GUIDELINE TITLE: Acute Liver Failure (Fulminant Liver Failure) - Clinical Guidelines
(also can be used for acute on chronic liver failure patients with noted caveats)

DISTRIBUTE TO: ALL Liver Service RELATED PROVIDERS

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☑ Patient Care  □ JCAHO
□ Nursing Practice  □ Title 22
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Effective Date: Reviewed or Revised: July 31, 2015
Unit/Department of Origin: Renown Inpatient Liver Service
Other Approval:
Policy/Procedure:

Acute Liver Failure Protocol

Timothy Halterman, MD; Robert Gish, MD

GOAL

- Provide optimal intensive care to patients with acute liver failure (ALF) which will include patients with fulminant and subfulminant liver failure who are being managed on the wards and in the ICU

OBJECTIVES

- Define and recognize acute (fulminant and subfulminant) liver failure (hereafter termed “ALF”)
- Promptly identify cause of ALF, when possible
- Identify common complications associated with ALF and appropriate strategies to prevent or manage related complications
- Rapidly triage ALF patients for possible transfer for transplant evaluation and listing, when appropriate
- Identify where this can be used for AoC, Acute on Chronic Liver Failure Patients

RESPONSIBLE PARTIES

- Gastroenterologists/Hepatologists
- ICU Attendings
- Hospitalists
- House staff
- Infectious Disease Consultant
- Nephrology Consultant
- Pharmacists
- Nutritionists
- Local Liver Transplant Centers
  1. Stanford transfer center phone number: 1-800-800-1551
  2. UCSF transfer center phone number: 1-415-353-9166
  3. CPMC transfer center phone number: 1-888-637-2762
SUMMARY and KEY POINTS FOR MANAGEMENT of ALF PATIENTS

1) First line testing for ALF cause
   a. Complete a full work up for viral hepatitis using HAV IgM, HBsAg, anti-HBc IgM, HCV Ab, HCV RNA, HEV IgM, if all tests negative, do HEV RNA blood and stool
   b. All patient needs to have a tox screen, acetaminophen level, alcohol blood level
   c. Autoimmune work up should include ANA, anti-F actin Ab, serum immunoglobulins, ANCA
   d. Abdominal US with Doppler to assess patency and size of portal and hepatic veins as well as liver and spleen size and presence of ascites

2) Second line testing for ALF cause
   a. Wilson Disease work up should be completed on any patient who is negative for first line testing including ceruloplasmin and 24 hour urine copper
   b. Liver Biopsy, transjugular preferred, with hepatic venogram, and pressure measurements, liver tissue to be sent for quant copper, path report to detail % necrosis, central veins, presence or absence of plasma cells

3) Daily labs should include CBC, CMP, INR, TEG, fibrinogen, lactate and PO4

4) Calculate MELD score daily

5) Monitor glucose every 2-6 hours and maintain glucose in 100-120 range with IV glucose D5 or if needed D10 as the risk of hypoglycemia is substantial in patients with ALF

6) Check AFP, ABG and calculate Kings criteria score (see below) on admit for prognostic purposes

7) Obtain blood and urine cultures on admit to rule out infection
   a. Do not use antibiotics empirically. Treat with broad spectrum antibiotics and antifungals if there are signs or symptoms of active infection

8) Check and grade mental status/Hepatic Encephalopathy daily using West Haven Score and treat accordingly. Do not use ammonia levels to guide therapy
   a. If stage III or IV hepatic encephalopathy, use hypothermia and induce hypernatremia (goal Na 150). Also consider mannitol if serum Osm <320 mOsm/L as well as hyperventilation if on ventilator

9) Use IV propofol for sedation and IV Fentanyl for analgesia. Avoid benzos, narcotics and central acting emetics

10) Elevate head of bed 30 degrees and sand bag head to minimize lateral movements

11) Avoid excessive stimulation. Minimize suctioning and other noxious stimuli

12) Avoid fluid overload to prevent pulmonary edema and prevention of intracranial hypertension

13) Use of coagulation products including FFP, cryoprecipitate and platelets should be ordered based on if patient is actively bleeding, having a high risk invasive procedure, or low fibrinogen level. Type of coagulation products given should be determined by TEG measurement. Coagulation products should not be given for asymptomatic elevated INR alone.

14) Treat all patients with IV NAC for 3 days (even if no history of acetaminophen exposure) then PO NAC until bilirubin is less than 5 mg/dL or INR decreases to less than 1.5 at doses in the same protocol used for Tylenol OD

15) If hypotensive with low MAP despite volume repletion with associated hepatic encephalopathy, initiate vasopressor in form of norepinephrine and trial of hydrocortisone, midodrine can be used for blood pressure support

16) Patients need supplemental nutrition to keep calorie intake between 2500-3000 cal per day
   a. Use 24 hour tube feeds
   b. Use IV intralipid 500 ml over 16 hours, to provide cholesterol and phosphatidyl choline for cell regeneration, this provides approx. 1000 cal per day

17) Early contact with liver transplant center in those with ALF if deemed to be liver transplant candidate

BACKGROUND
Acute (fulminant and subfulminant) liver failure (ALF) is a rare but serious clinical syndrome characterized by sudden loss of hepatic function in a person without evidence of preexisting liver
disease [1]. Exceptions to this definition include Wilson Disease, reactivation of hepatitis B, and autoimmune hepatitis [2]. ALF affects between 2,000 – 3,000 Americans per year [3]. Causes of ALF include, but are not limited to, drug or toxin induced liver disease, viral hepatitis, metabolic diseases, and vascular and/or ischemic liver disease, though as many as 20% of cases have no identifiable cause (See Table 1 & Figure 1). Acetaminophen overdose (APAP) is the leading cause of ALF. Patients at increased risk for APAP-induced ALF include those with concomitant alcohol use, malnutrition, or use of medications known to induce CYP 450 enzymes (e.g. phenytoin, carbamazepine, rifampin, etc.).

