ACUTE LIVER FAILURE: PATHOPHYSIOLOGIC BASIS, AND THE CURRENT AND EMERGING THERAPIES

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ABSTRACT

Acute liver failure (ALF) is a devastating condition that occurs in patients who previously had a normal liver. Although the outcome of patients with ALF has improved, without liver transplantation (LT) mortality rates remain in the range of 35-50% in different geographical areas and therefore, its treatment remains an unmet need. In the Western world toxic liver injury from acetaminophen remains one of the common causes but, in the East, hepatitis of unknown aetiology remains the most common cause. Treatment options are limited to meticulous attention to multi-organ support, use of N-acetyl cysteine, judicious use of antibiotics, and timely LT. This review describes the state-of-the-art techniques in the issues related to prognosis, outcome, and treatment of this devastating syndrome.

Keywords: Acute liver failure, intracranial hypertension, multi-organ failure, liver transplantation, N-acetylcysteine, acetaminophen.

INTRODUCTION

Acute liver failure (ALF) is a life-threatening clinical syndrome resulting from a rapid de novo hepatocellular necrosis in the absence of previous liver disease, and occurring within hours to up to 26 weeks of initial injury. Acute hepatic insult leads to a rapid loss of liver function and is characterised by severe coagulopathy and hepatic encephalopathy (HE), the two defining features of ALF. In clinical terms, any mental alteration in conjunction with a prolonged prothrombin time (PT >20 seconds) or International Normalised Ratio (INR >1.5), constitutes a diagnosis of ALF. Notable exceptions to this definition are some cases of Wilson’s disease (WD), autoimmune hepatitis (AIH), and reactivation of hepatitis B virus (HBV), where cirrhosis or chronic liver impairment may already be present but the clinical phenotype is one of ALF, which is indistinguishable from acute viral hepatitis.

Fulminant WD accounts for 6-12% of all patients with ALF referred for emergency transplantation. An early diagnosis of WD, ALF is critical for prognostication and subsequent need for liver transplantation (LT); the mortality rate in WD patients with ALF and HE approaches 100%. Typically, the combination of Kayser-Fleischer rings and a low serum caeruloplasmin (<0.1 g/l) level is usually sufficient to establish a diagnosis as other sophisticated biochemical tests of deranged copper metabolism are often not rapidly available. The Nazer score (based on serum bilirubin, aspartate aminotransferase [AST], and prolongation of PT), modified Nazer score (PT replaced by INR), and the Wilson Index (serum bilirubin, AST, INR, white cell count [WCC], and serum albumin) by Dhawan et al. are useful tools to identify patients with poor prognosis. Similarly, in 30-40% of cases the onset of AIH is acute, mimicking that of acute hepatitis due to other causes, constituting 2-16% of all causes of ALF. Viral hepatitis B is one of the most common causes of ALF worldwide. The presentation could be acute in the absence of previous liver impairment or a consequence of the reactivation of HBV replication in hepatitis B carriers undergoing immunosuppressive or cancer chemotherapy.
ALF is a rare condition, with a reported annual incidence in the developed world of 1-6 new patients per 1 million people. The aetiology of ALF varies widely around the world, with infections from hepatitis A, B, and E viruses accounting for most cases in the developing world. However, in the USA and much of Western Europe, viral hepatitis is on the wane, and drug-induced liver injury - such as acetaminophen toxicity - is by far the most common cause of ALF. Although identifying the underlying cause of the liver failure is important in order to modify the approach to management and to provide prognostic information, in 15–20% of cases, aetiology remains unclear even after an extensive clinical and laboratory assessment. The differential diagnosis of patients presenting abnormal liver function tests and decreased level of consciousness could be difficult; a patient's history, risk factors, clinical presentation, and general examination are fundamental to identify the underlying aetiology. Drugs, alcohol toxicity, WD, decompensated cirrhosis, and severe liver involvement of systemic infections (malaria, typhoid, leptospirosis, rickettsial infection, etc) are a few possible causes to take into consideration in this setting. Unabated hepatocellular necrosis leads to extra-hepatic end-organ damage, characterised by vasopoplegia and haemodynamic alterations, renal, pulmonary, and cerebral dysfunction representing a constellation of features resembling sepsis phenotype.

