Clinical Reviews

Recognition and Early Management of Acute Liver Failure

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Abstract

Acute liver failure (ALF) is a rare but frequently devastating condition, with the potential to disable virtually every organ and system in the body. However, if it is recognised swiftly, and if its specific complications are managed actively, a good outcome can be achieved, especially in the young. The first hours are crucial in stabilising the patient, optimising metabolic and cardiovascular parameters, and reducing the risk of permanent neurological injury or brain death. Simultaneous liason with a specialist unit will allow a planned, safe transfer and access to definitive treatment such as liver transplantation, should the patient require it.

This review highlights the clinical and laboratory features of ALF, emphasises aspects of early treatment which will aid short term survival, and makes recommendations concerning safe transfer to a liver unit. Information is also given to aid early counselling of relatives and next of kin.

Keypoints

- ALF should be considered in any patient with an unexplained reduction in conscious level
- ALF causes death by cerebral oedema with brain herniation, cardiovascular collapse and hypoglycaemia
- Aggressive fluid resuscitation is required, however sudden changes in serum sodium are dangerous; large volumes of dextrose should be avoided, saline is perfectly safe
- Vasopressor support should be instituted if blood pressure remains low after adequate fluid resuscitation; cerebral perfusion is of paramount importance
- All patients with ALF should be discussed with a liver unit, even if 'transplant criteria' are not met; these indicate advanced disease
- Encephalopathy in ALF is progressive; early, elective intubation is preferable to emergent intubation
- Specific and practical measures can be taken to reduce the risk of cerebral oedema

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Introduction

The cardinal features of ALF are encephalopathy (ranging from subtle changes in sensorium to coma) and coagulopathy, with or without jaundice.[1] Hypoglycaemia and lactic acidosis are subsidiary clues to a profound reduction in liver function. A large proportion of hepatocytes must be destroyed for these features to develop. Twenty-fold elevations of the transaminases aspartate aminotransferase (AST) and alanine aminotransferase (ALT) suggest hepatocellular necrosis, but do not necessarily imply ALF. It is the onset of encephalopathy that confirms ALF, as opposed to hepatocellular necrosis.

ALF by definition excludes patients with established chronic liver disease (such as those with decompensated cirrhosis), and it does not include patients with alcoholic hepatitis (AH). Despite the recent onset of jaundice and even encephalopathy in AH, over 50% will be cirrhotic already, and prone to associated complications such as variceal haemorrhage, spontaneous bacterial peritonitis and hepatorenal syndrome. Cirrhosis and AH will be covered in a future article.

The delay between the onset of illness (classically the onset of jaundice or symptoms), and the development of encephalopathy may be used to categorize liver failure.[2] If this delay is less than 7 days, the term ***hyperacute liver failure*** is used; a delay of 8-28 days is termed ***acute liver failure***; 5 to 26 weeks represents ***subacute liver failure***. Somewhat paradoxically the hyperacute type confers the greatest chance of spontaneous survival, although global organ dysfunction including cerebral oedema is far more likely. The progress of illness can accelerate at any time, and a long prodrome should not delay specialist assessment.

The major threats to life in the short term following the onset of ALF, are the consequences of reduced conscious level with an unprotected airway, cerebral oedema with tentorial herniation, and cardiovascular collapse. Unrecognised hypoglycaemia can also cause permanent brain injury, and should always be excluded as a cause of altered conscious level. Serious bleeding due to coagulopathy is not particularly common, and the administration of clotting factors or plasma is not usually recommended, given the great importance that the INR measurement plays in determining the patient's prognosis.

Clues to aetiology: rarely a textbook exercise

Although important in determining prognosis and definitive management, the cause of ALF is often difficult to establish in the initial stages.

Laboratory evidence of viral infection, autoimmune disease or more unusual causes may not become available for several days. Nevertheless, features in the history can provide vital clues, and these may be lost should the patient deteriorate and require intubation. Box 1 summarises the causes of ALF.

