

Standard ICU Care of Adult Patients with Acute Liver Failure at the University of Michigan

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Acute liver failure (ALF) is defined by the development of coagulopathy and encephalopathy within eight weeks of symptom onset in a patient without known underlying liver disease. The annual incidence of ALF in the United States is estimated at 2,000 cases per year (1). There are a multitude of known causes of ALF which vary widely by geographic region (2). In a prospective series of 308 consecutive ALF patients in the United States, acetaminophen hepatotoxicity was the most commonly identified etiology (39%), followed by indeterminate cases (17%), idiosyncratic drug reactions (13%), hepatitis B (7%), and hepatitis A (4%) (3). Spontaneous transplant-free survival was highest amongst patients with acetaminophen hepatotoxicity (68%) compared to patients with idiosyncratic drug reactions (25%) and indeterminate cases (17%).

ALF patients can have a highly unpredictable and dramatic clinical course. This necessitates aggressive medical management, anticipation of complications, and rapid evaluation and listing for emergency liver transplantation. As many as 80% of ALF patients will develop a bacterial infection during their hospital course with bacteremia noted in 26% (4). Fungal infections are also common in ALF patients, with rates as high as 32% reported (5). In multiple studies, the maximal degree of encephalopathy and coagulopathy have been shown to inversely correlate with survival. The King's College criteria are frequently used in decision making for liver transplantation and early arterial lactate levels appear to improve the PPV and NPV in acetaminophen patients (Table 1) (6, 7).

Cerebral Edema

The onset of encephalopathy (mental status changes) in ALF is often abrupt and can rapidly progress from subtle changes in mood and affect to seizures, obtundation, and decorticate posturing (**Table 2**). Encephalopathy in ALF patients is uniquely associated with the development of **cerebral edema** as opposed to portosystemic shunting of toxins

as seen in cirrhosis. As a result, the management is directed at lowering intracranial pressure in symptomatic patients. The etiopathogenesis of cerebral edema in ALF remains unclear, but two main theories have emerged. The “glutamine” hypothesis is based upon the observation that ammonia is detoxified by astrocytes in the brain to glutamine which can cause cellular swelling and brain edema (8). The second hypothesis contends that cerebral edema results from a loss of intracerebral vascular tone with unopposed cerebral vasodilation and associated increase in brain water and volume (8). Increased intracranial pressure resulting from cerebral edema in ALF is highly unpredictable and can lead to irreversible brain damage and is a leading cause of death. Physical signs of elevated intracranial pressure including papilledema, loss of pupillary reflexes, and clonus as well as CT findings of cerebral edema are **notoriously insensitive** and should not be used for clinical decision making (9). In addition to a heightened awareness and recognition of cerebral edema, epidural ICP monitoring and stepwise interventions can lead to improved outcomes in ALF patients with cerebral edema. Moderate hypothermia to 34° C via external cooling blankets and use of paralytic agents to prevent shivering has shown promise for patients with refractory cerebral edema but remains investigational (10, 11). The AASLD published a Position Paper in 2005 to assist clinicians with the management of ALF patients (12).

Stage I/II encephalopathy

- (I) Subtle change in behavior/ affect with minimal change in consciousness
- (II) Disorientation or inappropriate behavior/ asterixis

1. General Measures

- Admit to the CCMU
- Notify GI fellow and Transplant Surgery resident on call
E-mail rfontana@umich.edu and swelc@umich.edu for possible enrollment in US ALFSG Registry and treatment studies
- Bloodwork
 - CBCP with differential q 12 hours
 - Comprehensive panel q 12 hours
 - PT/INR, PTT, Factor V, arterial NH₃, arterial lactate q 12 hours
 - Type and cross X 2 (needed to list for LT), urinalysis
 - Urine and serum toxicology (ACM level as indicated)
 - Hepatitis serologies: Hepatitis B sAg, cAb, sAb; Hepatitis C PCR (Qualitative); Hepatitis A IgM
 - Ceruloplasmin, ANA, SmAb, SPEP
 - If clinically indicated, CMV PCR , EBV PCR, HSV PCR (Quant)
- Urgent Liver Transplantation evaluation (per GI fellow Table 4).
- Liver Ultrasound with doppler
- Chemsticks q 1- 2 hours
 - D10 drip and D50 bolus if glucose < 60 mg/dl
- Acid suppression: Protonix 20 mg po bid
- Drug dosing: Reduce dose of drugs metabolized in liver (per MICROMEDEX)
- Fever: Keep temperature < 100.0 ° F via cooling blankets (avoid ACM)
- Medical therapy for specific causes of ALF
 - Acetaminophen overdose: NAC 140 mg/ kg load; 70 mg/ kg q 4 hours (Table 5)
 - Budd-Chiari: IV heparin to maintain ACT of 200 to 300 seconds
 - Biopsy confirmed autoimmune hepatitis: IV solumedrol 20 mg q 8 hours

