Management of Acute Liver Failure: Update 2022

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Abstract

Abbreviated pathogenesis and clinical course of the acute liver failure syndrome. The pathogenesis and clinical course of the syndrome of acute liver failure (ALF) differs depending upon the etiology of the primary liver injury. In turn, the severity of the liver injury and resulting synthetic failure is often the primary determinant of whether a patient is referred for emergency liver transplantation. Injuries by viral etiologies trigger the innate immune system via pathogen-associated molecular patterns (PAMPs), while toxin-induced (and presumably ischemia-induced) injuries do so via damage-associated molecular patterns (DAMPs). The course of the clinical syndrome further depends upon the relative intensity and composition of cytokine release, resulting in an early proinflammatory phenotype (SIRS) and later compensatory anti-inflammatory response phenotype (CARS). The outcomes of overwhelming immune activation are the systemic (extrahepatic) features of ALF (cardiovascular collapse, cerebral edema, acute kidney injury, respiratory failure, sepsis) which ultimately determine the likelihood of death.

Acute liver failure (ALF) continues to carry a high risk of mortality or the need for transplantation despite recent improvements in overall outcomes over the past two decades. Optimal management begins with identifying that liver failure is indeed present and its etiology, since outcomes and the need for transplantation vary widely across the different etiologies. Most causes of ALF can be divided into hyperacute (ischemia and acetaminophen) and subacute types (other etiologies), based on time of evolution of signs and symptoms of liver failure; the former evolve in 3 to 4 days and the latter typically in 2 to 4 weeks. Both involve intense release of cytokines and hepatocellular contents into the circulation with multiorgan effects/consequences.

Management involves optimizing fluid balance and cardiovascular support, including the use of continuous renal replacement therapy, vasopressors, and pulmonary ventilation. Early evaluation for liver transplantation is advised particularly for acetaminophen toxicity, which evolves so rapidly that delay is likely to lead to death.

Vasopressor support, high-grade hepatic encephalopathy, and unfavorable (subacute) etiologies heighten the need for urgent listing for liver transplantation. Prognostic scores such as Kings

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Conflict of Interest
None declared.

Criteria, Model for End-Stage Liver Disease, and the Acute Liver Failure Group prognostic index take these features into account and provide reasonable but imperfect predictive accuracy. Future treatments may include liver support devices and/or agents that improve hepatocyte regeneration.

Graphical Abstract
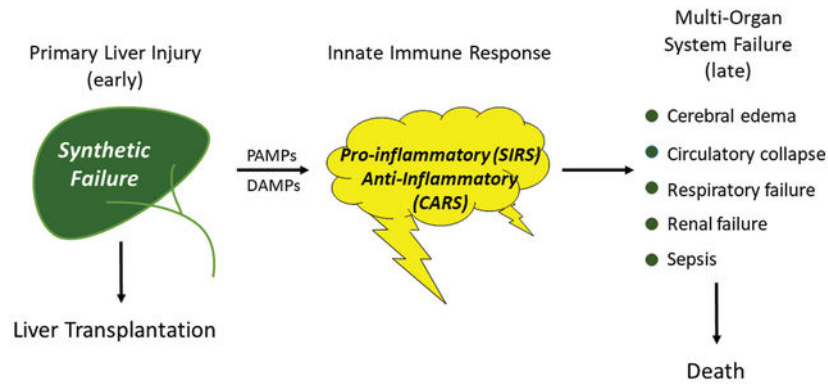
Keywords

encephalopathy; coagulopathy; hepatocyte injury; renal replacement therapy; prognostic score

The past 40 years has seen remarkable changes in all of medicine and in particular the management of patients with acute liver failure (ALF). ALF is the term applied to a cluster of diseases that all cause rapid evolution of liver injury to liver failure with similar signs and symptoms. Despite encompassing several etiologies, ALF remains an orphan or perhaps a super-orphan disease, affecting only approximately 2 to 3,000 per year in North America. Hallmark features include coagulopathy with increased prothrombin time/ international normalized ratio (INR) as well as altered mentation (hepatic encephalopathy [HE], graded for severity from 0 to 4). Interest in ALF remains high due to these dramatic presentation features as well as its high overall mortality. Prior to the 1980s and 1990s, more than 90% of patients with ALF died within weeks of disease onset.[1] With the advent of liver transplantation, outcomes began to improve but mortality still hovers around 30% in Europe and North America and is considerably higher in underdeveloped countries.[2,3] ALF is a distinct clinical entity which should not be confused with acute-on-chronic-liver-failure,[4] since the latter condition is characterized by the presence of underlying cirrhosis and complications thereof, while the definition of ALF excludes patients with cirrhosis except in specific conditions which present as ALF in a patient with unrecognized sub-clinical chronic liver disease (acute Wilson disease, acute autoimmune hepatitis [AIH], and reactivation of chronic hepatitis B). The current update will begin with a brief review of the overall spectrum (and evolution) of etiologies and their pathogenesis, before focusing on current management practices, and an assessment of current prognostic modeling and the role of liver transplantation for ALF.

Section I: Etiologies and Diagnosis

Case series beginning in the 1990s have highlighted the central role of acetaminophen (APAP; also called paracetamol in Europe) as the dominant etiology in Western countries, including North America, and much of Northern Europe.[5] Next most common is usually idiosyncratic drug-induced liver injuries (DILIs),[6] followed by viral hepatitis, and a raft of smaller numbers of cases of AIH, Wilson disease, ALF during pregnancy, and a host of even rarer agents.[7] By contrast, the Middle East, Asia, South America, and Africa (where records are available) vary from country-to-country with hepatitis B and E represented prominently, with many fewer DILI or APAP cases.[8] Herbal and dietary supplements (HDSs) have become a much larger problem in North America and in Asia in recent decades.[9]

Over the 20+ years of the Acute Liver Failure Study Group (ALFSG) registry, 1998 to 2018, there has been little change in the overall pattern of etiologies (Fig. 1). The incidence of APAP-induced ALF has remained steady over the years at around 46% of all adult cases. That said, there is some evidence from the United Kingdom that APAP has declined due to better public information concerning its toxicity and legal limitations on package size, neither of which have been implemented in North America. Over the two decades, the percentages in the ALFSG registry showed DILI remaining roughly steady at approximately 11%, hepatitis B 8%, and hepatitis A 3%. Over the 20-year period, however, hepatitis A and B initially began to decline somewhat, thought due to vaccination for the overall population, followed by a recent increase in the annual number of cases of infection of both A and B, apparently linked to the opioid crisis. An additional part of the increase in hepatitis B-related ALF is due to cases of reactivation in the setting of immunosuppressive medications, including cancer chemotherapy or other biologics.[10] Hepatitis A requiring hospitalization has increased in recent years in association with injection drug use and homelessness,[11] but this has not appeared to translate to more cases of full-blown hepatitis A-related ALF, at least in our experience: no hepatitis A ALF cases were registered between 2015 and 2019 by the ALFSG while nine acute liver injury (ALI) cases (INR 2.0, no encephalopathy) were recorded in the same period.[12] Within the overall DILI group, the mix of drugs implicated has evolved; antibiotics remain the most common overall group, but the incidence of HDSs has doubled in the past decade from 10 to 20%.[13] Overall, ALF due to HDS are associated with worse overall outcomes than other forms of DILI and will be discussed in more detail below. Certain agents are less commonly used and thus less frequently implicated. Medications that are declining in use/incidence include phenytoin, isoniazid, nitrofurantoin, and the early and toxic highly active antiretroviral agents.[13]

In summary, evolution of different etiologies over the past two decades has been relatively minimal for overall groups (APAP, DILI, AIH) while changes within the groups have been seen. We are not aware of differing trends in etiologies worldwide over this same time period.

Making the Correct Etiologic Diagnosis

It is vitally important to discern the correct etiology since antidotes and prognosis are both tied to the cause of the liver injury from first principles. *N*-acetylcysteine (NAC) is

the recognized antidote for APAP poisoning but ideally must be given within 12 hours of ingestion of a single dose with no clear timing requirement (early is best) for unintentional cases.[14] Other therapies such as corticosteroids (CS) for AIH and nucleoside analogs for hepatitis B are of uncertain value (see below), and do not preclude listing and ultimately transplantation.

