
Spont surv (%)	66	64	NS
Antidepress't	38	37	NS
History of depression	45	24	0.001
Narcotic cpd (%)	18	63	0.001
Multiple preps	5	38	0.001

Table 1. Intentional vs. Unintentional Overdoses: Clinical and Lab Features

As might be expected, suicidal ingestions that eventuate in acute liver failure are associated with late presentation, alcohol or other concomitant drugs that may cloud the sensorium delaying presentation, and consumption of larger total doses, indicating more serious intent rather than a gesture. Even with late presentation, N-acetylcysteine orally (and now available as an intravenous preparation, Acetadote®) may provide some protection against fatal injury and undoubtedly prevents a large number of deaths when given within 12 hours of ingestion (18).

Traditionally, acetaminophen poisoning carries a very good prognosis, even if hepatic failure has developed. However, one third of those reaching the threshold of encephalopathy still die and only 9% undergo transplantation (10). The spontaneous survival of the acetaminophen patients who develop encephalopathy (64%) exceeds that for most other forms of acute liver failure, such as idiosyncratic drug toxicity, where survival without transplantation is only ~20% (10). Nevertheless, because of the sheer number of cases, deaths due to acetaminophen toxicity constitute the most frequent cause of death in our study. Suicidal predilection or the history of previous suicide attempts, like substance abuse, will often preclude transplant consideration. Once acute liver failure develops, the outcome for either type of overdose, suicidal or unintentional, is similar.

Other issues associated with acetaminophen

By observing a large number of ALF cases, our registry has been able to characterize the typical disease presentations for each of the etiologies of ALF (Table 2). Acetaminophen cases are all hyperacute with time from onset of jaundice to encephalopathy of 1 day versus idioscyncratic drugs or viral hepatitis where longer intervals are seen. Accordingly, the acetaminophen ALF patients uniformly have very high aminotransferase levels and low bilirubins, while much lower aminotransferases and higher bilirubins characterize the more slowly evolving pictures.

	ACM n=475	Drug n=199	Indeterminate n=151	HepA/HepB n=31/75	All Others n=182
Age (median)	36	43	37	47/41	41.5
Sex (% F)	74	6	56	45/44	76
Jaundice (Days)	0	10	10	3/7	7
Coma ≥3 (%)	51	38	48	55/52	42
ALT (median)	4149	571	851	2404/1601	677
Bili (median)	4.5	21.6	23.0	11.9/20.8	15.2
Tx (%)	9	40	4	29/47	35
Spontaneous Survival (%)	64	26	27	58/24	30
Overall Survival (%)	71	63	65	84/64	60

Table 2. Comparison of clinical and lab values in the overall ALF registry by etiology.

Recent studies from our group and others highlight more subtle issues surrounding acetaminophen. Using a recently developed assay that reliably detects acetaminophen–

containing protein adducts released into the plasma by dying hepatocytes, 20% of both adult and pediatric ALF patients with indeterminate etiology (no cause discerned after extensive investigation and testing) were found to be due to unrecognized acetaminophen poisoning (21,22). Adducts are not found with acetaminophen use unless there is toxicity and the levels observed strongly implicate acetaminophen as the primary cause of the injury (Figure 3, Table 3); the quantity observed correlates very well with AST levels and with use of alcohol and poorer outcome (unpublished data).

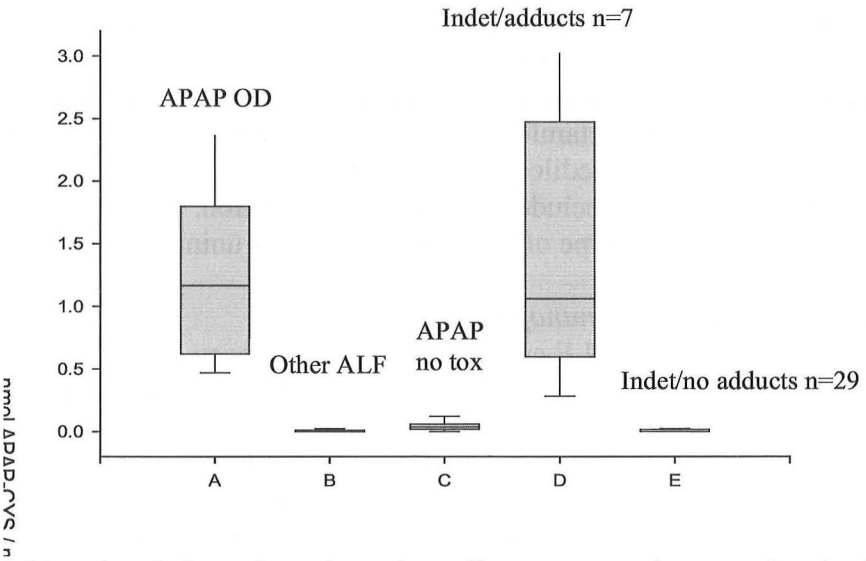


Figure 3. Adduct levels in patients in various disease categories associated with ALF.

Characteristic	Indeterminate Group with Adducts (N=7)									Indeterminate Group without Adducts (N=29)	
	Patient # 1	2	3	4	5	6	7	Range	Median	Range	Median
Age (year)	33	42	23	32	17	35	29	17-42	32	17-76	39
ALT (IU/L)	5,760	4,773	8,960	849	4,288	6,430	2,639	849-8,960	4,773	29 – 3,724	881
AST (IU/L)	14,580	11,029	18,928	1,569	6,465	8,850	1,629	1,549-18,928	8,850	42 –7,310	778
International normalized ratio (INR)	8.2	8.1	3.8	2.2	1.7	6.2	3.0	1.7-8.2	3.8	1.3 - 24.8	2.7
Bilirubin (mg/dl)*	2.2	6.7	7.1	10.9	8.5	2.5	5.3	2.2-10.9	6.7	1.8 - 52.2	23.7
Creatinine (mg/dl)**	3.8	2.9	3.4	3.9	0.5	2.2	3.6	0.5-3.9	3.4	0.7 - 6.3	1.4
Acetaminophen level (mg/L)	16	<10	<2	<10	0	N.D.	<10	0-16	-	0-15	-

Table 3. Lab data for 7 adduct positive patients with indeterminate ALF compared to the remainder of the indeterminate group.