2. Neurologic

- Assess airway/ gag reflex (Intubate as needed)

- Neuro checks q 1 to 2 hours
 - Glasgow Coma score every 4 hours (Table 3)
 - Head of bed > 30° from horizontal to minimize cerebral edema
- **Avoid all medications with sedative properties** (benzos, narcotics, benadryl)
 - Prefer short acting agent for severe agitation (midazolam 1-2 mg IV or propofol 5- 10 ug/ kg/min).
- Minimize valsalva and straining (raises ICP)
- Avoid lactulose (unless evidence of chronic liver disease) because of potential free water depletion (hypernatremia) and abdominal distention

3. Infection

- Blood, urine, and sputum cultures on admission to CCMU
- Diagnostic paracentesis for all patients with ascites, fever or leukocytosis (fluid for cell count with diff and bedside culture in blood culture bottles).
- Antibiotics for suspected infection
 - Unasyn 3.0 gm IV q 6 hours
 - If PCN allergic, Levofloxacin 400 mg q d
 - Fluconazole 100 mg p.o. q d if suspected/ proven fungal infection
- Admission & surveillance blood and urine cultures q 24 hours (as indicated)

3. Renal/ fluids

- Daily weights
- Una, Ucre if azotemia or oliguria
- Maintenance fluids: D5 0.9 NS at 100 cc/ hr
 - 0.9 NS 500 cc bolus for suspected/ confirmed hypovolemia
- Nephrotoxins: Avoid aminoglycosides, NSAID's (e.g. toradol), IV contrast dye
- Nutrition: enteral preferred over TPN (dophoff preferred due to aspiration risk)

4. Bleeding

- Prophylactic vitamin K 10 mg sq QD x 3 days
- Invasive procedure prophylaxis (central line, ICP, liver biopsy)
 - Transfuse FFP to INR < 1.5 immediately before
 - Transfuse platelets to > 50,000 immediately before
- **AVOID** maintenance FFP infusion **since** obscure prognostic value of INR / Factor V

Stage III/ IV Encephalopathy

- (III) Somnolent but arousable to vocal stimuli, marked confusion, incoherent
- (IV) Comatose, unresponsive to pain, decorticate/ decerebrate posturing, seizures

1. General measures

- Place arterial line
 - ABG, arterial NH₃, and arterial lactate q 12 hours
- Blood work
 - CBC with differential q 12 hours
 - Comprehensive panel, Mg +, osmolality q 12 hours
 - PT/ INR, Factor V, Fibrinogen q 12 hours
- Liver transplantation
 - Candidacy determined per GI and Transplant surgery
 - Notify Neurosurgery when patient listed as status 1 or with Stage 3/ 4 HE

2. Neurological

- Elective intubation for Stage III encephalopathy for Airway protection
 - Induction: Sodium pentothal and succinylcholine or cisatracurium
 - Ventilatory settings: Maintain PaO₂ > 70 mm Hg with low PEEP and FIO₂ < 40% if possible. Ventilatory rate to maintain PCO₂ 30 mm Hg
 - Mechanism: Hyperventilation causes cerebral vasoconstriction
 - Sedation: Propofol for agitation 5-10 ug/kg/min if clinically indicated
- Avoid surges in ICP
 - Keep HOB > 30 ° from horizontal
 - Minimal endotracheal suctioning
 - Minimize coughing, straining
 - Use cooling blankets to keep core temp < 37.0° C or 99.0° F
 - Transportation: Do not move patient out of ICU (bedside studies)
- Glasgow Coma scale q 4 hours.
 - Notify neurosurgery if patient no longer has purposeful movement to noxious stimuli or has evidence of decorticate/ decerebrate posturing
 - Blood products pre-operatively to place ICP monitor (Table 6)