There are two consistent clinical syndromes that account for all etiologies: "hyperacute" which includes APAP and ischemic liver injury, and "subacute" which includes nearly everything else: AIH, viral hepatitis, and DILI (Table 1).[7] The table highlights the differences between the hyperacute and subacute groups, in terms of onset, laboratory values, and outcomes, which are vastly different. The hyperacute group evolves over 2 to 4 days and resolution occurs by day 5 or 6.[7] In the case of APAP and most ischemic injuries, by day 5, either death or transplantation has occurred, or the patient is ready to be discharged! APAP cases are never subacute, and recovery rarely is prolonged to 2 weeks or more. By contrast, the subacute group typically has been ill for at least 2 weeks before seeking medical care or evolving tosigns of ALF. History-taking is vital to discern exposure to possible drugs, toxins, or viruses; however, since patients have altered sensorium, it may be difficult or impossible to obtain a reliable history. The availability of serologic testing for most viruses is paramount if clarity of diagnosis is to be obtained. A useful but not yet fully available test to determine exposure to APAP is the APAP-CYS adduct assay, which is currently "research only," while a point of care assay is under development.[15,16] After an overdose, blood levels of APAP disappear quite rapidly due to its short half-life (~ 6 hours), and levels are often undetectable upon arrival in the emergency department, raising uncertainty about the etiology of liver injury.[17] In contrast, APAP-CYS adducts, hepatocyte proteins covalently bound to the reactive metabolite of APAP (N-aminoparaquinoneimine), remain in the circulation as long as aminotransferases are elevated, up to 9 days.[18] Comparable specific diagnostic tests to determine definitively the causative agent in idiosyncratic DILI are not yet available but are under study.

Completing the Diagnostic Workup

The basic sequence of events in triaging patients with presumed ALF is as follows:

1.   Determine that ALF criteria are met (INR   1.5, any degree of encephalopathy.

2.   Search for etiology.

3.   Determine severity and need for liver transplant listing; if poor prognostic indicators are present, transfer to a liver transplant center.

4.   Start etiology-specific treatments and consider NAC.

5.   Set up general support measures and alerts for changes in status.

Determining an etiology requires extensive initial testing. A smartphone app provides a checklist for initial and daily laboratory testing to sort out etiology of each case (access as "ALF Checklist" in the App Store). The checklist process was summarized in 2016; a modified version of the admission and daily checklist is included in Tables 2 and 3.[19] A list of basic common etiologies and their appropriate tests precedes searching for more obscure conditions that are very rare.

What Constitutes Indeterminate ALF?

When no diagnosis is apparent, this "indeterminate" group, sometimes referred to as seronegative ALF, comprises a mélange of essentially undiagnosed etiologies. In rural communities in parts of Asia, indeterminate ALF may comprise more than 60% of cases[20] since serological testing is quite limited. In North America, indeterminate ALF was diagnosed by the ALFSG in 12% of registrants. However, upon further analysis of each case, the percent was diminished to around 5%, through thorough adjudication by a panel of expert hepatologists, additional serological testing, the use of the APAP-CYS adduct assay, and screening sera for viral genomes.[21] In many cases, the site investigator was uncertain between two diagnoses and chose "indeterminate ALF" to reflect this uncertainty. In the future, it is likely that nonbiased genomic sequencing with one sample will probe for most known viruses rather than the hit-or-miss testing we currently perform.[21] Despite the commonly held suspicion that occult viral infections were responsible for some indeterminate cases, searches for undiagnosed hepatitis viruses capable of causing ALF so far failed to disclose novel agents.[22]

Challenges to immediate diagnosis are real: patients have altered mentation (by definition), may not recall medications even if they are somewhat alert, and may not admit to overdosing as well. Thus, the APAP patient represents an ongoing diagnostic challenge. Use of the new APAP-CYS adduct assay will increase certainty of diagnosis once a point-of-care assay becomes available.[15,16]

As we look to the future, it is clear that the overall number of cases of ALF has not been increasing in most parts of the world and may actually be decreasing. Better education regarding the risks associated with APAP toxicity may be making some impact in the U.S. in terms of severity if not overall number of cases.[23] Outcomes have continued to improve in the past two decades with a decline in listing and liver transplantation accompanied by an increase in transplant-free survival.[3] These trends have occurred without a diminution of the severity of liver injury on presentation. Thus, improvements in intensive care as well as posttransplant management have evolved with greater experience with these difficult and challenging patients.

Section II: Management

Management Practices in ALF: A Developing Consensus Despite Weak Empirical Data

Although the management of patients with ALF remains unstandardized, general principles are emerging by consensus of experts in the field. Unfortunately, many of these principles are supported by weak empirical data. In 2007, the U.S. ALFSG comprehensively reviewed practices within the consortium,[24] many of which differed significantly. In 2016, the European ALF Consortium subsequently surveyed 22 liver transplant centers from 11 nations.[25] An overall approach to intensive care unit (ICU) management is outlined in Table 4. The etiologies of ALF in this report resembled those in the U.S., with approximately half of cases due to APAP overdose, 8% non-APAP idiosyncratic DILI, 5% viral, and 21% indeterminate etiologies. Although some management decisions were center-specific, many practices were quite similar; for example, intracranial pressure (ICP) monitoring

was selectively performed in most centers, usually for clinical evidence of intracranial hypertension (ICH). The ICP goal parameters were also similar, and treatment triggered by ICP greater than 25 mm Hg, with a goal cerebral perfusion pressure of 50 to 60 mm Hg. Mannitol was universally the first-line treatment. Interestingly, second-line therapy after failure of mannitol varied by center (increased sedation, followed by hypertonic saline [HTS] boluses), although there was a clear tendency for high-transplant volume centers to use HTS compared with low-volume centers (86 vs. 31%, respectively).

Other management practices were also identified consistently across centers. Roughly 80% administered NAC to patients with non-APAP ALF despite limited data supporting the practice.[26,27] Prophylactic antibiotics were uncommonly applied. Blood products (plasma and platelets) were generally not used without an indication, in only 5 and 16%, respectively, unless prior to ICP monitor placement (92 and 75%, respectively). Renal replacement therapy (RRT), usually continuous, was used by all centers. Interestingly, 55% of centers reported instituting RRT solely for treatment of hyperammonemia, as opposed to more traditional indications (acidosis, oliguria, volume overload).

Etiology-Specific Treatment

Steroids for suspected acute AIH: AIH is the most difficult etiology of ALF to identify accurately and carries a particularly poor prognosis (14% transplant-free survival in the ALFSG registry).[7] The international criteria for the diagnosis of chronic AIH were not developed for, and have not been validated in, patients with an acute presentation, and therefore are not readily applicable to patients with ALF. A simplification of the diagnostic criteria for chronic AIH has been adapted to the acute presentation, and include the presence of autoantibodies, hypergammaglobulinemia, a compatible liver histology, and the absence of viral markers.[28,29] Although useful, these criteria lack sensitivity and specificity, as the prevalence of autoantibodies in the acute presentation is only approximately 50 to 70%, and autoantibodies are frequently found in patients with other etiologies of ALF.[29–31] Liver biopsy features, which include those distinctive to the acute presentation, also lack sensitivity.[29]

Response to corticosteroids (CS) constitutes an important diagnostic feature of chronic AIH. Patients with severe acute presentations (coagulopathy without encephalopathy) may also respond to CS but have a poor prognosis overall.[32,33] Many clinicians have extrapolated these observations to patients with ALF and autoimmune features, a practice that has been referred to as "therapeutic brinksmanship."[32] Unfortunately, no randomized, placebo-controlled studies of CS in AIH-ALF have been performed, and less rigorous studies are not particularly supportive of the practice.[33,34] Consequently, guidelines regarding the use of CS in AIH-ALF have not advanced greatly. A study of CS therapy is currently underway for treatment of pediatric ALF, a disease that may be distinct from AIH-ALF in adults.

Without data-driven guidelines, an informal consensus has emerged regarding CS administration in suspected AIH-ALF. First, patients who present with, or evolve to, high-grade HE should be urgently evaluated for liver transplantation, and CS avoided, as CS rarely salvage such patients.[25] Second, the course of CS should be limited to roughly a week or two,[33] since longer application has been consistently shown to be futile and increases

the risk of infection. Third, despite the acute presentation, cirrhosis underlies many cases of AIH-ALF,[28] in which case liver transplantation may be the only viable long-term solution. De Martin et al[34] have identified a pattern of nonresponse to CS which predicts the need for urgent liver transplantation within 3 days of CS initiation, including the evolution of the INR and total bilirubin. In general, higher Model for End-Stage Liver Disease (MELD) score, INR, bilirubin, and encephalopathy grade at diagnosis predict CS failure.[32–35] Thus, the decision to list a patient for liver transplantation should be finalized within 3 days, and not more than 7 days, of CS administration. Evolution of encephalopathy may be the strongest indicator of the need for urgent transplantation, in which case CS should be forgone.

Antiviral agents for viral ALF: Nucleos(t)ide analogs for hepatitis B virus (HBV)-induced ALF have been assessed in several studies. The most scientifically rigorous study randomized 71 patients to receive lamivudine or placebo[36] but included patients with severe acute HBV (no encephalopathy). After 4 weeks, HBV deoxyribonucleic acid (DNA) titers were significantly lower in lamivudine-treated patients than placebo-treated controls, but otherwise, there were no clinically meaningful differences in the course of the two treatment groups. Other studies of DNA polymerase inhibitors in severe acute or fulminant HBV used historical controls, and some claim improvement in the poor transplant-free survival.[37–39] A Cochrane Database Review of pharmacologic interventions for acute HBV attempted to synthesize results from 7 randomized trials (lamivudine vs. placebo, 4 trials; lamivudine vs. entecavir, 1 trial; entecavir vs. no treatment, 1 trial; and interferon vs. no treatment, 1 trial), but concluded the data were highly biased, of low quality, and patient populations were excessively dissimilar.[40] Consequently, few data support the efficacy of any antiviral intervention in acute HBV; in patients with ALF, however, there is an emerging consensus that nucleos(t)ide analogs should be started on presentation to lower the risk of HBV infection of a transplanted liver. Herpes simplex virus causes ALF rarely but often with devastating severity. Acyclovir has been recommended based upon experience in small cases series.[41] Rescue of affected patients by acyclovir, with or without liver transplantation, is unusual.

