

Acute Liver Failure in Adults: An Evidence-Based Management Protocol for Clinicians

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Abstract: With the goal of providing guidance on the provision of optimal intensive care to adult patients with acute liver failure (ALF), this paper defines ALF and describes a protocol for appropriately diagnosing this relatively rare clinical entity and ascertaining its etiology, where possible. This paper also identifies the few known therapies that may be effective for specific causes of ALF and provides a comprehensive approach for anticipating, identifying, and managing complications. Finally, one of the more important aspects of care for patients with ALF is the determination of prognosis and, specifically, the need for liver transplantation. Prognostic tools are provided to help guide the clinician in this critical decision process. Management of patients with ALF is complex and challenging, even in centers where staff members have high levels of expertise and substantial experience. This evidence-based protocol may, therefore, assist in the delivery of optimal care to this critically ill patient population and may substantially increase the likelihood of positive outcomes.

Due to the complexity of clinical care for patients with acute and chronic liver disease, evidence-based protocols provide a means to improve delivery of care. This is particularly true when multiple specialties are involved in the care team, when physician coverage may change day-to-day or week-to-week, and when trainees (medical students, residents, and fellows) comprise part of the care team. The goal of the following protocol is to guide the provision of optimal intensive care to adult patients with acute liver failure (ALF), both fulminant and subfulminant, who are being managed in hospital wards and in the intensive care unit (ICU). The protocol is designed to help clinicians to define and recognize ALF; to promptly identify its cause, when possible; to identify common complications associated with ALF and appropriate strategies to prevent or manage these complications; and to rapidly triage ALF patients for liver transplantation evaluation and listing, where appropriate. This protocol is intended for the adult patient with ALF. Important differences may exist in management of the pediatric population, who may present with other signs of ALF without overt hepatic encephalopathy (HE); readers are directed to reviews specific to this patient population.^{1,2}

ALF (fulminant and subfulminant) is a rare but serious clinical syndrome characterized by sudden loss of hepatic function in a person without evidence of preexisting liver disease.³ Exceptions to this definition include Wilson disease, reactivation of hepatitis B virus infection, and autoimmune hepatitis.⁴ ALF affects approximately 2,000–3,000 Americans each year.⁵ Causes of ALF include drug-induced or toxin-induced liver disease, viral hepatitis, metabolic diseases, and vascular and/or ischemic liver disease; 15–20% of cases have no identifiable cause (Table 1).

Acetaminophen (APAP) is the leading cause of ALF. Patients who are at increased risk for APAP-induced ALF include those with concomitant alcohol use, malnutrition, or use of medications known to induce CYP450 enzymes (eg, phenytoin, carbamazepine, or rifampin). In 308 consecutive patients from 17 tertiary care centers participating in the US Acute Liver Failure Study Group, APAP was identified as the etiology of ALF in 40% of patients.⁶ The other etiologies identified, in ascending order of prevalence, were malignancy (1%), Budd-Chiari syndrome (2%), pregnancy (2%), Wilson disease (3%), hepatitis A virus infection (4%), autoimmune hepatitis (4%), ischemic hepatitis (6%), hepatitis B virus infection (6%), and idiosyncratic drug-induced liver injury (13%); 17% of cases were found to be indeterminate.

Definition of Acute Liver Failure

ALF is manifest by the presence of coagulopathy (international normalized ratio [INR] >1.5) and any degree of encephalopathy occurring within 24 weeks of the 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; the former 2 categories encompass fulminant hepatic failure, while subacute is also termed subfulminant. These categories can provide clues as to the underlying cause and prognosis of ALF (Table 2). Paradoxically, patients with HE that occurs within 8 weeks of the onset of symptoms (fulminant hepatic failure) have a lower mortality than those with a more gradually evolving course. Multiorgan failure is the most common cause of death (>50%) from ALF, with intracranial hypertension (ICH) and infection accounting for most of the other deaths in this patient population.⁹

Diagnosis of Acute Liver Failure

In patients with suspected ALF (those presenting with coagulopathy and HE in the absence of known underlying liver disease within a time frame compatible with ALF), the

following evaluation is recommended to help determine the etiology of liver failure. Determination of etiology assists in directing therapy and estimating prognosis.

Medical History

First, clinicians should obtain a detailed medical history from the patient and/or family, including first onset of symptom(s); all medications used over the last 6 months, including prescription medications, over-the-counter agents, herbal supplements, wild mushrooms, or other alternative/complementary therapies; a detailed history of current and prior substance use; current or prior depression (including assessment of suicidality), anxiety, psychosis, or other mental illness; viral prodrome; and recent travel.

Physical Examination

Second, a complete physical examination should be performed. Particular attention should be paid to the assessment of mental status, the neurologic examination, and the fundoscopic examination in patients with HE of stage 2 or greater.

Laboratory Tests

Third, a number of laboratory tests are recommended for the purposes of establishing an etiology and determining prognosis. Tests that should be performed on presentation are listed in Table 3.