<table>
<thead>
<tr>
<th>TABLE 1: ETIOLOGIES OF FULMINANT HEPATIC FAILURE [4, 5]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Viral</td>
</tr>
<tr>
<td>- HAV, HBV ± HDV, HEV, HSV, CMV, EBV, HVZ, adenovirus, hemorrhagic fever viruses</td>
</tr>
<tr>
<td>B. Drugs and toxins</td>
</tr>
<tr>
<td>- Dose-dependent: acetaminophen, carbon tetrachloride (CCl₄), yellow phosphorus, <em>Amanita phalloides</em>, <em>Bacillus cereus</em> toxin, sulfonamides, tetracycline, Ecstasy (methyldioxymethamphetamine), herbal remedies</td>
</tr>
<tr>
<td>- Idiosyncratic: halothane, isoniazid, rifampin, valproic acid, NSAIDs, disulfiram</td>
</tr>
<tr>
<td>C. Vascular</td>
</tr>
<tr>
<td>- Right heart failure, Budd-Chiari syndrome, veno-occlusive disease, shock liver (ischemic hepatitis), heat stroke</td>
</tr>
<tr>
<td>D. Metabolic</td>
</tr>
<tr>
<td>- Fulminant (acute) fatty liver of pregnancy, Wilson disease, Reye’s syndrome, galactosemia, hereditary fructose intolerance, tyrosinemia</td>
</tr>
<tr>
<td>E. Miscellaneous</td>
</tr>
<tr>
<td>- Malignant infiltration (liver metastases, lymphoma), autoimmune hepatitis, sepsis</td>
</tr>
<tr>
<td>F. Indeterminate</td>
</tr>
<tr>
<td>- Includes primary graft non-function in liver transplanted patients</td>
</tr>
</tbody>
</table>

Abbreviations: HAV, hepatitis A virus; HBV, hepatitis B virus; HDV, hepatitis D virus; HEV, hepatitis E virus; HSV, herpes simplex virus; CMV, cytomegalovirus; EBV, Epstein Barr virus; HVZ, herpes varicella zoster virus; CCl₄, carbon tetrachloride; INH, isoniazid; NSAIDs, non-steroidal anti-inflammatory drugs.
**Etiology of Acute Liver Failure in Adults**

![Etiology of Acute Liver Failure in Adults](image)

*FIGURE 1. Etiology of ALF in the 1,147 adult patients who were enrolled in the U.S. ALF Study Group database between January 1998 and July 2007 [6].*

**DEFINITION**

ALF is manifest by the presence of coagulopathy (INR > 1.5) and encephalopathy that occur within 26 weeks of first onset of symptoms in patients without underlying liver disease [7, 8]. The particular timing and severity of clinical presentation may be divided into hyperacute, acute, and subacute (which also includes the term subfulminant) categories which can provide clues as to the underlying cause and prognosis (see Table 2).

**TABLE 2**

Timing and Severity of Clinical Presentation & Clinical Prognosis

<table>
<thead>
<tr>
<th></th>
<th>Hyperacute (Fulminant)</th>
<th>Fulminant (acute)</th>
<th>Subfulminant (subacute)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice to Encephalopathy (time)</td>
<td>0 - 1 week</td>
<td>1 - 4 weeks</td>
<td>4 - 12 weeks</td>
</tr>
<tr>
<td>Severity of Coagulopathy</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Severity of Jaundice</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Degree of ICH</td>
<td>+++</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Survival without Liver Transplant</td>
<td>Good</td>
<td>Moderate</td>
<td>Poor</td>
</tr>
<tr>
<td>Typical Cause</td>
<td>Acetaminophen, HAV, HEV</td>
<td>HBV</td>
<td>Non-acetaminophen drug toxicity</td>
</tr>
</tbody>
</table>

+++ = High severity; ++ = Medium severity; + = Low severity; ICH = Intracranial hypertension.

Adapted from Bernal 2010 [9]

**Clinical Features of ALF**

Multiorgan failure (MOF) is the most common cause of death (>50%) from ALF, with intracranial hypertension (ICH) and infection accounting for most other deaths in this patient population [10].
Specific complications of ALF, their detection, and their management are discussed below:

**COMPLICATIONS OF ALF**

*Encephalopathy*

Severity of encephalopathy (see criteria below) may vary but is inversely correlated with the prognosis of ALF. Cerebral edema is common in ALF and one of the most common causes of death in this patient population. Although not entirely reliable, cerebral edema may be recognized clinically by the development of:

- systemic hypertension and bradycardia (Cushing reflex)
- decerebrate rigidity
- disconjugate eye movements
- loss of papillary eye movements

Controlling intracranial hypertension (ICH) and maintaining sufficient cerebral perfusion pressure (CPP) is essential to preserving neurologic function (see treatment).

