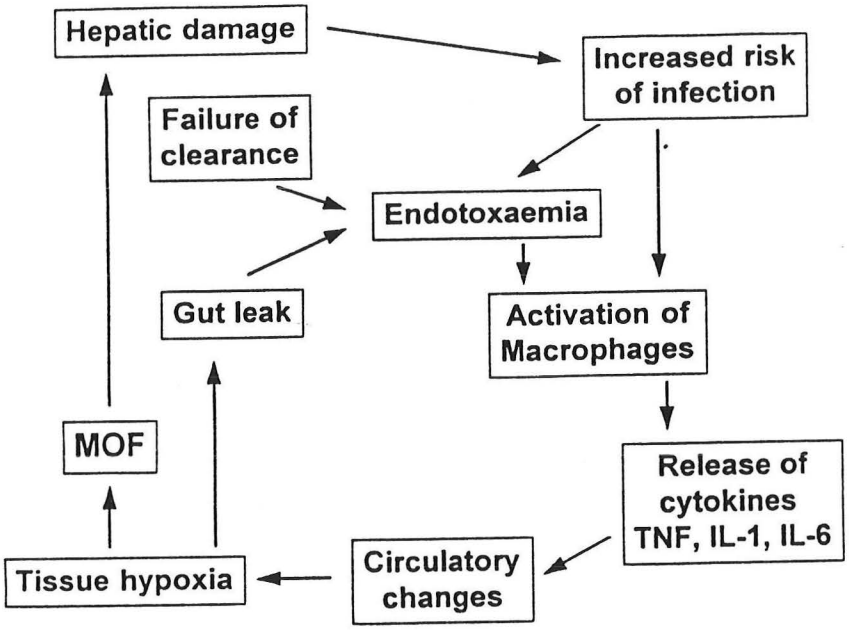
Acute Liver Failure:

Devastating Disease or Orphan Syndrome?



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Internal Medicine Grand Rounds

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June 11, 1998

About the speaker:

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An earlier and longer version of this document was submitted by the author in collaboration with his colleague, Dr. Frank V. Schiødt, as a chapter for the forthcoming edition of Schiff's Textbook of Liver Diseases.

I. INTRODUCTION

Acute liver failure (ALF) is an uncommon condition in which previously healthy people develop severe liver dysfunction, rapid onset of altered mentation, coma and frequently death. It is estimated that there are only 2,000 cases of acute liver failure in the United States annually, qualifying it as an orphan disease. Yet it continues to attract attention because of its sudden, devastating severity and its puzzling clinical picture. Many different agents occasionally cause severe hepatocyte injury. Once this is present, acute liver failure takes on common characteristics of dysfunction of kidneys, lungs, the circulatory system, and brain which are shared by all etiologies. The pathogenesis of multiple organ dysfunction in ALF is complex and poorly understood. Until recently, the disease demonstrated high mortality rates, from 80 to 97%. In the last decade, however, aggressive medical therapy, intensive monitoring, and the widespread use of orthotopic liver transplantation have improved survival considerably. Even with transplantation, overall survival is still around 50%. Current research directed toward development of an artificial liver springs from the need to treat acute liver failure. New surgical techniques such as split-liver and auxiliary liver grafts are in use at some centers, and other treatment modalities including a bio-artifical liver device, extracorporeal organ perfusion and human hepatocyte transplantation are being tested.

The topic was last covered at Grand Rounds on March 19, 1992. This lecture will provide both a framework for understanding acute liver failure, as well as a more detailed account of several new developments which are likely to impact our understanding of this puzzling condition in the next six to ten years.

II. DEFINITION

Trey and Davidson initially defined acute liver failure as the onset of altered mental status (hepatic encephalopathy) within eight weeks of initial symptoms of illness in an otherwise healthy individual (1). Since then, other definitions based on length of illness have been used to classify patients (2-4): hyperacute, < 7 days; acute, 7-28 days; and subacute, 28 days to six months, since length of illness seems to impact likelihood of survival. Patients with the shortest onset of illness tend to have the best prognosis and vice versa, those with longer evolutions to liver failure have a slower descent but are less likely to recover. Generally, coagulopathy and altered mentation go hand in hand, but occasionally prothrombin time prolongation will precede altered mentation. Other names sometimes applied to this condition include: acute yellow atrophy (an obsolete pathological term), fulminant hepatitis and fulminant hepatic necrosis, but the better umbrella term is acute liver failure, modified to indicate a specific time definition, if necessary.

III. ETIOLOGY

Many different etiologies can produce lead to ALF as shown in Table 1.

Table 1: Causes of acute liver failure

Viral

- Hepatitis A, B (± Delta), C, E
- Hemorrhagic fever viruses
- Cytomegalovirus
- Herpes simplex viruses

Drugs/toxins

Dose-related:

- Acetaminophen
- CCl_4, $CHCl_3$

Causes of acute liver failure, continued

Dose-related toxins
Amanita poisoning
Yellow phosphorus
Bacillus cereus emetic toxin
Cyanobacteria microcystins

Idiosyncratic:
Isoniazid, halothane, troglitazone, bromfenac, many other prescription medications
Reye's syndrome (salicylic acid)
Herbal medicines

Metabolic/genetic
Galactosemia
Fructose intolerance
Tyrosinemia
Neonatal iron storage disease
Wilson's disease
Alpha-1-antitrypsin deficiency

Neoplastic
Metastases: breast, melanoma, lung, lymphoma

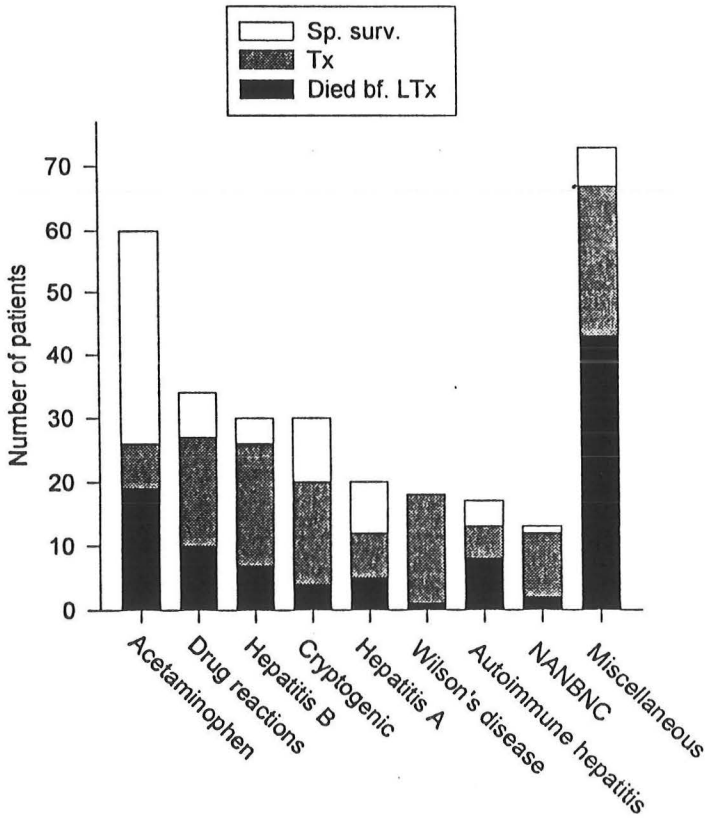
Pregnancy-related
Acute fatty liver of pregnancy
HELLP syndrome (hemolysis, elevated liver function tests,low platelets).