Management of Systemic Complications of ALF

Overall clinical management of the ALF syndrome is similar for different etiologies. The primary difference pertains to the special needs of patients with certain hyperacute versus subacute etiologies, specifically the critical mandate for rapid transplant listing of severely ill patients with APAP-induced ALF (hyperacute), and the more certain need for transplantation in all forms of sub-ALF, all of which have a dismal prognosis without liver transplantation. An overall management algorithm is shown in Fig. 2.

Fluids and hemodynamics: Upon initial admission to the hospital, patients with ALF are typically hypovolemic, particularly if the patient has been unconscious for any length of time. A hyperdynamic state with peripheral vasodilation ensues, the result of systemic inflammatory response syndrome (SIRS) and cytokine storm, and results in end-organ hypoperfusion including lactic acidosis and renal failure.[42] Intravenous normal saline should be administered promptly to restore blood volume and pressure to a mean arterial pressure (MAP) of greater than 65 mm Hg.[43] Assessment of end-organ perfusion should

also guide the MAP in an individual patient. Persistent hypotension/hypoperfusion should prompt a search for infection, and broad-spectrum antibiotics and vasopressors initiated; norepinephrine is preferred.[25] An inadequate response should prompt the addition of vasopressin. Relative adrenal insufficiency by abnormal short synacthen test has been shown in a majority of patients with ALF,[44] and hydrocortisone (300 mg intravenously) should be added in persistently hypotensive, euvolemic patients on maximal doses of vasopressors. Fluid-responsiveness (cardiac index increase of 15% after a colloid challenge) was identified in only 29% of critically ill patients with ALF,[45] suggesting that most patients have profound systemic vasodilation and an ineffective increase in cardiac preload after a volume challenge.

A relatively new strategy to manage vasopressor treatment failures has emerged: therapeutic plasma exchange (TPE). A multicenter, randomized, controlled study of "high-volume" TPE in 182 patients with ALF showed a higher cumulative proportion surviving compared with standard medical therapy (SMT).[46] In the cohort receiving TPE, MAP increased promptly after institution, remained significantly higher than baseline ($p < 0.0001$), and required lower doses of vasopressors, while MAP in the SMT cohort remained unchanged. End-organ dysfunction such as the need for RRT was significantly lower in the TPE cohort ($p < 0.0045$). A nonrandomized trial of "low volume" plasma exchange,[47] and a randomized study of "standard-volume" plasma exchange[48] have documented similar benefits. The mechanism(s) by which TPE improves hemodynamic instability in ALF are likely multiple, including removal of vasoactive inflammatory cytokines and repletion of beneficial factors found in plasma.[44] The former seems more likely, as treatment with the molecular adsorbent recirculating system (MARS), which uses an albumin dialysate, also improves MAP and end-organ function compared with matched controls.[49]

Cerebral edema (Table 5): In older series, complications of cerebral edema were a primary cause of death in patients with ALF. The two largest contemporary Western series of ALF, however, both documented dramatic decreases in the incidence of cerebral edema.[2,50,51] In the U.S. ALFSG registry, ICH decreased from 52 to 30%, and death from cerebral edema from 12 to 4.5%, in early (1998–2007) and recent (2008–2018) cohorts, respectively. Undoubtedly, many improvements in the intensive care of patients with ALF contributed to these decreases, primary among them, the early and widespread use of continuous RRT (CRRT), and maintenance of serum sodium at high-normal levels.

Monitoring ICP: The use of invasive ICP monitors also appears to be declining,[3] due to the waning incidence of cerebral edema, often-fatal bleeding complications after insertion of the device, and the fact that no study has documented improvement in outcome or neurologic function in ICP-monitored patients. Invasive ICP monitoring has thus been relegated to the exceptional liver transplant candidate with high-risk features predictive of cerebral edema (presence of SIRS, high-grade HE, serum ammonia > 100 μM, renal failure) and clinical evidence of ICH. An argument may be made that ICP monitoring serves to identify which patient with ALF should not undergo liver transplantation because of long-standing ICH, and high risk of intraoperative herniation or postoperative poor neurologic recovery (Fig. 3).

Unfortunately, noninvasive ICP monitoring remains an elusive goal in patients with ALF. For the reasons outlined above, studies of noninvasive ICP tests have not routinely used the gold standard of invasive pressure monitoring. In one study comparing noninvasive with invasive pressure monitoring, ultrasound-based tests were administered to a cohort of patients with ALF and grade 4 HE.[52] Neurointensivists blinded to the ICP by invasive monitor concluded that only transcranial Doppler flow velocities accurately detected an ICP greater than 20 mm Hg (area under the curve [AUC] 0.90), while optic nerve sheath diameter (AUC 0.59) and middle cerebral artery pulsatility index (AUC 0.55), did not. While the optic nerve sheath diameter technique has been shown to accurately reflect ICP in other disorders of ICH, the pathogenesis of cerebral edema in ALF is unique (cytotoxic edema and cerebrovascular vasodilation) and may not be amenable to detection by this technique.[52]

Management of serum sodium: The feasibility of prophylaxis against cerebral edema in patients with ALF was first shown by Murphy et al, in a prospective, randomized, placebo-controlled study of HTS to maintain mild hypernatremia (serum sodium 145–155 mM).[53] Patients who received HTS maintained lower ICPs by invasive monitoring, were less likely to develop ICP of 25 mm Hg or higher, and required lower doses of norepinephrine, than those who were managed at normal serum sodium levels. In patients with established cerebral edema, HTS (3% as a constant infusion to maintain serum sodium < 160 mM) was recently compared with 20% mannitol (1 g/kg bolus[es]).[54] The decline in ICP was approximately the same between groups but was measured by optic nerve sheath diameter and middle cerebral artery pulsatility index, results of which are questionable versus invasive ICP monitoring.[52] However, rebound in ICP and renal dysfunction were more common in mannitol-compared with HTS-treated patients, suggesting a possible ancillary rationale for choosing the latter agent. The unpredictable titration of serum sodium during HTS boluses or infusion may be more closely controlled using modifications of CRRT, as recently proposed.[55]

RRT for hyperammonemia: Another modification of standard ICU care in ALF patients has become the early application of RRT, usually CRRT, in moderately severely hyperammonemic patients. Although the association of serum ammonia greater than 200 μM with the development of ICH and cerebral herniation,[56,57] and greater than 100 μM with high-grade HE[58] has been recognized for decades, it has become more common to use RRT for the sole purpose of removing ammonia in ALF relatively recently. Blood and dialysate flow rates are the primary determinants of ammonia clearance.[59] CRRT with hemofiltration clears ammonia in proportion to the ultrafiltration rate ($r = 0.86$) and can decrease median arterial ammonia over 24 hours by more than 20%.[60] The cumulative duration of CRRT rather than hourly treatment intensity correlates with ammonia reduction most closely, suggesting that therapy should be started early and continued until ammonia levels are persistently less than 100 μM.[60] Continuous may be superior to intermittent RRT in lowering serum ammonia and is associated with improved transplant-free survival.[61]

Novel treatments for refractory cerebral edema: Based upon experience in children with hereditary forms of hyperammonemia, ammonia scavengers have been developed and tested in patients with ALF. L-ornithine L-aspartate (LOLA), a drug which provides

a substrate for glutamine synthesis from glutamate and ammonia, was studied in a randomized, placebo-controlled population with ALF.[62] Unfortunately, LOLA failed to lower serum ammonia more quickly than placebo and did not improve encephalopathy grade. These negative results were ascribed to gut glutaminases, which deamidate glutamine, returning ammonia back into the circulation.[63] A similar drug, L-ornithine phenylacetate (OPA), provides a substrate for glutamate synthesis (ornithine), and also binds ammonia through the action of glutamine synthetase.[64] In contrast to LOLA, the phenylacetate component of OPA binds glutamine and promotes its renal excretion before deamidation by glutaminases. In an open-label of patients with ALF and severe ALI, OPA was shown to promote renal excretion of ammonia in a dose-dependent manner and was deemed safe and well-tolerated.[64] Further randomized, placebo-controlled studies in ALF have yet to be performed.

