Current management for acute hepatic failure

Lakkana Rerksuppaphol\*<sup>™</sup>, Sanguansak Rerksuppaphol\*\*

\*Department of Preventive Medicine, Faculty of Medicine, Srinakharinwirot University

\*\*Department of Pediatrics, Faculty of Medicine, Srinakharinwirot University

Abstract:

Acute hepatic failure is one of the rare disease, but is life-threatening. The present review

summarizes about the acute hepatic failure in relation to various treatments available depending upon

the complications such as cerebral edema, hepatic encephalopathy, renal dysfunction etc. The gold

standard treatment for acute hepatic failure is "orthotopic liver transplantation". Other treatments

include uses of dialysis techniques to remove hepatotoxins, antibiotics and drugs for inflammatory

mediators depending upon various etiologies. As the present therapies are associated with various

drawbacks, some future therapeutic targets such as cannabinoid receptors, gene therapy and aquaporin

channels are also discussed which are in preclinical stages.

Keywords: Acute hepatic failure, coagulopathy, encephalopathy, cerebral edema, targets

Lakkana Rerksuppaphol

Department of Preventive Medicine, Faculty of Medicine,

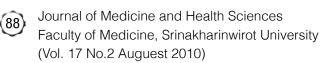
Srinakhariwirot University.

62 Moo 7, Rangsit-Nakorn Nayok Rd., NakornNayok, Thailand 26120

Telephone: 668 18483183

Facsimile: 663 7395275

Email: lakkana r@hotmail.com



# การรักษาภาวะตับวายเฉียบพลัน

ลัคนา ฤกษ์ศุภผล\*, สงวนศักดิ์ ฤกษ์ศุภผล\*\*

\*ภาควิชาเวชศาสตร์ป้องกันและสังคม คณะแพทยศาสตร์ มหาวิทยาลัยศรีนครินทรวิโรฒ

\*\*ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยศรีนครินทรวิโรฒ

# บทคัดย่อ

ภาวะตับวายเฉียบพลันพบได้น้อยแต่มีความรุนแรงถึงเสียชีวิต บททบทวนวรรณกรรมนี้มีจุด ประสงค์เพื่อที่จะรวบรวมการรักษาภาวะตับวายเฉียบพลันและภาวะแทรกซ้อน เช่น สมองบวม ภาวะ ผิดปกติของสมองจากตับวาย และไตวาย เป็นต้น ในปัจจุบันการรักษาภาวะตับวายเฉียบพลันที่ดีที่สุดคือ การปลูกถ่ายตับ การรักษาวิธีอื่น เช่น การฟอกสารพิษจากเลือด การใช้ยาปฏิชีวนะ และการให้ยาการอักเสบ จะพิจารณาตามสาเหตุของโรค เนื่องจากวิธีการรักษาที่มีในปัจจุบันยังมีข้อด้อย ทำให้ในปัจจุบันมีการ ศึกษาถึงแนวรักษาวิธีใหม่ที่มุ่งเป้าหมายเฉพาะ เช่น cannabinoid receptor ยีนบำบัด และ aquaporin channels เป็นต้น

#### **Definition**

Acute hepatic failure (AHF) also known as fulminant hepatic failure, is one of the rare, life-threatening and emergency diseased condition, encountered in patients without any pre-existing liver disease. Acute hepatic failure is defined as a condition in which there is a sudden loss of liver cell function with subsequent development of coagulopathy, jaundice and hepatic encephalopathy, associated with hyperbilirubinemia, electrolyte disturbance, cerebral edema and hemodynamic changes<sup>1,2</sup>.

### **Prevalence**

In children less than 3 years of age the indeterminate and metabolic abnormalities predominate. In adults and older children, drug especially induced toxicity, acetaminophen, predominates for AHF. Women's are more susceptible than men for AHF. Patients younger than 10 years and older than 40 years fare poorly. Acetaminophen cause is predominant in Europe, especially Great Britain, accounts for more than 50 % cases of AHF. In United States AHF cases are approximately 2000 annually. In developing countries AHF due to HBV infection predominates due to high prevalence of HBV. HEV associated AHF is predominant in women who are pregnant in regions such as Mexico, India, Central America, and the Middle East<sup>1</sup>.

