Acute Liver Failure: Updates in Pathogenesis and Management

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ABSTRACT
Acute liver failure (ALF) is a life-threatening illness precipitated by an acute liver injury in patients with no pre-existing liver disease. Acute viral hepatitis and drug-induced liver injury account for the majority of cases, the clinical course characterised by the development of coagulopathy and hepatic encephalopathy (HE), often progressing to multi-organ disease which is associated with high fatality rates. The outcomes have improved significantly over time with improving standards of organ system support and access to liver transplantation for the very sick. The King's College Hospital criteria (KCH) is the most commonly used tool for determination of prognosis and consideration for transplantation. Prompt diagnosis, immediate initiation of supportive care and aetiology-specific treatment, where applicable, and early discussions and transfer to transplant centre are keys to successful outcome.

KEYWORDS
Acute liver failure, fulminant hepatitis, critical care, hepatic encephalopathy, multi-organ failure, intensive care, liver transplantation.

DEFINITION AND CLASSIFICATION
Acute liver failure (ALF) is a rare, life-threatening illness, triggered by a de novo liver injury to a previously healthy liver, frequently progressing within hours and weeks to multisystem involvement and failure. Coagulation abnormalities of liver origin (elevated prothrombin time (PT) or International Normalised Ratio (INR) above 1.5) and mental alterations due to hepatic encephalopathy (HE) are the key defining clinical criteria required to make a diagnosis. ALF is a specific clinical entity in terms of the clinical phenotype, disease course, prognosis, and eligibility for emergency liver transplantation. This must be distinguished from secondary liver injury in sepsis or congestive cardiac disease or failure following major liver resection, none of which would qualify as ALF and would not be indications for emergency liver transplantation. Conversely, acute presentations of Wilson's disease, acute Budd-Chiari syndrome and some cases of autoimmune hepatitis may have undiagnosed chronic liver involvement but are treated as ALF because of the poor prognosis without transplantation in these conditions and clinical features consisting predominantly of coagulopathy and HE.

ALF is a rare condition with an estimated annual world-wide incidence of 1-6 patients per million population, with a further declining trend in incidence because of better vaccination programmes against viral hepatitis and fewer drug-induced cases, particularly those related to paracetamol toxicity, these being the two main aetiologies of ALF making up most cases world-wide, viral hepatitis in developing countries, and paracetamol toxicity predominantly in the Western world. The outcomes, both transplant-free and following transplantation, have continued to improve in the last decades owing to better understanding of the disease, a more refined organ system support platform, better aetiology-specific interventions and access to liver transplantation in severe cases.
Accurate prognostication to identify patients that are unlikely to survive without transplantation remains a challenge. The most commonly used tool, the King's College Hospital criteria (KCH) criteria, identified the ALF aetiology, patient age and the rapidity of desease progression defined by the time from jaundice development to onset of HE of 7 days (hyper-acute), 7-28 days (acute) and 28 days-12 weeks (sub-acute) as the major prognostic determinants. Sub-acute presentation is associated with the worst prognosis without liver transplantation. Disease duration of greater than 28 weeks is considered chronic liver failure.[1]

AETIOLOGY
Viral hepatitis (A, B, E) constitute the commonest cause of ALF in the developing countries and worldwide. Hepatitis B virus (HBV) is the most common encountered virus in most of Asia, Africa and the Amazon region while HEV is common in the Indian subcontinent. Drug-induced liver injury (DILI), in particular paracetamol toxicity which accounts for 50-70% of DILI cases, is the most common offender in developed world.
Other rarer causes include other viral infections (herpes simplex virus (HSV) 1 and 2, herpes virus 6, varicella, Epstein Barr virus, cytomegalovirus and parvovirus (erythrovirus) B19) specifically in immunocompromised patients, autoimmune hepatitis, metabolic disorders and pregnancy-related liver diseases. An underlying cause is not found in up to 20% of patients, referred to as 'indeterminate' or 'seronegative' ALF.