The induction of therapeutic hypothermia in ALF was pioneered by Jalan et al, to treat established, refractory ICH.[65,66] Candidates for hypothermia are usually awaiting liver transplantation, in grade 4 HE, and have an invasive ICP monitor in place. Although cooling patients to a core temperature of 32 to 34°C reliably decreases ICP, there are adverse effects of hypothermia particularly pertinent to patients with ALF to consider: increased risk of infection, exacerbation of coagulation abnormalities, and cardiac dysrhythmias. Therapeutic hypothermia has, therefore, been relegated to the most recalcitrant cases of ICH and is not a reliable bridge to liver transplantation in most cases. Prophylactic hypothermia has also received attention. In a randomized, multicenter study of management at low-normal (36°C) or hypothermic (33–34°C) conditions, patients with grade 4 encephalopathy and ICP monitors were followed until reaching a primary endpoint of ICP greater than 25 mm Hg or 72 hours of thermal management.[67] There were no differences in outcomes in patients managed under hypothermic versus normothermic conditions (primary endpoint met in 35% vs. 27%, respectively; $p = 0.56$). Although this study was very likely underpowered, prophylactic hypothermia cannot be advocated based upon these data.

Hemostatic abnormalities (Table 6): Patients with ALF appear to have a bleeding diathesis based upon often-markedly elevated INR and thrombocytopenia. Bleeding complications, often fatal, were commonly reported in early series of ALF (20–30% mortality). However, bleeding complications in a more contemporary series occurred in only 11% of the ALFSG cohort, with bleeding as a proximal cause of death recorded in only approximately 2% (7/10 deaths attributable to intracranial bleeding including complications of invasive ICP monitoring).[68] The explanation for the rarity of bleeding complications has been ascribed to "rebalanced hemostasis," a concept first identified in cirrhosis but more recently described in ALF.[69] Compensatory mechanisms for hemostatic deficiencies have been identified for each phase of coagulation, such that low procoagulant proteins are "rebalanced" by low anticoagulant proteins and increased levels of factor VIII.[68–71] The development of thrombocytopenia, which is partly SIRS-driven,[72] is "rebalanced" by SIRS-related hyperproduction of von Wille-brand factor,[73] the binding protein of platelets to endothelium, and by production of prothrombotic platelet-derived microparticles.[74]

Despite the fact that transfusion of platelets and plasma in patients with ALF has decreased with time,[3,68] bleeding complications have also decreased, suggesting that prophylactic

transfusions may not be indicated. However, it must be emphasized that hemostatic abnormalities unquestionably exist and may contribute to bleeding complications in ALF.[75] Therefore, the administration of plasma and platelets before an invasive procedure must be individualized by the clinician, with the following caveats. First, a platelet count of 60×10^9/L or higher is probably adequate for any invasive procedure except for ICP monitor placement, in which case individualized therapy discussed with the consulting neurosurgeon is mandatory. Considerations such as the presence of renal failure must be weighed. Second, there are no guidelines of plasma administration, or goal INR, to guide clinicians. Although an INR of 1.5 or lower is often stated as the goal of plasma infusion, there was no relationship between INR and bleeding complications in the ALFSG registry.[68] Clinicians must weigh the loss of the most important single clinical indicator of severity and trajectory of liver injury (the INR) by plasma infusion versus the perception of decreasing bleeding risk. Global hemostasis as assessed by thromboelastography[70,76] or rotational thromboelastometry[75] may be a useful adjunct to guide transfusion of platelets and plasma in patients with ALF but require further study as their sensitivity to subtle hemostatic derangements has not been adequately studied.

Section III: Prognostic Scoring and Liver Transplantation for Acute Liver Failure

Prognostic Scoring

Determining who can survive with best supportive care and who will succumb without liver transplantation remains a contentious area. Prognostic scoring systems attempt to balance sensitivity identifying patients who will die without liver transplantation with specificity aimed at avoiding unnecessary transplantation. Although no model performs perfectly, the hallmark of understanding prognosis in ALF depends on the etiology, laboratory and clinical markers of disease severity, and the tempo of disease. While the hyper-ALF seen with APAP provides the most dramatic laboratory derangements and highest risk for cerebral edema, ALF due to APAP also has the most favorable prognosis with the antidote NAC and supportive medical care whereas those with sub-ALF often due to idiosyncratic DILI, AIH, or indeterminate causes have the poorest outcomes without transplantation.[3] Historically, the King's College Criteria (KCC) have been used to predict need for transplantation in both APAP and non-APAP ALF though many additional scoring systems have been developed (Table 7).[77] Factor V was proposed early on as a more accurate measure than INR but is not used widely currently.[78] More recent studies have demonstrated that while having high specificity (94% in APAP; 82% in non-APAP), KCC lack sensitivity potentially failing to identify patients that will not survive without transplant. When KCC are compared with the Sequential Organ Failure Assessment (SOFA) score and MELD score in APAP ALF, SOFA was significantly better with AUC of 0.72 compared with KCC and MELD, with AUC of 0.65 and 0.58, respectively.[79] MELD score has been extensively studied in both APAP and non-APAP ALF cases with decreased spontaneous survival noted with MELD 33 or higher and 30 or higher, respectively.[80,81] A meta-analysis of 23 studies comparing the accuracy of KCC and MELD determined KCC predicted the need for transplant better in APAP cases whereas MELD performed better in non-APAP cases.[82] The first iteration of the ALFSG prognostic index used coma grade, INR, bilirubin, phosphorus, and levels of an

apoptosis biomarker, M30, and correctly identified those who were transplanted or died with sensitivity of 86%. This score is limited in clinical practice by availability of the M30 assay and did not outperform SOFA score in further analysis.[83,84]

Clinically, two readily available features on admission, coma grade and etiology of ALF, largely determine outcomes. Etiologies can be graded as favorable versus unfavorable (Fig. 4, Table 8) with advanced coma grade carrying a worse prognosis. The ALFSG subsequently developed a mathematical model available as a Web-based application (ALFSG Prognostic Index in the App Store) incorporating five clinical features: etiology (favorable vs. unfavorable), encephalopathy grade (low-grade 1–2, vs. high-grade 3–4), INR, bilirubin, and vasopressor use to successfully predict spontaneous survival with AUC of 0.843. This was superior to MELD (AUC 0.717) and KCC (AUC 0.560 for non-APAP, 0.655 for APAP) (Fig. 5).[85] The addition of lactate to bilirubin and etiology to create the Bilirubin Lactate and Etiology score,[86] as well as lactate when combined with creatinine may predict mortality better than MELD but has yet to be validated.[87] The Acute Physiology and Chronic Health Evaluation score has also been applied.[88]

Another more recent scoring system, the ALF early dynamic model, utilizes changes in ammonia, bilirubin, INR, and stage of encephalopathy over 3 days to predict outcomes more accurately.[89] Sequential monitoring of readily available laboratory values INR and lactate also have been employed by the King's College to discriminate between spontaneously recovering APAP ALF patients and those in need of liver transplant.[90] Serial monitoring of hepatic metabolic function with the ^{13}C-methacetin breath test predicted death or transplant with AUC of 0.88.[91] Additional biomarkers such as α fetoprotein,[92] phosphate,[93] human leukocyte antigen-DR expression,[94] Gc-globulin,[95] fatty acid binding protein,[96,97] and micro-ribonucleic acid levels[98] have been reported to improve existing prognostic models but are limited by clinical availability and external validation.

Liver volume less than 1,000 cm^3 determined by computed tomography may be a marker of irreversible massive necrosis predictive of development of high-grade encephalopathy and death in non-APAP ALF with 91% sensitivity and 63% specificity.[99] While clinical status may preclude liver biopsy in these patients, specimens with greater than 75% necrosis is associated with need for transplant or death in ALF due to AIH, drug, or viral hepatitis.[100–102]

In summary, there is no consensus on best scoring system. Clinical judgment of experienced hepatologists and transplant surgeons seems the best guide, using the prognostic indices as aids in elucidating the proper timing and appropriateness of liver grafting.

