Chapter 45
Approach to Acute Liver Failure in the ICU

45.1 Introduction

Acute liver failure (ALF) is a critical condition characterized by the rapid deterioration of liver function in patients without preexisting liver disease. This condition can progress rapidly and lead to life-threatening complications, including cerebral edema, coagulopathy, and multi-organ failure. The management of ALF in the intensive care unit (ICU) requires a systematic approach to stabilize the patient, prevent complications, and evaluate for potential liver transplantation. This chapter outlines a comprehensive approach to managing ALF, integrating the latest clinical guidelines and considerations [1, 2] [Ref: Algorithm 45.1].

Definition ALF is defined as the development of severe acute liver injury with encephalopathy and impaired synthetic function (INR of 1.5 or higher) in a patient without cirrhosis or preexisting liver disease and with an illness of fewer than 26 weeks duration.

45.2 Etiological Assessment

- Viral Causes: ALF can be triggered by viral infections like hepatitis B, A, E, herpes simplex virus, and cytomegalovirus (CMV). These infections are particularly relevant in certain geographic regions, and immunosuppressed patients (e.g., those undergoing chemotherapy) are at higher risk for viral reactivation leading to ALF.
- Drug-Induced Liver Injury (DILI): Acetaminophen remains the most common cause of ALF in developed countries; however, idiosyncratic reactions to other drugs, such as antibiotics, also contribute significantly to cases. A thorough

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review of the patient's medication history is critical to identify potential drug-related causes.
- Wilson's Disease and Other Specific Causes: Rare etiologies like Wilson's disease and acute Budd-Chiari syndrome should be considered, as these require specific diagnostic approaches. Early recognition of these conditions is essential, as they often necessitate urgent liver transplantation for improved outcomes.

45.3 Management

1. **Airway Management**
   - Decision Point: Is the patient able to maintain airway?
   - If no, intubate the patient to protect the airway. Intubation is crucial in patients with encephalopathy or altered mental status to prevent aspiration and ensure proper oxygenation and ventilation.
   - If yes, proceed with the management of hemodynamic stability and cerebral edema prevention.
2. **Prevention and Management of Cerebral Edema**
   - Head Elevation: Keep the head of the bed elevated at 30 degrees to reduce intracranial pressure (ICP) and minimize the risk of cerebral edema.
   - Serum Sodium Management: Maintain serum sodium levels between 145 and 155 mmol/L using hypertonic saline as needed. This approach helps to minimize cerebral edema, especially in patients with elevated ICP.
   - Intracranial Pressure Monitoring: Consider ICP monitoring in patients with advanced hepatic encephalopathy who are awaiting liver transplantation. This helps guide the use of osmotic therapies like mannitol or hypertonic saline.
   - Role of Hypothermia: Mild hypothermia may serve as a bridge therapy for patients with refractory intracranial hypertension, particularly in centers experienced with this technique.
   - Sedation: Sedating with Propofol can aid in controlling agitation and reducing cerebral metabolic demands, but careful monitoring is essential to avoid excessive sedation [3].
3. **Hemodynamic Support**
   - Maintain Mean Arterial Pressure (MAP) > 65 mm Hg: Adequate MAP ensures sufficient organ perfusion, especially in the setting of compromised liver function. Vasopressors may be used if required to maintain target pressures.
4. **Management of Hyperammonemia**

   Hyperammonemia is a hallmark of ALF and contributes significantly to the development of hepatic encephalopathy and cerebral edema. Elevated ammonia levels result from impaired liver function, which reduces the organ's ability to

detoxify ammonia produced by gut bacteria. In ALF, managing hyperammonemia is crucial to prevent worsening neurological status and other complications.