The acetaminophen adducts assay provides the smoking gun, evidence of specific hepatocyte damage due to acetaminophen, when historical data is lacking; we found 7 of 36 patients in our indeterminate group to have levels of adducts similar to those observed in suicidal cases, suggesting that it was a lack of history that made the case indeterminate; when the biochemical pattern was analyzed, the cases fit the profile of high ALT, low bilirubin observed in the known acetaminophen cases. Insufficient data may result from patient obtundation, or denial, whether purposeful or out of ignorance. Likewise, in patients with viral hepatitis, acetaminophen toxicity may enhance the likelihood of acute liver failure: of 72 ALF patients with bona fide acute hepatitis A or B, 9 (12%) had detectable adducts levels, albeit at a lower level than observed in suicidal overdoses. These patients had higher median ALT levels and lower bilirubins than those observed in the adduct-negative group, and, interestingly, had a considerably worse outcome (Table 4). Acetaminophen should definitely be excluded from use in situations of acute liver injury such as viral hepatitis on the premise that even therapeutic doses may result in additional injury in this setting.

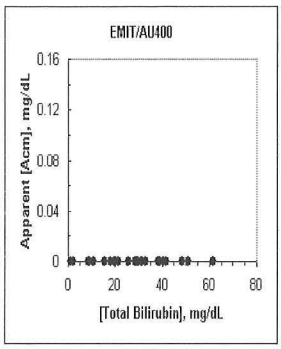
	ALT IU/L	T Bili mg/dL	[Add'ts]	Died* $p < 0.001$
AVH	1,580	19.8	0	27%
APAP-AVH	2,658	9.7	.45	67%
APAP	5,570	5.0	5.58	

Table 4. Clinical and laboratory data associated with the presence or absence of adducts in 72 patients with acute viral hepatitis.

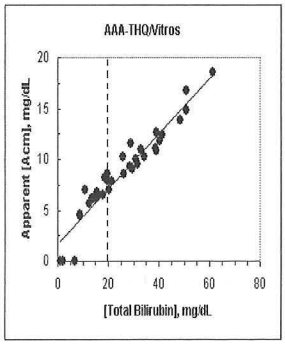
Whether acetaminophen dosing should be limited in the presence of chronic liver disease or cirrhosis remains unclear. A recent paper has questioned the use of 4 grams as the standard maximum daily dosing for acetaminophen (23). In nearly 100 healthy subjects observed over 10 days in a clinical research center setting, between 28 and 36% demonstrated significant hepatic enzyme elevations, up to 10x upper limit of normal, when given 4 gm/day daily in divided doses. No severe injury was observed but this remains of concern for those who use acetaminophen on a regular basis. Prudent management would suggest that doses within a 24-hour period be limited to half the suggested maximum of 4 gm, certainly in the presence of any chronic liver injury and perhaps in healthy subjects as well. However, two gm (4 Extra Strength tablets) represents an arbitrary but likely safer amount for most patients.

Another interesting aspect to this story concerns the use of acetaminophen quantitation assays to identify acetaminophen toxicity. Quantitative measures of acetaminophen in plasma are used to determine severity of overdose if the time of ingestion is known by plotting the level obtained on a nomogram. More recently, measuring acetaminophen in plasma has been used as a toxicology screening test as evidence of acetaminophen usage, regardless of the level obtained. As noted above, histories in ALF are notoriously unreliable for several reasons and in this and less severe settings, identifying acetaminophen use accurately has several implications: use of the antidote, NAC; proper assessment of causality when more than one possible agent is implicated; identification of occult suicidal ingestions. However, false positive assays have been demonstrated to

occur in patients with moderately severe liver disease; most clinicians are unaware of this. For example, a 71 yr old woman, admitted to Baylor with what turned out to be acute hepatitis A, denied acetaminophen use upon questioning while completely alert. On the second hospital day, an acetaminophen level came back as elevated at 15 mg/dL a low positive value. NAC was belatedly started; however, the level remained in the same range for several days, and a 1:1 dilution of her serum yielded no detectable acetaminophen. To evaluate this phenomenon further, we analyzed 36 non-acetaminophen ALF sera, all shown to be negative for the parent compound, acetaminophen, by highly specific gas chromatography/mass spectroscopy at nanogram amounts. We tested 6 assay systems finding between 0 and 21 of 36 positive, depending on the assay used. Colorimetric assays were subject to error whereas immunoassays were not. It has been thought that bilirubin interferes with the color reaction but we could not demonstrate a linear relationship to bilirubin in all the assay systems, so other substances found in serum of very ill patients that have similar increases in advanced liver disease like bilirubin may also be important (Polson J, submitted).



No interference (immunoassay)



Apparent linear interference due to bilirubin

Figure 4. APAP false positive results observed in 36 sera, comparing two different assay systems. The EMIT immunoassay does not show evidence of 'positive' APAP levels in the presence of bilirubin, while the AAA-THQ/Vitros enzyme/colorimetric assay does.

Idiosyncratic drug reactions

The developed world is particularly subject to rare acute liver failure due to idiosyncratic drugs reflecting the large number and variety of drugs we ingest. Still, prescription drugs are remarkably safe; the combined number of idiosyncratic drug cases thought to cause ALF in our series is dwarfed by the single agent, acetaminophen. Data from the ALFSG shows the difference in both clinical presentation and outcome for these cases as discussed in Table 2. The drug-induced ALF presentation is more subacute, the likelihood of survival is poorer, and this group more often receives liver transplants. Most frequently implicated drugs include antibiotics (most commonly anti-tuberculous medications, but also sulfa drugs and others). Next most common are non-steroidal anti-inflammatory agents and anti-convulsants. Drug toxicity has been reviewed here quite recently by Dr. Maddrey (February 9, 2006) and earlier by myself (24).

Viral hepatitis

Cases of viral hepatitis that develop hepatic failure represent a small fraction of viral hepatitis (~1%) and are largely comprised of hepatitis B, with hepatitis A less frequent

and hepatitis E quite prevalent in areas with poor sanitation. Recently, 4 patients died in an epidemic of more than 500 cases in the Pittsburgh area associated with food-borne contamination of green onions from Mexico at a TexMex chain (25). The reasons for individuals developing hepatic failure have included concomitant acetaminophen administration, associated other viruses such as hepatitis C (26) or an overactive immune response to acute hepatitis B infection (27). Outcome resembles that of other non-acetaminophen causes being quite dismal for hepatitis B but less so for hepatitis A (28).