The outcomes of ALF in developed countries have improved dramatically in the last 25 years, owing to better understanding of its aetiopathogenesis, and the advent and availability of emergency LT for those who progress to severe liver failure. Parallel advancements and evolving standards of care in evidence-based practices in organ-system support in the liver units and the intensive care units (ICU) have played a vital complimentary role in managing these complex patients. This has culminated in a significantly improved outcome for patients managed with medical treatment alone and those who received LT for the treatment of ALF, the latter showing a vast improvement in 1-year post LT survival rates from 36% in 1984 to approximately 80% currently in Europe.

### PATHOPHYSIOLOGIC BASIS OF ALF

#### Liver Injury

Acute liver injury is caused by both direct injury to the hepatocytes, and an innate immune-mediated response, mediated through activation of macrophages, dendrophages, and endocytosis, leukocytes, natural killer (NK) cells, and natural killer T (NKT) cells. These cells express receptors that are able to recognise pathogen-associated molecular patterns (PAMPs) in viral hepatitis and damage-associated molecular patterns (DAMPs) in toxin-mediated liver injury, leading to the activation of signal transduction pathways which determine the pattern of cytokines released, initially locally within the liver itself, spilling over to the systemic circulation eventually. The principle mode of hepatocyte death is through necrosis; particularly in the acetaminophen-induced liver injury. Recent studies also suggest a significant role of apoptosis in cell death of ALF, which is mediated through activation of caspases. Serum M30 antigen, a marker of apoptotic hepatocyte cell death, is significantly elevated in patients who die of ALF, thus making serum M30 antigen a potential biomarker for monitoring progression of liver injury, and the use of caspase or other apoptotic inhibitors as an important therapeutic target in preventing further cell death.

#### Extra Hepatic Injury

Irrespective of the aetiology, a large majority of the patients eventually go on to progress to various degrees of extra-hepatic organ involvement with some developing frank multiple organ failure. While intense systemic inflammatory response syndrome (SIRS), which develops in ALF - mediated by the pro-inflammatory cytokines released from the damaged liver and subsequent activation of endothelial, coagulation, and immunological systems and organ cross talk - seems to be largely responsible for distant organ damage, direct toxic injury may also occasionally contribute, as is seen in patients with acetaminophen toxicity who develop toxin-related acute renal tubular injury. The existence of a parallel compensatory anti-inflammatory response syndrome (CARS) - mediated by the anti-inflammatory cytokines, IL-4, IL-10, and transforming growth factor-β - is not only insufficient in counter-modulating this response, but acts to predispose to superimposed bacterial and fungal sepsis during the latter stages of the disease and late mortality.

Brain dysfunction in ALF deserves special mention as the pathophysiology of HE in ALF goes beyond the inflammatory response associated with the condition. The exact mechanisms are not fully understood, but alterations in cerebral...
blood flow (CBF) and cerebral autoregulation, circulating neurotoxins such as ammonia, systemic inflammation, and hypo-osmolality seem to play a major role. The consequences of HE can range from subtle neuropsychiatric alterations to full-blown cerebral oedema and intracranial hypertension (ICH). Increased CBF in conjunction with the loss of auto-regulation, results in cerebral hyperaemia leading to intracerebral hypertension. Ammonia is the most commonly studied neurotoxin in this context, with serum levels >124 µmol/L shown to be associated with a high incidence of cerebral oedema and raised intracranial pressure (ICP). and levels >150 µmol/L with cerebral herniation. It is produced from glutamine in the gut to then be metabolised chiefly in the liver into urea, which is excreted in the urine. Failure of this system and urea synthesis leads to elevated serum levels in liver failure.