5. **Ammonia Management**

- Lactulose Caution: While lactulose is frequently used in chronic liver disease to reduce ammonia levels, its role in ALF is less clear. Lactulose works by acidifying the gut and promoting the conversion of ammonia into ammonium, which is then excreted in the stool. However, in ALF, lactulose should be used with caution due to the potential for bowel distension and the risk of aspiration, especially in patients with altered mental status who are not intubated. Lactulose can increase the risk of abdominal bloating and discomfort, which can complicate care in the ICU setting.
- CRRT as Preferred Therapy: Continuous Renal Replacement Therapy (CRRT) is the preferred method for managing severe hyperammonemia in ALF patients. CRRT offers several advantages, including the ability to provide consistent removal of ammonia from the blood, management of fluid balance, and correction of acid-base imbalances. This is especially beneficial in ALF, where rapid changes in fluid status and electrolytes can exacerbate cerebral edema. CRRT is often initiated when ammonia levels are significantly elevated and not responding to conservative measures, making it a critical tool for ammonia control in the ICU.

Are Ammonia Levels Elevated (>100 μmol/L)?
If Yes:

- Initiate CRRT: When ammonia levels exceed 100 μmol/L, this is considered a threshold where the risk of cerebral edema increases significantly. Initiating CRRT at this point helps to actively reduce circulating ammonia, thus lowering the risk of further neurological deterioration. CRRT is especially indicated in cases where other methods like lactulose are ineffective or contraindicated.
- Adjust Serum Sodium Levels: Concurrently, maintaining serum sodium levels in the high-normal range (145–155 mmol/L) using hypertonic saline can help to reduce the risk of cerebral edema. This osmotic strategy helps to shift water out of the brain, countering the effects of ammonia-induced astrocyte swelling. Adjusting serum sodium is crucial in managing elevated intracranial pressure in patients with severe hyperammonemia.
- **If No:**
- Continue Monitoring: In cases where ammonia levels are below the threshold, it is essential to continue regular monitoring of ammonia levels and the patient's neurological status. Even moderate elevations in ammonia can lead to a gradual decline in mental status, and timely adjustments in management are critical. Frequent assessments help in detecting early signs of worsening encephalopathy, guiding the need for more aggressive interventions like CRRT or adjustment of sodium levels.

- Neurological Monitoring: Close monitoring of the patient's neurological status is crucial, as changes can indicate an increase in cerebral edema. Tools such as serial neurological exams, Glasgow Coma Scale (GCS) scoring, and consideration of intracranial pressure monitoring can help in detecting early signs of intracranial hypertension. This allows for prompt escalation in therapy if needed.

6. **N-Acetylcysteine (NAC):** Administering N-acetylcysteine (NAC) is often used in clinical settings to manage acetaminophen toxicity and in other off-label uses, such as treating non-acetaminophen-induced acute liver failure and certain oxidative stress conditions [4]. Below is a detailed approach to dosing NAC for different indications:

   Acetaminophen Overdose

- Oral Route:
  - Loading Dose: 140 mg/kg of NAC given as a single dose.
  - Maintenance Dose: 70 mg/kg every 4 hours for 17 doses (total duration: 72 hours).
  - The solution is typically diluted to 5% (diluted with a suitable liquid like water, juice, or cola) to improve palatability and reduce the risk of gastrointestinal side effects.
- Intravenous Route:
  - Loading Dose: 150 mg/kg over 60 minutes.
  - Second Dose: 50 mg/kg over 4 hours.
  - Third Dose: 100 mg/kg over the next 16 hours (total duration: 21 hours).
  - Some protocols may continue the infusion beyond 21 hours based on the patient's clinical status and acetaminophen levels.

   Key Considerations

- Adverse Reactions: Oral NAC is generally well-tolerated, though it may cause gastrointestinal discomfort, nausea, or vomiting. IV administration can cause anaphylactoid reactions in some patients, including rash, bronchospasm, and hypotension, particularly with rapid infusion rates.
- Monitoring: During IV administration, monitor liver function tests, serum electrolytes, and clinical signs of improvement or adverse reactions. For acetaminophen overdose, continue monitoring serum acetaminophen levels until they reach nontoxic levels and liver function normalizes.
- Dilution: When given intravenously, NAC should be diluted in dextrose 5% or sodium chloride solution to avoid vein irritation.