PATHOGENESIS
Irrespective of the aetiology of ALF, the common path to the damage involves an intense inflammatory surge mediated by the cytokines and other inflammatory mediators produced by damaged hepatocytes leading to severe impairment of the synthetic, metabolic and immune functions of the failing liver followed by progression to extrahepatic organ manifestations and multi-organ failure.
Encephalopathy: HE is generally multifactorial, and its mechanism is not well understood. The most prominent mechanistic processes include neuroinflammation with oxidative injury as part of systemic inflammation, superimposed insults from circulating and local neurotoxins, ammonia in particular, and osmotic perturbations such as hyponatremia. The reduced ability of the injured liver to synthesize urea causes glutamine excess in brain cells which leads to increased oxidative stress and subsequent astrocyte swelling. Alterations in cerebral blood flow with cerebral vasodilatation and hyperaemia, and a breached blood-brain barrier exacerbate this further. Cerebral oedema and intracranial hypertension (ICH) are the most dreaded complications of ALF and is considered the leading cause of death in advanced stages. However, the mortality rates from ICH is declining because of targeted monitoring and a proactive approach in managing the precipitating causes. High blood ammonia levels, particularly when associated with rapid increase, are associated with higher mortality. It was found that an arterial ammonia level of ≥ 124 umol/l can predict mortality and is associated with higher rates of complications. More recently, a level of ammonia >200 µg/dL is shown to be a strong predictor of severe cerebral oedema and brain herniation in patients with grades 3 and 4 HE, while values below 75 µg/dL or a falling ammonia level are rarely related to intracranial complications. Hyponatremia further contributes to development of cerebral oedema and ICH. A sodium target of 145-155mmol/L is desirable in the management of these patients.
Coagulopathy: The severely injured liver is unable to synthesize coagulation factors, which leads to prolonged INR. However, there is a simultaneous and proportional reduction in the production of natural anti-coagulant proteins such as proteins C, protein S and antithrombin, as well as increased production of endothelium derived pro-coagulants, factor VIII and von-Willebrand factor (vWF), all of which lead to an overall balanced haemostasis with little risk of spontaneous or invasive-procedure related bleeding. Platelet and fibrinogen derangements are more likely to predict bleeding risk in the setting of ALF. Correction of INR is generally not necessary for insertion of vascular lines. If invasive sensorineural monitoring is required (like invasive ICP monitoring), full correction of clotting factors is advisable.
Metabolic derangements: The most common metabolic complications are hypoglycemia, metabolic acidosis, renal failure and adrenal insufficiency. Hypoglycemia is usually the result of depletion of

glycogen stores and impaired gluconeogenesis in the liver. Metabolic acidosis is usually associated with paracetamol toxicity or result from circulatory impairment, sepsis and renal failure. Renal failure usually is the sequelae of circulatory failure, sepsis, disseminated intravascular coagulation or as a toxic effect in drug-induced liver injury. It occurs in about 50% of patients with ALF. Acute adrenal insufficiency is recorded in up to 65% of ALF patients. Steroid treatment reduces vasopressor requirement but is not associated with survival benefits while increasing infection risk. Other encountered metabolic abnormalities are hyponatremia, respiratory alkalosis and hypokalemia.

Cardiorespiratory changes: ALF patients tend to have a hyperdynamic high cardiac output state characterised by systemic vasodilatation and a low mean arterial pressure, which predisposes to tissue hypoperfusion. Most patients require aggressive fluid resuscitation in the initial stages and vasopressor support to maintain a mean arterial pressure of >70 mmHg. Respiratory alkalosis and hypoxemia are present in most cases of fulminant ALF, and is secondary to HE, sepsis, aspiration and acute lung injury.

Sepsis: Immune dysregulation and immune paresis predisposes to secondary microbial infections. Sepsis has emerged as the most common cause of death in ALF, surpassing cerebral complications which used to account for most fatalities a decade ago. Bacteraemia is reported in up to 80%, and fungaemia is found in up to 32% of ALF patients. The most frequent organisms associated are staphylococcus aureus, enterococci, Escherichia coli, Klebsiella bacilli and candida. Active surveillance and screening for infections and prompt aggressive treatment according to local protocols is vital. Antibacterial prophylaxis and anti-fungal prophylaxis (in high grades of HE) have been shown to improve cerebral complications and overall outcomes and should be used as routine.