Drug-induced ALF

It is important to determine if excess paracetamol has been ingested, intentionally or otherwise, because of the availability of an antidote (N-acetylcysteine) and because the prognostic markers used to identify those patients who will benefit from liver transplantation (LT) are quite different. Rapid onset of illness without prodrome, often in association with marked renal dysfunction and a spectacular transaminitis are the hallmarks of paracetamol induced liver failure; this accounts for over 50% of ALF cases in the UK. The timing of ingestion is important; the possibility of a 'staggered' overdose, over several days, should be actively excluded. In this scenario paracetamol levels can be deceptively low.

Even modest overdoses (which are frequently unintended, or even iatrogenic) can be harmful, especially if on a background of malnutrition, or enzyme induction by chronic alcohol ingestion or medication (eg. anticonvulsants).

The recent introduction of a drug may suggest an idiosyncratic reaction (Box 2). Specific enquiries about the use of herbal remedies should also be made, as a number of constituents have been associated with ALF[4] (Box 3). Most such reactions are idiosyncratic.

Paracetamol	54%
Seronegative hepatitis	17%
Hepatitis A or B	14%
Drug reaction	7%
Other causes	8%

There is significant geographical variation; for instance paracetamol accounts for only 2% in France, and viral hepatitis causes 55% of cases in Japan. In India Hepatitis E is responsible for 33% of cases.

Other causes:
Viral: cytomegalovirus, herpes simplex, Epstein-Barr
Metabolic: Wilson's disease, Reye's syndrome
Vascular: Budd-Chiari syndrome, ischaemic hepatitis
Pregnancy related: acute fatty liver, HELLP/toxaemia of pregnancy
Neoplastic: lymphoma, gross metastatic infiltration
Toxic: *aminata phalloides* mushroom

Box 1. Causes of ALF in UK[3]

Well recognised or common:
Paracetamol, isoniazid, rifampicin, NSAIDs, sulphonamides, sodium valproate, carbamazipine, Ecstasy

Less common:
Phenytoin, allopurinol, MAOIs, ketoconazole, methyldopa, amiodarone, tricyclic antidepressants, gold, propylthiouracil

The volatile anaesthetic agents halothane, isoflurane and enflurane have also caused ALF

Box 2. Drugs associated with ALF

Herbal remedy (toxic agent)	Usual use
Mediterranean glue thistle *(Atractylis gummifera)*	Multiple
Impila *(Callilepsis laureola)*	Zulu remedy, various
Chapparral leaf (*Larrea tridenta*)	Multiple
Chinese herbal medicines *(number of toxic agents)*	Multiple
Germander *(Neocleradone diterpenes)*	Weight reduction
Kava-kava *(Kava-lactone)*	Anxiolytic
Pennyroyal *(Pulegone)*	Abortifacient
'Mediterranena traditional remedy' *(Teucrium polium)*	Anti- *inflammatory*
Ma-huang *(ephedrine)*	Weight reduction

Box 3. Selected herbal remedies and dietary supplements reported to have caused fulminant hepatic failure or significant hepatocellular necrosis[4]

Infective hepatitis

Return from an area of high endemicity may suggest infection with a faeco-orally transmitted virus such as hepatitis A or E. Pregnant women who contract hepatitis E are at far greater risk of ALF, and mortality rates of 40% have been reported. Risk factors for blood borne virus transmission (eg. intravenous drug use, unprotected sexual intercourse, acupuncture, the possibility of poorly sterilised equipment when receiving hospital treatment abroad) will raise the possibility of hepatitis B infection (accounting for over 10% of cases in the UK).

Pregnancy

Presentation in the third trimester of pregnancy suggests acute fatty liver or a pre-eclampsia/eclampsia related syndrome. HELLP (haemolysis, elevated liver enzymes, low platelets) describes the features often seen in pre-eclamptic liver dysfunction, however the syndrome evolves in a variety of ways, the underlying vascular injury sometimes leading to hepatic infarction, haemorrhage or even rupture.

Ischaemic hepatitis

Massive hepatocyte loss may occur following circulatory disturbances or episodes of hypoxia, often in the context of pre-existing cardiac dysfunction, so called 'ischaemic hepatitis'.

Malignancy

Malignant infiltration, through replacement of normal liver tissue, can lead to ALF, and is usually seen in the elderly; lymphoma is a well recognised cause, normally presenting with increased alkaline phosphatase (ALP), although transaminases may also be significantly elevated.