Additional Tests to Consider

In patients with ALF of unknown etiology (“seronegative” ALF), additional laboratory studies to consider include autoimmune marker tests (antinuclear antibody, anti-actin antibody, quantitative immunoglobulins, and anti-soluble liver antigen); hepatitis E virus immunoglobulin (Ig)M testing (in patients with compatible travel history); and hepatitis C virus polymerase chain reaction (PCR) if risk factors are present. If Wilson disease is suspected, tests to consider include serum ceruloplasmin, serum copper level, 24-hour urine collection for quantitative copper, and slit-lamp ophthalmologic evaluation for the presence of Kayser-Fleischer rings (these tests should be done in all young patients with ALF and in those with Coombs-negative hemolytic anemia, low alkaline phosphatase levels, or splenomegaly). If a viral syndrome is identified or suspected, consider testing for herpes simplex virus 1/2 IgM (PCR also available), Epstein-Barr virus PCR, cytomegalovirus PCR, adenovirus PCR, and varicella-zoster virus IgM (in the setting of vesicular rash).

There are other diagnostic tests that may also be useful. A diagnostic transjugular liver biopsy should be considered for all unknown or non-APAP cases. Histology has not been shown to predict outcomes, although the liver biopsy may help to strategize immunosuppres-

Table 1. Differential Diagnosis of Acute Liver Failure (ALF)

Category	Etiology of ALF	Examples and/or common clinical features
Viruses	Hepatitis A virus	Rare in the United States; usually hyperacute in presentation; ALF is more common in older patients or those with underlying liver disease
	Hepatitis B virus \pm delta virus	Less common following widespread vaccination
	Hepatitis E virus	Occurs in those with a history of travel to endemic areas or direct exposure to those who have traveled to such areas, as well as those with exposure to porcine farm animals; has a higher risk during pregnancy, especially in the 3rd trimester
	Herpes simplex virus	Occurs in immunocompromised patients and rarely in those who have normal immune systems
	Varicella zoster virus	Manifested by a vesicular rash
	Cytomegalovirus	Rare and controversial as to the potential for causing ALF
	Epstein-Barr virus	
	Human herpesvirus-6	
	Adenovirus, Coxsackie B virus, hemorrhagic fever virus	Rare causes of ALF
Drugs	Idiosyncratic reactions	Isoniazid, nonsteroidal anti-inflammatory drugs, carbamazepine
	Dose-dependent hepatotoxicity	Acetaminophen, sulfonamides, tetracycline
	Herbal supplements	Patients' families must be asked explicitly about use.
Vascular diseases	Right heart failure	
	Sinusoidal obstruction syndrome	Most common following systemic chemotherapy in preparation for bone marrow transplantation
	Budd-Chiari syndrome	May not have classic presentation
	Ischemic hepatitis (shock liver)	Ischemia must be prolonged (such as with sepsis).
Toxins	<i>Amanita phalloides</i> toxin	More common in Europe than in the United States; gastroenteritis, renal failure, and pancreatitis are common features
	<i>Bacillus cereus</i> toxin	A foodborne illness ("fried rice syndrome")
	Carbon tetrachloride	Very rare
	Yellow phosphorus	
Metabolic diseases	Wilson disease	Most common in younger patients; typical findings include Coombs-negative hemolytic anemia, hypouricemia, and a low alkaline phosphatase level with a high bilirubin level
	Reye syndrome	Occurs in young children with viral syndrome and salicylate ingestion
	Acute fatty liver of pregnancy	Associated with defects in fetal and maternal mitochondrial long-chain 3-hydroxyacyl coenzyme A dehydrogenase ⁶²
Malignant infiltration	Metastatic breast cancer	The most common solid organ metastasis to cause liver failure
	Lymphoma	More common than leukemic infiltration
Autoimmune diseases	Autoimmune hepatitis	Accounts for approximately 5% of cases in the US ALF Registry

sion following liver transplantation in patients with autoimmune hepatitis. An abdominal ultrasound with Doppler can be used to confirm portal and hepatic vein patency. For patients with grade 3/4 HE, a noncontrast

computed tomography (CT) scan of the head should be considered. If the patient is a potential candidate for liver transplantation, both an echocardiogram and electrocardiogram should be done.

Table 2. Timing and Severity of Clinical Presentation and Clinical Prognosis in Patients with Acute Liver Failure

	Hyperacute (fulminant)	Acute (fulminant)	Subacute (subfulminant)
Time from jaundice to encephalopathy	0–1 week	1–4 weeks	4–12 weeks
Severity of coagulopathy	+++	++	+
Severity of jaundice	+	++	+++
Degree of ICH	+++	++	+/-
Likelihood of survival without liver transplantation	Good	Moderate	Poor
Typical cause(s)	Acetaminophen, HAV, HEV	HBV	Nonacetaminophen drug toxicity

—=none; +=low severity; ++=medium severity; +++=high severity; HAV=hepatitis A virus; HBV=hepatitis B virus; HEV=hepatitis E virus; ICH=intracranial hypertension.

