Objective: To provide a uniform platform from which to study acute liver failure, the U.S. Acute Liver Failure Study Group has sought to standardize the management of patients with acute liver failure within participating centers.

Methods: In areas where consensus could not be reached because of divergent practices and a paucity of studies in acute liver failure patients, additional information was gleaned from the intensive care literature and literature on the management of intracranial hypertension in non-acute liver failure patients. Experts in diverse fields were included in the development of a standard study-wide management protocol.

Measurements and Main Results: Intracranial pressure monitoring is recommended in patients with advanced hepatic encephalopathy who are awaiting orthotopic liver transplantation. At an intracranial pressure of ≥25 mm Hg, osmotic therapy should be instituted with intravenous mannitol boluses. Patients with acute liver failure should be maintained in a mildly hyperosmotic state to minimize cerebral edema. Accordingly, serum sodium should be maintained at least within high normal limits, but hypertonic saline administered to 145–155 mmol/L may be considered in patients with intracranial hypertension refractory to mannitol.

Data are insufficient to recommend further therapy in patients who fail osmotherapy, although the induction of moderate hypothermia appears to be promising as a bridge to orthotopic liver transplantation. Empirical broad-spectrum antibiotics should be administered to any patient with acute liver failure who develops signs of the systemic inflammatory response syndrome, or unexplained progression to higher grades of encephalopathy. Other recommendations encompassing specific hematologic, renal, pulmonary, and endocrine complications of acute liver failure patients are provided, including their management during and after orthotopic liver transplantation.

Conclusions: The present consensus details the intensive care management of patients with acute liver failure. Such guidelines may be useful not only for the management of individual patients with acute liver failure, but also to improve the uniformity of practices across academic centers for the purpose of collaborative studies. (Crit Care Med 2007; 35:2498–2508)

Key Words: acute liver failure; standardized care; intracranial pressure monitoring; hepatic encephalopathy; orthotopic liver transplantation
Acute liver failure (ALF), defined as the onset of hepatic encephalopathy and coagulopathy within 26 weeks of jaundice in a patient without preexisting liver disease, remains one of the most dramatic and highly mortal of all human afflictions. Nevertheless, the optimal management of patients with ALF remains very poorly defined and center-specific. Several reasons underlie the heterogeneous management of ALF, including the fact that ALF is a syndrome rather than a disease, representing the final manifestation of numerous etiologies. In addition, the syndrome is extremely difficult to study because of its high mortality and rarity (2,000 U.S. cases per yr) (1). The Adult U.S. Acute Liver Failure Study Group (ALFSG) was founded in 1997 to define the epidemiology and management of patients with ALF. Since its inception, the group has collected data on >1,100 patients with ALF from 23 prominent liver transplant centers. To more uniformly manage patients with ALF at participating centers, the ALFSG convened in December 2005 to review the available literature on the management of ALF, to compare the intensive care of patients with intracranial hypertension of various etiologies, and to compare practices within participating centers. Investigators in specialties outside of hepatology—including neuro-intensive care, nephrology, and coagulation—were invited to participate in formulating a standard study-wide management protocol. Where possible, the protocol was based upon literature pertaining to patients with ALF; where studies specifically examining ALF did not exist, management recommendations were derived from other literature. Recommended measures were defined as those in which evidence-based studies suggest possible benefit in the clinical course or outcome of patients with ALF. Measures without supporting clinical data, but which potentially may be of benefit based upon a reasonable rationale, or supported by literature not specifically pertaining to patients with ALF, were deemed insufficient data to recommend. Finally, measures which clinical studies suggest may be detrimental were not recommended. The protocol was approved by the 23 member sites on September 23, 2006, and revisions were approved on May 10, 2007.

The present protocol expounds on a previous position paper (2) sanctioned by the American Association for the Study of Liver Diseases. The position paper offers general guidelines targeted at nonintensivists, and is cited within the present protocol for completeness and to avoid duplication of publication.