Vascular
Budd-Chiari syndrome
Veno-occlusive disease
Ischemic shock liver

Miscellaneous
Autoimmune hepatitis
Primary graft nonfunction in liver transplanted patients
Heat stroke

Indeterminate

Until recently, little data regarding the breakdown of etiologies in the U.S. was available. A retrospective survey from July 1994 to June 1996 of 13 U.S. hospitals provided clinical and demographic information on all patients admitted with ALF (5). In two years, 295 patients with ALF were evaluated (Figure 1).



The most common single etiology was acetaminophen toxicity, comprising 20% of the overall group. This may be an underestimate, since most of the data was compiled from transplant lists, and many acetaminophen cases would not be listed for transplantation for a variety of reasons (expected better recovery, suicidal behavior). The U.S. data is compared to that from surveys in other countries in Table 2.

Causes of Acute Liver Failure Worldwide

	HAV	HBV	Drug	Acet	Wilson	Other
UK '93-94 n=342	2	2	2	73	1	19
France '72-90 n=502	4	32	17	2	2	44
India '87-93 n=423	2	31	5	0	0	62*
DK '73-90 n=160	5	31	17	19	2	17
U.S. '94-96 n=295	7	10	12	20	6	45

* Includes NANB, (hep E), and miscellaneous

Table 2.

Worldwide, the commonest cause of ALF is viral hepatitis, especially hepatitis B, but the incidence of other causes of ALF shows great variability from country to country (5-7). For example, acetaminophen overdose is by far the leading cause of ALF in the United Kingdom and is also the commonest cause in the United States and in Denmark. However, acetaminophen overdose is practically nonexistent in other countries, including France and India.

Viral-induced ALF may be caused by specific hepatotrophic viruses and rarely by other viruses (Table 1). **Hepatitis A** virus infection leading to ALF occurs in only 0.35% of acute hepatitis A cases in adults and is even rarer in children (8). A recent upsurge in cases of hepatitis A-related ALF is thought to result from the decreased prevalence of hepatitis A antibody in the U.S. population (9). Hepatitis A has been observed to cause ALF more frequently in patients with chronic hepatitis C, prompting a recent call for more routine hepatitis A vaccination of patients with hepatitis C infection (10). Elderly hepatitis A patients have a higher incidence of ALF and an even higher mortality, compared with younger patients. Fulminant hepatitis A carries a relatively good prognosis (~50% spontaneous survival).

Fulminant **hepatitis B** is common worldwide and is observed each year at least once at Parkland (11). For the most part, HBV is transmitted parenterally, either by blood transfusions, shared needles, or sexual contact. Acute hepatitis B leads to ALF in 1% of adult patients (12). The host's immunologic response to hepatitis B infection determines its course (11). Hepatocellular damage is caused by an immunologic attack on virus-infected hepatocytes; the virus itself does not seem to cause liver injury. In this model, fulminant hepatitis B may be the consequence of a very aggressive immunologic attack, as indicated by the study of Brechot et al (13) where HBV multiplication markers (HBeAg and HBV DNA) in serum were absent after onset of hepatic encephalopathy, indicating very rapid clearance of the virus. A heightened

immunologic response occasionally culminating in ALF may be observed with reactivation of latent chronic hepatitis B after abrupt withdrawal of chemotherapy or corticosteroids (14). In addition, ALF may be caused by HBV mutations in the precore region of the genome which preclude secretion of HBeAg (HBeAg negative mutants, 15,16).

Hepatitis C virus (HCV) seems to occasionally cause ALF in Taiwan (17) and Japan (18); however, hepatitis C is only rarely associated with ALF in Europe or North America (12,19). No cases of acute hepatitis C were found among 42 patients with NANB ALF in the United Kingdom (20), whereas HCV was implicated as a co-infection or super-infection in eight of 17 patients with HBsAg-positive hepatitis in France. The reason for these discrepancies is not clear. Recently, acute HCV reactivation similar to that described for hepatitis B has been observed following chemotherapy withdrawal, suggesting an immune-mediated mechanism for liver damage in hepatitis C (21). **Hepatitis D virus (delta)** (HDV) infection is only observed as a co-infection or as super-infection in patients with concomitant hepatitis B. HDV markers were more prevalent among patients with fulminant hepatitis B than in those with acute hepatitis B virus infection, indicating an increased morbidity with delta co-infection. In hepatitis D ALF patients, simultaneous co-infection is more common than super-infection of chronic hepatitis B carrier (22). ALF due to **hepatitis E virus** infection occurs almost exclusively in developing countries, constituting 42% of cases in a large study from India (7). Acute hepatitis E infection appears to have a much higher mortality rate in pregnant women (15 to 20%) than in nonpregnant individuals (1%) (23,24), although this has recently been disputed (7). **Hepatitis G** virus (GB virus C), is not clearly hepatotrophic (25), and seems to represent an innocent bystander virus which is not associated with significant liver disease or with acute liver failure. **Other viruses** like Ebstein-Barr virus (26), herpes simplex viruses (27), and cytomegalovirus are rare causes of ALF and usually occur in immunocompromised patients and children.

Drug-induced hepatoxicity leading to ALF carries a very high mortality without transplantation. Since the liver is the main metabolic organ for most drugs, it is not surprising that a large variety of drugs have been implicated. A few agents cause hepatic damage in a predictable dose-dependent fashion, the most prominent example being acetaminophen (paracetamol). **Idiosyncratic drug reactions** cause ALF in a fashion which is not dose-dependent and occur in only a small number (1:1,000 to 1:100,000) of patients who receive a given agent (28). Once again, there are significant differences in the proportion of idiosyncratic cases between developing and developed countries (Table 2). For example, the only drug reported as causing idiosyncratic liver injury in India is isoniazid, and this appears to be true for much of the developing world (7).

Acetaminophen is a very commonly used over-the-counter drug with more than one billion pills sold each year. Although acetaminophen is generally a safe drug when taken within recommended dosage (up to 4 grams per day) by otherwise healthy individuals, it has a narrow therapeutic window. Acetaminophen is a dose-dependent hepatotoxin and ingestion by a healthy person of as little as 10 grams of acetaminophen (150 mg/kg body weight) may lead to fatal hepatocellular necrosis. An effective antidote (N-acetylcysteine) is available, and spontaneous survival for acetaminophen-induced ALF has improved in recent years to at least 50% (5, 29).

Some individuals experience increased risk of developing acetaminophen-induced hepatotoxicity, due to induction of the cytochrome P450 system and/or

depletion of glutathione stores (30). High-risk patients include chronic alcoholics (31), malnourished or fasting individuals (32), and patients treated with other drugs which induce the P450 system, e.g., isoniazid or anticonvulsants (33). Following a number of case reports of severe toxicity due to 'therapeutic misadventures' with acetaminophen associated with chronic alcohol intake, we sought to establish the prevalence and clinical features of all forms of acetaminophen toxicity in a county hospital population, by performing a retrospective study identifying all patients admitted with potiential or actual acetaminophen toxicity at Parkland (34). Cases were divided into accidental and suicidal cases, based on the patients' histories. Tables 3 and 4 compare the demographic and clinical features of the accidental and suicidal cases.