Other causes

A variety of other etiologies have been implicated from autoimmune hepatitis (29), Budd-Chiari syndrome (hepatic vein thrombosis; 30), Wilson disease (31), pregnancy-associated liver failure (32), rapid evolution of metastatic or lymphomatous hepatic infiltration (33,34).

One unique presentation of acute liver failure worth noting is that associated with Wilson disease (WD), a genetic disorder of copper metabolism. Patients typically are unrecognized as having WD prior to the rapid evolution of deep jaundice and renal failure resulting from high plasma copper levels that lead to hemolysis and renal tubular injury. Outcome is invariably fatal without transplantation (35). We recently examined 16 cases of fulminant WD, to review how the diagnosis is best established. Of interest, conventional measures such as ceruloplasmin used to diagnose WD in the chronic setting are of little value here. Much better is a ratio of conventional lab tests: alkaline phosphatase:bilirubin. If the AP:Bili ratio is < 4 the sensitivity and specificity are 94 and 96% respectively. If one adds an AST:ALT ratio of < 2.2, the sensitivity and specificity reach 100%. The reasons for these unique variations in standard laboratory chemistries remain poorly understood but undoubtedly relate to the very high levels of plasma copper observed. These assays allow the most rapid diagnosis of WD by not relying on tests such as plasma, urine or tissue copper levels with slower turnaround times (Table 5).

Comparison of Screening Tests for WD in ALF

Group	*Screening Test*	*Sensitivity %*	*Specificity %*	*Likelihood Ratio*
Acute:	Cp[1] <20 by oxidase	21	84	1
	Cp <20 by nephelometry	57	63	2
	Hemoglobin <10	92	74	4
	AP:TB[2] ratio <4	92	96	22
	AP:TB ratio <4 + AST:ALT ratio >2.2	100	100	NA[3]
	Cu[4] >200	79	96	18
	AST:ALT ratio >2.2	93	86	7
Chronic:	Cp <20 by oxidase	71	97	21
	Cp <20 by nephelometry	71	79	3

[1] Ceruloplasmin; [2] Alkaline Phosphatase: Total Bilirubin; [3] Not applicable [4] Serum Copper

In the chronic liver disease group, zero subjects had an AP:TB r atio < 4, three subjects had Hg <10, one had Cu >200, and the AST:ALT ratio was an ineffective marker of WD.

Table 5. Standard lab values in patients with acute liver failure due to Wilson disease. The best single diagnostic test is the ratio of alkaline phosphatase to bilirubin.

Indeterminate cases

Despite our best efforts, in 15% of patients the diagnosis eludes us. To date, our group has looked for other viruses using specific and sensitive assays including parvovirus B19, hepatitis E virus (36), hepatitis C virus, SEN V virus (37), herpes simplex virus or occult HBV infection (38), and none of these appear to be responsible for United States cases, except for HSV in a very few instances. Unrecognized acetaminophen toxicity is clearly implicated and there may be unrecognized autoimmune disease, since testing for autoantibodies and/or biopsy may not be performed routinely in this setting. Occult and unreported drugs or toxins may be responsible in certain instances; another virus responsible for cases of acute liver failure seems unlikely at this point.

Pathogenesis

A unique syndrome of multi-organ failure appears following massive hepatic necrosis, characterized by altered mentation and, in the many advanced cases, cerebral edema. Characteristic features include coagulopathy, hypoglycemia, hypophosphatemia, low systemic vascular resistance, renal failure, bleeding, frequent infections and occasionally cardiac arrhythmias. The massive necrosis and loss of function clearly creates a cytokine storm about which little is known. Both pro-apoptotic (soluble Fas ligand [sFas] and TNF-alpha) and anti-apoptotic (hepatocyte growth factor [HGF] and IL-6) marker levels are elevated more than 10-fold in all forms of ALF compared to healthy controls or patients with other liver diseases such as hepatitis C (39). A surrogate marker for apoptotic activity, M-30 antigen, is also markedly elevated in ALF patients the levels correlating with outcome, being higher in those who die or are transplanted than in survivors without transplantation. One interesting observation is that many of the features, such as the shock like state, appear to improve with removal of the necrotic liver; however, rendering a patient anhepatic is not compatible with life for more than a few hours and cannot be considered acceptable without a readily available hepatic graft (40,41). It is not clear whether necrotic materials such as cellular actin in the circulation (42), the cytokines themselves, or possibly simply loss of hepatic function is responsible for this dire clinical picture. That ALF is a multi-organ process is highlighted by a recent study that showed in 184 patients that serum troponin-I levels were elevated indicating myocardial injury in 74% of patients with ALF across all etiologies; higher levels of troponin-1 were associated with poorer outcomes (43). Additional studies from our group have highlighted some of these numerous derangements: ferritin levels exceeding 100,000 mg/dL are not unusual (44), Gc globulin, an actin scavenger that mops up circulating cellular actin is diminished to $< 10\%$ of that observed in healthy controls (45,46), and levels of serum osteopontin (a novel phosphoglycoprotein found in hepatic macrophages that serves as a chemokine involved in the Th1 immune response during acute liver injury) are markedly elevated (47). Recent evidence suggests that the systemic inflammatory response syndrome (SIRS) components can be elicited in a great many ALF patients and are associated with a poorer prognosis when present as one might expect (48). The study referred to showed that acetaminophen patients were particularly prone to progression of coma and poorer outcomes if they developed new components of the SIRS syndrome (e.g., fever, increased neutrophil count) after hospital admission.

Clinical Management

The backbone of management of the ALF patient is good coma care. However, some special features deserve mention. Rapid evaluation (Table 6) and initiation of antidotes where feasible are needed: N-acetylcysteine for acetaminophen poisoning, penicillin G and silybinin for mushroom poisoning and delivery of the fetus in the cases of pregnancy induced ALF are standard of care (Table 7). Once the diagnosis of ALF is confirmed (by the finding of coagulopathy and encephalopathy in the setting of acute hepatitis) and a careful search for etiology is undertaken (Figure 5), attention should be turned to consideration of the need to list for transplantation. Patients with ALF are uniquely considered as having the highest priority for transplantation (UNOS Status 1) based on their penchant for rapid deterioration. In our series, patients received a liver graft on (median) day 1 after transplant listing, and if no liver was available, died on (median) day 3, emphasizing that emergent listing is often not enough to guarantee a good outcome, given the current shortage of available organs (10). A detailed review of the management issues involved is beyond the scope of this presentation but has been well summarized recently (49).