GENERAL MANAGEMENT

Patients with evidence of acute liver injury should be admitted to the hospital when accompanied by significant hepatocellular insufficiency (e.g., international normalized ratio >1.5). Because neurologic deterioration may be very rapid, patients should be moved to an intensive care unit at the onset of hepatic encephalopathy, and a discussion should ensue between the referring physician and intensivists at the nearest liver transplant center regarding timely transfer after stabilization. Such discussion should include whether endotracheal intubation should be performed before transfer. To establish a diagnosis, estimate disease severity, and predict the need for orthotopic liver transplantation (OLT), a battery of initial tests should be performed on arrival at the transplant center (2).

Etiology-Specific Treatments. Specific treatments (antidotes) for ALF have been systematically studied only for acetaminophen overdose. N-acetylcysteine (NAC) administration is recommended even if there is doubt concerning the timing, dose ingested, or plasma concentration of acetaminophen, and should not be withheld even if the ingestion was 48–72 hrs before presentation (3). Oral NAC is recommended as first-line therapy only in patients with mild (grade 1) hepatic encephalopathy; intravenous NAC should be administered to patients with >grade 1 encephalopathy, hypotension, or other reason that oral dosing might not be tolerated (e.g., vomiting, compromised airway, postoperative state, ileus). Doses for oral NAC administration should include a 140 mg/kg loading dose, followed by 70 mg/kg every 4 hrs. Doses for intravenous NAC administration vary according to protocol; one suggested schedule includes a 150 mg/kg load for 15–60 mins (usually in 5% dextrose, but any crystalloid is acceptable), followed by a maintenance infusion (e.g., 12.5 mg/kg per hr for 4 hrs, then 6.25 mg/kg per hr). NAC administration is recommended until there is firm evidence of improved hepatic function (resolution of hepatic encephalopathy, improving coagulopathy [international normalized ratio <1.5], and declining transaminases). The length of NAC administration should be determined by clinical improvement or outcome (death or liver transplant) rather than by time or serum acetaminophen levels; it should be emphasized that this period of time may extend well beyond 72–96 hrs.

Except for women with acute fatty liver of pregnancy or the hemolysis–elevated liver enzymes–low platelet syndrome, in whom prompt delivery of the fetus readily reverses ALF (4), there are generally insufficient data to recommend specific therapies for ALF due to other etiologies. However, etiology-specific measures are recommended by the ALFSG based upon anecdotal experience, relative innocuousness of the measures, and the high mortality of the clinical syndrome (Table 1) (2).
Infection remains one of the principal causes of death in patients with ALF and may be subtle in clinical presentation (19). The most common site of bacterial infection is the lung, followed by urinary tract and blood, and the most commonly isolated organisms are Gram-positive cocci (Staphylococcus, Streptococcus) and enteric Gram-negative bacilli (20). Fungal infections, particularly Candida, may be present in one third of patients with ALF (21). Intravenous catheter-related sepsis represents a major source of avoidable infectious complications in patients with ALF (22); consequently, unnecessary intravenous catheters are to be avoided. 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 (23). Therefore, there are insufficient data to recommend the routine use of antibiotic prophylaxis in all patients with ALF, particularly those with early stage hepatic encephalopathy. Although randomized studies exploring the use of daily bacterial surveillance cultures (blood and urine) and chest radiographs do not exist, such studies are recommended on the basis that patients with ALF frequently do not exhibit signs of infection, and early diagnosis of infection may improve outcome (20, 23). Empirical administration of antibiotics is recommended in the following circumstances where infection or the likelihood of impending sepsis is high: a) surveillance cultures reveal significant isolates (19); b) progression of, or advanced stage (III/IV), hepatic encephalopathy (22); c) refractory hypotension; or d) presence of systemic inflammatory response syndrome components (temperature >38°C or <36°C, white blood count >12,000 or <4,000/mm³, pulse >90 beats/min) (24). Empirical antibiotic (bacterial and antifungal agents) also are recommended for patients listed for OLT, because developing infection often results in delisting and immunosuppression is imminent, acknowledging that specific data to support this practice do not exist. It should be recognized that the risk of developing infection with resistant organisms will increase with longer waiting times.

There are insufficient data to recommend specific antimicrobial agents for the indications above. However, broad-spectrum coverage for Gram-positive and Gram-negative bacteria, such as with a third-generation cephalosporin, should be chosen with consideration of patient-specific isolates from surveillance cultures, as well as historical hospital-specific isolates. Vancomycin is specifically recommended in all patients with possible intravenous catheter–related sepsis and/or risk factors for infection with methicillin-resistant Staphylococcus aureus. An antifungal agent also is recommended in any patient without prompt improvement in signs of infection after institution of antibacterial agents. Aminoglycosides are not recommended on the basis of risk of nephrotoxicity.

