Management of acute liver failure

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An ideal therapy for acute liver failure (ALF) would be the successful promotion of liver regeneration, with spontaneous recovery from the disease. However, in spite of advances in our understanding of the process of regeneration and potential candidate compounds for clinical testing, we currently lack the ability to influence this process in the patient with ALF. Thus, therapeutic efforts are directed at three levels:

- Administering specific therapies for individual causes of ALF
- Supporting the patient by treating the multiple complications of the syndrome
- Evaluating artificial and bio-artificial support systems within the context of randomized controlled clinical trials.

Elements of this article reflect the efforts of the Acute Liver Failure group and more specifically of its Clinical Protocol committee in defining a common management protocol for the disease (Stravitz T, Kramer AH, Davern T, et al; unpublished). Due to the complexity and length of the topic, this article will not touch upon the indications for emergency liver transplantation.

**Specific therapies in ALF**

*N-acetylcysteine* (NAC) has received the greatest attention, in view of its role in the management of patients with acetaminophen-induced ALF. While its mechanisms of action as an antidote to acetaminophen poisoning are well characterized, the pathways by which it may be effective when administered late in the course of the disease are less clear. In humans, an improvement in regional hemodynamics and oxygen transport with subsequent lessening of the incidence of multiorgan failure was postulated. More recently, a quantitative MR spectroscopic technique in rodent liver noted an improved mitochondrial tricarboxylic acid cycle metabolism, independent of the capacity to restore glutathione stores. Anti-oxidant effects may be important in the reported improvement of renal function in cirrhosis. In the absence of conclusive evidence of its efficacy in non-acetaminophen-induced ALF, the ALF group continues to carry out a double-blind randomized controlled trial of NAC. The drug (or placebo) is administered for 3 days at a dose of 150 mg/day. The trial has enrolled 75% of its targeted goal of 200 subjects; the results are awaited with interest.

*Acyclovir* via the intravenous route should be started if herpetic hepatitis is suspected. The clinical history is important, including the presence of high fever, compatible exposure, skin lesions and an immuno-suppressed state (pregnancy, post-chemotherapy). Acyclovir may induce nephrotoxicity when given at high dose.

*Delivery of the fetus* may stop the liver injury in acute fatty liver of pregnancy/HELLP syndrome, a therapeutic measure increasingly based on the pathophysiology of the condition.

*Oral charcoal and i.v. penicillin* are used for intoxication with *Amanita phalloides*, an approach not evaluated in clinical trials.

*Lamivudine* was reported to improve the outcome of fulminant hepatitis B in a multicenter evaluation. However, a historical control group was utilized and the temporal relation between therapy and outcome is uncertain.

*Corticosteroids* have not shown clinical efficacy in this disease. In patients with fulminant autoimmune hepatitis, the efficacy of corticosteroids is questionable.

**The patient in the Intensive Care Unit**

The patient with acute liver injury who develops encephalopathy is admitted to an ICU. Patients with acute injury but who do not develop encephalopathy have a good prognosis; in a series of 68 patients, only 8 individuals ultimately deteriorated, a course that could be predicted by measuring the activity of factors V and VII.

*Nutritional support* is frequently overlooked in patients with ALF, a hypercatabolic state. Glucose administration is the norm in order to avoid hypoglycemia, but hyperglycemia can easily develop, as ALF is an insulin-resistant state. Hyperglycemia worsens the outcome of patients in the ICU and should be avoided.

*Infection* is a frequent complication of patients with ALF and should be sought and treated. The most common organisms are Gram-positive (staphy-
Blei

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Fig 1: Temporal relationship between de­
tection of first infection and progression to
stage III-IV HE in both acetaminophen and
non-acetaminophen groups. Symbols above
continuous line represent patients in whom
microbiologically confirmed infection was
detected before or within 24 hours of pro­
gression to stage III-IV HE (filled symbols),
and symbols below continuous line repre­
sent patients with microbiologically con­
firmed infection detected after 24 hours of
progression to stage III-IV HE.


dications may also occur. The full role of this therapy
awaits the results of randomized controlled trials.

Gastrointestinal bleeding can be prevented by
the use of H2-receptor antagonists; by inference,
proton pump inhibitors may also be used.

Renal failure is frequent in patients with ALF
and may be the result of severe arterial vasodilata­
tion as a result of infection and/or liver failure itself.
The clinical picture may evolve into acute tubular
necrosis. Assessment of intravascular volume may
be performed using central venous catheters, but
may require more specialized approaches in the ICU.