	Recommended	Optional
General tests	CBC, differential, hemoglobin, platelets Blood type and screen Chemistries (electrolytes§, glucose, BUN, creatinine*, liver chemistries) PT*/PTT, fibrinogen Ammonia (preferably arterial)‡ Amylase, lipase HIV antibody Arterial blood gas*	AFP Lactate* Ferritin Factors V,VII, VIII
Etiology-specific tests	Acetaminophen level Toxicology screen Viral serologies: HAV (IgM and total), HBV (HBsAg, anti-HBc (IgM and total), anti-HCV, anti-CMV, anti-EBV, anti-HSV 1/2 Pregnancy test (females) Autoimmune serologies (ANA, ASMA, anti-LKM), immunoglobulin levels Ceruloplasmin	HBV DNA HCV RNA CMV DNA EBV DNA HSV DNA† anti-HEV anti-HDV Serum and urine copper Slit-lamp eye exam Troponin Brain natriuretic peptide
Other tests	Chest X-ray EKG Echocardiogram Doppler ultrasound of liver and blood vessels	Transjugular liver biopsy Abdominal CT Head CT EEG

Table 6. Initial evaluation for acute liver failure patients.

The ALF Study Group has also developed and adopted a standardized protocol now in use throughout the group centers. In most instances, since ALF is an orphan disease, the level of evidence is not sufficiently high to ensure that the recommendations are truly evidence-based and best practices are invoked in many situations. Controversial management issues that are commonly of concern include provision of clotting factors (we generally do not treat the laboratory abnormalities unless active bleeding is present);

intracranial pressure (ICP) monitoring (center dependent); treatment of cerebral edema (mannitol provides short-term improvement, while hypothermia remains unproven but promising). Figure 5 provides a brief algorithm for initial triage of the ALF patient

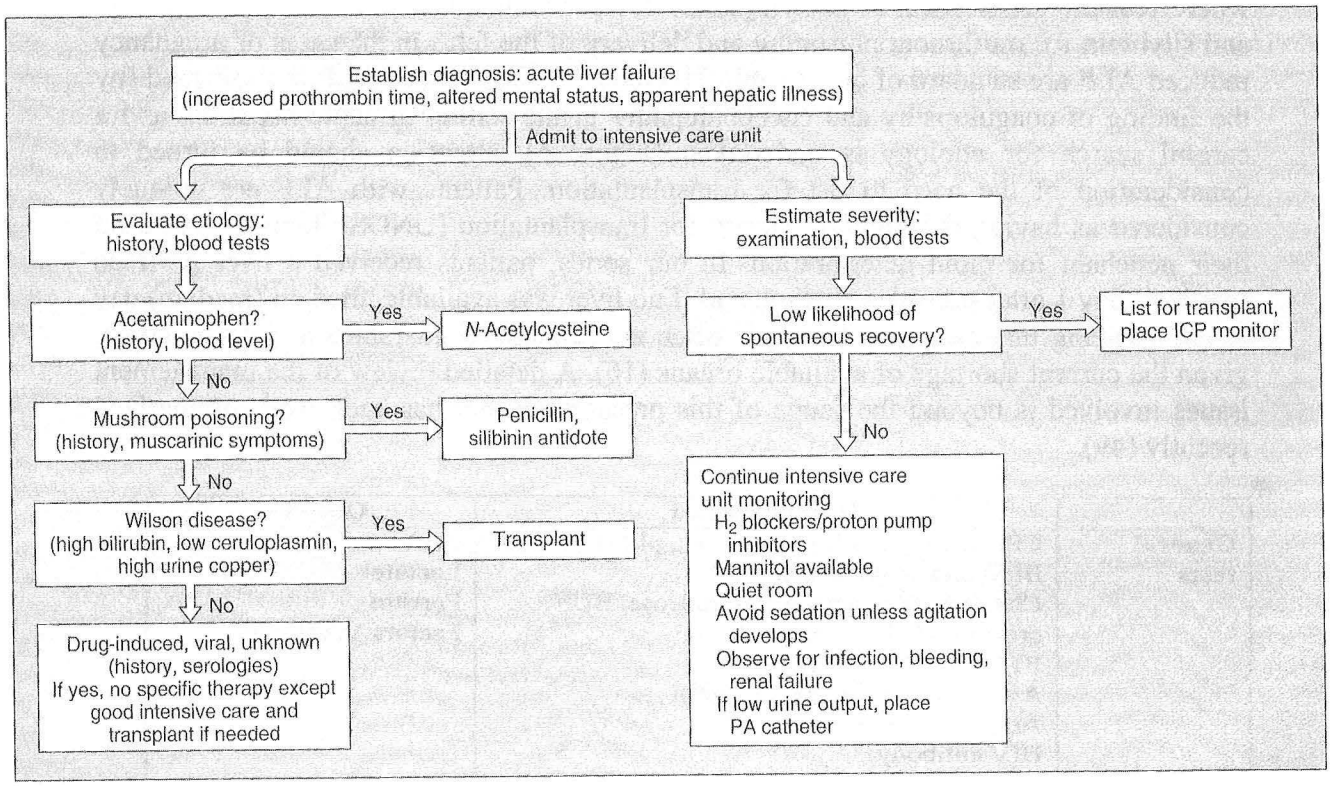


Figure 5. Management algorithm for ALF patients.

Role of intracranial pressure monitoring

We studied retrospectively the possible impact of ICP monitoring in 332 patients that reached advanced grades of encephalopathy. The results suggested that use of ICP monitoring was center dependent reflecting, among other things, the confidence level of the neurosurgeon, since a burr hole in the skull is needed and can be hazardous in the presence of severe coagulopathy. Patients in whom a monitor was placed generally received more aggressive mannitol and other treatments when evidence was available clinically of increased ICP levels, and were more likely to be listed for transplantation, but outcomes did not appear to differ in the two groups (50).