Adapted with permission from Bernal W, et al.⁶³

Table 3. Recommended Laboratory Tests for Establishing Etiology and Determining Prognosis of Acute Liver Failure

<ul style="list-style-type: none"> • Hepatic panel • Complete blood count with differential • Prothrombin time/international normalized ratio • Metabolic panel • Magnesium level • Phosphorus level • Amylase and lipase levels • Toxicology screen (including acetaminophen and salicylate levels) • Factor V level⁶⁴ • α-fetoprotein level • Arterial lactate level⁶⁵ • Arterial blood gas level • Arterial ammonia level (in patients with stage 2 or greater hepatic encephalopathy) 	<ul style="list-style-type: none"> • Viral hepatitis serologies: <ul style="list-style-type: none"> - Hepatitis B surface antigen (hepatitis delta immunoglobulin (Ig)G if surface antigen is positive) - Hepatitis B core IgM - Hepatitis A IgM - Hepatitis E IgG (if positive, ribonucleic acid testing should be ordered in select patients) - Hepatitis C antibody • HIV antibody • Blood and urine cultures • Urinalysis • Blood type • Serum pregnancy test (for patients with childbearing potential) • Thromboelastogram⁴⁷
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Treatment and Management of Complications

As shown in Table 4, there are only a few identified therapies that may be effective for specific causes of ALF. In addition to determining the need for liver transplantation, clinicians need to anticipate, identify, and manage complications of ALF in order to achieve optimal outcomes in these patients.

Hepatic Encephalopathy

Hyperammonemia plays a critical role in the pathogenesis of HE and cerebral edema (CE), although venous ammonia level has a poor correlation with clinical status. Measurement of arterial ammonia level can be used very selectively, due to high cost and painful sampling; a level above 200 g/dL is associated with a higher

risk for cerebral herniation.¹⁰ The role of conventional treatments for HE in chronic liver disease (lactulose and/or rifaximin [Xifaxan, Salix Pharmaceuticals] or sodium benzoate) remains unclear but can be considered on a case-by-case basis, with treatment guided by clinical assessment of encephalopathy severity rather than blood ammonia level. For assessment of severity, the West Haven criteria for encephalopathy separate symptoms related to altered mental status into 5 grades: Grade 0 (no abnormality detected); Grade 1 (trivial lack of awareness, euphoria or anxiety, shortened attention span, impairment of addition or subtraction); Grade 2 (lethargy or apathy, disorientation to time, obvious personality change, inappropriate behavior); Grade 3 (somnolence to semistupor, responsiveness to stimuli, confusion, gross disorientation, bizarre behavior); and

Table 4. Etiology-Specific Therapy for Patients with Acute Liver Failure

Etiology	Therapy	Reference(s)
Acetaminophen	Oral NAC: 140 mg/kg loading dose, then 70 mg/kg every 4 hours until discontinued by hepatology or transplantation surgery attending physician	Smilkstein MJ, et al ⁶⁶ Smilkstein MJ, et al ⁶⁷
	IV NAC: 150 mg/kg loading dose, 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 transplantation surgery attending physician	Buckley NA, et al ⁶⁸ Keays R, et al ⁶⁹
<i>Amanita phalloides</i> (mushroom intoxication)	Charcoal: via NGT every 4 hours alternating with silymarin Penicillin G: 1 g/kg/day IV and NAC (Dosing as for acetaminophen overdose.) Silymarin: 300 mg PO/NGT every 12 hours Legalon-SIL: 5 mg/kg/day IV (given in 4 divided doses) or 5 mg/kg IV loading dose followed by 20 mg/kg/day via continuous infusion	Broussard CN, et al ⁷⁰ Floersheim GL, et al ⁷¹
Herpes simplex virus	Acyclovir: 10 mg/kg IV every 8 hours (using IBW) adjusted for kidney function	Peters DJ, et al ⁷²
Cytomegalovirus	Ganciclovir: 5 mg/kg IV every 12 hours (using IBW) adjusted for kidney function	
Autoimmune hepatitis	Methylprednisolone: 60 mg/day IV	Kessler WR, et al ⁷³
Hepatitis B virus	Entecavir (taken on an empty stomach) or tenofovir at standard renal-adjusted doses	
AFLP/HELLP	Delivery of fetus	Mabie WC ⁷⁴ Castro MA, et al ⁷⁵

AFLP/HELLP=acute fatty liver of pregnancy/hemolysis-elevated liver enzymes-low platelet syndrome; IBW=ideal body weight; IV=intravenous; NAC=*N*-acetyl cysteine; NGT=nasogastric tube; PO=by mouth.

Grade 4 (coma).^{11,12} Neomycin should never be used to treat HE in patients with ALF due to risk for ototoxicity and nephrotoxicity. Accepted dosing recommendations for conventional treatments are listed below.