Wilson's disease presents a unique diagnostic problem, in that most patients (typically young) presenting with the features of ALF in fact have established liver fibrosis. Breaking the rule concerning the absence of prior liver disease, these patients are managed as though they have ALF, and usually require LT. Such patients may therefore have stigmata of chronic liver disease, including ascites and

splenomegaly. Clues to diagnosis are family history, Kaiser-Fleischer rings and acute, sometimes severe, Coombes-negative haemolysis. The rings are present in about 50% of patients presenting acutely, but require slit lamp examination for accurate identification.

Autoimmune hepatitis (AIH), like Wilson's, can present acutely after a long subclinical course. These patients are typically young women, and may have other immune mediated diseases (eg. diabetes mellitus, thyroid dysfunction, coeilac disease). Raised gamma globulins are typically found, and anti-smooth muscle or anti-nuclear antibodies may be present.

Accidental poisoning by the Death Cap mushroom *(Amanita phalloides)* is rare in the UK but more common in continental Europe. A history of ingestion should be sought, and abdominal symptoms (nausea and vomiting, diarrhoea and cramps) may predominate. Silymarin (the major ingredient of milk thistle) is advised as an antidote, however LT is often required.

Seronegative hepatitis is the term used to define those patients in whom, even after comprehensive testing, including biopsy, the cause remains unclear. This commonly affects middle aged women, and follows a less acute course. It has a poor prognosis.

Recognizing the syndrome: clinical, laboratory and radiological features

Clinical Findings

I. Encephalopathy

Initially alert patients can slide through each grade of encephalopathy in the space of an hour or two. Euphoria, fluctuating confusion, or slurred speech (grade I), followed by drowsiness with the continued ability to converse (grade II) leads to sleep from which the patient can be roused but without being able to hold a conversation, or extreme agitation or violence (grade III) before becoming unrouseable and comatose (grade IV). 90% of patients in grade III will go on to grade IV. Repeated assessments are therefore vital.

II. Cerebral oedema

Cerebral oedema is common in ALF, affecting 25-35% of those with grade III , and 65-75% of those with grade IV encephalopathy. Determining its onset without invasive cerebral monitoring is extremely difficult. The classic signs of intra cranial hypertension (ICH), such as papilloedema, bradycardia with hypertension and respiratory arrest, signify advanced cases.

Earlier signs include bursts of systemic hypertension, a tendency to bradycardia and sluggish papillary reaction or dilation. Fixed pupillary dilation, generalised hypertonicity and decorticate or decerebrate posturing, arrhythmias, hypotension and large temperature changes are signs of impending death.

III. Abdominal signs

Tenderness in the right upper quadrant is a common but non-specific finding. A liver edge is frequently palpable, although a shrinking liver (through ongoing hepatocyte loss) is a poor prognostic sign. A palpable liver may indicate infiltration by tumour, or be suggestive of chronic disease with cirrhotic change (in Wilson's for instance). Congestion, through hepatic vein obstruction in Budd Chiari syndrome (BCS), or due to cardiac failure, may also cause hepatomegaly.

The presence of ascites does not exclude ALF as those patients with a more gradual course may accumulate fluid. Fluid is to be expected in BCS, and is usually an exudate.

Laboratory tests

The tests recommended for patients with suspected liver failure are summarised in Box 4.

I. Coagulopathy

Haemostatic derangements are universal in ALF, and the extent of coagulopathy is of prime importance in deciding who will benefit from LT. Prothrombin time (PT) and INR are the most frequently employed measures, prothrombin being a senstitive marker of protein synthesis in the liver. An INR of over 1.5, in the context of liver injury, is enough to suggest significant synthetic dysfunction.

The coagulopathy in ALF is also reflected in prolonged activated partial thromboplastin time and low fibrinogen levels. This indicates a multifactorial basis to the coagulopathy, which is not fully understood. Accelerated fibrinolysis, disseminated intravascular coagulation and reduced fibrinogen production may all play a part.

In the absence of other laboratory clues a raised INR may be the only indication of liver dysfunction.