Sedation and Analgesia. Psychomotor agitation frequently contributes to intracranial hypertension in patients with ALF, especially as patients progress to stage III/IV hepatic encephalopathy (25). Pain also may increase intracranial pressure (26). Therefore, adequate analgesia and judicious sedation is required in patients who progress to stage III/IV hepatic encephalopathy, particularly before placement of invasive devices, such as intracranial pressure monitors or endotracheal tubes.

There are insufficient data to recommend a standard agent for sedation in patients with ALF. However, it should be recognized that both propofol and benzodiazepines, the most commonly used sedatives, increase γ-aminobutyric acid–ergic neurotransmission, and therefore may exacerbate hepatic encephalopathy.
transfusion requirements, obscures the trend of prothrombin time as a prognostic marker, and risks volume overload (39). The administration of cryoprecipitate is recommended in patients who have significant hypofibrinogenemia (<100 mg/dL). Anti fibrinolytic agents such as aminocaproic acid should be considered in patients with clinical evidence of a hyperfibrinolytic state (diffuse mucosal and puncture wound oozing) and supporting laboratory evidence, such as an increased clot lysis time (40).

A common practice has become to administer recombinant factor VIIa (rFVIIa) in circumstances where fresh frozen plasma has failed to correct prothrombin time/international normalized ratio to an acceptable level, or the patient has become volume overloaded, before invasive procedures with a high risk of bleeding (e.g., transjugular liver biopsy or placement of an ICP monitor) (41). Fresh frozen plasma should be administered before rFVIIa to replete other constituents of the clotting cascade, with cryoprecipitate if fibrinogen is <100 mg/dL. rFVIIa (40 μg/kg) should be administered immediately before a planned procedure. The procedure should be performed within 30–60 mins, although the effect of rFVIIa usually persists for >2 hrs (42). The use of rFVIIa may increase the risk of thrombotic complications in patients with ALF (43, 44), especially in higher doses (90 μg/kg) or after repetitive dosing (36). rFVIIa should not be given to patients with a history of myocardial infarction, stroke, or unstable angina within 2 wks, or with active deep venous thrombosis. Patients with ALF due to pregnancy, Budd-Chiari syndrome, or suspected malignant infiltration of the liver also should not receive rFVIIa. In subjects with persistent coagulopathy despite fresh frozen plasma who have contraindications to rFVIIa, plasma exchange is effective and should be considered (45).

The incidence of upper gastrointestinal bleeding in ALF patients has been shown to be decreased by gastric acid suppression with intravenous histamine-2 receptor antagonists (46). Therefore, intravenous histamine-2 blockers, or by inference, proton pump inhibitors (intravenous or oral), are recommended.

Assessment of Prognosis and Liver Transplant Listing Criteria. The ability to predict the likelihood of spontaneous recovery or death without OLT remains of paramount importance in patients with ALF. Many criteria have been proposed to anticipate the probability of death without OLT (Table 2), but there are insufficient data to recommend a particular scheme, given none have been found to be adequately sensitive and specific. A cursory assessment regarding transplant candidacy should be made on admission to the intensive care unit by the transplant and intensive care teams with specific consideration of poor prognostic factors included in the King’s College criteria (Table 2). If no immediate contraindications are identified, an expedited OLT evaluation should be undertaken without delay (47). In addition to the schemes outlined in Table 2, the etiology and rapidity of evolution of ALF also must be considered, because the likelihood of spontaneous recovery without OLT decreases dramatically with the more subacute presentations of fulminant hepatitis B, idiosyncratic drug reactions, and ALF of undetermined etiology (58).