Liver Support

Over the past three decades a variety of liver support devices have surfaced in early clinical trials only to falter and disappear from view. Many incorporated hepatocyte cartridges but either cell volumes were inadequate or the machines were too cumbersome to be feasible in the setting of a rare, rapidly evolving critical illness. Albumin-based dialysis systems, such as the MARS has been recommended for management of ALF patients particularly those with APAP injury. Equivocal results have led most centers to use these systems

selectively, if at all.[49] A recent meta-analysis of liver support devices discerned no difference in mortality between various support devices and standard medical treatment (SMT) in non-APAP ALF.[103]

Outcomes of Liver Transplantation

Mortality rate in ALF has improved greatly through the years, primarily with increased availability of liver transplantation. In the King's College experience of over 3,300 patients between 1973 to 2008, the survival rate increased from 16.7 to 62.2%.[2] Approximately half of non-APAP ALF patients will be transplanted, although ALF represents less than 10% of all liver transplants in Europe and the United States.[104] One-year posttransplant survival of ALF is less than chronic liver disease but comparable to critically ill high MELD patients at over 80%.[105] Risk factors for death after transplant for ALF in the European registry include male gender, donor age, recipient age, ABO incompatible graft, and small graft.[104] Additional risk factors for poor outcomes in the United Network for Organ Sharing (UNOS) database include obesity, creatinine greater than 2 mg/dL, and history of life support. The highest risk of death is in the first 3 months related to infection including fungal, neurologic complications, and multisystem organ failure.[106] In the European registry, noncompliance and repeated suicide resulted in graft loss and death 10 times more likely in APAP ALF than those transplanted for other etiologies.[104] Among those in the large ALFSG registry (N = 2,264), only 22% of APAP ALF patients were listed for liver transplant and were twice as likely to die waiting for an organ compared with other etiologies.[107] This finding was replicated in the UNOS database with APAP etiology associated with waitlist mortality but did not result in worse posttransplant outcomes after adjusting for disease severity. Most deaths occurred in the same hospitalization highlighting the need for timely and appropriate selection for transplant.[108]

Living donor liver transplant may be an option to combat organ availability though ethical concerns exist regarding expedited donor evaluation and undue coercion given the unique urgency of ALF patients. Such patients currently account for only 1% of the adult-to-adult living donor liver transplant evaluations in the United States with 1-year survival of 70%.[109] In Asia where deceased donors are rare, living donor liver transplantations for ALF have a 1-year survival of 79%. Western transplant centers have more recently reported comparable complication rates to deceased donor transplantation.[109,110] While more spontaneous recoveries of ALF are being achieved in recent years with supportive care, identifying those who will benefit from liver transplantation remains the ultimate task recognizing the limitations of current prognostic models.

Conclusion

Significant progress has been made over the past two decades in understanding and managing ALF. The incidence of ALF may be declining since several etiologies are less likely overall: DILI, hepatitis A and B, among others. The incidence of APAP ALF, however, does not appear to be declining. Spontaneous survival has improved in recent years owing to disease specific treatments such as NAC and improved critical care management including early initiation of CRRT. Despite numerous prognostic scoring systems, there is

not one perfect prediction model and when to list and transplant for ALF remains a highly complex decision. The outcomes of patients transplanted for ALF are comparable to those transplanted for chronic liver disease. Management in the future is likely to include novel liver support devices,[111] the possibility of stem cell mobilization to populate the damaged liver,[112] and other agents which promote liver regeneration.[113]

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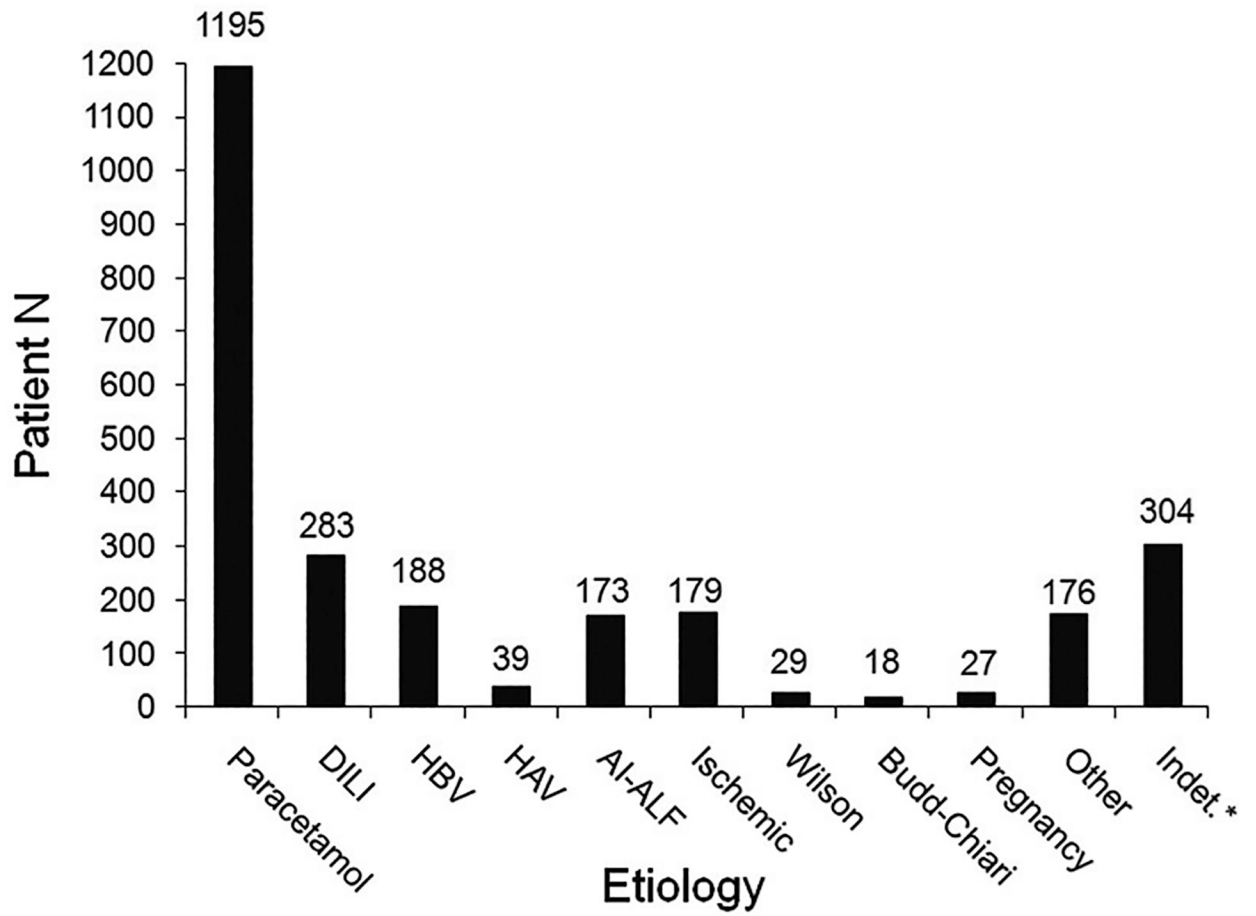
Fig. 1.
Incidence of specific etiologies of acute liver failure (ALF) as determined by the site principal investigator (PI) in the Adult Acute Liver Failure Study Group Registry: January 1998–March 2019.
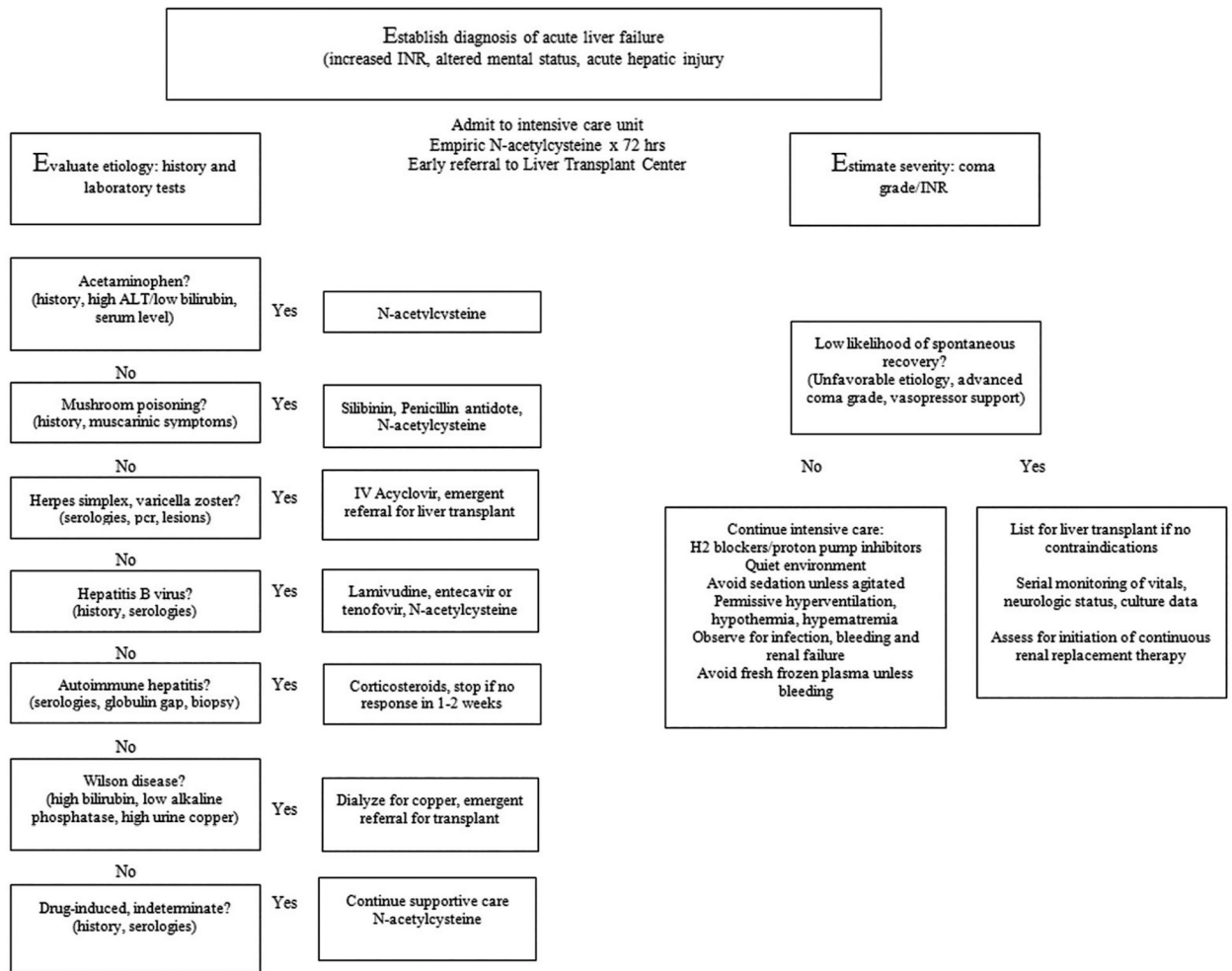
Establish diagnosis of acute liver failure
(increased INR, altered mental status, acute hepatic injury