Role of transplantation

There is no clear therapy for this devastating clinical syndrome. Prior to 1980, ALF series demonstrated survival in less than 10%. Small series of cases subjected to new experimental treatments (e.g., heparin!) showed that occasionally patients do survive; however, controlled trials were virtually impossible to perform and the state of the art (referring to these small uncontrolled trials) was said to be "Be published or perish (51)." In this setting, transplantation seemed nothing short of a miracle. In the current era, overall survival is approximately 67%, a considerable improvement in the last 3 decades.

However, transplants are only performed on 25% of patients admitted to the ALF study (Figure 6).

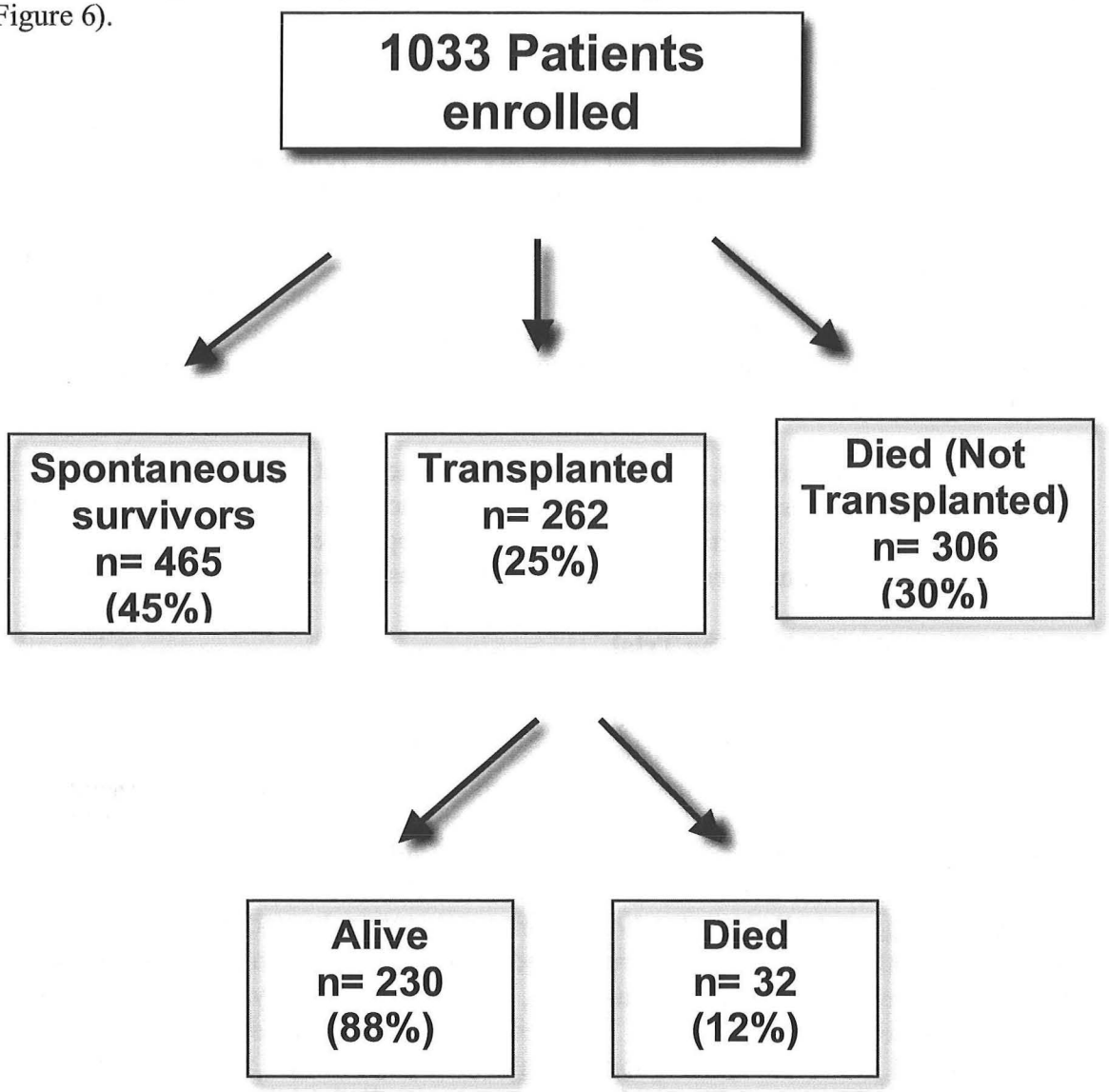


Figure 6. Outcomes after admission to the ALF Study for 1033 patients enrolled between 1998 and 2005.

The reasons for this include the difficulties in obtaining organs in a timely fashion, as well as the changing mix of etiologies, the change from hepatitis B to a predominance of acetaminophen making up most of the change. It should be noted that nucleoside analogues for acute liver failure due to hepatitis B appear to improve the outcomes (52),

but a controlled trial has not, and probably never will be, performed. Even in the transplant era, nearly 30% of patients do die with ALF. Reasons for the failure to transplant more patients have included lack of available organs, late presentation and too rapid deterioration, substance abuse issues, repeated suicidal behavior or other organ system involvement (malignancy, heart failure) that would preclude grafting in any case. Patients undergoing transplantation for ALF are typically young and otherwise healthy and thus should be quite optimal candidates compared to their cirrhosis counterparts. Nevertheless, short term and one year survival figures are below that for cirrhotic patients (91% at 3 weeks in our study), in part because of the extreme emergency conditions often encountered. There is no option for deferring transplant in these patients until a more optimal condition can be developed. Similarly, living related donations might solve the organ shortage; however, it is extremely difficult to prepare a donor adequately and perform the surgery in a timely fashion.

Despite full physical recovery, many patients have some mental impairment that may be life long. Because of these considerations, we are conducting a long-term follow-up study of patients with ALF to ascertain how much loss of cognitive abilities follows from the exposure to the conditions of encephalopathy and increased brain edema.