Current requirements for listing a patient with ALF for OLT within the United States must be consistent with Section 3.6.4.1 of the Policies and Bylaws of the United Network for Organ Sharing (available at http://unos.org). However, it must be emphasized that these policies are neither objective nor verifiable, nor are they amenable to prospective operational definition. The critical criteria include a) age ≥18 yrs; b) a life expectancy without a liver transplant of <7 days; c) onset of hepatic encephalopathy within 8 wks of the first symptoms of liver disease; d) the absence of preexisting liver disease; e) residence in an intensive care unit; and f) at least one of the following: ventilator dependence, requiring renal replacement therapy, or an international normalized ratio >2.0. Patients with acute decompensated Wilson disease also may be listed for OLT because of their universally poor prognosis for spontaneous recovery.

Nutrition. ALF is a catabolic state characterized by negative nitrogen balance and, consequently, immunodeficiency (59). Patients with ALF also exhibit increased resting energy expenditure compared with healthy controls (60). Therefore, nutritional support is recommended in patients with ALF, although essentially no studies exist to guide therapy (60, 61). Enteral nutrition should be administered whenever possible, with higher caloric density feeds preferred to avoid excessive free water and hypo-osmolality, which may exacerbate cerebral edema (see below). Parenteral nutrition (35–40 kcal/kg per day) (61), delivered by a dedicated central venous catheter, should be reserved for patients with specific contraindications to...
enteral nutrition. Monitoring for blood glucose should be performed at frequent regular intervals by finger stick (e.g., every 1–2 hrs). Intravenous glucose infusion (1.5–2.0 g/kg per day) is recommended in patients who develop hypoglycemia. Although single center clinical trials have suggested that the maintenance of tight glycemic control reduces mortality in critically ill patients (62, 63), and hyperglycemia may exacerbate intracranial hypertension in patients with ALF (64), ALF patients are at high risk for hypoglycemia. Thus, until further information is available, it is recommended that insulin infusions be used to maintain blood glucose levels <150 mg/dL, while also strictly avoiding hypoglycemia. Approximately 40 g protein per day (0.5–1.0 g/kg per day) also should be administered (65). There are insufficient data to recommend the use of branched-chain amino acids, which are also limited by cost (66). Lipid emulsions appear to be safe in ALF patients, and are recommended as a concentrated source of calories in volume-overloaded patients (61).

Seizure Prophylaxis and Surveillance. Nonconvulsive seizure activity has been documented in a high proportion of patients with ALF and advanced stages of hepatic encephalopathy (67). However, there are insufficient data to recommend prophylactic anticonvulsants in all patients with ALF because two studies using prophylactic phenytoin have reached conflicting conclusions (67, 68). It should be noted that propofol or benzodiazepine infusions used for sedation also provide potent antiseizure prophylaxis.

The performance of electroencephalogram, not necessarily continuously, is recommended for the following indications (68): a) grade III or IV hepatic encephalopathy; b) sudden unexplained deterioration in neurologic examination; c) myoclonus; or d) to titrate therapy when barbiturate coma is used to manage cerebral edema.

Treatment of Circulatory Dysfunction. In hypotensive patients with ALF, volume status should be assessed and hypovolemia corrected before the administration of vasopressors. Vasopressors are recommended for severe systemic hypotension (systolic blood pressure <90 mm Hg; mean arterial pressure <65 mm Hg) or to maintain a cerebral perfusion pressure (CPP) (equivalent to mean arterial pressure – ICP) of 50–80 mm Hg. Norepinephrine or dopamine are recommended, with norepinephrine preferred, because the former may provide a more consistent and predictable increase in cerebral perfusion than the latter in patients with traumatic brain injury (69). Low-dose dopamine is not recommended, as it has not been shown to be effective in decreasing the risk of renal failure in patients with systemic inflammatory response syndrome and early renal dysfunction (70). Epinephrine has been shown to decrease mesenteric blood flow in severe septic shock, and therefore may compromise hepatic blood flow in patients with ALF (71, 72). Vasopressin and analogs are not recommended, because they directly cause cerebral vasodilation and may exacerbate intracranial hypertension (73).

Relative adrenal insufficiency occurs frequently in patients with ALF, and may contribute to cardiovascular collapse (74). Moderate doses (200–300 mg/day) of hydrocortisone have been shown to improve the vasopressor response to norepinephrine in hypotensive patients with sepsis (75) and ALF (76). A trial of hydrocortisone should be considered in ALF patients with persistent hypotension despite a volume challenge and norepinephrine. Because of conflicting results in clinical trials, there are insufficient data to recommend the use of agents which purportedly improve peripheral tissue oxygenation, such as prostacyclin (77) and N-acetylcysteine (78, 79).

