Acute Liver Failure Protocol

1. **Identification of ALF and notifying consult team:**

   Acute liver failure (ALF) should be suspected in a patient presenting with an International Normalized Ratio (INR) greater than 1.5, with or without overt encephalopathy. Patients typically should not have underlying chronic liver disease and illness should be <26 weeks duration; exceptions to this include patients with Hepatitis B reactivation, autoimmune hepatitis flare, and Wilson disease. [1]

   A careful history is needed to elicit the underlying etiology as this may be help with prognostication and management. Patients should be asked about ingestion of acetaminophen, NSAIDs, enhancement/herbal supplements, mushroom ingestion, antibiotic use, drug/alcohol use or any new medications initiated in the preceding 8-12 weeks. Note: while alcohol alone does not cause acute liver failure, heavy alcohol use may lower the threshold for acute liver injury/failure due to other drugs. [2]

   Additionally, a detailed medical history and social history is needed as these may both be pertinent in regards to underlying etiology of ALF, as well as potential transplant candidacy.

   Please notify the Hepatology fellow via Halo at "HFH Hepatology" once the above history has been gathered. The fellow will then determine whether the patient may be a potential transplant candidate and provide further recommendations.

2. **Workup/lab monitoring**:
   (Order sets -> Pre-liver transplant and Acute Liver Injury/Failure Admission Order Set)

Initial/one time labs	**q1 hour**	**On admission and q4-6 hours in the ICU/q12 in the GPU**	**On admission and q12 hours**
Toxicology Screen	Glucose Fingersticks	Liver Profile	Complete Blood Count
Phosphatidylethanol (PEth)	Neurochecks*	Chemistry Panel	
Ethyl glucoronide		Phosphorus	
Acetaminophen level		Coagulation Profile	
Salicylates		ABG with lactate*	
Ammonia			
Hepatitis A Antibody: IgM and Total			

Hepatitis B Core Antibody: IgM and Total			
Hepatitis B Surface Antibody			
Hepatitis B Surface Antigen			
Hepatitis C Antibody			
Hepatitis B DNA			
Hepatitis C RNA			
HIV 4th Generation Antigen/Antibody Combo			
EBV PCR			
CMV PCR			
HSV PCR			
Syphilis Serology			
Varicella Zoster Antibody IgM, Serum			
Ceruloplasmin			
Iron and TIBC			
Monoclonal Protein Serum Screen			
ANA screen and titer			
Immunoglobulins			
Autoimmune panel			
Alpha-1-antitrypsin			
Alpha Fetoprotein, non-maternal			
Carbohydrate Ag 19-9			
CEA			
ABO/RH Type and Antibody Screen x 2			
Thyroid Screen			
Infectious workup (repeat as indicated if change in clinical status): Blood cultures – if being evaluated for transplant Urinalysis and urine culture (if positive UA) Paracentesis (if ascites present) with ascitic fluid studies and culture COVID-19			

Chest X-ray			
Ultrasound of liver with doppler studies			
CT liver wwo contrast (if no renal dysfunction. If renal dysfunction present, discuss performing an MRI with Hepatology team)			
2D echocardiogram with right heart protocol and bubble study			

*ABG with lactate - only if patient is in the ICU

*Neurochecks – can be done q4 when patient is on the GPU

3. **General medical management:**

   - All patients without contraindications should be placed on IV N-acetylcysteine (NAC). This should be continued for a duration of at least 72 hours; however, if INR is not <2 and Tylenol level is still detectable, the infusion should be continued beyond 72 hours. Note: contraindications to use include a history of anaphylactoid/hypersensitivity reaction to NAC. NAC should be used with caution in patients with congestive heart failure; please contact HFH pharmacy to discuss utilizing a reduced volume of dilution vs switching to PO NAC if the patient can swallow. [3-5]
   - Vitamin K 10 mg IV x 3 days if INR is >2.
   - Avoid correction of coagulopathy with FFPs/cryoprecipitate in the absence of bleeding or invasive procedure as this can contribute to significant volume overload which can complicate potential transplant
   - Thromboelastography (TEG) should be used (in addition to standard coagulopathy parameters) for accurate assessment of degree coagulopathy prior to invasive procedures to determine need for correction
   - Use Kcentra if correction of coagulopathy is needed prior to invasive procedures (including dialysis line placement) to avoid large volume administration of FFP/cryoprecipitate or if FFP/cryoprecipitate administration will lead to delays in care
   - PUD prophylaxis: Daily PPI on an empty stomach, 30-60 min prior to meals
   - If glucose is <60 mg/dL, administer D50 bolus + D10 drip
   - Ensure hepatic dosing of medications
   - I/O, minimize fluids
   - Etiology specific therapies:
     -Budd Chiari – IV heparin
     -Autoimmune hepatitis – IV solumedrol 20 mg every 8 hours or PO prednisone 40-60 mg/day