Specific Therapies Undergoing Trial

The ALFSG has, since 1999, undertaken a trial of N-acetylcysteine for the treatment of those cases of acute liver failure not due to acetaminophen. After acetaminophen overdose, N-acetylcysteine replenishes mitochondrial and cytosolic glutathione stores, and has been shown in patients and in experimental animals to prevent or ameliorate the degree of injury and cell death (53-55). Intravenous or oral NAC improves survival in patients with acetaminophen-induced ALF (56-58). Evidence of benefit, even when given as late as 72 hours after overdose, led to its use in a few non-acetaminophen ALF cases (59). A small uncontrolled study showed improvement in hemodynamics and oxygen transport in both acetaminophen (n=12) and non-acetaminophen (n=8) patients (60). Mean arterial pressure, oxygen consumption, and oxygen delivery increased, as did the oxygen extraction ratio. As a result, intravenous NAC is now used at King's College Hospital (KCH) in the United Kingdom and elsewhere as standard treatment for all acute liver failure, but has never been subjected to a controlled trial. A second study (61) confirmed the earlier findings concerning hemodynamics, and showed a significant increase in cyclic guanine monophosphate (cGMP) levels suggesting that NAC may cause vasodilation by increasing soluble guanylate cyclase activity (62,63). However, a more recent study from Edinburgh failed to demonstrate improved hemodynamics with NAC: patients with ALF in Grade IV coma on a ventilator were given intravenous NAC with no improvement in blood pressure or cardiac output (64). Nevertheless, all patients were in an advanced disease state and were ventilated and sedated, factors that may have precluded a beneficial effect and they certainly did not represent a cross-section of ALF. NAC had been widely used in the US as an oral preparation (Mucomyst®) and intravenous NAC infusion (Acetadote®) has been available in the US since 2004, specifically for use in acetaminophen overdoses. However, IV NAC appears to be prescribed widely in the emergency room setting because of concerns that acetaminophen toxicity might be missed or that NAC might have some beneficial effect as described

above. While missing acetaminophen cases would be a serious clinical error and there may be a need to use the drug in some instances, patients with APAP toxicity, as shown above, have a very specific and nearly unique pattern of very high aminotransferases and low bilirubins after a short illness. Thus, a deeply jaundiced patient who has been sick for several weeks is not likely to be suffering from acetaminophen poisoning.

Our NAC study is a double blind, randomized trial of N-acetylcysteine vs. placebo for the treatment of non-acetaminophen ALF, testing the safety and efficacy of a short course (72 hours) of intravenous N-acetylcysteine in patients with acute liver failure for whom no antidote or other specific treatment is available. Patients admitted to study sites meeting carefully defined criteria for acute liver failure and who are thought not to have acetaminophen toxicity, mushroom poisoning, pregnancy-related liver failure, or malignancy are eligible. We stratify according to coma grade (I-II vs. III-IV) and randomize in blinded fashion each patients to receive, by intravenous route, either 5% dextrose in water or a solution of 5% dextrose in water containing N-acetylcysteine, beginning at a dose of 150 mg/kg bodyweight in 200 ml 5% dextrose over one hour, and in declining doses over a total of 72 hours (65). Patients randomized to placebo will receive volume-matched 5% dextrose infusions. Care of patients and consideration of transplantation or other clinical decisions will not be affected by the study or the use of study drug or placebo. To date, 175 out of a planned 210 have been enrolled—we remain blinded to the results. The study will conclude on August 31, 2006.

Bioartificial liver assist devices

An artificial liver device that would replace the diverse functions of the liver is an unmet need that seems far in the future. A number of groups have designed membrane-containing cartridges filled with hepatocytes from human cell lines or porcine livers, allowing plasma to flow by the cells. Some improvement in encephalopathy has been observed but no real improvement could be demonstrated in overall survival in a controlled trial (66,67). A recent meta-analysis further demonstrated the scarcity of data and the lack of convincing efficacy (68). Several centers have experimented with extracorporeal transgenic pig livers or cadaver livers deemed unfit for transplantation but these techniques have not gained general acceptance (69,70). Finally, early experimentation is underway using infusions of hepatic stem cells that are said to be non-immunogenic; human trials are expected to begin in India in 2007 (71).

Summary

Acute liver failure challenges our best clinical and surgical skills because of its rarity, rapid progression and frequently bad outcomes. The small numbers of patients do not readily lend themselves to controlled trials and are studied only with great difficulty. Nevertheless, descriptive information aids our understanding of what to expect and where small gains might be made in this condition. Patients are particularly vulnerable to infection, bleeding and cerebral edema and seek medical care typically with very advanced hepatic injury. It is unlikely that there is one overall therapy that will improve hepatic function and restore hepatocyte mass in this condition. Rescue therapies that provide temporary liver support, or other treatments short of transplantation that don't enhance hepatic regeneration, are likely to fail unless there is reconstitution of functional

hepatic mass, probably via stem cells. Most of our efforts in treating ALF in 2006 should be directed toward ameliorating the damage in various etiologic categories. Possible targets might include, for acetaminophen, further education regarding the risk of acetaminophen liver injury, unbundling the narcotic compounds, limiting package size or requiring blister packs; for hepatitis B, prompt use of nucleoside analogues when acute hepatitis B becomes severe.

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) 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.
5) 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.
6) Polson J, Lee WM. AASLD Position Paper: Acute Liver Failure. Hepatology 2005,41:1179-97.
7) Stravitz RT, Kramer AH, Davern T, Shaikh OS, Caldwell SH, Mehta RL, Blei AT, Lee WM, and the ALFSG. Management of acute liver failure: Recommendations of the acute liver failure study group.
8) Rolando N, Philpott-Howard J, Williams R. Bacterial and fungal infection in acute liver failure. Semin Liver Dis 1996;16:389-402.
9) Vaquero J, Polson J, Chung C, Helenowski I, Schiodt FV, Reisch J et al. Infection and the progression of hepatic encephalopathy in acute liver failure. Gastroenterology 2003;125:755-764.
10) 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.
11) Acharya SK, Dasarathy S, Kumer TL, Sushma S, Prasanna KSU, Tandon A et al. Fulminant hepatitis in a tropical population: clinical course, cause, and early predictors of outcome. Hepatology 1996;23:1448-55.
12) Zimmerman HJ, Maddrey WC. Acetaminophen (paracetamol) hepatotoxicity with regular intake of alcohol: analysis of instances of therapeutic misadventure. Hepatology 1995;22:767-773.
13) 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.
14) Shakil AO, Kramer D, Mazariegos GV, Fung JJ, Rakela J. Acute liver failure: clinical features, outcome analysis, and applicability of prognostic criteria. Liver Transpl 2000;6:163-169.
15) Schiodt FV, Rochling FA, Casey DL, Lee WM. Acetaminophen toxicity in an urban county hospital. N Engl J Med 1997;337:1112-1117.
16) Rumack BH. Acetaminophen misconceptions. Hepatology 2004;40:10 –5.