Lactulose Lactulose should be administered at a dose of 30–60 mL given orally (PO) or via nasogastric tube (NGT) every 2–6 hours, titrated to maintain 3–4 soft stools (approximately 800 mL liquid stool) daily. In patients without good response to oral lactulose or those in whom there is clinical concern for ileus, an alternative approach is to administer lactulose via 150-mL enema plus 350 mL of tap water every 6–8 hours. Particular caution should be used to avoid overdistention of the bowel in ALF patients in need of liver transplantation to reduce the risk of surgical complications.

Rifaximin Doses of 550 mg of rifaximin can be given PO or via NGT every 12 hours.

Sodium benzoate Doses of 5 g of sodium benzoate can be given PO every 12 hours (not widely available).

Management of Cerebral Edema and Intracranial Hypertension

ICH due to CE remains one of the primary causes of morbidity and mortality in patients with ALF, with

the highest incidence in patients with more acute presentations (shorter jaundice-to-encephalopathy intervals).^{7,13} Risk factors for development of ICH include younger age, renal dysfunction, and need for inotrope support.¹⁰

Suggested Plan for Management of All Adult Patients with Acute Liver Failure

To lessen the risk for development or worsening of CE, consideration of the following is appropriate for all ALF patients.

Adjust Head Position Elevate the head of the bed 30°, and maintain the head in a neutral position.^{14,15} Avoid having the patient's head lying to the side. Sandbags can be placed around the head in order to minimize lateral movements and keep the neck straight.

Avoid Fluid Overload and Excessive Stimulation Minimize suctioning and other noxious stimuli.

Correct Hypercapnia and Hypoxia The goal is a carbon dioxide partial pressure of 30–40 mmHg, although achieving this goal is likely beneficial only in the first 48 hours.

Treat Fever Aggressively Cooling blankets, fans, or other noninvasive devices may be used. However, avoid

the use of nonsteroidal anti-inflammatory drugs and APAP, both of which are not recommended. Mild spontaneous hypothermia (35–36.5°C), such as that observed during continuous renal replacement therapy (CRRT), should not be treated, as it may be therapeutic.

Assess the Patient for Infection A full work-up for infection is imperative, and careful use of antibiotics is advised, ideally with guidance from an infectious disease (ID) consultant.

Perform a Head Computed Tomography Scan A head CT scan is recommended in patients who progress to stage 3/4 HE or who experience an acute change in mental status. Clinicians should recognize that CT scans are relatively insensitive to ICH.^{16,17}

Consider an Intracranial Pressure Monitor However, the indication for placement of an intracranial pressure (ICP) monitor remains 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% to 20%, depending on the depth of insertion, and the use of an ICP monitor has resulted in death in up to 5% of cases.¹⁸ ICP monitor placement should only be undertaken in centers with appropriate support, including an experienced neurosurgical service and the ability to aggressively manage coagulopathy. Placement of an ICP monitor is typically only considered in patients listed for liver transplantation with stage 3/4 HE, although some centers also insert ICP monitors in nontransplantation candidates with advanced-stage HE in whom intensive medical management offers a reasonable likelihood of spontaneous survival (eg, patients with APAP-induced ALF).

Suggested Plan for Management of Patients with Intracranial Hypertension

For patients with clinically suspected or proven ICH, the following treatments can be considered.

Mannitol Boluses of mannitol (0.25–0.5 g/kg via an intravenous [IV] route) should be administered when ICP is 25 mmHg or above for longer than 10 minutes in patients with preserved renal function. Check serum osmolality every 6 hours. Mannitol boluses may be repeated if ICP remains above 25 mmHg and serum osmolality is below 310 mOsm/L.

Induced Moderate Hypothermia Moderate hypothermia may decrease ICP in ALF patients with ICH refractory to mannitol and may stabilize ICP during liver transplantation.^{19–21} While data for this therapy are promising, further controlled trials are needed to confirm

benefit, better quantify risk, and determine the ideal target population for this intervention.^{19–22} Moderate hypothermia may be achieved with a surface cooling device or via direct core cooling using an endovascular heat-exchange catheter (according to institution-specific availability and expertise). The risks of moderate hypothermia include cardiovascular instability, shivering, bleeding, and/or infection. In order to minimize the risk of worsening coagulopathy, the recommended target range for cooling is 34.5–35°C.^{23,24} Management of shivering with therapeutic hypothermia is paramount to avoid an iatrogenic increase in ICP. At our institution, a protocol for management of shivering has been developed in conjunction with our institution's neurocritical care specialists; a similar approach would be recommended whenever therapeutic hypothermia is to be used.

The patient should be gradually rewarmed (at a rate of 0.2–0.5°C per hour) to the goal temperature of 37°C at the time of surgery. When direct core cooling is employed, surgeons should be aware of the risk of significant bleeding from the endovascular catheter site during liver transplantation. Consider leaving the sheath in place until after reperfusion of the liver and resolution of coagulopathy, which may be preferable to removal of the catheter and sheath in the operating room by the transplantation surgery team. Correction of coagulopathy can be assessed by thromboelastogram (TEG).