**TABLE 3: Grade of Hepatic Encephalopathy**
West Haven Criteria Used to Grade HE Severity

<table>
<thead>
<tr>
<th>Grade 0</th>
<th>Lack of detectable changes in personality or behavior</th>
<th>No asterixis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Trivial lack of awareness, shortened attention span, sleep disturbance, altered mood</td>
<td>Asterixis may be present</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Lethargy, disorientation to time, amnesia of recent events, impaired simple computations, inappropriate behavior, slurred speech</td>
<td>Asterixis is present</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Somnolence, confusion, disorientation to place, bizarre behavior, clonus, nystagmus, and positive Babinski sign</td>
<td>Asterixis is usually absent</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Coma; unresponsive to verbal or noxious stimuli</td>
<td></td>
</tr>
</tbody>
</table>

Reference [4]

Coagulopathy

The principle hematologic derangements of ALF include reduced platelet number and function as well as reduced circulating levels of fibrinogen and coagulation factors II, V, VII, IX, and X (factors VII and V, in particular) manifesting as elevated INR (formally termed prolonged prothrombin time (PT)). The severity of INR prolongation varies according to the etiology of ALF (see figure below from [11]). Because INR is an important prognostic indicator in ALF, controlling INR with fresh frozen plasma (FFP) is only generally indicated to control bleeding or prevent bleeding associated with invasive procedures (see separate document on the TEG procedure and its utility). Recent clinical data suggest that spontaneous and clinically significant bleeding in ALF is rare (about 5%) and spontaneous intracranial hemorrhage occurs <1% in the absence of insertion of an intracranial pressure monitoring device [11]. Most bleeding in this patient population occurs from mucosal lesions (superficial gastric erosions, nasopharynx, urogenital) [11]. Therapeutic tools for management of coagulopathy in ALF include FFP, cryoprecipitate, recombinant activated factor VII (rFVIIa), exchange plasmapheresis, platelet concentrates, and vitamin K. With severe coagulopathy, it can be difficult to correct the INR to 1.5 or less with FFP and risks of this approach include volume overload (may be managed with exchange transfusion) and hypersensitivity reactions. While there are data to support combined use of FFP and rFVIIa to correct INR, the optimal dosing schedule and risk for thrombotic complications are not
established at this time. Severe hypofibrinogenemia (<100 mg/dL) should be treated with administration of cryoprecipitate.

**WORK-UP OF PATIENTS WITH ALF**

- Obtain detailed **medical history** from patient and/or family, including:
  - First onset of symptom(s)
  - All medications used over the last 6 months including prescription medications, OTC/herbals, wild mushrooms, or other alternative/complementary therapies
  - Detailed history of current and historical substance use including alcohol use
  - Depression/suicidality
  - Viral prodrome
  - Recent travel

- **Initial Laboratory tests**: Hepatic panel, CBC with differential, PT/INR, comprehensive metabolic panel, Magnesium, phosphorus, complete toxicology screen, Factor V level, AFP, arterial lactate, ABG, arterial ammonia level, acetaminophen level, HbsAg (Hepatitis Delta IgG if HsAg +), HBcAb IgM, HAV IgM, HEV IgG (if + may order HEV RNA in selected pts), HCV Ab, HCV RNA PCR, HIV Ab, blood and urine cultures, urinalysis, amylase/lipase, blood type (x2), serum pregnancy test if female, TEG

- Suggested labs if unknown etiology (“seronegative” ALF) : ANA, Anti-actin Ab (F-actin), Quantitative immunoglobulins, Anti-SLA (soluble liver antigen), ceruloplasmin, 24-hour urine for copper, Anti HEV IgM, HEV RNA by PCR in stool and blood

- If viral syndrome identified or suspected: consider HSV 1/2 IgM (PCR also available), EBV PCR, CMV PCR, adenovirus, HBV PCR and HCV PCR

- Consider diagnostic transjugular liver biopsy for all unknown or non-acetaminophen cases. (Note: histology has not been shown to predict outcomes, although with AIH the liver biopsy helps to strategize immunosuppression)

- Abdominal US with Doppler to confirm portal and hepatic vein patency

- Chest X-ray
- Non-contrast head CT if grade 3-4 hepatic encephalopathy (HE)
- Echocardiogram and EKG if potential liver transplant candidate

**DIAGNOSIS**

The proposed work-up above may identify patients with APAP-induced liver injury, viral hepatitis, Wilson disease, and autoimmune liver disease. The tables below review the patterns of drug induced liver injury (DILI) and herbal supplements reported to cause ALF. This information may be helpful in determining etiology in patients without an identifiable cause after the work-up above.
### TABLE 4: Overview of Drug-Induced Liver Injury Patterns