MANAGEMENT OF CEREBRAL EDEMA AND INTRACRANIAL HYPERTENSION

Intracranial hypertension due to cerebral edema remains one of the primary causes of morbidity and mortality in patients with ALF (80), with highest incidence in patients with more acute presentations (i.e., a jaundice-to-encephalopathy interval of <4 wks) (58). A head computed tomography is recommended in patients with ALF who progress to stage III/IV hepatic encephalopathy or experience an
acute change in mental status, or before ICP monitor placement. Although a head computed tomography will frequently demonstrate cerebral edema in ALF patients with advanced-stage hepatic encephalopathy (81), it is insensitive to intracranial hypertension (82, 83); therefore, its principal value is to rule out other uncommon intracranial pathology, most importantly bleeding. The physician must consider the potential risk of moving a patient from the intensive care unit to the computed tomography scanner.

The indications for placement of an ICP monitor remain one of the most contentious issues in managing patients with ALF, because there are no randomized, controlled studies to guide the physician. Indeed, ICP monitoring in nonrandomized subjects has not been shown to improve survival (84, 85). Therefore, there are insufficient data to recommend ICP monitor placement in all patients with ALF. However, most members of the ALFSG place ICP monitors in patients with advanced (stage III/IV) hepatic encephalopathy with the belief that monitoring improves the management of cerebral edema and provides important prognostic information regarding neurologic recovery after OLT (84, 85). Therefore, ICP monitor placement should be considered in all patients listed for OLT with stage III/IV hepatic encephalopathy. 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 acetaminophen-induced ALF).

Bleeding complications attributed to the placement of ICP monitors occur in 10% to 20% of patients with ALF, but are often mild and of questionable clinical significance (84–86). Therefore, treatment of the bleeding diathesis before insertion is recommended as outlined above. There are insufficient data to recommend a standard intracranial location for ICP monitor placement. While it has been observed that placement of ICP monitors in the epidural space may decrease the incidence of bleeding complications (84, 86), such monitors are less accurate than those that traverse the dura and they tend to overestimate ICP (87). Due to the risk of bleeding, intraventricular placement should be avoided. ICP monitor placement is not recommended in patients with mild hepatic encephalopathy (stages I/II), or with clinical evidence of diencephalic herniation and/or intractable arterial hypotension, in whom death is imminent.

**Management of Intracranial Hypertension: General Recommendations.** A quiet environment with limited stimulation is recommended for ALF patients with evidence of cerebral edema. Chest physiotherapy and endotracheal suctioning also may need to be minimized, and prophylactic intravenous lidocaine before endotracheal suctioning may be considered (88). To decrease ICP, the head should be maintained in a neutral position (89), and the head of the bed should be elevated to 30 degrees (90, 91), which will also reduce the risk of ventilator-associated aspiration pneumonia (92). During elevation of the head of the bed, mean arterial pressure should be maintained to avoid decreasing the cerebral perfusion pressure (93). Trendelenburg position, head flexion, head rotation, and sudden change of position to supine should be avoided except when necessary for placement of a central venous catheter (89).

Hyperventilation-induced hypocapnia induces cerebral vasoconstriction, decreases ICP (94, 95), and may improve cerebrovascular autoregulation (96). Spontaneous hyperventilation, therefore, which is usual in patients with ALF, should not be treated. However, prophylactic hyperventilation is not recommended in patients with ALF, because vasoconstriction can reduce cerebral oxygen utilization (94) and had no effect on the development of cerebral edema in one study (97). Consequently, maintenance of a PCO₂ between 30 and 40 mm Hg is a reasonable goal. Acute hyperventilation, however, is recommended as emergency rescue therapy of patients with evidence of diencephalic herniation.