- Non-contrast Head CT prior to ICP monitor (r/o intracranial bleed)
- ICP monitoring
 - ICP monitor placed and calibrated by Neurosurgery
 - CPP= MAP – ICP Goal to maintain CPP > 60 mm Hg
 - ICP recorded on vital sheet by RN every hour when ICP < 20 mm Hg and every 15 min if ICP > 20 mm Hg.
 - RN to notify service if persistent rise in ICP of 5 mm Hg or greater
- **Mannitol**
 - **Indications:** First line therapy for persistent surges in ICP > 10 minutes not responding to hyperventilation
 - **Mechanism:** Draws fluid into intravascular space
 - **Dose: 0.5 – 1.0 g / kg IV bolus over 5 minutes**
 - Caution: Monitor serum osmolarity q 4 hours
 - Withhold if serum osmoles > 320 mOsm/ l
 - Lasix (10-40 mg IV) if fluid overload/ hyperosmolar from mannitol
 - Mannitol may be ineffective and lead to pulmonary edema if acute renal failure present
- **Pentobarbital**
 - **Indications:** 2nd line therapy if ICP not improved with hyperventilation and mannitol
 - **Mechanism:** Reduces cerebral oxygen utilization
 - **Dose: 100 – 150 mg bolus over 15 minutes**
 - Continuous infusion: 1-3 mg/ kg / hr
 - Serum pentobarbital level q 8 hours
 - Keep blood level 20 –35 mg/l
 - Caution: Infusion can lead to systemic hypotension (use dopamine as needed to maintain CPP > 60 mm Hg)
- **Moderate Hypothermia**
 - Indications: Cerebral edema refractory to hyperventilation, mannitol, and pentobarbital

- Mechanism: Reduces cerebral oxygen utilization/ blood flow
- **Lower core temperature to 33-34 ° C using cooling blankets**
 - Discontinue phenobarbitol drip if you plan to utilize hypothermia
 - Apply cooling blankets to whole body
 - Monitor core temperature using rectal thermometer
 - Sedation: Paralytic agent required to prevent shivering (Atracurium 300-600 ug/kg/hr along with propofol)
 - Lower core temperature down to 34° C to maintain CPP
 - Delay of up to 1 hour to see reduction in ICP
- Caution: Cardiac arrhythmias (Bradycardia), worsening coagulopathy, hypotension, infections
- **Seizures**
 - Hypoglycemia: Assess and treat with D50 and D10 drip
 - Neurology consult for EEG monitoring
 - If seizures/ PLEDS on EEG
 - Dilantin: 18 mg/ kg loading dose over 30 minutes then 100 mg q 8 hrs
 - Monitor free dilantin levels q d per neurology
 - Pentobarbitol : 3mg/kg IV bolus for refractory seizures

3. Hemodynamics/ Inotropes

- Dopamine/ levophed as needed to maintain adequate MAP and CPP > 60
 - Initiate to maintain SBP > 90 and CPP > 60 mm Hg
- Swan-Ganz when ICP monitor placed or inotropes required
- Caution: Cushing's reflex (hypertension, bradycardia) may be forerunner of impending uncal herniation

4. Renal/ fluids

- Acute renal failure in ALF multifactorial (ATN, hepatorenal, pre-renal)
 - Nephrology consult if oliguria/ progressive azotemia
 - CVVH preferred over hemodialysis due to hemodynamic instability
- Hyponatremia: Calculate and correct free water deficit
 - Avoid rapid Na correction (< 5 Meq change / 12 hour)

5. Infection

- Bacterial infections from lines, catheters common
 - Empiric antibiotics for suspected infection, leukocytosis, or fever
 - Unasyn 3.0 g q 6 hrs for enteric organisms
 - If PCN allergic, Levaquin 400 mg q d
 - Vancomycin 1.0 gm q 24 –48 hrs for suspected line infection
- Fever
 - Daily surveillance blood and urine cultures
 - Keep body temperature < 99.0° F to minimize cerebral blood flow
 - Cooling blanket preferred over acetaminophen / NSAID's

Table 1 King's College criteria for Liver Transplantation in ALF**Acetaminophen Hepatotoxicity****Non-Acetaminophen ALF**

Arterial lactate > 3.5 4 hrs after resuscitation

Or

PH < 7.30 or arterial lactate > 3.0 12 hrs
after resuscitation

Or

INR > 6.5 (PT > 100 sec)
Serum creatinine > 3.4 mg/dl
Stage 3 or 4 encephalopathy

INR > 6.5 (PT > 100 sec)

Or any 3 of the following:

INR > 3.5 (PT > 50 sec)
Age <10 or > 40 years
Serum bilirubin > 17.5 mg/dl
Duration of jaundice > 7 days
Etiology: drug reaction**Table 2- Stages of Encephalopathy in ALF**

Stage	Spontaneous Survival	Mental Status
I	70%	Mild changes in mood; mildly slurred speech; disorder of sleep rhythm, fluctuant, mild confusion
II	60%	Accentuation of stage I encephalopathy; I nappropriate behavior; mild somnolence
III	40%	Somnolent, but arousable to verbal command; marked confusion, incoherent speech
IV	20%	Unarousable to painful stimuli (comatose)

Table 3 Glasgow Coma Scale

A) Eye opening

- 4 = spontaneously
- 3 = to verbal command
- 2 = to painful stimuli
- 1 = none

B) Verbal response

- 5 = oriented
- 4 = confused
- 3 = inappropriate speech
- 2 = incomprehensible words
- 1 = none

C) Motor Response

- 6 = obeys commands
- 5 = localizes pain
- 4 = flexor withdrawl
- 3 = abnormal flexion
- 2 = extensor posture
- 1 = none

Glasgow Coma Score = A + B + C

** Use best response

Table 4: Evaluation for Liver Transplantation

<u>STUDY</u>
Medical/ Surgical evaluation GI/ Hepatology consult Transplant surgery consult Transplant social work
Bloodwork Type and cross x 2 (needed to list for transplant per UNOS) PT/INR, Factor V AFP, CBC + plts, comprehensive
Cultures/Microbiology Blood and peritoneal fluid as indicated PPD and candida
Serologies HIV CMV/HSV/EBV/Toxo titers Hepatitis B sAg, sAb, cAb HCV RNA PCR Hep A IGM/ IGG
Imaging Liver USN with Doppler (bedside) Chest x-ray
Cardiac Evaluation as Indicated EKG Bedside Dobutamine echo (if CAD risk factors) Bedside 2-D surface echo with doppler (no CAD risk)

All studies should be completed within 24 hours of admission to ICU

Table 5: IV N-acetylcysteine for Acetaminophen overdose

For patients with ACM toxicity that are intolerant of oral NAC (e.g. ileus, refractory N/V) or with pregnancy, there is an FDA approved formulation of NAC (Acetadote) that can be given intravenously

IV Acetadote infusion protocol

Dose 1. Loading dose: 150 mg/ kg NAC in 200 ml D5W over 1 hour

Dose 2. 50 mg/kg NAC in 500 ml D5W over 4 hours

Dose 3. 125 mg/kg NAC in 1000 ml D5W over 19 hours

Dose 4. 150 mg/kg NAC in 1000 ml D5W over 24 hours

Dose 5. 150 mg/kg NAC in 1000 ml D5W over 24 hours

Caution

1. NAC is contraindicated in patients with **sulfa allergy**
2. If ACETADOTE is not available, standard oral NAC can be mixed for intravenous administration using a leukopore filter
3. IV NAC can lead to anaphylactoid/ hypersensitivity reactions with rash, wheezing in up to 3% of treated patients (15).
4. Hold and reduce infusion rate by 50% if subject intolerant
 - Administer fluids, IV benadryl, IV steroids as needed

Table 6: ICP monitor protocol in ALF patients

1. Consult Neurosurgery when ALF patient with Stage III/ IV encephalopathy admitted to ICU
2. ICP monitors to be placed in ALF patients with Stage $\frac{3}{4}$ encephalopathy with possibility of recovery with medical or surgical interventions
 - Patient should have either 1) non-purposeful movement to painful stimuli 2) decorticate or decerebrate posturing or 3) no response to painful stimuli while off sedation for at least 2 hours
3. Preoperative assessment
 - Non-contrast head CT before ICP placement (R/o intracranial bleed)
 - Coagulation abnormalities
 - Transfuse platelets to keep > 50 k
 - Transfuse Cryoprecipitate if fibrinogen < 100 mg/dl
 - Transfuse 2 to 4 units of FFP to INR < 1.5
 - If INR > 1.5 after 4 units FFP, rFVIIa infusion per protocol **
4. ICP monitor placement and calibration per Neurosurgery
 - Page Neurosurgery if
 - Unable to obtain adequate ICP tracing
 - Unexplained sustained increase in ICP
5. ICP management per ALF management guideline