Demographics of ACM Intoxication

	Accidental N = 21	Suicidal N = 50	P
Age (years)	36 (16-54)	26 (14-83)	0.12
Gender (f/m)	11/10	37/13	0.098
Ethnic background	(as/blk/his/nat Amer/cauc)		
	0/11/4/1/5	4/9/9/0/28	0.009
ACM dose (gm)	12 (2-30)	20 (3-125)	0.009
ACM dose < 4 g	3 (14%)	2 (4%)	0.15
Acute EtOH	44%	39%	0.77
Chronic EtOH	63%	25%	0.009

Table 3.

Clinical Features of ACM Intoxication

	Accid (21)	Suic (50)	P
Presentation > 24 h	64%	14%	0.001
Peak ACM (med)	7 mg/L	126 mg/L	<0.001
Peak ALT (IU/L)	1,964	26	<0.001
Peak ALT >3,500	52%	14%	0.002
Peak PT (sec)	18.0	13.8	0.038
Rec'd NAC	76%	80%	0.76
Hep coma	33%	6%	0.006
Died	19%	2%	0.025
Cost	$5,897	$6,899	0.60

Table 4.

Ingestions with suicidal intent occurred in 50 patients (median dose 20 gm), while 21 patients had 'accidental' toxicity while attempting pain relief (median dose 12 gm; $p < 0.03$ cf. group S). Alcohol was a cofactor (either acute or chronic ingestion or both) in 22/50 (44%) of the suicidal and 13/21 (62%) accidental patient group. Two suicidal and three accidental toxicity patients had ingested $\leq$ 4 gm acetaminophen/24 hr. Accidental ingestions were more likely to be fatal (4/21 vs. 1/50; $p < 0.025$), and led to higher aminotransferase levels (52% $\geq$ 3,500 IU/L), significantly more severe illness, longer stays but similar median costs. Acetaminophen hepatotoxicity, both accidental and suicidal, accounted for 12% of all overdoses and 40% of all instances of acute liver failure at Parkland, occasionally leading to severe liver injury even at doses within the therapeutic range. We recommend that patients who are drinking or have chronic liver disease limit their daily intake to 2 gms. Two recent pediatric series of accidental acetaminophen overdoses have been reported, mainly involving infants and small children (35,36). Reasons for accidental overdosing discovered in these studies included: use of adult tablets instead of pediatric, teaspoon instead of dropper, too many doses per day, etc. Public and physician education to increase awareness seems warranted to reduce the risks associated with acetaminophen.

Other dose-dependent hepatotoxic agents include carbon tetrachloride and tetrachlorethylene, yellow phosphorus, an ingredient of fireworks in some Asian countries (37). Bacterial toxins represent a new class of hepatotoxic agents. The emetic toxin of *Bacillus cereus*, a foodborne pathogen, has been reported to have caused fatal ALF in a 17-year old boy after ingesting spoiled food (38). An epidemic of

ALF affecting more than 100 patients occurred at a dialysis center in Brazil caused by microcystins, toxins produced by cyanobacteria found in the reservoir water used in dialysate solutions (39).

Idiosyncratic drug reactions are presumed to occur in susceptible individuals via formation of neoantigens (drug-protein adducts), which may serve as targets for the host's immunologic attack, or may directly interrupt normal cellular function. Also implicated in the pathogenesis of severe drug reactions are genetically variant P450 isozymes, rapid acetylation, or extensive alcohol use (28). Two new agents to watch in 1998 which have led to significant numbers of reports in their first year after FDA approval are troglitazone (Rezulin®), and bromfenac (Duract®).

Idiosyncratic reactions are not confined to FDA approved drugs; in recent years, intake of herbal medicine such as *jin bu huan* (40), *chaparral* (41), or *germander* (42) has been associated with the development of ALF. Many patients only reluctantly admit ingestion of such drugs; therefore, a careful and specific medication history is of great importance, emphasizing non-prescription drugs.

Pregnancy may very occasionally cause ALF (Table 5).

Table 5. Severe liver disease in pregnancy.

Synd	Assoc Pre-eclampsia	Trime-ster	Symptoms	Lab values	Maternal mortality	Fetal mortality	Tr'tm'nt
AFLP	50 %	3rd	jaundice, abdominal pain, nausea, confusion	ALT < 500 IU/L, low glucose	~15 %	~15 %	Delivery
HELLP	Always	2nd or 3rd	same as above	dec Hgb, AST/ALT (200-500 IU/L), dec plts	1-3 %	~35 %	Delivery
Hepatic rupture	Usually	2nd or 3rd	severe RUQ epigastric pain hypotension	Resembles HELLP	~60 %	~60 %	Arterial emboli-zation and delivery
Viral hepatitis	No	Any	nausea, vomiting, fever,fatigue	ALT > 1000 IU/L, ≠ bilirubin	same as non-preg., exc. hep.E	same as non-preg. hep E 50%	Watchful waiting

Acute fatty liver of pregnancy (AFLP) occurs in 0.008% of all pregnancies and is associated with the presence of pre-eclampsia in half of the cases (43). Liver failure typically develops late in the third trimester. Characteristically, transaminases are moderately elevated, seldom reaching levels >500 IU/L. The HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) occurs in 0.1 to 0.6% of pregnancies and is always associated with pre-eclampsia (44). Although maternal mortality is lower than for AFLP, fetal mortality is higher for the HELLP syndrome. Prompt delivery is a

key element in the treatment of pregnancy-related ALF, since this will usually improve the condition rapidly. However, a clear distinction between pregnancy-related ALF and viral hepatitis must be made, since delivery is not necessarily indicated in the latter, and viral hepatitis is the most frequent cause of jaundice in pregnancy. Hepatic rupture is a very rare occurrence in pregnancy (45), with high maternal and fetal mortality and, similar to the other forms of liver failure in pregnancy, a close link to eclampsia. It requires immediate treatment, usually hepatic artery ligation or embolization.

Metabolic causes of ALF include inborn errors of metabolism, such as galactosemia, fructose intolerance, or tyrosinemia, and possibly neonatal hemochromatosis all typically appear in the first year of life. In addition, Wilson's disease and alpha-1-antitrypsin deficiency are clinically evident most commonly in older children and adolescents (46). Fulminant Wilson's disease, though infrequent, is of particular interest because it appears to be uniformly fatal without transplantation. This diagnosis constituted 7% of acute liver failure observed in our recently reported US multicenter series (5). The typical age at presentation is 15 to 20 years (47). Virtually all patients have underlying (unrecognized) cirrhosis, and it could be argued that Wilson's disease does not fulfill criteria for ALF since it is not an acute process, though previously unrecognized. A prominent feature of fulminant Wilson´s disease is severe hyperbilirubinemia, caused by copper-induced hemolysis. Low alkaline phosphatase levels have been noted in some patients but are not universal. Penicillamine therapy is not effective for fulminant Wilson´s disease, and liver transplantation must be performed in a timely fashion (47).