DIAGNOSIS

Diagnosis is usually made by clinical and laboratory features, showing essentially evidence of acute liver injury associated with coagulopathy and encephalopathy. Diagnostic laboratory and imaging baseline investigations are shown in table (1) and should be done in every patient with ALF presentation.

MANAGEMENT

Initial management: Early multi-disciplinary team management consisting of hepatology, critical care and liver transplant surgeons is crucial. Management of severe cases should ideally be carried out in a tertiary centre with the experience and facility of performing emergency liver transplantation.[2] A summary of intensive care management strategies is shown in figure (1).

Aetiology-specific management: Every measure should be done to diagnose the underlying eitiology, and specific management should start immediately.[2] This specifically include N-acetylcysteine (NAC) for treating paracetamol overdose, antiviral treatment for viral hepatitis-related ALF (lamivudine for HBV, and acyclovir for HSV), and immunosuppression for autoimmune hepatitis. NAC has been shown to improve outcomes even in non-paracetamol aetiologies, when used early in the illness before progression to higher HE grades.

Cardiovascular support: Aggressive fluid replacement with invasive cardiac monitoring and intravenous vasopressors are usually required. General data from large randomised trials favour the use of balanced crystalloids as the best option. Starch-based solutions are better avoided due to the risk of renal impairment. If fluids are not effective in treating shocked patients, or if there is a risk of over infusion, vasopressors can be used. Steroids can be sometimes used in treating refractory shock with other vasopressors.

Respiratory support: Endotracheal intubation and ventilation support are essential in higher grades of encephalopathy (grade 3 and above) and is performed electively for airway protection, modulation of CO_2 tension and control of agitation. This can be done in less grades of encephalopathy if there is a respiratory indication as respiratory infections or adult respiratory distress syndrome (ARDS).[3]

Neurological support: Early elective intubation in patient with encephalopathy grade greater than 2 and measures to control cerebral complications form the basic tenets of cerebral management, achieved by maintaining adequate sedation, normocapnia, normoglycemia and moderate hypothermia.[3] A target aim of a serum sodium of 145-155mmol/L is desirable and is usually achieved by a continuous infusion or boluses of 30% hypertonic saline. Rescue treatment with mannitol can be used in refractory cases. Early renal replacement therapy must be considered in patients with ammonia level above 150 umol/l. Other ammonia lowering strategies such as L-Ornithine L-Aspartate (LOLA) has never been shown to be effective. Intracranial pressure monitoring using an ICP bolt may be required in some cases, but its benefit on patient survival is questionable, lacking evidence and is

associated with more risk of bleeding and infections. Algorithm for management of grade 3 and 4 HE is highlighted in figure (2).

Renal support: Renal support is often required for renal and extra-renal indications such as hyperammonaemia, temperature control and fluid balance. Overhydration is often associated with worsening cerebral oedema. Continuous modes of dialysis confer better haemodynamic and cerebral control.

Coagulopathy: Although ALF patients have presumably high risk of bleeding, major bleeding is uncommon despite highly elevated prothrombin times. Routine correction, therefore, is not recommended unless there is evidence of major bleeding. It is important to note that PT provides an important guide to monitoring liver's synthetic function and is an important component of transplant criteria and must not be corrected unless absolutely necessary.

Sepsis: Active surveillance and screening for infections are necessary. Prophylactic broad-spectrum antibiotics and antifungals should be routinely used to prevent invasive bacterial and fungal infections. The antibiotics used should follow the local policies and protocols depending on the local sensitivity patterns.

Metabolic and nutritional support: Frequent blood glucose monitoring and replacement with low-volume high-concentration glucose preparations is essential to avoid cerebral oedema. Every attempt should be done to promote oral or enteral feeding. Parenteral nutrition is not recommended due to increased risk of sepsis unless enteral feeding is not possible or contraindicated.