### **Categories**

Hepatic failure is characterized into three categories: Hyperacute hepatic failure is a condition in which hardly it takes 7 days from jaundice to encephalopathy development, associated with severe cerebral edema. Acute hepatic failure is the second category, in which from jaundice to encephalopathy existence takes 8 to 28 days, associated with high incidence of cerebral edema and poor prognosis. The third category is the subacute hepatic failure, in which jaundice to encephalopathy develops within 5 to 12 weeks, with low incidence of cerebral edema and poor prognosis<sup>3</sup>.

## Diagnosis

The patient must be diagnosed for mental status, prolongation in prothrombin time  $\geq$  4-6 min and international normalized ratio (INR)  $\geq$  1.5 and blood pH > 7.3<sup>4</sup>.

## **Etiology**

Acute hepatic failure is caused mainly by viral hepatitis and acetaminophen induced drug toxicity. Viral hepatitis includes infection due to Hepatitis A, B, D, and E viruses and other viruses also such as cytomegalovirus, herpes simplex virus, varicella zoster virus, Epstein barr virus and yellow fever virus<sup>5</sup>. Drug induced acute

90

hepatic failure includes medications and herbs causing hepatotoxicity such as acetaminophen, troglitazone, kava kava. Stevens-Johnson syndrome is a type of liver injury caused by drugs such carbamazepine, phenytoin, halothane and erythromycin etc. Some drug metabolites such as ketoconazole, isoniazid, sodium valproate are injurious to liver<sup>6</sup>. Mushroom poisoning mainly caused by Amanita phalloides causes hepatic injury due to a toxin known as lpha amatinin toxin <sup>7</sup>. Other hepatotoxins include chloroform, tetracycline, aflatoxin, carbontetrachloride and yellow phosphorus<sup>5</sup>. Wilson disease, which is an autosomal recessive disorder, in which there is dysfunction in the copper transporters such as ATPase and ATP7B leading to copper accumulation in the liver and central nervous system, is one of the leading causes of acute hepatic failure 8. Budd-Chairi syndrome and sinusoidal syndrome are the ones which causes decreased hepatic blood flow, may lead hepatic hypoxia and ultimately to acute hepatic failure. Other causes

include Acute fatty liver of pregnancy, HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) and autoimmune hepatitis<sup>5</sup>.

## **Current Management strategies**

Various prognostic models have been defined which includes King's College Hospital (KCH) criteria and the Model for End Stage Liver Disease (MELD) Score. KCH criteria includes parameters for acetaminophen and nonacetaminophen induced AHF. The various criteria's measured are arterial pH < 7.3, prothrombin time (INR >6.5), age, serum creatinine and bilirubin levels >300  $\mu$ mol/L. MELD score is applied to end stage liver disease, includes three biochemical parameters serum creatinine, bilirubin and INR for prothrombin time. Some other prognostic models are liver biopsy, computed tomographyderived liver volume and biliary carnitine. Various levels of prognostic markers for AHF are enlisted in Table 1<sup>9</sup>.

Table 1 Various prognostic markers with cut-off levels and consequences during acute hepatic failure

Cut-off levels	Remarks	
100 mg/L	Low levels, Serum Gc globulin synthesized in	
	liver is responsible for actin clearance during	
	cell necrosis and tissue injury	
40 mg/L	Levels are decreased	
	100 mg/L	

Arterial blood lactate	3.5 mmol/L	Hyperlactemia, due to increased lactate	
		production and decreased clearance	
Arterial blood	124 $\mu$ mol/L	Hyperammonia causes intracranial	
ammonia		hypertension, hepatic encephalopathy,	
		cerebral edema	
Serum phosphate	2.5 mg/dl	Hypophosphataemia, related to hepatic	
		regeneration and severity of liver damage	
Serum alpha-	3.9 <b>µ</b> g/L	Higher levels are favourable for hepatic	
fetoprotein		regeneration after liver injury	
AHF associated with	n autoimmune	azathioprine <sup>10</sup> . Drugs and dose recommended	
hepatitis is treated with corticosteroid therapy		during treatment for acute hepatic failure are	
including prednisone alone or in combination with		presented in Table 2.	