Hypertonic Saline Boluses of hypertonic saline (HTS) have been increasingly used with efficacy similar or superior to mannitol.^{25–28} Many HTS preparations and dosing strategies have been employed to treat CE, including 23.4% saline (30 mL) and 7.5% saline (2.0 mL/kg) boluses repeated every 2–3 hours.²⁸ Serum sodium levels should be monitored every 6 hours. HTS has also been administered prophylactically as a constant infusion (a 30% solution at a rate of 5–20 mL/hr) to ALF patients with high-grade encephalopathy. For this purpose, use of 3% sodium chloride to achieve a serum sodium level of 145–155 mmol/L is recommended. In 1 small, randomized trial, the incidence and severity of ICH was reduced in patients with induced hyponatremia.²⁹ To reduce the risk of osmotic demyelination, do not correct or change serum sodium more than 12 mmol/L in 24 hours or 16 mmol/L in 48 hours.

Barbiturate Coma Barbiturate coma is now rarely used and has been replaced by propofol sedation. The risks of induced coma include hypotension, hypothermia, immunosuppression, hypokalemia, prolonged coma, and ventilator-associated pneumonia. Vasopressors can be used to maintain cerebral perfusion pressure (CPP) above 50 mmHg and are usually required.

Sedation and Analgesia

Controlling pain (analgesia) and minimizing agitation (anxiolysis) are important in controlling ICP.^{30,31} Propofol is relatively short-acting, decreases cerebral blood flow, and lowers ICP.³² Given these benefits, propofol is generally the preferred agent when sedation of ALF patients is necessary. Bispectral index monitoring is advised in this patient population.

Seizure Prophylaxis and Surveillance

Nonconvulsive seizure activity has been documented in a high proportion of patients with ALF and advanced stages of HE.³³ Clinicians should consider performing an electroencephalogram (EEG) for the following indications: grade 3/4 HE; sudden, unexplained deterioration in neurologic examination; and myoclonus.³⁴ Continuous EEG monitoring, where available, may be considered in cases where there are intermittent, unexplained neurologic findings that may be missed with standard EEG.

In a single study evaluating prophylactic use of antiepileptic medications in the setting of ALF, CE and survival were no different among patients treated with phenytoin versus controls; however, we believe this area deserves further investigation.³⁴ Given the noninvasive nature of EEG examinations and the potential benefit of identification and management of seizure activity in this patient population, we advocate a low threshold for performing EEGs, pending further research.

Mechanical Ventilation

High levels of positive end-expiratory pressure (PEEP) may increase ICP and decrease hepatic blood flow in patients with ALF.³⁵ In neurocritical care patients, however, the effects of PEEP on ICP are inconsistent and not always clinically important.³⁶ In general, the lowest PEEP that achieves adequate oxygenation should be applied in patients with ALF.

Treatment of Circulatory Dysfunction

Ensuring adequate volume resuscitation is important. The indications for vasopressors are systolic blood pressure below 90 mmHg (mean arterial pressure [MAP] <65 mmHg), or when needed to maintain a CPP of 50–80 mmHg. (CPP=MAP–ICP.) Norepinephrine is the preferred vasopressor in this population since it may provide a more consistent and predictable increase in cerebral perfusion than other inotropic agents.³⁷

A trial dose of hydrocortisone should be considered in patients with ALF who have persistent hypotension despite volume challenge and norepinephrine treatment. Hydrocortisone (50 mg IV every 6 hours or 100 mg IV every 8 hours) has been shown to improve the vasopressor response to norepinephrine in hypotensive patients with sepsis and ALF.^{38,39}

Vasopressin and vasopressin analogues are not recommended because they directly cause cerebral vasodilation and may exacerbate ICH.³⁹ Epinephrine is also not recommended; it has been shown to decrease mesenteric blood flow in patients with severe septic shock and, therefore, may compromise hepatic blood flow in patients with ALF.^{40,41}

Infection Prophylaxis and Surveillance

Infection remains one of the principal causes of death in patients with ALF and may be subtle in its clinical presentation.⁴² Even in the absence of signs or symptoms of infection, patients with ALF who are being considered for liver transplantation should have cultures taken daily from blood and urine, plus cultures taken every 3 days (at minimum) from other sites (sputum, stool, and radiographically identified fluid collections). Additionally, it is ideal to have the patient followed by a transplant ID specialist, when available, for ongoing evaluation and management.

Prophylactic parenteral and enteral antimicrobial regimens are not generally recommended because they have not been shown to improve outcomes or survival in patients with ALF, although key studies may have been underpowered.⁴³ When surveillance cultures reveal significant isolates, anti-infective medications should be initiated based on the isolated organism, as directed by the ID consultant.⁴² Empiric administration of antibiotics is recommended when infection or likelihood of impending sepsis is high. Specifically, empiric antibiotics should be administered if any 1 of the following conditions are met: progression of, or advanced (stage 3/4) HE; hypotension; or presence of 2 or more systemic inflammatory response syndrome components (temperature >38°C or <36°C, white blood cell count >12,000/mm³ or <4,000/mm³, pulse >90 beats/min, respiratory rate of >20 breaths/min, or an arterial carbon dioxide tension level of <32 mmHg).^{44,45}