INR/PT and FBC
Urea & Electrolytes/Liver function tests
Phosphate/Calcium/Magnesium

Arterial blood gas with lactate
Arterial ammonia
Amylase

Diagnostic
Paracetamol level
Toxicology screen
Hepatitis screen (anti-Hep A IgM, Hep B Sag, anti-Hep B Core IgM); anti-Hep E IgM/G if appropriate history
Caeruloplasmin/urinary copper excretion
Autoantibodies (anti nuclear~, anti smooth muscle~, anti liver kidney~) and immunoglobulins

Additionally,
HIV and hepatitis C status will be necessary if LT is to be considered

Box 4. Ideal laboratory investigations in ALF

II. Liver function tests

Hepatocellular necrosis results in massive elevations in AST and ALT, although the value of these markers does not relate to the severity of dysfunction. Values over 40 times the upper limit of normal are characteristic. Following an acute and finite insult (eg. ischaemia, paracetamol) a daily fall is expected, however a steady fall can also indicate the inexorable loss of liver mass due to ongoing damage (eg. drug reaction, autoimmune or viral hepatitis). AST is not specific to hepatocytes, and a disproportionately high value should prompt investigations into rhabdomyolysis (CPK, myoglobinuria) .

Alkaline phosphatase and gamma glutaryl transferase are not useful in recognising ALF, although a very cholestatic profile may accompany certain drug reactions (e.g. penicillin-clavulanic acid). In Wilson's disease ALP is often normal or low, for reasons unknown.

III. Electrolytes

Hyponatraemia and hypokalaemia are common, the latter especially requiring attention to avert arrhythmias. Hyponatraemia becomes especially relevant in the prevention and management of cerebral oedema. Aggressive dextrose infusions, on the misguided assumption that patients with liver disease should not receive saline, can lead to profound drops in serum sodium, increasing the risk of cerebral oedema.

Profound hypophosphataemia also occurs, and needs correcting. Interestingly low phosphate may predict liver regeneration through the avid hepatocyte uptake for ATP production. Hypomagnesaemia can also occur after aggressive resuscitation, and predisposes to cardiac arrhythmias.

IV. Arterial Blood Gas Analysis

The degree of acidosis, and the contribution made by lactate to the base deficit, is as important as the information given concerning oxygen and carbon dioxide exchange. Hyperlactataemia results from impaired clearance in the liver and increased production in the poorly perfused periphery (through anaerobic respiration). The degree of elevation has been shown to have predictive value in ALF (see 'Recognizing those with poor prognosis').

Oxygenation is rarely problematic in the very early phase of ALF, although significant respiratory failure can ensue over the following 2 to 3 days. ALF is a cause of acute respiratory distress syndrome (ARDS), and if severe the chance of LT can be prejudiced. Centrally driven hyperventilation may result in hypocapnia and respiratory alkalosis, and this may be exacerbated by hypokalamia.

Radiology

An urgent ultrasound up is helpful, with a few provisos. Parenchymal heterogeneity, even nodularity, in the liver of a patient with encephalopathy and coagulopathy would classically indicate cirrhosis. However these changes can be seen in ALF, particularly in those with a subacute course, due to foci of hepatic regeneration. Such findings should not therefore exclude the diagnosis. Ascites may also be compatible with the diagnosis. Evidence of portal hypertension (such as recanalisation of the umbilical vein, or splenomegaly) would not be expected in ALF however, unless Wilson's disease or AIH were being considered.

An appearance suggestive of infiltration or multiple metastases may prompt an urgent CT scan, which may avert an unnecessary transfer.

Absent or reduced flow in the draining hepatic veins will support Budd-Chiari syndrome. Abnormalities in the portal vein are more unusual, but may help explain an ischaemic pattern of injury.

Management

For the best chances of survival patients with ALF require care in a specialised unit where liver transplantation can be undertaken if required. To reduce the risk of death in the referring hospital, or in transit, specific measures to minimise circulatory instability, cerebral oedema and electrolyte fluctuations are necessary. Some aspects of early management merge with those that will be instituted in the referral unit, or in the local ICU should a delay to transfer occur.

Circulation

Hypotension in ALF arises from inappropriate vasodilatation, resulting in relative hypovolaemia. Fluid resuscitation with colloid or saline will frequently improve the situation. 2–3 litres may be required initially. Young patients are unlikely to manifest evidence of fluid overload. Despite this vasopressor support with norepinephrine is often needed (starting dose of 0.1μg/kg/min). Adequate systemic blood pressure becomes increasingly important when raised ICP co-exists, to maintain cerebral perfusion pressure.