Artificial liver support and plasma exchange: Novel extracorporeal liver support devices have been described as potential tools for maintaining liver function, detoxification, improving albumin function, modulating inflammation through removal of cytokines and other inflammatory mediators, thus augmenting liver regeneration to aid natural recovery or bridging to liver transplantation. Unfortunately, none of the currently available artificial liver support systems have shown any survival benefit, except high volume plasma exchange. In a randomised clinical trial, high volume exchange of up to 2-3 plasma volume for 3 consecutive days was associated with improved transplant-free survival especially in patients in whom liver transplantation was contraindicated for medical or psychosocial reasons.[4] Other extracorporeal modalities which target improvement of albumin function and immune modulation have shown some promise in an animal study of paracetamol induced ALF (DIALIVE study).[5]

Liver transplantation: Super-urgent listing for liver transplantation is required for the poor-prognostic group of patients. The King's College Hospital (KCH) criteria highlighted in table 2 is the most commonly used for patient selection.[6] As per the European liver transplant registry 8% of organs are used for ALF with 1-year survival rates close to 80%. Because of the poor specificity, the KCH criteria is modified to incorporate persistent hyperlactataemia after aggressive fluid resuscitation as an additional component which has improved its sensitivity and specificity. The other criteria frequently used is the French Clichy criteria (table 2), derived from a cohort of acute HBV related ALF, for non-paracetamol aetiologies. More recently, new scores have been proposed for better selection of liver transplant candidates, especially in paracetamol-related ALF, incorporating the chronic liver failure organ failure score (CLIF-OF score) and the severity of circulatory disturbance measured by the maximum noradrenaline requirements.[7] Liver transplantation is generally contraindicated in cases of irreversible brain damage, uncontrolled sepsis and presence of active malignancy. Because of limited organ availability and the life-long dependence on immunosuppression, it is important to identify patients who can potentially recover without transplantation. . Early spontaneous survivors tend to have better long-term outcomes than those who receive liver transplantation

FUTURE PERSPECTIVES

Further research is required to establish prognostic scores to predict outcomes after liver transplantation and to prevent transplantation in futile patients. Better listing criteria are still needed. Cellular and tissue-based extracorporeal liver support systems are an exciting area of research with still further need for trials to establish survival and overall benefits.

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Table (1): Criteria of liver transplantation in Acute Liver Failure.

<table>
<tr><th colspan="2">King's College Criteria (KCH)</th></tr>
<tr><th>Paracetamol overdose</th><th>Non-paracetamol aetiologies</th></tr>
<tr><td>1. Irrespective of grade of encephalopathy:
Arterial pH <7.25 following volume resuscitation >24 hours post overdose
OR
2. All of the following:
Grade 3 or 4 encephalopathy
PT >100 sec
Serum Creatinine >300 µmol/L
OR
3. The extended KCH criteria
Serum lactate >3.5 mmol/L after early resuscitation
Serum lactate >3.0 mmol/L 24 hours post overdose, and adequate volume resuscitation</td><td>1. Irrespective of grade of encephalopathy:
PT >100 sec
OR
2. Presence of encephalopathy + any 3 of the following:
Age <10 or >40
Aetiology Non-A non-B, drug reaction
Jaundice to encephalopathy>7 days
PT >50 sec
Serum Bilirubin >300 µmol/L</td></tr>
<tr><th colspan="2">Clichy Criteria (Non-paracetamol)</th></tr>
<tr><td colspan="2">1. Confusion/coma + Factor V concentration <20% + Patient Age <30 years
Or
2. Confusion/coma + Factor V concentration <30% + Patient Age >30 years</td></tr>
</table>

Table (2): Initial assessment of patients presenting with acute liver failure.

