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Review

Pathophysiology and management of acute liver failure

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SUMMARY

This is a review of the latest up to date information on Acute Liver Failure, a multi organic syndrome sometimes with a fatal outcome, if not diagnosed and treated at the right time. The review pays attention to some special features of the syndrome and all the new technical progress for a cure. There is also special mention about ALF and the main causes of ALF in the Greek population.

Key words: Paracetamol overdose, fulminant hepatic failure, transplantation, ALF during pregnancy

INTRODUCTION

The term acute liver failure (ALF) was first used by Trey and Davidson in 1970. ALF is a rare but dramatic clinical syndrome in which a previously normal liver fails within days to weeks. Based on data from the Liver Unit at King`s College Hospital, London, O`Grady et al.[3] proposed a classification with three different subgroups for ALF: "hyper-acute", "acute" and "subacute" liver failure. A number of conditions can cause this sudden severe liver cell dysfunction, which finally triggers a multi-organ response. The mortality is high despite considerable progress having being made during recent years, including intensive multi-organ support and liver transplantation.

AETIOLOGY AND PROGNOSIS

Paracetamol overdose is the major cause of acute liver failure in the UK, USA, Scandinavian and Mediteranian countries. The overall mortality of paracetamol-induced ALF is almost=40%, being much higher in those with profound coagulopathy and renal failure[7]. It takes at least 10gr of paracetamol to produce ALF, the usual being more than 30gr. Patients with chronic alcohol abuse and those taking enzyme-inducing drugs can develop paracetamol toxicity at substantially lower plasma levels due to induction of the cytochrome P_{450} system and consequent increased production of the toxic metabolite N-acetyl-p-benzoquinoneimine [NAPQI]. N-acetyl-cysteine {NAC}, by repleting glutathione stores, is highly effective in preventing massive hepatic necrosis if given within 10 h of paracetamol overdose and reduces the severity of liver damage if given up to 15 h after drug ingestion.[9,10] Late administration of NAC in paracetamol-induced ALF seems to improve survival without a measurable effect on liver function.[11,12]

Different classes of drugs can cause idiosyncratic ALF. Antiepileptics such as carbamazepine and valproate are commonly involved. All antituberculous agents have been implicated. Halothane and corticosteroids are also known causes of ALF. Finally non-steroidal anti-inflammatory drugs, antifungal agents and recreational drugs have been implicated.

Viral hepatitis is the commonest cause of acute liver failure world-wide and in the Indian subcontinent alone it

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Abbreviations:

FHF: Fulminant hepatic failure
OLT: Orthotopic liver transplantation
ALF: Acute liver failure
KCH: King`s College Hospital
NAPQI: N-acetyl-p-benzoquinoneimine
NAC: N-acetyl-cysteine
H.E.L.L.P.: Haemolysis, Elevated liver enzymes, Low platelets
ICP: Intracranial pressure
CPP: Cerebral perfusion pressure
SPEAR: Selective parenteral and enteral antimicrobial regimen
FFP: Fresh frozen plasma
BAL: Bioartificial liver
ELAD: Extracorporeal liver assist device

was the indentified aetiology in over 90% of cases.[13] However, less than 1% of acute viral hepatitis leads to hepatic failure.[14-16] All primary hepatotropic viruses can cause acute hepatic failure with a different incidence in different countries[14-16]. Hepatitis A-related ALF has a better prognosis {70% survival} than hepatitis B which produces a more severe clinical syndrome {40% survival}.[14] The term non-A non-B hepatitis is used in cases with clinical features suggestive of viral aetiology in the absence of any identified pathogen.[16-19] Non-A non-B-induced ALF follows a subacute course of illness and has the worst prognosis of viral causes {<20% survival }[5,15]. Hepatitis C virus is a rare, but now well documented, cause of ALF in European countries and the USA.

Special mention should be given to ALF due to hepatitis E during pregnancy.