The safety of Swan-Ganz catheterization is increas­
ingly questioned and is seldom used nowadays in
the management of ALF.

At this time, vasoconstrictive therapy for renal
failure cannot be recommended to counteract the
arterial vasodilation. In the experimental animal,
vasopressin, acting through V2 receptors, has been
shown to increase brain edema by inducing cerebral
hyperemia. Terlipressin, increasingly utilized for pa­
tients with cirrhosis and the hepatorenal syndrome,
was found to increase intracranial pressure, even in
bleeding was observed, such hemorrhage has been
observed in spite of its use. Thrombotic compli­
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lococcus, streptococcus) and Gram-negative bacte­
teria. Fungal infections occur in 30% of patients, pre­
dominantly Candida. Vigorous surveillance, includ­
ing daily blood/urine cultures and chest X-ray, may
improve outcomes through early detection. Special

care of i.v. lines is recommended, including the need

Antibiotics can be administered via 3 approaches:

Prophylactic. Combination parenteral and enteral
antimicrobial prophylactic regimens have not been
shown to improve outcome or survival. They are
not recommended for routine use.

Therapeutic. Responding to positive antimicro­
bial isolates or an abnormal chest X-ray.

Pre-emptive. Antibiotics should be administered
even in the absence of positive antimicrobial cul­
tures when clinical deterioration is noted, with pro­
gression of hepatic encephalopathy or with the
presence of SIRS (systemic inflammatory response
syndrome). The latter may also reflect the presence
of systemic inflammation as a result of cytokine
release and activation.

Coagulation abnormalities are a prominent fea­
ture of ALF, the result of synthetic dysfunction
(vitamin K-dependent factors), platelet abnormalities
and fibrinolysis. However, overt bleeding is rare. It
is incorrect to correct an abnormal coagulation
test solely due to its presence In fact, current tests
of coagulation in cirrhosis may not adequately re­

The major risk of hemorrhage occurs at the
time of skin/tissue piercing for invasive procedures/
diagnostic tests. While fresh frozen plasma is often
used for this purpose, there are risks of volume
overload. Recombinant factor VII has been used at
the time of placement of ICP monitors at a dose
of 40 mcg/Kg. A second dose was used when the
goal of reaching an INR of <1.5 was not obtained.

While in this series of 15 patients no intracranial

Fig 2: Rats infused with ammonia (NH3) develop brain edema. Ammonia + Vasopressin (VP) group reveals greater brain water and ICP at 105 min than other three groups.
the absence of an elevation of arterial pressure.\textsuperscript{25} Failure of cerebral vascular autoregulation is common in patients with severe encephalopathy, and all agents that increase arterial pressure have the potential of increasing cerebral blood flow and worsening cerebral edema.

Renal replacement therapy\textsuperscript{26} has become the standard approach to support patients with renal failure who exhibit uremia, volume overload and other metabolic derangements (acidosis, hyperkalemia). Intermittent hemodialysis is tolerated poorly and may aggravate cerebral edema due to fluid shifts. Continuous RRT, such as continuous veno-venous hemofiltration (CVVH), is recommended. Removal of ammonia is more likely with the use of CVVH-D (D for dialysis).

Circulatory failure is a more advanced expression of the arterial vasodilatory state and is an ominous clinical development. A critical reduction of arterial pressure (MAP <65 mmHg) may adversely affect the perfusion of individual organs. In the case of the brain, a cerebral perfusion pressure (MAP – intracranial pressure) of <40 mmHg has a high probability of resulting in brain ischemia. Adrenal insufficiency should be excluded, as it may contribute to cardiovascular collapse.\textsuperscript{27} Hydrocortisone supplementation may improve the response to norepinephrine, the usual agent used to treat such circulatory insufficiency.

The brain in ALF. Four distinct clinical situations need to be considered.

Development of encephalopathy. Encephalopathy is a defining condition of ALF but its presence should not be automatically equated with the “natural” progression of liver failure. Precipitant factors should be sought, including the development of GI bleeding, the use of antiemetics with sedative properties, and infection. With respect to therapy of mild encephalopathy, there is insufficient data to recommend the use of lactulose, an agent whose effectiveness in the encephalopathy of cirrhosis has also been questioned. It may cause ileus and its use in advanced stages of encephalopathy is probably futile. No data is available on the use of rifaximin in this condition.