Miscellaneous and vascular causes of ALF are listed in Table 1 and include Budd-Chiari syndrome (48), veno-occlusive disease (VOD) (49), autoimmune hepatitis (50), heart failure (51), acute graft failure after liver transplantion (52), heat stroke (53). Budd-Chiari syndrome is characterized by occlusion of the hepatic veins due to sludging or hypercoagulability and presents with acute right upper quadrant pain and ascites (48). Portocaval shunts or transplantation may be needed, particularly if the course of disease is rapid. VOD occurs almost exclusively in patients following bone marrow transplantion, appearing rapidly in the post-transplant period, the combined result of pretransplant chemotherapy and radiation. VOD is a complication in 54% of all bone marrow-transplanted patients, and 39% of VOD patients die (49). The patients typically develop hepatomegaly, ascites, and abnormal liver function tests, in the immediate post-transplant period, resembling Budd-Chiari syndrome. Reye´s syndrome is associated with the use of salicylates (54) but is extremely rare in adults. In this condition, ALF is thought to occur as a result of inhibition of long chain fatty acid oxidation.

Malignancy may sometimes cause ALF, usually by massive hepatic infiltration from metastases (55) or lymphoma (56). It is important to establish the diagnosis rapidly, since liver transplantation is contraindicated in these cases. Fatal outcome is observed in almost all patients.

Indeterminate is the term reserved for patients with ALF for whom a specific cause cannot be found. This group comprised 17% of the patients in our U.S. retrospective study (Figure 1). Possible causes would include environmental factors, unrecognized drugs, bacterial toxins or an elusive hepatotrophic ALF virus(es). The multi-center ALF study currently in progress will allow collection of sera and extensive epidemiological information from a large number of indeterminate cases to discover new etiologic agents.

IV. CLINICAL FEATURES

Cerebral symptoms and signs

Hepatic encephalopathy, the hallmark feature of ALF, occurs in the absence of portal hypertension. In patients with acute liver disease it is important to rule out non-hepatic causes of coma; e.g., barbiturate or benzodiazepine (co)intoxication, or meningitis. The exact cause of the encephalopathy in ALF remains unclear. Unlike cirrhotic patients, ALF patients will often become agitated prior to onset of coma.

Hepatic encephalopathy grades I and II represent mild decreases of level of consciousness (Table 6), whereas grades III and IV are more severe, carrying a much higher mortality. It is important to note that progression from mild alterations in mentation to deep coma may occur extremely rapidly.

Table 6: Hepatic encephalopathy, classification of coma grades.

COMA GRADE	CHARACTERISTICS
I	Slighty altered mental status, inverse sleep rhythm, personality changes.
II	Confusion, drowsiness, asterixis.
III	Stupor, incoherence, sometimes agitation.
IV	Comatose, gradually more unresponsive. Decerebrate posturing, seizures, ultimately areflexia.

Cerebral edema, first described in detail by Drs. Ware and Combes at Southwestern in 1971 (57), is a unique and common complication of ALF, occurring in up to 80% of patients with hepatic coma grade IV. Cerebral edema may be caused by cytotoxic mechanisms (impaired cellular osmoregulation leading to cell swelling), vasogenic mechanisms (increased permeability of the blood brain barrier), or both (58). Serum ammonia is elevated in most patients with ALF; however, ammonia levels do not correlate with encephalopathy grade. The diagnosis of cerebral edema may be difficult to establish, since clinical signs of cerebral edema (decerebrate posturing, systemic hypertension, or pupillary abnormalities) are typically observed only in advanced disease (59). Computerized tomography scans of the brain are not particularly helpful in this setting because of low sensitivity (60), although one study has suggested possible diagnostic benefit (61). A high level of suspicion is necessary when establishing the diagnosis of cerebral edema. Cerebral edema often leads to intracranial hypertension in the fixed confines of the cranium. Cerebral herniation of the uncus across the falx cerebrum developed in 25% (4/16) in the original descriptive study (57).

Cerebral blood flow (CBF) is reduced in most patients with ALF, but the reduction in CBF does not correlate with the level of hepatic encephalopathy. CBF is controlled by the tone in pial arterioles, regulated via baroreceptors and PaO_2 and $PaCO_2$. Loss of cerebral autoregulation has been demonstrated both in ALF animal models and in some patients with ALF (62). These pathophysiologic changes may leave the brain markedly susceptible to cardiovascular fluctuations. Close monitoring

and maintenance of mean arterial pressure (MAP) and CPP within normal physiologic ranges is crucial, both in the intensive care unit and during transplantation surgery. Despite full recovery otherwise, instances of long-term neurological sequelae are occasionally observed due to periods of inadequate cerebral perfusion pre- or intra-operatively.

Other clinical features

The liver is central to the metabolism of amino acids, proteins, lipids, and carbohydrates, detoxification of endogenous and exogenous compounds, and bile excretion among others. **Hypoglycemia** is a frequent problem in ALF, due to impaired gluconeogenesis and low hepatic glycogen production, and may require large quantities of glucose intravenously as replacement. A variety of **acid-base disturbances** occur in ALF: respiratory alkalosis is common, due to a centrally-mediated hyperventilation, while metabolic acidosis may occur early in acetaminophen-induced ALF (63) for unclear reasons, whereas acidosis occurring later in the course of illness is usually caused by hyperlactatemia (64).

The presence of a severe **coagulopathy** is the second hallmark of ALF, and often antecedes evolution to hepatic coma. Loss of clotting factors II, V, VII and IX due to decreased hepatic synthesis results in marked prolongation of both the prothrombin time and the activated partial thromboplastin time. Daily measurement of the prothrombin time is a reasonable guide to recovery, since improvement (in the absence of large volume plasma transfusions) rapidly reflects improved synthetic function. Disseminated intravascular coagulation (DIC) has been observed in ALF; however, consumption of coagulation factors is difficult to separate from the severe synthetic dysfunction observed. Of note, platelet counts are <100,000/μL in the majority of patients, and there is clear evidence of activation of platelets and fibrinolysis (65).

Hyperdynamic syndrome. One of the key features of ALF is the presence of a hyperdynamic circulatory syndrome, characterized by increased cardiac output and low systemic vascular resistance resembling septic shock (66,67). The pathophysiology is not yet understood, but ALF seems to induce the release of vasodilating substances possibly nitric oxide (68). Cardiac output is often two times higher in ALF patients than in normal individuals, and systemic vascular resistance is decreased in ALF, to ~65% of normal values. The clinical consequences of the hyperkinetic circulation syndrome is a strong tendency to arterial hypotension and decreased susceptibility to inotropic drug support. Arterial hypotension, defined as systolic blood pressure < 85 mm Hg, is present in 20% of patients with ALF and may be difficult to treat in some of them. **Tissue hypoxia** as evidenced by hyperlactatemia and metabolic acidosis, occurs typically in patients with grade III or IV ALF (64,68).