17) Whitcomb DC, Block GD. Association of acetaminophen hepatotoxicity with fasting and ethanol use. JAMA 1994; 272(23):1845-1850
18) Makin AJ, Williams R. Acetaminophen-induced hepatotoxicity: predisposing factors and treatments. Adv Intern Med 1997; 42:453-483.
19) 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.
20) Shayiq RM, Roberts DW, Rothstein K, Snawder JE, Benson W, Ma X et al. Repeat exposure to incremental doses of acetaminophen provides protection against acetaminophen-induced lethality in mice: an explanation for high acetaminophen dosage in humans without hepatic injury. Hepatology 1999;29:451-463.
21) Davern II, TJ, James LP, Hinson JA, Polson J, Larson AM, Fontana RJ, Lalani EK, Munoz S, Shakil AO, Lee WM and the ALFSG. Measurement of serum acetaminophen-protein adducts in patients with acute liver failure. Gastroenterology 2006:130:687-94.
22) James LP, Alonso EM, Hynan LS, Hinson JA, Davern TJ, Lee WM, Squires RH and the Pediatric Acute Liver Failure Study Group. Detection of acetaminophen-protein adducts in children with acute liver failure of indeterminate cause. Pediatrics 2006;118:e676-681.
23) Watkins PB, Kaplowitz N, Slattery JT, Colonese CR, Colucci SV, Stewart PW, Harris SC. Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen per day. JAMA 2006;296:87-93.
24) Lee WM. Medical Progress: Drug-Induced Hepatotoxicity. N Engl J Med 2003;349:474-85.
25) Wheeler C, Vogt TM, Armstrong GL, Vaughan G, Weltman A, Nainan OV, et al. An outbreak of hepatitis A associated with green onions. N Engl J Med 2005;353:890-97.
26) Vento S, Garofano T, Renzini C, Cainelli F, Casali F, Ghironzi G, Ferraro T, et. al. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. N Engl J Med 1998;338:286-90.
27) Woolf IL, Sheikh NE, Cullens H, Lee WM, Eddleston ALWF, Williams R, Zuckerman AJ. Enhanced HBsAb production in pathogenesis of fulminant viral hepatitis type B. Br Med J 1976;2:669-671.
28) Schiødt FV, Davern TJ, Shakil OA, McGuire B, Samuel G, Lee WM. Viral hepatitis-related acute liver failure. Am J Gastroenterol 2003;98:448-53.
29) Czaja AJ. Treatment of autoimmune hepatitis. Semin Liv Disease 2002; 22:365-378.
30) Ringe B, Lang H, Oldhafer K-J, Gebel M, Flemming P, Georgii A, et al. Which is the test surgery for Budd-Chiari syndrome: venous decompression or liver transplantation? A single center experience with 50 patients. Hepatology 1995;21:1337-44.
31) Roberts E, Schilsky ML. A practice guideline on Wilson disease. Hepatology 2003; 37:1475-1492.

32) Ockner RS, Brunt EM, Cohn SM, Krul ES, Hanto DW, Peters MG. Fulminant hepatic failure caused by acute fatty liver of pregnancy treated by orthotopic liver transplantation. Hepatology 1990;11:59-64.
33) Rowbotham D, Wendon J, Williams R. Acute liver failure secondary to hepatic infiltration: a single centre experience of 18 cases. Gut 1998;42: 576-80.
34) Agarwal K, Jones DE, Burt AD, Hudson M, James OF. Metastatic breast carcinoma presenting as acute liver failure and portal hypertension. Am J Gastroenterol 2002;97:750-751.
35) Korman J, Volensky I, Balko J, Webster J, Lee WM, Squires RH, Schilsky M, et al. Screening for Wilson Disease in Acute Liver Failure: A Comparison of Currently Used Tests. Submitted
36) Lee WM, Brown KE, Young NS, Dawson GJ, Schlauder GG, Gutierrez RA, Fontana R, Rossaro L, Davern T, Lalani E and the Acute Liver Failure Study Group. Brief Report: No evidence for hepatitis E or parvovirus B19 Infection in patients with acute liver failure. Dig Dis Sci 2006;ePub:September 9.
37) Umemura T, Tanaka E, Ostapowicz G, Lee WM, Heringlake S, Manns MP, Tassopoulos NC, et al. Investigation of SEN virus infection in patients with cryptogenic acute liver failure, aplastic anemia and acute and chronic non-A-E hepatitis. J Inf Dis 2003;188:1545-52.
38) Teo EK, Ostapowicz GA, Hussain M, Lee WM, Fontana RJ, Lok ASF and US ALF Study Group. Hepatitis B infection in patients with acute liver failure in the United States. Hepatology 2001; 33:972-76.
39) Rutherford AE, Hynan LS, Forcione DG, Blackard JT, Gorman AR, Lee WM, Chung RT and the ALF Study Group. Serum apoptotic markers in acute liver failure: a pilot study. Submitted.
40) Dominguez Fernandez E, Lange K, Lange R, Eigler FW. Relevance of two-stage total hepatectomy and liver transplantation in acute liver failure and severe liver-trauma. Transplant Internat 2001;14:184.
41) Lee WM. Total hepatectomy for acute liver failure: don't take out my liver! Gastroenterology 1994;107:894-97.
42) Lee WM, Galbraith RM. The extracellular actin-scavenger system and actin toxicity. N Engl J Med 1992;326:1335-41.
43) Parekh NK, Satyanaranyara R, Stravitz RT, McGuire B, McCashland T, Hynan LS, Lee WM and the ALF Study Group. Elevated troponin I levels in acute liver failure: Is myocardial injury an integral part of the acute liver failure? Submitted.
44) Korman J, Schilsky ML, Stravitz RT< Chung RT, Hassanein T, Shakil AO, Balko J, Lee WM and the ALF Study Group. Serum ferritin levels in acute liver failure: possible value in determining prognosis. Submitted.
45) Lee WM, Galbraith RM, Watt GH, Hughes RD, Hoffman BJ, Williams R. Predicting survival in fulminant hepatic failure using serum Gc protein concentrations. Hepatology 1995;21:101-5.
46) Schiødt FV, Rossaro L, Stravitz RT, Shakil OA, Chung RT, Lee WM, and the ALF Study Group. Gc-globulin and prognosis in acute liver failure. Liver Transplant 2005;11:1223-27.