For patients hospitalized less than 72 hours, empiric, broad-spectrum antimicrobial coverage may include piperacillin/tazobactam (3.375 g IV every 8 hours infused over 4 hours) plus vancomycin (20–25 mg/kg IV loading dose followed by 1 g IV every 12 hours, adjusted by the pharmacy to maintain a trough concentration of approximately 15 mg/L) and fluconazole (a single dose of 200 mg, administered PO or IV, followed by 100 mg/day administered PO or IV). For patients hospitalized longer than 72 hours and/or those with a complex medical history, ID consultation should be requested (with a transplantation ID specialist, if available, or the general ID consult service). Any central IV lines placed at an outside hospital should be removed and replaced.

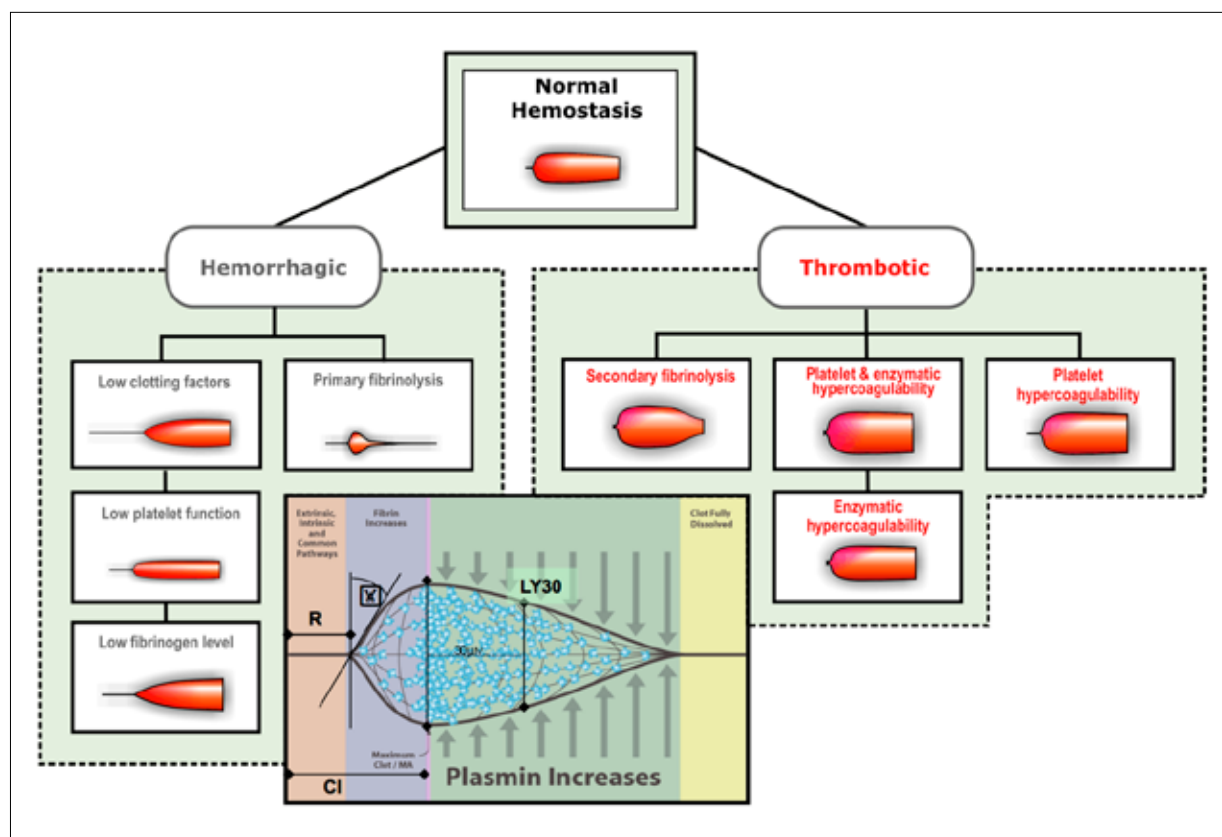


Figure 1. Using results from thromboelastogram (TEG) analysis, the TEG decision tree is used to arrive at a coagulopathy diagnosis and to distinguish between primary and secondary fibrinolysis and between platelet-induced versus enzymatic hypercoagulability. Comparing the patient's TEG analysis results to the decision tree depicted above allows clinicians to assess the patient's net coagulation profile and, in cases of increased risk for bleeding, to target the correct type of blood products for management.

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Correction of Bleeding Diathesis

By definition, patients with ALF are coagulopathic, but spontaneous, clinically significant bleeding is uncommon (<10%).⁴⁶ 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 of complications. TEG measures the time to initial fibrin formation, the rate of clot formation, the quality/strength of the clot, and clot lysis. A schematic of TEG results is shown in Figure 1.