<table>
<thead>
<tr>
<th>Histological pattern</th>
<th>Differential diagnosis</th>
<th>Common drugs involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute hepatitis and cholestatic hepatitis</td>
<td>Viral hepatitis, autoimmune hepatitis, Wilson disease, sclerosing cholangitis</td>
<td>See table 3</td>
</tr>
<tr>
<td>Acute liver failure</td>
<td>Autoimmune hepatitis, viral hepatitis, Wilson disease</td>
<td>Isotretinoin, monoamine oxidase inhibitors, anticonvulsants (phenytoin, valproate), antibiotics (sulfonamides, cotrimoxazole, ketocconazole)</td>
</tr>
<tr>
<td>Necrosis with marked inflammation</td>
<td>Autoimmune hepatitis, viral hepatitis, Wilson disease</td>
<td>Acetaminophen, cocaine, MDMA (ecstasy), carbon tetrachloride</td>
</tr>
<tr>
<td>Necrosis with little or no inflammation</td>
<td>Herpes simplex or adenoviral hepatitis, Wilson disease, malignant infiltration</td>
<td>Tetracycline, nucleoside analogues</td>
</tr>
<tr>
<td>Microvesicular steatosis with little or no inflammation</td>
<td>Acute alcohol intoxication, Reye syndrome, fatty liver of pregnancy</td>
<td>Lignocaine, risperidone, tramadol, aciclovir, tegafur, tamoxifen, methotrexate</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>Autoimmune hepatitis, chronic viral hepatitis, Wilson disease</td>
<td>Chlorpromazine, clonazepam</td>
</tr>
<tr>
<td>Drug-induced autoimmune hepatitis</td>
<td>Autoimmune hepatitis</td>
<td>Acetaminophen, cocaine, MDMA (ecstasy), carbon tetrachloride</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>Sepsis, cardiac failure, shock, large duct obstruction, benign intrahepatic cholestasis, intrahepatic cholestasis of pregnancy</td>
<td>Bacterial, fungal, viral, drug-induced, autoimmune</td>
</tr>
<tr>
<td>Bile duct cholestasis</td>
<td>Viral hepatitis, large duct obstruction</td>
<td>Anabolic/androgenic steroids, oestrogenic steroids, NSAIDs (nimesulide, piroxicam)</td>
</tr>
<tr>
<td>Cholestatic hepatitis (cholestatic or hypersensitivity cholestasis)</td>
<td>Viral hepatitis, large duct obstruction</td>
<td>Chlorpromazine, clonazepam</td>
</tr>
<tr>
<td>Granulomatous hepatitis</td>
<td>Infecions, sarcoidosis, primary biliary cirrhosis, tbc, metal toxicity</td>
<td>Isotretinoin, interferon, phenytoin, allopurinol (also see box 2)</td>
</tr>
<tr>
<td>Steatosis/sinusoidal steatosis</td>
<td>Diabetes, obesity, Wilson disease, hepatitis C</td>
<td>Alcohol, steroids, total parenteral nutrition, gold, cholestasis, hydrocarbons, chemotherapeutic agents (5-fluorouracil)</td>
</tr>
<tr>
<td>Macrophage cholestasis</td>
<td>Diabetes, obesity, Wilson disease, hepatitis C</td>
<td>Alcohol, steroids, total parenteral nutrition, gold, cholestasis, hydrocarbons, chemotherapeutic agents (5-fluorouracil)</td>
</tr>
<tr>
<td>Microvesicular steatosis</td>
<td>Fatty liver of pregnancy, carcinoma deficiency, Reye syndrome</td>
<td>Alcohol, steroidal, total parenteral nutrition, gold, cholestasis, hydrocarbons, chemotherapeutic agents (5-fluorouracil)</td>
</tr>
<tr>
<td>Steatohepatitis</td>
<td>(See macrovesicular steatosis differential)</td>
<td>Alcohol, steroidal, total parenteral nutrition, gold, cholestasis, hydrocarbons, chemotherapeutic agents (5-fluorouracil)</td>
</tr>
<tr>
<td>Vascular abnormalities</td>
<td>Myelosclerosis, venous outflow obstruction, right heart disease</td>
<td>Oxalates, pyrrolidine alkaloids, chemotherapy for ALL</td>
</tr>
</tbody>
</table>

*ALL: acute lymphoblastic leukaemia; MEMA, 3,4-methylenedioxymethylamphetamine; NSAID, non-steroidal anti-inflammatory drug.*

### TABLE 5: Herbal Products with Known Hepatotoxicity

<table>
<thead>
<tr>
<th>Herbal product</th>
<th>Intended use</th>
<th>Biopsy findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chelmar leaf (creosote bush, Larrea tridentata)</td>
<td>Antimicrobial, anti-aging, skin conditions</td>
<td>Acute hepatitis, cholestasis, hepatocellular necrosis</td>
</tr>
<tr>
<td>Germander (Teucrium scorpiodes)</td>
<td>Antispasmodic, anti-inflammatory, abdominal ailments, obesity</td>
<td>Acute hepatitis, centrilobular necrosis, rarely chronic liver disease with cirrhosis</td>
</tr>
<tr>
<td>Penstemon (Jawae californicum, Hedeoma pulegioides), &quot;snap pea&quot;</td>
<td>Emmunomodulator, antiflame agent for pets</td>
<td>Centrilobular necrosis</td>
</tr>
<tr>
<td>Glue thistle (Cynachum gomphocarpum), found in Mediterranean region and North Africa</td>
<td>Antibacterial, antiviral, anti-inflammatory</td>
<td>Centrilobular necrosis, parenchymal necrosis</td>
</tr>
<tr>
<td>Chin bu hun (lycopodium zonatum), marketed as anodyne tablets in 1990s</td>
<td>Sleep aid, analgesic</td>
<td>Acute hepatitis, chronic hepatitis, microvesicular steatosis</td>
</tr>
<tr>
<td>Kava (Piper methysticum)</td>
<td>Stress relief, anti-anxiety, sleeping aid, premenstrual syndrome</td>
<td>Acute hepatitis, fulminant hepatitis</td>
</tr>
<tr>
<td>Mitale (Phoradendron and Vaccum geis)</td>
<td>Digestive aid, heart tonic, sedative</td>
<td>Acute hepatitis</td>
</tr>
</tbody>
</table>

[12]
TREATMENT OF ALF

General Pharmacologic Treatment
IV NAC should be administered to every patient with ALF with unclear etiology per acetaminophen protocol (listed below in table 6) until INR less than 1.5.

Etiology Specific Therapies
There are very few identified therapies that may be effective for specific causes of ALF and these are shown in Table 6, below.