Laboratory tests
Coagulation: Prothrombin time/INR **Chemistries:** sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate glucose AST, ALT, alkaline phosphatase, GGT, total bilirubin, albumin creatinine, blood urea nitrogen, creatine kinase, Arterial blood gas, Arterial lactate, Amylase and lipase Ammonia (arterial if possible) **Haematology:** Complete blood count, Blood group and Rh factor **Toxicology:** Acetaminophen level, Toxicology screen **Viral aetiology:** Viral hepatitis serologies including hepatitis A, B, C and E. Serology for Epstein-Barr, Herpes simplex and Varicella zoster viruses. Serology for Human immunodeficiency virus HIV-1, HIV-2. **Autoimmune:** ANA, ASMA, Immunoglobulin levels **Others:** Ceruloplasmin level (if Wilson disease is suspected) Pregnancy test (in females in child-bearing period)
Imaging
Abdominal ultrasound scan with doppler

INR: international normalised ratio, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma glutamyl transferase, ANA: anti-nuclear antibodies, ASMA: anti smooth muscle antibodies.

Figure (1): Summary of initial intensive care management of patients with acute liver failure.

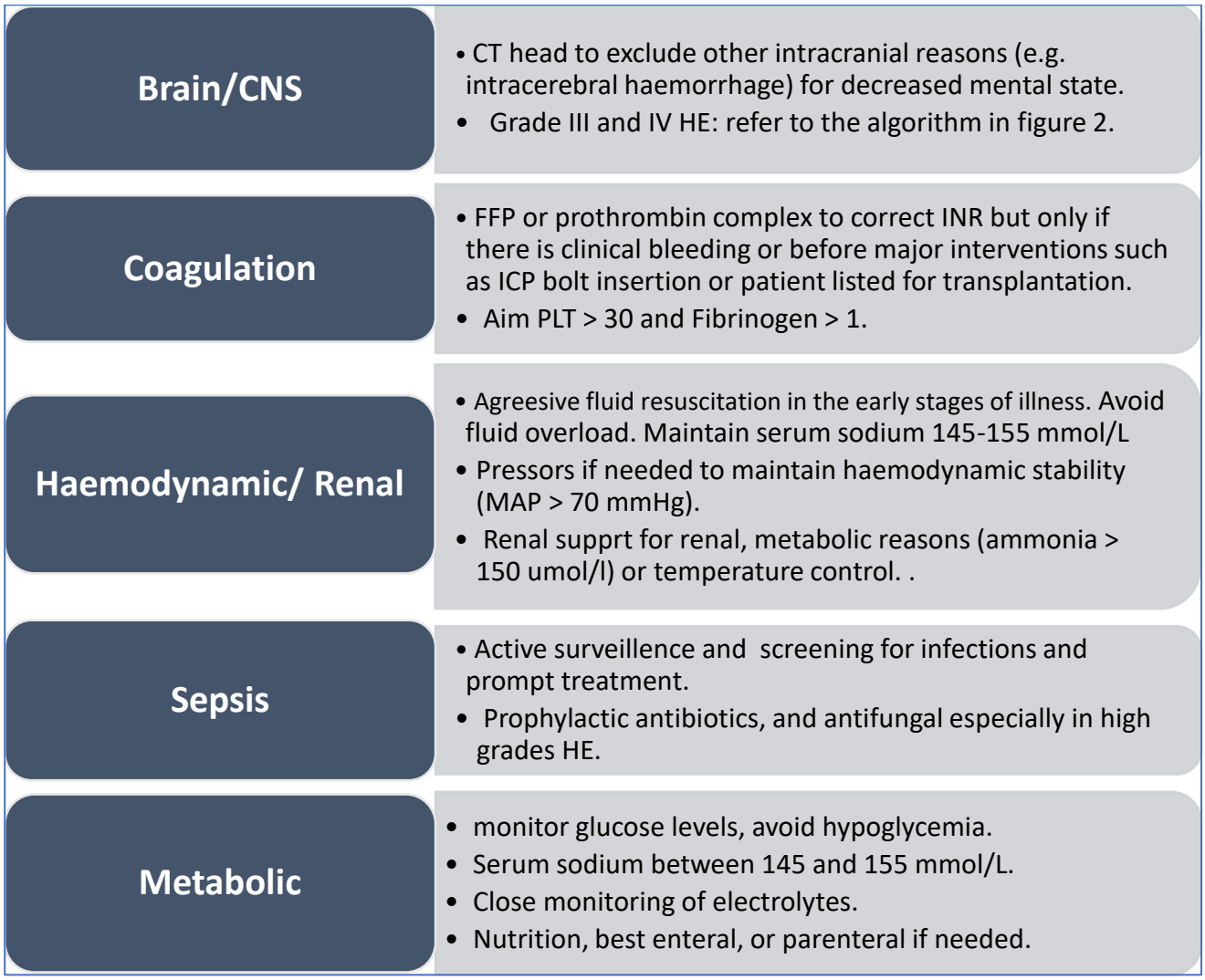
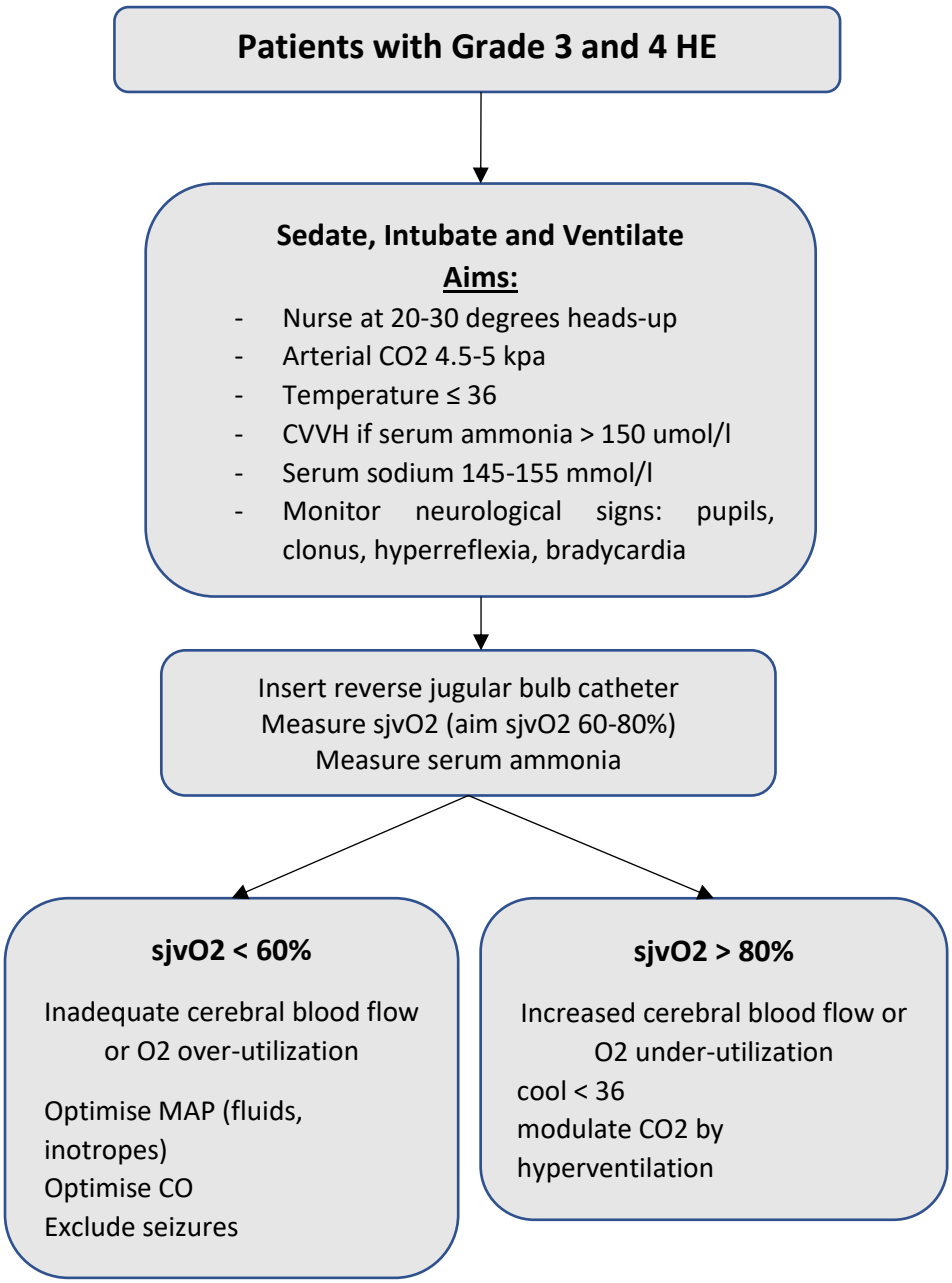


