

Current management for acute hepatic failure

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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

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บทคัดย่อ

ภาวะตับวายเฉียบพลันพบได้น้อยแต่มีความรุนแรงถึงเสียชีวิต บททบทวนวรรณกรรมนี้มีจุดประสงค์เพื่อที่จะรวบรวมการรักษาภาวะตับวายเฉียบพลันและภาวะแทรกซ้อน เช่น สมองบวม ภาวะผิดปกติของสมองจากตับวาย และไตวาย เป็นต้น ในปัจจุบันการรักษาภาวะตับวายเฉียบพลันที่ดีที่สุดคือการปลูกถ่ายตับ การรักษาวิธีอื่น เช่น การฟอกสารพิษจากเลือด การใช้ยาปฏิชีวนะ และการให้ยาการอักเสบจะพิจารณาตามสาเหตุของโรค เนื่องจากวิธีการรักษาที่มีในปัจจุบันยังมีข้อด้อย ทำให้ในปัจจุบันมีการศึกษาถึงแนวรักษาวิธีใหม่ที่มุ่งเป้าหมายเฉพาะ 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^{1,2}.

Prevalence

In children less than 3 years of age the indeterminate and metabolic abnormalities predominate. In adults and older children, drug induced toxicity, especially 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 East¹.

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 prognosis³.

Diagnosis

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

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 virus⁵. Drug induced acute

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 as carbamazepine, phenytoin, halothane and erythromycin etc. Some drug metabolites such as ketoconazole, isoniazid, sodium valproate are injurious to liver⁶. Mushroom poisoning mainly caused by *Amanita phalloides* causes hepatic injury due to a toxin known as α amanitin toxin⁷. Other hepatotoxins include chloroform, tetracycline, aflatoxin, carbontetrachloride and yellow phosphorus⁵. 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 failure⁸. 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 hepatitis⁵.

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 non-acetaminophen induced AHF. The various criteria's measured are arterial pH < 7.3, prothrombin time (INR >6.5), age, serum creatinine and bilirubin levels >300 μ 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 tomography-derived liver volume and biliary carnitine. Various levels of prognostic markers for AHF are enlisted in Table 1⁹.

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

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

Arterial blood lactate	3.5 mmol/L	Hyperlactemia, due to increased lactate production and decreased clearance
Arterial blood ammonia	124 μ mol/L	Hyperammonia causes intracranial hypertension, hepatic encephalopathy, cerebral edema
Serum phosphate	2.5 mg/dl	Hypophosphataemia, related to hepatic regeneration and severity of liver damage
Serum alpha-fetoprotein	3.9 μ g/L	Higher levels are favourable for hepatic regeneration after liver injury

AHF associated with autoimmune hepatitis is treated with corticosteroid therapy including prednisone alone or in combination with azathioprine¹⁰. Drugs and dose recommended during treatment for acute hepatic failure are 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	20-50 mg/kg/day/per oral	Not recommended
Activated charcoal	50 mg per oral	Not recommended
N-acetyl cysteine	Loading dose:140 mg/kg per oral 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	Same as in adults
Prednisone	5-60 mg/kg/day per oral, bid / qid, tapered in 2 weeks	4-5 mg/m ² /day per oral bid / qid, tapered in 2 weeks

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
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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 effect¹¹. Drug induced liver injury has been associated with the induction of proinflammatory cytokines mainly tumor necrosis factor (TNF- α), which in turn activates mitogen-activated protein kinases, c-Jun-N-terminal kinases (JNK). Various hepatotoxic drugs such as acetaminophen, chlorpromazine were studied in primary mouse hepatocytes pretreated with proinflammatory cytokines such as TNF- α , lipopolysaccharide or lipoteichoic acid. It was found that there were elevated levels of alanine aminotransferases,

which were reduced when treated with a JNK inhibitor¹².

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 indomethacin¹. Cerebral edema had been shown to be associated with increased ammonia levels which activate Na-K-Cl 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 cultures¹³.

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 AHF¹⁴ .

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 administration¹ . There is neuroendocrine activation and arterial vasodilatation in AHF associated with renal failure, is treated with plasma volume expanders, especially with albumin and vasopressor agents such as vasopressin analogues telipressin or noradrenaline¹⁵ .

Mushroom poisoning is treated with Penicillin G (250 mg/kg/day) and Silibinin (20-50 mg/kg/day) is useful in early stages¹ .

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 models¹⁶ .

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 injury¹⁷. 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 resistance¹⁹.

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 patient²⁰.

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 (TGF β) and osteopontin. Also genes regulating necrosis are also targets such as fibrinogen like protein 2 and inflammatory genes nuclear factor (NF κ B). Factors responsible for liver regeneration such as epidermal growth factor, hepatocyte growth factor, TGF α , lymphotoxin β , 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 hemorrhagic virus²¹.

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 soon²².

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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