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Therapy</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>NAC Oral: 140 mg/kg load, then 70 mg/kg Q 4 h until discontinued by hepatology or transplant surgery attending physician</td>
<td>[13]</td>
</tr>
<tr>
<td></td>
<td>NAC IV: 150 mg/kg load, then 50 mg/kg IV over 4 hours, then 100 mg/kg IV over 16 hours as a continuous infusion until discontinued by hepatology or transplant surgery attending physician</td>
<td>[14, 15]</td>
</tr>
<tr>
<td>Amanita phalloides</td>
<td>Charcoal per NGT every 4 hours alternating with silymarin Penicillin G: 1 g/kg/d IV and NAC (as for APAP overdose). Silymarin 300mg PO/NGT every 12 hours OR Legalon-SIL 5mg/kg/day IV (give in 4 divided doses) not FDA approved, requires IRB and emergency access number via FDA</td>
<td>[16, 17]</td>
</tr>
<tr>
<td>Herpes Simplex Virus (HSV)</td>
<td>Acyclovir: 10 mg/kg IV q8 hours (using IBW) adjusted for kidney function</td>
<td>[18]</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Ganciclovir 5 mg/kg IV q12h hours (using IBW) adjusted for kidney function</td>
<td></td>
</tr>
<tr>
<td>Autoimmune Hepatitis</td>
<td>Methylprednisolone 60 mg/day IV</td>
<td>[19]</td>
</tr>
<tr>
<td>HBV</td>
<td>Entecavir (take on empty stomach) or Tenofovir at standard renal adjusted doses</td>
<td>See HBV Liver Transplant protocol</td>
</tr>
<tr>
<td>AFLP/HELLP</td>
<td>Delivery of fetus</td>
<td>[20, 21]</td>
</tr>
</tbody>
</table>

AFLP/HELLP = acute fatty liver of pregnancy/hemolysis-elevated liver enzymes-low platelet syndrome; AIH = autoimmune hepatitis; Amanita phalloides = mushroom intoxication; HBV = hepatitis B virus; HSV = herpes simplex virus; NAC = N-acetylcysteine.

MANAGEMENT OF COMPLICATIONS OF ALF

Hepatic Encephalopathy
Hyperammonemia plays a critical role in pathogenesis of HE and cerebral edema (CE), though venous ammonia has a poor correlation with clinical status (see figure below). Arterial ammonia can be used very selectively, due to cost and painful sampling (>200g/dL associated with higher risk cerebral herniation). The role of conventional treatment for HE in chronic liver disease (lactulose and/or rifaximin or sodium benzoate) remains unclear but can be considered on a case-by-case basis and treatment directed according to encephalopathy grade, not blood ammonia level. Neomycin should never be used for HE.

- **Lactulose** 30-60 ml PO every 2-6 hrs titrated to maintain 3 - 4 soft stools (~800ml liquid stool/day). Alternative: Lactulose 150ml enema + 350ml tap water PR every 6 -8 hours. *Particular caution should be used to avoid over-distention of the bowel in ALF patients in need of liver transplant to reduce risk of surgical complications*

- **Rifaximin** 550mg PO/per NGT every 12 hours
• **Sodium Benzoate** 2 to 5 gm PO every 12 hours

<table>
<thead>
<tr>
<th>Median Ammonia Levels (umol/L)</th>
<th>Correlation with Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial 60 80 85 140 210</td>
<td>0.61 (0.47-0.74)*</td>
</tr>
<tr>
<td>Venous 50 65 65 120 190</td>
<td>0.56 (0.42-0.71)*</td>
</tr>
</tbody>
</table>

West Haven HE Grade


**Note:** Median ammonia levels shown above are extrapolated from a graph.

**Management of Cerebral Edema (CE) & Intracranial Hypertension (ICH)**

Intracranial hypertension due to cerebral edema remains one of the primary causes of morbidity and mortality in patients with ALF [22], with the highest incidence in patients with a more acute presentation (shorter jaundice-to-encephalopathy interval) [7]. Suggested plan for management for all ALF patients:

- Elevate head of bed 30 degrees [23] and sand bag head to minimize lateral movements
- Avoid excessive stimulation, minimize suctioning and other noxious stimuli
- Maintain head in neutral position [24]. Avoid having the patient head laying to the side (e.g. keep neck straight)
- Avoid fluid overload

For patients with clinically suspected or proven intracranial hypertension consider:

- **Mannitol** (0.25-- 0.5 gm/kg IV boluses) should be administered when ICP ≥ 25 mmHg for > 10 minutes in patients with preserved renal function. Check serum osmolality every 6 hours. Mannitol boluses may be repeated if ICP remains > 25 mmHg and serum osmolality < 310-315 mosm/L.

- **Induced moderate hypothermia** may decrease ICP in ALF patients with ICH refractory to mannitol [25, 26], and stabilize ICP during OLT [27].
  - Surface cooling
  - Risks include cardiovascular instability, shivering, bleeding and/or infection
  - In order to minimize risk of worsening coagulopathy[28, 29], the recommended target range for cooling is between 34.5-35.5°C
  - Management of shivering: It is of utmost importance to manage shivering, if present. The first line management of shivering is with propofol infusion, if patient is hemodynamically stable, and surface counter-warming measures.
  - Gradually warm patient to 37 degrees over 6-8 hours before surgery.
Hypertonic saline (HTS) boluses have been increasingly used with efficacy similar or superior to mannitol [30-33].