Agitation. A unique feature of the encephalopathy of ALF, in contrast to that of cirrhosis, is the development of agitation and mania, even at stages where consciousness appears relatively preserved. Such patients need to be sedated in order to avoid self-inflicted injury. Agitation can also be seen in intubated patients with more advanced encephalopathy, a situation that may aggravate intracranial hypertension. While propofol and benzodiazepines can be used to treat agitation, propofol is preferred due to its shorter half-life, the reduction of cerebral blood flow and the absence of increase in intracranial pressure.\textsuperscript{28}

Seizures. Myotonic seizures are described in ALF. Subclinical seizure activity may be present when sought with continuous EEG\textsuperscript{29} and was postulated to aggravate the development of brain edema. The use of phenytoin appears controversial as two clinical studies have reached opposite conclusions.\textsuperscript{29,30}

Brain edema and intracranial hypertension. Although an increase in brain water has now been shown in both acute and chronic liver failure,\textsuperscript{31} the
unique development in ALF is the rise in intracranial pressure, culminating in cerebral herniation and death. The pathogenesis of brain edema is complex and has been extensively studied in the laboratory. It involves the interplay between an osmotic alteration in astrocytes, a metabolic disturbance in this cell (characterized by the development of anaerobic glycolysis and oxidative stress) and the development of cerebral hyperemia. Because of the frequent association of infection/inflammation with the progression to deep encephalopathy (and hence the development of brain edema), cytokines may play a pathogenic role at several levels, including engagement of receptors in the cerebral vascular endothelium (green stars), via vagal afferents into brain, and through selected areas void of the blood-brain barrier.

Brain edema occurs in patients with severe HE. Its management is controversial. 

i. Arterial ammonia of >150 μmol/L in patients with stage III/IV encephalopathy places the patient at risk of cerebral herniation, a risk that is considerably higher with values >200 μmol/L.

ii. A CT scan is recommended to exclude other intracranial pathology. It has a low sensitivity to detect brain edema.

iii. ICP monitoring is a subject that still elicits controversy. The risk of intracerebral hemorrhage, almost 10% (with 2/58 deaths) in a recent series from the ALF group, is lower than the 22% seen in the early ‘90s. A randomized controlled trial of ICP monitoring may never be performed. In the ALF study, the outcome of liver transplantation was examined in patients with and without ICP monitoring (45 subjects per group). While survival post-

transplant was similar in both groups, the patients with ICP monitoring were treated more frequently for the presence of brain edema. Elevations of intracranial pressure >60 mmHg may be silent and thus, neurological damage may be manifest several months after the transplant procedure. The ALF group is currently examining this question in a prospective manner.

Brain edema is more prominent in a subset of patients with ALF: Those with a rapid clinical course (eg. Acetaminophen-induced liver injury), severe hyperammonemia of >200 ug/dl, hyponatremia <125 meq/L (potentiates hyperammonemia-induced brain edema) and those who acquired an infection. In patients who are candidates for liver transplantation, ICP monitoring may assist in the decision to cancel the procedure due to futility as well as manage ICP intraoperatively. Most, but not all, centers avoid its use in the management of patients who are not candidates for liver transplantation.

i. General measures are important for management: a quiet environment, head of the bed to 30°, avoidance of volume expansion. Fever worsens intracranial hypertension and should be treated. Infusion of hypertonic saline has been proposed to prevent the development of intracranial hypertension. Mannitol is used to treat a high ICP and 0.5 g/Kg appears to be the appropriate bolus dose. Serum osmolarity should be monitored. Barbiturate coma is seldom utilized, as it may result in arterial hypotension.

ii. Goals of therapy include an ICP < 20 mmHg and a CPP of 50-80 mmHg, based on approaches to
high ICP in other conditions. While successful transplantation has been done with CPP <40 mmHg, this should be viewed as the exception rather than the rule. A CPP <40 mmHg for more than 2 hours or severe (>40 mmHg) sustained intracranial hypertension refractory to therapy are ominous signs.

**Artificial/bioartificial support in ALF**

Bioartificial support appears as a more attractive proposition, with the possible replacement of liver. Extracorporeal liver perfusion (pig, human) has a long history of isolated success, but essentially is not a feasible option at most centers around the world. Thus, the results of the largest clinical trial in ALF ever, where a bioartificial liver was evaluated (pig hepatocytes + charcoal hemoperfusion), were awaited with great interest. The differences were not statistically significant and the Data and Monitoring Board of the trial recommended its early cessation due to futility. Post-hoc analyses showed a trend towards better outcomes in the patients with ALF (as subjects with primary non-function after transplant were also included in the primary analysis). Such an approach was criticized and the study is viewed as a negative trial.