Stravitz and colleagues recently published their experience using TEG to assess coagulation profiles among patients with acute liver injury (defined as INR ≥ 1.5 ; $n=37$) and ALF (acute liver injury + HE; $n=14$).⁴⁷ Despite the fact that the mean INR value in this study population was 3.4 (range, 1.5–9.6), mean and median

TEG parameters were within normal limits for the entire study population. TEG has also been reported to decrease the requirement for fresh frozen plasma (FFP) transfusion during liver transplantation.⁴⁸

Prophylactic FFP transfusion to improve coagulopathy in patients with ALF is not recommended, as it does not reduce the risk of significant bleeding or transfusion requirements; it obscures the trend of INR as a prognostic marker; and it risks volume overload.^{49,50} However, in the setting of profound coagulopathy (INR >7 with TEG confirming marked prolongation in the rate of clot formation), FFP transfusion to maintain INR between 5 and 7 is advised. Cryoprecipitate is administered to keep fibrinogen in the low-normal range and can be adjusted according to TEG results. The recently published study by Stravitz and colleagues also suggested that thrombocytopenia, when present,

may be the most significant contributor to a coagulopathic state identified by TEG.⁴⁷

Factor VII Protocol for Active Bleeding or Invasive Procedure Recombinant activated Factor VII (rFVIIa) is preferred in patients who require correction of coagulopathy for clinically significant bleeding or invasive procedures. Administration of rFVIIa (40 mcg/kg) is recommended prior to an invasive procedure with a high risk of bleeding (eg, transjugular liver biopsy or placement of an ICP monitor) in circumstances where FFP transfusion has failed to correct prothrombin time (PT)/INR to an acceptable level or the patient has become volume overloaded.⁵¹ A baseline coagulation panel—including PT/partial thromboplastin time (PTT) ratio, INR, fibrinogen, calcium, and magnesium—should be drawn if INR is above 1.5. The use of blood products may be indicated in patients with coagulopathy (PT, INR, or activated PTT [aPTT] >1.5 baseline [ie, PT of 15 sec and/or aPTT >45 sec] or fibrinogen level <150 mg/dL) and surgery or bleeding requiring transfusion of red blood cells postoperation. rFVIIa may be used as rescue therapy for severe bleeding when correction of coagulopathy with FFP and/or other products has failed. rFVIIa should be administered as a 1-mg IV bolus over 2–5 minutes. For the best results, it should be given 90 minutes prior to the procedure. A repeat coagulation panel should be drawn within 1 hour of rFVIIa administration. If INR does not decrease to baseline or INR is above 1.5, consider repeating the dose. The use of prophylactic rFVIIa is not generally recommended.

Stress Ulcer Prophylaxis

The incidence of upper gastrointestinal bleeding in ALF patients has been shown to be decreased by gastric acid suppression.⁵² Proton pump inhibitors (IV or PO) are recommended.

Plasmapheresis

Plasmapheresis is a treatment that is now reserved for patients with Wilson disease who do not respond to standard interventions, including chelation therapy and supportive care. Plasmapheresis has been used successfully for rapid removal of copper.⁵³ Most, if not all, patients with ALF due to Wilson disease require liver transplantation, without which they will remain at risk of death; nonetheless, supportive interventions are critical as a bridge to transplantation. Important supportive interventions include management of hyperglycemia or hypoglycemia and, possibly, more intensive management of neurologic complications, since some patients may have preexisting neurologic disease.

Nutrition

ALF is a catabolic state. Nutritional support, preferably administered via an enteral route, is recommended. Approximately 80–100 g of protein per day should be administered unless there is profound coma.⁵⁴ Addition of IV intralipids is recommended to supplement caloric intake when enteral feeding does not meet goals. Alternatively, all nutrition may be provided via a parenteral route in the case of ileus, bowel obstruction, or other situations where the enteral route is inaccessible.

Serum Glucose Control

Hypoglycemia and hyperglycemia should be avoided in patients with ALF. Glucose should be monitored every 2–6 hours. If the glucose level is below 100 mg/dL, begin D10 infusion and maintain a serum glucose level above 100 mg/dL and less than 140–180 mg/dL.

Renal Replacement Therapy: Management of Fluids and Electrolytes

The superiority of CRRT versus intermittent renal replacement therapy (IRRT) is an area of some controversy in the literature.⁵⁵ However, there are specific conditions in which CRRT has been proposed as the preferred modality, including combined acute renal and hepatic failure (because of the beneficial impact of CRRT on cardiovascular stability and ICP) and acute brain injury (because of the ability of CRRT to prevent CE).^{56–60} Patients with ALF who have suspected or proven CE should be treated with CRRT rather than IRRT due to the risk for worsened CE with IRRT (even in hemodynamically stable patients).^{57,61}

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 into the internal jugular vein is recommended unless the patient has significant ICH, 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 CE. Phosphorus should be monitored regularly (every 6 hours) and repleted aggressively. Continuous infusion of sodium phosphate should be considered in most patients but should be avoided in patients receiving CRRT. Use caution when creatinine clearance is less than 50 mL/min. Sodium phosphate should be mixed to a concentration of 100 mEq in either 1,000 mL of sterile water or D5W

