The Newcastle upon Tyne Hospitals NHS Foundation Trust

Guidelines for the management of Acute Liver Failure
Liver Transplant Unit, Institute of Transplantation, Freeman Hospital

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1 Introduction

All referrals of patients with acute liver injury (ALI) and acute liver failure (ALF) should be discussed with the consultant hepatologist of the week at the first available opportunity and within 24 hours, or urgently in the case of a patient approaching transplant criteria.

2 Criteria for transfer

Every patient is different and should be discussed with the Hepatology Consultant. The following is a rough guide to define criteria for transfer of patients with ALI/ALF:

2.1 Paracetamol:

- Significant hypoglycaemia
- Acidosis (pH<7.3 following resuscitation)
- Lactate >2.5 mmol/L
- Hypotension (MAP <60 mmHg)
- Any grade of encephalopathy
- PT > 50 seconds
- INR/PT rising
- Acute renal impairment (acutely elevated Creatinine 200 umol/L or new onset oligo-anuria) with raised INR (>3).

2.2 Non-paracetamol:

- INR >2
- Any grade of encephalopathy
- Bilirubin >300 umol/L
- Acutely elevated creatinine >133 umol/L on the background of increasing bilirubin or INR.

3 Guidelines on ICU management

This part of the document deals specifically with the ICU management of ALF

3.1 ICU admission criteria

One or more of the following:

- Grade II/III or generally worsening encephalopathy
- Need for mechanical ventilation
- Need for cardiac support
- Need for renal support
- Listed for liver transplantation
- Generally unmanageable on the ward.

Special situation

Patients transferred from another intensive care unit. Prior to acceptance of such patients, discussion must take place between the ICU and the ward teams. In general, these patients should come directly to the ICU but each case will be different. Direct admission to the ICU is required:

- If the patient is coming from another ICU, then unless there is a very good reason, the patient should go directly to Ward 37 ICCU
- If the patient has encephalopathy, impending or established acute renal failure or significantly deranged acid-base balance, the patient must go to ICU even if transferred from a non-critical care ward in the referring hospital.

Good communication between all involved in patient care is vital.

3.2 Investigations

(If not already done on the ward or by the referring hospital)

- FBC, U&E, LFTs, Glucose, Amylase, Creatine Kinase (CK), Ca^{++}, Mg^{++}, PO_4^-
- Clotting profile (including fibrinogen and FDP) 6-hourly
- Group & Save
- Arterial blood gases including lactate levels
- Arterial ammonia (or venous when on general ward)
- Viral Hepatitis serology (as advised by the liver team)
- Other viral serology (CMV, EBV, HSV, Varicella Zoster)
- Autoantibodies, immunoglobulin profile
- Iron studies if indicated
- Septic screen: blood cultures, throat swab, M/CSU, HVS and sputum
- Drug screen: paracetamol and salicylate levels, urine toxicology
- Other tests in specific situations: For example, copper studies (serum and urinary copper & plasma ceruloplasmin) if Wilson's disease suspected, characterised by young patient, previous history of neuropsychiatric illness, typically low Alkaline Phosphatase levels (bilirubin : alkaline phosphatase ratio >2), and evidence of haemolysis. Slit-lamp examination should be sought for Kayser-Fleischer rings.
- Imaging: This will be guided by specific presentation, however, a Doppler ultrasound examination of liver should be routine
- Liver biopsy: should be considered in patients with an unclear diagnosis, particularly in patients with sub-acute presentation of acute liver failure,

and acute on chronic liver failure without known liver aetiology but this will be decided on a case by case basis.

4 Management of Acute Liver Failure

The basic principles of management are to provide supportive treatment until spontaneous recovery of native liver function or the patient is listed for liver transplantation.

4.1 Specific therapy

N-acetylcysteine (NAC)

NAC is a glutathione precursor acting to restore glutathione stores in the treatment of paracetamol-induced ALF, thus limiting formation and accumulation of N-acetyl-p-benzoquinoneimine (toxic metabolite of paracetamol) as well as enhancing non-toxic sulphate conjugation. NAC may also improve systemic haemodynamics, tissue oxygen delivery, and act as scavenger of free radicals and an anti-inflammatory agent [1].