**Thirty-day survival in acute liver failure**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>n</th>
<th>Control* n (%)</th>
<th>BAL* n (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>171</td>
<td>53/86 (62)</td>
<td>60/85 (71)</td>
<td>0.259</td>
</tr>
<tr>
<td>FHF/SHF</td>
<td>147</td>
<td>44/74 (59)</td>
<td>53/73 (73)</td>
<td>0.117</td>
</tr>
<tr>
<td>PNF</td>
<td>24</td>
<td>9/12 (75)</td>
<td>7/12 (58)</td>
<td>0.667</td>
</tr>
</tbody>
</table>

*Survivors/total patients

Therapeutic hypothermia. In the experimental animal, mild hypothermia (32°-33°C) prevents the development of brain edema and intracranial hypertension. Its effects are mediated by the prevention of the development of cerebral hyperemia as well as reducing anerobic glycolysis and oxidative stress in astrocytes. Furthermore, survival of anhepatic animals is enhanced by the presence of hypothermia (reviewed in Ref 44).

Interest in the use of therapeutic hypothermia for humans encompasses several areas of critical care, including brain trauma, resuscitation post-cardiac arrest, and other acute neurological conditions. Two limited experiences in human ALF, using mild hypothermia for intractable intracranial hypertension, show effectiveness in the control of a high ICP. Patients were successfully bridged to liver transplantation and neurological recovery was complete. Evaluation of the effectiveness of hypothermia awaits the results of clinical trials, where some of the complications associated with the treatment, such as infection and coagulopathy, could be examined within the context of ALF itself.

Concern has been expressed whether hepatic regeneration would be impaired in humans with ALF subjected to mild hypothermia. Recent studies in an animal model of acetaminophen-induced injury indicate the continued presence of regenerative activity at 33°C. Furthermore, survival was enhanced after hypothermia was applied once the liver injury was fully developed. Hepatocyte apoptosis/necrosis was decreased and sinusoidal integrity remained intact. Mild hypothermia may exhibit positive effects on liver injury.

**Large-volume plasmapheresis.** A Scandinavian-UK randomized controlled trial is exploring the potential benefits of large-volume plasmapheresis in patients who predominantly have acetaminophen-induced ALF. Dr. Fin Larsen, principal investigator of the trial, provided a preliminary analysis of 120 patients entered into the study. Baseline characteristics of all major parameters were similar between the groups. A multiple regression analysis considered plasmapheresis and liver transplant as independent variables (one-third of patients underwent transplantation). Preliminary assessment of survival analysis in four groups of patients, with and without liver transplantation, with and without large-volume plasmapheresis, will be presented during the course. The study plans to enroll 180 patients into the trial.

**Extracorporeal albumin dialysis.** This approach has been mainly utilized in patients with cirrhosis with acute-on-chronic liver failure. The rationale behind such treatment is the removal of albumin-bound toxins. The putative toxin that is being eliminated has not been defined, though several candidates can be listed, including bile acids, nitric oxide and metals (such as copper). A robust finding in pathophysiological studies is the increase in systemic vascular resistance associated with such therapy, indicative of the removal of a vasodilating substance.

Three trials have been performed with the use of MARS, one of the available ECAD systems (the other, Prometheus, may provide a larger surface of
exchange). In two of them, hepatorenal syndrome and overall survival were improved in patients with acute-on-chronic liver failure. It is difficult to fully interpret both studies in view of the small number of patients. A recently completed study in patients with severe encephalopathy showed a significant improvement of mental state in the group treated with ECAD. The nature of the substance removed was indirectly assessed; significant differences in ammonia levels were noted, without changes in the levels of tryptophan; benzodiazepine levels were not detected in either group.

Could ECAD be used for patients with ALF? Scattered experiences reveal control of ICP with MARS, but in these cases, body temperature was not carefully controlled. A large clinical trial in ALF is ongoing in France, where approximately half of the targeted number has been enrolled. The trial is expected to be completed by the end of 2007.

**Final comment**

We are living the era of large clinical trials in ALF, many of which are currently in progress. These are complex studies, performed in critically ill patients and that require expertise in ICU management. Efforts to enroll patients in such trials should be viewed as a task of the entire GI/Hepatology community, as prompt referral will enhance the ability to see these studies to completion. It is through such efforts that we will arrive to a rational, evidence-based approach to the management of this challenging condition.

**References**


**Liver Transpl** 2005;11:1550-5.


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