The high mortality is secondary to hormonal and immunological changes of pregnancy. Steroid hormones (estrogen and progesterone) may promote viral replication and may also have direct inhibitory effects on hepatic cells which predispose to hepatic dysfunction. They also induce immunosupression. Their accumulatory effect can produce severe liver damage and ALF.[78]

Ingestion of the Amanita Falloides mushroom is a relatively common cause of acute liver failure in Mediteranian countries, Ingestion of as few as three mushrooms may prove fatal. Symptoms start 6-18 h after ingestion and are characterized by severe abdominal cramps, vomiting and watery diarrhoea, The clinical condition usually responds to fluid and electrolyte replacement unless clinical and biochemical signs of acute liver failure become established, usually 3-4 days later, Intravenous penicillin plus silibinin is the commonly used antidote and should be started as soon as the diagnosisis has been made.

Wilson's disease is a common cause of ALF. Presence of Kayser-Fleischer rings, in a young jaundiced patient with, Coombs negative haemolytic anaemia are indicative of the disease. Liver biochemistry usually shows high plasma bilirubin with relatively low plasma transaminase activity and mildly increased or normal alkaline phosphatase activity. A ratio of alkaline phosphatase activity to bilirubin of less than 2 is highly suggestive of the condition[23].Urinary copper excretion is high. Plasma caeruloplasmin is usually low.

Reye`s syndrome is another rare cause of liver failure, mainly in children between 5 and 15 years. It has been characterized by the development of acute encephalopathy with cerebral oedema and diffuse fatty change of the liver/ It usually follows a viral febrile illness and is strongly associated with the use of salicylates in the management of pyrexia.[24]

H.E.L.L.P. syndrome {haemolysis, elevated liver enzymes, low platelets } can be seen in pregnant women. It is more common in women with hypertension or pre-eclampsia. Spontaneous rupture of the liver can occur.

Malignacies may present as ALF. These can be due to metastatic involvement of the liver (occult breast cancer, gastric cancer,[83] occult bronchogenic cancer,, metastasis from lung /prostate[89]), due to primary liver malignancy (primary fibrolamellar carcinoma,, primary hepatic lymphoma, primary hemangioendothelioma)or due to hematologic malignancies (non-Hodgkin's lymphoma, leukemia).[80]

Mechanisms proposed to explain ALF due to neoplastic or paraneoplastic aetiology are sepsis, hepatic ischemia caused by obstruction of hepatic blood flow by infiltrating neoplastic cells,[81] and hepatic anoxia.[79]

Although the presence of a neoplasm is an absolute contraindication for liver transplantation, some forms, such as lymphoproliferative diseases[79] or small cell lung cancer[82] may respond to chemotherapy with improved hepatocellular function.

Furthermore, conditions such as Budd-Chiari, sepsis, ischaemic hepatitis and autoimmune chronic hepatitis can occasionally manifest themselves as acute liver failure.

With regards to Greece, the major cause of ALF is hepatitis B virus(52%). Other causes are Wilson's disease(4%), ischaemic hepatitis(4%), drugs inducing ALF (12%), coinfection with HBV and HCV(4 %), Amanita mushrooms ingestion (4%) and cryptogenic (16%).[75]

The prognosis of ALF depends on the etiology and the clinical course of the disease. HAV, HBV, paracetamol-induced and ischaemic ALF have a relatively good spontaneous survival rate of 36%, whereas idiosyncratic drug reactions and indeterminate causes have only 14% spontaneous survival rate.[86]

Table 5 shows in detail the survival rate reported with high grade hepatic encephalopathy.

CLINICAL PRESENTATION OF ACUTE LIVER FAILURE

The initial clinical presentation depends upon the cause and the time between toxic insult and hospitalization. Patients may present with non-specific symptoms such as malaise, nausea, vomiting, abdominal pains and dehydration and

often even after a careful history and examination the diagnosis of acute liver damage may initially be missed, until liver biochemistry and clotting screen become available.

CLINICAL COURSE OF ALF

The clinical course of acute liver failure is that of progressive multi-organ failure. The severity of clinical signs and illness depends upon the adverse metabolic consequences of loss of liver function, the systemic effect of toxins from the necrotic liver and the rate and degree of regeneration. In addition, and as a result of toxic injury, the immune system is compromised with development of secondary bacterial infections and endotoxaemia giving rise to a picture similar to that of septic shock.