NAC is a versatile agent with multiple therapeutic applications in the ICU and emergency settings, and careful dosing and monitoring are crucial to ensure its safety and efficacy.

45.4 Management of Complications

Coagulopathy:

- Treat active bleeding or if any procedures are planned. Coagulopathy in ALF is common due to impaired production of clotting factors by the liver.
- Consider transfusion of blood products such as fresh frozen plasma (FFP) or platelets if clinically indicated.

Infection Management:

- Empirical Antibiotics: Initiate broad-spectrum antibiotics empirically due to the high risk of infections in ALF patients. Infection remains a major cause of morbidity and mortality in this population.
- Fungal Infection Considerations: Given the risk of fungal infections in ALF, especially in cases of prolonged ICU stay, antifungal agents should be considered for high-risk patients.

45.5 Transplant Criteria and Timing

Liver transplantation is often the definitive treatment for patients with ALF who do not show signs of spontaneous recovery. Determining which patients may benefit from transplantation is crucial, as timing can significantly impact outcomes. Using structured criteria and ensuring early coordination with liver transplant centers helps optimize the chances of survival and recovery.

Prognostic Scoring Systems:

- MELD Score (Model for End-Stage Liver Disease): The MELD score is widely used to assess the severity of liver disease and prioritize patients for transplantation based on their risk of mortality without a transplant. It considers laboratory values such as serum bilirubin, serum creatinine, and INR (International Normalized Ratio). In ALF, the MELD score can help identify patients at high risk of deterioration. While MELD is traditionally used for chronic liver diseases, recent evidence suggests it can also be valuable in ALF, especially when combined with clinical judgment to assess overall prognosis.
- King's College Criteria (KCC): KCC is a well-established set of criteria specifically designed for predicting outcomes in ALF. It helps clinicians identify patients who are unlikely to recover without transplantation. The criteria include parameters such as arterial pH, serum lactate, prothrombin time, and the presence of encephalopathy. For example:
  - In acetaminophen-induced ALF, KCC criteria include factors like arterial pH < 7.3 or the presence of severe coagulopathy (INR > 6.5) alongside renal failure and grade 3 or 4 encephalopathy.

  - In non-acetaminophen ALF, KCC looks at prolonged prothrombin time (INR > 6.5) or the presence of grade 3 or 4 encephalopathy, often combined with other markers such as bilirubin levels.

- Use of Scoring Systems in Practice: Both MELD and KCC provide valuable guidance but should not be the sole determinants of transplantation decisions. A holistic evaluation of the patient's condition, including the speed of clinical decline, comorbidities, and response to supportive care, should complement these scores. This integrated approach allows for better prediction of outcomes and decision-making regarding the timing of liver transplantation [5].