- Many preparations and dosing strategies of HTS have been employed to treat cerebral edema, including 23.4% saline (30 ml) and 7.5% saline (2.0 ml/kg) boluses repeated every 2-3 hours [33]. NOTE: 3% hypertonic saline is used for head injury patients.

- Serum sodium should be monitored every 6 hours. HTS has also been administered prophylactically to ALF patients with high grade encephalopathy as a constant infusion (3%, 5-20 ml/hr) NOTE: For this purpose, recommend use of 3% sodium chloride to achieve a serum sodium of 145-155 mmol/L. In one small, randomized trial, the incidence and severity of intracranial hypertension was reduced in those patients with induced hypernatremia [34].

- Do not correct or change serum sodium >10-12 mmol/L in 24 hours or 16 mmol/L in 48 hours to reduce risk of osmotic demyelination

Barbiturate coma is now rarely used and has been replaced by propofol

- Correct hypercapnea & hypoxia (goal PCO₂ of 30-40 mmHg, likely only beneficial in first 48hrs)

- Fever should be treated aggressively with cooling blankets, fans, or other non-invasive devices, but NSAIDS and acetaminophen are not recommended. Full work-up for infection is imperative and careful use of antibiotics is advised (ideally with guidance from ID consultant)

- Mild spontaneous hypothermia (35-36.5 degrees Celsius), such as that observed during continuous renal replacement therapy, should not be treated (may be therapeutic)

- Head CT is recommended in patients who progress to stage III/IV HE or experience an acute change in mental status (recognizing that CT is relatively insensitive to ICH)[11, 35]

- The indications for placement of an ICP monitor remain one of the most contentious issues in managing patients with ALF as there are no randomized, controlled studies to guide management. The risk of bleeding from ICP monitors is reported to range from 4-20% depending upon the depth of insertion and resulted in death in up to 5% of cases [36].

- ICP monitor placement is rarely used and should only be considered in patients listed for OLT with stage III/IV hepatic encephalopathy after a detailed team discussion. Some centers also insert ICP monitors in non-OLT candidates with advanced stage hepatic encephalopathy in whom intensive medical management offers a reasonable likelihood of spontaneous survival (e.g. in patients with APAP-induced ALF).

Sedation and Analgesia

- Analgesia/Anxiolysis: Controlling pain and minimizing agitation is important in controlling ICP [37, 38]. Fentanyl continuous infusion is the analgesic of choice in ALF if needed.

- Propofol is relatively short-acting, decreases cerebral blood flow and lowers intracranial pressure [39]. As such, it is generally considered the preferred agent for sedation in ALF when necessary.

- Avoid benzodiazepines, long-acting narcotics and central acting antiemetics.
Seizure prophylaxis and surveillance

- Nonconvulsive seizure activity has been documented in a high proportion of patients with ALF and advanced stages of hepatic encephalopathy [40]

- The performance of EEG is recommended for the following indications [41]:
  - Grade III or IV hepatic encephalopathy
  - Sudden unexplained deterioration in neurologic exam
  - Myoclonus

Mechanical Ventilation

- High levels of positive end-expiratory pressure (PEEP) may increase ICP and decrease hepatic blood flow in patients with ALF [42]. However, in neurocritical care patients, the effects of PEEP on ICP are inconsistent and not always clinically important [43]. In general, the lowest level of PEEP that achieves adequate oxygenation should be applied in patients with ALF.

Treatment of Circulatory Dysfunction

- Ensure adequate volume resuscitation

- Indications for vasopressors
  - SBP < 90 mmHg (MAP < 65) OR to maintain a cerebral perfusion pressure (CPP) of 50 – 80 mmHg. (CPP = mean arterial pressure [MAP] - intracranial pressure [ICP]) in cases where ICP monitoring is performed

- Norepinephrine is the preferred vasopressor since it may provide a more consistent and predictable increase in cerebral perfusion than other pressors [44]

- A trial dose of hydrocortisone should be considered in patients with ALF with persistent hypotension despite volume challenge and norepinephrine. Hydrocortisone 50mg IV q6h or 100mg IV q8h have been shown to improve the vasopressor response to norepinephrine in hypotensive patients with sepsis [45] and ALF [46]

- Vasopressin and analogues are NOT recommended, as they directly cause cerebral vasodilation and may exacerbate intracranial hypertension (46)

- Epinephrine is NOT recommended. Epinephrine has been shown to decrease mesenteric blood flow in severe septic shock, and therefore may compromise hepatic blood flow in patients with ALF [47, 48].

Infection Prophylaxis and Surveillance

- Infection remains one of the principal causes of death in patients with ALF and may be subtle in clinical presentation [49]. As such it is recommended that patients with ALF being considered for liver transplant be cultured daily from blood and urine and, at a minimum, every 3 days from other sites (sputum, stool, radiographically identified fluid collections) in absence of signs or symptoms of infection. Additionally, when available, it is ideal to have the patient followed by the ID specialist for ongoing evaluation and management.

- Prophylactic parenteral and enteral antimicrobial regimens have not been shown to improve outcome or survival in patients with ALF, although key studies may have been underpowered [50]
- When surveillance cultures reveal “significant isolates”, anti-infectives should be initiated based upon the isolated organism as directed by the ID consultant [49]

- Empiric administration of antibiotics is recommended when infection or likelihood of impending sepsis is high (any one of the following conditions are met):
  - Progression of, or advanced stage (III/IV), hepatic encephalopathy [51]
  - Refractory hypotension
  - Presence of systemic inflammatory response syndrome (SIRS) components (temperature >38 or <36°C, WBC >12,000 or < 4,000/mm³, pulse >90 beats/min) [52].