Generally, maintenance of eutherma (36.5–37.5°C) is recommended in patients with ALF, because fever exacerbates intracranial hypertension (25) and is independently associated with worse outcome in patients admitted to neurologic intensive care units (98). Fever should be treated aggressively with cooling blankets, fans, or other noninvasive devices, but nonsteroidal anti-inflammatory drugs and acetaminophen are not recommended because of possible nephro- and gastric mucosal toxicity, and possible potentiation of liver injury, respectively. Shivering, which may also increase ICP, should be treated with increased sedation, or with small doses of meperidine (12.5–25 mg). Mild spontaneous hypothermia (35–36.5°C), such as that observed during continuous renal replacement therapy, should not be treated. At this time, there are insufficient data to support the routine use of prophylactic hypothermia in patients with ALF. However, the induction of hypothermia may be considered in the treatment of intracranial hypertension refractory to mannitol (see below).

Cerebral edema in ALF results primarily from astrocyte swelling (cytotoxic cerebral edema) rather than a leaky blood brain barrier (vasogenic cerebral edema) (99). While vasogenic cerebral edema may respond to corticosteroids, cerebral edema in ALF has not been shown to improve after their administration (100); therefore, corticosteroids are not recommended.

**Management of Intracranial Hypertension: Specific Recommendations.** The absolute values and duration of abnormal ICP and CPP for optimal neurologic recovery after ALF have not been well defined. Therefore, there are insufficient data to recommend strict pressure goals. Suggested ICP based upon experience of individual liver transplant centers in patients with ALF (83, 101), and of other centers in patients with traumatic brain injury (102), include an ICP of <25 mm Hg and CPP between 50 and 80 mm Hg. There are also insufficient data to recommend criteria of ICP and CPP to contraindicate OLT, because rare cases of complete neurologic recovery after severe, prolonged, intracranial hypertension have been reported (103). It has been observed that severe (>40 mm Hg), sustained, intracranial hypertension refractory to medical therapy and/or a CPP <40 mm Hg for >2 hrs are associated with brainstem herniation or poor neurologic recovery after OLT (83). However, if a patient’s pupils remain reactive and a liver graft becomes available, some transplant surgeons would proceed with OLT (103).

The administration of mannitol is recommended as first-line therapy for intracranial hypertension. Mannitol should be administered when ICP ≥25 mm Hg for >10 mins, after the validity of the ICP calibration is confirmed. There are insufficient data to recommend a standard dose of mannitol to be administered. A range of doses (0.25–1.0 g/kg intravenous boluses) has been used both in patients with brain injury (104) and ALF (94, 105). Because lower doses reduce the risk of...
severe osmotic disequilibrium and dehydration, and may be as effective as higher doses (104). 0.25–0.5 g/kg boluses are recommended. Serum osmolality should be assessed every 6 hrs, and mannitol boluses may be repeated if ICP remains >25 mm Hg and serum osmolality <320 mOsm/L. It should be noted that serum osmolality correlates poorly with mannitol concentrations, and a normal osmolar gap may be a more accurate measure of adequate mannitol clearance before the administration of subsequent doses (106).

There are insufficient data to recommend a standard therapy of intracranial hypertension refractory to mannitol. However, the following may be considered in the following order based upon ease and safety of administration, and efficacy based upon the available literature.

**Hypertonic saline** boluses have been used increasingly in neurocritical care patients, with efficacy similar or superior to mannitol (107–111). Many preparations and dosing strategies of hypertonic saline 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 hrs to 3 hrs (111). Serum sodium should be monitored at frequent intervals. Hypertonic saline also has been administered prophylactically to ALF patients with high grade encephalopathy as a constant infusion (30%, 5–20 mL/hr) to achieve a serum sodium of 145 mmol/L to 155 mmol/L. In one small, randomized trial, the incidence and severity of intracranial hypertension was reduced in those patients with induced hyponatremia (112). Although hyponatremia of short duration is not a contraindication to administering hypertonic saline in patients with ALF, the rate of correction should be inversely proportional to the duration of hyponatremia to minimize the risk of osmotic demyelination.

**Induced moderate hypothermia** (32–33°C) may decrease ICP in ALF patients with intracranial hypertension refractory to mannitol (113), and stabilize ICP during OLT (114). Increasingly, units within the ALFSG have used hypothermia to bridge patients with osmotherapy-refractory intracranial hypertension to OLT, although the practice is not universally endorsed. Further studies also must document the safety of the practice, which may increase the risk of cardiovascular instability and/or infection.