ALF may contribute to increased susceptibility to **infection** in many ways, including decreased opsonin function and complement deficiency, leukocyte dysfunction, impaired Kupffer cell function, bacterial gut translocation, release of immunosuppressive cytokines or endotoxin, TNF, and iatrogenic causes, such as placement of indwelling catheters or nasogastric tubes (12). Infections may worsen the course of ALF greatly and are a very common cause of death. Bacterial infection occurs in 80% of the patients (69); the sources of infection were blood (bacteremia), respiratory tract, urinary tract, skin wounds or intravascular catheters. *Staph. aureus* was the most common organism found, followed by *Staph. epidermidis*, and streptococcal species. In a retrospective Danish study (70), 44% of 72 patients with ALF were infected, with gram positive bacteria accounting for ca. 80% of the organisms

found, results similar to the 61% gram positives observed in bacteremic ALF patients from the United Kingdom. Usual clinical features of infection (fever, leukocytosis) were absent in ca. 30% of infected patients. Infection may manifest in some patients only as worsened hepatic encephalopathy. Gram negative bacteria, like *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella* species, accounted for the remaining bacteria found (69). Fungal infections occur in a third of the patients, often together with bacterial infections, typically appearing late in the course of the disease, after antibiotic treatment. *Candida albicans* is the most frequent fungal organism found, and the mortality is high. Fungal infection is a bad prognostic sign, and either precludes transplantation or complicates post-operative recovery.

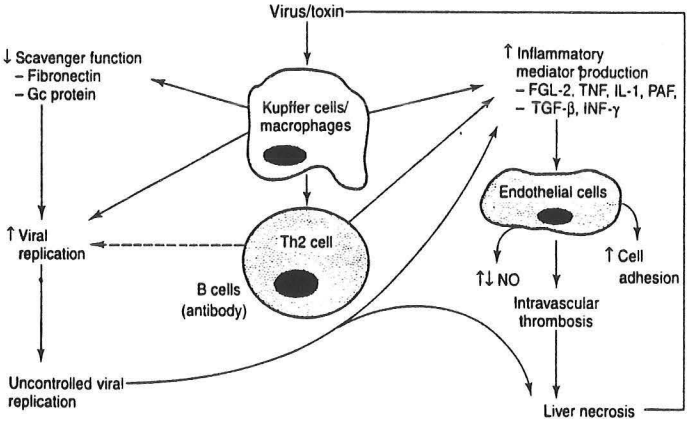
Renal failure occurs in more than half of the patients with ALF (67) and is also a bad prognostic sign. The cause may be either prerenal azotemia, acute tubular necrosis, toxic renal effect from a toxic hepatic agent (acetaminophen, *Amanita*-poisoning), hepatorenal syndrome, or combinations of these causes (66). Renal failure in ALF is defined as a urinary output less than 300 mL/24 hours and a serum creatinine >300 mmol/L (3.4 mg/dL). Blood urea nitrogen levels do not reflect the severity of renal dysfunction, because of impaired hepatic urea production. Electrolyte derangement is common and close monitoring of plasma sodium, potassium, magnesium and calcium is important. Hypophosphatemia is most frequently observed in acetaminophen overdose but is present in all forms of ALF (71). Fluid balance may require dialysis: continuous arteriovenous dialysis is preferable to hemodialysis since there is less effect on vascular instability observed with the former.

Pulmonary edema may complicate the course of ALF in ~40% of the patients, especially when cerebral edema is present (72). Careful management of fluid intake and use of diuretic agents has been recommended. **Adult respiratory distress syndrome (ARDS)** is less frequently seen (73). The mortality in ALF increases when ARDS is present (74), in part because ARDS may contraindicate transplantation.

V. PATHOGENESIS

In recent years, an improved understanding of the mechanisms leading to hepatic failure has emerged. Although the initial stimulus for liver failure may differ for each etiology, some similarities exist, with regard to involvement of the cytokine network (75). Activation of Kupffer cells seems to play a pivotal role in this setting (Figure 2), as an important site for release of cytokines, eicosanoids, and for the uptake of scavengers (76).

Figure 2. Vicious cycle of acute liver failure.



The most important of the cytokines are believed to be interleukin-1 (IL-1), IL-6, and tumor necrosis factor-alpha (TNF-α). These pro-inflammatory monokines mediate the upregulation of other related mechanisms, including adhesion molecules (e.g., Mac-1) (77) and nitric oxide (78). Although endotoxemia is frequent, it is not universal. Thus, an understanding of the MODS syndrome observed must still take into account different etiologies. Since several inflammatory cascades come into play, it is currently unclear whether manipulation of one system, i.e., prostaglandins, can favorably affect the evolution of the entire MODS picture (79).

Actin release into the circulation characterizes all forms of MODS, and release of actin may prove toxic to the circulatory environment (80,81). Decreased levels of the actin-scavengers gelsolin and Gc-globulin have been demonstrated in a variety of conditions associated with actin release into the circulation, and the lack of these scavenger proteins may predispose patients to intravascular obstruction with actin filaments released from dying hepatocytes (82-86). The most marked decreases in gelsolin and Gc-globulin levels are observed in acute liver failure, although low levels have been observed also in septic shock, myocardial infarction and crush injuries (87,88). Measurement of Gc-globulin levels has been suggested as a useful prognostic indicator of survival in ALF (Figure 3) (89).

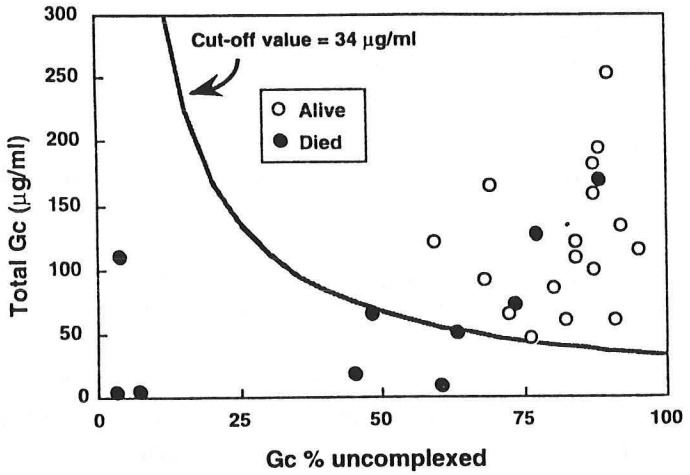


Figure 3. Gc results for 27 patients with acute liver failure. Data points represent the calculated product of total and percentage of uncomplexed protein. The curved line represents all product values equal to 34 µg/mL, the cutoff value. All of those above the line would be predicted to survive. The prognosis was correctly predicted for all patients except three (upper right), all of whom died late of sepsis, not ALF.

Recent evidence points to a role for actin itself in creating the microcirculatory disturbances. Sera from patients with ARDS were recently observed to be toxic to pulmonary endothelial cells in culture. These sera contained filamentous actin. The apparent harmful effect of actin could be abrogated by addition of recombinant gelsolin (which breaks down the actin filaments), to the culture medium (90). Sera from ALF patients also can be shown to contain actin filaments. Microvascular disturbances in the peripheral circulation leading to arteriovenous shunting appear to cause tissue hypoxia and the resultant lactic acidosis.