NAC should be commenced at the earliest opportunity, regardless of the blood results and paracetamol concentrations. The Prescott nomogram cannot be applied to staggered overdose. NAC should be considered even in delayed presentations of paracetamol overdose as improved outcome has been reported even when administered more than 24h after ingestion of paracetamol [2]. There is growing evidence of the benefit of NAC even in non-paracetamol aetiologies specifically for those with lower grades of encephalopathy [3].

If in doubt, commence treatment. N-acetylcysteine administration can be life-saving, and adverse reactions and unpleasant side effects are rare.

4.2 Coagulation issues

Prothrombin Time (PT) and International Normalised Ratio (INR) are the most sensitive indicators of liver synthetic function, and are routinely utilised to assess the severity of the liver damage. They provide valuable information regarding disease progression (continuing deterioration or path to recovery), and form the basis for determining prognosis and the need for transplantation. **For patients awaiting a decision RE possible super-urgent listing for liver transplantation, any consideration of administration of clotting factors to correct abnormality needs prior discussion at consultant level, as this may delay the option to consider listing.**

Anecdotally, elevated INR has been linked with significant risk of bleeding, particularly during invasive procedures, such as insertion of lines. Recent evidence, however, points towards a rebalanced or preserved haemostasis in patients with liver disease including those with acute liver failure, with minimal risk of spontaneous and intervention-related bleeding [4].

General principles guiding correction of INR in these patients therefore should take into account the following:

- **Avoid correction unless absolutely necessary**, such as before insertion of intracranial pressure monitor. Insertion of vascular catheters can be achieved with minimal risk without correction of INR
- Low platelets and fibrinogen are bigger risk factors for bleeding and should be corrected
- TEG may provide a global idea of bleeding risk and must be used more widely.

However, the final decision on aspects of clotting correction should remain with the person actually carrying out the procedure.

Recommended level of coagulation correction

For line insertion:

- Ideally the left IJ or right femoral veins should be used for central access in patients likely to be listed for super-urgent liver transplantation. (Large bore by-pass catheters are likely to be needed during transplant and these are best sited in right IJ and left femoral, for logistical reasons)
- Correction of INR is usually not necessary unless clinical bleeding present. Venous lines should be inserted under ultrasound guidance
- Correct platelets to > 30,000 x 10^9/L
- Correct fibrinogen to > 1 g/L.

Wherever possible, lines should be placed as early as possible (preferably whilst the patient is still on the ward and more stable) – consideration should also be given to using a multi- lumen CVC. A vascath should be inserted early so that it can be used as large bore access and for renal replacement therapy when required.

Once on ICU, correction of clotting for line insertion/removal will be at the discretion of ICU Consultant in consultation with the liver team.

4.3 Metabolic / electrolyte issues

Hypoglycaemia is common. Blood glucose should be checked hourly. A background of 40mls per hour 20% dextrose delivered by central venous access may be necessary to maintain blood glucose on admission. Where profound hypoglycaemia occurs, 20 ml boluses of 50% dextrose may be used for rapid correction. Early enteral feeding may help control blood sugar as well as providing GI mucosal protection.

In general, 5% Dextrose MUST be avoided as maintenance fluid as this can lead to severe **hyponatraemia** and worsening cerebral oedema and seizures. Cerebral oedema in ALF is more prominent in hyponatraemic patients [5].

Phosphate, magnesium and other electrolytes should be monitored regularly. Aim to keep sodium 140-145 mmol/L (higher, 145-150 mmol/L, if cerebral

oedema or intracranial hypertension present), phosphate > 1 and magnesium > 0.8.

4.4 Cardiovascular and haemodynamic support

Invasive monitoring / line insertion

All ALF patients on ICU will have central venous access, and an arterial catheter for continuous blood pressure monitoring and frequent blood sampling for blood gas analysis and other tests.

A vascath is also required in the majority of patients and should be inserted early along with other lines. Internal jugular or femoral sites are preferred (see above for choice of side). The subclavian route is avoided because of increased risk of pneumothorax. Use of ultrasound guidance for vascular access, and strict asepsis for all invasive procedure, must be adhered to at all times. *Patients transferred from other hospitals must have their lines replaced at the earliest opportunity*.

Haemodynamic management

ALF shares many features of sepsis and septic shock, and is characterised by a hyperdynamic state with profound vasodilation and hypotension. The broad principles of haemodynamic management revolve around aggressive fluid resuscitation, followed by institution of vasopressors where required. To aid optimal resuscitation some form of cardiovascular monitoring may be necessary. The choice will be dependent upon the current preferred device in the ICU.