**Barbiturate coma**, induced by pentobarbital (3–5 mg/kg intravenous loading bolus followed by 1–3 mg/kg per hr intravenous infusion) or thiopental (5–10 mg/kg loading bolus followed by 3–5 mg/kg per hr), also has been advocated in patients with ALF refractory to mannitol (83, 115). Potential severe adverse effects—including hypotension, hypothermia, immunosuppression, hypokalemia, and prolonged coma—mandate physician experience with the induction of barbiturate coma, and vasopressors to maintain cerebral perfusion pressure >50 mm Hg usually are required.

**Indomethacin** (25 mg infused intravenously over 1 min) also has been shown to acutely decrease ICP and increase CPP by causing cerebral vasoconstriction (116, 117). Indomethacin therefore may be considered as salvage therapy in patients with intracranial hypertension refractory to the above measures.

**OTHER SPECIAL PROCEDURES**

**Mechanical Ventilation.** Recommended indications for endotracheal intubation include respiratory failure (hypoxemia, hypercapnia), airway protection in the setting of advanced encephalopathy (stage III/IV), agitation, and imminent ICP monitor placement. Laryngoscopy and endotracheal intubation may be associated with transient elevation in ICP and appropriate countermeasures (induction of anesthesia followed by constant sedation) are recommended.

There are insufficient data to recommend a standard mode of delivering mechanical ventilation to patients with ALF. Patients with ALF often develop acute respiratory distress syndrome with disease progression to cerebral edema (118), often in the setting of infection as part of systemic inflammatory response syndrome (24). Generally, tidal volume and plateau pressure should be limited (6 mL/kg predicted body weight and <30 cm H2O, respectively) in intensive care unit patients with established acute lung injury, and low tidal volumes also may decrease the risk of progression to acute respiratory distress syndrome (119, 120). It must be appreciated that decrements in tidal volume will decrease minute ventilation and increase PCO2, and thereby increase ICP. Therefore, in patients with low tidal volumes, the respiratory rate should be increased to maintain a stable PCO2.

High levels of positive end-expiratory pressure also may increase ICP in patients with ALF, and decrease hepatic blood flow (121). However, in neurocritical care patients, the effects of positive end-expiratory pressure on ICP are inconsistent and not always clinically important (122). In general, the lowest level of positive end-expiratory pressure that achieves adequate oxygenation should be applied in patients with ALF.

**Renal Replacement Therapy (RRT); Management of Fluids and Electrolytes.** The evaluation of acute renal failure in patients with ALF should include analysis of urine sodium, which is low (<10 mEq/L) in prerenal azotemia and functional renal failure (hepatorenal syndrome) and high in acute tubular necrosis. Microscopic examination of the urine should be performed to detect casts and renal tubular cells, which suggest acute tubular necrosis. Assessment of intravascular volume by measurement of central venous pressure, or pulmonary capillary wedge pressure via pulmonary artery catheter, may be considered, but these measures poorly reflect intravascular volume (123). An intravenous fluid challenge (crystalloid and colloid; 1–1.5 L) is recommended to exclude prerenal azotemia, but large volumes of glucose-containing solutions should be avoided in consideration of the risk of hyperglycemia.

There are insufficient data to recommend specific criteria to start or discontinue renal replacement therapy (RRT) in patients with ALF. However, the decision to start RRT should be based upon the level of renal dysfunction, fluid balance, and metabolic derangements, and a need to create space for intravenous colloid (e.g., fresh frozen plasma) or parenteral nutrition. Goals of RRT should be clearly delineated before initiation of RRT. Conversely, a plan for discontinuing RRT also should be agreed upon before its institution, particularly in the event that a patient is no longer considered for OLT or fails to spontaneously improve (124).

Patients with ALF frequently tolerate intermittent hemodialysis poorly because of hemodynamic instability and fluid shifts. Furthermore, intermittent hemodialysis may increase ICP (125). Therefore, most members of the ALFSG prefer continuous RRT (126), even in hemodynamically stable patients (127). Mannitol removal may be accomplished by high volume continuous venovenous hemofiltration, but has not been well studied; conventional hemodialysis or continuous venovenous hemodiafiltration may be required for this purpose (128). A dedicated double-lumen catheter inserted in the internal jugular vein is recommended, un-
less the patient has significant intracranial hypertension, in which case the femoral route is preferred. If the catheter remains in place for >7 days, a tunneled catheter should be considered. Catheters should be locked with saline or citrate. During continuous venovenous hemofiltration, heparin anticoagulation should be avoided because of the risk of bleeding, and citrate is recommended, although ionized serum calcium must be monitored carefully. Bicarbonate buffer solutions are recommended, because citrate and lactate both require biotransformation to bicarbonate in the liver.