CEREBRAL MANIFESTATIONS

Encephalopathy. Severe liver injury results in impairment of cerebral function that ranges from abnormal mentation,, with drowsiness, euphoria and confusion, to deep coma. The diagnosis of encephalopathy is clinical, and a commonly used scoring system is shown in Table 2.General measures for the treatment of chronic hepatic encephalopathy, such as withdrawal of dietary protein, lactulose and neomycin, are neither useful nor practical in severe acute encephalopathy.

Cerebral oedema. Cerebral oedema occurs in 75-80% of patients with ALF and grade 4 encephalopathy, and is the primary cause of death in these patients.[26-28] ICP may increase rapidly before any clinical signs appear and may result in brain death before any treatment can be initiated.[30] The clinical signs suggestive of raised intracranial pressure {ICP} are summarized in Table 3. ICP monitoring has been used extensively throughout the world in patients with ALF in order to indicate appropriate therapy as necessary. Above 20 mmHg is usually associated with cerebral oedema and should be treated as an emergency.

Cerebral perfusion pressure (CPP) (which is the difference between mean arterial pressure and intracranial pressure) should be above 60 mmHg. A CPP below 40 mmHg is critical and has been associated with significant neurological damage ranging from residual neurological deficits to brain death.

Treatment of cerebral oedema

Mannitol

The use of mannitol has been shown to improve survival in patients with ALF complicated by grade 4 encephalopathy[31]. Acting as an osmotic agent, it reduces brain water and decreases ICP. A dose of 0.5-1 g {20% solution}/kg weight is administered over 20 min when clinical signs of raised ICP occur {in cases where ICP monitoring is not available}, or when ICP increases above 20 mmHg. The dose may be repeated as necessary, provided that adequate diuresis occurs and serum osmolality remains below 320 mOsm. In patients with oliguria and renal failure, mannitol should be used only in combination with renal replacement therapy.

Corticosteroids and L-ornithine L-aspartate

Several randomized studies have demonstrated that corticosteroids have no beneficial effect in cerebral oedema in ALF, or produce any improvement in survival rates[32-34.] LOLA has shown no benefit in encephalopathy in ALF

N-Acetylcysteine

There is increasing evidence that N- acetylcysteine {NAC} is of benefit not only in paracetamol-induced ALF, but in all aetiological groups. Even though NAC has no direct effect on ICP, it may reduce cerebral oedema by increasing cerebral blood flow and enhancing tissue oxygen consumption[11,12]. In addition, NAC may exert its beneficial effect due to its action as a free radical scavenger.

Infection

Patients with ALF are prone to sepsis because host defence mechanisms are impaired, with development of endotoxinaemia as an immediate consequence of acute liver injury. Invasive procedures and insertion of intravascular

Table 1. Classification of liver failure [O`Grady et al., 1993]

	Hyperacute liver failure	Acute liver failure	Subacute liver failure
Prognosis	moderate	poor	poor
Encephalopathy	yes	yes	yes
Duration of jaundice {days}	0-7	8-28	29-72
Cerebral oedema	common	common	infrequent
Prothrombin time	prolonged	prolonged	least prolonged
Bilirubin	least raised	raised	raised

Table 2. Staging of hepatic encephalopathy

Grade	Clinical symptoms	Outcome {survival %}
I	Slow mentation	70%
II	Inappropriate behaviour {confusion, euphoria} or drowsiness	60%
III	Permanent somnolence	40%
IV	Coma	20%

Table 3. Clinical signs of raised inracranial pressure

1. Systolic hypertension {paroxysmal or sustained}
2. Bradycardia
3. Increased muscle tone, opisthotonos, decerebrate posturing
4. Pupillary abnormalities {sluggish or absent response to light}
5. Brain stem respiratory patterns, apnoea

lines are common sources of bacteraemia in these patients. In a study by the "Lever Unit" of Barcelona's University Hospital, the isolated microorganisms are predominantly Gram-positive bacteria {70%} with a striking incidence of Staphylococcus aureus {36%} followed by Gram- negative bacteria, especially E. coli. Other groups reported Gram-negative bacteria as being the leading cause of infection.[35]

Fungal infections complicate the course of ALF in about a third of patients[36] and are predominantly due to Candida albicans. They do present late in the course of illness and should be suspected if deterioration in the level of consciousness, persistent leukocytosis over 20 x 10^9/L or pyrexia unresponsive to broad spectrum antibiotics develop after an initial improvement.