Fluid therapy

Patients often need aggressive fluid resuscitation in the early stage of the illness. A mixture of crystalloid and colloids are used, clinical end points being restoration of end organ perfusion (improving acidosis, good urine output and other clinical signs), achievement of stable trends of central venous pressure and saturation, arterial blood pressure and cardiac output.

Care should be taken to avoid fluid overload as many patients will develop renal failure with oliguria, and over resuscitation can produce adverse effects on brain swelling and intracranial pressure (ICP).

Vasopressors

Failure of response to fluid resuscitation often indicates the need for vasopressors, noradrenaline being the vasopressor of choice. Consider vasopressin (0.6-2.4units/hour) as a second line agent.

Inotropes

Inotropic support may be considered for patients with a low cardiac output state. An echocardiogram should be sought in this situation to determine cardiac function.

Steroids

There is some evidence of relative adrenal insufficiency in ALF and acute on chronic liver failure (ACLF) as is in sepsis, but the evidence base for steroid supplementation in these patients is weak. However, in patients on high-dose vasopressors (e.g noradrenaline >0.3mcg/kg/min), steroids (hydrocortisone 200-300mg daily, either as intermittent doses or a continuous infusion of 10mg/hr) should be considered and commenced early (within 6hours of development of vasopressor-resistant shock).

4.5 Ventilatory support and sedation

Indications for mechanical ventilation

Elective tracheal intubation and ventilation are recommended for patients with grade III/IV or worsening encephalopathy. This is not to treat respiratory failure necessarily but for airway protection and control of plasma CO_2.

Other indications for elective intubation may be before transferring a sick ALF patient, or when the patient is aggressive and generally unmanageable, putting themselves at risk by preventing necessary treatment.

Intubation / ventilation

Special precaution should be taken to avoid venous engorgement with endotracheal tube ties. Tubes will be routinely taped rather than tied.

Ventilation guidance: lung-protective ventilatory strategy, low tidal ventilation and limiting inflation pressures to minimise risks of volu- and baro-trauma.

Mode of ventilation not crucial – volume or pressure controlled ventilation.

Aim for normocapnoea ($paCO_2$-4.0 -5 kpa), and normoxia (paO_2>10kpa).

Sedation

Sufficient sedation must be ensured to avoid cough on suctioning, stimulation during patient turning and chest physiotherapy.

Requirements in grade III/IV encephalopathy are less than grade I/II. Sedative requirement may increase as ‘improvement’ occurs. Sedation should be assessed regularly.

Drugs choices are:

a. Propofol
b. Fentanyl or remifentanil
c. Midazolam

Standard practice is to use a combination of fentanyl and propofol. The choice of sedatives used will be decided by the duty ICU Consultant. Consider paralysis with neuromuscular blocking agents if necessary – boluses should be used prior to any nursing intervention i.e. patient turning, chest suctioning, physiotherapy or any patient intervention where concerns about raised ICP exist. Where there is evidence of acutely elevated ICP, a continuous infusion of cisatracurium is likely to be needed to reduce the risk of surges caused by straining/coughing.

4.6 Renal support

Renal failure is common, occurring in 50% of ALF patients, with incidence rising as high as 75% in paracetamol toxicity. It is multifactorial, often a combination of prerenal (hypotension and hypovolaemia, hepatorenal) and renal (direct tubular effect of paracetamol toxins, nephrotoxic antibiotics and contrast agents that might be used for radiological interventions) injuries.

General measures

Optimisation of BP and volume status.

Avoidance of nephrotoxic drugs / contrast agents.

Renal replacement therapy (RRT)

*Support is commonly required and should be **instituted early***.

Continuous therapy (CRRT) is preferred for haemodynamic stability.

Indications for CRRT

Usual indications of metabolic acidosis, hyperkalaemia and fluid overload etc.

Extra-renal indications include hyperammonaemia > 150umol/L, refractory intracranial hypertension / cerebral oedema and temperature control.

Method of CRRT

Continuous veno-venous haemofiltration (CVVH) or diafiltration (CVVHD) – follow ICU CVVH guidelines.