-Hepatitis B – Entecavir 1 mg daily (can use Tenofovir if Entecavir is unavailable)
***Please note that despite above therapies, transplant evaluation may still be pursued in the appropriate setting.[2, 6]

4. **Encephalopathy management:**

Encephalopathy in ALF is thought to occur partly due to glutamine (a metabolite of ammonia) accumulation in astrocytes and subsequent cerebral edema. This is a different mechanism than that of hepatic encephalopathy, seen in chronic liver disease. Cerebral edema, if advanced, can lead to irreversible brain damage and is a leading cause of death in the ALF population if not addressed promptly. No single clinical tool is sensitive enough to detect early cerebral edema and this condition can develop abruptly; thus a low index of suspicion is needed.[7]

General management (applies to all patients):

If the patient is a potential transplant candidate, a multidisciplinary team including Hepatology, Neurology/Neuro ICU, and Transplant Surgery should be notified of the patient's status via the Halo group "HFH ALF Team".

- Neuro checks every hour (includes checking for asterixis)
- Maintain head of bed at >30 degrees
- Avoid bilateral neck lines. If needs a Udall for RRT, PICC preferred for central access instead of IJ. Femoral lines are a last resort but may be need to be considered if patient has refractory cerebral edema
- Maintain neck midline
- Lactulose titrated to 2-3 soft bowel movements per day; avoid excessive diarrhea as this can lead to free water loss and colonic distension
- Continuous EEG for advanced encephalopathy or if mental status not accounted for by degree edema seen on imaging
- For sedation, pain control, or treatment of suspected alcohol withdrawal, short acting agents should be used with hepatic dose adjustment. Consult pharmacy for guidance.
- Hold sedation at least once a day, and if clinical situation warrants can consider pausing for additional assessment

Grade 1/2 encephalopathy (mild confusion/lethargy & disorientation with asterixis):

- Arterial line
- Serial arterial ammonia q 24
- If NH3 >50 (new/acute), medical therapy with lactulose/rifaximin titrated to 2-3 soft bowel movements per day
- If NH3 greater than 150 or if patient unable to take PO, consult Nephrology for consideration of RRT [10, 11]

- Ensure euvolemia

Grade 3/4 (somnolence/coma):

- Intubation and mechanical ventilation. Avoid high PEEP.
- Continuous EEG +/- antiepileptics per Neurology
- Arterial line
- Serial arterial ammonia q 12
- If NH3 >50 (new/acute), medical therapy with lactulose/rifaximin titrated to 2-3 soft bowel movements per day
- If NH3 greater than 150 or patient unable to take PO, consult Nephrology for consideration of RRT [10, 11]
- Hemodynamic monitoring to ensure euvolemia

Management of cerebral edema:

Any changes in mental status from baseline, presence of neurologic deficits, Cushing's triad (hypertension, bradycardia and irregular respirations) should prompt a STAT CT of the head to assess for cerebral edema, as well as a Neurology consultation. Patient should be transported down to CT by primary team, and Neurology should be notified as patient is being rolled down for CT for expedited read.

- Initial management:
  - Normothermia (external cooling) – avoid shivering due to increase in ICP[12]
  - Central line insertion for hemodynamic monitoring
  - Maintain PCO2 30-35[13]
  - Serum electrolytes every 6 hours
  - Increase sodium by 5 mEq from current level
  - If patient is undergoing SLED, increase Na bath to 150-155
- Further medical management with Mannitol/Hypertonic saline per Neuro ICU
- If no improvement despite medical management, patients should be transferred to the Neuro ICU for intracranial pressure monitoring. This is per Neuro ICU discretion and may depend on whether the patient is a transplant candidate

5. **Electrolyte management and RRT:**
   - Ensure all fluids/drips are in isotonic solution (including NAC)
   - Strict intake/output measurements
   - All fluids/drips should be in isotonic solution.
   - Avoid hyponatremia, hypokalemia and hypomagnesemia.

- Consult nephrology early for consideration of RRT if creatinine begins to rise, oliguria, fluid overload/positive fluid balance and/or in the presence of absolute indications for RRT (volume/electrolyte disturbances)
- If NH3 greater than 150 or patient unable to take PO, consult Nephrology for consideration of RRT
- Consider CRRT as opposed to iHD

6. **Transplant evaluation**.
   The Hepatology team will determine whether to proceed with a full transplant evaluation. If the decision is to pursue a transplant evaluation, the following should be completed to determine transplant candidacy:
   - Complete transplant evaluation labs as above (Order sets -> Pre-liver transplant and Acute Liver Failure Labs/Imaging)
   - Consult Transplant Surgery
   - Consult Transplant Psychology
   - Consult Social Work
   - Consult Cardiology (if age 50 or greater)
   - The need for additional testing or consultations will be determined by the Hepatology team
   - Once a transplant evaluation has been initiated, the transplant team will meet daily to discuss the patient's status and transplant evaluation progress/decision regarding transplantation

References:

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