- Empiric antimicrobial coverage for patients hospitalized < 72 hours
  - **Piperacillin/tazobactam** 3.375gm IV q8h (adjust for renal fxn) infused over 4 hours
  - **Vancomycin** 20-25mg/kg IV loading dose followed by vancomycin 1gm IV q12h (adjusted by pharmacy to maintain target trough ~ 15)
  - **Fluconazole** 200mg PO/IV x1 dose followed by 100mg/day

- For patients hospitalized > 72 hours and/or in those with complex medical history, ID consultation should be called

- Remove and replace any central IV lines placed at an outside hospital

**Correction of the Bleeding Diathesis**

- Patients with ALF are, by definition, coagulopathic, but spontaneous, clinically significant bleeding is uncommon (<10%) [53]

- TEG is recommended to best characterize coagulopathy in this patient population so as to target appropriate factor administration and minimize transfusions that may result in unnecessary IV volume, expense, and risk for complication

- TEG measures time to initial fibrin formation, rate of clot formation, quality/strength of clot, and clot lysis. A schematic of TEG results is shown below.

- Prophylactic FFP to improve coagulopathy in ALF is **NOT** recommended, as it does not reduce the risk of significant bleeding nor transfusion requirements, obscures the trend of INR as a prognostic marker, and risks volume overload. [54, 55]
- Cryoprecipitate is administered to keep fibrinogen in the low normal range (adjusted according to TEG results)

Schematic of TEG Results
Recombinant activated Factor VII (rFVIIa) is preferred in patients who require correction of coagulopathy for clinically significant bleeding or invasive procedures.

**FACTOR VII PROTOCOL FOR ACTIVE BLEEDING OR INVASIVE PROCEDURE**

- The use of prophylactic recombinant Factor VIIa is **NOT** generally recommended
- rFVIIa (40 mcg/kg) is recommended in circumstances where FFP has failed to correct PT/INR to an acceptable level, or the patient has become volume overloaded, prior to invasive procedures with a high risk of bleeding (e.g., trans-jugular liver biopsy or placement of an ICP monitor)[56].
- Draw baseline coagulation panel (PT/PTT, INR, fibrinogen, calcium, magnesium) if INR is >1.5
- The use of blood products is indicated in:
  - Patients with coagulopathy (PT, INR, or aPTT > 1.5 baseline (i.e. PT.15 seconds; aPTT > 45 seconds) or fibrinogen < 150 mg/dL) AND
  - Surgery or bleeding requiring RBC transfusion post-operation
- rFVIIa may be used as rescue therapy for severe bleeding when there is failure to correct the coagulopathy with FFP and/or other products as indicated
- Administer rFVIIa 1 mg IV bolus over 2 – 5 minutes. For best results, try to give 90 minutes prior to procedure whenever possible
- Draw a repeat coagulation panel within 1 hour of administration
- If the INR does not decrease to baseline or the INR is >1.5, consider repeating the dose

**Stress Ulcer Prophylaxis**

- **Proton pump inhibitors** (IV or PO) are recommended. The incidence of upper gastrointestinal bleeding in ALF patients has been shown to be decreased by gastric acid suppression [57]

**Nutrition**

- ALF is a catabolic state; nutritional support, preferably via an enteral route, is recommended. Approximately 40 gm protein/d (0.8-1.0 gm/kg/d) should be administered [58] as well as IV intralipids to achieve 30-35 kcal/kg/day energy intake.

**Serum Glucose Control**

- Hypoglycemia and hyperglycemia should be avoided
- Monitor glucose every 2 – 6 hrs
- Begin D10 infusion if glucose <100mg/dL and maintain serum glucose >100 mg/dL.

**Renal Replacement Therapy (RRT): Management of Fluids and Electrolytes**
Superiority of continuous versus intermittent renal replacement therapy is an area of some controversy in the literature [59]. However, specific conditions in which CRRT has been proposed as the preferred modality include combined acute renal and hepatic failure because of a beneficial impact on cardiovascular stability and intracranial pressure [60-63] and acute brain injury because of prevention of cerebral edema [60]

- Based upon the above, patients with ALF who have suspected or proven cerebral edema should be treated with CRRT rather than IRRT due to risk for worsened cerebral edema with IRRT (even in hemodynamically stable patients) [61, 64].
- During CRRT, heparin anticoagulation should be avoided because of the risk of bleeding, and citrate is recommended, although ionized serum calcium must be carefully monitored. Bicarbonate buffer solutions are recommended, since citrate and lactate both require biotransformation to bicarbonate in the liver.
- A dedicated double-lumen catheter inserted in the internal jugular vein is recommended, unless the patient has significant intracranial hypertension, in which case the femoral route is preferred. Catheters should be locked with saline or citrate.
- Hyponatremia should be strictly avoided as it may exacerbate cerebral edema.
- Monitor phosphorus regularly (q6hrs) and replete aggressively. Consider sodium phosphate continuous infusion. Avoid if on CRRT. Use caution when CrCl < 50ml/min.
  - Mix Sodium Phosphate 100meq in either 1000ml sterile water or D5W (10 Meq/100ml). Start infusion at 30 ml/hr & titrate to maintain serum phosphate goal 3 – 4.5 mg/dL