The role of antibiotic prophylaxis with or without selective gut decontamination has been studied. The most important reservation about the early use of wide spectrum antimicrobials such as ceftazidime and flucloxacillin is the development of multiresistant bacterial infection.

Selective parenteral and enteral antimicrobial regimen {SPEAR}, has shown a 30% reduction in the overall frequency of infection compared with those who received antimicrobial treatment when clinically indicated.[37] Furthermore, there was no statistically significant difference in the rates of infection between patients receiving SPEAR and those given antibiotics on admission.

The administration of oral non-absorbable antibacterials {Rifacol} for selective decontamination of the gut does not appear to improve survival in patients already receiving prophylactic systemic antibacterials.[38]

Coagulopathy

Coagulopathy is almost universal in ALF. It is the result of inadequate synthesis enhanced consumption of clotting factors and their inhibitors, and platelet abnormalities. Prothrombin time is one of the best indicators of changing liver function, and therefore its prophylactic correction is contraindicated,[39] especially if the patient is going to be considered for OLT. Prothrombin time may be influenced for at least 24 h after administration of fresh frozen plasma {FFP} and under those circumstances, measurement of factor V or VII should be considered.[40] Severe haemorrhage requiring blood transfusion is rare, with a decreased incidence from 30% to 10% in recent years.[41,42] In particular, the incidence of bleeding from the upper gastrointestinal tract, which is the most common site of bleeding significantly reduced by the use of H_2 antagonists and sucralfate.[43,44] Prophylactic use of FFP does not improve outcome,[45] and correction of coagulopathy with FFP or other specific factor concentrates is only indicated in cases of significant bleeding, before surgery and in invasive procedures such as liver biopsy or insertion of an ICP catheter. Central venous catheterization of the internal jugular vein is safer than the subclavian vein and does not need correction of coagulopathy.[46]

Renal manifestations

Oliguric renal failure complicates paracetamol-induced ALF in 70% of cases with grade 4 encephalopathy, as well

Table 4. Indications for transplantation in acute liver failure {King`s College Hospital criteria}

Paracetamol	Non-paracetamol
Arterial ph < 7.30 or H^+ >50	Prothrombin > 100 s
{ph < 7.25 if receiving NAC}	
OR{in the absence of the above}:	
All three of the following :	Any three of the following :
1. Prothombin time > 100 s	1. Unfavourable aetiology {i.e. drugs, non-A, non-B
2. Serum creatinine > 300 μmol/L	2.Jaundice > 7 days before encephalopathy
3. Grade 3 / 4 encephalopathy	3.Age < 10 or > 40 years
	4.Prothrombin time > 50 s
	5. Serum biltrubin >300 μmol/L

Table 5. Survival after Acute Liver Failure confirm the aetiology. Survival after Hepatic encephalopathy grade III-IV (John O´ Grady. Acute Liver Failure. Comprehensive Clinical Hepatology.2000)

Cause	Rate percent (%)
Wilson	1
Drug hepatitis	2,5
Seronegative hepatitis	20
Hepatitis B	38
Paracetamol overdose	56
Hepatitis A	67
Hepatopathy of pregnacy	98

as in 30% of non-paracetamol cases. In non-paracetamol cases,[28,47-49] renal failure appears early after severe liver injury with rising serum creatinine and oliguria[50]. It is usually associated with advanced encephalopathy and often fungal infection, and is a predictor of poor outcome[50]. Renal replacement therapy is still the treatment of choice when creatinine is above 400 μmol/L, in cases of fluid overload, acidosis, hypercalaemia and in conjunction with mannitol administration when oliguric renal failure develops.