It is recommended that an exchange rate of at least 35ml/kg/hr is used. Anecdotally, there **may** be some benefit in using higher rates of up to 45ml/kg/hr for the acute liver failure patient.

Anticoagulation: usually not required as patients are auto-anticoagulated. However, if circuits clot frequently, anticoagulation may be necessary. Heparin may be less effective due to reduced serum antithrombin III level. Epoprostenol (0-5ng/kg/min) may be used either alone or in combination with low–dose heparin. We do not currently use citrate in acute liver failure patients.

4.7 Cerebral support

Cerebral oedema represents the most serious complication of ALF, occurring, in varying severity, in up to 80% of patients with ALF, being more prominent in the hyperacute variety. Up to 40% of patients on the emergency transplantation list have been reported to die as a result of cerebral oedema and herniation before receiving transplantation. The exact pathophysiological mechanism of cerebral complications in ALF is not fully understood, but involves various vasogenic and cytotoxic pathways triggered by neurotoxins and inflammatory mediators. Ammonia has been implicated as the major neurotoxin responsible for the cerebral complications of ALF [6], with contribution from inflammatory cytokines in the presence of a systemic inflammatory response (SIRS) and sepsis [7].

Death from cerebral herniation occurs even in ACLF (~5-7% of patients), with an estimated incidence of cerebral oedema in 20% of ACLF patients.

Signs of raised ICP

Early signs: Hyperreflexia, Clonus, Extensor posturing, Teeth grinding, Opisthotonus.

Late signs: Pupillary abnormalities, sustained arterial hypertension / bradycardia.

Basic considerations in management of cerebral oedema

Early clinical signs of cerebral irritability are lost once the patient is sedated, pupillary and vasomotor abnormalities are late signs, often difficult to interpret and can occur from a variety of reasons.

The speed of progression from grade I to grade IV encephalopathy should not be underestimated and may occur within only a few hours.

Some form of ICP or cerebral oxygenation monitoring is useful – although not associated with improved survival, they can guide management manoeuvres.

Monitoring of ICH / cerebral oedema

The practice of invasive cerebral monitoring in ALF varies greatly amongst centres, some using aggressive multimodal monitoring for all patients with grade III/IV coma, while others avoid invasive monitoring altogether because of the risk of intra-cerebral bleeding and the clear lack of data demonstrating a mortality benefit and possibly harm. We at FRH use invasive monitoring on a case by case basis after thorough discussion between the liver transplant anaesthetists, hepatologists and the ICU team.

Ammonia measurement

Ammonia levels have been shown to predict risk of death from increased ICP. Arterial ammonia levels should be measured at admission and 24 hour

intervals in patients with an arterial line or when they develop hepatic encephalopathy.

ICP monitors

Measuring ICP has no overall survival benefit and insertion is not without risk. The overall complication rate for an extradural system is about 4% including fatal haemorrhage in 1% of patients. Complication rates are much higher for subdural and parenchymal systems.

CT head scan

Not sensitive in detecting early cerebral oedema or elevated ICP and a single study showed CT not to be helpful in management but should be considered if there are focal signs or unexplained encephalopathy.

EEG

Useful in detecting seizures in sedated and paralysed patients.

4.8 Management of cerebral oedema & raised ICP

General measures

- **Commence secondary brain injury chart**
- Ensure adequate sedation and analgesia. Consider paralysis, when turning, suctioning etc.
- Nurse head-up (20-30 degrees)
- Avoid cerebral venous engorgement
- Neutral neck position
- Beware occlusive tracheal tube ties
- Minimise intervention, especially patient turning and tracheal suction
- Maintain normoxia (paO_2>10kPa) and normocarbia ($paCO_2$-4.5-5kPa)
- Minimal PEEP to achieve target paO_2
- Limit peak/plateau airway pressure to <35cmH_2O
- Normovolemia (avoid excessive fluid)
- ***Na^+ 145-150mmol/L.***

Invasive Monitoring

If an ICP bolt is inserted (which is on a case by case basis), the liver transplant anaesthetist will formulate a management plan for:

1. Cerebral perfusion pressure
2. Treatment plan if raised ICP/low CPP
3. Parameters for platelet count, PT and fibrinogen

Specific therapies available to treat ICH

Mannitol (20%)

Associated with survival benefit in ALF
Bolus preferable to continuous infusion: 2.5-5ml/kg mannitol 20%.
Plasma osmolality must be checked (in lab) after every bolus (keep <320mosmol/l)
Care should be taken in oliguric patients as it may lead to hypervolemia and pulmonary oedema. If the patient is on CRRT, remove three times the volume administered.