Admit to intensive care unit
Empiric N-acetylcysteine x 72 hrs
Early referral to Liver Transplant Center

Evaluate etiology: history and laboratory tests

Estimate severity: coma grade/INR

Acetaminophen?
(history, high ALT/low bilirubin, serum level) — Yes → N-acetylcysteine

No

Mushroom poisoning?
(history, muscarinic symptoms) — Yes → Silibinin, Penicillin antidote, N-acetylcysteine

No

Herpes simplex, varicella zoster?
(serologies, pcr, lesions) — Yes → IV Acyclovir, emergent referral for liver transplant

No

Hepatitis B virus?
(history, serologies) — Yes → Lamivudine, entecavir or tenofovir, N-acetylcysteine

No

Autoimmune hepatitis?
(serologies, globulin gap, biopsy) — Yes → Corticosteroids, stop if no response in 1-2 weeks

No

Wilson disease?
(high bilirubin, low alkaline phosphatase, high urine copper) — Yes → Dialyze for copper, emergent referral for transplant

No

Drug-induced, indeterminate?
(history, serologies) — Yes → Continue supportive care N-acetylcysteine

Low likelihood of spontaneous recovery?
(Unfavorable etiology, advanced coma grade, vasopressor support)

No / Yes

Continue intensive care:
H2 blockers/proton pump inhibitors
Quiet environment
Avoid sedation unless agitated
Permissive hyperventilation, hypothermia, hypernatremia
Observe for infection, bleeding and renal failure
Avoid fresh frozen plasma unless bleeding

List for liver transplant if no contraindications
Serial monitoring of vitals, neurologic status, culture data
Assess for initiation of continuous renal replacement therapy

Fig. 2.
Algorithm for managing patients in the intensive care unit with acute liver failure.

Fig. 3.
Head computed tomography (CT) scans of a 32-year-old man with acute liver failure
of indeterminate etiology who died of progressive cerebral edema. At admission (*left*),
the brain appeared normal; 48 hours later (*right*), there was diffuse loss of gray-white
differentiation, effacement of sulci, and obliteration of the basal cisterns, consistent with
severe diffuse edema and transtentorial herniation with brainstem compression. This patient
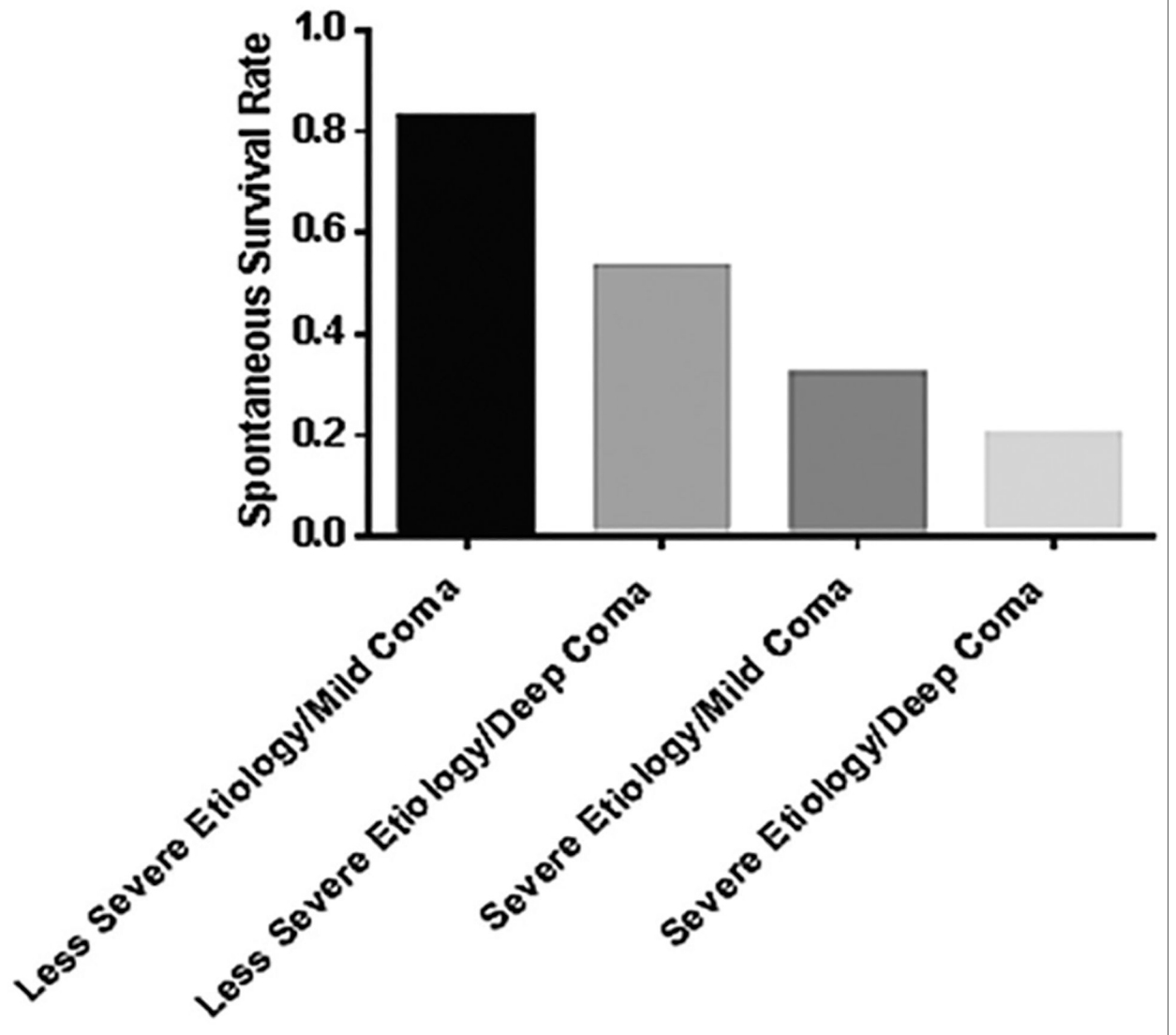died during attempted liver transplantation.