<table>
<thead>
<tr>
<th>Infusion Rate (ml/hr)</th>
<th>NaPhos (Meq/hr)</th>
<th>NaPhaos (Meq/24hr)</th>
<th>NaPhos (mmol/hr)</th>
<th>NaPhos (mmol/24hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>2</td>
<td>48</td>
<td>1.5</td>
<td>36</td>
</tr>
<tr>
<td>25</td>
<td>2.5</td>
<td>60</td>
<td>1.9</td>
<td>46</td>
</tr>
<tr>
<td>30</td>
<td>3</td>
<td>72</td>
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</tr>
<tr>
<td>35</td>
<td>3.5</td>
<td>84</td>
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<td>62</td>
</tr>
<tr>
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<td>4</td>
<td>96</td>
<td>3</td>
<td>72</td>
</tr>
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<td>45</td>
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<tr>
<td>50</td>
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<td>120</td>
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<td>91</td>
</tr>
<tr>
<td>55</td>
<td>5.5</td>
<td>132</td>
<td>4.1</td>
<td>98</td>
</tr>
<tr>
<td>60</td>
<td>6</td>
<td>144</td>
<td>4.5</td>
<td>108</td>
</tr>
<tr>
<td>65 (maximum)</td>
<td>6.5</td>
<td>156</td>
<td>4.9</td>
<td>118</td>
</tr>
</tbody>
</table>

Phosphorus Infusion Rate

<table>
<thead>
<tr>
<th>Serum Phosphorus (mg/dL)</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.5</td>
<td>Increase 30ml/hr</td>
</tr>
<tr>
<td>1.5 - 2.4</td>
<td>Increase 20ml/hr</td>
</tr>
<tr>
<td>2.5 – 2.9</td>
<td>Increase 10ml/hr</td>
</tr>
<tr>
<td>3.0 - 4.5</td>
<td>No Change</td>
</tr>
<tr>
<td>4.6 –5.0</td>
<td>Reduce 10ml/hr</td>
</tr>
<tr>
<td>5.1 - 5.5</td>
<td>Hold for 2 hours then reduce 20ml/hr</td>
</tr>
<tr>
<td>&gt; 5.5</td>
<td>Hold</td>
</tr>
</tbody>
</table>

- Other electrolyte concentrations (potassium, magnesium, bicarbonate) should be kept within the normal range.

Suggested Daily Monitoring

In addition to routine daily laboratory testing, the following are recommended for close monitoring of patients with ALF:
ABG daily
Lactate BID
TEG Daily
Electrolytes BID-QID (Goal serum sodium in 145-155 rage, as above)

PROGNOSIS & CRITERIA FOR LIVER TRANSPLANTATION

- Current UNOS criteria for Status 1A listing include:
  1. age 18 years or greater
  2. a life expectancy without a liver transplant of less than 7 days
  3. onset of hepatic encephalopathy within 8 weeks of the first symptoms of liver disease
  4. the absence of pre-existing liver disease
  5. residence in an ICU
  6. at least one of following: ventilator dependence, requirement for renal replacement therapy, or an INR > 2.0. (Patients with decompensated Wilson disease may also be listed for status 1A because of their universally poor prognosis for spontaneous recovery)

- King’s College Criteria (positive predictive value approximately 90%, negative predictive value 50-60%, meaning that these criteria are better able to predict patients with a poor prognosis than those with a good prognosis. See Table below)
- MELD > 30 predicts poor prognosis (currently not used by UNOS for priority listing for ALF)
- Paul Brousse (Clichy) criteria (for ALF secondary to HBV)
  - Grade III-IV HE and
  - Factor V level <20% (if younger than 30)
  - Factor V level <30% (if older than 30)
<table>
<thead>
<tr>
<th>Scheme</th>
<th>Etiology</th>
<th>Criteria for Liver Transplantation*</th>
<th>Reference</th>
</tr>
</thead>
</table>
| King’s College Criteria     | APAP     | Arterial pH < 7.30  
OR All of the following:  
1) PT > 100 sec (INR > 6.5), and  
2) creatinine > 3.4 mg/dl, and  
3) grade 3/4 encephalopathy | [65]      |
|                             | Non-APAP | PT > 100 sec (INR > 6.5)  
OR Any 3 of the following:  
1) NANB/drug/halothane etiology  
2) Jaundice to encephalopathy > 7 days  
3) Age < 10 or > 40 y.o.  
4) PT > 50 sec (INR > 3.5)  
5) Bilirubin > 17.4 mg/dl |           |
| Factor V                    | Viral    | Age < 30 y: factor V < 20%  
OR Any age: factor V < 30% and grade 3/4 encephalopathy | [66, 67]  |
| Factor VIII/V Ratio         | APAP     | Factor VIII/V ratio > 30 | [68]      |
| Liver Biopsy                | Mixed    | Hepatocyte necrosis > 70% | [69]      |
| Severity Index              | HBV, NANB | See reference | [70]      |
| Arterial Phosphate          | APAP     | > 1.2 mmol/L | [71]      |
| Arterial Lactate            | APAP     | > 3.5 mmol/L | [72]      |
| Arterial Ammonia            | Mixed    | > 150-200 μmol/L | [73]      |
| APACHE II Score             | APAP     | Score > 15 | [74]      |
| MELD/ΔMELD Score            | APAP     | MELD > 33  
ΔMELD > -0.4 | [75]      |

APAP = acetaminophen; HBV = hepatitis B virus; NANB = non-A, non-B viral hepatitis; MELD = Model for End-Stage Liver Disease; Mixed = mixed etiologies. *Times of data collection vary between studies. See individual references.
REFERENCES


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