Hypertonic saline

Reduces ICP and improves CPP without altering MAP in traumatic brain injury. Currently there is limited data for its use in ALF but serves to maintain hypernatremia (Na^+ 145-150 mmol/L) and may be beneficial in severe encephalopathy. A continuous infusion should be used to maintain sodium levels or can be used as a bolus (3mls/kg 2.7% sodium chloride). Osmolality should be calculated and kept < 320mosmol/L and once serum sodium >155mmol/l further benefit likely to be limited. Use of high flow CVVH will effectively reverse the effects of hypertonic saline boluses over a period of a few hours so regular checks of serum sodium and osmolality are needed. Equally there is likely to be continued benefits in bolus use with time on CVVH.

Care should be taken in correcting sodium levels acutely in the setting of hyponatraemia to prevent neurological complications.

Hypothermia

Moderate to severe hypothermia has been shown to reduce ICP and improve MAP in patients with intractable intracranial hypertension [8]. Hypothermia reduces circulating ammonia, brain uptake of ammonia and conversion to glutamine by the astrocytes causing reduced astrocyte swelling and cerebral oedema. It also reduces cerebral oxygen requirement for metabolism .

We aim for mild hypothermia in all patients with ALF (core temperature 35-36^0 C) and aggressively treat fever. In cases of difficult to control ICP, lower temperatures to 33^0 C can be used after discussion with the liver transplant anaesthetist/ICU team. **Other options** are to be considered on a case by case basis. Early filtration may be considered if cerebral oedema is a problem, usually in the absence of an adequate response to diuretics. Patients usually to be kept in a negative balance titrated against the haemodynamics.

- Hyperventilation - Only when cerebral hyperaemia is suspected and should be for short duration only
- Barbiturates - Thiopentone (2.5%) is the most commonly used barbiturate. It reduces ICP but may also cause severe hypotension and therefore

reduction in CPP. Except in exceptional circumstances, this approach should not be used
- High dose indomethacin 25mg bolus
- Exclude seizures.

4.9 GI and nutrition

Early enteral nutrition is recommended. It has been agreed by all to start feed early and increase as tolerated. No specific feed is recommended. Close liaison between ITU and liver team will help in stopping feed in time and aspirating residual feed should the patient need to go to theatre urgently for transplantation or other reasons.

Stress-ulcer prophylaxis with H_2-antagonist to be commenced.

4.10 Antimicrobial prophylaxis

ALF patients are highly susceptible to infections, with proven rates of up to 80% and 30% for bacterial and fungal infections, respectively. Fungal infections are more common in patients with advanced encephalopathy.

Pre-transplant prophylaxis - commence cefuroxime 750mg TDS (may need dose adjustment according to renal function) and liposomal amphotericin (AmBisome) at 1mg IV test dose, then 1mg/kg IV OD.

Refer to the Liver Unit Antimicrobial Guidelines for further details

4.11 Drug index

1. Cefuroxime 750mg TDS
2. Amphotericin (AmBisome) at 1mg IV test dose, then 1mg/kg IV OD
3. N-acetylcysteine (NAC) – 10g in 50ml (neat) infusion to run centrally. Maintenance dosage 150mg/kg over 24 hours. Refer to latest NAC policy for loading doses if this has not been commenced on admission to ITU
4. Vitamin K 10mg IV OD for three days
5. Forceval 1 PO/NG OD (multivitamin and trace elements)
6. Ranitidine 50mg IV TDS.

5 Emergency Liver Transplantation

Liver Transplantation is the definitive treatment in ALF patients who meet the criteria for transplantation. Patient selection is usually based on KCH (King's College Hospital) prognostic criteria. The criteria are based on the aetiology of ALF, age of the patient and the rapidity of progression.

Even after listing, suitability and requirement for transplantation should be regularly reviewed because of the progressive nature of the disease and in up to 1 in 10 listed patients may recover without transplantation. Therefore, it is imperative that even after listing, the clotting (INR) is not corrected unnecessarily and be used to monitor progress of disease.

Post-transplant, a plan will be in place by the on call liver transplant anaesthetist for full management strategies.

6 References

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