Fig. 4.
As noted in the table, prognosis depends on etiology but also on hepatic encephalopathy (HE) grade. Favorable etiologies and lower HE grades are associated with better transplant-free survival than unfavorable etiologies and advanced HE.
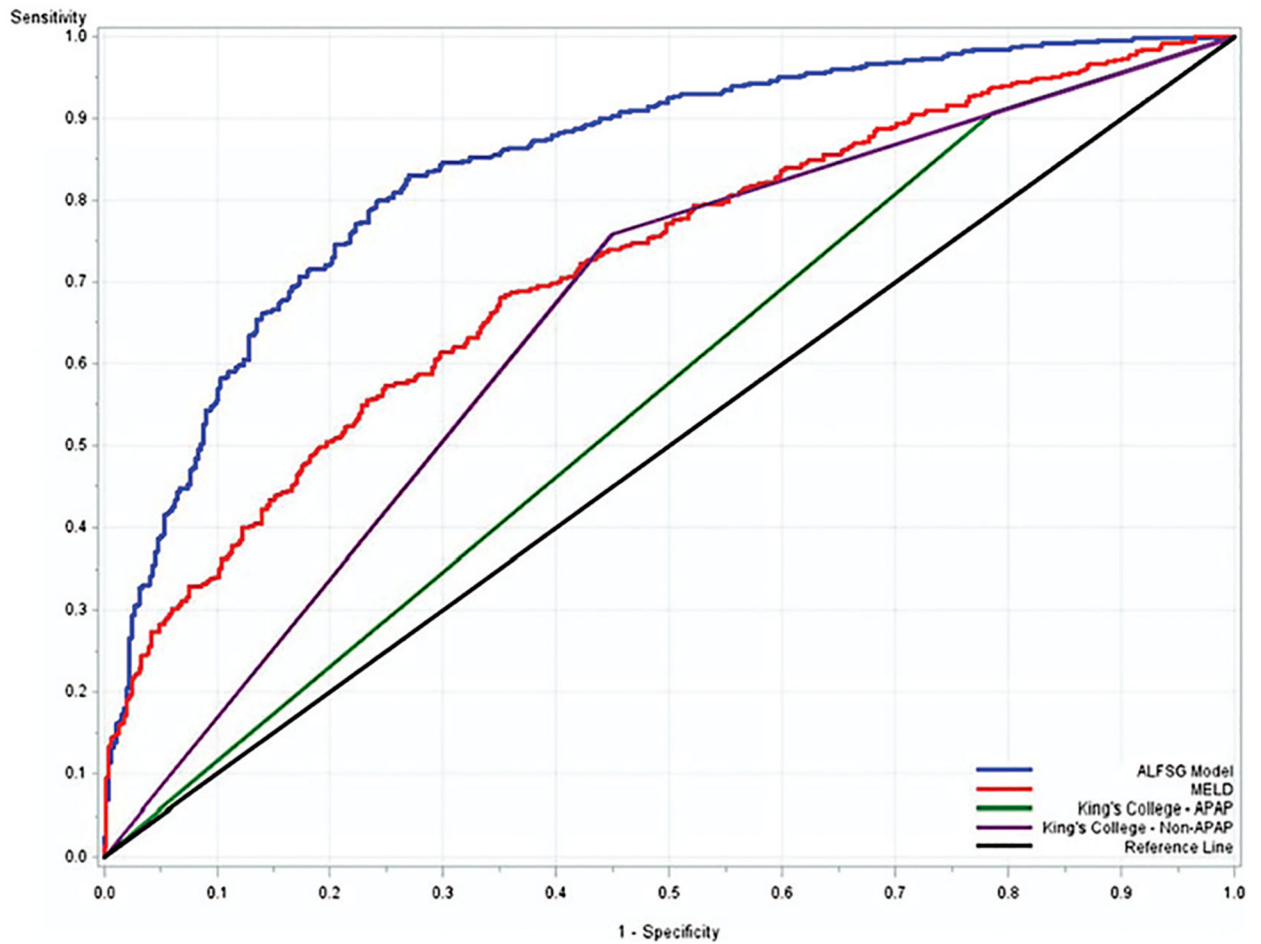
Fig. 5.
Area under the receiver operator curves (AUROC) comparing the Acute Liver Failure Study Group (ALFSG) prognostic index model to the King's College Criteria (KCC) and Model for End-Stage Liver Disease (MELD) score, in predicting 80% survival. ALFSG model outperformed KCC and MELD in this analysis. Model c-statistics: ALFSG model = 0.843; MELD = 0.717; King's College Criteria acetaminophen (APAP) (0.560), King's College Criteria non-APAP (0.655).

Table 1

Clinical and laboratory features of the different etiologies of acute liver failure

Clinical feature	Etiology of ALF, N = 2,614							
	Paracetamol, N = 1,195	Ischemia, N = 181	DILI, N = 283	AI-ALF, N = 173	HBV, N = 188	HAV, N = 39	Pregnant, N = 27	All others, N = 528
Age (median years)	37	53	47	46	45	50	31	40
Gender (% female)	75	58	67	81	45	44	100	64
Jaundice-coma (median days)	1	2	12	16	8	4	7	7
HE grade 3 (%)	54	56	36	27	51	54	54	44
ALT (median IU/L)	3,780	2,311	654	404	1,410	2,229	43	758
Bilirubin (median mg/dL)	4.3	3.8	19.6	22.8	19.2	12.0	9.0	16.2
Transplanted * (%)	9	2	39	57	40	33	4	36
Transplant-free survival * (%)	65	57	24	14	19	51	78	22
Overall survival * (%)	72	58	58	63	53	77	82	55

Abbreviations: AI, autoimmune; ALF, acute liver failure; ALT, alanine aminotransferase; DILI, drug-induced liver injury; HAV, hepatitis A virus; HBV, hepatitis B virus; HE, hepatic encephalopathy.

Note: Striking differences are seen between the two hyperacute etiologies (paracetamol and ischemia) and all other etiologies in terms of time from onset to failure, liver laboratory values, and outcomes.

*
indicates outcome 21 days after admission for ALF to the study site hospital

Table 2

Items to be considered on admission and daily in all cases of ALF

Neuro checks every 1–2 hours
Head of the bed at 30°
Head in neutral position
Minimize stimulation (tracheal suctioning, chest physiotherapy, sternal rubbing)
Consider N-acetylcysteine (NAC) IV
CXR and surveillance cultures (blood, urine, sputum) on admission and every 24–48 hours
Monitor blood glucose every 1–2 hours
Avoid nephrotoxic drugs (aminoglycosides, NSAIDs, neomycin, etc.) and IV contrast
DVT prophylaxis (sequential compression device) despite coagulopathy
PPI for stress ulcer prophylaxis
Communication: (1) intensivist and/or transplant hepatologist, (2) nurse, (3) patient's family

Abbreviations: ALF, acute liver failure; CXR, chest X-ray; DVT, deep vein thrombosis; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton-pump inhibitor.

Table 3

Diagnostic testing based on possible etiologies of ALF

Possible etiology	Diagnostic items to do in all cases of ALF	Diagnostic items to consider	Specific therapies[a]
Drug/toxin	• Obtain 6-month medication/toxin/ingestion history including OTC supplements, herbals, wild mushrooms, weight loss drugs • Urine and serum toxicology screens • Acetaminophen level	Consider liver biopsy	Acetaminophen toxicity: NAC Mushroom poisoning: charcoal, NAC, penicillin G, and/or silibinin[b]
Viral	• Anti-HAV IgM • HBsAg, anti-HBc IgM,HBV DNA (quantitative) • Anti-HCV, HCV RNA	Anti-HEV HSV DNA EBV DNA CMV DNA Anti-HDV/HDV RNA	HBV: Nucleos(t)ide analog HSV: Acyclovir
Autoimmune	• Antinuclear antibody • Anti-smooth muscle antibody/anti-actin antibody • Immunoglobulin G	Anti-liver/kidney microsomal antibody Liver biopsy	Consider corticosteroids
Vascular Budd–Chiari ischemia	• Abdominal ultrasound with Doppler	CT/MRI Assess for hypercoagulable state including search for malignancy Interventional radiology consultation Echocardiography/ECG	Budd–Chiari: Anticoagulation, TIPS
Wilson	• Check for hemolytic anemia (high indirect bilirubin), low alkaline phosphatase, renal failure, acidosis	Ceruloplasmin 24-hour urine for copper Serum copper Ophthalmology consultation to look for Kayser–Fleischer rings	Consider early CRRT
AFLP/HELLP		β-HCG Obstetrical consultation Ultrasound for fat	Early delivery
Malignancy		CT/MRI Liver biopsy	
Indeterminate		Liver biopsy	

Abbreviations: AFLP, acute fatty liver of pregnancy; ALF, acute liver failure; β-HCG, beta-human chorionic gonadotropins; CMV, cytomegalovirus; CRRT, continuous renal replacement therapy; CT, computed tomography; DNA, deoxyribonucleic acid; EBV, Epstein-Barr virus; ECG, electrocardiogram; HAV, hepatitis A virus; HBc, hepatitis B core; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HELLP, hemolysis, elevated liver enzymes and low platelets; HEV, hepatitis E virus; HSV, herpes simplex virus; IgM, immunoglobulin M; MRI, magnetic resonance imaging; NAC, N-acetylcysteine; OTC, over-the-counter; RNA, ribonucleic acid.

[a]NAC should be administered to all patients with ALF and encephalopathy grade I/II regardless of etiology, and for all cases of suspected acetaminophen toxicity.

[b]Not United States Food and Drug Administration (FDA) approved.

Table 4

ICU management

1. Neurologic

Abrupt deterioration in mental status?

Yes: Head CT to look for intracranial hemorrhage

Serum sodium < 145 mMol/L?

Yes → Consider using hypertonic saline for prophylaxis of intracranial hypertension to maintain serum Na between 145–155 mMol/L; carefully monitor rate of Na rise; discuss serum Na goal with health care team if patient on CRRT

Intubated, agitated or in pain?

No → Avoid sedating medications (benzodiazepines, narcotics, central-acting anti-emetics)

Yes → Use propofol and/or fentanyl

Spontaneous hypothermia (34–37°C)?

Yes → Do not warm patient

Encephalopathy grade III/IV?

Yes → Consider mannitol 0.25–1.0 g/kg IV q6 hours if serum osmolality < 320 mOsm/L or hypertonic saline boluses for treatment of suspected intracranial hypertension

Yes → Consider intracranial pressure monitoring

■ Goal intracranial pressure < 25 mm Hg

■ Goal cerebral perfusion pressure 50–80 mm Hg

2. Pulmonary

Encephalopathy grade III/IV?

Yes → Intubate; prefer low tidal volume ventilation to avoid acute lung injury

Intubated and spontaneously hyperventilating?

Yes → Do not correct ventilation

3. Infectious disease

(1) Progression of encephalopathy or grade III/IV or (2) SIRS or (3) clinical deterioration or (4) patient listed for transplant? Surveillance cultures daily

Yes/positive surveillance culture → Consider broad-spectrum antibiotics

4. Cardiovascular

Mean arterial pressure (MAP) < 75 despite volume repletion AND encephalopathy grade III/IV?