47) Srungaram P, Pezzia C, Webster J, Balko J, Attar N, Lee WM and the ALF Study Group, Serum osteopontin levels reflect degree of liver necrosis in acute liver failure. Gastroenterology 2006;
48) Vaquero J, Polson J, Chung C, Helenowski I, Schiodt FV, Reisch J, Lee WM, Blei AT and the Acute Liver Failure Study Group. Infection and the progression to deep hepatic encephalopathy in early fulminant hepatic failure. Gastroenterology 2003;125:755-64.
49) Polson J, Lee WM. AASLD Position Paper: Acute Liver Failure. Hepatology 2005,41:1179-97.
50) Vaquero J, Fontana RJ, Larson A, Bass N, Davern TJ, Shakil OA, Han S, Harrison EM, Stravitz TR, Muñoz S, Brown R, Lee WM, Blei AT. Complications and use of intracranial pressure monitoring in patients with acute liver failure and severe encephalopathy. Liver Transplant 2005; 11:1581-89.
51) Benhamou JP. Fulminant and subfulminant hepatic failure: definition and causes. In: Williams R. Hughes RD. Eds. Acute liver failure: improved understanding and better therapy. London. Miter Press, 1991:6-10.
52) Tillmann HL, Hadem J, Leifeld L, Zachou K, Canbay A, Eisenbach C, et al. Safety and efficacy of lamivudine in patients with severe acute or fulminant hepatitis B, a multicenter experience. J Viral Hepat. 2006;13:256-63.
53) Prescott LF, Illingworth RN, Critchley JAJH, Stewart MJ, Adam RD, Proudfoot AT. Intravenous N-acetylcysteine: the treatment of choice for paracetamol poisoning. BMJ 1979;ii:1097-1100.
54) Smilkstein MJ, Bronstein AC, Linden C, Augentein WL, Kulig KW, Rumack BH. Acetaminophen overdose: a 48-hour intravenous N-acetylcysteine treatment protocol. Ann Emerg Med 1991;20:1058-1063.
55) Smilkstein MJ, Knapp GL, Kulig KW, Rumack BH. Efficacy of oral Nacetylcysteine in the treatment of acetaminophen overdose. N Engl J Med 1988;319:1557-1562.
56) Keays R, Harrison PM, Wendon JA, Forbes A, Gove C, Alexander GJM, Williams R. Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. BMJ 1991;303:1026-1029.
57) Vale JA, Proudfoot AT. Paracetamol (acetaminophen) poisoning. Lancet 1995;346:547-552.
58) Perry HE, Shannon MW. Efficacy of oral vs. intravenous N-acetylcysteine in acetaminophen overdose: results of an open-label clinical trial. J Pediatr 1998;132:149-52.
59) Harrison PM, Keays R, Bray GP, Alexander GJM, Williams R. Improved outcome of paracetamol-induced fulminant hepatic failure by late administration of acetylcysteine. Lancet 1990;335:1572-1573.
60) Harrison PM, Wendon JA, Gimson AES, Alexander GJM, Williams R. Improvement by acetylcysteine of hemodynamics and oxygen transport in fulminant hepatic failure. N Engl J Med 1991;324:1852-1857.
61) Harrison P, Wendon J, Williams R. Evidence of increased guanylate cyclase activation by acetylcysteine in fulminant hepatic failure. Hepatology 1996;23:1067-1072.

62) Wood KS, Ignarro LJ. Hepatic cyclic GMP formation is regulated by similar factors that modulate activation of purified hepatic soluble guanylate cyclase. J Biol Chem 1987;262:5020-5027.
63) Schneider J, Lutun P, Boudjema K, Wolf P, Tempé J-D. In vivo evidence of enhanced guanylyl cyclase activation during the hyperdynamic circulation of acute liver failure. Hepatology 1994;19:38-44.
64) Walsh TS, Hopton P, Philips BJ, Mackenzie SJ, Lee A. The effect of N acetylcysteine on oxygen transport and uptake in patients with fulminant hepatic failure. Hepatology 1998;27:1332-40.
65) Makin AJ, Wendon J, Williams R. A 7-year experience of severe acetaminophen-induced hepatotoxicity (1987-1993). Gastroenterology 1995;109:1907-16.
66) Demetriou A, Brown RS, Busuttil RW, Fair J, McGuire BM, et al. Prospective, Randomized, Multicenter, Controlled Trial of a Bioartificial Liver in Treating Acute Liver Failure. Ann Surg 200;239:660–70.
67) Jalan R, Sen S, Williams R. Prospects for extracorporeal liver support. Gut 2004;53:890-98.
68) Liu J, Khaergard LL, Asl-Nielsen B, Gluud C, Artificial and bioartificial support systems for liver failure: a Cochrane Hepato-Biliary Group Protocol. Liver 2002;22:433.
69) Chari RS, Collins BH, Magee JC, DiMaio JM, Kirk AD, Harland RC, et al. Brief report: treatment of hepatic failure with ex vivo pig liver perfusion followed by liver transplantation. N Engl J Med 1994;331:234-237.
70) Horslen SP, Hammel JM, Fristoe LW, Kangas JA, Collier DS, Sudan DL, et al. Extracorporeal liver perfusion using human and pig livers for acute liver failure. Transplantation. 2000;70:1472-8.
71) www.vestatherapeutics.com

Appendix:

List of sites and PI's in the Adult Acute Liver Failure Study Group

•UT Southwestern	Lee
•U Washington	Larson
•UCSF	Davern
•Mt. Sinai NYC	Martin
•Univ Nebraska	McCashland
•Baylor Dallas	Murray
•Univ Pittsburgh	Shakil
•Northwestern Univ	Blei
•OHSU, Portland	Zaman
•UCLA	Han
•Michigan	Fontana
•Univ Alabama Birmingham	McGuire
•Mass General	Chung
•Columbia/Cornell NYC	Brown/Schilsky
•VCU	Stravitz
•Mayo Clinic: Rochester, Jax,	Hay, Satyranarana
•UC Davis	Rossaro
•Einstein Philadelphia	Munoz
•MUSC Charleston	Reuben
•Pennsylvania	Reddy
•UCSD	Hassanein
•Duke	Smith