VI. PATHOLOGY

Liver tissue for histopathologic examination is infrequently obtained in ALF patients. The severe coagulopathy contraindicates liver biopsy, even if performed during infusion of fresh frozen plasma. Transjugular liver biopsies may be helpful in excluding metastatic tumors, but biopsies have little prognostic value. Liver tissue may be obtained from explanted liver, by autopsy, or from patients in the restitution phase (91). Although the findings depend somewhat on the underlying etiology, widespread hepatocyte necrosis is a prominent feature in most cases. Acetaminophen typically causes a centrilobular necrosis, although panlobular necrosis is seen in the most severe intoxications (92). In survivors of acetaminophen-induced ALF, liver biopsies at five months follow-up showed only minimal pathological changes, including centrilobular parenchymal pallor, irregular multilayered cell plates, and pigment-swollen Kupffer cells (92). Most viral infections or drug-induced injury cause a widespread pan-lobular injury. Occasionally, nodular regeneration is observed, typically in subacute cases.

Rarely, necrosis may be very sparse or even absent. Instead, microvesicular fatty deposition within hepatocytes is the prominent feature, as seen in acute fatty liver of pregnancy (43), fialuridine, valproic acid, microcystin toxicity and Reye's syndrome. In these cases, mitochondrial damage leads to impaired aerobic glycolysis and small vesicle fat deposition within cells, a picture distinctly different from fatty liver as observed in the alcoholic or diabetic obese patient.

Venocclusive disease demonstrates a distinct picture of central vein thrombosis and obliteration, sinusoidal dilatation and congestion, centrilobular hemorrhage and hepatocellular necrosis, which may be valuable diagnostically and lead to specific therapy for this entity, such as anticoagulation.

VII. INITIAL TRIAGE, MONITORING AND TREATMENT

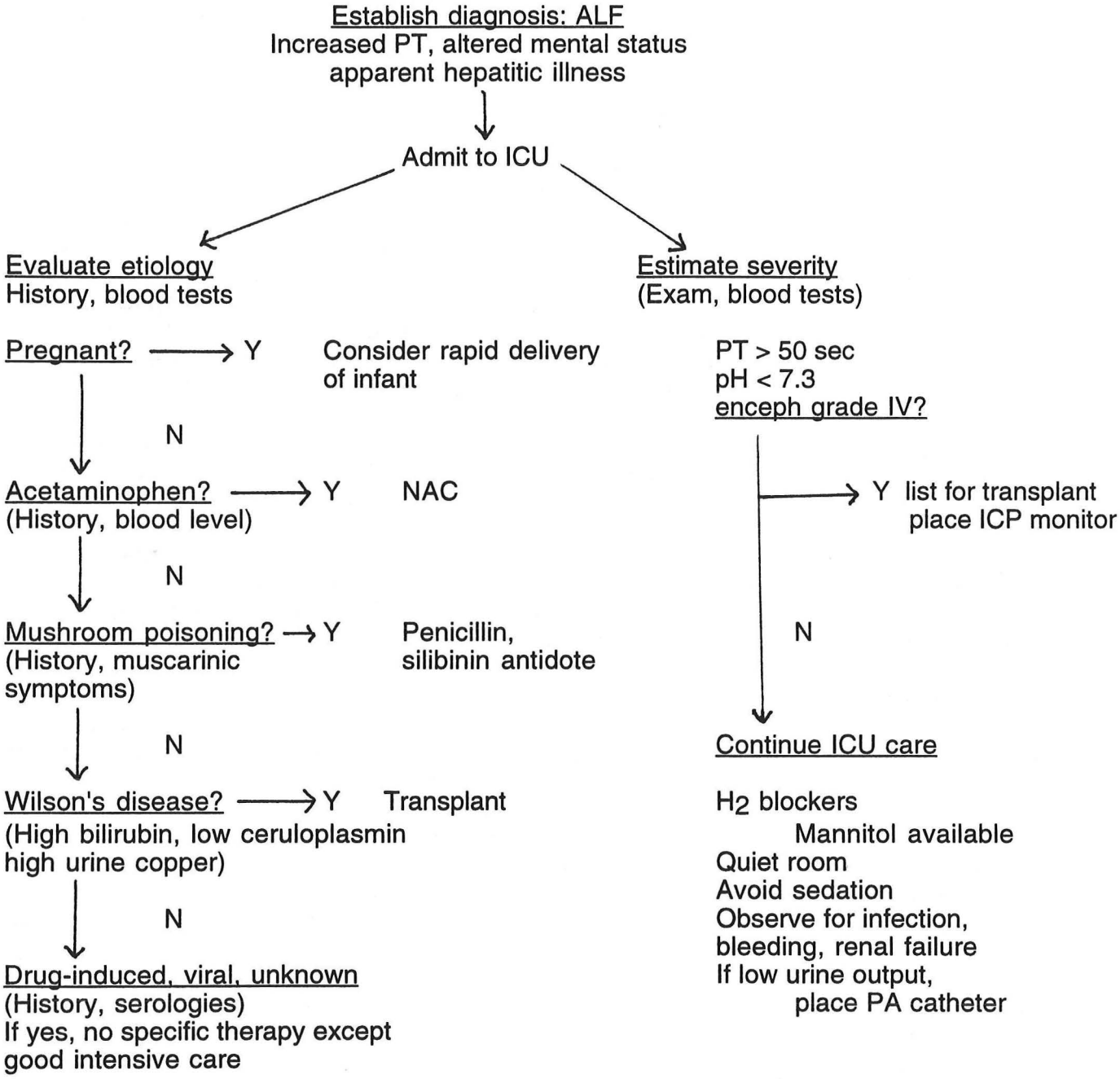
As soon as the diagnosis of ALF is established (altered mental status and coagulopathy documented), it is important to establish the cause. Acetaminophen overdose and *Amanita* poisoning demand immediate and specific antidotes. Rapid delivery of the infant is recommended for pregnancy-related causes such as acute fatty liver of pregnancy. Failing a treatment specific for the condition, patients are assessed for transfer to a liver transplantation unit or listing for transplantation (Figure 4). On the other hand, it is also important to establish the diagnosis of malignancy-induced ALF, since liver transplantation is obviously contraindicated in this condition.

Patients with ALF should ideally be transferred to a transplantation center with the experience and necessary equipment to monitor patients optimally (93). Treatment of ALF patients is a multidisciplinary task, including hepatologists, anesthesiologists, nephrologists, transplant surgeons, immunologists, and others. All patients need to be closely followed for changes in level of consciousness, since deterioration may develop very rapidly and may require immediate treatment, such as intubation and onset of mechanical ventilation. Maintenance of blood glucose, electrolytes, and hemoglobin within normal levels is crucial.

Of utmost importance is the treatment of cerebral complications in ALF. Direct intracranial pressure (ICP) monitoring is frequently recommended in patients with suspected cerebral edema or intracranial hypertension, but is not uniformly performed. Placement of extradural ICP catheters is considered safer than subdural catheters (94,95), with fewer complications (hemorrhage, infection). On the other hand, subdural

ICP monitors are more accurate than epidural (96), and some authors (94) have pointed out that, after the initial "learning process", the complication rate for subdural catheter placement decreases considerably.