Cardiovascular manifestations

The clinical syndrome produced in ALF resembles that of septic shock in many aspects; it is characterized by hypotension due to low systemic vascular resistance with increased cardiac output.[51]

The haemodynamic abnormalities of ALF begin with microcirculatory disturbances that lead to abnormal oxygen transport and utilization. The management consists of fluid replacement under monitoring of pulmonary artery wedge pressure and cardiac output; if fluids fail to restore the circulation, vasopressors are required. Noradrenaline [norepinephrine] and sometimes adrenaline [epinephrine] are the most commonly used vasopressors, while the use of angiotensin 2 is reserved for more refractory cases. Despite the efficacy of vasopressors in maintaining mean arterial pressure, their use is severely limited by the fact that they decrease tissue oxygen consumption[52]. In this respect the coadministration of prostacyclin, a microcirculatory dilator, or of N-acetylcysteine may overcome this adverse effect.

Metabolic changes

Hypoglycaemia is a common manifestation in ALF, due to severe impairment of glucose homeostasis. Metabolic acidosis in paracetamol overdose is independent of renal function and is the most important predictor of outcome[4]. In other aetiologies of ALF, a centrally induced respiratory alkalosis is more common. Other metabolic abnormalities such as hypophosphataemia and hypomagnesaemia are not uncommon and should be treated as required.[49]

ALF is characterized by profound metabolical dysfunction due to loss of liver cell function.. Parenteral nutrition is desirable in such cases. Glucose is given for the prophylaxis or treatment of hypoglycemia (2-3 g kg^{-1} d^{1}) and lipids (0,8-1,2 g kg^{-1} d^{1}) as energy supply. Amino acid use to support protein synthesis has proven unhelpful.[85]

Haematologic manifestations

A rare but life-threatening condition is hepatitis-associated aplastic anemia (HAA).

In this syndrome, marrow failure follows the development of ALF. This entity which is mediated by immunological mechanisms occurs either concurrently or within 6 months of an ALT increase to at least five times the upper limit of the reference range. The treatment include hematopoietic cell transplantation and immunosuppressive therapy.[77]

Pulmonary complications

The main pulmonary complications include pulmonary edema, pneumonia and tracheobronchitis. Although the exact mechanisms are not clear enough, it is believed that central mechanisms, vascular lesions caused by metabolic and toxic factors, and increased susceptibility to infections are the leading pathogenesis in this domain of complications.[84]

PHARMACOLOGICAL THERAPY

Except for the symptomatological treatment of ALF mentioned above, there are also specific therapies which conform the aetiology.

Penicillin G is used early at the course of Amanita's mushrooms ALF.

Lamivudine, although controversial is used in ALF caused by HBV. Intravenous acyclovir is given to HSV- related hepatitis (mostly seen among immunosuppressed and pregnant patients). Finally, plasmapheresis and chelation therapy is given to ALF caused by Wilson's disease.

TRANSPLANTATION IN ALF

OLT is the most effective means of therapy for patients with ALF whose prognostic evaluation suggests a < 20% chance of survival with medical management alone. NIDDK reported a 70% patient survival rate in the early post-transplant period and a 60% graft survival rate at 3 years.

In Greece there are about 100 cases of ALF per year. Often there is a delay in the diagnosis and patient's referral to a specialized center. The decision to offer OLT in such patients is quite difficult. If the patient recovers without the need for OLT, with pharmacologic therapy only, his liver will return normal. On the other hand, transplantation implies the need for lifelong immunosuppression. Under this circumstance the correct timing for reference to a specialized center is "a must". This should be done if: Prothrombin time is more than 20 sec, (INR >2), bilirubin > 100 μmol/L, hypoglycemia, encephalopathy and/or developing renal failure.[91] The selection of patients that should be referred to a transplant center for OLT is a crucial medical decision and is currently based on two sets of prognostic indicators which can be applied relatively easily. The first set comes from King`s College Hospital in London {Table 4}.[4]

The second set, from Clichy, France, was based on patients with viral ALF who had developed confusion or coma, and is a combination of grade 3 or 4 encephalopathy with the levels of factor 5 in blood and age[25]. Both sets were tested retrospectively in 81 patients with ALF, and the reported results were poorer than in the original report.[53]

MELD score in ALF

An important issue is the time of listing a patient with ALF for a super-urgent OLT.[54-55] The time needed for a suitable donor organ to become available can be as long as 48 h, and because ALF patients may deteriorate suddenly, they should be evaluated with a view to being listed for OLT as early as possible.