Electrolyte abnormalities of all types frequently accompany ALF, especially when complicated by renal failure, and may be particularly deleterious. Monitoring of serum electrolyte concentrations (once or twice daily) and prompt correction of abnormalities is recommended. Hyponatremia should be strictly avoided, because it may exacerbate cerebral edema. As noted above, a relative restriction of free water is recommended; for example, by administering higher caloric density enteral feeds and/or more concentrated glucose infusions in ALF patients with hypoglycemia. Although there are insufficient data to advise a rate of correction of serum sodium, the risk of osmotic demyelination may be lower than in other patient populations because of the short duration of hyponatremia. Therefore, hypertonic saline boluses or continuous RRT may be employed for this purpose (126), with adjustment of the rate of correction for the length of time of hyponatremia. Other electrolyte concentrations (phosphate, magnesium, bicarbonate) should be kept within the normal range.

Maintenance of euvolemia in ALF is recommended to avoid hemodynamic instability and underperfusion of critical vascular beds. Unfortunately, central venous pressure and pulmonary capillary wedge pressure reflect intravascular volume unreliably, and hypotensive ALF patients should first receive a volume challenge, as above. In volume-unresponsive subjects, echocardiography or other non-invasive measures of intrathoracic blood volume should be considered.

MANAGEMENT OF ALF DURING AND AFTER OLT

Many complications of ALF persist or become more acute during OLT. Unfortunately, there are insufficient data from clinical trials to recommend any specific management decision pertaining to OLT in ALF patients. However, based upon practices in the published literature and the experiences of centers in the ALFSG, the following guidelines have been endorsed.

**Intraoperative and Postoperative Monitoring.** ICP frequently increases during dissection of the native liver and during reperfusion of the graft (114), especially if the patient has experienced intracranial hypertension before OLT (129). Furthermore, intracranial hypertension may persist during the first 10–12 hrs after OLT for ALF (130). Therefore, if an ICP monitor has been placed before OLT, ICP should be continuously monitored during and early after OLT. OLT should not be delayed, however, for placement of an ICP monitor after an organ has become available, as long as the patient’s pupils remain active and the patient is not posturing (131). Monitoring in the operating suite also should include continuous arterial pressure. As in the case of pre–liver transplant patients, pressure goals include ICP <25 mm Hg, mean arterial pressure >90 mm Hg, and CPP 50 mm Hg to 80 mm Hg, and norepinephrine is preferred for pressor support (114). Osmotherapy with mannitol should be administered for ICP >25 mm Hg for >10 mins, and serum sodium should be maintained between 140–150 mmol/L.

**Graft Selection Considerations.** Survival after OLT for ALF decreases markedly after patients have progressed to stage IV hepatic encephalopathy (131). Therefore, in patients deemed to have poor prognosis by the schemes outlined in Table 2, OLT must be performed as soon as an organ becomes available and not delayed. In general, ABO-identical grafts are preferred, but ABO-compatible grafts have nearly comparable 1-yr survival after OLT for ALF and should be used without hesitation (132). The gravity of the clinical situation must dictate whether to use an ABO-incompatible graft, because 1-yr graft survival is decidedly lower (132). Evaluation of a possible living donor may be entertained by transplant centers with extensive experience with living donor liver transplantation in cirrhotic patients. Such an expedited evaluation has been shown to be feasible in the setting of ALF, with outcomes as good as OLT with a deceased donor graft (133).

**Other Surgical Considerations.** Transplant surgeons generally tailor other decisions regarding the surgical management of ALF patients to the particular clinical situation. Venovenous bypass has been advocated by some authorities (132), but not others (114), to minimize swings in cerebral perfusion during clamping of the inferior vena cava and portal vein, as well as during reperfusion. Similarly, hepariectomy of the native liver with temporary portocaval anastomosis may be considered in ALF patients with toxic liver syndrome (134–136).

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APPENDIX

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