Figure (2): Algorithm for management of grade 3 and 4 HE.



QUESTIONS

Question 1

A 48-year-old man presented to emergency department with acute onset of vomiting and confusion. Three days previously he had taken an unknown quantity of paracetamol. On clinical examination he was confused, Glasgow Coma Scale 13/15, slightly jaundiced, with a 'flapping tremor', T 38.0^{0}C, HR 105 beats/min, and BP 134/88 mmHg. On abdominal examination, the liver was not palpable and there was no detectable free fluid.

Investigations

Hb 145 g/L (130–180)
MCV 98 fL (80–96)
WCC 5.7 x10^9/L (4.0–11.0)
Platelets 130 x10^9/L (150–400)
U 15.7 mmol/L (2.5–7.0)
Cr 168 µmol/L (60–110)
Bili 38 µmol/L (1–22)
ALT 2145 U/L (5–35)
AST 1639 U/L (1–31)
ALP 126 U/L (45–105)
Albumin 34 g/L (37–49)
INR 1.9 (<1.4)
Arterial blood gases (on breathing room air)
PO2 11.8 kPa (11.3–12.6)
PCO2 3.1 kPa (4.7–6.0)
pH 7.20 (7.35–7.45)
bicarbonate 18 mmol/L (21–29)
lactate 2.3 mmol/L (0.5–1.6)

In addition to the evidence of hepatic encephalopathy, which feature confirms the diagnosis of acute liver failure?

A. Raised transaminases
B. Glasgow Coma Scale result
C. Prolonged INR
D. High bilirubin
E. Blood gas results

Correct answer: C.

Question 2

You are the medical on-call in a gastroenterology ward and received a call about a 29-year-old female presented with paracetamol-induced hepatotoxicity with acute liver failure. She is conscious with a GCS of 15/15, normal renal function, INR of 2, ALT of 4000 IU/L and serum lactate of 2.8 (0.5–1.6). She was started on N-acetyl Cysteine and you recommended IV fluid hydration. You had a feedback 24 hours later informing you that her transaminases started to improve with an ALT of 2000 IU/L and her INR is now 1.8 but her repeated lactate is increasing to 4 mmol/L despite adequate IV fluids and normal renal function. She remained entirely conscious.

What is the best recommendation that you would give?

A. Continue NAC and IV fluids in the local hospital
B. Stop NAC and continue IV fluids in the local hospital
C. Start continuous renal replacement therapy
D. Contact the nearest liver transplant centre for possibility of transfer
E. Discharge as there are no risk signs or need for organ support

Correct answer: D.

Question 3

A 32-years-old man presented to the emergency department with jaundice and mild confusion. The diagnosis of acute liver failure was made, but further investigations failed to identify a cause as all the liver screen and abdominal images were negative. Following admission, his confusion progressively deteriorated and developed grade 3 HE, and he required transfer to the intensive care unit. On ICU, he was intubated, on high dose of vasopressor support and he required continuous renal replacement. He spiked a temperature of 38.2^0C and his inflammatory markers were raised. Antibiotics were started for a confirmed positive blood culture. Two days later his temperature improved, and his inflammatory markers settled but he still required high vasopressor support and hemofiltration, and his pupils started to be dilated with sluggish reactivity.

Which of the following is a contraindication for liver transplantation in this patient?

A. High dose of vasopressor requirements
B. Presence of infection
C. Unknown etiology of ALF
D. Continuous renal replacement therapy
E. Irreversible brain damage

Correct answer: E.