Table 5. Proposed Schemes for Assessing Prognosis and the Need for Orthotopic Liver Transplantation in Patients with Acute Liver Failure

Scheme	Etiology	Criteria for liver transplantation*	Reference(s)
King's College criteria	APAP	Arterial pH <7.30 OR All of the following: • PT >100 sec (INR >6.5) • Creatinine level >3.4 mg/dL • Grade 3/4 encephalopathy	O'Grady JG, et al ⁷⁶
	Non-APAP	PT >100 sec (INR >6.5) OR Any 3 of the following: • NANB/drug/halothane etiology • Time from jaundice to encephalopathy >7 days • Age <10 years or >40 years • PT >50 sec (INR >3.5) • Bilirubin level >17.4 mg/dL	
Factor V	Viral	Age <30 years: factor V <20% OR Any age: factor V <30% and grade 3/4 encephalopathy	Bernuau J, et al ⁷⁷ Bernuau J, et al ⁷⁸
Factor VIII/V ratio	APAP	Factor VIII/V ratio >30	Pereira LM, et al ⁷⁹
Liver biopsy	Mixed	Hepatocyte necrosis >70%	Donaldson BW, et al ⁸⁰
Severity index	HBV, NANB	See reference.	Takahashi Y, et al ⁸¹
Arterial phosphate level	APAP	>1.2 mmol/L	Schmidt LE, Dalhoff K ⁸²
Arterial lactate level	APAP	>3.5 mmol/L	Bernal W, et al ⁶⁵
Arterial ammonia level	Mixed	>150–200 μ mol/L	Clemmesen JO, et al ⁸³
APACHE II score	APAP	Score >15	Mitchell I, et al ⁸⁴
MELD/ Δ MELD score	APAP	MELD score >33 Δ MELD score >–0.4	Schmidt LE, Larsen FS ⁸⁵ Kremers WK, et al ⁸⁶
BiLE score	Mixed	Bilirubin level (mmol/L)/100 + lactate level (mmol/L) + etiology (+4 indeterminate etiology, Budd-Chiari syndrome, or phenprocoumon toxicity; +2 APAP toxicity; +0 all other etiologies) Score >6.9 predictive of death or need for liver transplantation	Hadem J, et al ⁸⁷

APACHE II=Acute Physiology and Chronic Health Evaluation II; APAP=acetaminophen; BiLE=Bilirubin-Lactate-Etiology; HBV=hepatitis B virus; INR=international normalized ratio; MELD=Model for End-Stage Liver Disease; Mixed=mixed etiologies; NANB=non-A, non-B viral hepatitis; PT=prothrombin time.

*Times of data collection vary among studies. See individual references.

(10 mEq/100 mL). The infusion should be started at a rate of 30 mL per hour and titrated to maintain a serum phosphate goal level of 3–4.5 mg/dL.

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

Suggested Daily Monitoring

In addition to routine daily laboratory testing, the following assessments are recommended for close monitoring of patients with ALF: arterial blood gas (daily), lactate testing (twice daily), TEG (daily), and electrolyte testing (2–4 times daily; goal serum sodium level is 145–155 mmol/L, as described above).

Although the recommendation for daily monitoring via TEG is not evidence-based, per se, it is supported by recent data.⁴⁷ Also, in our experience, performing TEG daily may help to avoid unnecessary blood product transfusions and associated intravascular volume overload.

Prognosis and Criteria for Liver Transplantation

One of the most important, yet difficult, aspects of care for patients with ALF is determination of the need for urgent liver transplantation. We recommend early and rapid evaluation for transplantation candidacy, but the final decision regarding whether to list a patient with a Status 1A priority should be made based on input from multiple members of the liver transplantation care team (hepatologists, surgeons, social workers, and, in some cases, psychiatrists). Current United Network for Organ Sharing criteria for Status 1A listing include: (1) age 18 years or greater, (2) life expectancy without liver transplantation of less than 7 days, (3) onset of HE within 8 weeks of the first symptoms of liver disease, (4) absence of preexisting liver disease, (5) residence in an ICU, and (6) at least 1 of the following criteria: ventilator dependence, requirement for renal replacement therapy, or INR above 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 should be used to aid in the assessment of prognosis (Table 5). These criteria have a positive predictive value of approximately 90% and a negative predictive value of 50–60%, meaning that they are better able to predict patients with a poor prognosis than those with a good prognosis. Other criteria for estimation of prognosis are also shown in Table 5.

Conclusions

Management of patients with ALF, even in busy transplantation centers, is complex and challenging. An evidence-based protocol may therefore assist in delivery of optimal care to this patient population. This protocol has been reviewed by the entire transplantation team at the University of California–San Diego's Center for Hepatobiliary Disease and Abdominal Transplantation,

and it serves as a reference for all members of the care team involved in care of individuals with ALF. This protocol will be periodically reviewed and updated as new data are published and/or as experience with this protocol brings to light areas that may be improved.

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(Continued on page 212)

(Continued from page 172)

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