Yes → Begin vasopressors (prefer norepinephrine over epinephrine or vasopressin)

Yes → Consider trial of hydrocortisone

5. Renal

1) Oliguria or (2) rise in creatinine > 0.3 mg/dL or (3) ammonia > 150 μM or (4) volume overload or (5) established/suspected intracranial hypertension?

No → Consider renal consultation/early hemodialysis

Yes → Initiate CRRT (CRRT preferred over intermittent HD even if hemodynamically stable)

6. Hematology

Clinically significant bleeding?

No → Do not correct INR

Yes → Correct thrombocytopenia, hypofibrinogenemia and coagulopathy

Planned invasive procedure?

No → Do not correct INR, if possible upon consultation with intensivists/radiologists/neurosurgeons

Yes → Correct thrombocytopenia and hypofibrinogenemia (INR does not predict bleeding risk in patients with ALF)

7. Endocrine

Glucose < 80 mg/dL?

Yes → Dextrose

Glucose > 180 mg/dL?

Yes → Insulin

8. Gastrointestinal

Enteral feeding possible (PO or NG)?

Yes → Begin as early as possible if no evidence of gastroparesis

9. Early transplant evaluation

Encephalopathy?

Yes → Consult transplant center/transplant hepatologist early

Potential liver transplant candidate?

Yes → Begin transplant evaluation per center protocol

All criteria for Status IA listing met?

All 3 of following criteria must be met:

1	Onset of encephalopathy within 8 weeks of first symptoms of liver disease
2	In the ICU
3	(a) INR > 2 or (b) intubated or (b) on CRRT

Yes→ Consider listing, in consultation with transplant team

Abbreviations: ALF, acute liver failure; CRRT, continuous renal replacement therapy; CT, computed tomography; HD, hemodialysis; ICU, intensive care unit; INR, international normalized ratio; IV, intravenous; Na, sodium; NG, nasogastric; PO, per oral; SIRS, systemic inflammatory response syndrome.

Note: Items to be checked on admission and daily.

Table 5

Management of cerebral edema

Prevention of cerebral edema
• Allow spontaneous hyperventilation
• Allow spontaneous hypothermia; generally, do not warm a patient with spontaneous low core temperatures
• Initiate renal replacement therapy early, particularly in patients with risk factors for developing cerebral edema (serum ammonia > 100–150 µM, high-grade encephalopathy, presence of SIRS, oliguria, AKI)
• Maintain serum sodium at high-normal levels (145–155 mM)
Management of established cerebral edema
• Mannitol (0.5–1.0 g/kg body weight IV) bolus(es)
• Hypertonic saline bolus(es)
• Remove more volume and ammonia (CVVH)
• Maintain cerebral perfusion pressure with norepinephrine (CPP > 60 mm Hg)
• Consider therapeutic plasma exchange
• Consider deeper sedation (propofol)
• Consider ammonia scavenging agent (sodium phenylacetate, sodium benzoate; Ammonul)
• Consider therapeutic hypothermia (core temperature 32–34°C)

Abbreviations: AKI, acute kidney injury; ALF, acute liver failure; CPP, cerebral perfusion pressure; CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; HTS, hypertonic saline; ICP, intracranial pressure; IV, intravenous; MAP, mean arterial pressure;

OPA, L-ornithine phenylacetate; SIRS, systemic inflammatory response syndrome.

Note: The optimal management plan for cerebral edema in patients with ALF is undoubtedly prevention. In addition to the usual positional maneuvers (elevation of the head-of-bed; neutral neck rotation), patients should be allowed to hyperventilate such that their PCO_2 decreases to 30–40 mm Hg and allowed to be hypothermic (usual in patients on CVVH). CRRT should be initiated early in patients with risk factors for developing cerebral edema. Serum sodium should be raised to high-normal.

In patients with established cerebral edema, mannitol or HTS boluses should be administered promptly, and CVVH continued. If an ICP monitor is placed, the CPP should be maintained > 60 mm Hg by increasing the MAP with norepinephrine. Therapeutic plasma exchange should be considered, as this will not only improve the MAP, but will remove ammonia from the circulation. As desperate measures,

deeper sedation with propofol and/or therapeutic hypothermia may be considered. Although not studied in patients with ALF, sodium phenylacetate/sodium benzoate (Ammonul) might be considered as an ammonia scavenging agent. The compound has been studied in children with urea cycle defects and acute hyperammonemic crises and is commercially available; OPA is not.

Table 6

General recommendations for blood component transfusion prior to an invasive procedure in patients with ALF

Hemostatic parameter	Transfusion/Infusion	Threshold to replete
INR	Plasma	Unknown
Platelet count	Platelets	$< 60 \times 10^9$/L
Fibrinogen	Cryoprecipitate	< 100 mg/dL
Hemoglobin	RBCs	< 7 g/dL

Abbreviations: ALF, acute liver failure; INR, international normalized ratio; RBC, red blood cell.

Note: Although the cause of much consternation to clinicians caring for patients with ALF, the implication of an elevated INR in estimating bleeding risk is unclear.[68] Before an invasive procedure, we suggest considering the transfusion of 1–2 units of plasma shortly before the procedure, then proceeding with the procedure without repeating the INR.

Platelets should be transfused if peripheral counts are $< 60 \times 10^9$, with consideration of a higher threshold for transfusion in the setting of renal failure. Fibrinogen should be repleted with cryoprecipitate or fibrinogen concentrate if blood concentration is < 100 mg/dL. Red blood cells (RBCs) should be transfused if the hemoglobin is < 7 g/dL. These recommendations are primarily made on the basis of studies in patients with cirrhosis rather than ALF.[76] In a patient with ALF who is actively bleeding, all blood components should be repleted, including plasma.

Table 7

Parameters for predicting mortality and need for liver transplantation in patients with ALF

Test or index	Etiology of ALF	Threshold for poor prognosis, need for liver transplantation	Reference
King's College Criteria	Paracetamol	Arterial pH < 7.30 *or* all of the following: **1** PT > 100 s (INR> 6.5) **2** Creatinine > 3.4 mg/dL3. Grade ¾ encephalopathy	O'Grady et al, 1989
	Non- paracetamol	PT > 100 s (INR > 6.5) *or* any three of the following: **1** Non-A, non-B hepatitis, drug, or halothane etiology **2** Jaundice to encephalopathy > 7 d **3** Age < 10 or > 40 y **4** PT > 50 s (INR > 3.5) **5** Bilirubin > 17.4mg/dL	
Factor V (Clichy criteria)	Viral	Age < 30 y: factor V < 20% *or* Any age: factor V < 30% *and* grade ¾ encephalopathy	Bernuau et al, 1986; 1991
Liver biopsy	Mixed	Hepatocyte necrosis > 70%	Donaldson et al, 1993
Arterial phosphate	Paracetamol	> 1.2 mmol/L; sensitivity 89%, specificity 100%	Schmidt and Dalhoff, 2002
Serum lactate	Paracetamol	> 3.5 mmol/L postresuscitation	Bernal, 2002 [114]
APACHE II score	Paracetamol	Score > 15; sensitivity 82%, specificity 98% Score > 20; sensitivity 68%, specificity 87%	Mitchell et al, 1998
MELD score	Paracetamol Non-paracetamol	Score > 33 Score 30	Schmidt and Larsen, 2007 Yantorno et al, 2007
SOFA score	Paracetamol	Score 12	Cholongitas et al, 2012
BiLE score	Mixed	Score > 6.9	Hadem et al, 2008
Volumetric CT	Non-paracetamol	Liver volume < 1,000cm^3	Zabron et al, 2018
ALFSG prognostic index[a]	Mixed	Continuous variables: Favorable/unfavorable, encephalopathy grade, use of pressors (Y/N), INR, bilirubin	Koch et al, 2016

Abbreviations: ALF, acute liver failure; ALFSG, Acute Liver Failure Study Group; APACHE, acute physiology, age and chronic health evaluation; BiLE, Bilirubin-Lactate-Etiology score; CT, computerized tomography; mixed, mixed etiologies; INR, international normalized ratio; MELD, Model for End-stage Liver Disease, PT, prothrombin time; SOFA, Sequential Organ Failure Assessment.

[a] The ALFSG prognostic index, in contrast to the other indices listed, is designed to predict transplant-free survival rather than death/need for liver transplantation (see text).

Table 8

Etiologies divide nicely into those that are favorable (> 50% transplant-free survival) and those that are unfavorable (< 50% survival without transplantation)

Favorable prognosis	
• APAP	66%
• Ischemia	66%
• Pregnancy	55%
• Hepatitis A	56%
Unfavorable prognosis	
• Drugs	27%
• Indeterminate 25%	27%
• Autoimmune	26%
• Hepatitis B	26%
• Wilson disease	0%

Abbreviation: APAP, acetaminophen.