An arterial catheter should be inserted, together with reliable, large bore venous cannulae. Central venous catheterisation is frequently avoided due to the coagulopathy However internal jugular line insertion by an experienced operator or femoral venous lines are generally safe.

Invasive cardiovascular monitoring helps direct fluid and vasopressor therapy. The PiCCO system ('pulse-induced contour cardiac output') employs an easily inserted femoral arterial line, which in conjunction with cold boluses injected through an internal jugular veinous line gives useful information about cardiac index, intravascular blood volume and lung water. This intervention, or similar, may be indicated if care on the ICU is required before transfer to optimise fluid therapy.

Cerebral Oedema

The risk of cerebral oedema is greater in those with rapid onset (hyperacute) illness, the young (who have less 'space' within the fixed cranium), those with sepsis, and those with hyponatraemia. A very high blood ammonia (>150mmol/L) also predicts cerebral oedema.

Recognition and Early Management of Acute Liver Failure

Accurate estimation of ICP is only possible with invasive monitoring, and this is unlikely to be initiated outside a tertiary unit. Even without clinical signs of raised ICP, measures can be taken to reduce the risk of onset in those who appear at risk. High quality evidence concerning the management options in this condition is hard to come by, given the great difficulty in undertaking randomised trials.

Patients with sufficient encephalopathy to be at risk of ICH will have been intubated for airway protection. Sedation is required, and Propofol, which reduces metabolic demands in the brain and may reduce ICP,[5] is the favoured agent (50 to 150 mg/hr).

Additionally, the following factors can be addressed:

- Posture: positioning the head in the midline, with the angle of the body 20°degrees from horizontal will aid cerebral venous outflow.
- Normocapnia [pCO2 4.5-5 kPa]: the traditional approach of hyperventilation and low pCO_2, although effective in short term reduction of cerebral blood flow and ICP, can lead to cerebral vasospasm and increased risk of brain injury.
- Body temperature: avoid fever
- Avoidance of stimulation: surges in ICP are seen in monitored patients who are exposed to stimuli such as loud noise, suctioning and excessive movement.

If pupillary abnormalities (progressive dilation, or dilation with sluggish reaction to light) or other neurological signs evolve, and tentorial herniation appears imminent, specific measures can be employed:

- Mannitol: 0.5g/kg boluses may be administered and repeated, but serum osmolarity should be monitored so that 320mosm/L is not exceeded. To prevent fluid overload a 500ml diuresis (or negative balance if being haemofilitered) should be obtained after each bolus.
- Hypothermia: a core temperature of 32°-33°C, achieved with active cooling, can bring about prolonged reductions in ICP.[6] There are concerns about increased susceptibility to infection, cardiovascular instability and bleeding with hypothermia of this degree. In practical terms <35°C would seem a sensible compromise.
- Hypernatraemia: serum sodium in the range 145-155mmol/L has been shown to have a beneficial effect on ICP.[7] This target can be achieved with continuous central infusion of 30% NaCl, with regular monitoring. A slow bolus of 20ml 30% sodium chloride may also be administered for possible surges in ICP.

Following transfer, an extradural pressure monitor (or 'bolt') may be inserted if ICH is suspected, or if there are high risk features. Indomethicin may be considered if the measured ICP is resistant to first line approaches. Their use would not normally be advised outside a specialist unit.

Lactic acidosis and renal failure

Even in the absence of established renal failure, renal replacement therapy is often required for the management of acidosis, which may be profound. Continuous veno-venous haemofiltration through a vascular catheter is the preferred method as it has a less detrimental haemodynamic impact.[8] The dialysate fluid should be bicarbonate buffered, given the inability of the diseased liver to metabolise lactate or acetate. To bring about a significant benefit in metabolic state a moderate to high plasma exchange rate is sometimes required (4-6L per hour). Anticoagulation may not be required, however epoprostenol ('*Flolan*') is the preferred agent should filter clotting occur.