Absolute contraindications to OLT include uncontrolled intracranial hypertension where permanent neurological damage and/or brain death is likely, refractory systemic hypotension, sepsis and adult respiratory distress syndrome. The presence of ongoing psychiatric illness and social or behavioural problems that may affect compliance to treatment post-OLT especially in cases with suicidal intent, may be considered as relative contraindications to OLT.

The increasing shortage of human organs for transplantation has resulted in an intensified effort to maintain patients` stability while awaiting OLT. In this aspect several modalities have been proposed, such as total hepatectomy, mild hypothermia, xenotransplantation, heterotopic liver transplantation, extra-corporeal human or animal allograft as well as hepatocyte transplantation and administration of hepatic growth factors.[58,59]

There is increasing evidence that removal or devascularization of the failing liver stabilizes the clinical condition of patients with ALF[60-62]. Total hepatectomy with portacaval shunt is said to correct cerebral oedema and haemodynamic abnormalities, providing a window of stability in the critically ill patient awaiting OLT. This window is limited to 24-36 h. A number of centres have used total hepatectomy as a form of temporary treatment to delay clinical deterioration. The total hepatectomy is potentially life-saving, but has only short-lived beneficial effects.

LIVING RELATED LIVER TRANSPLANTATION IN ALF

BIOARTIFICIAL LIVER

In view of the potential for complete recovery of native liver in ALF, a liver support system to bridge the time to recovery would theoretically be the best treatment option. Several biological and non-biological liver support systems have been developed. Non-biological systems include haemodialysis, charcoal and resin haemoperfusion, blood and plasma exchange, and have been extensively used but have not been proved effective enough to alter the course of illness[65-67]. Biological liver support systems using liver tissue were first tested several years ago, but it was not until recently that they were further developed and clinically tested for their ability to synthesize coagulation factors and proteins and to detoxify blood. A bioartificial liver {BAL} or extracorporeal liver assist device {ELAD} consists of a mass of liver cells placed in a hollow fibre bioreactor perfused by the patient`s own blood or plasma. Several systems have been developed, using different cell lines {primary mammalian hepatocytes or immortalized hepatocyte lines}, with or without a plasmapheresis system connected to the bioreactor.[69-72] Clinical results so far have been disappointing.

MARS (Molecular Absorbent Recirculating System) an extracorporeal albumin dialysis machine that removes albumin-bound substances (benzodiazepines, billirubin, bile acids, cooper, protoporphyrin) and water –soluble substances (ammonia, Urea, creatinine, IL-6)[88] is potentially beneficial as a scavenger for substances with an injurious role in liver failure. It has been used in the treatment of liver failure to enable native liver regeneration or as a bridge to liver transplantation in acute or chronic cases.[87] Predictors of survival in MARS treated patients are aetiology of liver failure, grade of encephalopathy, factor V and ALT levels.[87] Positive prognostic factors after treatment with the MARS method include the Glasgow Coma

Scale score >11, intracranial pressure <15 mm Hg, lactate level< 3mmol /L, TNF-a <20 pg/m, IL- 6< 30 pg/ ml and a hemodynamic change from hyperkinetic to normal kinetic state.[90]

In conclusion ALF, despite all the advances in intensive care and the development of a variety of new treatment modalities, remains a condition with high mortality, which is best managed in specialist centers. Of the variety of new treatments, OLT appears to be the only one that has made a significant impact so far in improving outcome. Bioartificial liver support systems and hepatocyte transplantation, although still at an early stage of development and clinical application, are new and exciting treatment options which may change the management of acute liver failure in the future.

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