45.6 Early Referral to Transplant Centers

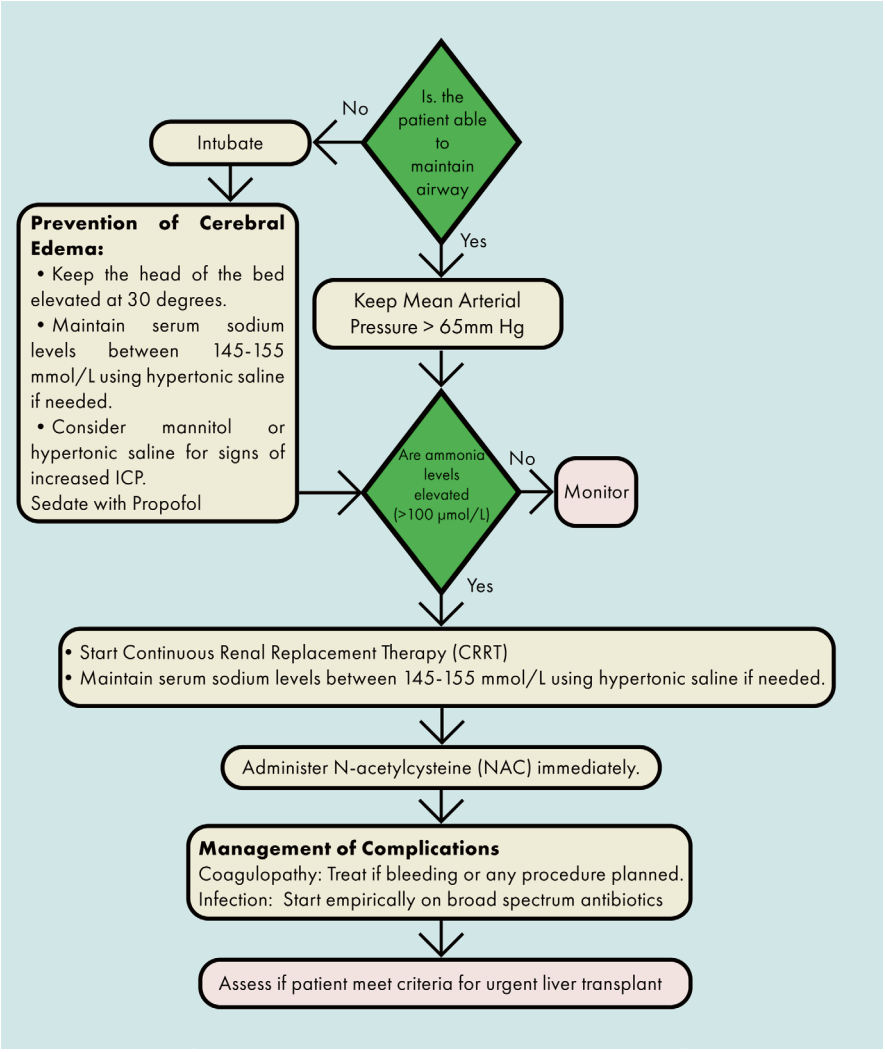
- Importance of Timely Communication: Early referral to a liver transplant center is crucial for patients with ALF, as the window for intervention is often narrow. Delayed referral can limit options, especially if complications like cerebral edema or multi-organ failure develop, which can preclude successful transplantation.
- Rapid Assessment and Coordination: Coordination with transplant centers allows for timely evaluation of the patient's eligibility for transplantation, pretransplant optimization, and access to advanced therapies, such as extracorporeal liver support systems. This coordination is particularly important for patients who show signs of rapid clinical deterioration or meet the prognostic criteria for poor outcomes.
- Stabilization and Transfer: In situations where a patient requires transfer to a liver transplant center, stabilizing the patient's condition before transfer is essential. This includes securing the airway if there is altered mental status, maintaining hemodynamic stability with vasopressors if needed, and initiating therapies like CRRT for hyperammonemia. Ensuring a smooth and safe transfer can prevent further complications during transport and enable immediate evaluation upon arrival.
- Consultation for Transplantation Decision-Making: Even if the patient's condition appears to stabilize temporarily, involving a transplant center early allows for a more comprehensive evaluation and helps in determining the ideal timing for listing the patient for transplantation. This proactive approach can provide a critical advantage, especially if the patient's condition worsens unexpectedly.

45.7 Conclusion

The management of acute liver failure in the ICU is a complex and dynamic process that requires vigilance, prompt intervention, and a multidisciplinary approach. This protocol emphasizes securing the airway, preventing cerebral complications,

maintaining hemodynamic stability, and addressing complications such as coagulopathy and infection. A key component of the approach is recognizing patients who may benefit from urgent liver transplantation, as it often remains the definitive treatment for those with irreversible liver damage. Incorporating considerations like specific etiologies, tailored infection management, and advanced care measures helps improve outcomes in this critical condition.

Algorithm 45.1: Approach to acute liver failure in the ICU



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