Table 2 Drugs and dose recommended during treatment for acute hepatic failure

Drugs	Dose recommended		
	Adul	Pediatric	
Penicillin G (DOC for Mushroom poisoning)	1 mg/kg/d or 1.8 million U/kg/d IV	Not recommended	
Silymarin Activated charcoal N-acetyl cysteine	20-50 mg/kg/day/per oral 50 mg per oral Loading dose:140 mg/kg per oral	Not recommended  Not recommended  Same as in adults	
	Maintenance dose:70 mg/kg per oral, 4h after Loading dose and 17 doses administered, if emesis occurs within 1 h of administration, repeat dose Given IV also		
Prednisone	5-60 mg/kg/day per oral, bid / qid, tapered in 2 weeks	4-5 mg/m <sup>2</sup> /day per oral bid / qid, tapered in 2 weeks	



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Azathioprine

1 mg/kg/day per oral for 6-8 wk; increase by 0.5 mg/kg 4week until response or dose reaches 2.5 mg/kg/day

Initial dose: 2-5 mg/kg/day per oral IV Maintenance dose:1-2 mg/kg/day per oral /IV

DOC: drug of choice, IV: intravenously, bid: bis in die, qid: quater in die

N-acetyl cysteine (NAC) is one the most prominent clinical treatment available for acetaminophen-induced AHF cures hepatic encephalopathy, cerebral edema and neurological abnormalities. This drug is also studied in mice in non-acetaminophen induced AHF in model of azoxymethane induced liver injury. NAC was found to be effective in this preclinical model of non-acetaminophen induced AHF with normalization of brain and hepatic glutathione levels, improved neurological outcomes and reduction in proinflammatory cytokines, thus suggesting anti-inflammatory and anti-oxidant effect 11 . Drug induced liver injury has been associated with the induction of proinflammatory cytokines mainly tumor necrosis factor (TNF-CL), which turn activates mitogen-activated protein kinases, c-Jun-N-terminal kinases (JNK). Various hepatotic drugs such as acetaminophen, chlorpromazine were studied in primary mouse hepatocytes pretreated with proinflammatory cytokines such as TNF-Q, lipopolysaccharide or lipoteichoic acid. It was found that there were elevated levels of alanine aminotransferases,

which were reduced when treated with a JNK  $inhibitor^{12}$ .

There is increased intracranial pressure and cerebral herniation in AHF and monitoring of cerebral blood flow using jugular bulb catheter is promising. Some of the treatment used for to reduce intracranial pressure is use of hyperventilation, propofol sedation, hypertonic saline, mannitol and indomethacin<sup>1</sup>. Cerebral edema had been shown to be associated with increased ammonia levels which activate Na-K-CI cotransporters in turn causing imbalance in cellular homeostasis leading to astrocyte swelling. Cycloheximide, N-nitro-l-arginine methyl ester and uric acid significantly were found to decrease astrocyte swelling in cultures<sup>13</sup>.

For the treatment of coagulopathy, fresh frozen plasma, platelets and cryopreservate infusions are utilized. There is decrease in coagulation factors II, V, VII and X, anticoagulant proteins such as protein C, protein S and antithrombin III. platelet dysfunction, while there is elevated levels of factor VIII and plasminogen activator inhibitor-1. Apart from

this there are other hemodynamic abnormalities such as thrombocytopenia, hypofibrinogenemia, dysfibrinogenemia etc. are associated with AHF <sup>14</sup> .

Renal failure is one of the complications associated with AHF, systemic inflammatory response syndrome (SIRS) and elevated phosphate levels, preventing hepatic regeneration causes renal dysfunction. Also there is hyperinsulinaemia and depletion of glycogen stores, thus requiring continuous glucose administration . There is neuroendocrine activation and arterial vasodilatation in AHF associated with renal failure, is treated with plasma volume expanders, especially with albumin and vasopressore agents such as vasopressin analogues telipressin or noradrenaline<sup>15</sup>.

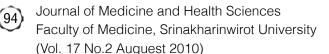
Mushroom poising is treated with Penicillin G (250 mg/kg/day) and Silibinin (20-50 mg/kg/day) is useful in early stages <sup>1</sup>.

Aquaporins (AQPs) are family of water selective channels have been implicated in fluid elimination, which is needed during cerebral edema in AHF. AQP4 and AQP9 have been implicated as the emerging anti-edema targets validated in transgenic mouse and brain edema models<sup>16</sup>.