Sepsis

80% of patients with ALF develop positive bacterial cultures, and in 30% fungal infection is reported.[9] ALF is highly immunosupressing, and the need for ventilation and vascular lines raises the risk of infection. It is standard practise to give all patients who fulfil poor prognostic criteria prophylactic broad spectrum anti-bacterial and anti-fungal cover (eg. Tazocin 4.5g tds iv, Fluconazole 50mg od po/iv.)

Coagulopathy

Prophylactic repletion of clotting factors has not been shown to improve outcome, and will make prognosis more difficult to judge. Thrombocytopenia correlates better with bleeding episodes, and can be corrected without concern for the important prognostic indicators. Disseminated intravascular coagulation is likely to have a role in the low platelet counts seen in some cases, and treatment with cryoprecipitate may be indicated if fibrinogen is low with evidence of bleeding.

N-acetylcysteine (NAC)

In paracetamol poisoning there is a well established protocol for prescribing NAC (150mg/kg over 15 minutes, 50mg/kg over 4 hours, 100mg/kg over 16 hours). There is also a definite role for NAC in delayed presentation, even following the onset of liver dysfunction. Reductions in the onset of encephalopathy, and a survival benefit, have been shown.[10] NAC should therefore be given if paracetamol poisoning is a possibility, whatever the time scale.

Even without evidence of paracetamol induced liver injury NAC may be beneficial, improving liver perfusion and oxygen transport. Its use, although not routine, has become common in non-hyperacute cases of liver failure, and may be recommended after consultation with a liver unit (150mg/kg over 24 hours, ongoing prescription). A large randomised trial of NAC in non-paracetamol associated liver failure is under way.

Adrenocortical dysfunction

The vasopressor sparing effect of steroids has been recognised in circulatory shock for some time, and evidence exists for their use in ALF. Adrenocortical insufficiency, demonstrated with abnormal short synacthen tests, was found in 62% of ALF patients, the 60 minute increment being significantly lower in those

requiring norepinephrine, and especially in those who died or required LT. Administration of a supraphysiologcal dose (300mg hydrocortisone/24hrs) was associated with a lower vasopressor requirment.[11]

A short synacthen test followed by empirical hydrocortisone is therefore appropriate in the face of rapidly escalating vasopressor dose.

Glucose Control

The possibility of hypoglycaemia must remembered; hourly blood glucose measurement is recommended. A continuous 10% dextrose infusion will minimise this risk. Conversely, hyperglycaemia has been associated with a higher incidence of ICH,[12] and should be avoided.

Prophylaxis against GI bleeding

Patients with ALF have all the factors that have been shown to be associated with GI bleeding risk in the critically ill (mechanical ventilation, renal failure, sepsis), and in addition a profound coagulopathy. Overt bleeding will require replenishment of platelets and clotting factors. Prophylaxis with an IV proton pump inhibitor or an H2 antagonist is recommended.

Identifying patients with poor prognosis & when to refer

Although ALF may resolve spontaneously with supportive treatment, a proportion will die without transplantation. Identifying these patients is of vital importance. Intuitively those with more severe coagulopathy and encephalopathy will do worse; however other factors are important. The Kings College criteria (Box 5) are based on an analysis of 588 patients with ALF who were managed medically between 1973 and 1985. Factors associated with non-survival were identified, and a model to guide decision making was constructed; this was validated on a further cohort between 1986 and 1987.[13] More recent work has highlighted the prognostic value of persistent metabolic acidosis and a high arterial lactate following adequate volume resuscitation.[14] The criteria for paracetamol induced and non-paracetamol induced ALF are quite different.

Clearly, discussion with and transfer to a liver unit should **not** be delayed until these criteria are met. Early referral of patients whose markers appear to be progressing towards these levels will enable transfer to be planned as appropriate, and also facilitate discussions about pre-transfer management. This is particularly true for Paracetamol induced liver dysfunction, in whom liver failure may occur quickly. In such cases, if only one of the criteria is being approached (eg. creatinine has reached 200μmol/L, the patient becomes oliguric, or the INR reaches 3 and continues to rise), referral is warranted.