Recent clinical and experimental data, however, suggest a much more complex inter-organ traffic involved in the production and metabolism of ammonia, opening up new possibilities for therapeutic interventions, which can be targeted at various stages of its metabolism, thus achieving reduction in ammonia production and enhanced elimination. Skeletal muscles provide a minor alternative site for ammonia metabolism, by converting ammonia through glutamine synthetase activity to glutamine. Glutamine that is produced can undergo reconversion into ammonia and glutamate by the enzyme glutaminase, present in the kidneys and gut. Ammonia that reaches the brain is converted to glutamine by the astrocytes, which in high concentrations exert an osmotic effect leading to oedema and causing oxidative stress from reactive oxygen species. Systemic inflammation, particularly in the presence of sepsis, further impairs central nervous system (CNS) function by causing oxidative injury, endothelial damage with increased permeability of cerebral vasculature, and alterations in blood flow, leading to further brain swelling and raised ICP.

**PRINCIPLES OF MANAGEMENT**

The key management principles of ALF are complex and require a team of highly trained hepatologists, intensivists, and transplant surgeons. Establishing a diagnosis of the underlying insult is crucial in determining specific therapy options for certain aetiologies, which could result in the cessation of the damage process and may even reverse liver failure. For example, in the case of acute HBV infection, more than 95% of patients may seroconvert spontaneously, while the remaining 5% with severe acute or protracted hepatitis (defined as prolonged PT and deep jaundice persisting for >4 weeks) may benefit from nucleoside/tide analogue treatment. The Budd-Chiari syndrome (acute hepatic vein thrombosis), inherited or acquired, is an uncommon cause of ALF characterised by a pro-coagulant state, where therapeutic options include: anticoagulation, performance of transjugular intrahepatic portocaval shunting, or LT.

HELLP syndrome and acute fatty liver degeneration constitute two severe complications occurring during pregnancy. Early recognition of these syndromes and prompt delivery of the foetus are critical in achieving good outcomes. The overall prognosis and the spontaneous recovery of liver function in pregnancy-associated ALF is excellent with only a minority of patients requiring LT. Interventions are primarily aimed at optimising organ perfusion to promote spontaneous liver regeneration and recovery, while efforts are directed towards reduction and amelioration of liver injury through liver-specific therapy wherever applicable, along with early diagnosis and treatment of new complications, and timely identification of those who are unlikely to improve with medical management alone and would need emergency LT.

**MONITORING AND GENERAL MEASURES**

ALF patients should ideally be nursed in dedicated liver units, with clear escalation plans for early admission to ICU, particularly when they develop higher grades of HE (≥Grade 3) requiring airway protection, or are in need of advanced cardiovascular, pulmonary, renal, or cerebral support. However, simple protocol-based management, focused on maintaining metabolic homeostasis with an attention to detail on nutrition, glucose levels, oxygenation, blood pressure control, and maintenance of serum electrolytes, is crucial. Most patients in ICU require insertion of central venous lines and arterial accesses for closer haemodynamic monitoring, and provision of therapy such as vasopressors and renal support. Elevated PT in ALF does not necessarily predict bleeding risk and should not be routinely corrected for insertion of vascular catheters, thus allowing it to be used to monitor synthetic liver function.
Controversy continues to rage about the use of ICP transducers to monitor ICP but the current recommendations state they should be used with caution, only inserted by experts after correction of coagulation. Fatal intra-cerebral haemorrhage has been reported in up to 10% of patients with ICP monitoring. Epidural or sub-dural transducers are preferred as they are associated with lower risks of haemorrhage and infective complications. While invasive CNS monitoring and cerebral optimisation have failed to translate to survival benefit, Keays et al.\textsuperscript{20} have shown delayed cerebral death in Grade 4 HE patients managed with invasive monitoring with survival time improving 6-fold from 10 hours to 60 hours, thus arguing for an extra amount of time for a graft to become available.