Various detoxification methods including adsorbents have been in use for AHF to remove toxins from the liver due to accumulation or

generation or lack of elimination. Thus removal of toxins will further prevent the liver damage. Various proinflammatory mediators, ammonia, cytokines, aromatic amino acids and nitric oxide increase the capillary permeability and may lead to cerebral edema and severe liver injury 17. Among these the various techniques used are HemoCleanse-DT or Liver dialysis unit uses charcoal as adsorbent for binding of toxins and Single pass albumin dialysis (SPAD) uses albumin as adsorbent. These are examples of open loop dialysis, while closed loop systems include the Molecular adsorbent recirculating system (MARS) and Fractionated plasma separation, absorption and dialysis system (Prometheus) 18.

Orthotopic liver transplantation (OLT) is one of the most recommended treatments also known as "Gold standard" for AHF. This measure when treated along with Hepatitis B immunoglobulin (HBIG) combined with the nucleoside analog Lamivudine (LAM) was found to be reducing graft rejection and improved patient survival rate. LAM inhibits DNA polymerase of virus and Hepatitis B virus (HBV) replication. The major limitation is the development of mutation in the gene of HBV polymerase at tyrosine-methionine-aspartate-aspartate locus. Adefovir, a nucleoside analog of adenosine monophosphate is useful in LAM resistant cases, but is associated with nephrotoxicity on prolong use.



Other drugs such as Entecavir, a carboxylic analog of guanosine and Tenofovir disoproxil fumarate, a nucleoside analogue which is a reverse transcriptase inhibitor, were used instead of Adefovir due to nephrotoxicity or development of mutant resistance<sup>19</sup>.

But this measure is associated with the limitation of limited matched liver donors, costly treatment and use of immunosuppressive agents for entire life. So there is a need for the development of new therapies for the treatment of AHF. Thus various synthetic liver support devices such as dialysis and hemoperfusion removing low molecular weight hepatotoxins. This type of treatment is useful in hepatic encephalopathy as it found that low molecular weight toxins are present, which can be easily removed. But it was observed that these synthetic measures solely will not be sufficient for AHF. Thus, some biological support systems in conjunction with synthetic measures were thought to be more fruitful. Hence, hepatocyte isolation and cell culture made possible for the supply of hepatocytes which will perform the synthetic hepatic functions. Some of the studies done were in spleen of six patients cryopreserved hepatic cells were injected, who showed improvement in hepatic encephalopathy and biochemical parameters, but died afterwards. Also, other systems developed were bioartificial liver and extracorporeal liver assist device were some of the other works done by scientists. But all these biological measure were found be associated with development allergy, shock and sometimes death of patient <sup>20</sup>.

One of the land mark in this is gene

therapy for hepatic failure. Various genes which are targeted are the genes regulating apoptosis such as death receptors Fas, tumor necrosis factor receptor (TNFR) and TNF related apoptosis inducing ligand receptor (TRAIL), protein A20 and cytokines tumor growth factor (TGFeta) and osteopontin. Also genes regulating necrosis are also targets such as fibrinogen like protein 2 and inflammatory genes nuclear factor (NFKB). Factors responsible for liver regeneration such as epidermal growth factor, hepatocyte growth factor, TGF $\alpha$ , lymphotoxin $\beta$ , Interleukin (IL-1) and IL-6) are some more targets. Gene therapy is a technique in which the genetic material is transferred into cells, tissues or organ with techniques such as Gene gun, Electroporation, Sonoporation and Hydrodynamics-based gene transfer. This causes gene repair, gene augmentation, gene substitution or interference in the gene expression. This target had not reached in clinical trails stage, is in preclinical stage only, but will replace soon OLT. The various animal models used in preclinical studies are surgical, drug-induced and viral animal models. The surgical model includes hepatectomy and devascularisation. Drug-induced includes concanavalin A, acetaminophen, galactosamine, carbon tetrachloride and thioacetamide and Viral models include hepatitis B virus, murine hepatitis virus strain 3 and rabbit harmorrhagic virus<sup>21</sup>.

Cannabinoid receptors which are G-protein coupled receptors are one the targets in limelight. CB1 antagonist and CB2 agonist have been found to be effective in AHF animal model such as thioacetamide, where overexpression of CB2 receptors were reported. CB2 agonists showed improved neurological function during hepatic encephalopathy, was found to be associated with stimulation AMP-activated protein kinase involved in neuroapoptosis and neuroregeneration and CB2 receptors also showed anti-fibrinogenic property. This will be also one of target in clinical trails soon <sup>22</sup>.

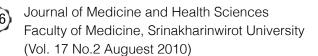
## Conclusion

The present treatments are not satisfactory and need further exploration in relation to the understanding of pathophysiology and thus the various targets.

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