Figure 4. Algorithm for triage, diagnosis and treatment of the patient with acute liver failure. It is first necessary to perform the three 'E's"--establish the diagnosis, evaluate the etiology, and estimate the severity of the illness.



The patient should be placed with the head 10 to 20 degrees elevated.

Maneuvers that may increase ICP should be avoided, including tracheal suction, other forms of stimulation, or rapid position changes. Use of sedation is controversial but is usually avoided so that mental status may be assessed. An agitated mental state associated with grade III coma may sometimes require the use of sedatives, but these should be used sparingly if at all.

Mannitol is the first-line drug when treating cerebral edema and intracranial hypertension (83, 98), given as a rapid infusion of 100 to 200 mL of a 20% mannitol solution (0.3 to 0.4 g/kg body weight). Mannitol increases the plasma osmolarity and thus decreases the intracellular water content in the brain. Caution must be advised in the case of renal failure; mannitol may accumulate in astrocytes and cause increased swelling (rebound phenomenon).

Renal failure should be treated with hemodialysis only in the case of gross fluid overload or severe uncontrollable electrolyte derangement (11). Conventional hemodialysis or hemofiltration (over 4 to 5 hours) may have serious effects on blood pressure and tissue perfusion, due to the rapid fluid and electrolyte changes (99). Significant ICP increases and peaks and concomitant falls in mean arterial pressure due to dialysis may cause a critical reduction in cerebral perfusion pressure, disposing to cerebral ischemia. Continuous arteriovenous hemofiltration or continuous arteriovenous hemofiltration with dialysis, on the other hand, does not appear to affect ICP or MAP adversely and should be the preferred mode of renal substitution in ALF (100). It is important to avoid nephrotoxic drugs, such as aminoglycosides; dopamine infusion may be instituted in an attempt to improve renal blood flow but adequate studies of its use have not been performed.

Hypoglycemia should be avoided by close monitoring of blood glucose levels (often 6 to 8 times per day), and use of hypertonic (20%) glucose if levels below 60 mg/dL are observed. Fifty percent glucose infusion may be necessary, if renal failure and fluid overload is a problem.

The question of nutrition in ALF is difficult and sparsely studied. Even though patients with ALF are hypercatabolic, protein restriction is recommended (101).

Unfortunately, specific antidote treatment is available only for a few etiologies. N-acetylcysteine (NAC), is highly effective for acetaminophen overdose when given within 10 to 24 hours after a single dose ingestion. NAC is considered safe even in established hepatic disease; furthermore, both retrospective and prospective studies of late NAC infusion have demonstrated improved hemodynamics and survival in patients with established hepatic encephalopathy (102,103). The use of N-acetylcysteine for non-acetaminophen ALF is disputed; however, a controlled trial in this setting seems justified, and will begin later this year. For *Amanita* poisoning, penicillin and silibinin infusion seem effective, penicillin via its antagonistic effect on the mushroom toxin, amatoxin, and silibinin by blocking the hepatocellular uptake of amatoxin (104).

Therapy for the overall condition acute liver failure

A large number of treatments have proved ineffective in ALF. Corticosteroids were long thought to be helpful due to their immunosuppressive effect; however, three studies failed to show any beneficial effect on survival, and steroids are no longer used. Other ineffective treatment options in ALF include exchange transfusion, hyperimmune globulin infusion for fulminant hepatitis B, insulin and glucagon infusion, asanguinous-hypothermic total body perfusion, prostaglandin E_2 infusion, and charcoal hemoperfusion.

High volume plasmapheresis (68,105) has been attempted in a few centers. It

involves the concomitant filtration of the patient's plasma and replacement with donor plasma, up to 15 to 20% of body weight. Improved hemodynamics, intracranial pressure, and hepatic coma grade have been observed. A controlled trial has never been performed, but it is possible that high volume plasmapheresis might serve as a bridge to transplantation.

Use of hepatocytes as liver support

Another approach in the treatment of ALF is the use of hepatocytes in various forms as liver replacement therapy. Two extracorporeal liver assist devices have been studied, both using hepatocytes incorporated in hollow fiber cartridges. Sussman et al (106) used a human hepatoblastoma cell line (C3A) with whole blood passing through a cartridge with heparin as an anticoagulant. Improvement in prothrombin time, ALT levels, and galactose elimination capacity has been reported in a pilot study (107), but no effect on survival has been observed. Rozga et al (108) have used plasmapheresis in combination with a charcoal column and porcine hepatocytes in a cartridge device. Although initial results were promising, controlled studies demonstrating efficacy have yet to be performed. A large multi-center trial of this bio-artificial liver (BAL) is about to begin (108). Since the device includes only a small quantity of cells (ca. 50 gm), it seems unlikely to provide adequate support for the failing liver.

Use of a whole liver in an extracorporeal circuit has been attempted, employing human organs unsuitable for grafting (109). If a xenogeneic organ such as that of a pig is employed, the organ becomes injured within one half hour by hyperacute rejection, with damage to endothelial cells, leading to increased resistance to blood flow, thrombosis and non-function. Hyperacute rejection can be abrogated by the use of a transgenic animal in which human CD44, decay accelerating factor, a part of the complement cascade, is inserted into the pig genome. This transgenic model has been developed and, when used in an extracorporeal circuit, does not demonstrate hyperacute rejection at least over periods of several hours. An initial clinical study using transgenic pigs as a bridge to transplantation is underway, and forms the preliminary step toward consideration of xenotransplantation (110). Intuitively, a whole organ perfusion would offer a substantial amount of replacement cells, in a less artifical environment than that of the hollow fiber cartridge, but is extremely costly given the need to raise and have constantly available transgenic animals. It should be noted that both the BAL and the transgenic pig clinical trials have been suspended by the FDA due to concerns regarding a porcine retrovirus. Treated patients have not demonstrated exposure to such a virus on extensive testing; it seems likely that the suspension will soon be reversed.

Interest in hepatocyte transplantation has increased recently with some encouraging preliminary reports of uncontrolled trials using infusion of human hepatocytes in the splenic artery or portal vein. This might have applicability for chronic hepatic insufficiency as well (111,112). No controlled trials have been attempted.

Total hepatectomy has been advocated for the treatment of the vascular instability and MODS aspects of ALF. It is postulated that much of the systemic effects observed are generated by the necrotic liver. Indeed, blood pressure can be observed to improve in some patients during the anhepatic period prior to liver graft insertion. This remains controversial and, lacking an available donor, there seems little rationale for removing the native liver with no specific replacement plan (113-115).