It is likely that arterial ammonia levels (>150 µmol/L) and/or jugular venous oxygen tension (<65 mmHg or >85 mmHg) may help to identify patients at particular risk of developing intracranial hypertension (ICH).\textsuperscript{21} The decision about invasive ICP monitoring should be on a case-by-case basis, assessing the risks and benefits of the procedure. At our institution all patients with Grade 3 HE have reverse jugular catheters, while ICP bolt is reserved for hyperacute presentation, persistent hyperammonaemia >150 µmol/L, pupillary changes, fluctuations in reverse jugular saturations, and features of hyperexcitability such as sustained clonus (Figure 1). The patient’s neck should be maintained in a neutral position with the head of the bed elevated to 30° to facilitate venous drainage.

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**Figure 1: Management of Grade 3/4 hepatic encephalopathy in acute liver failure.**

- Serum ammonia >150 µmol/L?
- High risk of cerebral oedema?
- Impaired renal function?
- Consider CVVHF

**General Aims**
- pH 7.35-7.4
- PCO$_2$ 4.5-5
- Avoid hypertension
- Glucose 4-6 mmol/L
- Temperature 35°C
- Serum Sodium 145-150 mmol/L

- Pupillary abnormalities
- Haemodynamic instability
- Renal failure
- Clonus
- Hypereflexia

- Why is cerebral blood flow insufficient for metabolic demands?
  - Consider seizures
  - Optimise MAP, cardiac output

**SjO$_2$ 60-70%**
- Normal pupils
- No Clonus

**SjO$_2$ <60**

- Why is cerebral blood flow insufficient for metabolic demands?
  - Consider seizures
  - Optimise MAP, cardiac output

**Sedate**
- Ventilate

**Insert reverse internal jugular venous catheter**

**Measure jugular bulb venous saturation (SjO$_2$)**

**Consider ICP monitor insertion**
- Maintain CO$_2$ 4.5-5
- Temperature <36°C

**Treat sustained ICP >25 mmHg**
- Mannitol
- Bolus hypertonic saline
- Indomethacin, if hyperaemic (high SjO$_2$)
- Hypothermia (32-35°C)
- Short term hyper-ventilation in incipient cerebral herniation with high SjO$_2$
Infections and Sepsis in ALF

Immune paralysis, neutrophil dysfunction, and bone marrow suppression seen in ALF predispose patients to secondary bacterial infection and sepsis, with evidence of culture-positive bacterial and fungal infections in up to 70% and 30% of patients, respectively. Pneumonias, urinary tract infections, intravenous and other catheter-related blood stream infections, and spontaneous gut bacterial translocation constitute the most common sources of sepsis driven by organisms such as enteric Gram-negative bacilli, Gram-positive cocci, and Candida species. Superimposed sepsis (infection with SIRS) leads to further deterioration of HE and cerebral oedema, and cardiovascular and renal failure precluding transplantation occasionally, and is associated with a poorer outcome. A rigorous surveillance process to detect and treat infections early is imperative in the management of these patients. Prophylactic antibiotic therapy, though routinely used, has not shown survival benefit, but is associated with a significant reduction in the infection rates and the intensity of SIRS thereof, with improved cerebral oxygenation and circulatory stability. Prophylactic antifungal therapy is usually reserved for Grades 3/4 HE. Broad spectrum antimicrobial therapy is commenced in all patients at the time of admission and is modified periodically according to the organism identified and the sensitivity reports.

Modulating Liver Injury

N-acetylcysteine (NAC) is the most commonly used liver-specific therapy in acetaminophen toxicity, helping to replenish exhausted glutathione stores in the liver and promoting metabolism of N-acetyl p-benzoquinoneimine (NAPQI), the toxic metabolite of acetaminophen responsible for liver toxicity. While the best evidence of its effectiveness is reserved for early commencement following acetaminophen toxicity (within 24 hours), even delayed therapy (after 24 hours) produces improvement in the haemodynamic and cerebral oxygenation parameters. In addition, in the early stages of HE (Grade 1-2) NAC has also been shown to exert beneficial effects in non-acetaminophen aetiologies of ALF. Other liver-specific therapies, such as lamivudine and intravenous immunoglobulin (IVIG) in hepatitis B, or acyclovir in herpes simplex virus-related liver failure, and corticosteroids in AIH, although routinely used, have failed to demonstrate substantial beneficial effect, partly because of the rarity of occurrence of these diseases and the associated wide variations in the severity of illness, which makes conducting randomised trials to establish best practise and the evidence base difficult.