Table 7: Recombinant FVIIa infusion protocol

- **Indication:** To reduce risk of peri-operative bleeding in ALF patients with persistent hypoprothrombinemia despite FFP infusion requiring urgent ICP monitor placement or other invasive surgery/ procedure with high risk of bleeding
 - **Mechanism of action:** Localized clot formation in areas of tissue factor release. rFVIIa in the presence of tissue factor activates FIX to FIXa which activates FX to FXa resulting in activation of prothrombin (FII) to thrombin (FIIa). Typically enhances clot formation for 2 to 8 hours with a t1/2 of 2 hours.
 - **Contraindications:** Budd-Chiari, known or suspected malignancy, history of DVT/ PE, Pregnancy, hypersensitivity to Vitamin K or mouse, bovine, or hamster proteins
 - **Administration:**
 - 4 units of FFP to have been previously infused with persistent INR > 1.5
 - Cryoprecipitate to be given for patients with fibrinogen < 100 mg/dl immediately before rFVIIa
 - Dose: * **80 ug/kg rFVIIa** IV bolus over 2 to 5 minutes immediately prior to ICP placement (provides up to 4 hour window to place ICP monitor)
 - Do not wait to confirm correction of INR post-infusion since short half-life
 - **Lab Studies**
 - **Pre-infusion:** CBC + platelets, PT, aPTT, Factor V, fibrinogen, D-dimer
 - **1 hour (60 min) post-infusion:** CBC + platelets, PT, aPTT, Factor V
 - **4 hour (240 min) post-infusion:** CBC + platelets, PT, aPTT, Factor V
 - **8 hour (480 min) post-infusion:** CBC + platelets, PT, aPTT, V
- * Vial sizes are 1200, 2400, and 4800 ug. Always round up or down to nearest vial size.

References

- 1) Hoofnagle JH, Carithers RI, Shapiro C, Ascher N: Fulminant hepatic failure: a summary of a workshop. *Hepatology* 1995, 21:240-252.
- 2) Ostapowicz G, Lee WM. Acute hepatic Failure: A western perspective. *J Gastroenterology and Hepatology* 2000, 15:480-88.
- 3) Ostapowicz G, Fontana RJ, Schiodt FV, et al Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Annals of Internal Medicine* 2002; 137: 947-954,
- 4) Rolando N, Harvey F, Brahm J, et al: Prospective study of bacterial infection in acute liver failure: an analysis of fifty patients. *Hepatology* 1990, 11:49.
- 5) Rolando N, Harvey F, Brahm J, et al: Fungal infection: a common, unrecognized complication of acute liver failure. *J Hepatol* 1991, 12:1.
- 6) O'Grady JG, Alexander GJ, Hayllar KM, Williams R: Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989, 97:439-445.
- 7) Bernal W, Donaldson N, Wyncoll D, Wendon J. Blood lactate as an early predictor of outcome in paracetamol-induced acute liver failure: A cohort study. *Lancet* 2002; 359: 558-563.
- 8) Blei A, Larsen F: Pathophysiology of cerebral edema in fulminant hepatic failure. *J Hepatol* 1999, 31:771-776.
- 9) Munoz SJ, Robinson M, Northrup B, et al. Elevated intracranial pressure and computed tomography of the brain in fulminant hepatocellular failure. *Hepatology* 1990, 13: 209-212.
- 10) Jalan R, Camink SWE, Deutz NEP, et al. Moderate hypothermia for uncontrolled intracranial hypertension in acute liver failure. *Lancet* 1999; 354: 1164-68.
- 11) Jalan R, Damink SWM, Deutz NEP, et al. Restoration of cerebral blood flow autoregulation and reactivity to carbon dioxide in acute liver failure by moderate hypothermia. *Hepatology* 2001; 34: 50-54.
- 12) Polson JP, Lee WM. AASLD position paper: The management of acute liver failure. *Hepatology* 2005;41:1179-97.
- 13) Herman GD, Meijer K, DeWolf JT, et al. Reduced transfusion requirements by recombinant factor VIIa in orthotopic liver transplantation. *Transplantation* 2001; 72: 402-405.
- 14) Shami VM, Caldwell SH, Hespenheide EE, et al. Recombinant activated Factor VII for coagulopathy in fulminant hepatic failure compared with conventional therapy. *Liver Transplantation* 2003; 9:138-144.
- 15) Kao LW, Kirk MA, Furbee RB, et al. What is the rate of adverse events after oral N-acetylcysteine administered by the intravenous route to patients with suspected acetaminophen poisoning? *Ann Emerg Med* 2003; 42: 741-750.