Paracetamol related cases:

- pH < 7.3 following volume resuscitation and >24 hours post ingestion

or

- PT > 100 (INR >6.5) plus creatinine > 300 mcmol/l plus grade III/IV encephalopathy within a 24 h time frame

Non-paracetamol related:

Encephalopathy

with INR > 6.5 (PT > 100)

or, with THREE of the following:

- age < 10 yrs or > 40 yrs
- jaundice for > 7 days prior to the development of encephalopathy
- serum bilirubin > 300 mcmol/l
- INR > 3.8 or PT > 50 seconds
- aetiology: non A non B or drug induced

Strongly consider transplantation in paracetamol related cases if arterial lactate >3.5 mmol/l after early fluid resuscitation.

Box 5. King's College Criteria

Liasing with the liver unit

Before contacting the liver unit it is important to have the relevant information to hand; the following should provide a useful checklist.

- Likely aetiology (if known)
- Timing and magnitude of initial insult (e.g. time / quantity of paracetamol overdose)
- Serial INR measurements (and timing in relation to initial liver insult)
- Renal Function (urea, creatinine and potassium) and peak ALT /AST
- Acid-base status (including lactate)
- Circulatory status: blood pressure, fluid / vasopressor requirements, urine output
- Ventilatory status: respiratory rate, pO2, etc
- Neurological status: conscious level, grade of encephalopathy, pupil responses

Ensuring Safe Transfer to the Liver Unit

Airway protection

Most patients with ALF will require intubation for transfer, even if in a low grade of encephalopathy at the

Cardiovascular:
Arterial line, colloid/crystalloid (avoid large volumes 5% dextrose), norepinephrine (made up prior to departure, eg. 5mg/50mls)

Neurological:
Pupil size and response, mannitol 0.5g/kg (eg. 50mls of a 20% bag over 10 minutes), 1% propofol infusion, fentanyl infusion, hypertonic saline after d/w referral unit, if available (eg. 5mls/hr of 30% Sodium Chloride)

Metabolism:
Frequent blood glucose monitoring, 10% dextrose infusion, 50% dextrose to hand
Sodium Bicarbonate if profound acidosis

Ventilation:
Elective intubation almost always required, normal tidal volumes for size, aim for normocapnia

Box 6. Inter-hospital transfer: monitoring, fluids and drugs

outset. Deteriorations can occur rapidly, leading to risk of aspiration or hypoxia during the journey. Simultaneous cardiovascular and metabolic derangement increases the risks of emergent intubation.

Ventilation

Even with paralysing agents, fine tuning of ventilatory parameters with portable units during transfer can be difficult. Normocapnia, obtained with tidal volumes appropriate to weight and size, is desirable.

Circulation

An arterial catheter is ideal. Assuming appropriate fluid resuscitation has taken place, ongoing hypotension should be treated with a vasopressor, as above. It is sensible to take norepinephrine and more colloid with the patient, in case of further deterioration.

Cerebral oedema

Any pupillary changes may herald rising intracranial pressure due to cerebral oedema. In transit this can be managed with appropriate sedation (propofol and an opiate such as fentanyl) and mannitol boluses. Unnecessary movement or other stimulation should be avoided. Core temperature should be kept below 36°C.

Informing the family

In the early stages, accurate assessment of prognosis is very difficult. If transplantation criteria appear to have been clearly fulfilled, and this option has been mentioned to the family, it is important to emphasise the grave nature of the illness, and to emphasise that LT does not equate to a cure. The multi-organ nature of ALF means that patients may succumb to respiratory and cardiovascular complications, or to sepsis.

It is also important that LT is not presented as the only chance of survival. Recovery without LT can occur, and after detailed assessment it may be concluded that the chance of survival with LT is no different to that associated with aggressive medical management. Younger patients fair better during and after major surgery; advancing age, especially if accompanied by cardiac or respiratory co-morbidities, begins to tip the balance against LT.

Survival rates after LT are 60-65% overall, however figures of 75% to over 90% at one year have been reported (in North Amercia), and with increasing expertise such outcomes are increasingly likely to be achieved.[15]

Underlying psychiatric conditions, commonly seen in the context of paracetamol poisoning, do not preclude referral, transfer or LT. Judgments about the ability of the patient to cope with LT and its consequences often need to be made in conjunction with the patient's family, psychiatrist and social worker. Such judgements are usually best taken in the liver unit after detailed evaluation of the patient's medical condition has been undertaken.

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