Circulatory Dysfunction

Circulatory failure is universal in severe disease and is characterised by systemic vasodilatation, vasoplegia and hypotension (despite increased cardiac output), and not infrequent subclinical myocardial dysfunction. Aggressive fluid therapy to maintain circulatory volume and tissue perfusion is achieved by rapid infusion of crystalloid or colloid solutions. The role of human albumin solution (HAS) as a plasma expander, and as a drug with potential extra-oncotic effects such as stabilisation of endothelial function, drug handling, and anti-inflammatory and anti-oxidant effects, is yet to be studied in ALF. However, in the wake of recently published studies demonstrating the ill effects of starch solutions in patients with sepsis, HAS could be considered for resuscitative purposes in hypovolaemic patients not responsive to crystalloids alone. Caution must be exercised to avoid hypervolaemia with albumin as this can lead to a deleterious effect on ICP.

Vasopressors are required for the volume-unresponsive shock, norepinephrine being the vasopressor of choice. Vasopressin, and its analogue terlipressin, can be used as a second-line agent in combination with norepinephrine but can be associated with increases in ICP. The target of therapy is difficult to define and at present is arbitrarily based upon maintaining adequate cerebral perfusion. Most units would aim for a mean arterial pressure of 65-70 mmHg. In refractory shock, corticosteroids may have a role especially when administered early in the course of illness. This is to treat relative adrenal insufficiency associated with ALF.

Respiratory Support

Oro-tracheal intubation for airway protection and invasive mechanical ventilation to manoeuvre blood carbon dioxide (CO₂) tension is the norm for those who progress to Grade 3/4 HE. Although temporary hyperventilation can be undertaken to reduce ICP, prolonged periods of hyperventilation is not advised and can be deleterious. Mechanical ventilation exposes patients to a spectrum of ventilator-associated complications (VAC) -
such as ventilator associated pneumonias, acute lung injury (ALI), and acute respiratory distress syndrome (ARDS) - and the risks of baro, volu, and bio-trauma. Protective lung ventilation strategy is the gold standard for managing most acute lung injuries in the ICU but a careful balancing act is required when dealing with ALF patients. While high positive end expiratory pressure (PEEP) may be necessary to optimise recruitment of lung units and prevent atelectasis to improve oxygenation, high PEEP in conjunction with low tidal ventilation and low inflation pressure can adversely impact on cerebral oedema and ICH secondary to venous engorgement from high transmitted pressure, and cerebral vasodilation due to elevation in CO₂ (permissive hypercapnia).

Renal Support

Renal support is commonly required as >50% of patients develop acute kidney injury (AKI), with incidence of AKI rising to as high as 75% in patients with ALF due to acetaminophen overdose. The cause of renal failure in this setting is multifactorial, including dehydration, direct drug nephrotoxicity, hypotension, sepsis, and hepatorenal syndrome. Management includes avoidance of nephrotoxic agents, treatment of infections, and maintenance of euvoalaemia and adequate renal perfusion. While the primary objectives of the renal support is to control azotaemia, treat electrolyte abnormalities and metabolic acidosis, and maintain fluid balance, it is also highly effective in removing ammonia, and achieving normo/hypothermia and control fever. Continuous modes of dialytic therapy are preferred to avoid large fluid shifts and cerebral complications associated with it.³²