VIII. LIVER TRANSPLANTATION

Liver transplantation for ALF has never been subjected to a controlled trial, but is generally accepted as an important treatment option. In our recent retrospective study of 13 hospitals around the U.S., 12 of which were transplant centers, 41% of ALF patients received a liver graft (5). A major dilemma in the treatment of patients with ALF is the decision to list for transplant and the timing of the transplantation. As recently stated, the time between "too early" and "too late" may be very short (101). Survival after transplantation is somewhat diminished (~65% at one year) in comparison to elective transplantation for chronic liver disease (~85-95% at one year), owing to the persistence of fungal infections, cerebral edema and other "pre-op" complications unique to ALF patients. The correct timing of liver transplantation is therefore crucial. Optimally, liver transplantation should be performed only in those patients who would not survive spontaneously. The figure of 20% survival has been used as a "benchmark" for prognostic criteria. Recovery is typically rapid and complete with transplantation but necessitates life-long immunosuppression. It has been estimated that only 10-20% of patients with ALF receive a transplant (12).

Long term survival for children transplanted for ALF is comparable with that of adults (46). Liver transplantation will correct the underlying defect in metabolic diseases such as Wilson's disease, alpha-1-antitrypsin-deficiency, and others (47). For acetaminophen-induced ALF, liver transplantation seems to have a more limited role (5, 116); transplantation rates are low, at 10-15%, partly because of the good prognosis for this etiology, as well as the rapid course of the disease which leaves little time for transplantation.

Auxiliary liver transplantation is now a treatment option for ALF (117). The aim is to provide a temporary support until the native liver recovers. The native liver is left in situ and regenerates in 68% of > 3 mo survivors and immunosuppression can be withdrawn in most of these patients, leaving the donor liver to be removed surgically or to atrophy (117). Split liver grafts are also being performed, in which the left or right lobe is removed, and a replacement inserted, preserving part of the native liver so that reconstitution may take place. Many technical problems have limited application of this technique. In pediatric patients < 2 years of age, many approaches have been attempted to obtain the proper size liver, including reduced-size transplantation, split-liver transplantation (two recipients receive grafts from a single donor), and living related donor (118). Split-liver transplantation is associated with the highest mortality and complication rate. **Contraindications** for liver transplantation include irreversible brain damage, uncontrolled bacteremia, HIV-infection, malignancy or the presence of failure in any other organ which would prevent a satisfactory outcome. **Complications** of transplantation include residual brain damage from previous cerebral edema. Aplastic anemia has been reported as an uncommon complication following liver transplantation, occurring in children with previous NANB ALF (119).

IX. PROGNOSIS AND OUTCOME

Until a decade ago, ALF was associated with a very high mortality; 30/31 (97%) in a series from Dallas (120), 94% in a Mayo Clinic series (121), and mortality rates < 80% were rarely reported. In the last decade, however, the mortality rate has improved considerably at least in the most experienced liver centers. This improvement is probably due to two factors: 1) the advent of urgent liver transplantation in the mid 1980's, and 2) more aggressive medical therapy (inotropic support, antibiotic treatment)

and monitoring, including invasive procedures such as epidural/subdural ICP monitoring, Swan-Ganz catheters.

The survival rate depends to a large extent on the etiology (Figure 1). Acetaminophen intoxication and fulminant hepatitis A are associated with survival rates around 50%. Idiosyncratic drug reactions, and indeterminate cases, on the other hand, are associated with much lower survival rates, under 20% (63). For Wilson's disease, survival without transplantation is rare because of the accompanying cirrhosis, as confirmed by a recent American retrospective series (5), in which not one out of 18 patients survived without transplantation.

Time from symptoms/jaundice to onset of hepatic encephalopathy is important as indicated by the improved survival observed in those cases listed as hyperacute (<7 days). The hepatic encephalopathy grade on admission also influences the mortality rate; survival is much higher for patients with maximum hepatic coma grade I or II than for grade III or IV (1,5). Coma grade on admission seems to have a greater influence on outcome for acetaminophen patients; patients with deep coma (hepatic coma grade III or IV) on admission had lower survival rate than patients who presented with grade 0 to II in our retrospective study, presumably because of less likelihood of obtaining a transplant in a timely fashion. Late-onset hepatic failure, or subacute hepatic failure, represents an exception to this rule (3).

The presence and number of complications experienced influence the mortality rate (122). Age also may influence outcome, although this is more controversial; age <10 years and >40 years have been considered to be poor prognostic indicators (7,73). However, in our recent American ALF series age did not differ between survivors and nonsurvivors, and many survivors were older than 40 years.

The search for prognostic indicators

The ideal marker of outcome should be available very early in the course, easy to measure or estimate, and 100% accurate. Such a marker is not presently available now and will probably not be available in the near future. The Kings' College Hospital criteria for liver transplantation are used in most liver centers (63). These criteria were developed after review of 588 patients, creation of a logistic regression model, and subsequent testing in another 175 patients from the same unit. Criteria differ for acetaminophen-induced ALF versus nonacetaminophen-induced ALF, reflecting the slightly different clinical syndromes and different prognoses for these two conditions but utilize readily available clinical and laboratory data (6). Other prognostic markers have been suggested (123-131). As reviewed earlier, Gc-globulin, an actin-scavenger, is greatly reduced in ALF (82), and both free (uncomplexed) Gc-globulin levels (89) and total Gc-globulin levels (124) have been used as prognostic indicators. The presence of automated assays available in any hospital laboratory should make these assays useful, if further prospective testing verifies the value of measuring Gc levels early in the hospital stay. Serial prothrombin time measurements in acetaminophen-induced ALF showed that a continuous rise of prothrombin values from day 3 to day 4 or a high absolute value was an accurate indicator of death (125). The degree of liver necrosis observed by transjugular biopsy is not useful in predicting outcome (126). The arterial ketone body ratio which reflects the redox potental of hepatic mitochondria has been suggested to be of value, a ratio <0.60 predicting poor outcome accurately in one study (127). However, only 19 patients were included, and the usefulness of this ratio in a larger group of patients have not yet been confirmed. A large Indian series recently published used a model with high predictive accuracy; however, whether this has wider

applicability outside of the Indian subcontinent remains to be determined (7).

Except for the King's College criteria, none of the above mentioned prognostic markers/models have been tested in independent learning and assessment sets. Each model will probably best fit for the patients used to create the model. A large multicenter prospective study is needed to test all available models, but these will be compromised by the use of transplantation which alters spontaneous outcome statistics.

XII. FUTURE RESEARCH

Larger multicenter trials are needed to collect data, determine more accurate prognostic models and test new therapies. We have recently formed a multi-center group to study acute liver failure, comprised of 14 sites around the United States. The study group began January 1, 1998 to collect prospective data, serum samples and tissue for the use of investigators interested in further characterizing the etiologies, clinical features and treatment for this most puzzling orphan disease. The group will begin a pilot study of the use of N-acetylcysteine for non-acetaminophen induced ALF, based on earlier work from Kings College Hospital suggesting that use of NAC was beneficial in reversing the hemodynamic alterations in this condition (103). It should be recognized that all treatment trials currently contemplated will suffer from the bias induced by liver transplantation, since transplantation alters the "natural course" of the disease, and actual outcome does not reflect untreated outcome. No currently available liver assist device can be advocated based on current information. All other treatments referred to above are clearly experimental. Given the great shortage of donor organs in the U.S. currently, a method of hepatic support which would allow regeneration of the native liver should hold a high priority, since it would prove highly effective in reducing the need for transplantation for this critically ill group of patients.

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