HE and ICH

HE and cerebral oedema with ICH is the most devastating complication of ALF, occurring more commonly and in a more severe form in hyperacute presentations. Despite significant improvement in the understanding of its pathophysiology, and the overall management of CNS complications of ALF, ICH still accounts for up to 25% of deaths in ALF. The basic tenets of cerebral management in ALF are similar to that in traumatic brain injury, with additional measures undertaken to control hyperammonaemia. Prevention and treatment of secondary insults, such as hypotension and hypoxia, are vital, along with maintenance of adequate cerebral perfusion and controlling ICP. Avoidance and treatment of hypo-osmolality, hyponatraemia being the main offender, through osmotherapy with mannitol or hypertonic saline to achieve higher serum sodium (>145 mmol/L) levels is associated with less severe cerebral oedema.³³

Adequate sedation and treatment of subclinical seizures helps to reduce cerebral metabolic requirement for oxygen, thus preventing ischaemic injury. However, there is no role for prophylactic anticonvulsants.³⁴ ICH, in association with increased CBF (cerebral hyperaemia), is managed with short periods of hyperventilation to induce hypocapnoea and cerebral vasoconstriction, moderate hypothermia, and occasionally cyclo-oxygenase (COX) inhibition therapy (indomethacin).³⁵ Ammonia lowering strategies currently utilise extracorporeal removal techniques and induction of hypothermia. Hypothermia creates a state of ‘hibernation’ reducing metabolic rate and therefore ammonia production. It also leads to reduced ammonia uptake by the brain, and has been shown in animal studies and in small case series to effectively control refractory ICH.³⁶ Pharmaceutical interventions - such as lactulose, branched chain amino acid and non-absorbable antibiotic, and L-ornithine L-acetate (LOLA), which enhances ammonia detoxification in the muscle - whilst effective in cirrhotics, failed to show benefit in ALF.³⁷

Prognosis and Selection for LT

LT is the mainstay of treatment in the poor prognosis group. Early identification of those with poor prognosis is crucial. Multiple scoring systems (Table 1) have evolved through the years to accurately prognosticate and act as selection criteria for LT. King’s College Hospital (KCH) criteria³⁸ remains the most widely used and is based on factors indicative of poor prognosis, such as the extremes of age, rapidity of progress as defined by the jaundice-encephalopathy interval, and the aetiology of ALF with the spectrum ranging from spontaneous recovery most unlikely in WD to very good outcome for pregnancy-related ALF. The extended KCH criteria for acetaminophen poisoning has further improved its sensitivity and is based on refractory hyperlactataemia post fluid resuscitation.³⁹ The French Clichy criteria - which were developed in ALF patients with acute HBV infection,⁴⁰ and are based on the presence of confusion/coma, patient age, and Factor V levels - are used in difficult cases of non-acetaminophen aetiologies. Other indicators, such as serum phosphate levels, Gc-globulin, alpha-fetoprotein levels, and liver volume assessments (particularly in
subacute ALF), are occasionally used. Although the criteria developed at KCH are the most commonly applied in this setting, a recent meta-analysis of studies reporting their performance in non-paracetamol aetiologies concluded that different aspects of KCH criteria in this setting require further improvement. Similarly, a systematic overview of the actual models for prediction of poor outcome in patients with ALF suggest that the models have shown inconsistent reproducibility, prognostic accuracy, and inability to predict mortality in ALF. The need for a better prognostic model remains high.

FUTURE DIRECTIONS

Development of Novel Biomarkers to Monitor Progression of ALF

Current strategies under investigation include use of peripheral biomarkers to determine whether specific therapies, such as inhibitors of apoptosis (caspase inhibitors) or modulators of inflammation (Toll-like receptor 4 and 9 inhibitors), are likely to be useful for the prevention of progression of liver injury. Ornithine phenylacetate (OP) promotes urinary excretion of glutamine produced in the

Table 1: Classification of acute liver failure (ALF) and criteria for liver transplant (LT).

<table>
<thead>
<tr>
<th>Classification of ALF – clinical features and prognosis in the subgroups</th>
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<tbody>
<tr>
<td>Hyperacute</td>
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<tr>
<td>Jaundice to Encephalopathy</td>
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<tr>
<td>Prothrombin time (PT) rise</td>
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<tr>
<td>Cerebral oedema / Intracranial hypertension</td>
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<tr>
<td>Prognosis (without LT)</td>
</tr>
</tbody>
</table>

| Typical aetiology | Acetaminophen, Hepatitis E & A | Hepatitis B | Non-acetaminophen drugs, seronegative or indeterminate hepatitis |

King’s College Hospital (KCH) criteria for emergency or super-urgent LT

**Acetaminophen overdose**

1. Irrespective of grade of encephalopathy:
   Arterial pH <7.25 following volume resuscitation >24 hours post overdose
   Or
   2. All of the following:
   Grade 3 or 4 encephalopathy
   PT >100 sec
   Serum Creatinine >300 µmol/L
   Or
   3. The extended KCH criteria
   Serum lactate >3.5 mmol/L after early resuscitation
   Serum lactate >3.0 mmol/L 24 hours post overdose, and adequate volume resuscitation

**Non-acetaminophen aetiologies**

1. Irrespective of grade of encephalopathy:
   PT >100 sec
   Or
   2. Presence of encephalopathy + any 3 of the following:
   Age <10 or >40
   Aetiology NANB, drug reaction
   Jaundice to encephalopathy >7 days
   PT >50 sec
   Serum Bilirubin >300 µmol/L

**Clichy criteria for emergency LT** (non-acetaminophen aetiology only)

1. Confusion/coma + Factor V concentration <20% + Patient Age <30 yrs
   Or
   2. Confusion/coma + Factor V concentration <30% + Patient Age >30 yrs
muscles as phenylacetylglutamine (PAGN), and has been shown to significantly reduce serum ammonia levels and brain oedema in a chronic liver failure rodent model, and to attenuate rise in ICP in a porcine model of ALF. There are no studies yet in humans. Newer agents such as N-methyl-D-aspartate (NMDA) receptor antagonist memantine, an inhibitor of the glutamate NMDA receptor preventing binding of the extracellular brain glutamate and development of brain oedema, etanercept, a TNF-α neutralising molecule, and minocycline, a broad-spectrum tetracycline antibiotic, which is a potent inhibitor of microglial activation reducing neuroinflammation, are some of the exciting therapeutic options which have shown promise in experimental models but are under further evaluation in the human setting.

**New Targets for Pharmaceutical and Extracorporeal Interventions**

Artificial and bioartificial liver support systems are aimed at supplementing standard intensive care for patients with liver failure, supporting either regeneration of the patient’s native liver or bridging to transplantation. The premise and the concept of an ideal extracorporeal liver support device hinges on the ability to detoxify the blood, perform synthetic, metabolic, and immune functions, and remove and/or inhibit production of inflammatory signalling molecules (e.g. cytokines), thereby breaking the vicious circle of liver injury leading to production of inflammatory mediators and further propagation of liver injury; the ultimate aim being stimulation and promotion of liver regeneration. Unfortunately, as of now, none of the currently available artificial or bioartificial devices have shown much promise in the context of ALF, except a regime of enhanced or high volume plasmapheresis (>10 L of plasma removed and replaced per day). This demonstrated a clinical improvement in HE, hepatic and CBF, and even a survival benefit when used for up to 10 days. Although this seems like a promising intervention, the definitive role of plasmapheresis needs further evaluation before it is adopted as a standard clinical care for ALF patients.

**CONCLUSIONS**

ALF is a reversible and, therefore, treatable condition. Huge in-roads have already been made in improving the understanding of the disease process and its treatment, as evidenced by a significant reduction in mortality and morbidity. Further research towards unravelling the pathophysiological processes underlying ALF, development of biomarkers for early diagnosis and prediction of disease progression and novel drugs to halt the disease process, and advances in the organ support system in intensive care, including the on-going search for an ideal extracorporeal liver support device, remain the unmet needs. The emergence of drugs that target apoptosis, inflammation, and the new stem cell strategies also provide exciting new opportunities to improve patient outcome.

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